

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

## Restricted Rotation in Aryl Amines. XVIII. Resolution of N-Carboxymethyl-N-methyl-3-bromomesidine

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N-Carboxymethyl-N-methyl-3-bromomesidine has been synthesized and resolved. The active form has a half-life of 0.47 hr. in boiling methyl acetate (b.p. 57°).

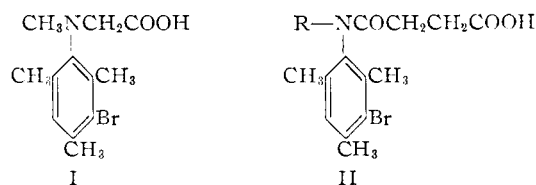
A large number of aromatic amines has been described in which the existence of restricted rotation between the amine nitrogen and the ring has been established through resolution of the compounds or isolation of *cis-trans* isomers. The amine nitrogen atom in all cases has been substituted by two different groups. No molecule in which a hydrogen is present on the nitrogen has as yet been observed to have restricted rotation. In addition to the substituents on the nitrogen, groups in each of the positions in the aromatic nucleus *ortho* to the amine usually are necessary. Only a few compounds are known in which a single large *ortho* group has been demonstrated as adequate to block free rotations; the resulting optically active substances are relatively unstable.<sup>2</sup>

The pairs of groups on the nitrogen atom which have been employed in successful resolutions are: CH<sub>3</sub><sup>3-7</sup> and C<sub>2</sub>H<sub>5</sub><sup>4</sup> with COCH<sub>2</sub>CH<sub>2</sub>COOH; CH<sub>3</sub><sup>8-12</sup>, C<sub>2</sub>H<sub>5</sub><sup>8,10,11,13</sup>, *i*-C<sub>3</sub>H<sub>7</sub><sup>14</sup>, *n*-C<sub>4</sub>H<sub>9</sub><sup>8</sup>, *n*-C<sub>10</sub>H<sub>21</sub><sup>8</sup>, C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub><sup>8,10,11</sup>, C<sub>2</sub>H<sub>5</sub>OOCCH<sub>2</sub><sup>8,11</sup>, HOOC-CH<sub>2</sub><sup>8,11,15,16</sup>, NCCH<sub>2</sub>CH<sub>2</sub><sup>10</sup>, HOOCCH<sub>2</sub>CH<sub>2</sub><sup>10</sup> and HOCH<sub>2</sub>CH<sub>2</sub><sup>17</sup> with SO<sub>2</sub>Ar; CH<sub>3</sub> with SO<sub>2</sub>-CH<sub>3</sub><sup>18</sup>; CH<sub>3</sub><sup>2a,2b</sup> and C<sub>2</sub>H<sub>5</sub><sup>2a</sup> with COCH<sub>2</sub>; Ar with COC<sub>6</sub>H<sub>5</sub><sup>19</sup>; and CH<sub>2</sub>CH<sub>2</sub>CO C(CH<sub>3</sub>)<sub>2</sub>CO.<sup>20</sup> It is noteworthy that in all instances at least one of the groups on the nitrogen has a carbonyl or sulfonyl function attached to the nitrogen. Such a group may be shown by models to provide a substantially greater blocking effect than an alkyl or carboxymethyl.

(1) An abstract of portions of theses submitted by Dale C. Blomstrom, Cincinnati Chemical Co., Fellow, 1950-1951; Standard Oil Co. of Indiana Fellow, 1951-1952, and K. V. Y. Sundstrom, Cincinnati Chemical Co. Fellow, 1951-1952 and 1952-1953, to the Graduate College of the University of Illinois, 1953, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

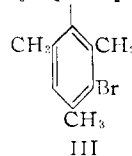
- (2) (a) C. Buchanan and S. H. Graham, *J. Chem. Soc.*, 500 (1950);  
 (b) W. H. Mills and R. M. Kelham, *ibid.*, 274 (1937).  
 (3) R. Adams and L. J. Dankert, *THIS JOURNAL*, **62**, 2191 (1940).  
 (4) R. Adams and H. W. Stewart, *ibid.*, **63**, 2859 (1941).  
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 (9) R. Adams and M. Rothstein, *ibid.*, **71**, 1620 (1949).  
 (10) R. Adams and N. K. Nelson, *ibid.*, **72**, 132 (1950).  
 (11) R. Adams and B. Englund, *ibid.*, **72**, 135 (1950).  
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 (13) W. H. Mills and J. G. Breckenridge, *J. Chem. Soc.*, 2209 (1932).  
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 (15) W. H. Mills and K. A. C. Elliot, *J. Chem. Soc.*, 1291 (1928).  
 (16) R. Adams and J. R. Gordon, *THIS JOURNAL*, **72**, 2458 (1950).  
 (17) J. Glazer, M. M. Harris and E. E. Turner, *J. Chem. Soc.*, 1753 (1950).  
 (18) R. Adams and J. B. Campbell, *THIS JOURNAL*, **72**, 128 (1950).  
 (19) M. M. Jamison and E. E. Turner, *J. Chem. Soc.*, 1646 (1938).  
 (20) R. Adams and D. C. Blomstrom, *THIS JOURNAL*, **75**, 2375 (1953).

