in 50 cc. of water until no more ammonia was evolved (*ca.* two days). Acidification with hydrochloric acid and evaporation to dryness gave white powders which were ground in a mortar and exhaustively extracted with dry ether. Recrystallization of the ether extracts from hot water gave mesaconic acid in both cases, m. p. 197–198° (uncor.), neutral equivalent, 65.8 (theory, 65.0). Citraconic anhydride, when subjected to the same treatment, also gave only mesaconic acid, which did not depress the melting point of the above hydrolysis products.

*cis-* **and** *trans-***Methyl β-Cyanocrotonates.**—By an analogous procedure, 400 g. of methyl acetoacetate yielded 371 g. (75%) of its cyanohydrin, b. p. 116–118° (11 mm.), $n^{25}$D 1.4332. Dehydration of 270 g. with 216 cc. of thionyl chloride gave the two isomers of methyl β-cyanocrotonates: III, b. p. 82–83° (22 mm.), f. p. 22.5°, $n^{25}$D 1.4543, and IV, b. p. 112–113° (22 mm.), f. p. 24.5°, $n^{25}$D 1.4566. The yield of both isomers was 74%.

*Anal.* Calcd. for $C_6H_7O_2N$: C, 57.6; H, 5.64; N, 11.20. Found for III: C, 57.53; H, 5.75; N, 11.18. Found for IV: C, 57.32; H, 5.81; N, 11.08.

*cis-* **and** *trans-n-***Butyl β-Cyanocrotonates.**—In a similar fashion, 475 g. of *n*-butyl acetoacetate yielded 391 g. (70%) of *n*-butyl acetoacetate cyanohydrin, b. p. 138–142° (17 mm.), $n^{25}$D 1.4318. Dehydration gave a 68% yield of the two isomers of *n*-butyl β-cyanocrotonate: V, b. p. 66–67° (1 mm.), f. p. −36°, $n^{25}$D 1.4515 and VI, b. p. 80–81° (1 mm.), f. p. below −78°, $n^{25}$D 1.4519.

*Anal.* Calcd. for $C_9H_{13}O_2N$: C, 64.65; H, 7.84; N, 8.38. Found for V: C, 64.26; H, 8.07; N, 8.21. Found for VI: C, 63.25; H, 8.02; N, 8.55.

## Summary

The methyl, ethyl, and butyl esters of *cis* and *trans* β-cyanocrotonic acid have been synthesized and their structures and configurations elucidated.

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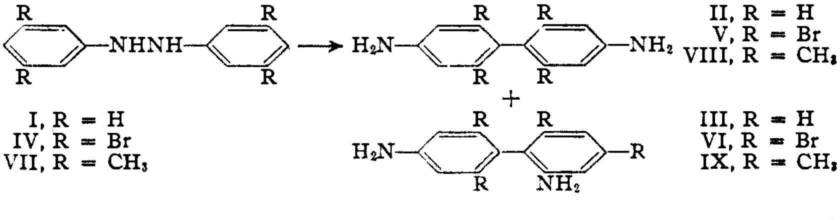
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, AND THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

# The Rearrangement of 3,3',5,5'-Tetramethylhydrazobenzene

BY ROBERT B. CARLIN

The acid-catalyzed rearrangement of hydrazobenzene (I) to benzidine (II) was first recognized by Hofmann.[1] Schmidt and Schultz[2] showed that benzidine was accompanied in the rearrangement products by a small amount of an isomeric base, diphenyline (III). The rearrangements of many substituted hydrazobenzenes have since been studied and the experimental results generalized.[3] Although Robinson[4] has proposed an electronic interpretation of the benzidine rearrangement, he was unable to consider the effects of steric factors upon the course of the reaction because of the scarcity of available evidence bearing upon this phase of the problem. A study of the rearrangements of 3,3',5,5'-tetrasubstituted hydrazobenzenes, in which the substituents are bulky atoms or groups, should serve to furnish some of the required information. The investigation which forms the subject of this report was undertaken in order to determine the effect of the methyl groups in 3,3',5,5'-tetramethylhydrazobenzene (VII) upon the course of its rearrangement. Particular care was taken to observe any of the four manifestations of the hindering effect of the methyl groups which might occur.

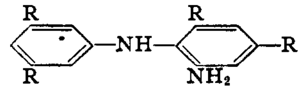


I, R = H
IV, R = Br
VII, R = $CH_3$

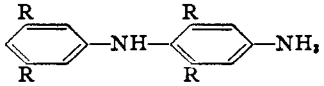
II, R = H
V, R = Br
VIII, R = $CH_3$

III, R = H
VI, R = Br
IX, R = $CH_3$

It might be expected that the rearrangement of any such substituted hydrazobenzene to the corresponding 2,2',6,6'-tetrasubstituted benzidine should be hindered to a certain extent by the presence of the bulky groups occupying all ring positions *ortho* to the carbon atoms engaged in the formation of the new carbon-to-carbon bond. This hindrance, if sufficient to modify the normal electronic effects, might manifest itself by: (1) an increase in the amount of diphenyline, which should be less highly hindered, at the expense of the benzidine; (2) formation of semidines (*e. g.*, X and XI); (3) increased disproportionation of the hydrazobenzene 2ArNHNHAr → ArN=NAr + 2ArNH$_2$; (4) more drastic conditions required to bring about reaction. Numerous attempts have been made to isolate semidines from the rearrangement products of *p*-unsubstituted hydrazobenzenes, but only one has been reported to be successful. Nölting and Werner[5] indicated that traces of *o*-semidine (X, R = H) were formed along with benzidine and diphenyline, by the rearrangement of hydrazobenzene in benzene solu-



X



XI

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[1] Hofmann, *Proc. Roy. Soc.* (London), **12**, 576 (1863).

