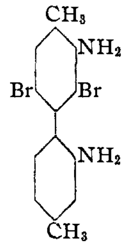
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

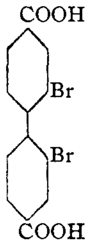
Stereochemistry of Diphenyls. XXXIX.[1] Synthesis of Active 2,6-Dibromo-3,3'-diamino-4,4'-ditolyl

BY W. I. PATTERSON[2] AND ROGER ADAMS

It has been established with an abundance of experimental evidence that diphenyl molecules with two groups of proper size and character, substituted in the 2,2' positions and with no substitution in the 6,6' positions, may be resolved. A compound has now been prepared and resolved in which two groups are substituted in the 2,6 positions and no substitution is present in the 2',6' positions. It is 2,6-dibromo-3,3'-diamino-4,4'-ditolyl (I).



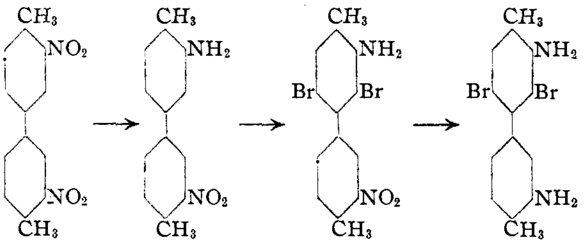
I



II

The brucine salt of this substance mutarotated and the active forms slowly racemized in solution. The rate of racemization of the active compound is less than that of the 2,2'-dibromo-4,4'-dicarboxydiphenyl (II)[1] but deductions from comparing the data are unjustified, since the substituents in the two molecules apart from the 2,2',6,6' positions are distinctly different and it has been demonstrated that such substituents markedly affect the rate of racemization of easily racemized diphenyls.

The compound was prepared by the partial reduction of 3,3'-dinitro-4,4'-ditolyl (III). The resulting 3'-nitro-3-amino-4,4'-ditolyl (IV) was brominated to the 3'-nitro-2,6-dibromo-3-amino-4,4'-ditolyl (V). That both bromines are in the same ring was determined by oxidation of the molecule to 3-nitro-4-methylbenzoic acid. On reduction the diamine was produced and resolved through the brucine salt.



III IV V I

Experimental

4-Amino-2-nitrotoluene.—This compound was prepared in 70% yield by the reduction of 2,4-dinitrotoluene in alcoholic ammonia solution with hydrogen sulfide.[3]

4-Iodo-2-nitrotoluene.—Diazotization of 4-amino-2-nitrotoluene in dilute sulfuric acid solution followed by treatment with aqueous potassium iodide according to the usual method gave 4-iodo-2-nitrotoluene in 75% yield.[4]

3,3'-Dinitro-4,4'-ditolyl.—A mixture of 100 g. of 4-iodo-2-nitrotoluene, 100 g. of nitrobenzene and 100 g. of copper bronze was refluxed for five hours and filtered from the excess copper and copper iodide, which was washed with several portions of hot benzene. The filtrate was steam distilled to remove the nitrobenzene and the insoluble residue was extracted with 100 cc. of boiling benzene. The precipitate which separated on cooling was recrystallized once from benzene and once from acetic acid. The product[4] thus prepared amounted to 20 g. (39%), and was used directly for the preparation of 3-amino-3'-nitro-4,4'-ditolyl.

3-Amino-3'-nitro-4,4'-ditolyl.—A stream of hydrogen sulfide was passed for one hour through a suspension of 20 g. of 3,3'-dinitro-4,4'-ditolyl in 2 liters of boiling 95% alcohol containing 3 g. of sodium hydroxide. The mixture was refluxed for seven hours longer, the alcohol removed on a water-bath, and the dark oily residue extracted with two 700-cc. portions of boiling petroleum ether (b. p. 60–110°). The extracts were cooled thoroughly in an ice-bath before filtering. The crude product was purified by extracting with hot 95% ethyl alcohol, which left behind unchanged starting material, sulfur and other by-products. The alcoholic solution of the amine was concentrated to a small volume; 100 cc. of acetone was added followed by 4 cc. of concentrated hydrochloric acid. The voluminous precipitate which separated completely in a few minutes was filtered and air dried; on warming this with 100 cc. of 95% ethyl alcohol containing 5 cc. of concentrated aqueous ammonia, solution occurred. After cooling in an ice-bath the yellow crystalline precipitate was filtered, washed with a little alcohol and once with water to remove any ammonium chloride contamination. Two crystallizations from alcohol gave about 10 g. (60%) of pure 3-amino-3'-nitro-4,4'-ditolyl, m. p. 108–109°.

