[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Polyalkylbenzenes. XXXIV.[1] The Reaction between Polymethyl-*p*-methoxyanilines and Formaldehyde

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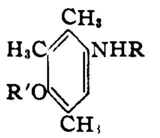
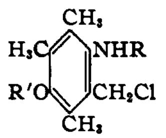
If the reaction between formaldehyde, hydrochloric acid, and a polymethyl-*p*-aminophenol or some derivative of it (I, II, III) could be controlled in such a way that simple chloromethylation resulted, the products, such as IV, would be of great value as starting materials for synthesis of 6-hydroxytetrahydroquinolines, the nitrogen analogs of the tocopherols. The reaction between simple aromatic amines and formaldehyde, under a variety of conditions has been rather extensively studied[3]; in general, when the *p*-position of the aromatic amine is occupied by a substituent, the primary products have included *o*-aminobenzylanilines, *o,o'*-diaminodiphenylmethanes, and substances produced from these by further action of formaldehyde: hydroxytetrahydroquinazolines, dihydroquinazolines, tetrahydroquinazolines, the N-methyl derivatives of the original amines, and "Troeger's base," the last type obtained only from *p*-toluidine, *p*-anisidine, and *p*-phenetidine.



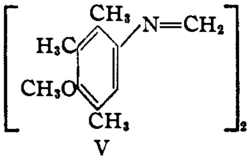
I, R' = CH_3; R = H
II, R' = CH_3; R = —CHO
III, R' = CH_3; R = Ac



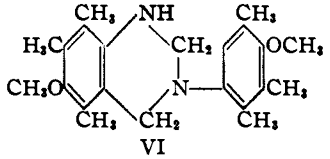
IV

When either 2,3,5-trimethyl-4-methoxyaniline (I) or its formyl derivative (II) was subjected to the action of formaldehyde and hydrochloric acid at room temperature for some sixty hours, it was converted in a yield of 86%, into a basic compound, A. Two other basic compounds, B and C, resulted when dilute hydrochloric acid was used and the time of the reaction was reduced. No compounds corresponding to IV were even obtained.

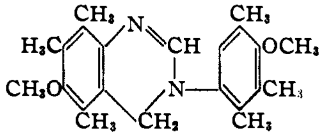
Base A was isolated from the reaction mixture as the hydrochloride, which could not itself be recrystallized, for it was insoluble in non-polar solvents, and solvolyzed in polar solvents. The free base A, however, was easily purified and the analytical values and molecular weight of it and of its hydrochloride showed that two molecules of amine, and two or three molecules of formaldehyde, were involved in the formation of A. On the basis of the analytical values, and in analogy with previous work described in the literature, four structures for A had to be considered: the azomethine dimer V; the tetrahydroquinazoline VI; the dihydroquinazoline VII; and the "Troeger's base" VIII.



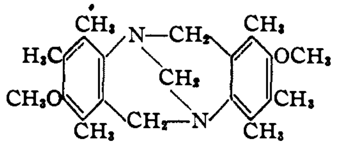
V



VI

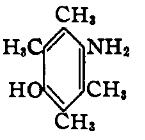


VII

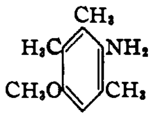


VIII

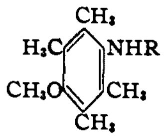
VIIIa, OH in place of OCH_3



IX



X



XI, R = H
XII, R = CH_3

Base A failed to react with acetic anhydride and sulfuric acid at 100°, and was unaffected by the action of sodium and alcohol, of stannous chloride and hydrochloric acid, or of hydrogen in the presence of Raney nickel catalyst. Moreover, base A was unchanged by boiling alcoholic sodium hydroxide, and when boiled in hydrochloric acid and acetic acid, the only effect was a partial cleavage of the methoxyl groups to hydroxyl groups (VIIIa). These properties showed that no amino hydrogen atom was present in A, and that the grouping —N═C was also absent; the structure VIII for A was strongly indicated. Final proof that structure VIII was the correct one was obtained when A was reductively cleaved by action of hydriodic acid and phosphorus at 170°; there resulted, in 71% yield, 2,3,5,6-tetramethyl-4-aminophenol, IX. On one occasion, the temperature during the reductive cleavage of A reached 280°, and in this case, the product was the hydrocarbon durene, a tetramethylbenzene. Thus, base A is a "Troeger's base"—and is the only example of such

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(1) XXXIII, THIS JOURNAL, 65, 1594 (1943).

(2) Abstracted from a thesis by W. M. Schubert, presented to the Graduate Faculty of the University of Minnesota, in partial fulfilment of the requirements for the Ph.D. degree, August, 1947.