[2] Schmidt and Schultz, *Ber.*, **11**, 1754 (1878).

[3] Jacobson, *Ann.*, **428**, 76 (1922).

[4] Robinson, *J. Chem. Soc.*, 220 (1941).

[5] Nölting and Werner, *Chem. Ztg.*, **18**, 1095 (1894).

tion. Since the formation of *o*-semidines (X) or *p*-semidines (XI) related to 3,3',5,5'-tetrasubstituted hydrazobenzenes, unlike the formation of benzidines and diphenylines, should be comparatively free from hindrance by the substituents, any inclination toward semidine formation on the part of unsubstituted hydrazobenzene should be greatly augmented when the substituents are present. Cleavage of substituted hydrazobenzenes has been observed frequently,[3] particularly in the case of *p,p'*-disubstituted hydrazobenzenes. This reaction always accompanies rearrangement, although it is usually relatively unimportant.

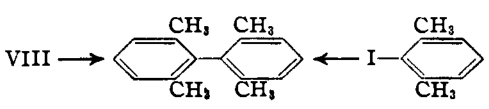
Apparently, no study of the rearrangement products of 3,3',5,5'-tetrasubstituted hydrazobenzenes has been undertaken previously. Meyer, Meyer and Taeger[6] found that 3,3',5,5'-tetrabromohydrazobenzene (IV) was rearranged much less easily than the unsubstituted parent compound and that the rearrangement was accompanied to an unusual extent by cleavage. Two isomeric diprimary amines were isolated from the rearrangement products. The base formed in larger amount was assigned the benzidine structure (V); while its isomer, found only in traces, was given the diphenyline structure (VI). Although, in the light of previous knowledge,[3] these structures appeared most probably correct, they were not proved. Nölting and Stricker[7] treated VII with hydrochloric acid and reported that the hydrochloride of the base which was formed could be diazotized and coupled with compounds, such as naphthionic acid, to produce dyes. The base itself was not otherwise investigated.

The rearrangement of VII by 10% hydrochloric acid proceeded smoothly and without difficulty, as Nölting and Stricker had observed. The crude product was a solid from which two isomeric bases were isolated and separated in 81% yield. Of the 19% of material remaining after the two bases had been removed from the product, about 2% was the 3,3',5,5'-tetramethylazobenzene; and it was then reasonable to assume that at least an equivalent amount of *sym*-xylidine, the other disproportionation product, was present, although it could not be identified. The remainder of the reaction product was a red gum from which no pure compound could be obtained. Evidently the presence of the methyl groups had neither interfered with the ease with which rearrangement occurred nor caused excessive disproportionation of the hydrazo compound.

Examination of the two bases which comprised the major portion of the rearrangement product disclosed that they were the "normal" products, the benzidine (VIII) and the diphenyline (IX). The ratio of VIII to IX from all rearrangements carried out in aqueous solution was consistently about 3:2. In one experiment in which the medium was 95% ethanol saturated with hydrogen chloride, the ratio of benzidine to diphenyline in the product was 5:8. Van Loon[8] showed that the benzidine-to-diphenyline ratio is lower when hydrazobenzene is rearranged in alcohol solution than it is when water is the solvent. Since, however, the benzidine-to-diphenyline ratio from the rearrangement of hydrazobenzene itself in aqueous solutions has never been reported to be less than 4:1, it seems possible that the much smaller ratio of the two homologs VIII and IX formed by rearranging VII may be ascribed to the greater steric hindrance involved in the formation of VIII as compared to that involved in the formation of IX.

No compound having the properties of a semidine was ever found among the rearrangement products of VII, although every attempt was made to isolate and identify such a substance. It is unlikely, therefore, that X and XI (R = $CH_3$) were present in appreciable amount.

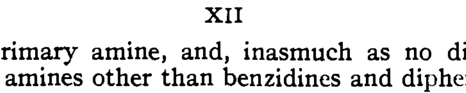
The structure of the benzidine (VIII) was proved by its deamination to the crystalline 2,2',6,6'-tetramethylbiphenyl and the synthesis of the latter by means of the Ullmann reaction.



The deamination of VIII, carried out by reducing the tetrazonium salt with hypophosphorous acid,[9] occurred in only 20% yield. The principal product of the reaction was a red resin from which the biphenyl could be separated only by virtue of its volatility in a high vacuum. Meyer, Meyer and Taeger[6] apparently encountered similar difficulties when they attempted to deaminate V. They were able to convert it to the corresponding tetrabromobiphenyl in only 11% yield, and they reported that this substance was accompanied in the product by quantities of a red-brown resin.

