[Contribution from the Department of Chemistry of Iowa State College]

THE SYNTHESIS OF N-METHYL-3-ISOPROPYL-4-DIMETHYLAMINOPHENYL CARBAMATE AND SOME RELATED DERIVATIVES

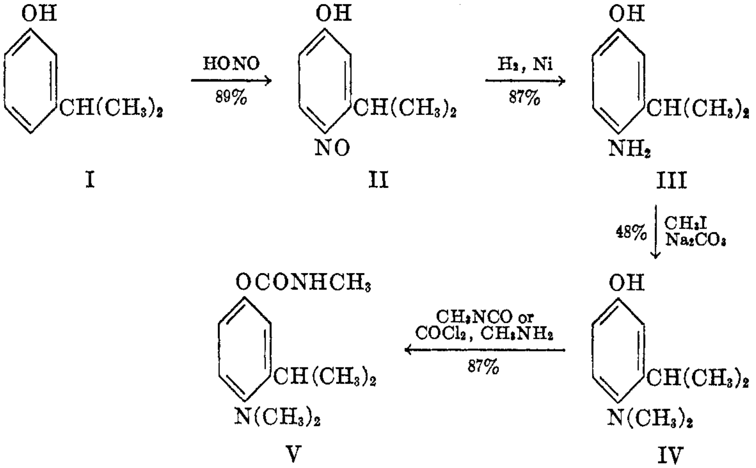
HENRY GILMAN, SOUREN AVAKIAN, R. A. BENKESER, H. S. BROADBENT,
R. M. CLARK, GEORGE KARMAS, F. J. MARSHALL, S. M. MASSIE,
D. A. SHIRLEY, and L. A. WOODS

Received November 11, 1953

As a part of a broad program of synthesis and biological evaluation of quaternary ammonium salts of aminoaryl carbamates we undertook to (a) study the various synthetic routes to N-methyl-3-isopropyl-4-dimethylaminophenyl carbamate and (b) to synthesize related type compounds for evaluation. These type compounds have been shown to possess marked cholineësterase-inhibitory activity like physostigmine (1).

The synthesis of N-methyl-3-isopropyl-4-dimethylaminophenyl carbamate was carried out as indicated in Figure I starting with *m*-isopropylphenol. As a prerequisite to this phase of the problem we made a rather thorough study of various synthetic routes to *m*-isopropylphenol. The most useful method from the standpoint of laboratory manipulation was the route shown in Figure II which used *m*-hydroxybenzoic acid as the starting material.

Fig. I



A second satisfactory but somewhat longer route started from the nitration of isopropylbenzene and proceeded as shown in Figure III.

A third route involved the preparation of *p*-acetaminoisopropylbenzene (XIV) as above followed by bromination and the sequence shown in Figure IV.

Another sequence of reactions starting with the isopropylation of chlorobenzene was evaluated. This sequence is shown in Figure V.

Fig. II

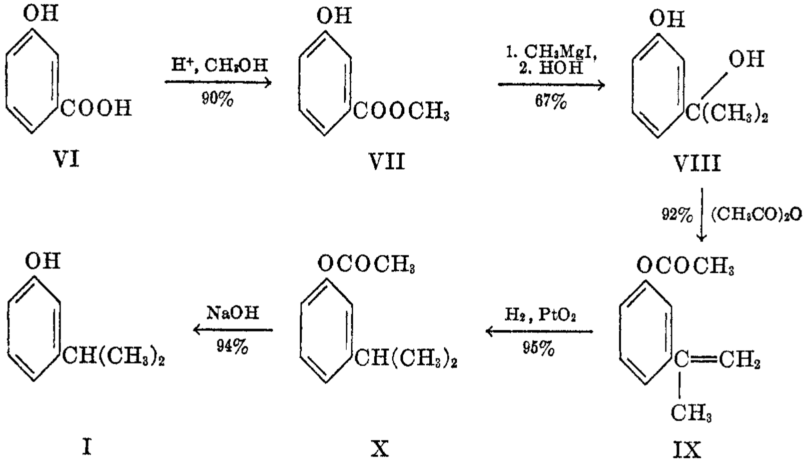
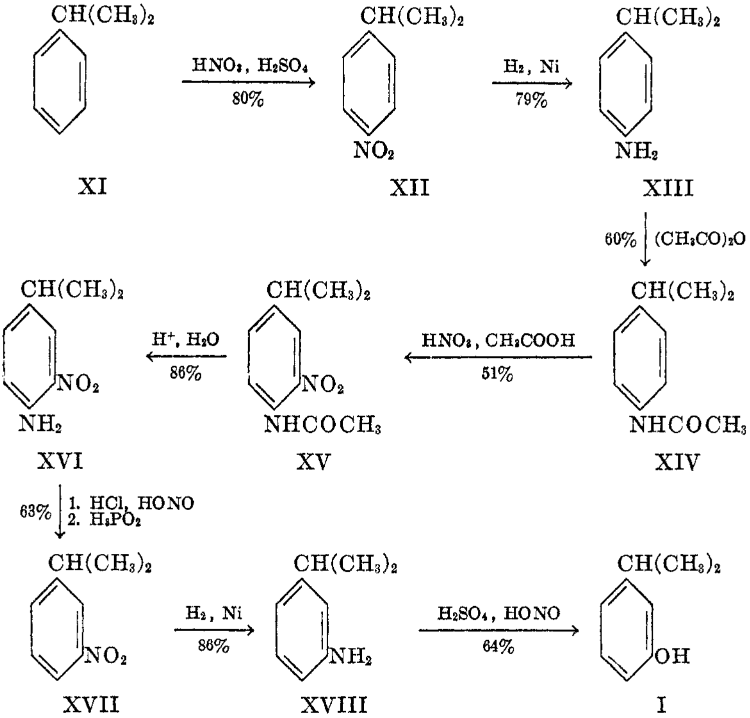


Fig. III



A last synthesis started with *m*-bromophenol and proceeded through *m*-methoxyphenylmagnesium bromide as shown in Figure VI.

