of ice water and was dried *in vacuo* at 100° over phosphorus pentoxide; 1.1 g. (48.2% of the theoretical yield) of crystals was obtained which melted at 200–205°. Several recrystallizations from hot water to a constant microbiological activity gave silky needles which melted at 206–208°.

Anal. Calcd. for $C_{10}H_{16}O_4N_2$: C, 52.63; H, 7.07; N, 12.27. Found: C, 52.62; H, 7.43; N, 12.12.

Methyl Ester: A. By Esterification with Methanol and Hydrochloric Acid.—A solution of 100 mg. of (VI) in 10 cc. of dry methanol was saturated with dry hydrogen chloride and the solution was refluxed for one hour. The methanol was removed *in vacuo* and two 10-cc. portions of fresh methanol were added to the residue and successively removed by evaporation *in vacuo*. The oily residue was then dissolved in two cc. of ice water, the solution was layered with 10 cc. of ethyl acetate, and solid potassium carbonate was added to bind most of the water. The ethyl acetate solution was decanted from the solid residue, filtered through a layer of potassium carbonate and the solvent was removed on the steam-bath. The resulting crystalline ester was purified by recrystallization from a mixture of dioxane and ether, and melted at 114–116°.

Anal. Calcd. for $C_{11}H_{18}O_4N_2$: C, 54.52; H, 7.49; N, 11.55; OCH_3, 12.81. Found: C, 54.39; H, 7.39; N, 12.10; OCH_3, 13.20.

B. By Treatment of the Acid Chloride of Oxybiotin with Methanol.—*dl*-Oxybiotin (100 mg.) was dissolved in two cc. of thionyl chloride and the solution was kept at room temperature for one hour. The thionyl chloride was removed *in vacuo* and the residue was refluxed for thirty minutes with 5 cc. of methanol. The methanol was removed *in vacuo* and the ester was isolated and purified as described under A.

Anal. Calcd. for $C_{11}H_{18}O_4N_2$: C, 54.52; H, 7.49; N, 11.55. Found: C, 54.37; H, 7.31; N, 11.90.

***cis-dl*-3,4-Diamino-2-tetrahydrofuranvaleric Acid Sulfate (VII).**—A mixture of 600 mg. of *dl*-oxybiotin, 12 g. of $Ba(OH)_2 \cdot 8H_2O$ and 60 cc. of water was heated in a sealed tube to 140–150° for twenty hours, and 522 mg. (66.1% of the theoretical yield) of the sulfate (VII) was isolated in the usual manner.[14] The compound was purified by recrystallization from dilute methanol and melted at 252–255° with decomposition.

Anal. Calcd. for $C_9H_{18}O_3N_2 \cdot H_2SO_4$: C, 36.00; H, 6.71; N, 9.32; S, 10.68. Found: C, 35.76; H, 6.63; N, 9.00; S, 10.77.

***dl*-Oxybiotin (VI) by Phosgene Treatment of (VII).**—A solution of 100 mg. of (VII) was dissolved in two cc. of a 10% solution of sodium bicarbonate, was cooled in an ice-bath and a slow stream of phosgene was passed into the solution until it became acid to congo red. The *dl*-oxybiotin, which crystallized, was collected and recrystallized from a small amount of water; 46 mg. (60.5% of the theoretical yield) of needles melting at 205–207° was obtained which did not depress the melting point of an authentic sample of *dl*-oxybiotin.

Anal. Calcd. for $C_{10}H_{16}O_4N_2$: C, 52.63; H, 7.07; N, 12.27. Found: C, 52.78; H, 7.32; N, 12.40.

Acknowledgment.—The author wishes to express his thanks to Mrs. Florence Baker and to Miss Anna Bridgwater for their valuable assistance throughout this work.

Summary

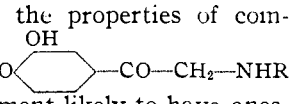
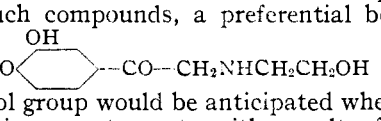
The total synthesis of *dl*-oxybiotin (hexahydro-2-oxo-1-furo[3,4]imidazole-4-valeric acid) has been described.

PITTSBURGH, PENNSYLVANIA RECEIVED MAY 26, 1945

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

Amines Related to Epinephrine. II. Some More Amines of the "Eprocaine" Type

BY RALPH HILL[1] AND GARFIELD POWELL

Looking further into the properties of compounds of the type  where —NHR is a fragment likely to have anesthetic activity,[2] we anticipated that the introduction of $C_6H_5COO(CH_2)_x$— as R, or this group with aryl substituents, would produce compounds having anesthetic activity and possibly also pressor activity.[3] Such compounds should give salts with appreciable water solubility, and would be closely related to procaine when the aryl substituent is $—NH_2$. For the preparation of such compounds, a preferential benzoylation of  on the alcohol group would be anticipated when the benzoylating agent reacts with a salt of the amine.[3,4] This method, in fact, was successfully employed with *p*-nitrobenzoyl chloride but did not work out, with benzoyl chloride. The N-benzoyl derivative, however, was easily obtained. Though the rearrangement of N derivatives to O derivatives is less commonly observed than the reverse rearrangement, it has been effected, by the use of alcoholic hydrogen chloride, in at least two instances.[5] On attempting this method, which would give the compounds sought, with N-benzoyl-(3,4-dihydroxyphenacylamino)-ethanol we obtained what we believe to be a dihydroparoxazine and its salt. Such dihydroparoxazines occurring not as a part of a fused ring system have hitherto not been described in the literature.