(3) (a) Maffei, *Gazz. chim. ital.*, 58, 261 (1928); 59, 3 (1929); (b) Wagner, THIS JOURNAL, 54, 660, 3698 (1932); 57, 1296 (1935); (c) Wagner and Eisner, *ibid.*, 56, 1938 (1934); 59, 879 (1937); (d) Simons, *ibid.*, 59, 518 (1937); (e) Spielman, *ibid.*, 57, 583 (1935); (f) Miller and Wagner, *ibid.*, 63, 832 (1941).

a base completely substituted in the benzene rings.[4]

When I, formaldehyde and dilute hydrochloric acid were allowed to react at 65–70° for fifteen minutes, the yield of A was reduced to 25% and there appeared a greater yield of a lower-melting (137–138°) base, B; when the reaction was carried out at 50° for eight minutes, the yield of B was nearly doubled and no A at all resulted. The filtrate, after removal of B, deposited crystals of the hydrochloride of a third base, C, melting at 136–137°, almost the same temperature as B. Base B was converted into base C by the action of sodium and alcohol. Base B failed to react with acetic anhydride, whereas base C was converted to a monoacetyl derivative, soluble in dilute hydrochloric acid. These facts showed that the group —N=C was present in B and the group —NHCH— as well as a tertiary N atom, were present in C. Finally, base B, when reductively cleaved by action of hydriodic acid and phosphorus at 170°, gave a mixture of 2,3,6-trimethyl-4-aminophenol and 2,3,5,6-tetramethyl-4-aminophenol (IX) in a yield of 71%. These facts establish the structure of B as the dihydroquinazoline VII, and the structure of C as the tetrahydroquinazoline VI.

The question as to how the three bases VI, VII, and VIII are related chemically is difficult to decide. The fact that the yield of VIII increased with time at the expense of VI and VII may mean that the latter bases are intermediates in the formation of VIII; the fact that VI was precipitated (as the hydrochloride) from the acidic filtrate after removal of VII may mean that VI is formed later than, and perhaps by reduction of VII. The tetrahydroquinazoline VI was converted into VIII by action of formaldehyde and hydrochloric acid, or by action of formic acid, alone or in the presence of hydrochloric acid. Hence, VI is probably an intermediate in the formation of VIII, but a reduction must have occurred when VI was converted into VIII by action of formic acid. Some sort of oxidation process must have occurred during the formation of the dihydroquinazoline VII; it may have resulted from a condensation of formic acid with an *o*-aminobenzylamine, formed earlier in the reaction and the evidence, though indirect, indicates that VII is a precursor of VI. Thus, action of formalin and 4% hydrochloric acid upon I for eight minutes at 50° produced VII in 52% yield, and no VI or VIII was isolated; when the temperature was maintained at 65–70°, and the reaction time was prolonged to fifteen minutes, VII, VI, and VIII were produced in yields of 31, 7, and 25%, respectively. However, VII was not converted into VIII by action of formaldehyde, formic acid, and hydrochloric acid, so VII is certainly not a direct precursor of VIII.

Many attempts, and under a great variety of conditions, were made to condense 2,3,6-trimethyl-4-aminophenol, its N-formyl, N-acetyl derivatives and their *o*-methyl ethers (I, II, III) with dienes (isoprene, 2,3-dimethylbutadiene), allylic halides (allyl bromide, isoprene hydrobromide, α-methallyl bromide), and an allylic alcohol (methylvinylcarbinol), but without any success. In the great majority of experiments, the starting material was recovered unchanged or else the reaction consisted merely in cleavage of the N-acyl group. Likewise, no success attended any of the many attempts to introduce an aldehyde group into the vacant position of these compounds: zinc cyanide and hydrochloric acid, or N-methyl formanilide and phosphorus oxychloride, were without significant action. No useful product resulted when the free aminophenol or its *o*-methyl ether were condensed with β-methoxybutanone-2, and finally, the acetanilide III could not be chloromethylated.

In connection with the work on the structures of the bases derived from I, a comparative study was made of the action of formaldehyde and hydrochloric acid upon 2,3,6-trimethyl-4-methoxyaniline, X (a position isomer of I), and upon 2,3,5,6-tetramethyl-4-methoxyaniline, XI. Neither of these methoxyanilines was affected by the action of warm formaldehyde and hydrochloric acid and X was recovered unchanged after it was heated in a mixture of paraformaldehyde, acetic acid, hydrochloric acid and phosphoric acid. The completely substituted aniline XI, however, under the latter conditions, gave a good yield of the methylaniline XII. This is the first case in which a methylaniline has been obtained as the major product of the action of formaldehyde upon an aromatic amine.

Experimental Part[5,6]

2,3,5-Trimethyl-4-aminophenol, m. p., 149–152°, was prepared from 2,3,5-trimethylphenol by the method of Smith, Hoehn and Whitney.[7]

Trimethylquinone was prepared from the above aminophenol by the procedure of Carlin[8] and was converted into the 1-*p*-nitrophenylhydrazone by the procedure of Smith and Irwin.[9]

2,3,5-Trimethylquinone-1-semicarbazone.—A solution of trimethylquinone (10 g.) and semicarbazide hydrochloride (7.5 g.) in alcohol (40 cc.) and water (60 cc.) was allowed to stand at room temperature for a few hours. The yellow semicarbazone (12.7 g., 78%) was removed and crystallized from alcohol; it then melted at 252–253° (dec).

Anal. Calcd. for $C_{10}H_{13}O_2N_3$: C, 57.97; H, 6.32. Found: C, 58.09; H, 6.50.

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[4] The failure of the Troeger's base A to react with acetic anhydride is noteworthy for all other such bases so far prepared react rather readily. The benzene rings of base A, however, are completely substituted, and molecular models of this base indicate that there should be a considerable hindrance to attack at the nitrogen atoms. Such hindrance is not present in the tetrahydroquinazoline (Base C) which readily undergoes acetylation.

