The picrate from water melted at 159–160°; Holmen and Carroll[9] report 156–157°.

**4-*n*-Butylamino-2-chlorobenzoic Acid.**—A mixture of 34.3 g. of 4-amino-2-chlorobenzoic acid, 30 g. of 1-bromobutane and 13.2 g. of potassium hydroxide in 250 ml. of 75% alcohol was refluxed overnight. An additional portion of 13.2 g. of potassium hydroxide and 30 g. of 1-bromobutane was added and refluxing continued for eight hours. The solution was then concentrated *in vacuo*, poured into 200 ml. of water, made basic with potassium hydroxide and extracted with ether. Acidification of the aqueous portion gave 20 g. of solid which was extracted with 3 l. of boiling water and allowed to crystallize and the procedure repeated with the mother liquor. The crystals so obtained were recrystallized from 95% alcohol three times, leaving 7.5 g. of 4-*n*-butylamino-2-chlorobenzoic acid, white crystals, m.p. 112–114°.

*Anal.* Calcd. for $C_{11}H_{14}O_2NCl$: N, 6.16. Found: N, 6.04.

The residue from the water extraction solidified. It was recrystallized twice from absolute alcohol to give 4-di-*n*-butylamino-2-chlorobenzoic acid, white crystals, m.p. 127–129°.

*Anal.* Calcd. for $C_{15}H_{22}O_2NCl$: N, 4.94; Cl, 12.49. Found: N, 4.86; Cl, 12.58.

**2,6-Dichloro-4-nitrobenzoic Acid.**—Twelve grams of purified 2,6-dichloro-4-nitrotoluene was dissolved in 50 ml. of pyridine and 40 ml. of water. The mixture was brought to the boiling point and 4.3 g. of potassium permanganate was added. Five additional portions of 4.3 g. were used after the permanganate was consumed. Following the removal of the manganese dioxide, the filtrate was concentrated *in vacuo* to one-fourth its volume. Addition of concentrated HCl precipitated an oil which solidified. Treatment with aqueous sodium hydroxide served to separate 6 g. of unreacted material. After reacidification 2 g. of yellow crystals was obtained. Repeated recrystallization from water and drying gave crystals which sintered at 157°, then melted at 172–174°.

*Anal.* Calcd. for $C_7H_3O_4NCl_2$: N, 5.93. Found: N, 5.93.

In attempting to prepare 2-diethylaminoethyl 4-amino-2,6-dichlorobenzoate by procedure II, 7 g. of 2,6-dichloro-4-nitrobenzoic acid was refluxed for four hours with 25 g. of thionyl chloride. The esterification with the crude acid chloride proceeded in poor yield. However, a portion of 2,6-dichloro-4-nitrobenzoic anhydride could be recovered from the solution. The yellow needles, from alcohol, melted at 190–191.5°.

*Anal.* Calcd. for $C_{14}H_4O_7N_2Cl_4$: N, 6.17. Found: N, 6.26.

**4-Amino-2,6-dichlorobenzoic Acid.**—Following the procedure of Kuhn,[7] 1.9 g. of 2,6-dichloro-4-nitrobenzoic acid and 1.5 g. of 5% palladium-on-charcoal were added to 60 ml. of methanol. Then with stirring, 1 g. of hydrazine hydrate in 5 ml. of methanol was added during five minutes. After standing over the weekend, the solution was filtered and concentrated to 10 ml. This was poured into 25 ml. of water and acidified. The product was twice crystallized from water, yielding 0.4 g. of cream-colored crystals, m.p. 178–179° dec.

*Anal.* Calcd. for $C_7H_5O_2NCl_2$: N, 6.80. Found: N, 6.45.

**N-[2-(2-Chloro-4-nitrobenzoxy)-1-propyl]-N-cyclohexyl-2-chloro-4-nitrobenzamide.**—In the preparation of 1-cyclohexylamino-2-propyl 2-chloro-4-nitrobenzoate by procedure III, the aminoalcohol was incompletely neutralized and the ester-amide was obtained as a by-product. The cream-colored solid, from chloroform–ether, melted at 156.5–158°.

*Anal.* Calcd. for $C_{23}H_{23}O_7N_3Cl_2$: N, 8.02. Found: N, 7.88.

**2-Diethylaminoethyl 4-Hydroxylamino-2-nitrobenzoate Hydrochloride.**—Six-tenths of a gram of 2-diethylaminoethyl 2,4-dinitrobenzoate hydrochloride in 20 ml. of alcohol and 1 ml. of 3 *N* ammonia was treated at room temperature for 30 minutes with hydrogen sulfide, filtered and the solution concentrated. Yellow needles, 0.2 g., crystallized from alcohol, m.p. 170–172°. The compound gave the Tollens test for the hydroxylamino group.