The behavior of 2-iodo-1,3-xylene in the Ullmann reaction has evidently not been described previously. The reaction was extremely slow and incomplete, and it was not possible to separate the product from unchanged iodoxylene. The biphenyl could be isolated only after the iodoxylene had been hydrogenated to *m*-xylene.

Examination of the isomer of VIII disclosed that it could not possess either semidine structure X or XI (R = $CH_3$), since the base formed a bis salicylal derivative (XII). It must therefore be



XII

a diprimary amine, and, inasmuch as no diprimary amines other than benzidines and diphenylines have been detected in the rearrangement

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(6) Meyer, Meyer and Taeger, *Ber.*, **53**, 2034 (1920).

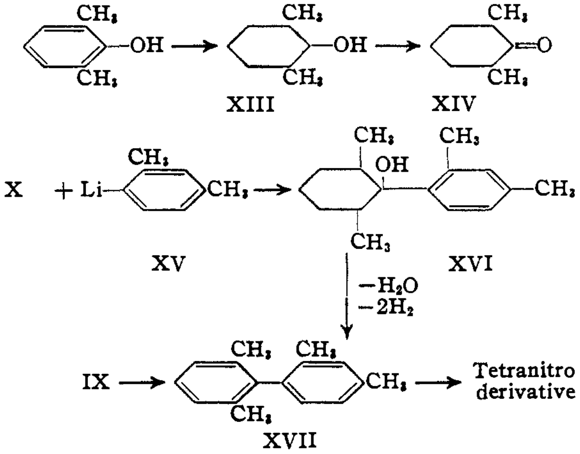
(7) Nölting and Stricker, *ibid.*, **21**, 3142 (1888).

(8) Van Loon, *Rec. trav. chim.*, **23**, 84 (1904).

(9) Kornblum, "Org. Syn.," **21**, 30 (1941).

products of hydrazobenzenes, the structure IX was strongly indicated. The deamination of the base, carried out by the hypophosphorous acid procedure, gave a liquid product in 29% yield which formed a crystalline tetranitro derivative. The formation of a liquid deamination product was in itself evidence favoring the structure IX for the base; for, had the base been 2,2',4,4'-tetramethyl-6,6'-diaminobiphenyl, the only possible structure other than IX, it should have given as its deamination product 2,2',4,4'-tetramethylbiphenyl, a crystalline solid which melts at 41°.[10]

The structure of the base was established by synthesis of the biphenyl XVII. The liquid product of the synthesis gave a tetranitro derivative identical with that obtained from the deamination product of the base.



Whereas the addition of XV to XIV occurred in 90% yield, the iodomagnesium Grignard reagent corresponding to XV reacted with XIV to form a product from which 60% of XIV was recovered and from which only traces of XVI could be obtained. Evidently enolization of the ketone was the chief reaction. It has recently been shown[11] that organo-lithium compounds undergo more addition to and cause less enolization of branched ketones than do the corresponding Grignard reagents.

The carbinol (XVI) proved unexpectedly difficult to dehydrate. Although it was simultaneously dehydrated and dehydrogenated by sulfur at 250°, attempts to prepare 1-(2,4-dimethylphenyl)-2,6-dimethyl-1-cyclohexene by the action of potassium acid sulfate or of acetic anhydride on the carbinol failed. An investigation of the action of dehydrating agents on XVI and similar carbinols is contemplated.

The only evidence of the hindering effect of the methyl groups of VII upon the course of its rearrangement is to be found in the unusually low ratio of benzidine to diphenyline in the product. It is possible that even this effect may be ascribed to the electronic, rather than to the steric, properties of the methyl groups. A study of the rearrangements of other 3,3',5,5'-tetrasubstituted hydrazobenzenes is now being carried out. The proper selection of substituents should make it possible to decide, on the basis of the results, whether their electronic or steric properties are responsible for their effects upon the course of the benzidine rearrangement.

## Experimental[12,13]

**3,3',5,5'-Tetramethylhydrazobenzene (VII).**—To a stirred suspension of 25 g. of zinc dust in a boiling solution of 10 g. of 5-nitro-1,3-xylene (Eastman Kodak Co.) in 40 cc. of ethanol, a solution of 15 g. of sodium hydroxide in 50 cc. of water was added dropwise. The alkali was added at such a rate that the solution boiled vigorously. Partial crystallization of the azo and hydrazo compounds occurred occasionally, and ethanol was added as required to bring these compounds into solution. After about half of the alkali had been added, it was necessary to heat the reaction mixture in order to maintain steady boiling. When all of the alkali had been added, the solution was still colored, and it was therefore boiled, with frequent additions of 1-g. quantities of zinc dust, for four hours. The mixture was rapidly filtered through a large, preheated Buchner funnel into 150 cc. of 30% acetic acid to which about 0.5 g. of sodium bisulfite had been added. The insoluble sludge from the reaction mixture was twice stirred and boiled with 20-cc. portions of ethanol, and the extracts were also filtered into the acetic acid solution. The mixture in the filter flask was cooled to 10°, and the buff-colored product was collected by filtration and immediately dissolved in 75 cc. of boiling petroleum ether (b. p. 60–110°). The petroleum ether solution was poured from the slight water layer and filtered. On cooling, the solution deposited VII as glistening white needles. After drying, the product weighed 7.4 g. (92%); m. p. 122–124°.