[5] All melting points are corrected.

[6] Microanalyses by Roger Amidon, Jay S. Buckley, W. H. T. Hunter and Sherman Sundet.

[7] Smith, Hoehn and Whitney, THIS JOURNAL, **62**, 1863 (1940).

[8] R. B. Carlin, Ph.D. Thesis, University of Minnesota, 1940, p. 80.

[9] Smith and Irwin, THIS JOURNAL, **63**, 1036 (1941).

1-(2,3,5-Trimethyl-4-hydroxyphenyl)-semicarbazide.—Sodium hydrosulfite (5 g.) in water (25 cc.) was added to a suspension of the above semicarbazone (1.22 g.) in boiling alcohol (35 cc.). The mixture became homogeneous and colorless at once; the white solid (1.12 g.) was removed from the cooled solution. It melted at 194° (dec).

Anal. Calcd. for $C_{10}H_{15}O_2N_3$: C, 57.40; H, 7.22. Found: C, 57.65; H, 7.38.

The white semicarbazide, or a solution of it in alcohol, slowly became yellow when exposed to air; the oxidation was quite rapid when the semicarbazide (0.3 g.) was dissolved in aqueous sodium hydroxide (20 cc., 5%) and exposed to air for one hour. The product (0.28 g., 93%) was the semicarbazone, m. p., and mixed m. p. 250–251° (dec).

2,3,5-Trimethylquinone-1-oxime.—Hydroxylamine hydrochloride (56 g.) in water (75 cc.) was added to a solution of crude trimethylquinone (115 g.) in methanol (325 cc.). The mixture was warmed (40–45°) to bring about complete solution and was then allowed to stand at room temperature for two days. The solid was removed and washed with water until free from acid. It weighed 114 g. (91%), melted at 177–179°, and was sufficiently pure for use in subsequent operations. The analytical sample, crystallized from aqueous ethanol (50%), melted at 181–182°.[10]

Anal. Calcd. for $C_9H_{11}O_2N$: C, 65.43; H, 6.71. Found: C, 65.62; H, 6.63.

N-(2,3,5-Trimethyl-4-hydroxyphenyl)-hydroxylamine.—The above oxime (25 g.) was stirred with sodium hydroxide (7.0 g.) in water (300 cc.) while sodium hydrosulfite (40 g.) was added. The temperature rose to 35°, and a solid separated. The mixture was cooled to 10°, the solid was removed, and washed with water containing a little sodium hydrosulfite. The crude solid melted at 100–103° (dec.), and was very unstable, becoming oxidized to the oxime when attempts were made to recrystallize it. In alkaline solution, the substance was oxidized in air rapidly and quantitatively to the oxime, but addition of excess sodium hydrosulfite to the alkaline solution converted the hydroxylamine quantitatively into 2,3,6-trimethyl-4-aminophenol, m. p. 134–136° (dec.).

2,3,5-Trimethylquinone-1-oxime-O-methyl Ether.—A solution of the oxime (23 g.) in water (175 cc.) and sodium hydroxide (9 g.) was stirred at room temperature as methyl sulfate (29 g.) was added dropwise (one hour). Stirring was continued for one hour, and then the solid was removed, washed with water, and crystallized from aqueous ethanol (350 cc., 60%). The product (21.7 g., 87%) melted at 82–83°; the analytical sample, crystallized again, melted at 83–84°.

Anal. Calcd. for $C_{10}H_{13}O_2N$: C, 67.02; H, 7.30. Found: C, 66.78; H, 7.57.

The oxime ether (2 g.) in methanol (15 cc.) was catalytically hydrogenated (Raney nickel 1 g.) at 60° in fifteen minutes under an initial hydrogen pressure of 1900 lb. to 2,3,6-trimethyl-4-aminophenol, isolated as the N-acetyl derivative (93% over-all yield), m. p., 211–212°. The oxime ether did not react with sodio malonic ester; instead, it underwent self-condensation in the presence of alkali to give, in poor yield, an amphoteric substance which melted at 213–214°. This substance gave a positive Folin-Denis test for phenols, but a negative vat test. It was analyzed, but was not investigated further.

Anal. Found: C, 70.79, 70.40; H, 6.59, 6.81; N, 9.27.

2,3,6-Trimethyl-4-aminophenol.—The aminophenol could be obtained by reductive cleavage of any of the 1-carbonyl derivatives of trimethylquinone. From the *p*-nitrophenylhydrazone (1.69 g.) in boiling alcohol (35 cc.) by action of sodium hydrosulfite (6 g.) in water (35 cc.): yield 0.43 g. (48%), m. p. 132–134° (dec.).[9] From the semicarbazone (1.22 g.) by action of stannous chloride (3 g.) and hydrochloric acid (3 cc.) in hot water (20 cc.) and alcohol (30 cc.): yield 0.23 g. (33%) of material of poor quality, m. p., 119–123° (dec.). From the semicarbazone (1.5 g.) in alcohol (10 cc.) by catalytic reduction (Raney nickel catalyst, 1 g.) at 95° under an initial hydrogen pressure of 1000 lb.: yield 0.89 g. (65%), m. p. 132–134° (dec). From the oxime (111 g.) dissolved in aqueous sodium hydroxide (110 g. in 1600 cc.) by action of sodium hydrosulfite (280 g.) at 20–30° (one hour): yield nearly quantitative; m. p. 135–137° (dec.). It is important, in this reduction, that enough alkali be present to keep the intermediate hydroxylamine in solution, otherwise the reduction stops at the first stage.

