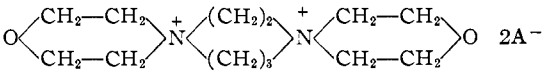
TABLE II (*Continued*)

(e) N,N'-Ethylene-N,N'-trimethylenedimorpholinium salts,  2A⁻

x	y	A⁻	M.p., °C.[a]	Yield, %	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Bromine, % Calcd.	Bromine, % Found
47		Bromide	326–327	14	$C_{13}H_{26}O_2N_2Br_2$	6.97	6.86	39.75	39.66
48		Picrate	277–278		$C_{25}H_{30}O_{16}N_8$	16.04	15.93		

[a] All compounds melted with decomposition except 42, 44 and 46. Compounds 18 and 20 were explosive. [b] The bromide and chloroplatinate have been prepared (ref. 4) but the melting points were not reported. O. Aschan (*Ber.*, **32**, 988 (1899)) obtained the iodide. The chloride has been prepared (ref. 6), but the melting point was not mentioned. It was stated (ref. 6) that the chloroaurate melted at 273–274° dec. [c] Ref. 5, m.p. over 300°.

75 cc. of isopropyl alcohol was refluxed for 24 hours. The precipitate was filtered and washed with isopropyl alcohol; yield 1.5 g. (12%). The salt was dissolved in a few cc. of water, the solution treated with Norite, filtered and the product precipitated with isopropyl alcohol; m.p. 279–280° dec.

The dipicrate precipitated when picric acid was added to an aqueous solution of the dibromide; m.p. 182–184°.

N,N',N,N'-Diethylenedipyrrolidinium Dibromide (Table II, 1).—In addition to the use of the general method described above, this compound was obtained directly from pyrrolidine and ethylene bromide.

A mixture of 35.5 g. (0.5 mole) of pyrrolidine, 20.0 g. (0.5 mole) of sodium hydroxide and 60 cc. of water was stirred, and 94.0 g. (0.5 mole) of ethylene bromide was added, dropwise, at such a rate that the material refluxed. The mixture was stirred and refluxed for 6 hours. After the product had precipitated from the cooled mixture, it was filtered and washed with alcohol; yield 24.5 g. (28%). It was dissolved in a small amount of water, the solution treated with Norite, filtered and the product precipitated with isopropyl alcohol; yield 22.9 g., m.p. 342–344°, mixed m.p. with material obtained by the use of the general method 342–344°.

In order to convert the dibromide into the dichloride, 5.0 g. of the former substance, dissolved in 50 cc. of water, was shaken with 4.8 g. of silver oxide for 3 hours. The filtered solution was neutralized with hydrochloric acid. The solution was concentrated to a small volume, cooled, and the product precipitated by the addition of isopropyl alcohol and then acetone; yield 2.7 g. A portion of the product was converted into the chloraurate and chloroplatinate.

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[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

2-(1-Hydroxypropyl)-amides of 1-Hydroxy-6-amino- and 1-Hydroxy-7-aminobenzo(f)quinoline-2-carboxylic Acids

BY F. F. BLICKE AND J. E. GEARIEN[1,2]

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The two basic amides mentioned in the title were obtained by interaction of the corresponding ethyl esters of the 2-carboxylic acids with 2-aminopropanol. The required acids were prepared by a series of reactions from acenaphthene.

The two basic amides described in this paper were prepared by interaction of the ethyl esters of the required 2-carboxylic acids with 2-aminopropanol. They were synthesized in order that they might be tested for oxytocic activity.

To obtain ethyl 1-hydroxy-6-aminobenzo(f)-quinoline-2-carboxylate (V), acenaphthene was oxidized to naphthalic anhydride[3] which was nitrated to produce 3-nitrophthalic anhydride.[4] Mercuration of the anhydride yielded a mixture of anhydro-3-nitro-8-hydroxymercuri-1-naphthoic acid and anhydro-6-nitro-8-hydroxymercuri-1-naphthoic acid.[5] When the mixture was heated with hydrochloric acid, a mixture of 6-nitro-1-naphthoic and 3-nitro-1-naphthoic acids was produced.[5] When the mixture was dissolved in acetic acid and the solution was cooled, most of the 3-nitro acid precipitated. The 3-nitro acid was converted into 3-nitro-1-naphthylamine[6] by the use of sodium azide and sulfuric acid. After acetylation of the amino group and reduction of the nitro group, 3-amino-1-acetylaminonaphthalene (I) was obtained.