In this investigation a successful attempt has been made to resolve an arylamine in which the nitrogen is substituted by a methyl and carboxymethyl. These two groups are smaller than any previously described but nevertheless cause hindrance in scalar models. The compound selected for study was N-carboxymethyl-N-methyl-3-bromomesidine (I), synthesized by the action of ethyl bromoacetate on N-methyl-3-bromomesidine followed by saponification. Cinchonidine reacted to give a single salt, indicating mutarotation. By decomposition of the salt, the dextro form of the acid was isolated. The half-life of the acid in boiling methyl acetate (b.p. 57°) was 0.47 hour. As anticipated, substitution of this pair of groups leads to a molecule which is relatively unstable as compared with the closely related mesidine derivatives II<sup>3,4</sup> and III.<sup>7</sup>



R = CH<sub>3</sub>    Half-life 9 hr., boiling *n*-butyl alcohol  
 R = C<sub>2</sub>H<sub>5</sub>    Half-life 28 hr., boiling *n*-butyl alcohol

C<sub>6</sub>H<sub>5</sub>SO<sub>2</sub>NCH<sub>2</sub>COOH



Half-life 8 hr., boiling *n*-butyl alcohol

### Experimental<sup>21</sup>

**N-Carboxymethyl-N-methyl-3-bromomesidine.**—N-Methyl-3-bromomesidine<sup>3</sup> was prepared by the procedure previously described, b.p. 159.5-161.5° (21 mm.).

A solution of 20 g. of N-methyl-3-bromomesidine and 8 g. of ethyl bromoacetate in 270 ml. of 75% ethanol was refluxed for 18 hours. A solution of 20 g. of sodium hydroxide in 30 ml. of water was added and the solution was refluxed for 2.5 hours. After distillation of 175 ml. of ethanol, 250 ml. of water was added and the solution was extracted three times with ether to remove unchanged starting material. Drying of this extract and passing in dry hydrogen chloride caused precipitation of 5.85 g. of N-methyl-3-bromomesidine hydrochloride. The aqueous layer was acidified with acetic acid and extracted with ether. The ether extract upon evaporation yielded 11.6 g. (92%) of white crystals. They were purified by recrystallization from petroleum ether (b.p. 80-100°); prisms, m.p. 107-108°.

*Anal.* Calcd. for C<sub>12</sub>H<sub>16</sub>BrNO<sub>2</sub>: C, 50.36; H, 5.64. Found: C, 50.51; H, 5.53.

(21) All melting points are corrected.

**Resolution and Racemization of N-Carboxymethyl-N-methyl-3-bromomesidine.**—A chloroform solution of 3.10 g. of N-carboxymethyl-N-methyl-3-bromomesidine and 3.20 g. of cinchonidine was evaporated *in vacuo* from 100 ml. to approximately 10 ml. The viscous residue was dissolved in 150 ml. of acetone by boiling under reflux for one hour. When the filtered acetone solution was allowed to stand overnight in a refrigerator, a colorless solid formed, which was removed by filtration and stored in a refrigerator. More solid crystallized out, as the solution stood at low temperature. Four crops were collected totaling in weight about 90% of the salt present; the melting point and rotation of each was essentially the same.

Crop	Time, days	Wt., g.	$[\alpha]^{25}_D$	M.p., °C.
1	1	2.995	-56.3°	157-158
2	2	1.229	-58.0	158-158.5
3	3	0.403	-57.2	157-158
4	6	0.995	-57.5	156-158

*Anal.* Calcd. for  $C_{12}H_{16}BrNO_2 \cdot C_{19}H_{22}N_2O$ : C, 64.13; H, 6.60. Found: C, 64.11; H, 6.78.

By repeated extraction of combined crops 1 and 2 with 20% aqueous hydrochloric acid to which ice was added, 1.5 g. of *d*-acid was isolated, m.p. 104-104.5°.

From 1.25 g. of the *d*-acid, 20 ml. of a solution in methyl acetate was prepared, which was used in racemization experiments at the temperature of boiling methyl acetate (57°). The previously described technique with sealed tubes<sup>22</sup> was employed.