An attempted rearrangement of *p*-isopropylphenol to the *meta* isomer in accordance with the work of Baddeley (2) was tried. While some *m*-isopropyl-

Fig. IV

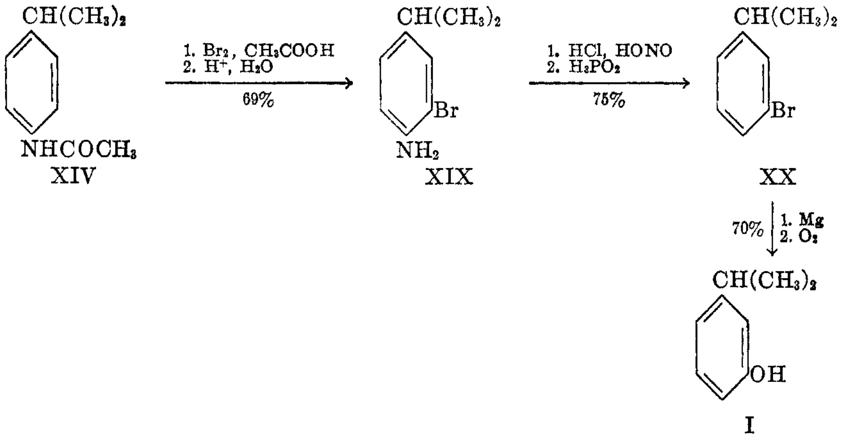


Fig. V

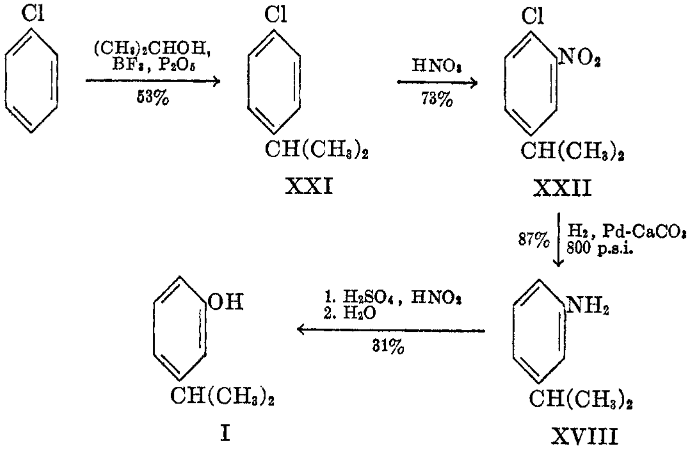


Fig. VI

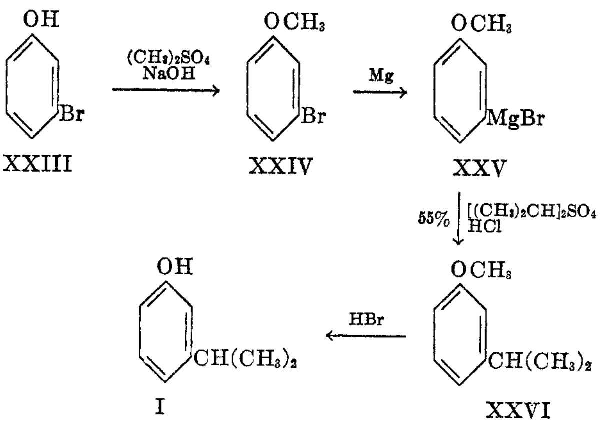


Fig. VII

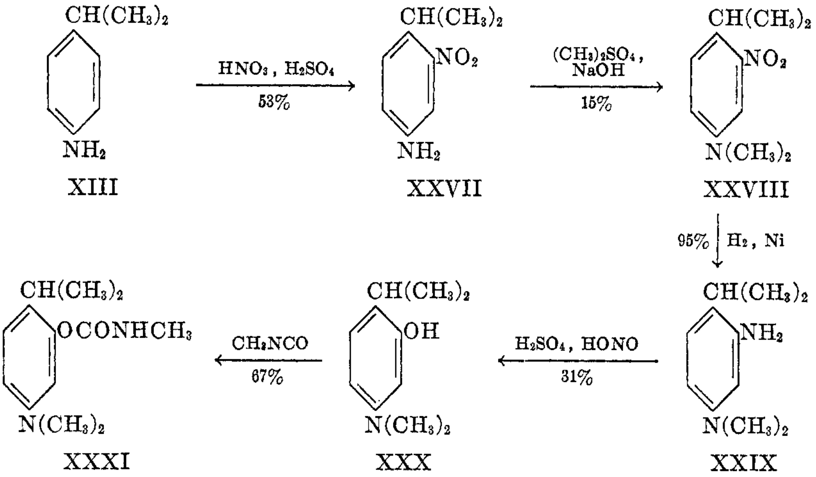


Fig. VIII

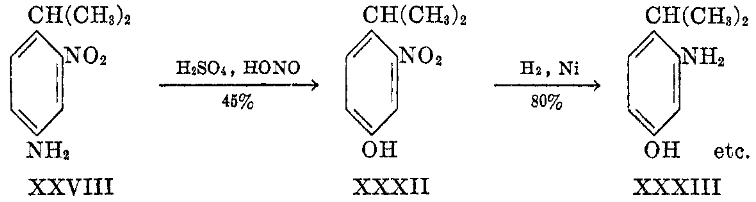
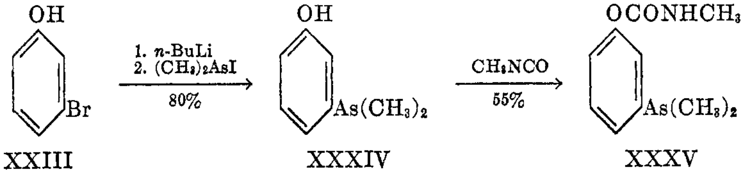


Fig. IX



phenol was formed, the yields in several runs were quite low, phenol being the major product.

3-Isopropyl-4-dimethylaminophenol was allowed to react with ethyl isocyanate and with phosgene and dimethylamine to give N-ethyl-3-isopropyl-4-dimethylaminophenyl carbamate and N,N-dimethyl-3-isopropyl-4-dimethylaminophenyl carbamate, respectively.

An isomer of the basic type carbamate (V)—namely, N-methyl-2-isopropyl-5-dimethylaminophenyl carbamate—was prepared by the sequence of reactions shown in Figure VII.

A second isomer of the basic type carbamate (V) was synthesized as shown in Figure VIII. The product is N-methyl-3-dimethylamino-4-isopropylphenyl carbamate.