From the oxime (18 g.) in methanol (125 cc.) by catalytic reduction (Raney nickel 2 g.) at 40–50° under an initial hydrogen pressure of 1200 lb.: yield quantitative; m. p. 133–136° (dec). The most convenient preparative method is that involving reduction of the oxime by action of sodium hydrosulfite and alkali.

2,3,6-Trimethyl-4-acetylaminophenol.—Crude trimethylquinone oxime (111 g.) was reduced by action of sodium hydrosulfite, as described above, and the wet cake of crude aminophenol was dissolved in hydrochloric acid (70 cc.) and water (1600 cc.) by warming. The solution was warmed with Norit, filtered, acetic anhydride (81.5 cc.) was added to the filtrate at 50°, followed by addition of a solution of sodium acetate (113 g.) in water (500 cc.). The solid was removed, washed thoroughly with water, and dried. It then weighed 95 g. (74% based on the oxime) and melted at 212–213°. The analytical sample, crystallized from aqueous ethanol (30%), melted at 213–214°.

Anal. Calcd. for $C_{11}H_{15}O_2N$: C, 68.37; H, 7.82. Found: C, 68.69; H, 7.87.

2,3,6-Trimethyl-4-formylaminophenol, m. p. 189–190° (9 g., 69%) was prepared by action of formic acid (40 cc., 87%) upon the aminophenol (11 g.) essentially according to the method of King[11] who reported the m. p. as 190–191°.

2,3,6-Trimethyl-4-(N,N-diformylamino)-phenol.—Phosphorus oxychloride (2 cc.) was added to a solution of the aminophenol (0.9 g.) in anhydrous formic acid (5 cc.). The solution was allowed to stand overnight, and was then poured into ice-water (50 cc.). The solid (0.6 g.) was removed and crystallized from aqueous methanol, when it melted at 153–154°.

Anal. Calcd. for $C_{11}H_{13}O_3N$: C, 63.76; H, 6.32. Found: C, 63.60; H, 6.51.

The substance was insoluble in dilute hydrochloric acid, but soluble in aqueous sodium hydroxide. The Folin–Denis test was positive. When warmed with hydrochloric acid (5%) it was hydrolyzed to the monoformyl derivative, m. p. 189–190°, and when refluxed for two hours with dilute acid, it was converted into the aminophenol, m. p. 133–135°.

2,3,6-Trimethyl-4-(N-acetyl-N-formylamino)-phenol.—Phosphorus oxychloride (5 cc.) was added to a solution of the acetylaminophenol (1 g.) in anhydrous formic acid (7 cc.), the mixture was allowed to stand overnight, and was poured into water. The solid (1 g.) was removed and crystallized from aqueous ethanol (40%), when it melted at 170–171°.

Anal. Calcd. for $C_{12}H_{15}O_3N$: C, 65.14; H, 6.82. Found: C, 64.97; H, 6.84.

The substance was insoluble in dilute acid, but soluble in dilute alkali, and the Folin–Denis test was positive. When warmed with dilute acid, it was hydrolyzed, first to the acetylaminophenol (m. p. 210–211°), and finally to the aminophenol (m. p. 132–134°).

2,3,5-Trimethyl-4-acetoxyformanilide.—This compound was obtained as the result of an attempt to bring about a condensation between the formylaminophenol and iso-

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[10] Karrer and Leiser, *Helv. Chim. Acta*, **27**, 678 (1944), report the m. p. as 182°.

[11] J. A. King, Ph.D. Thesis, University of Minnesota, 1942, p. 134.

prene hydrobromide. The formylaminophenol (1 g.), isoprene hydrobromide (2.5 g.), and stannic chloride were allowed to stand in acetic acid (10 cc.) at room temperature for a week, and then the mixture was poured into water. The solid was removed and washed with ether. There remained 0.9 g. of material (m. p. 154–160°) which, after two crystallizations from aqueous ethanol, melted at 171–172°. The material was insoluble in both dilute hydrochloric acid and dilute sodium hydroxide; the Folin–Denis test was negative.

Anal. Calcd. for $C_{12}H_{15}O_3N$: C, 65.12; H, 6.83; N, 6.33. Found: C, 65.02; H, 6.84; N, 6.15.

2,3,5-Trimethyl-4-methoxyacetanilide III.—The crude acetylaminophenol (90 g.) was dissolved in aqueous sodium hydroxide (32 g. in 1000 cc.), and to the well-stirred solution, methyl sulfate (65 cc.) was slowly (one and one-half hours) added dropwise. Stirring was continued for one and one-half hours longer, and the precipitate was removed, washed thoroughly with water, and dried. It weighed 90 g. (93%), melted at 169–170°, and was sufficiently pure for use in subsequent operations. The analytical sample, recrystallized from aqueous ethanol (30%) with the use of a little Norit, was white and melted at 170–171°.