This hydrazobenzene was extremely easily oxidized in air unless it was crystallized from petroleum ether. It could be recrystallized from ethanol saturated with hydrogen sulfide, but the product obtained in this manner was stable only for a few minutes. After recrystallization from petroleum ether, it could be kept for several days in a stoppered container. Recrystallization failed to raise the m. p. of the compound higher than 125°. Nölting and Stricker[7] reported the m. p. to be 124–125°.

*Anal.* Calcd. for $C_{16}H_{20}N_2$: C, 79.93; H, 8.41. Found: C, 79.79; H, 8.66.

**3,3',5,5'-Tetramethylazobenzene** was obtained in quantitative yield by boiling an ethanol solution of the hydrazo compound in an open vessel for ten minutes. On cooling, the solution deposited thick, orange-red needles, m. p. 138.5–139°. The m. p. given by Nölting and Stricker[7] was 136–137°.

**2,2',6,6'-Tetramethyl-4,4'-diaminobiphenyl (VIII) and 2,2',4,6'-Tetramethyl-6,4'-diaminobiphenyl (IX).**—To 300 cc. of boiling 10% hydrochloric acid through which nitrogen was being bubbled, 6.2 g. of the hydrazobenzene (VII) was added, with vigorous stirring. Most of the solid material dissolved within fifteen minutes, but a small amount remained undissolved even after the solution had been boiled for five hours. The nitrogen stream was discontinued, the mixture stoppered and allowed to stand overnight. The insoluble azo compound (0.07 g.) was collected by filtration and dried. On recrystallization from petroleum ether, it formed orange-red needles, m. p. 139°.

The filtrate from the azo compound was stirred and boiled with Norit for thirty minutes and then filtered. The colorless filtrate was cooled and treated with 20% sodium hydroxide until cloudiness appeared and then with

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(10) Ullmann and Meyer, *Ann.*, **332**, 45 (1904).

(11) Young and Roberts, THIS JOURNAL, **66**, 1444 (1944).

(12) All melting points are corrected.

(13) Microanalyses by Miss Theta Spoor, University of Illinois, and by Dr. Carl Tiedcke, Laboratory of Microchemistry, New York, N. Y.

a saturated solution of sodium acetate until precipitation was complete. The pinkish solid which separated was extracted from the aqueous solution with three 100-cc. portions of ether. The red ether solution was dried over Drierite and the ether removed and replaced by 20 cc. of benzene. The hot benzene solution was treated with 40 cc. of petroleum ether (b. p. 80–90°) and the resulting solution was allowed to cool. The fine, buff-colored needles (3.0 g.) which deposited were collected by filtration and dried; m. p. 160–165°. Repeated recrystallization of this material from 50% ethanol gave faintly yellowish, fern-like crystals of VIII, m. p. 167–168°.

*Anal.* Calcd. for $C_{16}H_{20}N_2$: C, 79.93; H, 8.41. Found: C, 79.74; H, 8.51.

The filtrate from VIII was concentrated to a volume of 15 cc. On cooling, the solution deposited pinkish crystals of IX (2.0 g.) which were collected by filtration, washed with petroleum ether (b. p. 30–40°), and dried; m. p. 140–142°. Several recrystallizations from benzene–petroleum ether gave small, white prisms, m. p. 143°. The yield of VII and IX combined was 5.0 g. (81%).

*Anal.* Calcd. for $C_{16}H_{20}N_2$: C, 79.93; H, 8.41. Found: C, 79.77; H, 8.43.

Only red oils were obtained when the filtrate and washings from IX were concentrated. Attempts to obtain pure compounds from these oils by the use of steam distillation, vacuum distillation, and high vacuum sublimation failed.

**Rearrangement of VII in Ethanol Solution.**—To a solution of 2.0 g. of VII in 30 cc. of ethanol, which had been prepared in a stream of nitrogen, dry hydrogen chloride was added until the solution was saturated. Passage of nitrogen through the solution was continued during the addition of hydrogen chloride, and the solution was allowed to boil. The solution was cooled, the vessel was stoppered, and the mixture was permitted to stand overnight. It was boiled gently for an hour and poured into 400 cc. of iced 10% sodium hydroxide. The precipitated solid was collected by filtration, dried, and dissolved in a boiling mixture of 10 cc. of benzene and 30 cc. of petroleum ether (b. p. 80–90°). The benzidine (VIII) crystallized from the cooled solution; weight 0.5 g.; m. p. 158–162°. The diphenyline (IX) was obtained by concentrating the filtrate from VIII; weight 0.8 g.; m. p. 140–142°.