We have prepared some types analogous to the carbamates mentioned above containing the dimethylarsino [$(CH_3)_2As$—] in place of the dimethylamino group. The basic synthetic method is illustrated by the preparation of N-methyl-*m*-dimethylarsinophenyl carbamate in Figure IX. The corresponding *ortho* isomer as well as the diethylarsino and N,N-dimethylcarbamate homologs were also prepared by this method.

The carbamates mentioned above were all converted to their quaternary ammonium salts (methiodides or methochlorides) for biological tests to determine toxicity. The results of these tests will be reported elsewhere.

EXPERIMENTAL[1]

Methyl m-hydroxybenzoate (VII). A mixture of 276 g. (2.0 moles) of *m*-hydroxybenzoic acid, 830 ml. of anhydrous methanol, and 55 ml. of concentrated sulfuric acid was refluxed for eight hours. The excess methanol was removed by distillation under reduced pressure from a hot water-bath, and the residue was poured on about 400 g. of crushed ice. The solid product was extracted with 1000 ml. of ether, and the ether solution in turn was extracted with three 100-ml. portions of saturated sodium bicarbonate solution and one 100-ml. portion of water. The ether solution was dried over sodium sulfate, the ether was removed by distillation, and the residue was heated to 90° at 2 mm. pressure. The oil solidified on cooling and was dried over phosphorus pentoxide at reduced pressure. The resulting ester weighed 274 g. (90% yield) and melted at 72° (3). Other runs of this preparation gave yields ranging from 88 to 95%.

m-Hydroxyphenyldimethylcarbinol (VIII). To the Grignard reagent prepared from 483 g. (3.4 moles) of methyl iodide, 80 g. (3.3 g.-atoms) of magnesium, and 1800 ml. of ether was added (two hours) with vigorous stirring and refluxing a solution of 152 g. (1.0 mole) of methyl *m*-hydroxybenzoate. The mixture was refluxed for an additional two hours and allowed to stand overnight. It was then added portionwise to a solution of 385 g. of ammonium chloride in 1200 ml. of water. The ether layer was separated and the residue was washed with ether. The combined ether solutions were distilled to remove the ether and the residue was boiled for 1½ hours with 1 l. of 10% aqueous sodium hydroxide solution. The resulting solution was filtered and acidified with hydrochloric acid. The precipitated solid was suspended in dilute sodium bicarbonate and after 12 hours it was removed by filtration to give 100 g. (67%) of carbinol melting at 97–101°. From another run using 1.33 moles of ester there was obtained a 60% yield of product melting at 101–103°. Von Auwers (4) reports this compound to melt at 105–106°.

m-Isopropenylphenyl acetate (IX). A mixture of 69 g. (0.46 mole) of *m*-hydroxyphenyldimethylcarbinol and 175 g. (1.73 moles) of acetic anhydride was heated under reflux for 10 hours. Fractionation of the resulting liquid gave 64.1 g. (80%) of product, b.p. 124–125°/12 mm., n_D^{20} 1.5322, d_4^{20} 1.053 (4).

A series of runs was made starting with ester in which the intermediate carbinol was not isolated. These gave *m*-isopropenylphenyl acetate in yields of 69–74% using 1.0 mole of ester.

m-Isopropylphenyl acetate (X). A mixture of 73 g. (0.42 mole) of *m*-acetoxyisopropenylbenzene, 105 ml. of absolute ethanol, and 0.4 g. of Adams' catalyst was shaken with hydrogen (25 minutes) in a steel bomb at 300 pounds pressure. After customary operations of filtration and washing, distillation gave 69.1 g. (94%) of product boiling at 107–108°/8 mm., n_D^{20} 1.4969, d_4^{20} 1.0096.

m-Isopropylphenol (I). A solution of 54 g. (1.35 moles) of sodium hydroxide in 270 ml. of water heated to 70° was mixed with 94.3 g. (0.53 mole) of *m*-isopropylphenyl acetate, and

---

[1] All melting and boiling points are corrected.

then 25 ml. of 95% ethanol was added. The mixture was stirred and refluxed for 45 minutes. After cooling, acidifying with hydrochloric acid, extracting with ether, and then washing the ether extracts with sodium bicarbonate solution, there was obtained 66.6 g. (94%) of *m*-isopropylphenol boiling at 109–110°/11 mm., m.p. 26°, n_D^{20} 1.5261 (5).

m-Isopropylphenol was also obtained by hydrogenolysis of *m*-hydroxyphenyldimethylcarbinol (VIII) over a chromium-copper-barium oxide catalyst at 1600 pounds pressure initially at 185° and finally at 212°. A solution of 30.2 g. (0.20 mole) of carbinol in 85 ml. of ethanol gave a 65% yield of the phenol.

The same sequence of reactions reported above was used on methyl *m*-methoxybenzoate leading to *m*-isopropylanisole which was demethylated to the desired phenol. The action of methylmagnesium iodide on the ester produced *m*-methoxydiphenylcarbinol, m.p. 36°, b.p. 119–120°/3.5 mm., in 83% yield. The reported m.p. is 34° (5, 6). Dehydration of the carbinol with acetic anhydride gave a 64% yield of *m*-isopropenylanisole, b.p. 102–105°/16 mm., d_4^{18} 0.9896, n_D^{20} 1.5453. Reduction with Adams' catalyst as before gave 95% of *m*-isopropylanisole (4, 5) which was demethylated in 81% yield by refluxing in 48% hydrobromic acid for 16 hours.

m-Isopropylphenol via nitration of 4-acetaminoisopropylbenzene. Isopropylbenzene was nitrated in accordance with the directions of Haworth and Barker (7). 4-Nitroisopropylbenzene, b.p. 126–133°/13–14 mm., was obtained in 80% yield. Reduction of the nitro compound over Raney nickel at 50 pounds hydrogen pressure gave 79% of 4-aminoisopropylbenzene, b.p. 222–225°/740 mm., 109–111°/15 mm. (7). Acetylation of the amine by refluxing with acetic anhydride in acetic acid gave 4-acetaminoisopropylbenzene (XIV), m.p. 98–100°, after one recrystallization from petroleum ether (b.p. 80–110°). The yield was 60%. Haworth and Barker (7) report m.p. 101–102°.