Condensation of I with diethyl ethoxymethylenemalonate (II)[7] yielded 1-acetylamino-3-naphthylaminoethylenemalonate (III) which, when heated, cyclized to ethyl 1-hydroxy-6-acetylaminobenzo(f)-quinoline 2-carboxylate (IV, IV'). Treatment with hydrochloric acid eliminated the acetyl group whereby the ester, ethyl 1-hydroxy-6-aminobenzo-(f)quinoline-2-carboxylate (V) was obtained. The structure of the ester V was established by removal of the amino group which converted it into a compound of known structure, ethyl 1-hydroxybenzo-(f)quinoline-2-carboxylate.[8,9]

The ethyl ester V reacted with 2-aminopropanol to form the desired 2-(1-hydroxy)-propylamide (VI).

Ethyl 1-hydroxy-7-aminobenzo(f)quinoline-2-carboxylate was obtained by the preparation of the following series of intermediates: 2-*p*-toluenesulfon-

(1) This paper represents part of a dissertation submitted by J. E. Gearien in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan, 1949.

(2) Parke, Davis and Company Fellow.

(3) C. Graebe and F. Gfeller, *Ber.*, **25**, 652 (1892).

(4) C. Graebe and N. Briones, *Ann.*, **327**, 84 (1903).

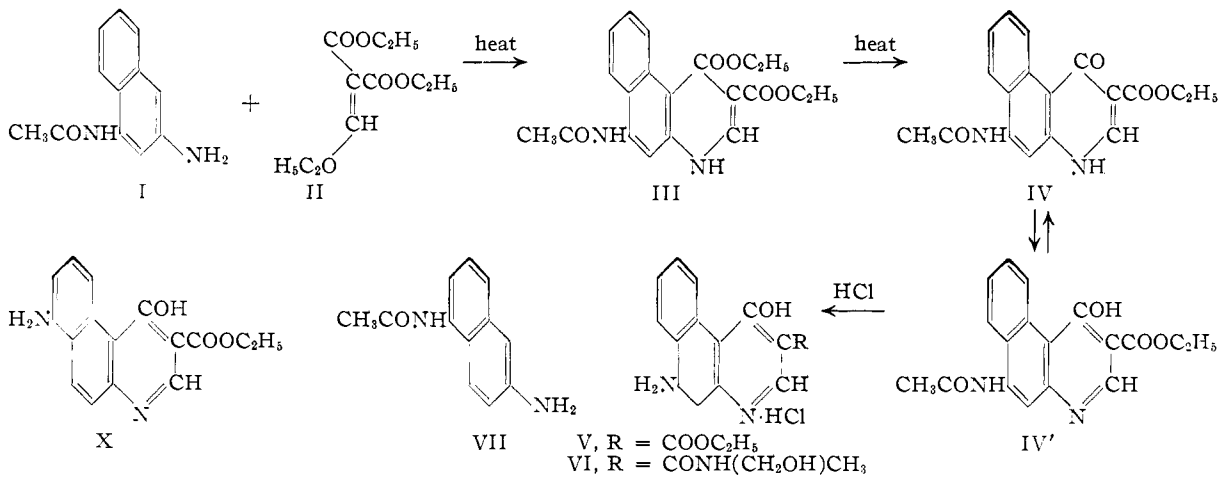
(5) G. J. Leuck, R. P. Perkins and F. C. Whitmore, THIS JOURNAL, **51**, 183 (1929).

(6) This compound had been obtained by V. Vesely and K. Dvorak (*Bull. soc. chim.*, **33**, 327 (1923)) by a different process. See also ref. 5.

(7) R. C. Fuson, W. E. Parkham and L. J. Reed, *J. Org. Chem.*, **11**, 194 (1946).

(8) A. C. Mueller and C. S. Hamilton, THIS JOURNAL, **65**, 1017 (1943).

(9) R. E. Foster, R. D. Lipscomb, T. J. Thompson and C. S. Hamilton, *ibid.*, **68**, 1327 (1946).



ylaminonaphthalene[10] → 1,6-dinitro-2-*p*-toluenesulfonylaminonaphthalene[11] → 1,6-dinitronaphthalene[12] → 6-nitro-1-naphthylamine.[12] We also obtained 6-nitro-1-naphthylamine by the following process. The mixture of 6-nitro-1-naphthoic acid and 3-nitro-1-naphthoic acid, mentioned above, from which most of the 3-nitro acid had been removed, was esterified with ethanol. The insoluble ethyl ester of the 6-nitro acid, which separated from the cooled reaction mixture, was hydrolyzed, and the 6-nitro acid was treated with sodium azide and sulfuric acid whereby 6-nitro-1-naphthylamine was obtained. The last-mentioned compound was acetylated to form 6-nitro-1-acetylaminonaphthalene[13] which was reduced to 6-amino-1-acetylaminonaphthalene (VII).