**Bis Salicylal Derivative (XII) of Base (IX).**—To a boiling solution of 0.5 g. of IX in 5 cc. of ethanol was added a hot solution of 0.5 g. of freshly distilled salicylaldehyde in 5 cc. of ethanol, and the resulting solution was boiled for 3 hours. When the cooled solution was diluted with 50 cc. of water and the resulting mixture was shaken with ether, 0.3 g. of a bright yellow, crystalline solid, m. p. 201–205°, separated. The ether solution was filtered, washed twice with 5% hydrochloric acid, three times with a 5% solution of sodium bicarbonate, and dried over Drierite. When the ether solution was concentrated, another 0.2 g. of small yellow crystals separated, m. p. 192–203°. After two recrystallizations from ethanol–benzene, bright yellow platelets of the bis salicylal derivative (XII), m. p. 208°, were obtained.

*Anal.* Calcd. for $C_{30}H_{28}O_2N_2$: C, 80.32; H, 6.29; for mono salicylal derivative, $C_{23}H_{24}ON_2$: C, 80.19; H, 7.03. Found: C, 80.49; H, 6.32.

**2,2',6,6'-Tetramethylbiphenyl. A. By Deamination of VIII.**—The procedure given by Kornblum[9] was followed. A solution of 2.36 g. of the benzidine (VIII) in 30 cc. of water and 3.4 cc. of concentrated hydrochloric acid was tetrazotized with a solution of 1.45 g. of sodium nitrite in 5 cc. of water. The cold solution of the tetrazonium salt was treated with 30 cc. of 30% hypophosphorous acid. The reaction mixture was kept at 0° for eight hours and at room temperature for fourteen hours and was then extracted three times with ether. The ether solution was washed three times with 10% sodium hydroxide, once with water, and was dried over Drierite. The solvent was removed, and the residue was subjected to sublimation in a high vacuum. The temperature of the oil-bath surrounding the sublimation apparatus was raised from 25 to 120° during the course of the sublimation. The powdery white sublimate (0.82 g.), which melted over a wide range, was resublimed at room temperature. Only a part (0.42 g.) of the material was volatile. This sublimate was composed of shiny, white needles, m. p. 64–66°; yield, 20%.

The solid residue from the sublimation of the biphenyl could be sublimed only at higher temperatures, and the sublimates appeared to be amorphous and were always impure. Two fractions, m. p. 60–100° and 145–160° were obtained. The residue from the first sublimation was an extremely tough, red glass which was not examined.

**B. From 2-Iodo-1,3-xylene by the Ullmann Reaction.**—Eastman Kodak Co. 2-iodo-1,3-xylene was purified by steam distillation from 10% sodium hydroxide and fractionation under reduced pressure through a Widmer column. The fraction chosen for use in the Ullmann reaction was faintly pink; b. p. 87° (3 mm.); $n^{20}_{D}$ 1.6038.

A stirred mixture of 5.62 g. of iodoxylene and copper metal (J. T. Baker Chemical Co., precipitated powder) was heated in a metal bath at 240–265° for forty-eight hours. The cooled mixture was extracted with ether, the solution was filtered, the solvent removed, and the residue was steam distilled. The distillate was extracted with ether, the ether solution was dried over Drierite, and the ether removed. The residue was distilled, and two fractions, b. p. 230–240° and 240–261°, were collected. The more volatile fraction was composed principally of unchanged iodoxylene. The higher boiling fraction was dissolved in a solution of 2 cc. of 10% sodium hydroxide in 30 cc. of ethanol, about 1 g. of Raney nickel was added, and the mixture was shaken for one hour with hydrogen at a pressure of 40 pounds. The mixture was filtered free of nickel and diluted with water until glistening white plates of the tetramethylbiphenyl separated; weight 0.45 g.; m. p. 66–67°. An additional 0.1 g. of product, m. p. 63–65°, could be obtained by concentrating the mother liquors from the first crop of crystals; yield, 21%. Recrystallization of the substance m. p. 66–67° from ethanol failed to raise the m. p. A mixture of a sample of this material with one of m. p. 64–66° obtained by deaminating VIII had the m. p. 65.5–66.5°.

*Anal.* Calcd. for $C_{16}H_{18}$: C, 91.37; H, 8.63. Found: C, 91.34; H, 8.86.

No product could be obtained unless the iodoxylene was purified in the manner described above.

**2,6-Dimethylcyclohexanol (XIII).**—The hydrogenation of 61 g. of 2,6-xylenol (Shell Development Co., m. p. 44.5°) was carried out using a modification of the procedure given by Ungnade and Nightingale[14] for the hydrogenation of phenols. To the molten xylenol was added 75 mg. of sodium, and the mixture was warmed until the metal dissolved. The molten mixture was poured into a nickel bomb liner, and about 4 g. of Raney nickel was added. The hydrogenation was carried out with an initial hydrogen pressure of 1850 pounds. The maximum temperature was 190°, attained after one and one-half hours, when the hydrogenation was complete. The contents of the bomb and liner were poured out and the bomb and liner rinsed with benzene. The solution of the product in the benzene used as the rinse was filtered free of nickel, washed twice with 10% sodium hydroxide and once each with a 5% solution of sodium bicarbonate and with water, and dried over potassium hydroxide. The benzene was removed and the residue distilled. The main fraction (46.8 g.; 73%) had a b. p. 171–173°; $n^{20}_{D}$ 1.4625. Skita[15] hydrogenated 2,6-xylenol in the presence of platinum and obtained a product which had a b. p. 172°; $n^{20}_{D}$ 1.4612. Apparently the compound reported by Skita was a stereoisomer of the one obtained in this experiment, for the latter formed a **phenylurethan**, m. p. 132°, whereas Skita obtained a phenylurethan m. p. 158°. Anziani and Cornubert[16c] isolated stereoisomeric specimens of 2,6-dimethylcyclohexanol which formed phenylurethans melting, respectively, at

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[14] Ungnade and Nightingale, THIS JOURNAL, **66**, 1218 (1944).

