

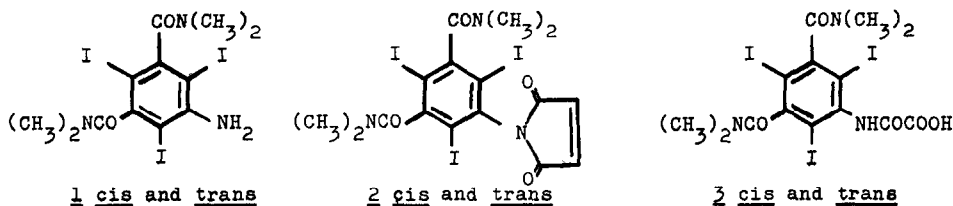
RESTRICTED ROTATIONAL ISOMERS III. cis- AND trans-3',5'-(DIMETHYLCARBAMOYL)-2',4',6'-
TRIIODOOXALANILIC ACID AND THEIR N-METHYL DERIVATIVES*

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In our two previous papers the cis and trans isomers of 5-amino-2,4,6-triiodo-N,N',N'-tetramethylisophthalamide (1) were discussed and the assignment of the configurations was made by preparation of the trans isomer in optically active form (1) and by examination of the nmr spectra of cis- and trans-2,4,6-triiodo-5-maleimido-N,N,N',N'-tetramethylisophthalamide(2)(2). Our present paper presents additional evidence for the assignment of these configurations and describes a benzene derivative which has three positions with restricted rotation.



When the cis- or trans-isophthalamide 1 was treated with ethyl oxalyl chloride in dioxane and the resulting ester hydrolyzed in aqueous sodium hydroxide, cis- or trans-3',5'-(dimethylcarbamoyl)-2',4',6'-triiodoxalanilic acid (3) was obtained, mp 204-209° (dec) and 201-211° (dec), respectively. These acids were examined by thin layer chromatography (tlc)** and gave single different spots at Rf 0.33 and 0.40, respec-

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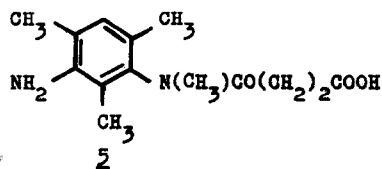
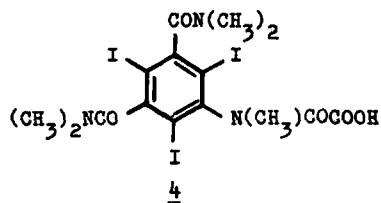
**Tlc was done on pre-coated plates (Silica Gel F254, E. Merck Ag.). Two passes in a chloroform:methanol:formic acid (72:14:14) system were made.

ively. The configuration of the trans-oxalanilic acid 3 was confirmed by resolution through the brucine salt. One enantiomer was obtained pure as the salt: $([\alpha]_D^{25} - 18.1^\circ, \text{DMF, mp } 216\text{--}222^\circ \text{ dec})$ and was converted to the acid $([\alpha]_D^{25} + 0.5^\circ, \text{DMF, mp } 217\text{--}220^\circ \text{ dec})$. This acid was also prepared in optically active form from (+)-5-amino-2,4,6-triiodo-N,N,N',N'-tetramethylisophthalamide (1)(1) $([\alpha]_D^{25} + 22.0, \text{DMF})$ under the mild conditions already described and its rotation was low when recorded at the sodium D line $([\alpha]_D^{25} + 0.4, \text{DMF, mp } 221\text{--}226^\circ \text{ dec})$. The optical rotatory dispersion spectra of these two samples of resolved trans-3 were essentially identical and followed the base line closely between 350-650 m μ . A pronounced negative rotation was noted between 250-300 m μ and reached a minimum at 263 m μ $([\alpha]_{263}^{25} - 3000^\circ, \text{DMF})$. This is possibly a result of a negative Cotton effect in this region which could not be recorded below 263 m μ since the sample was absorbing too much light below this wavelength.

Further evidence for the assignment of the configurations of the isomers resulted when the cis- and trans-oxalanilic acids 3 were N-methylated. Treatment of the cis-acid 3 with dimethyl sulfate in dilute sodium hydroxide by the procedure of Holtermann and coworkers (3) gave 3',5'-(dimethylcarbamoyl)-2',4',6'-triiodo-N-methyloxalanilic acid (4). Examination of the crude product by tlc* showed two spots in about a 1:1 ratio. One component (4A), mp 306-310° (dec), was separated by fractional crystallization from methanol and the other (4B), mp 236-238° (dec), was obtained pure by fractional crystallization of the methyl esters from methanol and hydrolysis back to the acid. Both of these compounds gave the correct analysis for the N-methyloxalanilic acid structure 4, had similar ir and nmr spectra, and showed single different spots with tlc* at Rf 0.23 and 0.35, respectively.