Anal. Calcd. for $C_{12}H_{17}O_2N$: C, 69.51; H, 8.27. Found: C, 69.56; H, 8.34.

2,3,5-Trimethyl-4-methoxyaniline I.—Crude III (89.5 g.) was refluxed overnight with water (1000 cc.) and hydrochloric acid (200 cc.). A little Norit was added, and the solution was filtered. The colorless filtrate, cooled and neutralized with sodium hydroxide, deposited a solid which was removed, washed and dried. It weighed 63 g. (88%) and melted at 106–107°. The analytical sample, recrystallized from aqueous ethanol (40%), melted at 108–109°.

Anal. Calcd. for $C_{10}H_{15}ON$: C, 72.70; H, 9.15. Found: C, 72.82; H, 9.47.

2,3,5-Trimethyl-4-methoxyformanilide II.—Methyl sulfate (4.5 cc.) was added dropwise and with stirring to a solution of the crude formylaminophenol (5.5 g.) in aqueous sodium hydroxide (50 cc., 4%). The solid (4.8 g.) was removed, washed with water, and dried. It melted at 142–144°; after crystallization from ethyl acetate, it weighed 4 g. (69%) and melted at 146–147°.

Anal. Calcd. for $C_{11}H_{15}O_2N$: C, 68.37; H, 7.82. Found: C, 68.47; H, 8.04.

2,3,5-Trimethyl-4-acetylaminophenol, m. p. 184–186°, was prepared in 81% yield from the aminophenol by the method of Smith, Hoehn and Whitney.[7]

2,3,6-Trimethyl-4-methoxyacetanilide (22 g., 90%), m. p. 176–178°, was prepared from the above acetylaminophenol in alkaline solution by action of methyl sulfate, as described for the isomeric methoxyacetanilide. The analytical sample, crystallized from aqueous ethanol (50%), melted at 181–182°.

Anal. Calcd. for $C_{12}H_{17}O_2N$: C, 69.51; H, 8.27. Found: C, 69.60; H, 8.39.

2,3,6-Trimethyl-4-methoxyaniline X.—The above crude methoxyacetanilide (21 g.) was hydrolyzed by refluxing it for thirty-six hours with water (300 cc.) and hydrochloric acid (100 cc.). The solution was diluted with water (300 cc.), decolorized with Norit, and neutralized with sodium hydroxide. The solid was removed, washed, and dried, when it weighed 14 g. and melted at 73–74°. The material was sublimed under 2–3 mm., when it formed white needles (13 g., 75%) melting at 74–75°.

Anal. Calcd. for $C_{10}H_{15}ON$: C, 72.70; H, 9.15. Found: C, 72.62; H, 9.14.

2,3,5,6-Tetramethyl-4-aminophenol IX.—A solution of sulfanilic acid (21.5 g.) and sodium carbonate (6.5 g.) in water (100 cc.) was cooled (12°) and mixed with a solution of sodium nitrite (7.4 g.) in water (20 cc.). The whole was poured, with stirring, into a mixture of cracked ice (80 g.) and hydrochloric acid (21 cc.) and allowed to stand for thirty minutes. The sludge of diazonium salt was added to a stirred mixture of durenol (15 g.) and sodium hydroxide, (20 g.) in water (100 cc.) and then allowed to stand overnight. Sodium hydrosulfite (40 g.) was added and the mixture was stirred and heated to 60–70° for about thirty minutes, when the red color disappeared. The mixture was cooled (20°) and the solid was removed and washed several times with water containing a little hydrosulfite. The crude product was light in color, weighed 15.5 g. (94%), and melted at 175–179°.[12]

2,3,5,6-Tetramethyl-4-acetylaminophenol (18 g., 91%, m. p. 260–262° dec.) was prepared from the crude aminophenol (15.5 g.) by acetylation in hydrochloric acid (9.1 cc. in 250 cc. of water) by action of acetic anhydride (11.7 cc.) and sodium acetate (15 g.) as described above. The analytical sample, recrystallized from aqueous ethanol, melted at 262–263°.

Anal. Calcd. for $C_{12}H_{17}O_2N$: C, 69.52; H, 8.27. Found: C, 69.68; H, 8.37.

2,3,5,6-Tetramethyl-4-methoxyacetanilide.—The above acetylaminophenol (18 g.) was dissolved in aqueous sodium hydroxide (6 g. in 200 cc. of water) and methylated by action of methyl sulfate (12 cc.) as described before. The crude product melted at 211–213°, and weighed 21 g. (95%). The analytical sample, recrystallized from aqueous methanol (80%), melted at 215–216°.

Anal. Calcd. for $C_{13}H_{19}O_2N$: C, 70.55; H, 8.65. Found: C, 70.57; H, 8.73.

2,3,5,6-Tetramethyl-4-methoxyaniline XI.—The above crude methoxyacetanilide (14 g.) was refluxed with hydrochloric acid (100 cc.) and water (300 cc.) for forty hours. The solution was diluted with water (300 cc.), decolorized with Norit, and made alkaline by addition of aqueous sodium hydroxide. The solid was removed, washed, and dried; it weighed 10 g. and melted at 60–65°. This material, sublimed under 2–3 mm., gave a white sublimate (6.7 g., 65%) which melted at 68–69°.