[15] Skita, *Ber.*, **56B**, 2234 (1923).

[16] (a) Cornubert and de Demo, *Compt. rend.*, **197**, 843 (1933); (b) Cornubert and Anziani, *ibid.*, **217**, 197 (1943); (c) Anziani and Cornubert, *ibid.*, **217**, 233 (1943).

132° and 158°. They did not give physical constants of the carbinol from which the former was prepared.

**2,6-Dimethylcyclohexanone (XIV).**—To a stirred solution of 45.7 g. of 2,6-dimethylcyclohexanol (XIII) in 120 cc. of acetic acid, a solution of 155 g. of sodium dichromate and 44 cc. of concentrated sulfuric acid in 240 cc. of water was added at such a rate that the temperature of the mixture was maintained between 55 and 60° throughout most of the addition. The temperature dropped somewhat after about three-fourths of the oxidizing agent had been added, and the last fourth was added quite rapidly. Stirring was continued for three hours after all the chromic acid solution had been added. The reaction mixture was treated with a solution of 135 g. of sodium hydroxide in 200 cc. of water, and the viscous mass which resulted was steam distilled until 500 cc. of distillate had been collected. The water layer was saturated with sodium chloride, the crude product separated from the brine, and the latter extracted with three 50-cc. portions of ether. The ether extracts were combined with the crude product, and the solvent was removed. The residual liquid was shaken mechanically for sixteen hours with a solution of 35 g. of semicarbazide hydrochloride and 40 g. of sodium acetate in 105 cc. of water to which 10 cc. of 10% sodium hydroxide had been added. The crude solid semicarbazone (38.5 g., 59% from the cyclohexanol) was collected by filtration and recrystallized from a mixture of 35 cc. of absolute ethanol and 700 cc. of benzene. Although 26.4 g. of glistening white needles was obtained, the material was not pure but was apparently a mixture of the semicarbazones, m. p. 183° and 197°, respectively, of stereoisomeric specimens of XIV reported by Cornubert and de Demo,[16a] for the m. p. of the product of recrystallization was 178–184°. Concentration of the filtrate from the first crop of semicarbazone gave 9.9 g. of white needles, m. p. 171–175°. The total yield of purified semicarbazone was 36.3 g. (57%). No effort was made to separate the stereoisomeric semicarbazones. The oxidation of a single stereoisomer of the cyclohexanol (XIII) to a mixture of stereoisomeric cyclohexanones (XIV) is in accord with the observation of Cornubert and Anziani[16b] that a mixture of stereoisomers is obtained regardless of the source material or the nature of the preparation of XIV.

The recrystallized semicarbazone mixture was treated with 500 cc. of 12% sulfuric acid, and the ketone (XIV) was steam distilled from the mixture. The product was extracted from the distillate in the manner described above, the ether solution dried over Drierite, and the ether removed. Distillation of the residual liquid gave 1 g. of material b. p. 168–170° and 22.2 g. of a clear, colorless liquid, b. p. 170–172°; $n^{20}$D 1.4500. Skita[15] reported a b. p. of 174°, but no refractive index appears to have been reported. The over-all yield of ketone from the carbinol was 49%.

In agreement with the report of Cornubert and de Demo[16a] and contrary to that of Skita,[15] it was not found possible to prepare a bisulfite addition product of XIV. The crude semicarbazone mixture was best recrystallized from benzene–absolute ethanol. An attempt to effect recrystallization from dilute ethanol resulted in the hydrolysis of a considerable portion of the semicarbazones, with the regeneration of XIV.

**1-(2,4-Dimethylphenyl)-2,6-dimethyl-1-cyclohexanol (XVI).**—About one-fourth of a solution of 36.4 g. of 4-iodo-1,3-xylene (Eastman Kodak Co., purified by the same procedure used for the purification of 2-iodo-1,3-xylene) in 75 cc. of absolute ether was added to a stirred mixture of 2.4 g. of cut lithium in 40 cc. of absolute ether under a stream of dry, oxygen-free nitrogen. The reaction started within a minute, and the remaining iodoxylene solution was added at such a rate that gentle boiling was maintained. After the iodoxylene had been added, the mixture was stirred and boiled for four hours. Stirring was continued, and a solution of 15 g. of 2,6-dimethylcyclohexanone (XIV) in 35 cc. of absolute ether was added rapidly enough to cause the solution to boil. After the reaction mixture had been permitted to stand overnight under a nitrogen stream, it was poured, with stirring, into 200 cc. of iced 10% sulfuric acid. The ether solution was separated, the aqueous layer was extracted with three 30-cc. portions of ether, and the extracts were added to the original ether solution. The combined ether solution was washed with a saturated solution of sodium bisulfite, with a 5% solution of sodium bicarbonate, with water, and was dried over Drierite. The ether was removed, a little dry benzene was added to and distilled from the residual liquid to remove traces of water, and the liquid was distilled under diminished pressure. Most of the distillate (25 g., 88%) was a colorless, somewhat viscous liquid, b. p. 132–133° (4 mm.); $n^{20}$D 1.5337.