The trans-oxalanilic acid 3 was methylated in the same manner. Recrystallization of the crude product from methanol gave material (4C), mp 253-260° (dec), which had the correct analysis for the structure 4, had an ir spectrum similar to those of 4A and 4B, and showed a single spot with tlc different from 4A and 4B at Rf 0.43. The nmr spectrum of 4C was not similar to 4A and 4B, and the spectra are shown in Fig. 1.

*Four passes in a chloroform:methanol:formic acid (86:7:7) were made.



The work of Adams and Dankert (4) established that the N-methylsuccinanilic acid 5 has restricted rotation about the nitrogen-aromatic carbon bond of the anilic acid. The N-methyloxalanilic acid 4 would likewise be expected to have restricted rotation about the nitrogen-aromatic carbon bond. This is in addition to the already established restricted rotation of the two dimethylcarbamoyl groups (1). N-methylation of

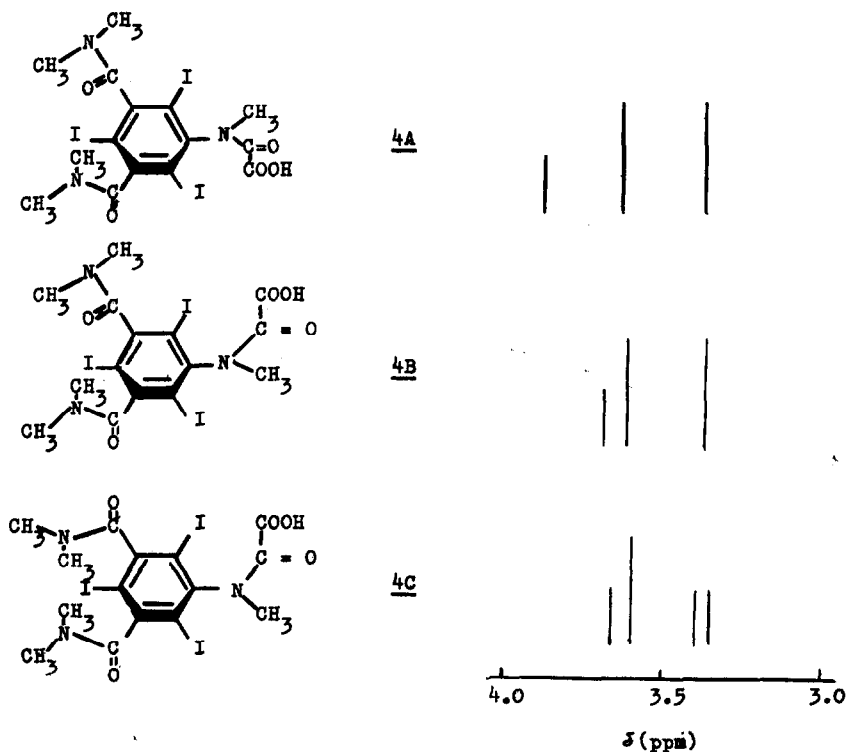


Fig. 1 Structures of 4A, 4B, and 4C and their nmr Spectra which were run in deuterated water on a Varian Model A60 spectrometer as the sodium salts. The spectra are shown schematically.

the cis-oxalanilic acid 3 could then produce two isomers and the nmr spectrum of each should show three signals in a ratio of 2:2:1. When the trans-oxalanilic acid 2 is methylated, one product would result and its nmr spectrum might show five equal signals. Two isomers were obtained from the cis-acid 3 and their structures, 4A and 4B, are shown in Fig. 1.

The nmr spectra of 4A and 4B are as expected and this again confirms the cis configuration of the dimethylcarbamoyl groups. The more polar isomer, 4A, is tentatively assigned the cis, cis structure and the less polar isomer, 4B, is assigned the cis, trans structure. One product was isolated from the methylation of the trans-acid 3 and its structure, 4C, also is shown in Fig. 1. The nmr spectrum of 4C showed four signals in a ratio of 2:1:1:1. The vertical methyls of the dimethylcarbamoyl groups of 4C are more easily affected by changes in structure than the horizontal methyls. Hence, the vertical methyls of 4C show their nonequivalence in the nmr spectrum while the horizontal methyls give only one signal. These results are compatible with a trans orientation of the dimethylcarbamoyl groups and confirm the trans structure.

We believe that the three isomers, 4A, 4B, and 4C represent the first case where three isomers result from three positions of restricted rotation around a single benzene ring. Adams and Englund prepared benzene derivatives which also had three restricted positions but since the three groups were identical, only two isomers resulted (5).

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