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"PROF. DR PARASKEV STOYANOV" VARNA
FACULTY OF PHARMACY
DEPARTMENT OF PHARMACEUTICAL CHEMISTRY

Tanya Nedelcheva Dimova

NEW AROMATIC IODONE DERIVATIVES - SYNTHESIS, STRUCTURE, PROPERTIES

ABSTRACT
of a dissertation for awarding the educational and scientific degree "doctor" in scientific specialty "Pharmaceutical Chemistry"

Scientific supervisors:
Associate Professor Iliyan Nikolov Kolev, Ph.D
Associate Professor Svetlana Fotkova Georgieva, Ph.D.

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The dissertation was discussed at a meeting of the Department of Pharmaceutical Chemistry and aimed to be defended before the Scientific Jury by a decision on Protocol No 64/24.11.2023. of the Faculty Council and a report with ent. No 108-705/28.11.2023 by prof. Dr. Petko Marinov, D.Sc. – Dean of the Faculty of Pharmacy at the Medical University – Varna, on the grounds of art. 24, para. 6 and Vol. 30, para. 3 of the RZRRB, art. 68, para 1 of the Rules for the Development of Academic Staff at the Medical University – Varna.

The dissertation work covers 101 pages, 29 figures, 75 diagrams and 10 tables. 213 titles were cited.

The experimental work on the dissertation was carried out at the Department of Pharmaceutical Chemistry at the Medical University - Varna.

The public defense of the dissertation will be held on 26.02.2024 at .....h. in the hall..... at an open session with a Scientific Jury consisting of:

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I. INTRODUCTION

Halogen substituted aromatic compounds have been used with undoubted success in organic and pharmaceutical synthesis. Rationally, the "design" of a wide variety of polysubstituted biphenyls, stilbenes and other derivatives can be successfully realized using this class of compounds. A number of halogenated compounds are also used for diagnostic purposes or the preparation of so-called tissue-imitating materials.

Therefore, the topic of this dissertation is aimed at the synthesis and detailed structural characterization of new iodo-, bromo- and mixed halogenossubstituted aromatic compounds – compounds with particularly great potential in the field of pharmaceutical synthesis and also in imaging.

Emphasis is also placed on the methods of growing monocrystals from each received compound, which undoubtedly prove their structure. In this regard, the toxicity of some of the resulting compounds has been determined. Separately, the possibility of making their real physical phantoms with application in contrast-enhanced mammography has been evaluated.

II. OBJECTIVE AND TASKS

Goal set:
To realize the synthesis of new iodo-substituted compounds and their bromine-containing analogues, as well as to evaluate their structural characteristics, toxicity and X-ray contrast properties.

In order to achieve this goal, the following tasks are set:
1. To synthesize new halogen substituted aromatics.
2. To establish the crystallization conditions and crystal structures of the newly obtained compounds.
3. To evaluate the photo-induced toxicity of some of the resulting iodo-containing compounds.
4. To assess the possibility of including diiodo-containing compounds in real, physical phantoms intended for contrast-enhanced mammography.
5. To propose new environmentally sound methods for the synthesis of the envisaged compounds.

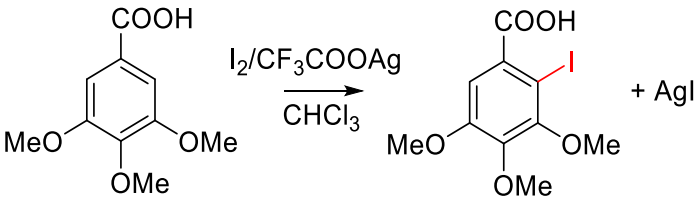
III. RESULTS AND DISCUSSION

Natural eudesmicacid was used as a precursor for the syntheses. The presence of the latter was found in the fruits of *Oleaeuropaea* and numerous representatives from *Eucalyptus spp*.

The acid was used as a precursor for the synthesis of several therapeutic agents - *Methoserpidine, Troxipide, Trimetozine, Trimethobenzamide, Hexobendine, Dilazep, Trimebutine*.

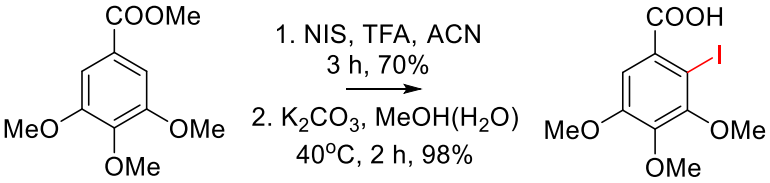
1. SYNTHESIS OF 2-IODO-3,4,5-TRIMETHOXY-BENZOIC ACID

The synthesis of 2-iodo-3,4,5-trimethoxybenzoic acid (ITMBA) is realized by the oxidation of 2-iodo-3,4,5-trimethoxybenzyl alcohol with the Jones reagent and our applications, a simpler and more effective method for direct iodination of 3,4,5-trimethoxybenzoic acid with the iodination system iodine-silver trifluoroacetate (I_2/CF_3COOAg; I_2/AgTFA) (Scheme 1).



Scheme 1. Iodization of 3,4,5-trimethoxybenzoic acid with Iodizing system I_2/CF_3COOAg in $CHCl_3$ medium.

ITMBA was also obtained as a result of hydrolysis of its respective ester (Scheme 2).

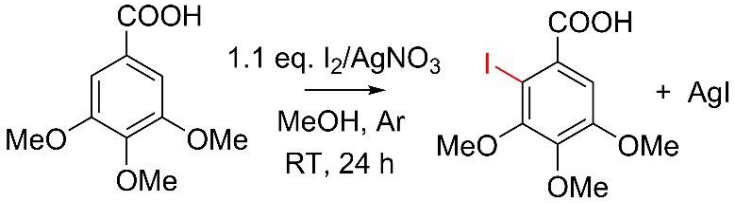


Scheme 2. Preparation of ITMBA from the methyl ester of 3,4,5-trimethoxybenzoic acid.

The I_2/CF_3COOAg system referred to is commonly used for halogenation of poorly activated and inactivated arenes – halo-substituted arenes and benzoic acid derivatives. The reaction conditions used by different authors are determined primarily by the reactivity capacity of the respective precursor (aromatic hydrocarbon); thus, for example, benzoic acid is iodinated in a medium of nitrobenzene at 150°C (with a yield of 84%), the methyl ester of 3,4,5-trimethoxybenzoic acid — in chloroform at room temperature (in 45% yield), and the iodination of the 3,4,5-trimethoxy-benzoic acid used by us — in boiling $CHCl_3$ (in 99% yield). Although, in most cases no detailed description of the experimental procedures is used, it is reasonable to assume that the iodination of arenes should be carried out in quantitative yield if the following conditions are observed: freshly prepared silver trifluoroacetate, inert atmosphere and strictly anhydride medium are used. The presence of traces of moisture (H_2O) in the reaction medium should prove to be the cause of hydrolysis of *the in situ* formed CF_3COOI to the corresponding lower active and unstable hypoiodist acid (HIO):

$$CF_3COOI + H_2O \longrightarrow CF_3COOH + HOI$$

The high toxicity of trifluoroacetic acid (CF_3COOH) forced us to revise the working protocol used. When working with the reagent pair $I_2/AgNO_3$, instead of I_2/AgTFA, we were able to obtain again the desired product, but in a much more convenient and environmentally friendly way (Scheme 3).

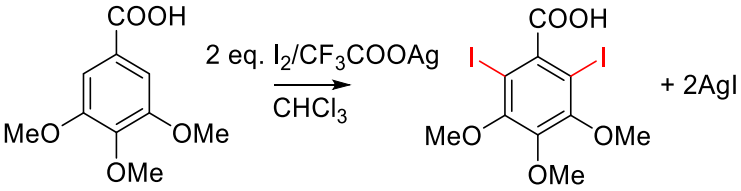


Scheme 3. ITMBA synthesis with Iodizing system $I_2/AgNO_3$ in methanol medium.

Objective confirmation of the suitability of this synthetic method was obtained by means of the ^1H NMR analysis of the raw product. Thus, instrumentally established the absence of undesirable impurities in the composition of the "raw" product; including the absence of unreacted TMBA. As pointed out in the literature review, pioneers in the use of $AgNO_3$ (as a co-agent) in direct iodination reactions of aromatic hydrocarbons are B. Hathaway *et al*. Furthermore, using the same reactant pair, M. Yusubov and co-authors were successful in "converting" a wide "gamma" aromatic hydrocarbons into aryl iodides under solid phase (mechano-chemical) conditions. However, for the first time, here, the potential of the iodizing system $I_2/AgNO_3$ in question was exploited in the targeted synthesis of ITMBA; an acid which was again mined in quantitative yield (+95%) and of extremely high purity (+98%).

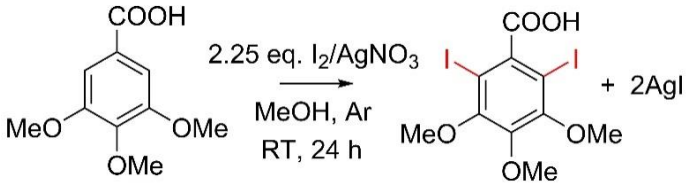
2. SYNTHESIS OF 2,6-DIIODO-3,4,5-TRIMETHOXYBENZOIC ACID

The synthesis of 2,6-diiodo-3,4,5-trimethoxybenzoic acid (DITMBA) was first realized by Kolev and co-authors. The authors propose an effective method for direct iodination of TMBA with Iodizing system I_2/AgTFA using a stoichiometric amount of it (Scheme 4).



Scheme 4. Synthesis of DITMBAwith Iodizing System I_2/AgTFA.

Instigated by the same limitations in the applicability of the used CF_3COOH, we decided to investigate the potential of the above reactant pair $I_2/AgNO_3$ in the synthesis of DITMBA (Scheme 5).



Scheme 5. Synthesis of DITMBA with Iodizing System $I_2/AgNO_3$.

With the introduction of this iodizing reagent, we were actually able to obtain again the desired product – DITMBA. The acid in question was obtained in a quantitative yield (> 95%); proved

in the conditions of repeated repetition of the presented experimental procedure. The purity of the target product was evaluated by means of 1H NMR analysis. In the spectra, of the "raw" products thus obtained, the presence of monoiodosic acid (ITMBA), and also that of the precursor used - TMBA.