Compound VII was condensed with diethyl ethoxymethylenemalonate to form diethyl 1-acetylamino-6-naphthylaminomethylenemalonate (VIII) which, when heated, yielded ethyl 1-hydroxy-7-acetylaminobenzo(f)quinoline-2-carboxylate (IX). After treatment of IX with hydrochloric acid, ethyl 1-hydroxy-7-aminobenzo(f)quinoline-2-carboxylate (X) was obtained which was condensed with 2-aminopropanol to produce the 2-(1-hydroxy)-propylamide. The structure of IX was established by deamination with the formation of ethyl 1-hydroxybenzo(f)quinoline-2-carboxylate.

The conversion of VII into X is analogous to the transformation of I into V.

Experimental

3-Nitro-1-naphthylamine.—3-Nitro-1-naphthoic acid[14] (10 g.) was dissolved in 75 cc. of concd. sulfuric acid, 75 cc. of chloroform was added, the mixture was stirred and 3.6 g. of sodium azide was added in small portions. After all of the gas had been evolved, the mixture was stirred for 30 minutes. During these operations the temperature of the mixture was maintained at 50°. The chloroform layer was separated and discarded. The acidic solution was poured onto ice whereby the insoluble amine sulfate precipitated. It was filtered and washed with water until free from acid. The sulfate was treated with 28% ammonia water and the brown solid was recrystallized from alcohol; yield 5.0 g. (55%), m.p. 136–137°.[15]

3-Nitro-1-acetylaminonaphthalene, prepared by the method of Hodgson and Holloway,[16] melted at 262–264°.[17]

3-Amino-1-acetylaminonaphthalene (I).—A mixture of 12.3 g. of stannous chloride dihydrate and 40 cc. of acetic acid was saturated with hydrogen chloride, stirred and the temperature of the mixture kept below 25° while 4.2 g. of 3-nitro-1-acetylaminonaphthalene was added in small portions. After all of the material had dissolved, the mixture was allowed to remain at room temperature for 8 hours. The precipitated tin complex was filtered, dissolved in 300 cc. of water, the solution was filtered and the product was precipitated by the addition of 20% sodium hydroxide solution; m.p. 184–186° after recrystallization from ethanol, yield 3.5 g. (96%).

Anal. Calcd. for $C_{12}H_{12}ON_2$: N, 14.00. Found: N, 13.83.

Diethyl 1-Acetylamino-3-naphthylaminomethylenemalonate (III).—A mixture of 3.5 g. of 3-amino-1-acetylaminonaphthalene, 20 cc. of nitrobenzene and 3.8 g. of diethyl ethoxymethylenemalonate[7] was heated at 150° for 30 minutes. The precipitate, which separated from the cooled solution, was washed with ethanol and then recrystallized from the same solvent; m.p. 233–235°, yield 5.5 g. (85%).

Anal. Calcd. for $C_{20}H_{22}O_5N_2$: C, 64.86; H, 5.99; N, 7.57. Found: C, 65.00; H, 6.27; N, 7.45.

Ethyl 1-Hydroxy-6-acetylaminobenzo(f)quinoline-2-carboxylate (IV).—A mixture of 2.5 g. of *pure* diethyl 1-acetylamino-3-naphthylaminomethylenemalonate and 15 cc. of diphenyl ether was refluxed for 15 minutes in such a manner that the ethanol formed during the reaction could distil from the mixture. The yellow, crystalline precipitate was separated by filtration from the hot mixture[18] and the product was refluxed with acetone in order to purify it; the colorless material melted above 360°, yield 2.2 g. (92%).

Anal. Calcd. for $C_{18}H_{16}O_4N_2$: N, 8.64. Found: N, 8.51.

Ethyl 1-Hydroxy-6-aminobenzo(f)quinoline-2-carboxylate (V).—The acetyl derivative (2.8 g.) and 10 cc. of concd. hydrochloric acid were heated on a steam-bath for 30 minutes. The amine hydrochloride precipitated when the mixture was cooled in an ice-bath; m.p. 281–283° after recrystallization from ethanol, yield 2.0 g. (83%).