*Anal.* Calcd. for $C_{16}H_{24}O$: C, 82.69; H, 10.42. Found: C, 82.66; H, 10.32.

**2,2′,4,6′-Tetramethylbiphenyl (XVII). A. By Dehydration and Dehydrogenation of XVI.**—A mixture of 16.5 g. of the carbinol (XVI) and 2.65 g. of sulfur was heated in a metal bath until, at 230°, gas began to be evolved. The temperature was gradually raised in order to maintain a steady evolution of gas. When a test with a dilute solution of lead acetate showed that the evolution of hydrogen sulfide had almost ceased, the mixture was allowed to cool, water was removed from portions of the apparatus where it had collected during the reaction, about 0.5 g. of fresh sulfur was added, and the mixture was again heated until hydrogen sulfide was evolved rapidly. This process was continued until the addition of fresh sulfur no longer caused appreciable amounts of hydrogen sulfide to be formed. The cooled mixture was dissolved in ether, and the ether solution was washed twice with 5% sodium hydroxide and once with water, and was dried over Drierite. The viscous, dark residue from the evaporation of the ether was distilled under diminished pressure. The distillate (7.8 g., 52%) was yellow and somewhat milky, b. p. 80–104° (5 mm.). It was dissolved in 200 cc. of petroleum ether (b. p. 40–60°), and the solution was allowed to trickle through an eight-inch column of silica gel. The solvent was removed and the residual liquid was distilled. The distillate (7.1 g., 48%) was colorless but still somewhat cloudy, b. p. 114–115° (5 mm.). Repeated redistillations, preceded by careful drying, failed to remove the cloudy appearance. The milkiness could be removed only by allowing the liquid to stand for a week over a few pieces of Drierite in a tightly stoppered container. The clear, colorless liquid had $n^{20}$D 1.5648.

*Anal.* Calcd. for $C_{16}H_{18}$: C, 91.37; H, 8.63. Found: C, 91.30; H, 8.71.

**The tetranitro derivative** was prepared by treating a mixture of 0.8 g. of the biphenyl (XVII) and 3.4 cc. of concentrated sulfuric acid with 3.4 cc. of concentrated nitric acid. The mixture was cooled and shaken during the addition of nitric acid. After the nitric acid had been added, the mixture was maintained at 45° for ten minutes and then poured onto 50 g. of cracked ice. The solid which formed (1.2 g.) was collected by filtration, washed with water, and recrystallized from acetic acid. The first crystalline fraction (0.1 g.) had a m. p. of 228–230°, and two more fractions (0.5 g.) of m. p. 218–225° and 213–221°, respectively, were obtained by concentrating the filtrate from the first fraction. The homogeneity of the first fraction was established by chromatographing its solution in a mixture of 50 cc. of benzene and 50 cc. of petroleum ether (b. p. 40–60°) through a 1.8 by 25-cm. column of activated alumina (Alorco, Grade A). The chromatogram was developed with 100 cc. of the same solvent, cut into four equal parts, and the parts eluted with acetone. Only the eluate from the topmost section contained an appreciable amount of material. After recrystallization from benzene–petroleum ether, this substance formed tiny, pale yellow needles, m. p. 237–238°.

*Anal.* Calcd. for $C_{16}H_{14}N_4O_8$: C, 49.23; H, 3.59. Found: C, 48.88; H, 3.46.

**B. By Deamination of IX.**—The deamination of 1.95 g. of IX was carried out by the procedure applied to the deamination of VIII. When the product was introduced into a sublimation apparatus and a high vacuum applied, a liquid collected on the cold finger. The distillate was obtained by raising the bath temperature slowly to 150°. The residue from the distillation was a dark, tough glass. The distillate was redistilled onto the cold finger in the sublimation apparatus; but this time the mixture was kept at room temperature. The distillate was washed from the cold finger with ether, the ether was removed, and the distillation at room temperature was repeated. Again the product was washed from the cold finger with ether. The ether was removed under diminished pressure and the residual liquid (0.5 g., 29%) was nitrated by means of a procedure identical with that described in part A. The crude nitration product was divided into fractions by recrystallization from acetic acid, and the first fraction, having a m. p. of 226–229°, was chromatographed in the manner described in part A. From the second quarter of the chromatogram a compound was obtained which, after recrystallization from benzene–petroleum ether, formed small, pale yellow needles, m. p. 235–237°. A mixture of this substance and that of m. p. 237–238° described in part A had a m. p. of 236–237°.