The experimental conditions which we originally proposed, however, can be considered again by most users as relatively difficult to reproduce. Therefore, we set out to investigate the potential of the $I_2/AgNO_3$ reactant pair for the iodination of the acid in question under much more favourable, from a synthetic point of view, conditions — in the absence of an argon atmosphere and without observing strictly anhydride conditions.

In most methodologies presented, the work with this reagent is conducted in a strictly anhydride environment, since the INO_3 solutions are not stable during prolonged storage, and its preparation should be carried out in situ in the presence of the organic "target"/reactant. In one of the methodologies, however, the reagent in question was obtained by mixing its two precursors into a mortar. With this in mind, it seems logical to assume that even in the presence of water (atmospheric moisture) the activity of the reagent should be retained in full.

Therefore we decided to investigate the potential of our modified methodology in the synthesis of the target diiodosesubstituted acid; without the need to strictly observe anhydride conditions. In this connection the reaction was not carried out in argon atmosphere. Separately, 100 μL of water was intentionally introduced to the reaction mixture.

Contrary to expectations, at the end of the envisaged 24-hour reaction interval, apparently, we register the quantitative depletion of the introduced iodine – a sign that carries primary information about the quantitative course of the planned reaction. Subsequently, convincing analytical/instrumental (FTIR and NMR) evidence has also been obtained regarding this.

As can be seen from Figure 1, the profiles (or spectral fingerprints) of the newly obtained and previously reported FTIR spectrum fully coincide; a circumstance that can be perceived as real evidence of the identity of the target product.

As the analysis in question could not provide information on the purity of the reaction product, a further study proved necessary. In order to obtain objective information about this parameter, the product was additionally subjected to ^{1}H NMR analysis (Figure 2).

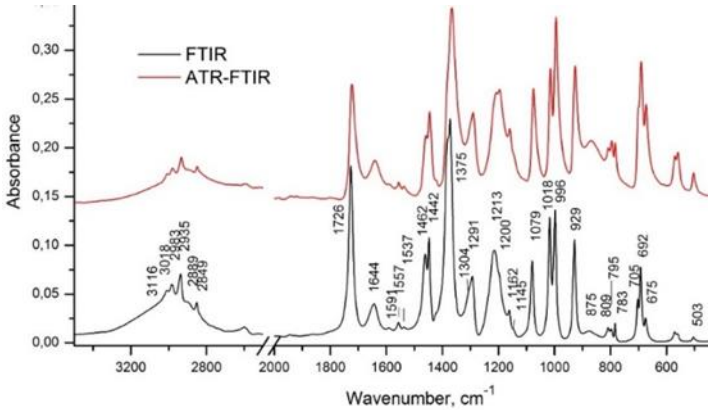


Figure 1. FTIR spectra of DITBA obtained in anhydrous methanol (black line) and water-methanol media (red line).

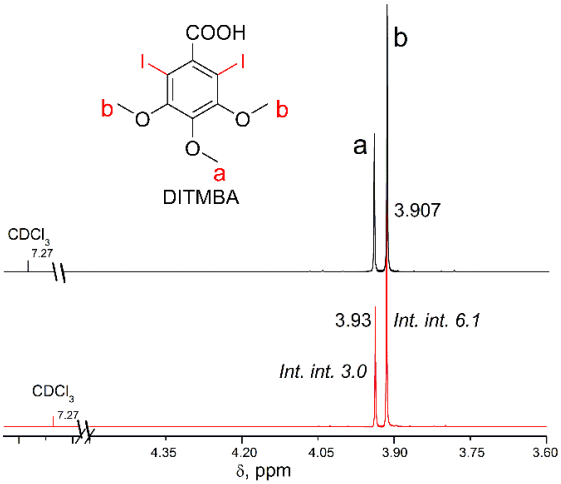


Figure 2. [1]H NMR spectra of DITBA obtained in anhydrous methanolic (black line) and water-methanol (red line) medium.

In the taken [1]H NMR spectrum (Figure 2) the presence of unreacted eudesmic acid, de facto, was not established. The same is true for monoiodoselocale (ITMBA) acid. Furthermore, the number and position of all the recorded resonance signals coincide with those reflected in our previous study.

Therefore, the presence of a minimum amount of water in the reaction mixture does not change the yield and purity of the desired product - DITMBA. Therefore, with full justification, it can be argued that, under the imposed experimental conditions, the goal set, namely, to provide a much more "convenient" method for the synthesis of diiodoselocalized eudesmic acid (2,6-diiodo-3,4,5-trimethoxybenzoic acid), has been successfully realized.

Moreover, the results obtained may have been used as evidence that in an aqueous methanolic environment, the in situ INO_3 reagent retains its activity/structural integrity. In addition, as indirect evidence of the same, the quantitative conversion of the introduced organic reactant can also be presented.

Therefore, the presented preparative methodology holds the potential to be optimal for the synthesis of the target DITMBA.

The potential of the reactant pair $I_2/AgNO_3$ is undoubted for the synthesis of ITMBA. The presented results even define it as preferred. These circumstances form the basis of our subsequent spectral and biological studies with larger amounts of the acids in question.

In addition, the inorganic residue (AgI) can easily "recover" the amount of silver consumed from the released inorganic residue (Scheme 6).

$$2\,AgI + Zn \longrightarrow 2Ag + ZnI_2$$

Scheme 6. Interaction between AgI and Zn.

In a transient study by our team, the main spectral (FTIR and NMR) features of DITMBA and more precisely of the carboxylic functional group in a di-ortho-iodine environment were presented and evaluated in detail, and with this the hypothesis was proposed that the same functional assumes orthogonal conformation relative to the benzene ring. Although all this is based on the optical behavior-structure relationship, we have not been able to obtain any real proof of these conclusions.

Therefore, the main focus of this dissertation development is not only on the implementation of a new, much more user-friendly

strategy for the synthesis of DITMBA, but also for the acquisition (growth) of its X-ray quality monocrystals.

Single crystal DITMBA growth

Losses in structural integrity of DITMBA crystals occurring during their "drying" (in a stream of dry argon) from the organic solvent used (the crystallization medium) can be perceived as a relevant factor hindering their subsequent SC-XRD analysis. The same is true for the solvent "crystal-bound" crystallites stored in dry glass vials, in which the organic solvent (toluene) used has the possibility to occupy their internal volume.

In an attempt to preserve the structural integrity of the DITMBA crystals thus obtained, all the relatively larger crystallites have been transferred, by means of tweezers, from the mother liquor into liquid paraffin. For this purpose, a suitable glass vial with a smaller internal free volume was also used. Thus processed, the crystals do not "at first glance" change their characteristics – transparency and integrity. Subsequently, their quality was instrumentally confirmed as fully acceptable. The acid in question, as will be presented below, crystallizes in the form of a toluene solvatomorph.

In addition, the unsalted crystalline form of the same acid was also successfully obtained. Our initial concerns, about the thermal instability of DITMBA, turned out to be completely unfounded. Unexpectedly, when recrystallizing the acid in boiling water, within a few minutes we get fine, needle-like crystals. The crystals obtained in this way are also structurally (SC-XRD) and spectrally (Raman and UV) characterized.

X-ray crystallography of DITMBA

DITMBA × toluene crystallizes in the P-1 space group with two molecules of acid and a toluene molecule in an asymmetric cell. In the absence of a crystal-incorporated solvent, DITMBA crystallizes in a space group P21/c; again with two molecules in an asymmetric cell.

In parallel with that reported earlier for ITMBA, the molecular structure of DITMBA solvatomorph, reveals a dimer arrangement of two independent molecules by means of hydrogen bonds between their COOH functionals (Figure 3). The carboxyl groups, in the structure of the "solvent-devoid" DITMBA, form a cathemal system of hydrogen bonds (Figure 4). In both cases, no parallel ring arrangement is observed as in the parent TMBA. In the DITMBA structure × toluene dimer the oxygen contacts, of the O-atoms involved in hydrogen bonding, are O1•••O7 2.6157(19) and O2•••O6 2.6158(19) Å, while the corresponding distances in the catemer DITMBA structure (no solvent included) they are longer, O1•••O7 2.641(2) and O2•••O6 2.682(2) Å respectively. In ITMBA these two O•••O distances are 2.627(9) Å, which is close to those of DITMBA × toluene dimer. It should be kept in mind that the structure of the monoiodo-substituted compound was determined at room temperature, whereas those of DITMBA specimens were determined at 123 K.

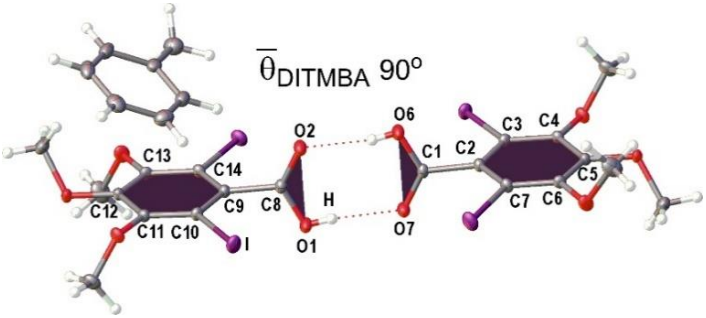


Figure 3. The dimeric structure of DITM × toluene

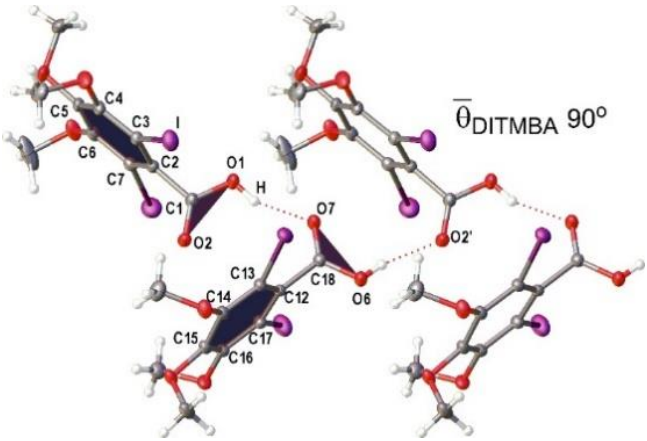


Figure 4. DITMBA catemer

In both DITMBA structures the carboxylic groups are perpendicularly oriented to the plane of their adjacent benzene rings. In the dimer solvatomorphic structure the deviations from the hypothetical (ideal) right angle are 2.84(7) and 4.85(7)°. In the DITMBA catemeric structure they are smaller - 0.04(7) and 1.96(7)°. In contrast, the double-walled angle between the carboxylic group midplanes and the benzene ring in the

previously reported monosubstituted equivalent of these acids, ITMBA, equals 14.3(5)º, making it orientationally semi-planar.