Anal. Calcd. for $C_{16}H_{15}O_3N_2Cl$: N, 8.79; Cl, 11.12. Found: N, 8.70; Cl, 11.10.

The free amine was obtained when the hydrochloride was triturated with 10% sodium carbonate solution; m.p. 267–269°.

Anal. Calcd. for $C_{16}H_{14}O_3N_2$: N, 9.93. Found: N, 9.81.

(10) H. H. Hodgson and E. W. Smith, *J. Chem. Soc.*, 1854 (1935).
(11) H. H. Hodgson and H. S. Turner, *ibid.*, 86 (1943).
(12) H. H. Hodgson and H. S. Turner, *ibid.*, 318 (1943).
(13) V. Vesely and K. Dvorak, *Bull. soc. chim.*, **33**, 327 (1923).
(14) When a mixture of 6-nitro-1-naphthoic acid and 3-nitro-1-naphthoic acid, obtained by the method described in the literature (ref. 5), was dissolved in acetic acid and the mixture was cooled, most of the 3-nitro acid precipitated. After filtration of this acid, the acids present in the filtrate were converted into their ethyl esters; the insoluble 6-nitro ester, which separated from the cold reaction mixture, was then hydrolyzed to the corresponding acid which was required for a later experiment.
(15) Reference 13, m.p. 136–137°.
(16) H. H. Hodgson and D. E. Holloway, *J. Chem. Soc.*, 123 (1945).
(17) Reference 13, m.p. 255°.
(18) The filtrate, as well as any material which separated from it, was discarded.

Deamination of Ethyl 1-Hydroxy-6-aminobenzo(f)quinoline-2-carboxylate.—A solution of 1.0 g. of V in 5 cc. of acetic acid was saturated with hydrogen chloride, cooled to 0°, stirred and 0.5 g. of isoamyl nitrite was added. After the mixture had been stirred for 10 minutes, it was poured into a stirred suspension of 5.0 g. of cuprous oxide in 25 cc. of ethanol. The mixture was heated at 70° for 15 minutes; during this time nitrogen was evolved. The hot mixture was filtered, the solvents were removed and the residue, ethyl 1-hydroxybenzo(f)quinoline-2-carboxylate, was recrystallized from ethanol; m.p. 271–272°, mixed m.p. with an authentic sample[9] 270–271°.

2-(1-Hydroxy)-propylamide of 1-Hydroxy-6-aminobenzo(f)quinoline-2-carboxylic Acid Hydrochloride (VI).—The ethyl ester (V, 1.5 g.) and 15 cc. of 2-aminopropanol were heated in a flask, fitted with an air condenser, for 4 hours. The ethanol, which formed during the reaction, was allowed to escape through the condenser. The excess amino alcohol was removed by distillation under reduced pressure. The gummy residue was dissolved in absolute ethanol and the solution was treated with hydrogen chloride. After recrystallization from methanol, the hydrochloride melted at 220–222°, yield 1.0 g. (60%).

Anal. Calcd. for $C_{17}H_{18}O_3N_3Cl$: N, 12.08; Cl, 10.20. Found: N, 11.97; Cl, 10.24.

6-Nitro-1-naphthylamine.—This amine was obtained by partial reduction of 1,6-dinitronaphthalene[11,12] and also by the following process. 6 Nitro-1-naphthoic acid[14] (7.0 g.) was dissolved in 50 cc. of concd. sulfuric acid, 50 cc. of chloroform was added and the mixture was treated with 2.5 g. of sodium azide in the manner described above. The amine was recrystallized from ethanol; m.p. 168–170°,[19] yield 4.0 g. (66%).

6-Nitro-1-acetylaminonaphthalene.—A mixture of 4.0 g. of 6-nitro-1-naphthylamine, 40 cc. of acetic acid and 3.2 g. of acetic anhydride was heated for 15 minutes on a steam-bath. The acetyl derivative precipitated when the mixture was cooled in an ice-bath; m.p. 236–238°,[20] yield 4.0 g. (83%).

6-Amino-1-acetylaminonaphthalene (VII).—This compound was prepared in the same manner as 3-amino-1-acetylaminonaphthalene from 4.0 g. of 6-nitro-1-acetylaminonaphthalene, 19.2 g. of stannous chloride dihydrate, 40 cc. of acetic acid and hydrogen chloride. The amine melted at 146–147° after recrystallization from ethanol; yield 2.1 g. (62%).