*Anal.* Calcd. for $C_{13}H_{19}O_5N_3 \cdot HCl$: N, 12.60. Found: N, 12.65.

**Pharmacological.**—Intradermal and topical anesthetic activities were measured on guinea pig wheal and rabbit cornea, respectively. Comparisons were made with procaine or cocaine, to each of which the value of unity was assigned. The acute toxicities were determined in albino mice.

NEWARK, N. J.

(9) R. E. Holmen and D. D. Carroll, THIS JOURNAL, **73**, 1859 (1951).

---

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

# Derivatives of Benzo[f]quinoline

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

RECEIVED DECEMBER 15, 1953

The preparation of 2-methylbenzo[f]quinoline and of the β-diethylaminoethyl ester and the 2-(1-hydroxy)-propylamide of 1-hydroxybenzo[f]quinoline-2-carboxylic acid has been described.

A quantity of benzo(f)quinoline-2-carboxylic acid was desired for the preparation of substituted amides which were to be tested for oxytocic activity. It was expected that 2-bromobenzo(f)quinoline could be converted into the corresponding cyano derivative and that the latter could then be hydrolyzed to the desired acid. However, we could not obtain the bromo compound by the method described in the literature.[3] It was then decided to synthesize the unknown 2-methylbenzo(f)quinoline in the hope that this substance could be oxidized to the 2-carboxylic acid. 2-Naphthylamine (I) was condensed with diethyl methylmalonate (II) to form 2-methylbenzo(f)quinoline-1,3-dione (III). When a portion of III was oxidized with sodium hypobromite,[4] 2-amino-1-naphthoic acid (IV) was produced. This experiment proved that a benzo(f)quinoline, not a benzo(g)quinoline had been obtained; the latter substance would have yielded 3-amino-2-naphthoic acid on oxidation.

Compound III reacted with phosphorus oxychloride to form 1,3-dichloro-2-methylbenzo(f)quinoline (V). Hydrogenation, in the presence of palladium, removed the nuclear chlorine atoms and 2-methylbenzo(f)quinoline (VI) was obtained.

(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) A. Claus and H. Besseler, *J. prakt. Chem.*, **57**, 60 (1898).

(4) We used this process since W. R. Vaughan (THIS JOURNAL, **68**, 324 (1946)) had shown that 2,4-dihydroxy-3-acetyl-7-chloroquinoline is oxidized by sodium hypobromite to 4-chloroanthranilic acid.

Attempts to oxidize the 2-methyl compound to the corresponding 2-carboxylic acid by the use of potassium permanganate or chromic oxide failed. Also unsuccessful were efforts to oxidize 2,3-dimethylbenzo(f)quinoline[5] to a dicarboxylic acid.[6]

The β-diethylaminoethyl ester (XIII) and the 2-(1-hydroxy)-propylamide (XIV) of 1-hydroxybenzo(f)quinoline-2-carboxylic acid were obtained in the following manner. 2-Naphthylamine (VII) was heated with diethyl ethoxymethylenemalonate (VIII) to produce diethyl 2-naphthylaminomethylenemalonate (IX). The last-mentioned compound, when heated at a higher temperature, was transformed into ethyl 1-hydroxybenzo(f)quinoline-2-carboxylate (X) which was then converted into the corresponding acid (XI) by hydrolysis. The potassium salt of the acid, treated with thionyl chloride, yielded the acid chloride which reacted with β-diethylaminoethanol to produce XIII, and with 2-aminopropanol to form XIV. The basic ester and the basic amide were obtained also from the ester X and the required alcohol.

The interaction of VII and VIII, at room temperature for more than 12 hours to produce IX, had been effected in 90% yield by Foster, *et al.*[7] We found that the condensation product IX could be obtained in 87% yield if the reaction was carried out at 100–150° for 2 hours.

The acid XI, isolated after hydrolysis of the ester X, had been obtained only in a crude state by Foster, *et al.*,[7] and they reported the melting point to be about 260°. We found that the pure acid melted at 297–299°. Decarboxylation of the crude acid by Foster, *et al.*,[7] yielded 1-hydroxybenzo(f)-quinoline which was converted into the corresponding 1-chloro derivative. We obtained these same reaction products by the use of the pure acid.