Vibration Analysis of DITMBA

In the preceding work of I. Kolev and co-authors associated with the same acid, it has been suggested that DITMBA molecules form a dimeric structure in the solid state. In the present thesis we provide crystallographie data which show that DITMBA molecules, lie in mutually perpendicular planes. As seen from Figure 4, the catemer possesses a plane of symmetry perpendicular to that organized by the C_6 residues. The first plane is characterized by *Cs* Symmetry. This means in practice that all vibrational motions are active and manifest in both the IR and Raman spectrum (Figure 5).

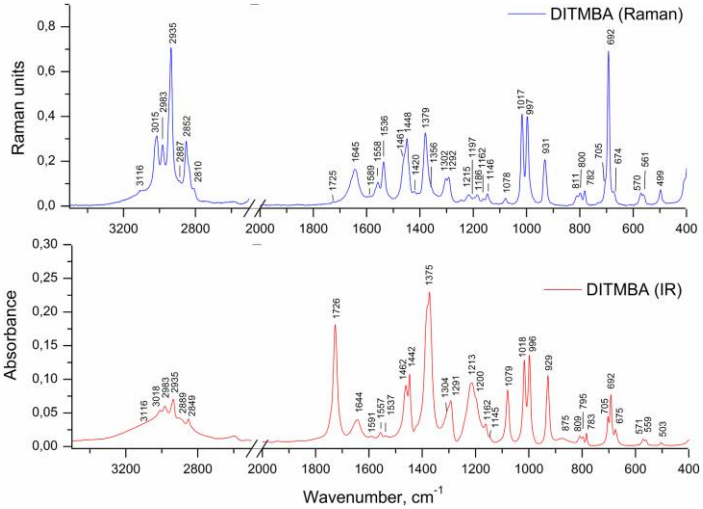


Figure 5. Raman (blue curve) and IR (red curve) spectra of DITMBA catamer in the region 3500 ÷ 400 cm^{-1}.

According to quantum-chemical calculations, two vibrational modes of the catemery-arranged carbonyl groups in the IR and Raman spectra are observed. One is asymmetric (1726 cm^{-1}) with greater intensity, and the other is symmetrical (1644 cm^{-1}) with lower intensity. The distance between them is approximately 82 cm^{-1}. The calculated Raman frequencies predict that the low-frequency band is significantly more intense than the high-frequency band. This is actually observed in the experimental Raman spectrum. The observed high-frequency band of H-linked DITMBA carboxyl groups can be explained not only by the ortho-effect present (see Figure 5), but also by the imposed electrostatic influence of C-I dipoles above them.

UV spectral analysis

Although the planar architecture of TMBA is profoundly affected by the ortho-positioned iodine atom, the distinctive electro-spectral features of this (parent) chromophore remain unaffected by it (Figure 6). Indeed, as can be seen from the presented figure, the spectrum of ITMBA somewhat resembles that of the parent (TMBA) acid. Furthermore, the system in question responds in an expected manner to the imposed steric/steric effect. In this regard, the observed “blue” shift of the main electron-transfer (ET) band by approximately 7 nm can be taken as a real experimental measure of the presence of weak steric interference imposed by the introduced iodine atom on the conjugated TMBA system. The same regularity is observed in the case of the isomorphous monobromo-substituted acid, where the substitution pattern is identical and the imposed steric effect is even less pronounced.

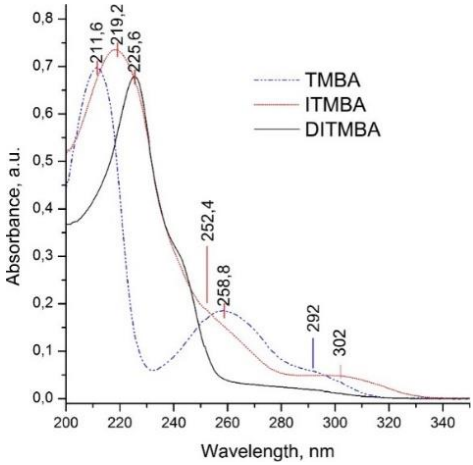


Figure 6. UV spectra of TMBA (blue, dashed curve), ITMBA (red curve) and DITMBA (black, solid curve).

With respect to the secondary ET band of the same product with much lower intensity, its maximum is offset approximately 7 nm in the "red" region; i.e. in the expected direction. The same applies to the most intense (benzenoid) band in the spectrum. The effective halogen atom involvement, in conjugation with the parent system, is in this case the most probable cause of the observed bathochromic offset of the bands in question. Of course, the influence of the remaining substituents in the total absorption profile (ITMBA) is difficult to assess, due to the "electron-amphoteric" nature (p-electrondonor and d-electronacceptoren) of the halogen atom considered. In the presented section the intensity changes of the observed strips are deliberately not discussed, given the expected experimental uncertainty in the sampling process.

As far as the DITMBA spectrum is concerned, a suigeneris spectral phenomenon is constituted in it (Figure 6). It has been suggested that the absence of ET banding in the DITMBA

spectrum seems fully justified when the considered double-walled angle, θ DITMBA (Figures 3 and 4), reaches its limiting value or, in other words, when the expected resonance interaction between carboxylic and aromatic functional is completely discontinued. The absorption band (λ_{max} 221 nm) recorded in the spectrum of the product in question is only evidence of the realized p-π electronic interactions between the "isolated" (from the presence of the carboxylic function) benzene chromophore and the other five +M substitutes.

Of course, the same phenomenon has been observed by other authors, but for differently substituted benzenoids - biphenyls, nitrobenzenes, acetophenones, etc., in which the involvement of the aromatic residue in the total conjugation is also completely discontinued. It would therefore be reasonable to assume that orthogonality (established in crystalline state) between the benzene ring and the carboxylic functional group in the iodine overcrowded DITMBA system is also inherent in dilute solutions of the acid in question.

In vitro analysis of cyto- and phototoxicity of DITMBA

The in vitro cytotoxicity and phototoxicity of DITMBA, ITMBA and TMBA were investigated using the 3T3 NRU assay. For this purpose, the cells used were incubated with the test substances in the concentration range from 15 to 4000 μg/ml for 24 hours under standard conditions. Cytotoxicity/ phototoxicity is expressed in % vs. negative control. The obtained results are presented in Fig. 7.

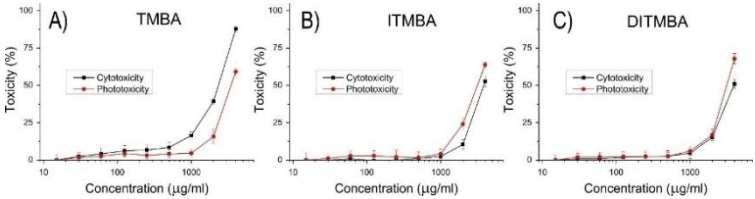


Figure 7. Dose-response curves for cytotoxicity and phototoxicity determined with the BALB 3T3 cell line. A) TMBA, B) ITMBA, C) DITMBA. The values were averaged ± SD from three independent experiments, n = 6.

Table 1. Mean values for CC_{50} and PIF value.

Cell line	Simple	Mean values for CC_{50} ± SD (µg/ml)		PIF*
		Cytotoxicity	Phototoxicity	
BALB 3T3	TMBA	2438.14 ± 65.74	3580.93 ± 61.84	0.68
	ITMBA	3854.91 ± 145.18	3298.76 ± 121.16	1.17
	DITMBA	3899.02 ± 101.38	3306.29 ± 85.43	1.18
	Acridine Orange**	5.51 ± 0.33	0.14 ± 0.06	39.3

** PIF (photoirritation factor), PIF < 2 is not phototoxic, PIF ≥ 2 and < 5 probable phototoxicity, PIF ≥ 5 phototoxic.*

*** Positive control (phototoxic compound).*

CC_{50}/PC_{50} values (50% cytotoxic/ phototoxic concentration) were calculated by nonlinear regression analysis based on the established dose-biological response relationships (Table 1). For each test compound, the obtained CC_{50} values can also be used to determine the so-called "CC_{50} values". PIF (photoirritation factor): PIF = CC_{50}/PC_{50}.

For all the compounds tested, the calculated PIF < 2, which demonstrates a high level of photosafety. The cytotoxicity of

ITMBA and DITMBA (CC_{50} = 3854.91 ± 145.18 and 3899.02 ± 101.38 μg/ml respectively) was significantly lower ($p < 0.001$) than that of TMBA (CC_{50} = 2438.14 ± 65.74 μg/ml). The results reveal that TMBA, ITMBA and DITMBA are safe for topical application.

In conclusion, it can be summarized that a new highly effective preparative method for the synthesis of 2,6-diiodo-3,4,5-trimethoxybenzoic acid (DITMBA) has been introduced. Being environmentally sound and high-yielding, this method may be used for the synthesis of significant quantities of the acid in question.

In addition, two methods have been successfully established allowing the crystallization of DITMBA in the form of toluene solvatomorph and of unsalted catemer. Thus, the limit of the DITMBA-specific ortho-effect adopted earlier found its crystallographic confirmation.

Moreover, as the results of the present and preceding vibration analysis show, most likely, with removal of the crystalline-incorporated toluene, a restructuring of the DITMBA dimer into a noncentro-symmetric catemer is realized.

On the other hand, the data from the UV analysis testify that even in a solution, the acid under discussion retains its specific orthogonal (or quasiorthogonal) configuration.

Since DITMBA acid is supposed to be photosensitive, we find that it shows no signs of photoinduced toxicity to the test cell line BALB/3T3 branch A31.

Figure 8 presents the experimental X-ray micrographs of an improvised phantom with radiocontrast agents at 40, 60, 80 and 100 kV. As seen with an increasing kV, a lower contrast of the

images is observed, which could be due to the increased probability of Compton's interaction. In addition, visually the contrast of NaDITMB is slightly lower compared to that of other substances.