Anal. Calcd. for $C_{11}H_{17}ON$: C, 73.69; H, 9.56. Found: C, 73.70; H, 9.69.

1,3,4,7,9,10-Hexamethyl-2,8-dimethoxy-5,11(6,12)-methanodibenzo-[b,f][1,5]-diazocine (R. I. No. 2651). VIII.—A mixture of I (5 g.), formalin (7 cc.) and hydrochloric acid (40 cc.) was shaken mechanically for twelve hours and then allowed to stand for forty-eight hours. The mixture was diluted to 500 cc. with water, and the solid (5.5 g.) was removed, washed with water, and dried. The nearly white hydrochloride was warmed with ethanol (50 cc.), aqueous ammonia (5 cc.) was added, and the mixture was diluted to 250 cc. with water. The crystalline solid (5.1 g., m. p. 184–190°) was removed, washed with water, and recrystallized from ethanol (250 cc.). There resulted 4.7 g. (86%) of white needles melting at 191–192°.

Anal. Calcd. for $C_{23}H_{30}O_2N_2$: C, 75.38; H, 8.25; N, 7.64; mol. wt., 336. Found: C, 75.40, 75.29; H, 8.43, 8.41; N, 7.72; mol. wt. (cryoscopically in benzene), 340.

Hydrochloride.—Somewhat impure VIII (0.4 g., m. p. 187–188°) was added to hydrochloric acid (2 cc.). Immediate solution occurred, then deposition of a solid in a very short time. The mixture was allowed to stand overnight, and the solid was removed and washed thoroughly with dry ether. The solid was shaken with ether (30 cc.) for thirty minutes, and was then shaken with petroleum ether (100 cc., b. p. 60–68°) overnight. The residual white, amorphous solid (0.3 g.) melted at 224–226°.

Anal. Calcd. for $C_{23}H_{30}O_2N_2{\cdot}HCl$: C, 68.29; H, 7.73; N, 6.95; Cl, 8.80. Found: C, 67.62; H, 7.83; N, 7.16; Cl (Volhard), 8.65.

Compound VIII (0.3 g.) was recovered unchanged after it was heated with acetic anhydride (3 cc.) and sul-

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[12] W. B. Irwin, Ph.D. Thesis, University of Minnesota, 1940, p. 65, prepared this compound by a somewhat different method and reported it to melt at 178–181°.

furic acid (1 drop) for one hour or when it was refluxed for two days with alcoholic sodium hydroxide. Compound VIII was also recovered (75–90%) when attempts were made to reduce it by action (a) of sodium and ethanol; (b) of sodium and butanol; (c) of stannous chloride and hydrochloric acid in acetic acid; (d) of hydrogen in the presence of Raney nickel catalyst at 85° and hydrogen pressure of 2300 lb. Action of zinc dust and hydrochloric acid, or of zinc chloride and hydrochloric acid, brought about no reduction but did convert VIII into a high-melting (301–302°) stable solid which was difficult to purify. This substance was apparently a double compound of VIII and zinc chloride, for it reacted with ammonia in aqueous methanol, regenerating VIII. No simple formula for this "stable hydrochloride" could be deduced from the analytical values.

Anal. Found: C, 59.14; H, 7.14; N, 6.49; Cl, 14.39.

Compound VIII was reductively cleaved when it (1 g.) was heated to 170° for twenty-one hours in a Carius tube with hydriodic acid (15 cc., 48%) and red phosphorus (0.1 g.). The cooled mixture was diluted to 100 cc. with water, hydrochloric acid (10 cc.) was added, and the mixture was filtered. The filtrate was made alkaline by addition of aqueous potassium carbonate, and the solid was removed, washed with water, and dried. It weighed 0.64 g. (71%) and melted at 174–177°. When mixed with authentic 2,3,5,6-tetramethyl-4-aminophenol (m. p. 179–181°), the substance melted at 176–178°. A portion (0.5 g.) of this aminophenol was dissolved in hydrochloric acid (50 cc., 3%), ferric sulfate (5 g.) was added, and the mixture was distilled with steam. The distillate contained duroquinone (0.43 g., 86%), m. p. and mixed m. p. 111–112°.

1,3,4,7,9,10-Hexamethyl-2,8-dihydroxy-5,11(6,12)-methanodibenzo[b,f][1,5]-diazocine (R. I. No. 2651). VIIIa.—A solution of VIII (1 g.) in acetic acid (10 cc.) and hydrochloric acid (10 cc.) was refluxed for forty-four hours. The cooled solution was diluted with water (20 cc.) and made alkaline with aqueous ammonia. The solid (0.65 g.) was removed and crystallized twice from carbon tetrachloride and once from methanol. It then melted at 279–280° (dec.) and weighed 0.25 g. The Folin–Denis test was positive.

Anal. Calcd. for $C_{21}H_{26}O_2N_2$: C, 74.52; H, 7.80. Found: C, 74.43; H, 8.01.

The filtrates from the recrystallizations of VIIIa, on evaporation, yielded 0.1 g. of unchanged VIII.