The basic ester XIII and the basic amide XIV were tested for oxytocic activity in the Parke, Davis and Company laboratories. The former substance was found to be inactive while the latter was only slightly active.

## Experimental

**2-Methylbenzo(f)quinoline-1,3-dione (III).**—A mixture of 14.3 g. of 2-naphthylamine, 34.8 g. of diethyl methylmalonate and 300 cc. of nitrobenzene was heated for 2 hours at 230–240° in such a manner that the alcohol which was formed distilled from the reaction mixture. The mixture was cooled, the precipitate was filtered and then dissolved in 10% sodium hydroxide solution. The alkaline solution was filtered and the filtrate was acidified with hydrochloric acid. The precipitated product proved to be so insoluble that it could be purified only by washing it with boiling alcohol; m.p. above 300°, yield 17 g. (75%).

*Anal.* Calcd. for $C_{14}H_{11}O_2N$: N, 6.22. Found: N, 6.04.

Sodium hydroxide (5.3 g.) was dissolved in 20 cc. of water, the solution was cooled to 5° and 10 g. of ice was added. The mixture was stirred, cooled in an ice–salt-bath and 2.4 g. of bromine was added, dropwise. After the addition of 3.6 g. of III, the mixture was stirred for 8 hours. The solution was cooled to 0° and acidified with hydrochloric acid whereupon 2-amino-1-naphthoic acid (IV) precipitated; m.p. and mixed m.p. with an authentic sample 126–128°.

**1,3-Dichloro-2-methylbenzo(f)quinoline (V).**—A mixture of 22.5 g. of III, 100 cc. of phosphorus oxychloride and 25 cc. of dimethylaniline[8] was refluxed for 3 hours. The phosphorus oxychloride was distilled from the mixture *in vacuo*. Benzene was added to the residue and then removed by distillation. The residue was treated with water and then recrystallized from acetone; yield 16 g. (62%), m.p. 133–135°.

*Anal.* Calcd. for $C_{14}H_9NCl_2$: Cl, 27.05. Found: Cl, 26.83.

**2-Methylbenzo(f)quinoline Hydrochloride (VI).**—Compound III (10.5 g.), dissolved in 150 cc. of alcohol, was hydrogenated under an initial pressure of 40 pounds in the presence of 1 g. of palladium-on-charcoal catalyst (10%).[9] The calculated amount of hydrogen was absorbed after 4 hours. After removal of the catalyst and the solvent, the residue was dissolved in ether, the solution was dried over anhydrous magnesium sulfate and then treated with hydrogen chloride; m.p. 275–276° in a sealed tube[10] yield 8 g. (88%).

*Anal.* Calcd. for $C_{14}H_{12}NCl$: N, 6.10; Cl, 15.44. Found: N, 5.93; Cl, 15.35.

The base melted at 82–84°.

**1-Hydroxybenzo(f)quinoline-2-carboxylic Acid (XI).**—A mixture of 22.0 g. of the ethyl ester, 15.5 g. of potassium hydroxide, 30 cc. of water and 250 cc. of ethanol was refluxed for 8 hours. After removal of the solvents, the potassium salt was dissolved in water, the solution was acidified with dilute hydrochloric acid and the precipitated acid was filtered.

In order to obtain a sample of pure acid, a portion of the potassium salt was recrystallized from water, then dissolved in water and the solution was acidified; the precipitated acid melted at 297–299°.[11]

*Anal.* Calcd. for $C_{14}H_9O_3N$: N, 5.86. Found: N, 5.73.

**Acid Chloride of 1-Hydroxybenzo(f)quinoline-2-carboxylic Acid (XII).**—Since the carboxylic acid failed to react with thionyl chloride in a satisfactory manner, the potassium salt was employed for the preparation of the acid chloride.

Sixteen grams of the acid, 4.5 g. of potassium hydroxide, 20 cc. of water and 200 cc. of ethanol were refluxed for 0.5 hour, about one-half of the alcohol was removed and the solution was cooled. The precipitated salt weighed 16 g. (91%).

Five grams of the potassium salt and 20 cc. of thionyl chloride were refluxed for 4 hours and the excess thionyl chloride was removed. Benzene was added to the residue and then removed by distillation in order to free the product from traces of thionyl chloride.

**β-Diethylaminoethyl 1-Hydroxybenzo(f)quinoline-2-carboxylate Dihydrochloride (XIII).**—(a) A mixture of the acid chloride, which had been obtained from 5 g. of the carboxylic acid, 8.4 g. of β-diethylaminoethanol and 70 cc. of benzene was refluxed for 2 hours. The precipitate, which consisted of a mixture of β-diethylaminoethanol hydrochloride and the desired ester, was filtered, washed thoroughly with water, and then recrystallized from ethanol; m.p. 187–189°, yield 4.7 g. (79%).