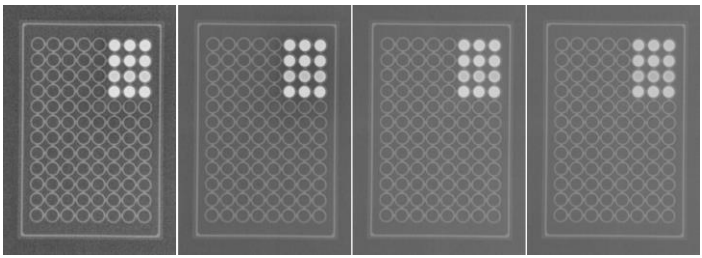


Figure 8. Xray images of the contrast phantom at 40, 60, 80 and 100 kVp (left to right). First row - Ultravist 350; second row - Omnipaque 350; third row – NaDITMB; fourth line - Ultravist 370.

Figure 9 presents the realized measurement of the different radiocontrast agents in the compiled phantom. The results of the analyzed areas with an area of 24.576 mm^2 for each contrast material are summarized.

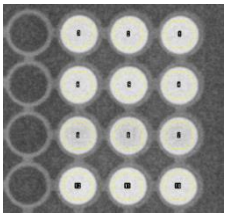


Figure 9. Measured "grey" values for the phantom imaged. The area chosen is the same for all contrast iodine agents and equals 24.576 mm^2. Zone 1-3 corresponds to Ultravist 350, zone 4-6 - to Omnipaque 350, zone 7-9 - to NaDITMB, while zone 10-12 presents Ultravist 370.

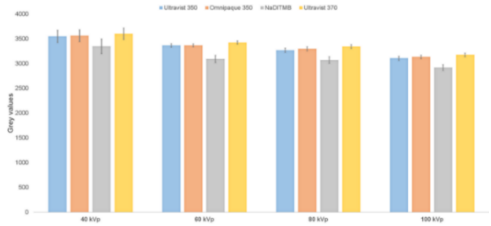


Figure 10. Measured "grey" values for the contrast materials depicted.

Comparing the individual values (in the "grey" scale) between the different contrasting materials (Figure 10) confirms the findings of the simulation study (Figure 9). While clinically used contrast materials demonstrate almost the same "grey" values, the proposed NaDITMB shows somewhat lower ones. This trend is maintained for all energy levels. At a very low energy (of 40 kV) it is obvious that the discrepancy between NaDITMB and Iohexol 350 (Omnipaque) as well as Ultravist 350 is immaterial. In fact, 40 kV represents the lower energy range of a general purpose radiographic technique, where the photon flux may be insufficient to produce images with reduced fluctuations. For the higher kV, the results convincingly demonstrate a smaller difference between NaDITMB and Omnipaque. This contrast becomes particularly evident with a maximum deviation of 8% at 60 kV on the X-ray beam.

The data of the present study can be summarized as follows: DITMBA can be used as an alternative to clinically used radiocontrast agents in the construction of new physical phantoms designed for contrast-enhanced mammography.

The data that support the findings of this study are publicly available at http://doi.org/10.5281/zenodo.8296786.

3. SYNTHESIS OF 2-IODO-3,4,5-TRIMETHOXY-BENZALDEHYDE

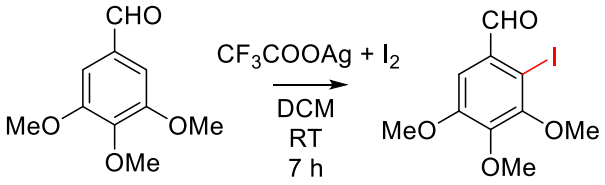
3,4,5-Trimethoxy Benzaldehyde - halogenation reactions (iodination, bromination), oxidation

Aromatic aldehydes are widely used in the production of medicinal substances, dyes, pesticides, etc. Thus, for example, 3,4,5-trimethoxy-benzaldehyde (ITMBD) is applied in the synthesis of Trimethoprim.

In this connection, Harfenist and also F. Ziegler obtained 2-iodo-3,4,5-trimethoxybenzaldehyde by oxidation of 2-iodo-3,4,5-trimethoxybenzyl alcohol with MnO_2 in benzene solution. The methodology was also used for the synthesis of 2-bromo-3,4,5-trimethoxybenzaldehyde. Alternatively, the method of oxidation of 3,4,5-trimethoxybenzaldehyde with pyridinium fluorochromate (PFC) in N,N-dimethylformamide (DMF) medium and in the presence of para -toluenesulfonic acid (TsOH).

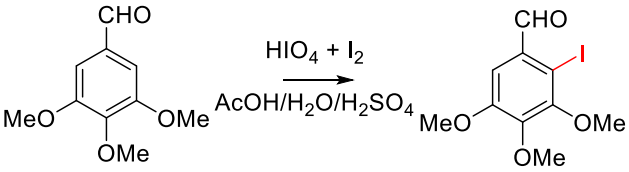
2-iodo-3,4,5-trimethoxy benzaldehyde

In this regard, 2-iodo-3,4,5-trimethoxybenzaldehyde (Scheme 7) was first prepared by Bradley et al. as to the solution of the reactant aldehyde in CH_2Cl_2, the authors added a previously prepared solution of silver(I) trifluoroacetate ($AgCOOCF_3$) and to the resulting mixture they subsequently added a saturated solution of iodine. The same methodology was used by M. Nunn et al.



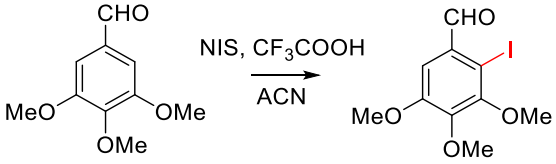
Scheme 7. Synthesis of 2-iodo-3,4,5-trimethoxybenzaldehyde by the Bradley method.

N. Nicolaus et al. replace Bradley's dichloromethane with chloroform. S. Rossington et al. iodinated the aromatic aldehyde using the method used by Suzuki et al. iodination system I_2/H_5IO_6 (Scheme 8).



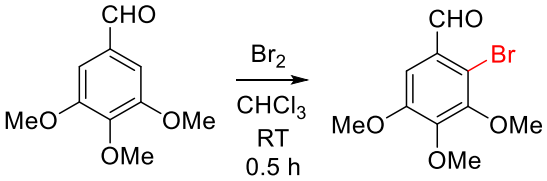
Scheme 8. Synthesis of 2-iodo-3,4,5-trimethoxybenzaldehyde using the reagent pair I_2/H_5IO_6.

W. Gao et al. prepared 2-iodo-3,4,5-trimethoxy-benzaldehyde using N-iodosuccinimide (NIS) as the iodination reagent (Scheme 9).



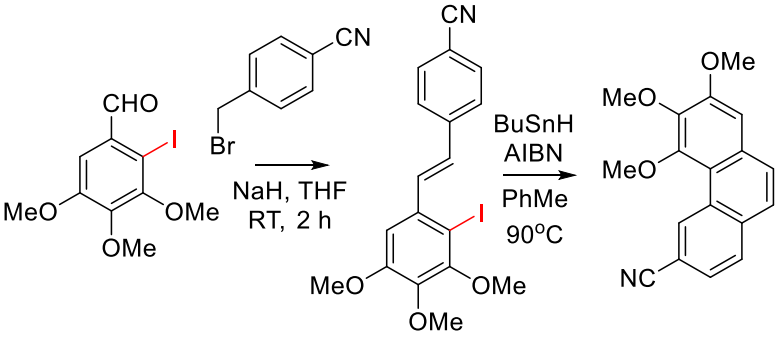
Scheme 9. Synthesis of 2-iodo-3,4,5-trimethoxybenzaldehyde with the iodination reagent N-iodosuccinimide (NIS).

M. Nunn synthesized 2-bromo-3,4,5-trimethoxy-benzaldehyde using the method developed by Brown et al. method of direct bromination of aldehyde with molecular bromine in chloroform medium. The authors obtained the product in 99% yield (Scheme 10).



Scheme 10. Synthesis of 2-bromo-3,4,5-trimethoxybenzaldehyde by Brown's method.

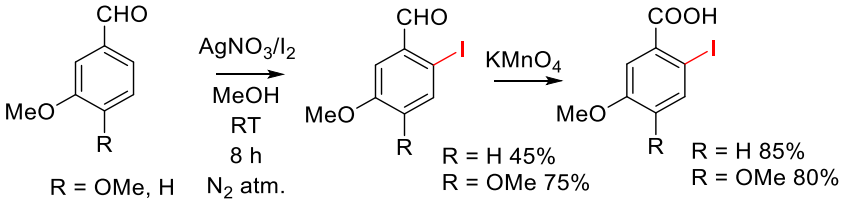
The iodinated aldehyde obtained by the same authors was used for the synthesis of other, much more complex compounds from a structural point of view - stilbene, phenanthrene derivatives (Scheme 11), etc.



Scheme 11. Synthesis of iodostilbene and 5,6,7-trimethoxy-3-phenanthrenecarbonitrile from ITMBD.

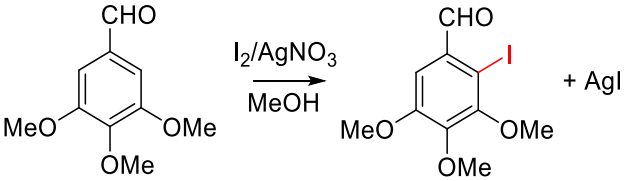
The opportunity to explore the potential of the $I_2/AgNO_3$ system in the synthesis of the title compound is again raised.

Using this iodination system, A. Ilangovan et al. succeeded in obtaining 2-iodo-5-methoxybenzaldehyde and 2-iodo-4,5-dimethoxybenzaldehyde (Scheme 12).



Scheme 12. Preparation of ortho-iodo-substituted derivatives of benzaldehyde and benzoic acid.

Indeed, using the indicated iodination system, we were able to obtain the desired aromatic aldehyde in quantitative yield (Scheme 13). ITMBD was isolated as pale yellow, acicular crystals in 85 to 92% yield; MP 55 ÷ 57°C; 66 ÷ 66.5°C; 68 ÷ 69°C.



Scheme 13. Synthesis of 2-iodo-3,4,5-trimethoxy-benzaldehyde (ITMBD) with the $I_2/AgNO_3$ system in methanol medium.

The molecular composition of the obtained product is determined by means of ATR-FTIR spectroscopy.

Vibrational analysis of ITMBD

Correlation of the vibrational frequencies was accomplished by comparative analysis of the recorded spectrum of 2-iodo-

3,4,5-trimethoxybenzaldehyde (ITMBD; Figure 11) with those of 3,4,5-trimethoxybenzaldehyde, 3,4,5-trimethoxy-benzoene acid (TMBA), 2-iodo-3,4,5-trimethoxy-benzoic acid (ITMBA) and related other derivs.