3-Nitro-4-acetaminoisopropylbenzene (XV). To a mixture of 100 g. of nitric acid (*d.* 1.50) and 36 g. of glacial acetic acid was added slowly 36 g. (0.20 mole) of 4-acetaminoisopropylbenzene. The reaction mixture was held at 5–10° during the addition and for two hours subsequently. The mixture was poured into 800 ml. of water and the precipitated solid was removed, dried, and extracted with three 150-ml. portions of boiling petroleum ether (b.p. 60–68°). Upon cooling the solution, there precipitated 22.3 g. (51%) of yellow needles, m.p. 78–79°.

Anal. Calc'd for $C_{11}H_{14}N_2O_3$: N, 12.61. Found: N, 12.37.

3-Nitro-4-aminoisopropylbenzene (XVI). A mixture of 48 g. (0.22 mole) of 3-nitro-4-acetaminoisopropylbenzene, 100 ml. of 95% ethanol, and 100 ml. of concentrated hydrochloric acid was heated under reflux for 1½ hours. On cooling there precipitated 40.3 g. (86%) of the amine hydrochloride, m.p. 131° (dec.). Liberation of the base gave a red oil, b.p. 141–143°/1 mm.

Anal. Calc'd for $C_9H_{12}N_2O_2$: N, 15.56. Found: N, 15.61.

3-Nitroisopropylbenzene (XVII). A suspension of 250 g. (1.15 moles) of 3-nitro-4-aminoisopropylbenzene hydrochloride in a mixture of 400 ml. of concentrated hydrochloric acid and 400 ml. of water was diazotized at 5° with 60–65 g. of sodium nitrite. The resulting mixture was filtered and poured rapidly into 1600 ml. of ice-cold 30% hypophosphorous acid (8). After standing in an ice-bath for 10 hours, the mixture was extracted with ether and the ether extracts in turn were extracted with 15% sodium hydroxide solution. The ethereal solution was dried and distilled to give 120 g. (63%) of 3-nitroisopropylbenzene, b.p. 94–98°/1 mm., n_D^{25} 1.5281.

Anal. Calc'd for $C_9H_{11}NO_2$: N, 8.49. Found N, 8.42.

3-Aminoisopropylbenzene (XVIII). Reduction of the nitro compound in 95% ethanol solution over Raney nickel in the usual fashion allowed formation of the amine in 86% yield. The product boiled at 222–224°/740 mm. and the index of refraction was n_D^{25} 1.5385.

Anal. Calc'd for $C_9H_{13}N$: N, 10.35. Found: N, 10.31.

The *acetyl* derivative melted at 78°.

The 3-aminoisopropylbenzene was diazotized and converted to *m*-isopropylphenol by customary procedures (9). The yield was 64%.

m-Isopropylphenol via bromination of 4-acetaminoisopropylbenzene. 4-Acetaminoisopropylbenzene was brominated and hydrolyzed in accordance with the procedure of Haworth and Barker (10) to form 3-bromo-4-aminoisopropylbenzene, b.p. 137–139°/16 mm., in 69% yield.

The 3-bromo-4-aminoisopropylbenzene was deaminated by diazotization and treatment with hypophosphorous acid as described above. There was obtained a 75% yield of 3-bromoisopropylbenzene, b.p. 97–98°/20 mm. (7).

The Grignard reagent was prepared from a mixture of 80 g. (0.40 mole) of 3-bromoisopropylbenzene and 62 g. (0.45 mole) of *n*-butyl bromide. A mixture of dry air and oxygen was passed through at 0°. After working up by customary procedures there was obtained 24.5 g. (42%) of *m*-isopropylphenol. Simultaneous oxidation of a mixture of cyclohexylmagnesium bromide and *m*-isopropylphenylmagnesium bromide (11) allowed formation of *m*-isopropylphenol in 70–74% yield.

m-Isopropylphenol via nitration of p-chloroisopropylbenzene. p-Chloroisopropylbenzene (XXI). Boron trifluoride was passed through a stirred solution of 180 g. (3.0 moles) of isopropyl alcohol and 1324 g. (12.0 moles) of chlorobenzene. The mixture was cooled in an ice-bath and placed under a reflux condenser. Passage of the gas was continued until white fumes appeared at the top of the condenser. Then 113 g. (0.75 mole) of phosphorus pentoxide was added as rapidly as possible. At the end of the exothermic reaction period, the ice-bath was replaced with an oil-bath and the reaction mixture was heated to 75–85° for seven hours. After cooling, the upper layer was separated and washed twice with 100 ml. of 10% sodium carbonate solution and once with 2000 ml. of water. Fractional distillation yielded 242 g. (53%) of product, b.p. 50.5–52°/1 mm., n_D^{20} 1.5132. Meyer and Bernhauer (12) report the boiling point as 190–195°/760 mm.

3-Nitro-4-chloroisopropylbenzene (XXII). To 115 g. (0.74 mole) of *p*-chloroisopropylbenzene was added 170 g. of fuming nitric acid (*d*. 1.5) at a rate to maintain the temperature at 0–5°. The mixture was stirred for 2½ hours, and near the end of this period the temperature was allowed to rise to 20°. After pouring into iced-water, extracting with ether, washing the extracts with 10% sodium bicarbonate solution, and drying over sodium sulfate, fractionation yielded 106.5 g. (73%) of the 3-nitro-4-chloroisopropylbenzene, b.p., 149–150°/20 mm. and 97–99°/1 mm., n_D^{20} 1.5463, d_4^{20} 1.2168. M_D (Calc'd): 51.60; M_D (Found) 52.0.

Anal. Calc'd for $C_9H_{10}ClNO_2$: Cl, 17.77. Found: Cl, 17.57 and 17.64.

The 3-nitro-4-chloroisopropylbenzene was simultaneously reduced and dehalogenated 800 pounds hydrogen pressure over a palladium-calcium carbonate catalyst. The yield of 3-aminoisopropylbenzene was 87%. Diazotization and conversion of the phenol has been described above.

m-Isopropylphenol via m-methoxyphenylmagnesium bromide. m-Bromophenol was converted to *m*-bromoanisole with dimethyl sulfate and sodium hydroxide (13, 14). Isopropyl sulfate was prepared in essential accordance with the procedure of Levaillant (15). To the Grignard reagent from 93.5 g. (0.50 mole) of *m*-bromoanisole was added 182 g. (1.0 mole) of freshly distilled isopropyl sulfate at such a rate as to maintain gentle reflux (one hour). The mixture was refluxed for 30 minutes, allowed to stand overnight, and hydrolyzed with iced dilute hydrochloric acid. The ether layer was separated, dried, and distilled to give 41.5 g. (55%) of crude *m*-isopropylanisole, b.p. 82–92°/13–14 mm. This compound was demethylated with 48% hydrobromic acid to give *m*-isopropylphenol.