3-(4-Methoxy-2,3,5-trimethylphenyl)-5,7,8-trimethyl-6-methoxy-3,4-dihydroquinazoline VII.—A solution of I (5 g.) in hydrochloric acid (40 cc., 4%) was prepared by warming the mixture on the steam-bath. The solution was cooled to 50° and formalin (4 cc.) was added. An oil separated almost immediately; the mixture was maintained at 50° for eight minutes, then it was quickly cooled (0°) and rubbed with a spatula. The solid was removed, washed with water (30 cc.) and dissolved in methanol (30 cc.). The solution was made alkaline with aqueous ammonia (5 cc.) and diluted with water (500 cc.). The product appeared as an oil which solidified when set aside in a refrigerator. The solid (3.4 g., m. p. 129–136°) was removed (filtrate, see preparation of VI below) and crystallized from *dry* petroleum ether (b. p. 60–68°). It then weighed 2.8 g. and melted at 136–138°. The analytical sample, crystallized once more from petroleum ether, melted at 138–139°.

Anal. Calcd. for $C_{22}H_{28}O_2N_2$: C, 74.97; H, 8.04. Found: C, 74.78; H, 8.06.

When the above preparation was duplicated, except that the temperature was held at 65–70°, and the reaction was allowed to proceed for fifteen minutes, there resulted VIII (1.39 g., 25%) and VII (crude, 2 g., recrystallized, 1.6 g., 31%). The dihydroquinazoline VII (0.3 g., 75%) was recovered unchanged (a) when it (0.4 g.) was heated for an hour in acetic anhydride (1 cc.); (b) when it was heated with 96% formic acid for an hour; and (c) when it was allowed to stand for a day at room temperature with formalin and hydrochloric acid.

3-(4-Methoxy-2,3,5-trimethylphenyl)-5,7,8-trimethyl-6-methoxytetrahydroquinazoline VI.—The first filtrate obtained in the first preparation of VII above, when allowed to stand overnight, deposited a crystalline hydrochloride (0.42 g., m. p. 163–164°). The salt could not be recrystallized, so it was analyzed directly.

Anal. Calcd. for $C_{22}H_{30}O_2N_2 \cdot HCl$: C, 67.59; H, 8.01. Found: C, 67.79; H, 8.31.

This salt (0.3 g.) was dissolved in a little methanol, and the solution was made alkaline with aqueous ammonia and diluted with water (25 cc.). The product appeared as an oil which soon solidified; the solid was removed and crystallized from petroleum ether (b. p. 40–70°). It weighed 0.15 g. and melted at 136–137°; when mixed with VII (m. p. 137–138°), the substance melted at 129–137°.

Anal. Calcd. for $C_{22}H_{30}O_2N_2$: C, 74.54; H, 8.54. Found: C, 74.70; H, 8.56.

1-Acetyl Derivative of VI.—The tetrahydroquinazoline (0.4 g.) in acetic anhydride (1 cc.) was heated on the steam-bath for one hour. The cooled solution was diluted with water (20 cc.), made alkaline with aqueous ammonia and allowed to stand for an hour. The solid (0.36 g.) was removed and crystallized twice from petroleum ether (10 cc., b. p. 40–70°). It then weighed 0.2 g., and melted at 136–137°. When mixed with VI (m. p. 136–137°) the substance melted at 110–120°.

Anal. Calcd. for $C_{23}H_{32}O_3N_2$: C, 72.64. H, 8.13. Found: C, 72.90; H, 8.33.

Conversion of VI to VIII. A.—The tetrahydroquinazoline (80 mg.) in formic acid (96%) was heated on the steam-bath for forty-five minutes. From the cooled and diluted solution there was obtained 50 mg. (54%) of VIII, m. p. and mixed m. p. 190–191°. **B.** The tetrahydroquinazoline (0.3 g.), in formic acid (0.3 cc., 87%) and hydrochloric acid (3 cc.) was maintained at room temperature for two days. From the cooled and diluted solution there was obtained 0.28 g. of VIII, m. p. and mixed m. p. 189–190°. **C.** A solution of the tetrahydroquinazoline (0.4 g.) and formalin (0.4 cc.) in hydrochloric acid (4 cc.) was maintained at room temperature for two days. The solution was diluted with water (30 cc.) and the solid was removed and dissolved in methanol (10 cc.). The methanol solution was made alkaline with ammonia (1 cc.) and diluted to 50 cc. with water. The solid was removed and crystallized from methanol; it weighed 0.32 g. (78%) and melted at 191–192° alone or when mixed with another specimen of VIII.

Reduction of VII to VI.—Sodium (2 g.) was added portionwise (thirty minutes) to a refluxing solution of VII (0.75 g.) in dry ethanol (30 cc.). The solution was cooled, neutralized with acetic acid, and diluted with water (150 cc.). The product (0.6 g.) separated as an oil which solidified on standing in a refrigerator overnight. The solid was removed and crystallized from dry petroleum ether (b. p. 60–68°), when it weighed 0.51 g. (75%) and melted at 136–137°, alone, or when mixed with VI from the above experiment.

