232–223° with darkening. When samples of this material and the original were mixed there was no change in the melting behavior.

The yellow product dissolved in alcohol with subsequent separation of colorless crystals. When dry hydrogen chloride was passed into this suspension the crystals first dissolved with subsequent separation of the yellow solid. When suspended in water or ether, the yellow substance did not dissolve but lost color immediately to give the same colorless crystals. The yellow substance itself seemed quite stable, suffering no apparent loss in color on standing for a week.

A quantity of the yellow substance was treated with alcohol, and the resulting colorless crystals filtered off, washed with alcohol until free from chloride, and recrystallized from alcohol; m. p. 225–227° with darkening. This was assumed to be the same substance as the dehydrated N-(3,4-dihydroxyphenacyl) N-(β-hydroxyethyl)-benzamide, with the melting point raised by better purification. The analysis indicated the loss of one molecule of water during the treatment with alcoholic hydrogen chloride.

The colorless product gave an emerald green color with ferric chloride solution. It was insoluble in 5% sodium carbonate solution.

Anal. Calcd. for $C_{17}H_{15}NO_4$: C, 68.7; H, 5.0. Found: C, 68.6; H, 5.2.

Summary

In attempting to bring about the rearrangement of a benzoyl group from N to O, by the use of alcoholic hydrogen chloride, compounds were obtained which appeared to be a dihydroparoxazine and its salt, of a type not hitherto described in the literature.

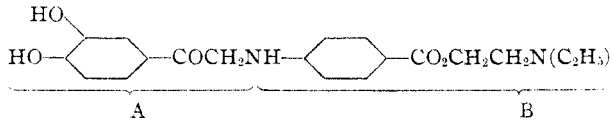
NEW YORK, N. Y. RECEIVED JANUARY 15, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

Amines Related to Epinephrine. III. Amines of the Eprocaine Type

BY LEO S. BIRNBAUM[1] AND GARFIELD POWELL

In this work we have varied the structure of eprocaine (I)[2] to give related compounds.

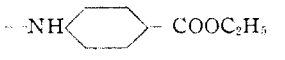


I

A B

In the first series of variations the group B was left unchanged, while A was varied by substitution of methoxyl for the phenolic groups and by replacement of the catechol radical by a phenyl, *p*-hydroxyphenyl or *p*-methoxyphenyl radical. The ketones thus obtained were reduced catalytically to the corresponding alcohols. In this series the isolation and characterization of the alcohols was difficult, the simple salts and usual derivatives being in general hygroscopic and difficult to purify.

In the second series of syntheses the group B of eprocaine was replaced by the benzocaine radical (II) and the same



II

variations were made in A as before. The compounds of this series were much more easily purified and characterized.

Experimental

β-Diethylaminoethyl *p*-Phenacylaminobenzoate Hydrobromide.—Procaine hydrochloride (2.7 g.) was refluxed for five hours with 2.0 g. of phenacyl bromide in 125 cc. of water. After cooling a fine white crystalline powder was filtered off and recrystallized from alcohol; yield 76% from procaine; m. p. 176°.

Anal.[3] Calcd. for $C_{21}H_{27}O_3N_2Br$: C, 57.9; H, 6.3. Found: C, 57.6; H, 6.4.

The free base, liberated by sodium carbonate solution is insoluble in water, slightly soluble in ether, soluble in ethyl and butyl alcohols and hot ligroin; m. p. 103–104°.

Anal. Calcd. for $C_{21}H_{26}O_3N_2$: C, 71.2; H, 7.3. Found: C, 71.1; H, 7.4.

The **picrate,** formed by the addition of an aqueous solution of picric acid to the hydrobromide and purified by recrystallization from alcohol, melted with decomposition at 181–182°.

Anal. Calcd. for $C_{27}H_{29}N_5O_8$: C, 55.6; H, 5.0. Found: C, 55.3; H, 5.2.

The **flavianate** melted with decomposition at 167°. We attempted to prepare the 3,5-dinitrobenzoyl derivative in an ether solution of the free base by the addition of an excess of 3,5-dinitrobenzoyl chloride. The precipitate which formed was recrystallized from alcohol. The yellow compound so obtained, m. p. 160–161°, gave a positive halogen test with alcoholic silver nitrate, and yielded 3,5-dinitrobenzoic acid with cold, dilute sodium carbonate solution. The analysis corresponded with a simple N-acyl derivative together with one mole of 3,5-dinitrobenzoyl chloride. *Anal.* Calcd. for $C_{35}H_{31}N_6O_{13}Cl$: C, 54.0; H, 4.0; N, 10.8. Found: C, 54.1; H, 4.2; N, 11.0.

Formulated as of ammonium salt type this compound would be unusually stable, and an alternative formulation as an enol ester hydrochloride of the N-acyl derivative is possible. The simple N-acyl derivative to be expected after treatment of this compound with cold sodium carbonate solution, could not be crystallized.

