and 0.5 g. of palladium black were suspended in 100 cc. of alcohol and reduced as before. The uptake of hydrogen was found to be 0.95 mole in thirty-six hours, the suspension of ketone having disappeared. The catalyst was filtered and the solvent removed *in vacuo*. The product was crystallized from nitromethane and washed with petroleum ether; m. p. 151°.

Anal. Calcd. for $C_{17}H_{19}NO_5$: C, 64.3; H, 6.0. Found: C, 64.8; H, 6.2.

Summary

Compounds of the eprocaine type with variations of the phenacyl group, and similar compounds with the benzocaine radical instead of the procaine radical, were prepared. Variations consisted in elimination of one or both phenolic hydroxyl groups, or substitution of one or both of them by methoxy groups, and also reduction of the phenacyl ketone group to the alcohol. Most of the reduced compounds of the eprocaine type were found to be very hygroscopic and difficult to obtain pure for analysis, and derivatives were hard to obtain. Eprocaine and compounds of this type were found to undergo reductive scission in acid media. With the benzocaine radical instead of the procaine radical, the compounds were easier to purify and identify. All the compounds of this type which were prepared were crystalline.

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Amines Related to Epinephrine. IV. Some γ-Aryl, γ-Hydroxypropyl Amines and Intermediate β-Aminopropiophenones

BY R. E. DAVIES[1] AND GARFIELD POWELL

In considering amines of the epinephrine type, in connection with studies of the relation of chemical constitution to physiological action, we have had occasion to prepare amines of the types $RCOCH_2CH_2NH_2$ and $RCH(OH)CH_2CH_2NH_2$, in which R is the phenyl, 4-hydroxy-phenyl, or 3,4-dihydroxyphenyl radical. Primary physiological testing[2] indicates that the activity of these amines is less in each instance than that of the corresponding amine with a two-carbon side chain. The method of synthesis of compounds of the type $RCOCH_2CH_2NH_2$ found most convenient was the reaction of β-chloropropionyl chloride with the appropriate phenolic ether, formation of the phthalimido compound and subsequent scission of the ether group or groups after hydrolysis to the amine. The β-aminopropiophenones so formed were reduced by the method of Kindler and Peschke,[3] involving the gradual addition of the ketone to the reducing chamber. The hydroxy amines so obtained were found to be difficult to characterize as free amine or simple salts, but derivatives were obtainable in each instance. The hydroxyamines bearing hydroxyl groups in the 4 or 3,4 positions of the benzene ring were found to be particularly unstable in ordinary manipulation. In some instances we report derivatives of these hydroxyamines. Since in the case of ephedrine, mono-acetylation gives rise to an O-acetyl derivative in certain circumstances,[4] we have examined one of our benzoyl derivatives prepared by the Schotten–Baumann method, and submit evidence that it is the N-benzoyl derivative. Presumably the other mono-benzoyl derivatives of the alcohol-amines herein reported are also N-benzoyl derivatives.

Experimental

β-Chloropropiophenone.—The method of Hale and Britton[5] was used for the preparation of this compound. The melting point, however, agreed with that reported by Conant and Kirner,[6] m. p. 49–50°; yield, 65–70%.

β-Phthalimidopropiophenone.—Hale and Britton[5] prepared this compound by heating β-chloropropiophenone with potassium phthalimide in sealed tubes. For the preparation of large quantities this method is very cumbersome and a modification was used. To a suspension of 82 g. of potassium phthalimide in 200 cc. of boiling xylene mechanically stirred, a solution of 50 g. of the chloroketone in 100 cc. of xylene was added dropwise. The addition was complete in one-half hour and refluxing was continued for one and one-half hours. The solution was filtered hot and on cooling the phthalimido compound separated. The material was sufficiently pure for further synthesis; m. p. 130°; yield 75–80%.

β-Aminopropiophenone Hydrochloride.—The phthalimido compound described above (58 g.) was added to a solution of 174 g. of concentrated hydrochloric acid in 232 g. of glacial acetic acid. After refluxing for sixteen hours, water was added and the whole refluxed for one-half hour with Norite. After filtering and evaporating to one-half the initial volume, phthalic acid separated. On continued evaporation the hydrochloride crystallized. The product was washed with acetone to remove traces of phthalic acid and recrystallized from absolute alcohol; m. p. 127°; yield 80%. Treatment with benzoyl chloride and potassium hydroxide gave a benzoyl derivative which on recrystallization melted at 94.5–95.5°.

Anal. Calcd. for $C_{16}H_{15}O_2N$: C, 75.8; H, 5.9. Found: C, 75.6; H, 6.0.