3-Isopropyl-4-nitrosophenol (II). To a solution of 208 g. (1.50 moles) of *m*-isopropylphenol in 1050 ml. of 95% ethanol was added 1200 ml. of concentrated hydrochloric acid. Then, 180 g. (2.6 moles) of sodium nitrite was added in small portions over a period of two hours, keeping the temperature at 5–8°. The mixture, containing a chocolate-brown precipitate, was stirred for 2½ hours and then diluted with an equal volume of water. The water should be added slowly and with stirring to reduce foaming. Subsequent to filtration and washing with water, there was obtained 221 g. (89%) of a light brown powder which melted with decomposition at 152°. Recrystallization from benzene gave yellow plates melting with decomposition at 153°. This purification appeared unnecessary for subsequent reactions, for the compound melting at 152° was sufficiently pure. In one preparation starting with 190 g. of *m*-isopropylphenol the yield of nitroso compound melting at 152–153° was 92%.

Anal. Calc'd for $C_9H_{11}NO_2$: N, 8.42. Found: N, 8.32.

3-Isopropyl-4-aminophenol (III). To a solution of 3-isopropyl-4-nitrosophenol in 250 ml. of isopropyl alcohol was added one tablespoon of Raney nickel catalyst, and the mixture was hydrogenated for 45 minutes under a pressure of 55–30 pounds of hydrogen. The products from four runs of the size mentioned were combined, and to them was added 200 ml. of 95% ethanol. The mixture was heated to boiling and filtered, and the solid was extracted with two 75-ml. portions of 95% ethanol. On cooling the combined ethanolic solutions, there was obtained 81 g. of grey needles which melted at 175–176° (1). Concentration of the filtrate to 200 ml. yielded 25 g. of brown needles melting at 174–175°. The total yield (106 g.) was 87%.

From a reduction of 66 g. of 3-isopropyl-4-nitrosophenol using Adams' catalyst, the yield of 3-isopropyl-4-aminophenol melting at 176–177° was 56 g. (95%). In three other reductions the yields were 84%, 83%, and 90%; methanol is a better solvent than ethanol in the platinum oxide reductions. The platinum oxide reduction procedure is recommended for smaller-sized runs.

3-Isopropyl-4-dimethylaminophenol (IV). (*a*). *By sodium carbonate and methyl iodide.* A mixture of 48 g. (0.318 mole) of 3-isopropyl-4-aminophenol, 1230 ml. of 95% ethanol, 200 g. of methyl iodide, and 50 g. of anhydrous sodium carbonate was refluxed for 18 hours. Then 100 g. of methyl iodide was added and refluxing was continued for five hours, and finally an additional 100 g. of methyl iodide was added and refluxing was continued for an additional five hours. The hot solution was decanted, and the salt was extracted with two 100-ml. portions of hot 95% ethanol. On concentrating the extracts together with the decanted solution to about 300 ml., there was obtained, on cooling, 63 g. of salt. This was heated in a 125-ml. Claisen flask, in a metal-bath at 270–320°, at 30 mm. pressure for about three hours or as long as any distillate came over. The distillate solidified in the receiver, and after recrystallization from petroleum ether (b.p. 60–68°) gave 27.5 g. (48%) of white prisms melting at 81–82°. After another crystallization the melting point was 83°.

Stevens and Beutel (1) gave no melting point of their compound. Identification was completed by the preparation of the hydrochloride which melted at 218–219°. This is in agreement with the m.p. reported by earlier workers.

The range of yield in several preparations was 41–60%. The procedure is a modification of the one used by Stevens and Beutel who report a yield of about 30%.

(*b*) *By methyllithium and methyl iodide.* A solution of 1.75 moles of methyllithium in 1100 ml. of ether (prepared from methyl chloride and lithium) was added, during one hour, to a stirred suspension of 151 g. (1 mole) of 3-isopropyl-4-aminophenol in 2000 ml. of ether, and the mixture was refluxed for 20 hours. A solution of 107 g. (0.75 mole) of methyl iodide in 50 ml. of ether was added during 1½ hours, and the mixture was refluxed for 1½ hours. Then, 1.1 moles of methyllithium in 650 ml. of ether were added during one hour, and the mixture was refluxed for one hour. This was followed by the addition of a solution of 156 g. (1.1 moles) of methyl iodide in 50 ml. of ether during 1¼ hours and refluxing for one hour, and then the addition of 1.1 moles of methyllithium and 1.1 moles of methyl iodide was repeated. Finally, methyllithium (0.68 mole in 400 ml. of ether) was added until a 70 ml. excess of solution had been added beyond gas evolution, and the mixture was refluxed for one-half hour; then 107 g. (0.75 mole) of methyl iodide in 25 ml. of ether was added during ¾ of an hour, and the mixture was refluxed for one-half hour. The clear red solution was cooled by ice and hydrolyzed by the addition of 600 ml. of water. The ether was separated, washed with 600 ml. of water, and dried over potassium carbonate. To this ether solution was added the ether extracts from acidification and extraction of the water layer. There was obtained 138 g. distilling at 99–103°/1–1.9 mm., and melting at 75–77°. Recrystallization from 500 ml. of petroleum ether (b.p. 60–68°) gave 126 g. (70%) of product melting at 79.5–80.5°. From the mother liquor there was obtained 6.1 g. melting at 76–78°. The total weight corresponds to a yield of 73.5%.

An orienting experiment showed that the combination of methylmagnesium iodide and methyl iodide was not effective in the dimethylation.

Methiodide of 3-isopropyl-4-dimethylaminophenol. White plates melting at 205° (dec.) separated when a mixture of 3-isopropyl-4-dimethylaminophenol and excess methyl iodide was allowed to stand at room temperature.

Anal. Calc'd for $C_{12}H_{20}INO$: I, 39.5. Found: I, 39.6 and 39.3.