The dihydrochloride was obtained when the ester, dissolved in absolute ethanol, was treated with the calculated amount of alcoholic hydrogen chloride. The salt precipitated upon the addition of dry ether. It melted at 150–152°, then solidified and melted at 273–275°.

*Anal.* Calcd. for $C_{20}H_{24}O_3N_2Cl_2$: Cl, 17.26. Found: Cl, 17.03.

(b) A mixture of 1.2 g. of X and 15 cc. of β-diethylaminoethanol was refluxed for 4 hours. An air condenser was attached to the reaction flask and the ethyl alcohol which was formed was allowed to escape through the condenser. After removal of the excess β-diethylaminoethanol by distillation, the residue was recrystallized from ethanol with the use of charcoal; m.p. 187–189°, yield 0.7 g. (47%).

**2-(1-Hydroxy)-propylamide of 1-Hydroxybenzo(f)quinoline-2-carboxylic Acid (XIV).**—(a) A mixture of 1.5 g. of X

(5) V. A. Petrow, *J. Chem. Soc.*, 693 (1942).

(6) It was reported by A. C. Mueller and C. S. Hamilton (THIS JOURNAL, **65**, 1017 (1943)) that 1-hydroxy-3-carboxybenzo(f)quinoline could not be obtained by oxidation of 1-hydroxy-3-methylbenzo[f]-quinoline.

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

(8) In the absence of dimethylaniline an unidentified halogen product was obtained. See J. Baddiley and A. Tophan, *J. Chem. Soc.*, 678 (1944).

(9) *Org. Syntheses*, **26**, 78 (1946).

(10) The material sublimed when heated.

(11) It was stated (ref. 7) that the crude acid melted about 260° with the loss of carbon dioxide.

and 15 cc. of 2-aminopropanol was refluxed for 4 hours. The alcohol which was formed was allowed to escape from the reaction mixture through an air condenser. The excess amino alcohol was removed *in vacuo*, the oily residue was dissolved in hot ethanol, the solution was treated with charcoal, filtered and the filtrate was cooled. The precipitated amide weighed 1.5 g. (88%), m.p. 220–222°.

*Anal.* Calcd. for $C_{17}H_{16}O_3N_2$: N, 9.46. Found: N, 9.28.

The amide, dissolved in absolute ethanol, was treated with alcoholic hydrogen chloride; when dry ether was added, the hydrochloride precipitated; m.p. 205–207° after recrystallization from ethanol.

*Anal.* Calcd. for $C_{17}H_{17}O_3N_2Cl$: N, 8.48; Cl, 10.65. Found: N, 8.46; Cl, 10.73.

(b) The acid chloride, obtained from 24 g. of the potassium salt of the carboxylic acid, was mixed with 50 cc. of benzene and added, slowly, to 26 g. of 2-aminopropanol, dissolved in 75 cc. of benzene. The mixture was refluxed for 3 hours whereupon an oily precipitate formed. After decantation of the benzene, the oil was washed with water and then allowed to remain under 50 cc. of 10% sodium carbonate solution for several hours. The solidified material was dried and recrystallized from ethanol; m.p. 220–222°, yield 11 g. (41%).

ANN ARBOR, MICHIGAN

---

[COMMUNICATION NO. 1646 FROM THE KODAK RESEARCH LABORATORIES]

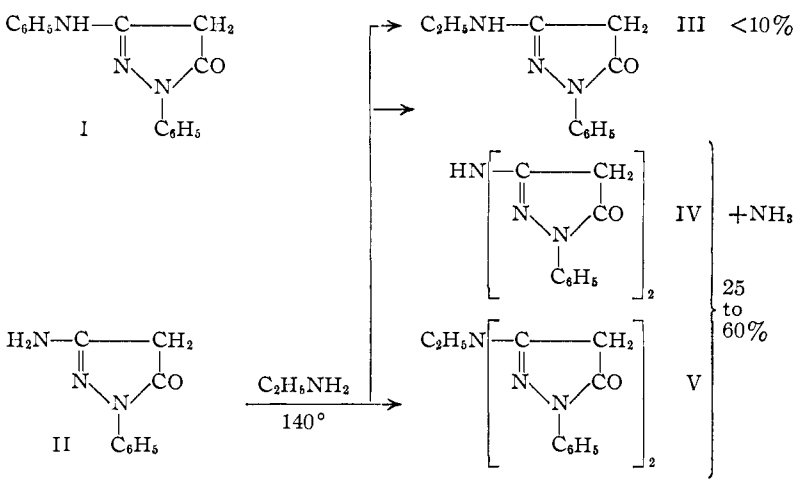
# The Reaction of 1-Substituted-3-amino-5-pyrazolones with Amines