**Action of Potassium Acid Sulfate on the Carbinol (XVI).**—A mixture of 21 g. of XVI and 268 mg. of freshly fused potassium acid sulfate was heated in an oil-bath under a pressure of 70–85 mm. until slow distillation of a milky liquid occurred. The temperature of the oil-bath was so regulated that the temperature of the distilling vapors was maintained between 190 and 200°. The distillate was dissolved in ether, and the solution was dried over Drierite. The ether was removed, and the dehydration procedure was repeated, using 200 mg. of potassium acid sulfate. This time, the distillate was clear and colorless. It was dissolved in ether, and the ether solution was washed with 5% sodium hydroxide and with water and dried over Drierite. After removal of the ether, the residual liquid was distilled under diminished pressure. Although there was some lower-boiling material, the only constant-boiling portion, which comprised most of the product, had a b. p. of 122–123° (3 mm.); $n^{20}D$ 1.5322. This substance had the composition of the unchanged carbinol.

*Anal.* Calcd. for $C_{16}H_{24}O$: C, 82.69; H, 10.42. Found: C, 82.63; H, 10.37.

The action of boiling acetic anhydride on XVI had similar results.

## Summary

1. The products of the rearrangement of 3,3′,5,5′-tetramethylhydrazobenzene (VII) in 10% hydrochloric acid have been shown to be 2,2′,6,6′ - tetramethyl - 4,4′ - diaminobiphenyl (VIII) and 2,2′,4,6′-tetramethyl-6,4′-diaminobiphenyl (IX).

2. The only abnormality of this rearrangement which might be attributed to the hindering effect of the methyl groups is the low benzidine (VIII) to diphenyline (IX) ratio in the product.

ROCHESTER, N. Y. RECEIVED MARCH 12, 1945

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF MIZZY, INC.]

# Esters of β-Alkylaminoethanols

BY JULIAN R. REASENBERG AND SAMUEL D. GOLDBERG[1]

Since the discovery that esters of β-monoalkylaminoethanols were suitable local anesthetics,[2] a considerable amount of work has been done on compounds of this type. Goldberg and Whitmore prepared the β-monoalkylaminoethyl and γ-monoalkylaminopropyl esters of *p*-aminobenzoic acid in which the alkyl group varied from ethyl to amyl in size. Goldberg, Ringk and Spoerri[3] prepared the α-alkyl substituted analogs of the above and Pierce, Salsbury and Frederickson[4] prepared the alkoxybenzoates of these amino alcohols. Kremer and Waldman[5] prepared the β-mono alkylamino β,β-dimethylethanols and attempted to esterify these. Pierce and his coworkers successfully esterified the last mentioned amino alcohols with alkoxybenzoic acids and obtained local anesthetics.[6] Since then, Ringk and Epstein[7] have prepared the *p*-aminobenzoates which Kremer and Waldman failed to prepare and in addition have extended some of the other series previously described.

In a recent patent and subsequent comprehensive series of papers, issued since this work was completed, Cope and Hancock have described aromatic esters of 2-alkylaminoethanols, monoalkylaminopropanols, and monoalkylaminobutanols.[8] The present paper deals with the esterification of β-monoalkylaminoethanols and β-monoalkylamino β,β-dimethylethanols with a number of aromatic acids to give esters. Also, since there is some confusion about the mechanism of the Schotten–Baumann reaction involved, an attempt has been made to elucidate the course of the reaction.

Ringk and Epstein[7] show that for the reaction of one mole of acyl chloride with one mole of β-monoalkylaminoethanol in aqueous alkali, two products are possible, namely, the β-hydroxy amide and the β-amino ester. Hancock and Cope[8d] have demonstrated that in the Schotten–Baumann reaction between an acid chloride and a β-alkylaminoalcohol, the main product is the amide. Our present work leads to a complete and independent agreement with the work of Cope. When the condensation is carried out by the method of Goldberg and Whitmore[2] only the β-hydroxy amide is formed, and, under the influence of strong acid, this amide undergoes a rearrangement to form the acid salt of the corresponding amino ester.

This rearrangement, or acyl shift, is more or

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[1] Present address: Graham Chemical Co., Jamaica 2, N. Y.

[2] Goldberg and Whitmore, THIS JOURNAL, **59**, 2280 (1937).

[3] Goldberg, Ringk and Spoerri, *ibid.*, **61**, 3562 (1939).

[4] Pierce, Salsbury and Frederickson, *ibid.*, **64**, 1691 (1942).

[5] Kremer and Waldman, *ibid.*, **64**, 1089 (1942).

[6] Pierce, Salsbury, Haden and Willis, *ibid.*, **64**, 2884 (1942).

[7] Ringk and Epstein, *ibid.*, **65**, 1222 (1943).

[8] (a) Cope, U. S. Patent 2,339,914, Jan. 25, 1944; (b) Cope and Hancock, THIS JOURNAL, **66**, 1448 (1944); (c) Cope and Hancock, *ibid.*, **66**, 1453 (1944); (d) Hancock and Cope, *ibid.*, **66**, 1738 (1944).