N-(β-Phenyl-β-hydroxy)-ethyl Procaine.—This was obtained from the preceding ketone by catalytic reduction with palladium black. The ketone, as hydrochloride in water solution, was shaken with 10% by weight of palladium black in hydrogen until approximately one mole of hydrogen was absorbed. Excess hydrochloric acid in this reduction leads to scission of the phenacylprocaine.[4]

(1) From a dissertation submitted in partial fulfillment of the requirements for the Ph. D. degree in Columbia University. See also *J. Org. Chem.*, **4**, 139 (1939).

(2) (a) Osborne, *Science*, **85**, 105 (1935); (b) Hill and Powell, THIS JOURNAL, **67**, 1462 (1945).

(3) For the analyses reported herein we are indebted to Mr. Saul Gottlieb.

(4) Eprocaine itself was found to undergo reductive scission readily, giving acetocatechol in good yield, even when reduced with cadmium-zinc amalgam in formic acid. This accords with previous experience (ref. 1) in acid reductions of compounds of the type $Ar{\cdot}COCH_2X$ in which X is a negative group or, in some instances, an amino or substituted amino group.

The aqueous solution of the reduced product gave no crystalline salts other than the *picrate*, m. p. 128–129°.

Anal. Calcd. for $C_{27}H_{31}O_{10}N_5$: C, 55.4; H, 5.3. Found: C, 55.5; H, 5.5.

Since the picrate of the ketone was distinctly different from the above, it was assumed that the free base, which was not crystalline and was somewhat soluble in water, was available from the picrate in approximately pure form though not further characterized. This difficulty of characterizing the alcohol is observed with other alcohols of this group, described below.

β-Diethylaminoethyl *p*-(*p*-Hydroxyphenacylamino)-benzoate Hydrochloride.—*p*-Hydroxy-ω-chloroacetophenone, m. p. 154°, (0.85 g.) was refluxed with 1.36 g. of procaine hydrochloride in 30 cc. of water for four hours. On cooling, the mixture was diluted with 20 cc. of water and extracted with ether to remove any unchanged phenol. The crude base, obtained by the addition of sodium carbonate, melted at 84–85°. The hydrochloride was obtained in low yield by the addition of alcoholic hydrogen chloride dropwise to an ether solution of the base. Recrystallized from butyl alcohol, the yield was 39%, m. p. 215–216°.

Anal. Calcd. for $C_{21}H_{27}N_2O_4Cl$: C, 62.0; H, 6.6. Found: C, 62.1; H, 6.8.

N-(β-Hydroxy-β-*p*-hydroxyphenyl)-ethyl Procaine.—As before, the above ketone hydrochloride was reduced with palladium black. One and two-tenths moles of hydrogen was absorbed in sixty hours. No salt could be obtained in a form suitable for clear distinction between the expected alcohol and a corresponding salt of the original ketone. A citrate, obtainable from the alcohol by mixing ether solutions of the reactants, not obtainable from the ketone, was analyzed for (2 moles base plus 1 mole citric acid and 3 moles water) but could not be recrystallized from solvents. Other salts were too hygroscopic for satisfactory handling.

β-Diethylaminoethyl *p*-(*p*-Methoxyphenacylamino)-benzoate Hydrochloride.—A mixture of 1.4 g. of procaine and 1.1 g. of *p*-methoxy-ω-bromoacetophenone was refluxed for five hours in 50 cc. of water. On cooling excess sodium carbonate was added. The free base was filtered, dried, and dissolved in ether. Methyl alcoholic hydrogen chloride was added dropwise to give a crystalline hydrochloride. This was recrystallized from butyl alcohol; yield 1.5 g. (65%); m. p. 169–170° (dec.).

Anal. Calcd. for $C_{22}H_{29}N_2O_4Cl$: C, 62.8; H, 6.9. Found: C, 62.7; H, 7.1.

On reduction as before a glass-like product was obtained, presumably the hydrochloride of N-(β-hydroxy-β-*p*-methoxyphenyl)-ethyl procaine. No other salts or derivatives of this product could be obtained in satisfactory condition for analysis.

β-Diethylaminoethyl *p*-(3,4-Dimethoxyphenacylamino)-benzoate Hydrochloride.—A mixture of 1.4 g. of procaine hydrochloride and 1.25 g. of ω-bromoacetoveratrone was refluxed in 40 cc. of water for three hours. Excess of ammonia was added and the free base which precipitated was filtered. Recrystallized from butyl alcohol, the base melted at 123°.

Anal. Calcd. for $C_{23}H_{30}O_5N_2$: C, 66.7; H, 7.3. Found: C, 66.5; H, 7.3.

The hydrochloride obtained by addition of alcoholic hydrogen chloride to a solution in butyl alcohol, melted at 168° (dec.) and was unstable, losing hydrogen chloride on attempted recrystallization.