Comparable behavior with acids to give a dihydroparoxazine was not shown with the unbenzoylated amine.

Experimental

β-Aminoethyl Benzoate Hydrochloride.—β-Chloroethylamine hydrochloride was prepared by treating ethanolamine hydrochloride with thionyl chloride.[6] The N-benzoyl derivative was prepared and converted to β-

(1) From a dissertation submitted in partial fulfillment of the requirements for the Ph.D. degree in Columbia University.

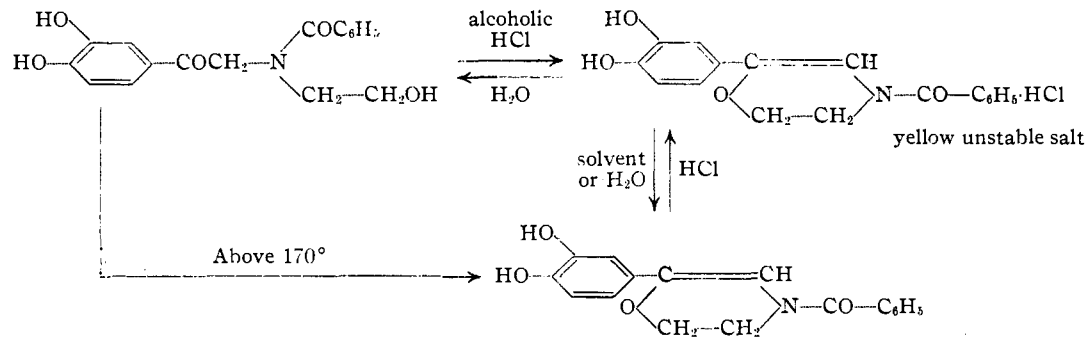
(2) Ralph Hill and G. Powell, THIS JOURNAL, **66**, 742 (1944).

(3) See Coles and Lott, *ibid.*, **58**, 1939 (1936).

(4) Rubin and Day, *J. Org. Chem.*, **5**, 54 (1940).

(5) Kanao, *J. Pharm. Soc. Japan*, **48**, 1074 (1928); Immediata and Day, *J. Org. Chem.*, **5**, 512 (1940).

(6) Ward, THIS JOURNAL, **57**, 914 (1935).



aminoethyl benzoate hydrochloride by rearrangement in boiling water.[7] Recrystallized from alcohol, the melting point was 135°.

β-Aminoethyl *p*-Nitrobenzoate Hydrochloride.—This was prepared by the same method as the previous compound, and recrystallized from alcohol; m. p. 201–203°.

Anal.[8] Calcd. for $C_9H_{11}N_2O_4Cl$: C, 43.8; H, 4.5. Found: C, 43.8; H, 4.6.

N-(β-Hydroxyethyl)-*p*-nitrobenzamide.—This was prepared by neutralizing a water solution of β-aminoethyl *p*-nitrobenzoate hydrochloride with sodium hydroxide solution.[9] The oily product, which separated out immediately and then crystallized in glistening plates, was not soluble in dilute hydrochloric acid, as the ester would be; m. p. 132–133°, recrystallized from water.

Anal. Calcd. for $C_9H_{10}N_2O_4$: C, 51.4; H, 4.8. Found: C, 51.5; H, 4.7.

β-Aminoethyl *p*-Nitrobenzoate Hydrochloride.—Two grams of N-(β-hydroxyethyl) *p*-nitrobenzamide was dissolved in about 50 cc. of saturated alcoholic hydrogen chloride solution, and allowed to stand for two days. During this time the product separated out in crystalline form. The crystals were filtered, washed with alcohol and recrystallized from alcohol; m. p. 201–203°. The melting point showed no depression when the substance was mixed with a sample of β-aminoethyl *p*-nitrobenzoate hydrochloride prepared by a known method (see above).

β-(3,4-Dihydroxyphenacylamino)-ethanol Hydrochloride.—A solution of 2 cc. of ethanolamine in 2 cc. of water was added slowly, with shaking and cooling, to a paste made by moistening 3 g. of chloroacetylcatechol with 95% alcohol. A dark reddish brown solution formed from which the ethanolamine salt of chloroacetylcatechol soon separated as light brown crystals. The salt was rearranged to the desired product by gently warming and shaking for several hours, and the resulting solution was concentrated under vacuum on a water-bath. The gummy residue was acidified with dilute hydrochloric acid and again concentrated under vacuum. Some difficulty was met in crystallizing the residue in the first run made, though in subsequent runs crystallization took place during the concentration. The first crystals formed in an alcoholic solution of the residue which had stood overnight. The main portion of the residue was then crystallized by working up with alcohol and seeding. The product was filtered, washed with alcohol and recrystallized from 90% alcohol; m. p. 195–196° (literature 197°[10]); yield 1.9 g., 48% of theoretical.