Anal. Calcd. for $C_{14}H_{14}O_2N_2$: N, 11.56; C, 69.39; H, 5.83. Found: N, 11.67; C, 69.36; H, 6.00.

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[1] For the last paper in this series see Searle and Adams, THIS JOURNAL, **56**, 2112 (1934).

[2] Submitted as part of a thesis for the Degree of Doctor of Philosophy in Chemistry at the University of Illinois.

[3] Beilstein and Kuhlberg, *Ann.*, **155**, 14 (1870).

[4] Turner, *J. Chem. Soc.*, 480 (1926).

3-Acetylamino-3′-nitro-4,4′-ditolyl.—Upon adding 0.35 g. of 3-amino-3′-nitro-4,4′-ditolyl to 2 cc. of acetic anhydride, a white precipitate separated immediately. After warming the mixture on a water-bath for thirty minutes, 5 cc. of acetic acid was added to give a clear solution; on cooling, this solution yielded 0.22 g. of colorless needles. Recrystallization from alcohol gave a product melting at 193.5°.

Anal. Calcd. for $C_{16}H_{16}O_3N_2$: N, 9.85. Found: N, 10.03.

2,6-Dibromo-3-amino-3′-nitro-4,4′-ditolyl.—To 5 g. of 3-amino-3′-nitro-4,4′-ditolyl in 50 cc. of glacial acetic acid at room temperature was added 6.5 g. of bromine at such a rate that very little precipitate formed. The clear solution, obtained by warming the mixture slightly, was concentrated *in vacuo* to a small volume, and the crystals filtered after cooling in an ice-bath for one hour. Two crystallizations from ethyl alcohol gave 5.8 g. of buff crystals melting at 139° (70%).

TABLE I

Fraction	Weight, g.	$[\alpha]^{25}_D$ [a]	$[\alpha]^{25}_D$
1	1.40	2.37	14.8
2	0.42	2.27	13.7
3	.42	1.95	11.8
4	.18	−1.12	−15.5

[a] Each fraction, except fraction 1 in which 0.40 g. was used, was made up to 5 cc. in methyl alcohol at 20° and the rotation measured in a 2-dm. tube with sodium light.

TABLE II

ROTATIONS OF THE *d*-BASE AND THE MUTAROTATION OF ITS *d*-CAMPHORSULFONATE

Substance	Solvent	Sample,[a] g.	α_D	$[\alpha]_D$[b]	Temp., °C.	α_E[c]	*k*[d]	Av. devn. of *k*	Half-life[e] period, min.
d-Amine[f]	Acetone	0.580	+0.18	+ 0.78	23	...	0.004286	±0.0006	70.2
d-Amine salt	Abs. EtOH	.2019	+1.28	+15.85	27	−0.05	.000242	± .00005	1242.8
	Abs. EtOH	.2000	+1.29	+16.12	27	− .075	.000252	± .00003	1214.3
	Abs. MeOH	.5000	+2.74	+13.70	30	−2.28	.000242	± .00003	1242.8

[a] All rotation solutions were made up to 5 cc. at 20°. [b] Rotations were measured in a 2-dm. tube with sodium light. [c] $\alpha_E = (\alpha_{t_1}^2 - \alpha_i\alpha_{t_2})/(2\alpha_{t_1} - \alpha_{t_2} - \alpha_i)$; where α_E is the equilibrium rotation; α_i the initial rotation, α_{t_1} and α_{t_2} the rotations at the times t_1 and t_2, and t_2 must always equal $2t_1$. [d] $k = 1/t \log_{10} (\alpha_i - \alpha_E)/(\alpha_t - \alpha_E)$. [e] $T = 1/k \log_{10} 2$, where T = half-life period. [f] The rotations of the *d*-amine varied considerably from sample to sample. The solutions were slightly colored and of such a tint that accurate readings were difficult to obtain.