γ-Phenyl γ-Hydroxypropylamine.—β-Aminopropiophenone hydrochloride (2 g.) dissolved in 50 cc. of water was allowed to drop into a suspension of 0.4 g. of palladium black in 15 cc. of water, the whole system being maintained under two atmospheres of hydrogen. The apparatus was constantly agitated until no more hydrogen was taken up. The solution was then evaporated under vacuum at not over 30°. To the sirup thus obtained a 30% solu-

(1) From a thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Done by Edwin J. Fellows, Temple University.

(3) Kindler and Peschke, *Arch. Pharm.*, **269**, 74, 581 (1931).

(4) Mitchell, *J. Chem. Soc.*, 1153 (1940).

(5) Hale and Britton, THIS JOURNAL, **41**, 841 (1919).

(6) Conant and Kirner, *ibid.*, **46**, 240 (1924).

tion of potassium hydroxide was added and the free amine was extracted immediately with benzene. Evaporation of the benzene yielded the solid amino-alcohol. This solid was washed with ether to remove unreduced ketoamine and γ-phenylpropylamine if present, yield 70%; m. p. 63.5–64.5°.

Anal. Calcd. for $C_9H_{13}ON$: C, 71.5; H, 8.6. Found: C, 71.5; H, 8.7.

Benzoyl Derivative.—The above amino-alcohol was subjected to the Schotten–Baumann reaction yielding a product which crystallized with difficulty from dilute alcohol; m. p. 85–86°.

Anal. Calcd. for $C_{16}H_{17}O_2N$: C, 75.3; H, 6.7. Found: C, 75.3; H, 6.9.

This was established as the N-benzoyl derivative by the following method. Three grams of the N-benzoyl derivative of β-aminopropiophenone was dissolved in 30 cc. of absolute alcohol and 30 g. of 2.5% sodium amalgam was added from time to time to the alcoholic solution. The temperature was held at 60–70° and the solution was neutralized from time to time with acetic acid. Evaporation of this solution and subsequent treatment with water yielded an oil which was recrystallized from dilute alcohol; m. p. 85–86°.

Anal. Calcd. for $C_{16}H_{17}O_2N$: C, 75.3; H, 6.7. Found: C, 75.3; H, 6.9.

A mixed melting point of the two benzoyl derivatives produced no lowering of the melting point; mol. wt. in camphor 228; calculated 255.

N-Carbamyl Derivative.—The amino-alcohol (0.5 g.) dissolved in the calculated amount of hydrochloric acid, was treated with 0.2 g. of potassium cyanate. After warming for five minutes and cooling, a solid separated which, when recrystallized from water, melted at 110–111°.

Anal. Calcd. for $C_{10}H_{14}O_2N_2$: C, 61.9; H, 7.3. Found: C, 61.9; H, 7.4.

N-Benzoyl O-Carbaniloyl Derivative.—The benzoyl derivative of the amino-alcohol was treated with phenyl isocyanate. A reaction took place immediately with formation of a flocculent precipitate. The product was recrystallized from alcohol and water; m. p. 122–123°.

Anal. Calcd. for $C_{23}H_{22}O_3N_2$: C, 73.7; H, 5.9. Found: C, 73.9; H, 5.8.

***p*-Methoxy-β-chloropropiophenone.**—Although this compound has been described in the literature, no detailed procedure for its preparation has been given. The procedure developed was a modification of the method of Freudenberg and Fikentscher.[7] β-Chloropropionic acid (60 g.) was refluxed with 54 g. of phosphorus trichloride for one hour. The crude product was decanted from the phosphorous acid and added to 90 cc. of carbon bisulfide. This solution was added to 83 g. of anhydrous aluminum chloride with cooling, and 67.2 g. of anisole in 120 cc. of carbon bisulfide was allowed to drop slowly into the mixture. The solution was then allowed to reflux gently for one hour, after which it was poured on ice and the product filtered; m. p. 63°; yield 50–60%. The melting point agrees with that of Kenner and Statham,[8] rather than that reported by Allen, Cressman and Bell.[9]

***p*-Methoxy-β-phthalimidopropiophenone.**—This compound was prepared in a manner analogous to that previously described. The compound is well identified by intermediates and the hydrolysis products described below; yield 70–75%; m. p. 140°.

***p*-Methoxy-β-aminopropiophenone Hydrochloride.**—The hydrolysis of the phthalimido compound was carried out as previously described; yield 75–80%; m. p. 169–170°.

Anal. Calcd. for $C_{10}H_{14}O_2NCl$: C, 55.7; H, 6.5. Found: C, 56.0; H, 6.5.

The **N-benzoyl derivative** was prepared by means of the Schotten–Baumann reaction; m. p. 104.5–105.5°.

(7) Freudenberg and Fikentscher, *Ann.*, **440**, 36 (1924).

(8) Kenner and Statham, *J. Chem. Soc.*, 299, 303 (1935).

(9) Allen, Cressman and Bell, *Can. J. Research*, **8**, 440 (1933).