BY B. GRAHAM,[1] W. RECKHOW AND A. WEISSBERGER

RECEIVED FEBRUARY 16, 1954

The reactions are investigated which occur when 1-substituted-3-substituted-amino-5-pyrazolones are heated with primary aromatic or aliphatic amines, $RNH_2$. Three types of compounds are obtained, namely, 1-substituted-3-amino-5-pyrazolones, 3,3′-imino-bis-(1-substituted-5-pyrazolones) and 3,3′-R-imino-bis-(1-substituted-5-pyrazolones). The latter compounds undergo cyclization condensations with ethyl *o*-formate or formaldehyde. A yellow compound obtained in the condensation of aniline with 1-phenyl-3-amino-5-pyrazolone is probably a trimeric condensation product of the latter.

The formation of 1-phenyl-3-anilino-5-pyrazolone (I) by the action of aniline on 1-phenyl-3-amino-5-pyrazolone (II) has been described by Weissberger and Porter.[2] When an attempt was made to synthesize 1-phenyl-3-ethylamino-5-pyrazolone (III) by the reaction of II with ethylamine, III was obtained in a low yield, while the principal products were 3,3′-imino-bis-(1-phenyl-5-pyrazolone) (IV), and 3,3′-ethylimino-bis-(1-phenyl-5-pyrazolone) (V).




Similar results were obtained with *n*-butylamine, *n*-amylamine and benzylamine. When II was heated with ammonia in a sealed tube, a 70% yield of IV resulted, and 1-(4-*p*-*t*-butylphenoxy-phenyl)-3-amino-5-pyrazolone, when refluxed with *n*-butylamine, yielded 3,3′-imino-bis-[1-(4-*p*-*t*-butylphenoxy-phenyl)-5-pyrazolone] in 13% yield. The 3,3′-imino-bis-(5-pyrazolones) are high melting, rather insoluble in organic media, and react with *p*-aminodialkylanilines in the presence of oxidizing agents to form bluish-magenta azomethine dyes.[3]

Jennen[4] prepared 3,3′-imino-bis-(1-*m*-chlorophenyl-5-pyrazolone) as a by-product in the synthesis of 1-*m*-chlorophenyl-3-amino-5-pyrazolone from *m*-chlorophenylhydrazine and ethyl β-amino-β-ethoxyacrylate.[5] A similar reaction in these Laboratories with phenylhydrazine and ethyl β-amino-β-ethoxyacrylate yielded 9% of IV and 34% of II. Ammonia was evolved during this reaction. The latter may account for the formation of IV from the principal product, II.

One might expect that cyclizations involving the reactive 4-positions of the two pyrazolone nuclei of the 3,3′-imino-bis-(5-pyrazolones) should proceed readily. Thus, 8-*n*-butyl-3,5-dioxo-2,6-diphenyl-2,3,4a,5,6,8-hexahydrodipyrazolo[3,4-b,4′,3′-e]-pyridine (VII) was obtained when *n*-butylimino-bis-(1-phenyl-5-pyrazolone) (VI) was treated with ethyl orthoformate; with formalin, 8-*n*-butyl-3,5-dioxo-2,6-diphenyl-2,3,3a,4,4a,5,6,8-octahydrodipyrazolo-[3,4-b,4′,3′-e]pyridine (VIII) was formed.

The reaction of 1-phenyl-3-amino-5-pyrazolone (II) with aniline[2] was reinvestigated to determine whether compounds of the types IV or V were formed along with 1-phenyl-3-anilino-5-pyrazolone (I). No 3,3′-imino-bis-(1-phenyl-5-pyrazolone) (IV) was isolated when II was refluxed with aniline until no more ammonia was evolved (two hours). When the reaction was stopped after 15 minutes, a

(1) Now at Stanford Research Institute, Stanford, Calif.

(2) A. Weissberger and H. D. Porter, THIS JOURNAL, **64**, 2133 (1942).

(3) A. Weissberger and H. D. Porter, *ibid.*, **65**, 52 (1943).

(4) J. J. Jennen, British Patent 636,988 (1950).

(5) B. Graham, H. D. Porter and A. Weissberger, THIS JOURNAL, **71**, 983 (1949).