Anal. Calcd. for $C_{14}H_{12}O_2N_2Br_2$: N, 7.00; Br, 39.96. Found: N, 6.91; Br, 39.93.

2,6-Dibromo-3-acetylamino-3′-nitro-4,4′-ditolyl.—A mixture of 0.5 g. of 2,6-dibromo-3-amino-3′-nitro-4,4′-ditolyl with acetic anhydride and sodium acetate in excess pyridine was refluxed for one hour, and then poured into water. Recrystallization from 70% alcohol gave a colorless product melting at 145.5–146°.

Anal. Calcd. for $C_{16}H_{14}O_3N_2Br_2$: N, 6.34. Found: N, 6.14.

Oxidation of 2,6-Dibromo-3-amino-3′-nitro-4,4′-ditolyl.—A solution of 1.5 g. of 2,6-dibromo-3-amino-3′-nitro-4,4′-ditolyl in 15 cc. of warm glacial acetic acid was treated with 5 g. of chromium trioxide in 70 cc. of hot acetic acid. Reaction occurred immediately. After warming on the water-bath for forty minutes, the acetic acid was removed *in vacuo* and the residue treated with water. A gummy precipitate resulted which was washed thoroughly with water to remove chromium salts. It was then extracted with dilute aqueous ammonia and the extract filtered through Norite. Acidification with hydrochloric acid yielded a gray powder, which on recrystallization from dilute alcohol gave a product melting at 186–187°. The melting point of 3-nitro-4-methylbenzoic acid prepared from *p*-toluic acid[5] was 187.5–188.5°. The mixed melting point of the two was 186–187.5°.

Anal. Calcd. for $C_7H_7O_4N$: neut. equiv., 181. Found: neut. equiv., 180.

2,6-Dibromo-3,3′-diamino-4,4′-ditolyl.—A solution of 2 g. of 2,6-dibromo-3-amino-3′-nitro-4,4′-ditolyl in 20 cc. of glacial acetic acid was treated with zinc dust in small portions as long as heat was evolved; finally the mixture was warmed to 50° for a few minutes to complete the reaction, and immediately filtered into 100 cc. of water; the zinc residue was washed with two 5-cc. portions of acetic acid. The crude red product was sucked as dry as possible on a Buchner funnel, and washed with five 10-cc. portions of carbon tetrachloride. One gram (55%) of colorless powder was obtained. It was purified by dissolving in a minimum amount of acetone and adding ten volumes of methyl alcohol. After standing overnight in the ice-box, crystals separated, m. p. 174–175°.

Anal. Calcd. for $C_{14}H_{14}N_2Br_2$: N, 7.57; Br, 43.20. Found: N, 7.63; Br, 43.33.

Resolution of 2,6-Dibromo-3,3′-diamino-4,4′-ditolyl.—To a solution of 1.48 g. of 2,6-dibromo-3,3′-diamino-4,4′-ditolyl in 20 cc. of acetone was added 0.93 g. of *d*-camphorsulfonic acid. After standing overnight in the ice-box, 1 g. (41%) of large rhombohedra had separated. Careful addition of carbon tetrachloride to the filtrate gave further quantities of the salt with essentially the same rotation, up to the final fraction; sometimes the salt was thrown out as an oil by the carbon tetrachloride; the oil would crystallize on standing for several hours after seeding with a crystal from the first fraction. A representative fractionation, starting with 2.4 g. of salt, is given in Table I.

Fractions 1, 2 and 3 were combined and recrystallized three times as follows: The material was dissolved in an equal weight of methyl alcohol, an excess of acetone was added, and the methyl alcohol completely removed with a current of dry air; addition of a little acetone and seeding with a crystal from the original product gave a crop of almost colorless crystals in a short time. The sample for

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[5] Fittig and Ramsay, *Ann.*, **168**, 251 (1873).

rotation and analysis was dried *in vacuo* over phosphorus pentoxide at 100°. This salt melted at 170–180°.

Rotation. 0.5000 g. made up to 5 cc. in methyl alcohol gave α_D, 2.86°; $l = 2$; $[\alpha]^{25}_D$ 14.3°.

Anal. Calcd. for $C_{24}H_{30}O_4N_2Br_2S$: N, 4.65; Br, 26.54; S, 5.32. Found: N, 4.54; Br, 26.18; S, 5.11.