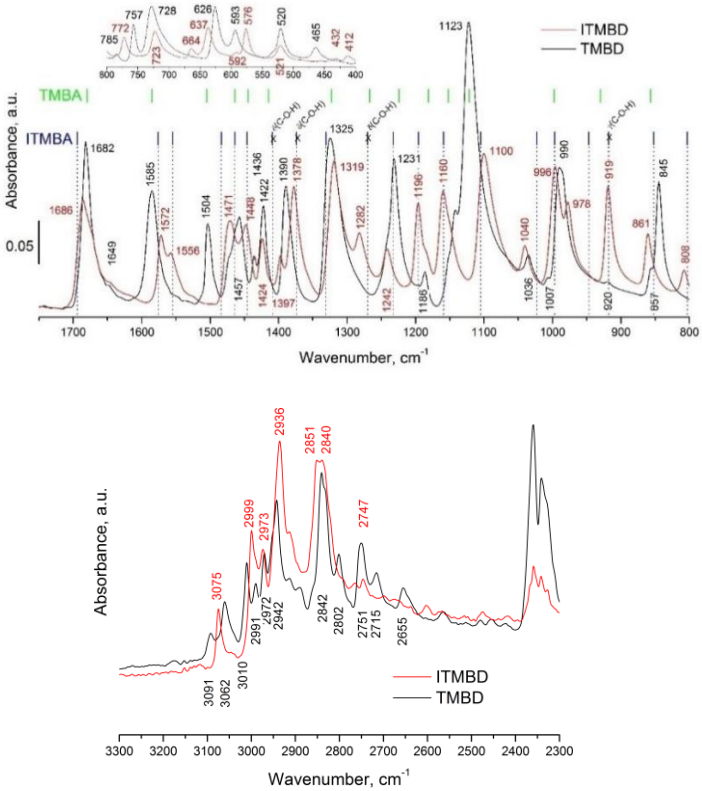


Figure 11. ATR-FTIR spectra of 2-iodo-3,4,5-trimethoxybenzaldehyde (red line) and 3,4,5-trimethoxybenzaldehyde (black line) in the region 3300 ÷ 400 cm-1; blue and green vertical lines represent the positions of the absorption maxima of ITMBA and TMBA.

In the ATR-FTIR spectrum of 2-iodo-3,4,5-trimethoxy benzaldehyde, the bands attributed to the asymmetric valence vibrations of the C-H bonds are observed at 2973 and 2936 cm^{-1}, and those associated with the symmetric valence C-H vibrations at 2840 cm^{-1}. It should be noted here that the spectrum of the product in question does not show the "halo" characteristic of carboxylic acids from 2400 to 2800 cm^{-1}, inherent to the asymmetric O-H···O valence vibrations which is a fact that negates the oxidation potential of the reagent used towards the CHO group present. Absorption bands characteristic of asymmetric and symmetric C-H deformation vibrations are found at 1488 and 1424 cm^{-1}, respectively. In addition, three medium- to high-intensity bands are observed at 990, 1100, and 1282 cm^{-1}. The latter can be rationally related to the vibrations of the three MeO groups present, namely: the symmetric and asymmetric O-CH_3 valence vibrations, as well as the vibrational motion of C-OCH_3 bonds. Bands observed in the spectrum of the product under consideration at 757, 728 and 432 cm^{-1} can be assigned to valence and deformation C-OCH_3 vibrations. On the other hand, the bands recorded at 1160 and 1196 cm^{-1} correlate well with the pendulum oscillations of CH_3 molecular residues. Two pairs of absorption bands in the 1650–1320 cm^{-1} region associated with the tangential vibrations of the aromatic C=C bond are usually present. According to the well-known Wilson notation, these bands are designated as 8a, 8b, 19a and 19b. In general, their position and their intensity are affected not only by the nature but also by the number and position of the substituents in the aromatic ring. In the spectrum of isomorphously substituted ITMBA, three of these bands are observed with medium intensity at 1577, 1554 and 1484 cm^{-1}, and in the spectrum of ITMBD at 1572, 1556 and 1471 cm^{-1}.

Interestingly, it is noted that the presence of the fourth band cannot be adequately attributed/established, because it is most likely "hidden" in the available bands characteristic of the methyl, asymmetric and symmetric C-H deformation vibrations or among the others those localized in the frequency interval of 1320 ÷ 1500 cm^{-1}.

According to G. Varsanyi, the frequency ranges of 14 (Kekule), 1 ("breathing") and 12 (deformation) vibrations are 1200–1260, 1120–1200 and 1020–1090 cm^{-1}, respectively. The frequency values of these motions present in the spectrum are recorded at 1242, 1186 (shoulder) and 1040 cm^{-1}.

The very weak to moderate intensity bands observed at 808, 785, 664, 637, 592, 521 and 412 cm-1 are attributed to the deformational CCC vibrations of the aromatic phenyl residue.

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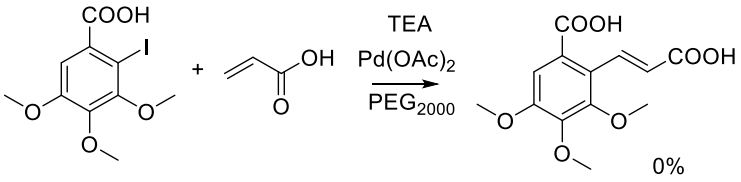
The very weak to moderate intensity bands observed at 808, 785, 664, 637, 592, 521 and 412 cm^{-1} are attributed to the deformational CCC vibrations of the aromatic phenyl residue.

We register the presence of an aldehyde group in the ATR-FTIR spectrum of ITMBD by the available absorption band with a maximum at 1686 cm−1. We use the significant change in the profile of the latter as an additional indication of the presence of an iodine atom in the molecular structure of the product. The observed shift in the "blue" region is indicative of the presence of a strong intramolecular, electrostatic interaction transmitted

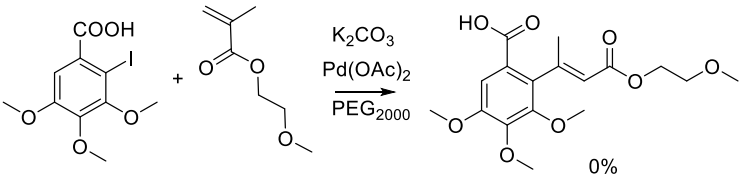
through the space between the adjacently positioned iodine and oxygen atoms. The increase in the frequency of vibrational C=O motions should also be related to the reduced participation of the latter in resonance interactions with the aromatic system. It should also be noted that a similar effect was found in the case of ITMBA.

Since the COOH functional could be the reason for the impossible participation of ITMBA in the Heck reaction, we decided to conduct analogous studies with the resulting ITMBD.

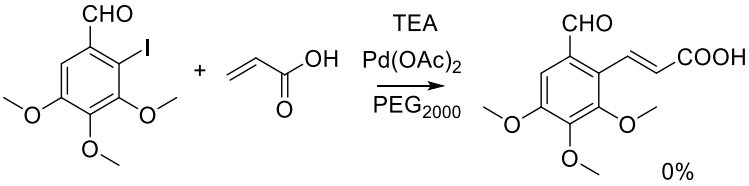
In none of the several reactions carried out with the indicated aldehyde, we were able to achieve the formation of the desired products (Schemes 14-16).



Scheme 14. Synthesis of 2-(2-carboxyvinyl)-3,4,5-trimethoxybenzoic acid.



Scheme 15. Synthesis of 3,4,5-trimethoxy-2-(3-(2-methoxyethoxy)-2-methyl-3-oxoprop-1-en-1-yl)benzoic acid.

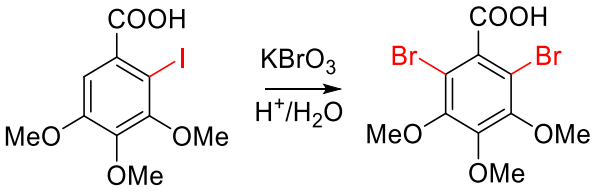


Scheme 16. Synthesis of 3-(6-formyl-2,3,4-trimethoxyphenyl)acrylic acid in the presence of TEA.

Therefore, as a reason for the impossibility of participation of ITMBA and ITMBD in the indicated reaction, we should highlight the steric nature of the available substituents (methoxy and carboxyl/aldehyde group), which prevent the participation of this type of substrates in C-C coupling with α-unsaturated esters and heartburn.

4. SYNTHESIS OF 2,6-DIBROMO-3,4,5-TRIMETHOXYBENZOIC ACID

Organobromine compounds are also highly valued precursors in organic and pharmaceutical synthesis. Their participation in homo- and cross-coupling reactions is indisputable and even preferred, given the inertness of this type of coupling to electromagnetic radiation from the visible part of the spectrum. A number of brominating agents are used for their synthesis, but only a few of them appear to be completely safe for the user-chemist and for the environment. Therefore, in the present section, a new and environmentally friendly method for the synthesis of 2,6-dibromo-3,4,5-trimethoxybenzoic acid (Scheme 17) is presented, although the latter can be freely purchased from various manufacturers.



Scheme 17. Synthesis of 2,6-dibromo-3,4,5-trimethoxy-benzoic acid

2,6-Dibromo-3,4,5-trimethoxybenzoic acid (DBrTMBA) was obtained in an attempt to synthesize a mixed halogen-substituted TMBA. Instead of the desired product (BrITMBA), one was separated, in the structure of which we registered the presence of two identical halogen (bromine) atoms by means of SC-XDR analysis. As the reason for the appearance of this compound, we present the manifestation of two consecutive reactions to the used acid/precursor - 2-iodo-3,4,5-trimethoxybenzoic acid, namely: that of the desired bromination and unexpected transhalogenation of iodine with a bromine atom. The synthesis in question was realized using KBrO3 in a sulfuric acid environment (Scheme 17).

$KBrO_3$ is a convenient source of molecular bromine. This reagent is used both for the bromination of deactivated aromatic compounds and in oscillatory reactions. It is soluble in water but almost insoluble in alcohol. For analytical purposes, it was dried at 100–110°C for 1 hour. $KBrO_3$ is a strong oxidizer (standard potential 1.44 V) with relatively low toxicity. During its storage, care must be taken that it does not come into contact with mineral acids and organic compounds.