The results of one run, which were very closely duplicated in a second run, were as follows: 0.0 hr.,  $\alpha_D +0.661^\circ$ ,  $[\alpha]^{25}_D +10.8^\circ$ ; 0.25 hr.,  $\alpha_D +0.417^\circ$ ,  $[\alpha]^{25}_D +6.82^\circ$ ; 0.5 hr.,  $\alpha_D +0.269^\circ$ ,  $[\alpha]^{25}_D +4.40^\circ$ ; 0.75 hr.,  $\alpha_D +0.166^\circ$ ,  $[\alpha]^{25}_D +2.72^\circ$ ; 1.0 hr.,  $\alpha_D +0.116^\circ$ ,  $[\alpha]^{25}_D +1.90^\circ$ ; 1.5 hr.,  $\alpha_D +0.032^\circ$ ,  $[\alpha]^{25}_D +0.8^\circ$ . From these data,  $t_{1/2} = 0.47$  hr.

(22) R. Adams and K. V. Y. Sundstrom, *THIS JOURNAL*, **76**, 5474 (1954).

URBANA, ILLINOIS

[CONTRIBUTION NO. T203, FROM THE RESEARCH LABORATORY, THE GOODYEAR TIRE AND RUBBER COMPANY]

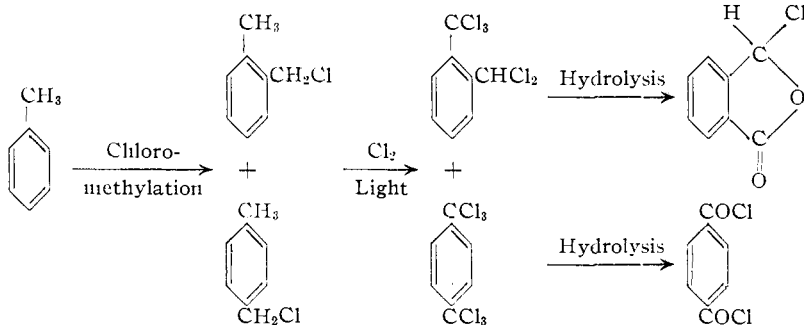
## The Chloromethylation of Toluene and Conversion of *p*-Xylyl Chloride to Terephthaloyl Chloride

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A study has been made of the chloromethylation of toluene, and a viscosimetric method has been developed for the determination of the percentages of isomers present in the reaction products. The mixtures of *o*- and *p*-xylyl chlorides ( $\alpha$ -chloro-*o*-xylene and  $\alpha$ -chloro-*p*-xylene) have been chlorinated in the side chains and it has been shown that hexachloro-*p*-xylene ( $\alpha, \alpha, \alpha, \alpha', \alpha', \alpha'$ -hexachloro-*p*-xylene) can be separated from the mixtures. Hexachloro-*p*-xylene has been converted to terephthaloyl chloride in high yields by means of hydrolysis with maleic acid.

The need for relatively large quantities of terephthaloyl chloride suggested that it might be obtained economically from toluene. The present investigation describes studies of the chloromethylation of toluene, chlorination of the resulting reaction products, separation of the mixtures of pentachloro-*o*-xylene ( $\alpha, \alpha, \alpha, \alpha', \alpha'$ -pentachloro-*o*-xylene) and hexachloro-*p*-xylene and hydrolysis of the latter compounds to acid chlorides. The transformations involved may be summarized by means of the equations



Although earlier investigators indicated that the chloromethylation of monoalkyl benzenes leads principally to *para* chloromethyl derivatives, Hill and Short<sup>2</sup> have shown that the introduction of a chloromethyl group into toluene, by the use of dichloromethyl ether or paraformaldehyde, affords a considerable amount of *o*-xylyl chloride (53 and

42%, respectively). Recently, Brown and Nelson<sup>3</sup> determined the ratio of isomers in the product obtained by chloromethylation of toluene using trioxymethylene in acetic acid at 60° with hydrogen chloride and zinc chloride. They obtained values of 34.7, 1.3 and 64.0 for the percentage distribution of the *ortho*, *meta* and *para* isomers, respectively.

In an attempt to increase the ratio of *para* to *ortho* substitution, a relatively extensive series of chloromethylation reactions of toluene was carried out. Approximately equal amounts of the two isomers resulted on zinc chloride catalysis under a wide variety of conditions. Other catalysts such as ferric chloride, aluminum chloride, stannic chloride, sulfuric acid, phosphoric acid and boron trifluoride did not alter the ratios of isomers more than a few per cent.

The mixtures of *o*- and *p*-xylyl chlorides (b.p., 96-98° (25 mm.)) cannot be separated by conventional distillation. Since the procedure of Hill and Short<sup>2</sup> for the analysis of mixtures of *o*- and *p*-xylyl chlorides consists of hydrolyzing the mixture and carrying out a thermal analysis of the derived xylyl alcohols, it does not lend itself to a study of a large number of samples. Accordingly, a new method was sought for the determination of the percentages of isomers present in the various reaction mixtures. Since the study described here was completed several

(1) Department of Chemistry, University of Missouri.  
(2) P. Hill and W. F. Short, *J. Chem. Soc.*, 1123 (1935).

(3) H. C. Brown and K. L. Nelson, *THIS JOURNAL*, **76**, 6292 (1953).