N-Methyl-3-isopropyl-4-dimethylaminophenyl carbamate (V). (*a*). *From methyl isocyanate.* After allowing 12 g. (0.067 mole) of 3-isopropyl-4-dimethylaminophenol and 12 g. (0.21 mole) of methyl isocyanate to stand for two days, the excess methyl isocyanate was removed under reduced pressure. Crystallization of the residual solid from petroleum ether (b.p. 60–68°) gave 13.8 g. (87%) of white plates melting at 87–88°. Recrystallization gave 13.2 g. (83%) of compound with the same m.p. and crystalline appearance. A mixture m.p. with the starting phenol (m.p. 82°) was below 65°.

Anal. Calc'd for $C_{13}H_{20}N_2O_2$: N, 11.87. Found: N, 11.61.

The *hydrochloride* was obtained as minute white crystals melting at 186–188° after crystallization from a mixture of ether and absolute ethanol.

Anal. Calc'd for $C_{13}H_{21}ClN_2O_2$: Cl, 13.02; N, 10.28.
Found: Cl, 13.01; N, 10.53.

(*b*). *From phosgene and methylamine.*[2] To a stirred solution of 54 g. (0.3 mole) of 3-isopropyl-4-dimethylaminophenol and 70 ml. of diethylaniline in 240 ml. of benzene, cooled in an ice-bath, was added over a period of five minutes a solution of 33 g. (0.3 mole) of phosgene in benzene. Anhydrous methylamine was passed into the mixture for about 45 minutes or until a small hydrolyzed sample of the reaction mixture gave an alkaline reaction with Methyl Red. Intermittent cooling with an ice-bath was necessary to keep the temperature of the reaction mixture below 40°. Subsequent to hydrolysis the benzene layer was washed with cold 5% sodium hydroxide and then with water. The benzene was evaporated, petroleum ether (b.p. 60–68°) was added, and there precipitated on cooling 21 g. of white minute crystals which melted at 88–90°. An additional 6.3 g., melting at 88–89°, was obtained from the mother liquors by concentration and crystallization, to give a total yield of 27.3 g. (39%). A mixture m.p. of this product with that obtained from the methyl isocyanate reaction was 85–86°.

Evaporation of the petroleum ether from the last crystallization gave a dark oil from which was obtained, subsequent to hydrolysis by heating with 10% potassium hydroxide, 3-isopropyl-4-dimethylaminophenol (mixture m.p.). This phenol, together with that obtained by neutralization of the original alkaline extracts of the benzene layer, amounted to 16.5 g. (31%). From another reaction carried out in a similar manner there was obtained 48% of carbamate and 26% of initial phenol.

Methiodide of N-methyl-3-isopropyl-4-dimethylaminophenyl carbamate. A solution of 102.6 g. (0.43 mole) of N-methyl-3-isopropyl-4-dimethylaminophenyl carbamate and 400 ml. of methyl iodide deposited 70 g. of solid after four days. The filtrate was refluxed overnight to give an additional 25 g. After refluxing for two more days, there was obtained 32.5 g.; and after standing for six days, an additional 14.5 g. separated, or a total of 142 g. (86%) in the period stated. It was later observed in a corresponding run, that about 100 g. of solid separated at the end of 30 hours of refluxing, more coming down subsequently. The reaction proceeds slowly in a solvent like dry benzene. The colorless prisms melt at 160–161°.

Anal. Calc'd for $C_{14}H_{23}IN_2O_2$: C, 44.5; H, 6.09; I, 33.6; N, 7.41.
Found: C, 44.5; H, 6.16; I, 33.8, 33.2, and 33.6; N, 7.58 and 7.33.

Methochloride of N-methyl-3-isopropyl-4-dimethylaminophenyl carbamate. A mixture of 40 g. (0.106 mole) of the methiodide, 530 ml. of water, three drops of concentrated hydrochloric acid, and the silver chloride from 40 g. of silver nitrate was stirred rapidly with exclusion of light for 20 hours. The reaction mixture was filtered and the filtrate was evaporated to a thick, viscous, colorless syrup under a water pump vacuum and at the temperature of a steam-cone. The residue was evaporated twice with 100-ml. portions of 1:1 absolute

---

[2] In general accordance with directions of Dr. A. L. Wilds (private communication).

ethanol-benzene during which time the product crystallized. The crystalline solid was triturated with acetone and filtered to give 27 g. (89%) of the methochloride. While this product gave a satisfactory nitrogen and chlorine analysis, some hydrolysis of the carbamate had apparently taken place during the above operation, and retreatment with methyl isocyanate was necessary.[3]

To 106 g. of the impure methochloride was added 230 ml. of nitromethane, and then 31.6 g. (0.555 mole) of methyl isocyanate. Stirring was started, and a solution of 2 ml. of glacial acetic acid and 2 ml. of triethylamine was added quickly. The mixture warmed quite rapidly and turned yellow. An ice-bath was used when the temperature reached 45°. The mixture was then stirred for two hours, cooled to 0°, and filtered. The solid was washed with 100 ml. of nitromethane and 200 ml. of acetone, and dried in a vacuum desiccator to constant weight. There was obtained 76 g. of the methochloride which gave a very faint phenol test and which melted at 174–176°. Another sample from a smaller-sized run melted at 178–180° and gave no phenol test.

Anal. Calc'd for $C_{14}H_{23}ClN_2O_2$: Cl, 12.38; N, 9.76.
Found: Cl, 12.30, 12.32, and 12.29; N, 9.78 and 9.65.

N,N-Dimethyl-3-isopropyl-4-dimethylaminophenyl carbamate. A solution of 180 g. (1 mole) of 3-isopropyl-4-dimethylaminophenol, 400 ml. of pyridine, and 128 g. (1.12 moles) of dimethylcarbamyl chloride was heated on a steam-bath for 24 hours, cooled, and then taken up in ether and water. Sodium hydroxide was added until the aqueous layer was neutral, and then an additional 500 ml. of 2% sodium hydroxide was added. The ether layer was separated and washed several times with water. After drying, the ether was removed by distillation, and then the pyridine was distilled off at 0.5 mm. pressure. Crystallization from petroleum ether (b.p. 60–68°) gave 216 g. (86.4%) of the carbamate melting at 67.5–68°.

