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RESTRICTED ROTATIONAL ISOMERS I. HINDERED TRIIODOISOPHTHALIC ACID DERIVATIVES*

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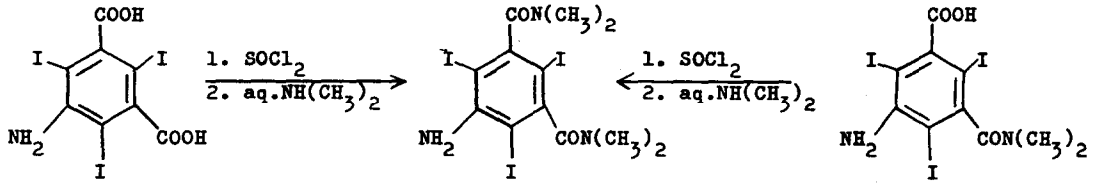
In our work which was directed toward the synthesis of new radiopaques, 5-amino-2,4,6-triiodo-N,N,N',N'-tetramethylisophthalamide (1) was prepared as an intermediate. Although the isophthalamide 1 was reported as a single compound, mp 240-243° (1), and our synthesis was similar to that described, two approximately equal spots were detected when the crude product 1 was examined by thin layer chromatography (tlc).** The isophthalamide 1 was obtained in two steps from 5-amino-2,4,6-triiodoisophthalic acid (2) (2). Treatment of 2 with thionyl chloride followed by aqueous dimethylamine gave the crude isophthalamide 1 in good yield. The acid 2 was obtained by iodination of 5-aminoisophthalic acid with sodium iododichloride. The two components in the crude 1



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were separated readily by fractional crystallization from methanol. The two compounds, 1A (mp 257-265°), and 1B (mp 241-258°) gave the correct analysis for the isophthalamide 1, had essentially identical uv spectra, had similar ir and nmr spectra, and showed single different spots with tlc** at Rf 0.62 and 0.67, respectively; 1A: uv max

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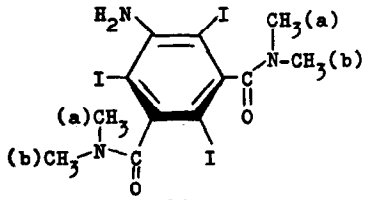
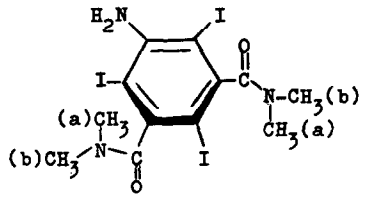
**Thin layer chromatography was done on pre-coated plates (Silica Gel F_{254}, E. Merck Ag.). An HOAc:MeOH:benzene (10:20:70) system was used.

(95% C_2H_5OH) 234 (ε 33,600) 267_{sh} (10,100), 321 mu (5,400); ir* (KBr) 3325, 1632, 1578, 1395, 1252, 1138, 747 cm^{-1}; and nmr (20% TFAA) δ 3.05 [S,6, $\underline{NCH_3}$ (a)], 3.32 ppm [S,6, $\underline{NCH_3}$ (b)]; 1B: uv max (95% C_2H_5OH) 235 (ε 34,000), 267_{sh} (10,000), 321 mu (5,000); ir* (KBr) 3325, 1632, 1588, 1400, 1383, 1265, 1156, 740 cm^{-1}, and nmr (20% TFAA) δ 3.06 [S,6, $\underline{NCH_3}$ (a)], 3.32 ppm [S,6 $\underline{NCH_3}$ (b)]. The properties of each compound are compatible with the structure 1 and each gave a mixture of the two components when it was heated at 100° in dioxane for 16 hr. The ratio of isomers (1A:1B), which was estimated by means of tlc, was about 1:5 after heating. On the basis of the examination of molecular models and work reported in the literature, we believe the two compounds are isomers of the structure 1 and are caused by restricted rotation around the two carbonyl carbon-aromatic carbon bonds. The isomers are represented by the structures 1A and 1B and may be looked upon as having a cis-trans relationship with regard to the oxygen atoms and also with regard to the vertical methyls in the dimethylcarbamoyl groups. In this case the cis isomer would be a meso compound and the trans isomer should be optically active. The least stable isomer, which also had the lower Rf on tlc, was tentatively assigned the cis structure (1A) and this was confirmed by the preparation of the higher Rf isomer (1B) in optically active form.