Reduction Cleavage of VII.—The dihydroquinazoline (1 g.) was heated at 170° for twenty-two hours in a Carius tube with hydriodic acid (15 cc., 48%) and red phosphorus (0.1 g.). The mixture was cooled, and the solid hydriodide (0.72 g.) was removed and washed with water. The combined filtrate and washings were neutralized with aqueous potassium carbonate and extracted twice with ether (35 cc. each time). The ether extract was immediately mixed with hydrochloric acid (3%) and placed in a flask arranged for steam distillation. The solid hydriodide was dissolved in methanol (25 cc.); the solution was neutralized with aqueous ammonia, diluted with water (150 cc.), and the solid was removed, washed with a little water, and added to the ether extract in the steam-distillation flask. The ether was carefully distilled from the mixture with a gentle current of steam, and then ferric sulfate (10 g.) was added and the mixture was steam distilled. The distillate was extracted with several portions of ether (total 70 cc.) and the combined yellow extracts were dried over sodium sulfate. Removal of the solvent left a yellow solid (0.58 g.). This solid was dissolved in methanol (4 cc.) and water (0.5 cc.). Hydroxylamine hydrochloride (0.25 g.) was added, and the mixture was allowed to stand at room temperature for one day. The mixture was diluted with water (30 cc.) and extracted with several portions of ether (total, 70 cc.). The combined ether extracts were then extracted three times with 15-cc. portions of aqueous sodium hydroxide (5%). The alkaline extracts, when neutralized with dilute hydrochloric acid, deposited 2,3,5-trimethylquinone-1-oxime (0.14 g., 16%) which, after one crystallization from aqueous alcohol (50%) melted at 180–182° alone or when mixed with an authentic specimen. The yellow ether solution remaining after the alkaline extraction was washed with water and evaporated. The residue (0.19 g., 21%) melted at 109–111° alone or when mixed with authentic duroquinone.

2,3,5,6-Tetramethyl-4-methoxy-N-methylaniline XII.—The tetramethylmethoxyaniline XI (0.8 g.) and paraformaldehyde (0.25 g.) were heated on the steam-bath for sixteen hours in a mixture of acetic acid (1 cc.), hydrochloric acid (1 cc.) and phosphoric acid (0.6 cc., 85%). The mixture was diluted with water (50 cc.), warmed to bring about complete solution, and decolorized with a little Norit. The cooled filtrate was made alkaline with aqueous sodium hydroxide (10%) and the precipitate (0.6 g., m. p. 77–82°) was removed and dissolved in ether (50 cc.). The solution was filtered and the solvent was allowed to evaporate. The residue was crystallized twice from aqueous ethanol (35%), when it melted at 83–85°. This was sublimed under 3 mm. pressure at a temperature of 70–80°. The first portion of the sublimate melted at 78–84°; the last portion at 84–87°. The high-melting fraction, when resublimed as before, gave 0.12 g. of material melting at 87–88°.

Anal. Calcd. for $C_{12}H_{19}ON$: C, 74.56; H, 9.91. Found: C, 74.51; H, 9.86.

The tetramethylmethoxyaniline XI (1.4 g., m. p. and mixed m. p., 63–65°) was recovered unchanged when it (2 g.) was shaken with formalin (2 cc.) and hydrochloric acid (15 cc.) at room temperature for five days. The material was recovered when the reaction mixture was diluted with water (150 cc.) and made alkaline with aqueous sodium hydroxide (10%). The same result was obtained when the experiment was repeated, but for seven hours at a temperature of 75°.

2,3,6-Trimethyl-4-methoxyaniline X (0.32 g.) and paraformaldehyde (0.1 g.) were heated on the steam-bath for fifteen hours in a mixture of acetic acid (0.5 cc.), hydrochloric acid (0.5 cc.) and phosphoric acid (0.25 cc., 85%). The mixture, processed as described above for the tetramethyl analog, yielded a sublimate (0.13 g.) which was unchanged X, m. p. and mixed m. p. 71–73°.

Summary

1. It has been shown that action of formaldehyde and hydrochloric acid upon 2,3,5-trimethyl-4-methoxyaniline produces three basic substances: a new highly substituted "Troeger's Base" VIII, a dihydroquinazoline VII, and a tetrahydroquinazoline VI. The relative amounts of these three bases depend upon the experimental conditions, particularly upon the temperature and the time.

2. The dihydroquinazoline VII has been reduced to the tetrahydro compound VI; the latter has been converted to the "Troeger's Base" VIII by action of hydrochloric acid and formaldehyde or formic acid, whereas the former was not affected by these reagents. The dihydroquinazoline VII therefore cannot be a direct precursor of the "Troeger's Base," whereas the tetrahydroquinazoline VI probably is an intermediate in its formation from the methoxyaniline.

3. Tetramethyl-*p*-methoxyaniline and 2,3,6-trimethyl-4-methoxyaniline gave no compounds analogous to those obtained from the 2,3,5-trimethyl compound. The trimethylaniline underwent no change, whereas the tetramethyl compound was converted into 2,3,5,6-tetramethyl-4-methoxy-N-methylaniline.

4. A convenient five-step synthesis of 2,3,6-trimethyl-4-aminophenol from 2,3,5-trimethylphenol has been developed, and several new derivatives of the aminophenol have been prepared and characterized.

5. Using as starting materials 2,3,6-trimethyl-4-aminophenol and several of its derivatives, a number of synthetic approaches to 6-hydroxy-2,2-disubstituted-1,2,3,4-tetrahydroquinolines, the N-analogs of the tocopherols, have been investigated. None of the reactions was successful.

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