$KBrO_3$ (including $NaBrO_3$) react quantitatively with KBr in dilute solutions of mineral acids (usually in those of sulfuric acid): $BrO_3^- + 5\ Br^- + 6\ H^+ \rightarrow 3\ Br_2 + 3\ H_2O$

The resulting *in situ* Br_2 is a convenient reagent for the bromination of alkenes and aromatic compounds. Methyl ketones, substituted cyclo-hexenones, thiophene, organoboron compounds, cyclopentamethylene-diphenyl tin compounds and also sulfonyl hydrazides have been successfully brominated with it.

Similar to 2,6-diiodo-3,4,5-trimethoxybenzoic acid (DITMBA) presented above, the crystal structure of the title dibromo compound is composed of hydrogen-bonded DBrTMBA molecules.

X-ray crystallography of DBrTMBA

DBrTMBA (Figure 12) crystallizes in monoclinic space group - P21/n. In each asymmetric cell (Z=4), the presence of only one molecule of the acid in question was found.

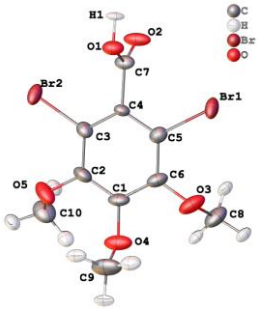


Figure 12. Structure and notation scheme of DBrTMBA.

According to the obtained data, the DBrTMBA crystal is transparent, colorless acicular, with dimensions of 0.08 × 0.06

× 0.03 mm^3 of DBrTMBA, suitable for SC-XRD analysis, was selected and mounted on a Rigaku Oxford Diffraction Super Nova diffractometer. The diffraction pattern was obtained using an AtlasS2 CCD detector, processed and finalized using CrysAlisPro (42.92a) software (Rigaku Oxford Diffraction, 2019). In contrast to the tightly connected, through a pair of hydrogen contacts, molecules of mono- and diiodo-3,4,5-trimethoxybenzoic acid (ITMBA and DITMBA.toluene), the resulting product does not form an H-bonded dimer structure in the solid state (Figure 13). . Instead, a continuous chain of hydrogen bonds (22281408_rev.cif) in crystallographic direction b is observed connecting the individual molecules of DBrTMBA. Therefore, from a structural point of view, the supramolecular structure of DBrTMBA resembles that of the previously reported DITMBA. The determined intermolecular hydrogen (O1—O2) bond distance in DBrTMBA is 2.617(5)Å (Figure 14).

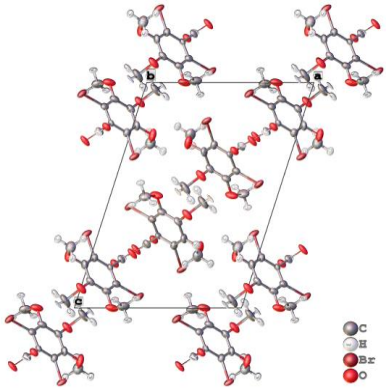


Figure 13. Packing of DBrTMBA along the crystallographic b-direction.

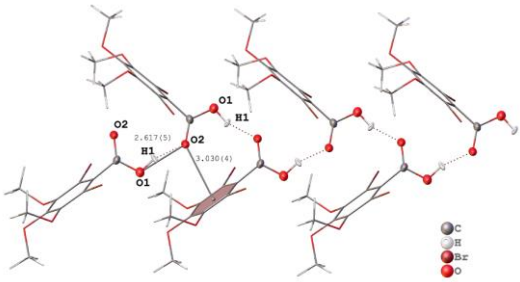


Figure 14. Syndiotactic arrangement of DBrTMBA molecules in crystallographic direction b.

Another interesting structural feature in this syndiotactic specimen, we can find in the contact (lp)—π(C6) interaction between the carbonyl-O2 atom and the geometric benzene center; of 3.030 (4)Å (Figure 14). This contact probably prevents the realization of a dimeric type of structure inherent to both ITMBA and the DITMBA × toluene sample. In the latter, the toluene solvent molecule most likely "prevents" the realization of this type of interaction. The carboxyl group of DBrTMBA (O1-C7-O2) adopts a configuration close to orthogonal (86.7(2)°) to the mean geometric plane of ring C6. The reported deviation is medial to the reported values for DITMBA catemer. In order to gain more detailed information about the crystalline DBrTMBA "packing" and the contribution of individual (closest) contacts to intermolecular interaction, a specialized software program (Crystal Explorer) was used, allowing Hirshfeld analysis to be carried out. Figure 19 (images C and D) presents the realized closest interaction contacts for DBrTMBA, namely hydrogen bonding and O(lp)—π(C6) type interaction in subfigure F. The properties of the hydrogen

contact are visualized by electrostatic potential mapping of the Hirshfeld DBrTMBA surface (E).

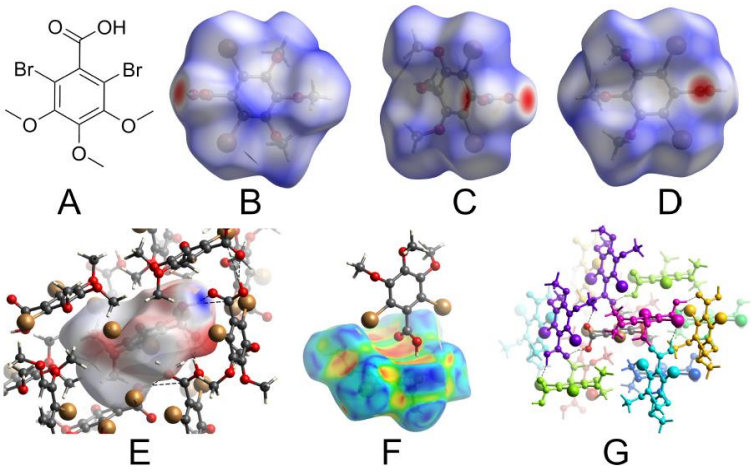


Figure 15. Chemical structure (A) and three differently oriented (B-D) DBrTMBA with d-Hirshfeld surface; (E) nearest contacts and electrostatic potential (−0.077, 0.252); (F) Hirshfeld surface curvature and (G) neighboring localized molecules.

In Figure 20-G, intermolecular interaction energies are presented in different colors. As expected, the strongest intermolecular interaction is realized in the contact H and O(lp)—π (C6) interaction (the purple colored neighboring molecule).

The fingerprint plots (Figure 16) present the differences in the degree of interatomic interaction for Br—H, O—H, H—H, and C—H bonds, revealing the high degree of Br—H and O—H interactions.

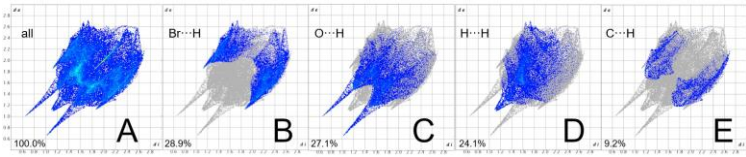


Figure 16. Hirshfeld surface fingerprint plots for DBrTMBA.

ATR- FTIR analysis of DBrTMBA

The vibrational frequencies of DBrTMBA were determined by comparative analysis of its IR spectrum data with those of DITMBA and of mixed, halogen-substituted BrITMBA (Figure 17). Thus, we can observe important spectral changes when replacing iodine with bromine atoms. As might be expected, this structural transformation mainly affects the vibrations of the benzene ring C-Br carboxyl group and to a lesser extent the vibrations of the H_3C-O groups.

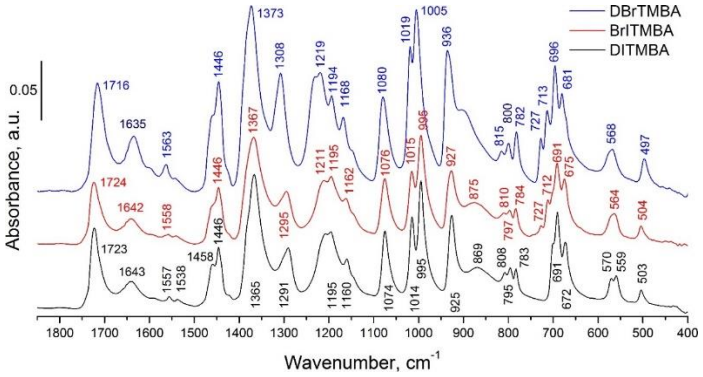


Figure 17. ATR-FTIR spectrum of DBrTMBA (blue line), DITMBA (black line) and BrITMBA (red line) in the 1800 ÷ 400 cm^{-1} range.

Vibrations of the phenyl ring

A significant change in the molecular force field is observed in the "breathing" benzene vibrations falling in the 1600 ÷ 1450 cm^{-1} region (Figure 17). Three of these bands of relatively high to medium intensity are detected in the presented spectrum.

The position and intensity of the indicated bands depend primarily on the nature, number and localization of the surrounding substituents. In the spectrum of DBrTMBA these bands are registered at 1601, 1563 and 1544 cm^{-1}, and in the spectra of DITMBA and BrITMBA samples - at 1588, 1557, 1538 and 1594, 1558, 1542 cm^{-1}.

The weak to medium intensity bands observed in the DBrTMBA spectrum at 904, 815, 696, 681, 568 and 497 cm^{-1} most likely characterize the benzene C=C-C deformation vibrations.

In the spectrum of DBrTMBA, the bands characteristic of the valence asymmetric and symmetric C-Br vibrations are observed at 713 and 727 cm^{-1} (Figure 17).

Features and specific spectral behavior of the DBrTMBA catemer

In the crystalline phase, similar to DITMBA, DBrTMBA molecules interact to form an infinite catemer-associate. In the IR-spectrum of DBrTMBA, the bands characteristic of ν(C=O) vibrations are observed at frequencies 1635 and 1716 cm^{-1} (Figure 17).

The unusual spectral behavior of the DBrTMBA catemer should be rationally attributed to two effects:

- that of the imposed steric effect of bromine atoms on the carboxyl functional, which causes an increase in the frequency of the valence ν(C=O) vibration, the out-of-plane γ (-O-H...O) and δ(C-O-H) vibrations (see Figure 17) and
- that of the available polarization effect (electrostatic interaction through space) between C-I dipoles with that of the carboxyl functional.