Anal. Calcd. for $C_{12}H_{12}ON_2$: N, 14.00. Found: N, 13.85.

(19) Reference 13, m.p. 167°.

(20) Reference 13, m.p. 232-233°.

Diethyl 1-Acetylamino-6-naphthylaminomethylenemalonate (VIII).—Two grams of 6-amino-1-acetylaminonaphthalene was heated, in an open flask, to 130° in an oil-bath and 2.2 g. of diethyl ethoxymethylenemalonate[7] was added. The mixture solidified after it had been heated for 10 minutes. The product melted at 188–190° after it had been recrystallized from ethanol; yield 2.2 g. (60%).

Anal. Calcd. for $C_{20}H_{22}O_5N_2$: N, 7.57. Found: N, 7.66.

Ethyl 1-Hydroxy-7-acetylaminobenzo(f)quinoline-2-carboxylate (IX).—A mixture of 2.2 g. of *pure* diethyl 1-acetylamino-6-naphthylaminomethylenemalonate and 10 cc. of diphenyl ether was boiled for 15 minutes. The mixture was cooled and the precipitated product was boiled with acetone in order to purify it; m.p. 280–282°; yield 1.8 g. (93%). The ester was found to be insoluble in all of the common organic solvents.

Anal. Calcd. for $C_{18}H_{16}O_4N_2$: N, 8.64. Found: N, 8.47.

Ethyl 1-Hydroxy-7-aminobenzo(f)quinoline-2-carboxylate (X).—A mixture of 2.0 g. of IX and 15 cc. of concd. hydrochloric acid was stirred and heated at 50°. After all of the material had dissolved, the mixture was heated for 15 minutes longer, diluted with 30 cc. of water and the free amine was precipitated by the addition of solid sodium carbonate. In order to purify the amine, it was dissolved in 10% hydrochloric acid, the solution was filtered and the product was precipitated with sodium carbonate; m.p. 234–236°, yield 1.1 g. (64%).

Anal. Calcd. for $C_{16}H_{14}O_3N_2$: N, 9.93. Found: N, 9.68.

Deamination of Ethyl 1-Hydroxy-7-aminobenzo(f)quinoline-2-carboxylate.—This process was carried out in the manner already described with 1.0 g. of ethyl 1-hydroxy-7-aminobenzo(f)quinoline-2-carboxylate. There was obtained 0.2 g. (20%) of ethyl 1-hydroxybenzo(f)quinoline-2-carboxylate after the material had been recrystallized from ethanol; m.p. 271–272°, mixed m.p. with an authentic sample[9] 270–271°.

2-(1-Hydroxy)-propylamide of 1-Hydroxy-7-aminobenzo(f)quinoline-2-carboxylic Acid Hydrochloride.—A mixture of 2.0 g. of the ethyl ester and 15 cc. of 2-aminopropanol was treated in the manner described above. Since the hydrochloride could not be recrystallized, it was extracted thoroughly with boiling ethanol; m.p. 225–227° dec., yield 1.4 g. (58%).

Anal. Calcd. for $C_{17}H_{18}O_3N_3Cl$: N, 12.08; Cl, 10.20. Found: N, 12.10; Cl, 10.37.

ANN ARBOR, MICHIGAN

[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RESEARCH LABORATORIES, THE WILLIAM S. MERRELL COMPANY]

Diuretics. α,α-Disubstituted 2-Piperidine-ethanols and 3,3-Disubstituted Octahydropyrid[1,2-c]oxazines

BY CHARLES H. TILFORD AND M. G. VAN CAMPEN, JR.

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A series of α,α-disubstituted 2-pyridine-ethanols were prepared and hydrogenated to yield the corresponding 2-piperidine-ethanols, which upon reaction with formaldehyde gave octahydropyrid[1,2-c]oxazines. The latter were reduced with aqueous formic acid to give α,α-disubstituted-1-alkyl-2-piperidine-ethanols. A number of the octahydropyridoxazines and piperidine-ethanols had diuretic and antifungal properties.

This investigation of α,α-disubstituted-2-piperidine-ethanols, their N-alkyl and oxazine derivatives was carried out with the purpose of developing new therapeutic agents. In most cases these products were prepared from α,α-disubstituted-2-pyridine-ethanols. Such pyridine-ethanols have been synthesized from α-picoline and ketones in the presence of phenyllithium[1-5] or sodamide.[6,7] Various monosubstituted piperidine-ethanols,[8-10]

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