Fraction 4 was the impure salt of the *l*-amine and was not purified further.

Impure salt of *l*-amine: *Rotation.* 0.1804 g. made up to 5 cc. in methanol at 20° gave α_D −1.12; $l = 2$; $[\alpha]^{25}_D$ −15.5°. On standing for fifty hrs., $[\alpha]^{25}_D$ −6.5°.

***d*-2,6-Dibromo-3,3′-diamino-4,4′-ditolyl.**—The pure salt was dissolved in the minimum amount of cold methyl alcohol and immediately poured into ice water containing an excess of aqueous ammonia. The precipitate was filtered and dried in a vacuum desiccator at room temperature. It melted at the same temperature as the racemic base, due, probably, to racemization before melting.

The mutarotation of the *d*-amine salt and the racemization of the free amine are given in Table II.

Summary

A 2,6-disubstituted diphenyl, 2,6-dibromo-3,-3′-diamino-4,4′-ditolyl has been prepared and resolved.

URBANA, ILLINOIS RECEIVED FEBRUARY 15, 1935

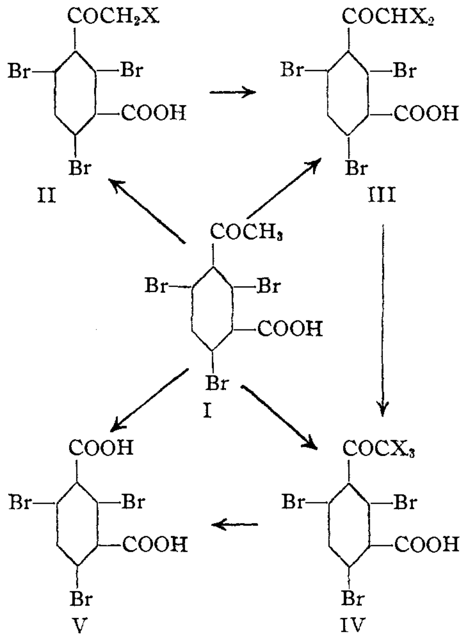
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

The Haloform Reaction. XV. Stepwise Halogenation

BY BENTON A. BULL, WM. E. ROSS AND REYNOLD C. FUSON

The mechanism of the haloform reaction has long been assumed to involve stepwise halogenation followed by chain cleavage of the trihalomethyl derivatives to a haloform and a salt. Because of the rapidity with which the reaction takes place it is extremely difficult to demonstrate the formation of intermediate derivatives. We have found that the introduction of steric hindrance diminishes the rate of the process and, by this means, it has been possible in a number of cases to interrupt the reaction at the last stage,[1] *i. e.*, to isolate the trihalomethyl ketones. In a single instance—one in which the hindrance was due to the presence of halogen atoms ortho to the ketone group—we were able to isolate a monohalomethyl derivative.[2] Subsequently, we have found that ketones which are soluble in alkali react in a manner better adapted for a study of the mechanism.[1] By incorporating both of these desirable features in a single molecule we have been able, in the present work, to interrupt the haloform reaction at each of the stages postulated above.

The compound in question is 2,4,6-tribromo-3-acetylbenzoic acid (I). It was prepared from the corresponding nitrile.[3] When treated for fifteen minutes with cold sodium hypobromite solution this acid was converted into 2,4,6-tribromo-3-monobromoacetylbenzoic acid (II, X = Br). Treatment of one hour's duration converted this compound as well as the original acid (I) into 2,4,6-tribromo-3-dibromoacetylbenzoic acid (III, X = Br). Each of these three compounds could, in turn, be converted into 2,4,6-tribromo-3-tribromoacetylbenzoic acid (IV, X = Br) by extending the time of treatment to twenty-four hours.



The keto-acid (I) was treated in a similar manner with cold sodium hypochlorite solution, but the monochloroacetyl derivative could not be isolated; in five minutes the dichloroacetyl derivative (III, X = Cl) had formed. Both this compound and I were converted into the corre-

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[1] See Johnson and Fuson, THIS JOURNAL, **56**, 1417 (1934), and preceding papers of this series.

[2] Fuson, Bertetti and Ross, *ibid.*, **54**, 4380 (1932).

[3] Fuson, Lewis and DuPuis, *ibid.*, **54**, 1119 (1932).