Ethyl *p*-Phenacylaminobenzoate.—Phenacyl bromide (10 g.) and 16.5 g. of benzocaine were refluxed in 100 cc. of 95% alcohol for five hours. On cooling, a precipitate settled out and was recrystallized from alcohol; m. p. 139–140°; yield 56%.

Anal. Calcd. for $C_{17}H_{17}NO_3$: C, 72.1; H, 6.1. Found: C, 72.0; H, 6.1.

The **hydrochloride** was prepared by passing dry hydrogen chloride into an ether solution of the base. It is readily decomposed in solvents to give the free base, and melts with loss of hydrogen chloride at about 140°.

N-β-Hydroxy-β-phenylethyl Benzocaine.—The above ketone (2.0 g.) was reduced in alcohol with 10% by weight of palladium black. One mole of hydrogen was absorbed in half an hour. The catalyst was removed, solvent alcohol distilled off, and the residue distilled under high vacuum. On standing the distillate crystallized; m. p. 71–72°. It was recrystallized from nitromethane.

Anal. Calcd. for $C_{17}H_{19}NO_3$: C, 71.6; H, 6.7. Found: C, 71.4; H, 6.5.

On heating the amino alcohol (0.4 g.) with 3,5-dinitrobenzoyl chloride (0.7 g.) at 140° for three and a half hours, a derivative was obtained which was crystallized from butyl alcohol and washed with methyl alcohol; m. p. 165–167°. The analysis corresponded to a dibenzoyl derivative, presumably an ester amide of 3,5-dinitrobenzoic acid.

Anal. Calcd. for $C_{31}H_{23}N_5O_{13}$: C, 55.3; H, 3.4. Found: C, 55.6; H, 3.6.

β-Phenylethyl *p*-(β-Phenylethylamino)-benzoate.—β-Phenylethyl iodide was prepared from β-phenylethyl bromide with sodium iodide in acetone; b. p. 108–110° at 11 mm. Phenylethyl iodide (4.6 g.) was refluxed in 15 cc. of water for fifteen hours with a mixture of 2.7 g. of *p*-aminobenzoic acid and 1 g. of sodium carbonate. The β-phenylethyl group was thereby introduced both as ester and amino substituents. The product was a thick oil which crystallized on cooling; yield 4 g. A hydrochloride was formed by adding dry hydrogen chloride in methyl alcohol. This was filtered and washed with petroleum ether; m. p. (sealed tube) 182–187° (dec.). This hydrochloride is soluble in ethyl alcohol. The free base, soluble in ether and acetone melts at 137–138°.

Anal. Calcd. for $C_{23}H_{23}NO_2$: C, 80.0; H, 6.7. Found: C, 80.1; H, 6.8.

Ethyl *p*-(β-Phenylethylamino)-benzoate Hydrochloride.—Benzocaine (4.3 g.) was heated with 12 g. of β-phenylethyl iodide[5] for fifty hours on a steam-bath. The product, a viscous red oil, was shaken with strong aqueous hydrochloric acid and ether, giving colorless crystals of the hydrochloride at the junction of the layers. The rather unstable hydrochloride was filtered and washed with ligroin; m. p. 174–176° (sealed tube).

Anal. Calcd. for $C_{17}H_{20}NO_2Cl$: C, 66.8; H, 6.6. Found: C, 66.9; H, 6.6.

Ethyl *p*-(*p*-Hydroxyphenacylamino)-benzoate.—*p*-Hydroxyphenacyl bromide (10.7 g.) and 16.5 g. of benzocaine were refluxed for one hour in 100 cc. of alcohol. Toward the end of the reflux period a solid separated. It was filtered after cooling and crystallized from alcohol; m. p. 214–216° (dec.); yield 77%.

Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.2; H, 5.7. Found: C, 67.9; H, 6.0.

N-(β-Hydroxy-β-*p*-hydroxyphenyl)-ethyl Benzocaine.—N-*p*-Hydroxy-phenacyl benzocaine (2 g.) was suspended in 100 cc. of alcohol with 0.2 g. of palladium black, and reduced as before. After seven hours more catalyst was added. After twelve hours 0.90 mole of hydrogen had been absorbed, and the suspended solid was then in solution. After removing the catalyst and solvent, the residue crystallized on standing. The product was recrystallized from nitromethane and washed with petroleum ether; m. p. 131–132°.

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.8; H, 6.3. Found: C, 67.7; H, 6.4.

Other preparations gave on occasion a product of the same composition, m. p. 158°. On grinding a specimen of the lower melting point with a few crystals of the higher melting product, dimorphism was indicated in that the mixture melted without previous softening at 158°.

N-(β-Hydroxy-β-3,4-dihydroxyphenyl)-ethyl Benzocaine.—N-3,4-Dihydroxyphenacyl benzocaine (2.0 g.)

(5) Benzocaine did not react with β-phenylethyl bromide, with or without the aid of various solvents.

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.

NEW YORK, N. Y. RECEIVED JANUARY 15, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

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).