1A

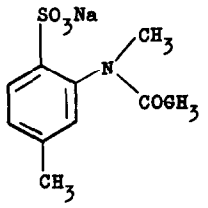


1B

Since the isophthalamides 1A and 1B have restricted rotation, we felt that 5-amino-2,4,6-triiodo-N,N-dimethylisophthalamic acid (3) (3) should also have restricted rotation and hence be optically active. This postulation was shown to be correct when the isophthalamic acid 3 [mp 275-280° dec.; reported 274.9-275.9 (3)] was resolved as the strychnine salt. One enantiomer was obtained pure as the salt ($[\alpha]_D^{25}$ -24.2°, DMF, mp 218-221°) and was converted to the acid ($[\alpha]_D^{25}$ +13.0°, DMF, mp 252-261° dec.). The other enantiomer was obtained by fractional recrystallization of the acid recovered from

*The prominent ir bands of both isomers are reported.

the salt residue and had a rotation almost equal and opposite ($[\alpha]_D^{25}$ -12.3°, DMF, mp 252-260° dec.) to the first. Each enantiomer of the isophthalamic acid 3 was converted to a mixture of the isophthalamides 1A and 1B by preparation of the acid chlorides in thionyl chloride followed by reaction with aqueous dimethylamine. In one case the starting acid 3 was recovered from a portion of the acid chloride and there was no appreciable loss of optical activity. The isophthalamides 1A and 1B were formed in about equal amounts from each of the two enantiomers of 3 and were separated by fractional crystallization from methanol. The two samples of the isophthalamide 1B obtained in this manner were optically active ($[\alpha]_D^{25}$ +21.2°, DMF, mp 247-258°; $[\alpha]_D^{25}$ -22.2°, DMF, mp 245-255°) while the samples of the isophthalamide 1A showed no significant rotation ($[\alpha]_D^{25}$ 0.2°, 0, DMF). The two enantiomers of the isophthalamic acid 3 and those of the isophthalamide 1B gave the correct analyses and were indistinguishable from the corresponding dl compounds with tlc. The racemization of the optically active isophthalamic acid 3 was studied in boiling n-butanol at 117° and the half-life was found to be about five hours. The equilibration of the optically active isophthalamide 1B to 1A and dl 1B was also studied in the same manner by rotational measurements and the half-life was about nine hours.



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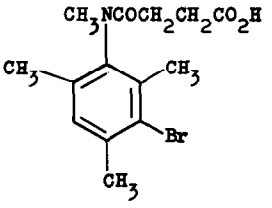

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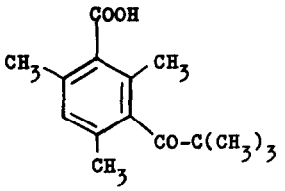
These stabilities are considerably greater than that of the benzene derivative 4 described by Mills and Kelham (4) and are comparable to that of the anilic acid 5 reported by Adams and Dankert (5). The racemization half-lives of 4 and 5 were 5.25 hours at 16.6° in water and nine hours in boiling n-butanol, respectively. Recently the benzoic acid 6 (6) was resolved by Pinkus and coworkers and has a half-life of approximately six minutes at room temperature. Adams and Tjepkema reported that the diaminomesitylene derivative 7 had cis and trans isomers and resolved the trans isomer

(7). In the last case the two isomers result from two points of restricted rotation around the benzene ring (7) and our isomers 1A and 1B are similar.



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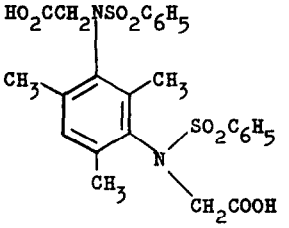

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We are further investigating the occurrence of isomers with analogs of the isophthalamides 1A and 1B.

Acknowledgement. The authors would like to thank Dr. R. K. Kullnig and his co-workers for the spectral data and rotations. The spectra were determined on a Cary 15 Ultraviolet Spectrophotometer and on a Perkin-Elmer 21 Infrared Spectrophotometer. The nmr spectra were determined on a Varian A-60 and TMS was used as external standard.

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