Anal. Calc'd for $C_{14}H_{22}N_2O_2$: N, 11.20. Found: N, 11.04.

A methiodide derivative prepared as described above in 65% yield melted at 159° (dec.).[4]

Anal. Calc'd for $C_{15}H_{25}IN_2O_2$: I, 32.38; N, 7.15.
Found: I, 32.40 and 32.41; N, 7.19 and 7.01.

The *methochloride* was prepared as described above except that no retreatment with dimethylcarbamyl chloride was necessary. The yield of colorless, hygroscopic solid, m.p. 174°, was 95%.

Anal. Calc'd for $C_{15}H_{25}ClN_2O_2$: Cl, 11.82; N, 9.32.
Found: Cl, 11.66 and 11.57; N, 9.32 and 9.23.

2-Nitro-3-aminoisopropylbenzene (XXVII). To 1050 ml. of concentrated sulfuric acid was added 101 g. (0.75 mole) of *p*-aminoisopropylbenzene and the resulting solution was cooled. To this solution was added slowly 68.5 g. of 69% nitric acid over a one-hour period with the temperature of the reaction mixture held in the range of −5° to 0°. After pouring on ice, there was precipitated 72 g. (53%) of 2-nitro-4-aminoisopropylbenzene which melted at 51–51.5° after a recrystallization from petroleum ether (b.p. 60–68°). This compound is mentioned in the patent literature (16), but no physical constants are given. Its structure is indicated since the other isomeric mononitration product, XVI, was described above.

Anal. Calc'd for $C_9H_{12}N_2O_2$: N, 15.55. Found: N, 15.61 and 15.62.

The *acetamino* derivative melted at 116–117° after crystallization from benzene.

2-Nitro-4-dimethylaminoisopropylbenzene (XXVIII). To 16.6 g. (0.13 mole) of methyl sulfate heated to 155° was added portionwise, with vigorous stirring, 10 g. (0.0577 mole) of crude 2-nitro-4-aminoisopropylbenzene. When addition was completed, the red mixture was cooled, treated with aqueous sodium hydroxide, and refluxed for a short time to hy-

---

[3] In general accordance with directions of Dr. C. S. Hamilton.

[4] J. R. Stevens and R. H. Beutel (ref. 1) report the melting point of this compound as 170°. However, a sample kindly provided by Merck and Co. showed the same melting point as ours.

drolyze the excess dimethyl sulfate. The ether extract of the free amines was concentrated, and the brown liquid residue was refluxed for 1½ hours with 7 ml. of acetic anhydride. This mixture was treated with dilute hydrochloric acid and extracted with ether to remove the acetyl derivatives of primary and secondary amines. Then the aqueous solution was treated with an excess of sodium hydroxide and extracted with ether to remove the 2-nitro-4-dimethylaminoisopropylbenzene of which 1.7 g. (15%) was obtained as an orange oil distilling at 175–177°/17 mm.

Anal. Calc'd for $C_{11}H_{16}N_2O_2$: N, 13.51. Found: N, 13.44.

2-Amino-4-dimethylaminoisopropylbenzene (XXIX). Reduction of 12.3 g. (0.06 mole) of the nitro compound under three atmospheres of hydrogen and with a Raney nickel catalyst gave the amine, b.p. 105–108°/1 mm., in 95% yield (10.5 g.).

Anal. Calc'd for $C_{11}H_{18}N_2$: N, 15.78. Found: N, 15.64.

2-Hydroxy-4-dimethylaminoisopropylbenzene (XXX). Diazotization of the amine followed by hydrolysis in the usual manner gave 31% of the corresponding hydroxy compound, b.p. 115–120°/1 mm., m.p. 120–121°.

Anal. Calc'd for $C_{11}H_{17}NO$: N, 7.81. Found: N, 7.38.

N-Methyl-2-isopropyl-5-dimethylaminophenyl carbamate (XXXI). Reaction of 2-hydroxy-4-dimethylaminoisopropylbenzene with methyl isocyanate in accordance with the procedure given above yielded 67% of the carbamate, m.p. 117–118°. A mixture melting point with the starting phenol, m.p. 120–121°, showed a sharp depression.

Anal. Calc'd for $C_{13}H_{20}N_2O_2$: N, 11.86. Found: N, 11.52.

The *methiodide* was formed in 95% yield and melted at 172–173° (dec.) after crystallization from a mixture of dry methanol and ether.

Anal. Calc'd for $C_{14}H_{23}IN_2O_2$: I, 33.6; N, 7.40.
Found: I, 33.5; N, 7.50.

2-Nitro-4-hydroxyisopropylbenzene (XXXII). Diazotization and hydrolysis of the corresponding amine (XXVII) gave the phenol in 45% yield. The product boiled at 113–115°/1 mm. and after crystallization from petroleum ether (b.p. 60–68°) melted at 58–59.5°.

Anal. Calc'd for $C_9H_{11}NO_3$: N, 7.74. Found: N, 7.57 and 7.57.

2-Amino-4-hydroxyisopropylbenzene (XXXIII). The nitro compound was reduced as described previously. The product was formed in 80% yield. It boiled at 130–135°/less than 1 mm. and melted at 102–103° after recrystallization from benzene-petroleum ether.

Anal. Calc'd for $C_9H_{13}NO$: N, 9.28. Found: N, 9.40.

2-Dimethylamino-4-hydroxyisopropylbenzene. Methylation of the amine by the stepwise procedure using methyllithium and methyl iodide as described above gave a 90% yield of light yellow syrup, b.p. 108–110°/less than 1 mm.

Anal. Calc'd for $C_{11}H_{17}NO$: N, 7.81. Found: N, 7.97.

N-Methyl-3-dimethylamino-4-isopropylphenyl carbamate. Reaction of the phenol and methyl isocyanate as described previously gave 73% of white prisms, m.p. 106–107°.

Anal. Calc'd for $C_{13}H_{20}N_2O_2$: N, 11.86. Found: N, 11.76.

The *methiodide* melted at 170–172° (dec.), and was formed in 67% yield.