Anal. Calcd. for $C_{10}H_{14}NO_4Cl$: C, 48.5; H, 5.7. Found: C, 48.6; H, 5.6.

β-(3,4-Dihydroxyphenacylamino)-ethyl *p*-Nitrobenzoate Hydrochloride.—One gram of *p*-nitrobenzoyl chloride was mixed with 1.3 g. of β-(3,4-dihydroxyphenacylamino)-ethanol hydrochloride in a large test-tube and heated to fusion on an oil-bath. It was found that a temperature of 150–155° was required. There was a steady evolution of hydrogen chloride. The mixture was heated for about half an hour, allowed to cool, and then extracted with about a liter of water by boiling for about fifteen minutes. Undissolved material was filtered off and the filtrate was concentrated to dryness under vacuum. The concentrate was crystallized by treating with about 20 cc. of alcohol. The crystals were filtered, washed with alcohol, and recrystallized from dilute acetic acid containing a little hydrochloric acid; m. p. 215–216° with darkening.

The product gave a positive test for halogen with silver nitrate. It gave an emerald green color with ferric chloride solution, indicating that the ortho-hydroxy groups were still intact. Hydrolysis with 15% hydrochloric acid gave *p*-nitrobenzoic acid and β-(3,4-dihydroxyphenacylamino)-ethanol hydrochloride.

Anal. Calcd. for $C_{17}H_{17}O_7N_2Cl$: C, 51.4; H, 4.3. Found: C, 51.4; H, 4.5.

N-(3,4-Dihydroxyphenacyl)-N-(β-hydroxyethyl)-benzamide.—Four grams of β-(3,4-dihydroxyphenacylamino)-ethanol hydrochloride was dissolved in about 20 cc. of water, and 3.1 g. of potassium carbonate was added. To the clear solution, 1.3 cc. of benzoyl chloride was added and the mixture was shaken for several hours. The product separated as a light brown oil, which gradually solidified. It was filtered off, washed with sodium bicarbonate solution followed by water, and air dried. The product was recrystallized from butyl alcohol; yield 2.5 g., 40% of theoretical; m. p. 171.5–172.5° to a clear liquid with evolution of gas. It resolidified gradually with slight darkening, then remelted at 223–224° with darkening. The first melting was a dehydration, as will be seen from the following section.

The substance here obtained was soluble in 5% sodium hydroxide solution. It could be recrystallized from ethyl alcohol, but not as efficiently as from butyl alcohol. It gave an emerald green color with ferric chloride solution, indicating the presence of the *o*-dihydroxy groups.

Anal. Calcd. for $C_{17}H_{17}NO_5$: C, 64.8; H, 5.4. Found: C, 65.0; H, 5.6.

2-(3,4-Dihydroxyphenyl)-4-benzoyl-5,6-dihydroparoxazine.—Two grams of N-(3,4-dihydroxyphenacyl) N-(β-hydroxyethyl)-benzamide was dissolved in about 25 cc. of saturated alcoholic hydrogen chloride solution. The separation of a solid began immediately, and appeared complete in about an hour. The solid was filtered and washed twice with ether, giving a light yellow crystalline product. On heating in the melting point apparatus, it gradually turned white at 100–145°, finally melting at 222–225° with darkening. It was found that the loss of color was accompanied by the loss of hydrogen chloride. This was determined by trapping the evolved gas in a solution of silver nitrate.

When the yellow product was refluxed with water for about an hour and a half, it was converted to the original compound, N-(3,4-dihydroxyphenacyl) N-(β-hydroxyethyl)-benzamide, melting at 170–171° to a clear liquid with evolution of gas, resolidifying, and finally melting at

(7) Gabriel, *Ber.*, **23**, 2493 (1890).

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

(9) Jacobs and Heidelberger, *J. Biol. Chem.*, **21**, 412 (1915).

(10) Hochster Farbw., German Patent 152,814, *Chem. Zentr.*, **75**, II, 270 (1904).

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.

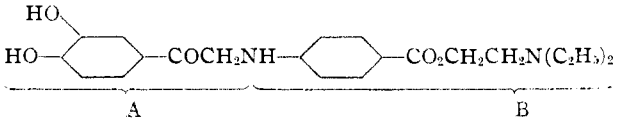
NEW YORK, N. Y. RECEIVED JANUARY 15, 1943

[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

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°.

Anál.[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 $C_{27}H_{29}N_5O_{10}$: 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·COCH$_2$X in which X is a negative group or, in some instances, an amino or substituted amino group.