Anal. Calcd. for $C_{17}H_{17}O_3N$: C, 72.1; H, 6.0. Found: C, 72.1; H, 6.2.

γ-(*p*-Methoxyphenyl) γ-Hydroxypropylamine.—The reduction of the ketone to the alcohol and subsequent operations were carried out as previously described. The ketoamine and γ-(*p*-methoxyphenyl)-propylamine are both soluble in ether and the product was purified by washing with ether; yield 65%; m. p. 116–117°.

Anal. Calcd. for $C_{10}H_{15}O_2N$: C, 66.3; H, 8.3. Found: C, 66.6; H, 8.5.

N-Benzoyl Derivative.—This compound was made by the Schotten–Baumann method on the above amino-alcohol, and recrystallized from alcohol; m. p. 97–98°.

Anal. Calcd. for $C_{17}H_{19}O_3N$: C, 71.6; H, 6.7. Found: C, 71.8; H, 6.9.

***p*-Hydroxy-β-aminopropiophenone Hydrochloride.**—The methoxyketoamine (20 g.) was heated with 100 g. of concentrated hydrochloric acid in a bomb tube for one hour at 150°. After evaporating to dryness and washing with acetone, the salt was dissolved in water and the free base was liberated with dilute ammonium hydroxide. The base was dissolved in dilute hydrochloric acid, evaporated, and recrystallized from dilute alcohol; yield 80%; m. p. 179–181°.

Anal. Calcd. for $C_9H_{12}O_2NCl \cdot H_2O$: C, 49.2; H, 6.4. Found: C, 49.4; H, 6.6.

The **N-benzoyl O-benzoyl derivative** was prepared by the Schotten–Baumann reaction; m. p. 176°.

Anal. Calcd. for $C_{23}H_{17}O_4N$: C, 74.0; H, 5.1. Found: C, 73.7; H, 5.0.

N,N-Diphenylcarbamyl Derivative.—The aminoketone hydrochloride (0.7 g.) was mixed with 2.3 g. of diphenylcarbamine chloride in 9.2 g. of pyridine. After heating a short time on a steam-bath all the material dissolved. Heating was continued for one hour, when the solution was poured into water with rapid stirring. After washing the separated mass with dilute hydrochloric acid and with sodium hydroxide, the residue was recrystallized from methyl alcohol and water; m. p. 124–125°.

Anal. Calcd. for $C_{35}H_{29}O_4N_3$: C, 75.7; H, 5.2. Found: C, 75.5; H, 5.5.

γ-(*p*-Hydroxyphenyl), γ-Hydroxypropylamine Hydrochloride.—The reduction of the ketoamine hydrochloride was carried out as previously described. The amino-alcohol hydrochloride was obtained as a hygroscopic glass. This glass was partially purified by treatment with absolute alcohol in which the ketoamine hydrochloride is insoluble.

Di-(N,N-diphenylcarbamyl) Derivative.—The partially purified product obtained above (0.7 g.) was mixed with 2.3 g. of diphenylcarbamine chloride in 9.2 g. of pyridine. After heating a short time on a steam-bath solution occurred. Heating was continued for one hour and the solution was then poured into water with rapid stirring. The resulting precipitate was washed with dilute hydrochloric acid and sodium hydroxide. The material was then subjected to steam distillation and the residue recrystallized from dilute methyl alcohol; m. p. 161–165° (dec.).

Anal. Calcd. for $C_{35}H_{31}O_4N_3$: C, 75.4; H, 5.6. Found: C, 75.3; H, 5.6.

β-Chloro-3,4-dimethoxypropiophenone.—This compound was prepared according to the method of Freudenberg and Fikentscher[7]; m. p. 113–114°.

β-Phthalimido-3,4-dimethoxypropiophenone.—The chloroketone described above is slightly soluble in xylene. The procedure is the same as in the previous cases except that the chloroketone is added in the solid state to the suspension of potassium phthalimide in boiling xylene; yield 75–80%; m. p. 172.5°.

3,4-Dimethoxy-β-aminopropiophenone Hydrochloride.—This compound was obtained by hydrolysis of the phthalimido compound as before described; m. p. 163–164°; yield 80–85%.

Anal. Calcd. for $C_{11}H_{16}O_3NCl$: C, 53.7; H, 6.5. Found: C, 53.7; H, 6.6.

The **N-benzoyl derivative** was prepared by the Schotten–Baumann reaction; m. p. 103.5–104.5°.

Anal. Calcd. for $C_{18}H_{19}O_3N$: C, 69.0; H, 6.1. Found: C, 69.2; H, 6.1.

γ-(3,4-Dimethoxyphenyl) γ-Hydroxypropylamine.—The reduction from ketone to alcohol and the subsequent operations were carried out as previously described. The oil, remaining after treatment with ether to remove unchanged ketoamine, could not be crystallized. An oxalate was obtained, however, by dissolving the oil in absolute alcohol and adding an alcoholic solution of oxalic acid. The resulting precipitate was recrystallized from alcohol; m. p. 185–186° (dec.).