The structural changes resulting from the manifested ortho-effect are expressed in the changes of the dihedral angle θ concluded between the planes of the carboxyl groups and the aromatic rings.

The valence O-H vibrations of the carboxylic DBrTMBA functional should be particularly sensitive to the established electronic-structure effects. However, the profile of the O–H bands is extremely complex in the crystalline state. In this and other cases, the valence O–H vibrations are represented by a significantly broad absorption band occupying the region from 3200 to 2500 cm^{-1}. The overlap of this broad O–H band with several $C–H_3$ bands present in the region (characteristic of the three present $–OCH_3$ groups) further complicates the correct assignment of the valence vibrations of these groups at 3146 and 3071 cm^{-1}. However, the characteristic out-of-plane γ(-O-H...O) vibration of the acid functional turns out to be significantly more informative and indicative of its strength. The observed high-frequency shift of this band in the DBrTMBA spectrum (at 937 cm^{-1}), compared to that in the DITMBA spectrum (at 925 cm^{-1}), is also accompanied by a slight increase in the former's intensity. The lack of conjugation between the acid functionals of DBrTMBA and DITMBA and

their benzene residues should reduce the intermolecular bonding forces, which would also cause their low-frequency shift. However, the C-I and C-Br dipoles of ITMBA and BrTMBA should exert a much stronger polarizing effect on their available carboxyl functionalities than those of DITMBA and DBrTMBA, due to the fact that the latter fall in a plane perpendicular to the plane of their aromatic rings. The result is expressed in the recorded weaker polarization of DITMBA and DBrTMBA C=O..H-O- "catemerically-bonded" groups due to the spatial arrangement of their C-I and C-Br dipoles. This explains the higher frequency of the observed out-of-plane γ(-O-H...O) band in the infrared spectra of the two catemer samples. The two δ(C–O–H) plane strain vibrations of ITMBA are localized at 1406 and 1373 cm^{-1}. The pair of plane strain δ(C–O–H) frequencies in the IR spectrum of DITMBA can be referred to as syn- and antiphase, corresponding to low and high intensity spectral bands. In contrast to the spectral data for ITMBA, those for δ(C–O–H) of DITMBA and DBrTMBA are observed at 1425 and 1365 cm−1 and 1425(7) and 1373 cm^{-1}. Comparing these data with those for TMBA, we find that the high-frequency band at 1425 cm^{-1} is intense, while the band at 1375 cm^{-1} is weakly intense. It is obvious that the change in coupling does not significantly affect the position of the out-of-phase, deformation oscillation, while the in-phase oscillation turns out to be more sensitive. The dipole C-I and C-Br electric field component has a significant effect on the transition dipole moment in the in-phase strain mode, which has an almost parallel direction to the dipole electric field component. Therefore, a noticeable change in the intensity of these stripes is registered here (Figure 17). Electronic factors such as induction and mesomeric effect of substituents also influence

the position of the carbonyl band for DBrTMBA. It is obvious that due to the steric effect of the two bromine atoms, the mesomeric effect of the substituents is probably much less pronounced and "confined" to the region of the aromatic ring system. It should be noted that the observed frequency shift of the carbonyl group in DBrTMBA, by analogy with the diiodo-substituted counterpart, may be further influenced by the strong electron-accepting effect of the three methoxy groups.

Vibrations of CH_3O- residues

Following the above scheme for comparing the spectral characteristics of ITMBA, DITMBA and DBrTMBA, we find that there is no significant difference in the position of the symmetric and asymmetric valence C-H bands characteristic of the three methoxy groups (Figure 18). The asymmetric and symmetric C-H deformation vibrations detected in the ATR-FTIR spectrum at 1458(9) and 1446 cm^{-1} for DITMBA (Figure 17), respectively, are similar to those for the same acid presented in Table 8 at 1462 and 1448 cm^{-1}.

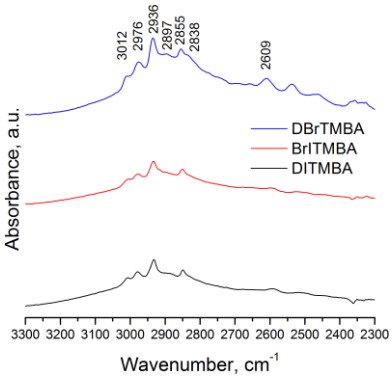
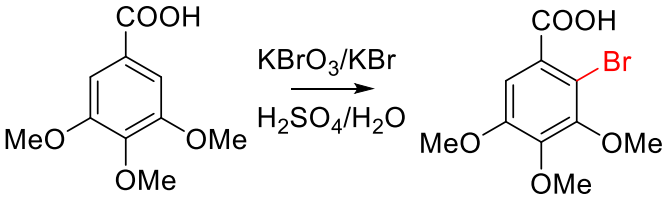


Figure 18. FTIR spectra of DBrTMBA, DITMBA and ITMBA in the high frequency region of 3300 ÷ 2300 cm^{-1}.

The three bands observed in the region 1100 ÷ 990 cm^{-1} in the ATR-FTIR spectra of DITMBA and DBrTMBA can be attributed to the valence symmetric and asymmetric vibrations of -O-CH_3 groups, which possess almost similar positions to those present in ITMBA spectrum (Figure 11). The frequency band at 1194 cm^{-1} can be attributed to the asymmetric valence CAr-O-CH_3 vibrations, while the one at 815 cm^{-1} - to the symmetric ones.

5. SYNTHESIS OF 2-BROMO-3,4,5-TRIMETHOXY-BENZOIC ACID

The synthesis of 2-bromo-3,4,5-trimethoxybenzoic acid (BrTMBA) is carried out using a $KBrO_3/KBr/H_2SO_4$ bromination system (Scheme 18). We obtain the compound in question in order to use it as a precursor for the synthesis of the mixed halogen-substituted 2-bromo-6-iodo-3,4,5-trimethoxy-benzoic acid (BrITMBA).



Scheme 18. Synthesis of BrTMBA

In order to establish the required amount of the brominating reagent used, we implement several successive syntheses. In the first synthesis, we put the necessary stoichiometric amount of each reagent (1 equivalent of $KBrO_3$) (Scheme 18). In the second synthesis, we use 1.1 equivalents of the reagent $KBrO_3$, and in the third – 1.2 equivalents of $KBrO_3$. We subjected the

three separate products obtained in this way to NMR analysis. For the first two products we report the presence of unreacted TMBA, and for the third - the absence of such (Figure 19).

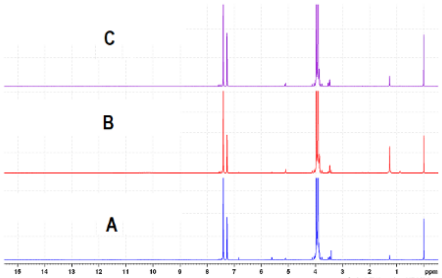


Figure 19. ^{1}H NMR spectra of BrTMBA prepared with (A) 1.0 equivalent $KBrO_3$, (B) 1.1 equivalent $KBrO_3$, and (C) 1.2 equivalent $KBrO_3$.

Therefore, for the synthesis of the target acid, it is necessary to use 1.2 molar equivalents of the inorganic oxidant in question. By adding an excess of this reagent, we compensate for any loss of elemental bromine that occurred during the TMBA bromination.

Although BrTMBA is present in the catalogs of most global producers, here we present a much more rational and safe method for its synthesis.

Separately, with the help of SC-XRD analysis, the crystal structure of the acid in question was established for the first time (Figure 20).

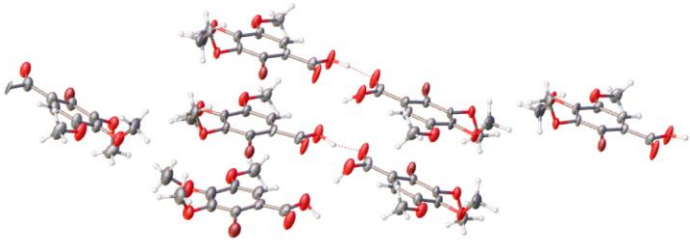


Figure 20. Crystal structure of BrTMBA.

X-ray analysis revealed that monobromo-zemestic acid crystallizes with seven conformationally different molecules in a unit cell (space group P1).

We further find that similar to ITMBA, BrTMBA molecules via their COOH groups also form centrosymmetric intermolecular associates/dimers.

The ATR-FTIR spectra of the two monohalogen substituted acids appear very similar to each other (Fig. 21).

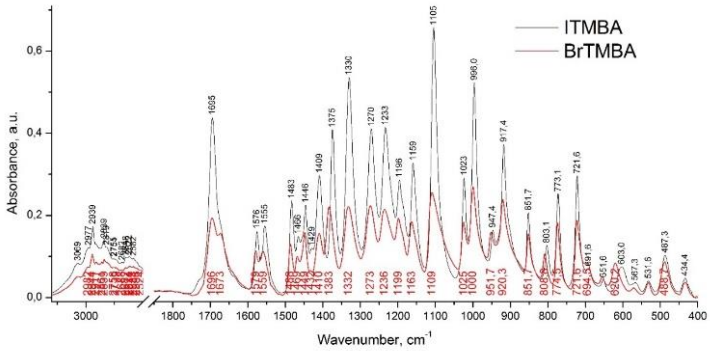


Figure 21. ATR-FTIR spectra of BrTMBA (red line) and ITMBA (black line).

Features and specific vibrational behavior of the COOH functional in the composition of BrTMBA.

In the crystalline phase, the molecules of ITMBA and BrTMBA interact with each other forming dimer associates. In the IR-spectrum of BrTMBA, the bands characteristic of the ν(C=O) vibration are observed at frequencies 1696 and 1673 cm^{-1}, and this one - in the spectrum of ITMBA - at 1695 cm-1 (Fig. 21).

The shift of the bands characteristic of the COOH functional of BrTMBA in the "blue" region should be attributed to two effects:

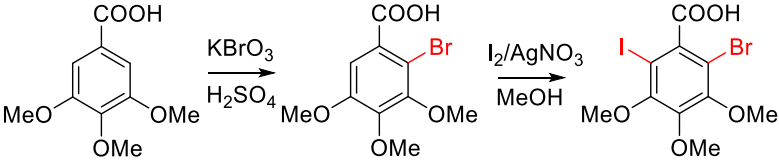
- that of the imposed steric effect of the bromine atom on the carboxyl functional, which causes an increase in the frequency of the valence ν(C=O) vibration, the out-of-plane γ (-O-H...O) and δ(C-O-H) vibrations (see Figure 26 , Table 9) and
- that of the available, polarization effect between the C-Br and C=O dipoles.