Anal. Calc'd for $C_{14}H_{23}IN_2O_2$: I, 33.6; N, 7.40.
Found: I, 33.5; N, 7.34.

m-Hydroxyphenyldimethylarsine XXXIV. *m-Bromophenol* (0.24 mole) in ether solution was treated with 0.48 mole of *n*-butyllithium for halogen-metal interconversion (17). To the resulting organolithium compound was added, over a ten-minute period, a solution of 70 g. (0.30 mole) of dimethyliodoarsine in 100 ml. of ether. Ten minutes after the addition was completed, the mixture was hydrolyzed and worked up by customary procedures to give 38 g. (80%) of *m*-hydroxyphenyldimethylarsine boiling at 87–90°/0.8 mm.

The *methiodide* was formed by mixing a solution of 15 g. of the *m*-hydroxyphenyldimethylarsine in 100 ml. of dry benzene and 25 ml. of methyl iodide. After 20 hours the solid product was removed and extracted twice with 300-ml. portions of boiling chloroform. The yield of salt was 15 g. It melted at 209–211°.

Anal. Calc'd for $C_9H_{14}AsIO$: I, 37.35. Found: I, 37.47 and 37.52.

Methiodide of N-methyl-m-dimethylarsinophenyl carbamate. A mixture of 12 g. (0.12 mole) of *m*-hydroxyphenyldimethylarsine and 10 g. (0.25 mole) of methyl isocyanate was allowed to stand at room temperature for three days. After removal of the excess methyl isocyanate under reduced pressure, the residue was dissolved in 200 ml. of dry benzene, and treated with 30 ml. of methyl iodide. The methiodide was filtered after standing for 26 hours, and crystallization from ethanol gave 10 g. (55%) of product melting at 187–189°.

Anal. Calc'd for $C_{11}H_{17}AsINO_2$: I, 32.0; N, 3.52.
Found: I, 31.91 and 32.21; N, 3.42.

o-Hydroxyphenyldimethylarsine. This was prepared in 47% yield by the procedure mentioned above for the *m*-isomer. The product boiled at 85–87°/0.3 mm.

The *methiodide* formed in the usual manner melted at 238–239° (dec.).

Anal. Calc'd for $C_{11}H_{17}AsINO_2$: I, 32.0; N, 3.52.
Found: I, 31.60 and 31.73; N, 3.69 and 3.71.

m-Hydroxyphenyldiethylarsine. This was prepared as described above in 51% yield from *m*-hydroxyphenyllithium and diethyliodarsine (18–20). The product distilled at 112°/0.15 mm.

The *methiodide* melted at 87–89°.

Anal. Calc'd for $C_{11}H_{18}AsIO$: I, 34.51. Found: I, 34.66 and 34.48.

Methiodide of N-methyl-m-diethylarsinophenyl carbamate. The product was prepared as described above and was a gummy solid which could not be crystallized.

Anal. Calc'd for $C_{13}H_{21}AsINO_2$: I, 29.88; N, 3.29.
Found: I, 29.32 and 29.45; N, 3.52 and 3.58.

Methiodide of p-hydroxyphenyldimethylarsine. This compound was prepared as described above from *p*-bromophenol. The over-all yield was 28% of product, m.p. 244–246°.

Anal. Calc'd for $C_9H_{14}AsIO$: I, 37.35. Found: I, 37.97 and 37.99.

Methiodide of N,N-dimethyl-p-dimethylarsinophenyl carbamate. To 6.8 g. (0.02 mole) of the methiodide of *p*-hydroxyphenyldimethylarsine dissolved in 30 ml. of chloroform and 12 ml. of pyridine was added 7 g. of dimethylcarbamyl chloride. The mixture was allowed to stand for one week with occasional shaking and was then poured into 200 ml. of ether. After agitation, the ether was decanted from the precipitated oil. An ethanolic solution of sodium hydroxide was added to the oil in ethanol until no more precipitate formed. The salt was removed, and the filtrate was poured into excess ether, which precipitated 5.6 g. of yellow prisms. Crystallization from absolute ethanol gave 4 g. (49%) of large yellow prisms melting at 226.5°.

Anal. Calc'd for $C_{12}H_{19}AsINO_2$: I, 30.9; N, 3.42.
Found: I, 30.9, 31.0, and 30.9; N, 3.44 and 3.63.

SUMMARY

The synthesis of the methochloride of N-methyl-3-isopropyl-4-dimethylaminophenyl carbamate, a compound with physostigmine-like activity, has been evaluated in detail, including several routes to the intermediate *m*-isopropylphenol.

A number of related type compounds, including some containing arsenic, was synthesized.

Ames, Iowa

REFERENCES

(1) Stevens and Beutel, *J. Am. Chem. Soc.*, **63**, 308 (1941).
(2) Baddeley, *J. Chem. Soc.*, 527 (1943).
(3) Baeyer and Villiger, *Ber.*, **35**, 3026 (1902).
(4) von Auwers, *Ann.*, **413**, 305 (1917).

(5) BEHAL AND TIFFENEAU, *Bull. soc. chim.*, [4] **3**, 317 (1908).
(6) EASSON AND STEDMAN, *J. Chem. Soc.*, 1096 (1933).
(7) HAWORTH AND BARKER, *J. Chem. Soc.*, 1302 (1939).
(8) ADAMS AND KORNBLUM, *J. Am. Chem. Soc.*, **63**, 194 (1941).
(9) MANSKE, *Org. Syntheses*, Coll. Vol. I, 2nd ed., 404 (1941).
(10) Ref. 7, p. 1299.
(11) KHARASCH AND REYNOLDS, *J. Am. Chem. Soc.*, **65**, 501 (1943).
(12) MEYER AND BERNHAUER, *Monatsh.*, **53/54**, 741 (1929).
(13) KOELSCH, *J. Am. Chem. Soc.*, **61**, 969 (1939).
(14) NATELSON AND GOTTFRIED, *J. Am. Chem. Soc.*, **61**, 1001 (1939).
(15) LEVAILLANT, *Compt. rend.*, **188**, 261 (1929).
(16) CHRISTIANSEN AND MONESS, U. S. Patent 2,140,509 (1939) [*Chem. Abstr.*, **33**, 2655 (1939)].
(17) GILMAN AND MOORE, *J. Am. Chem. Soc.*, **62**, 1843 (1940).
(18) MCKENZIE AND WOOD, *J. Chem. Soc.*, **117**, 406 (1920).
(19) BURROWS AND TURNER, *J. Chem. Soc.*, **117**, 1373 (1920).
(20) WIGREN, *Ann.*, **437**, 285 (1924).