Anal. Calcd. for $C_{24}H_{36}O_{10}N_2$: C, 56.3; H, 7.0. Found: C, 56.2; H, 7.1.

N-Benzoyl Derivative.—This derivative was prepared by the Schotten–Baumann reaction and was recrystallized from alcohol and water; m. p. 113°.

Anal. Calcd. for $C_{18}H_{21}O_4N$: C, 68.6; H, 6.7. Found: C, 68.6; H, 6.8.

3,4-Dihydroxy-β-aminopropiophenone Hydrochloride.—This compound was prepared by demethylation of the corresponding methoxy compound in a manner already described. The product was recrystallized from water; m. p. 240° (dec.).

The **tribenzoyl derivative** was prepared in the usual manner and recrystallized with difficulty from alcohol and water; m. p. 146–147°.

Anal. Calcd. for $C_{30}H_{23}O_6N$: C, 73.0; H, 4.7. Found: C, 72.7; H, 4.6.

The **N,N-diphenylcarbamyl derivative** was prepared in a manner similar to that for the 4-hydroxy compound. On recrystallization from alcohol the compound melted at 89–90°.

Anal. Calcd. for $C_{48}H_{38}N_4O_6$: C, 75.2; H, 5.0. Found: C, 75.3; H, 5.2.

γ-(3,4-Dihydroxyphenyl) γ-Hydroxypropylamine.—The corresponding ketone was reduced as previously described. The glass obtained by evaporation of the reduced solution was partially purified by treatment with alcohol in which the ketoamine hydrochloride was insoluble. The hydrochloride of the amino-alcohol could not be isolated.

Tetra-(N,N-diphenylcarbamyl) Derivative.—This derivative was prepared by a method previously described. The compound was recrystallized from butyl and ethyl alcohols; m. p. 145° (dec.).

Anal.[10] Calcd. for $C_{61}H_{49}O_7N_5$: C, 76.0; H, 5.1. Found: C, 75.7; H, 5.0.

Summary

A number of amines have been synthesized resembling nor-adrenalone, ephedrine and epinephrine in structure, but having a three-carbon side chain with the amine group on the terminal carbon atom. The nor-adrenalone type compounds, under primary testing, were found to have vasopressor activity.

(10) For analyses reported in this paper we are indebted to Mr. Saul Gottlieb.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

Amines Related to Epinephrine. V. Pyridine Compounds Analogous to Epinephrine, Adrenalene and Ephedrine

BY HARRY O. BURRUS[1] AND GARFIELD POWELL

We were interested in comparing the physiological action of compounds having a pyridine nucleus with the known activity of the corresponding compounds having a benzenoid nucleus. As pyridine is not entirely comparable with unsubstituted benzene, it seemed also necessary to make the comparison when the pyridine was substituted in the 2, 3 and 4 positions. Few such pyridine analogs of physiologically active benzenoid compounds have been prepared, even though the presence of the pyridine ring in such physiologically important types as the vitamin B complex, nucleic acids, and antibacterials included in the sulfa type drugs draws increasing attention to their potential usefulness. Even more rarely has the relative physiological activity of the isomeric 2, 3 and 4 substituted pyridine compounds been examined, in physiologically active pyridyl compounds or in pyridine analogs of other active compounds. The most notable exceptions are (1) the investigations of antipellagra activity of the various pyridine monocarboxylic acids and their derivatives,[2] (2) the pharmacological properties of the pyridyl-ethylamine dihydrochlorides,[3,4] (3) and those of the sulfa drugs.[5] In the first instance activity was found limited to the 3 position; and in the second case the 3 and the 4 ring substitutions produced compounds comparable to the phenylethylamine in pressor activity. The 2 substitution was markedly different in giving rise to an appreciable histamine-like activity. A pharmacological study in the third case has not been reported.

In a study of amines related to epinephrine we have prepared compounds with ketoethylamine, hydroxyethylamine and ethylamine groupings substituted in the 2, 3 and 4 positions on pyridine.

Owing to the fact that nor-ephedrine derivatives (isopropylamine types) have therapeutic properties that are in some respects more desirable than those of epinephrine derivatives (ethylamine types), we have sought also a method of preparation for this type of compound with a pyridine ring as the nucleus.

The procedure which was followed is outlined.

(1) From a dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Elvehjem, *Physiol. Rev.*, **20**, 249–271 (1940).

(3) Walter, Hunt and Fosbinder, THIS JOURNAL, **63**, 2771 (1941).

(4) Niemann and Hays, *ibid.*, **64**, 2288 (1942).

(5) Kolloff and Hunter, *ibid.*, **63**, 490 (1941).