The structural changes resulting from the manifested ortho-effect are expressed in the changes of the dihedral angle θ formed between the planes of the carboxyl groups and the aromatic rings.

As for the remaining absorption bands in the spectrum of BrTMBA, their position and relative intensity reveal the isostructural (identical substitution) nature of the two aromatic acids.

6. SYNTHESIS OF 2-BROMO-6-IODO-3,4,5-TRIMETHOXYBENZOIC ACID

The synthesis of 2-bromo-6-iodo-3,4,5-trimethoxybenzoic acid (BrITMBA) was accomplished via a two-step protocol (Scheme 19). For this purpose, we use the obtained monobromo derivative as a reactant for the synthesis of a mixed, halogen-substituted acid.



Scheme 19. Synthesis of BrITMBA.

The crystal structure of the resulting acid was established by SC-XRD analysis (Figure 22).

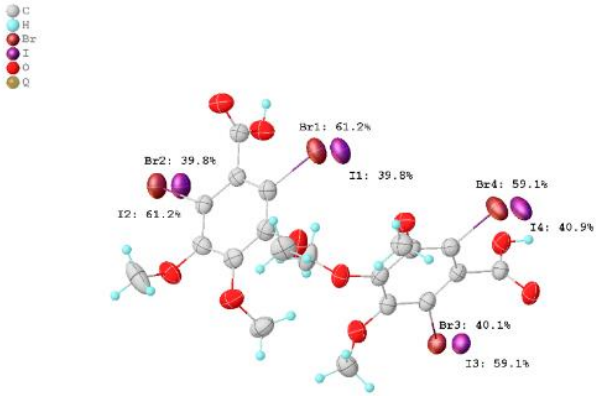


Figure 22. Crystal structure of BrITMBA

Similar to DBrTMBA and DITMBA, the mixed halogen representative crystallizes in an infinite, hydrogen-bonded catemer system. Analysis revealed the probable presence of

bromine and iodine atoms in each individual molecule. The observed arrangement of the molecules may be related to a spatial translation of individual catemer chains, in which each adjacent halogen atom appears "anti-halogen". Moreover, the unit cell of BrITMBA has radically different geometrical characteristics (size, volume) than those of its homosubstituted analogues - a = 7.3456(1) Å, b = 17.4928(3) Å, c = 21.0051(3) Å; V = 2699.04(7) Å3.

Features and specific spectral behavior of the BrITMBA catemer

In the IR spectrum of BrITMBA, the bands characteristic of ν(C=O) vibrations are observed at frequencies 1642 and 1724 cm^{-1} (Figure 17).

As reflected above, the unusual spectral behavior of the COOH functional from the composition of the DBrTMBA cathemer should be attributed to the imposed steric effect of the bromine and iodine atoms on the carboxyl functional and the available polarization effect between the C-I, C-Br and COOH dipoles. The induction effect of the halogen substituents (iodine and bromine atom) have a significant influence on the position of the DBrTMBA carbonyl band (Figure 17). It is obvious that due to the available steric effect, the mesomeric effect is interrupted, and such effect is present only between the aromatic, ring system and the remaining 5 substituents – halogen atoms and methoxy groups (Figure 23).

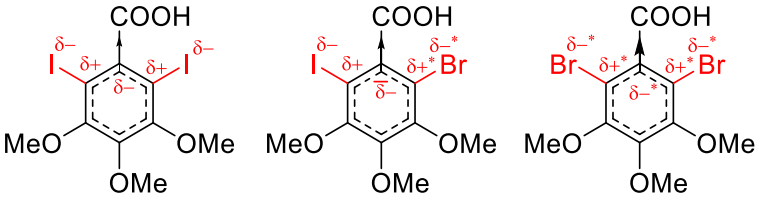
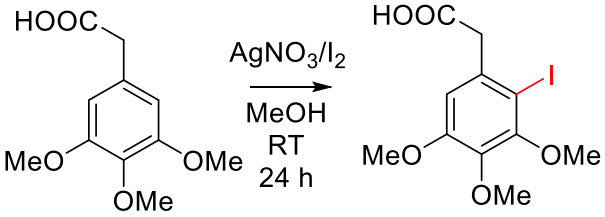


Figure 23. Difference in the electronegativity of C_{Ar} - atoms, carriers of COOH functionals in the three catemeric representatives – DBrTMBA, DITMBA and BrITMBA.

7. SYNTHESIS OF 2-IODO-3,4,5-TRIMETHOXY-PHENYLACETIC ACID

The synthesis of the title acid (IPhAA) is realized by means of the applied protocol for obtaining ITMBA, DITMBA and BrITMBA (Scheme 20).



Scheme 20. Synthesis of IPhAA

The molecular composition of the obtained product is determined by means of ATR-FTIR analysis.

Vibration analysis

The relation of the vibrational frequencies is carried out by means of a comparative analysis of the captured spectrum for IPhAA with those of PhAA, ITMBD and ITMBA.

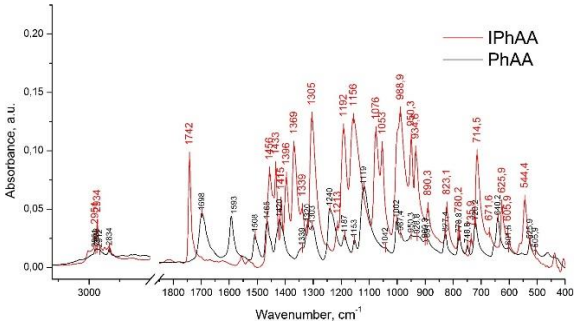


Figure 24. ATR-FTIR spectra of IPhAA and PhAA.

As can be seen from Figure 24, the infrared spectra of the recrystallized product IPhAA and the starting PhAA acid have radically different spectral profiles, even in the fingerprint region.

A clue to the successful introduction of an iodine atom into the aromatic system can also be found in the area of the aromatic C=C vibrations. In the spectrum of the iodo-substituted acid, the appearance of two new, low-intensity bands in the region 1520 - 1570 cm^{-1} - bands inherent to the tangential vibrations of the aromatic C=C bonds of 5-substituted aromatic systems are recorded. At 1213 and 1053 cm^{-1} we observe the aromatic 14 (Kekule) and 12 (strain) vibrations of IPhAA. We attribute the weak-to-moderate intensity bands reported at 823, 780, 672, 626, 606, and 544 cm^{-1} to the deformational CCC vibrations of the phenyl residue.

Absorption bands inherent to the asymmetric and symmetric C-H deformation vibrations are found, respectively, at 1456 и 1433 cm^{-1}.

V. CONCLUSIONS

1. New halogen-substituted compounds - 2-(2-iodo-3,4,5-trimethoxyphenyl) acetic acid (ITMPhAA) and 2-bromo-6-iodo-3,4,5-trimethoxybenzoic acid (BrITMBA) were synthesized.
2. The crystallization conditions and crystal structures of 2,6-diiodo-3,4,5-trimethoxybenzoic acid (DITMBA) and its toluene solvatomorph, as well as those of 2,6-dibromo-3,4,5-trimethoxybenzoic acid (DBrTMBA) and 2-bromo-3,4,5-trimethoxybenzoic acid (BrTMBA).

3. In vitro studies revealed the absence of photoinduced DITMBA toxicity against the tested BALB/3T3 cell line from clone A31.

4. The potential of the newly obtained sodium salt of DITMBA in the construction of real physical phantoms intended for contrast-enhanced mammography is evaluated.

5. The reactivity of the $I_2/AgNO_3$ reagent pair in the iodination of various aromatic substrates - 3,4,5-trimethoxybenzaldehyde, 3,4,5-trimethoxybenzoic acid and 2-(3,4,5-trimethoxyphenyl) acetic acid was established.

6. The inertness of the iodination $I_2/AgNO_3$ system in water-methanol medium and the reactivity of the latter in the synthesis of DITMBA were established.

7. A new environmentally friendly methodology for the synthesis of BrTMBA and DBrTMBA is proposed.

VI. CONTRIBUTIONS

1. The crystal structures of four homo- and heterohalo-substituted aromatic acids - DITMBA, BrTMBA, DBrTMBA and BrITMBA - have been established.

2. The tendency of undoped DITMBA and its isostructural DBrTMBA and BrITMBA analogues to form peculiar H-bonded systems of cathemeric type was found.

3. It was established that the determinant for the geometrical/conformational stability of DITMBA, DBrTMBA and BrITMBA molecules is the organized intermolecular O(lp)—π(C6) contact.

4. New and easy-to-implement protocols for the synthesis of bromo-, iodo-, and bromo-iodo-containing aromatic acids with inorganic reagents that are readily available and safe for the user and the environment have been introduced.

VII. PUBLICITY OF THE RESULTS

In publications referenced and indexed in world-renowned databases of scientific information:

1. Iliyan Kolev, Tanya Dimova, Ivan Iliev, Marin Rogozherov, Michael Bodensteiner, *Further findings concerning 2,6-diiodo-3,4,5-trimethoxybenzoic acid* (Part II), Journal of Molecular Structure, Volume 1294, Part 1, (2023), 136388, ISSN 0022-2860, https://doi.org/10.1016/j.molstruc.2023.136388

2. F. Meurer, T. Dimova, M. Bodensteiner, I. Kolev, *2,6-Dibromo-3,4,5-trimethoxybenzoic acid*, (2023), Acta Cryst. 79, ISSN 2056-9890, DOI: 10.1107/S2056989023007831.

In non-refereed peer-reviewed journals:

1. Tanya Dimova, Nadya Hadzhieva, Nadezda Nefedova, Iliyan Kolev, *Strategies in the synthesis of orto-diiodine-substituted aromatic acids*, Industrial Technologies, Vol. 8 (1) 2021, pp. 81-86

2. Iliyan Kolev, Tanya Dimova, *On the iodination of eudesminic acid with INO_3 in an aqueous-methanolic medium*, Scripta Scientifica Pharmaceutica, 2023, ISSN 0582-3250

FINANCING
Participation in a project under the "Science" Fund at the University of Medicine - Varna - No. 20023. Name of the project "Synthesis and structural analysis of new organoiodine compounds - potential X-ray contrast agents", led by Associate Professor Iliyan Nikolov Kolev, Ph.D.