two hours, when the initial blood-red color had changed to orange-yellow. On hydrolysis of the excess anhydride the acetate separated as a solid and was crystallized from benzene–ligroin; yield 5.12 g. (74%), m. p. 86.4–88.4°. The analytical sample (No. 12) consisted of pale yellow microprisms.

**Reductive acetylation** (No. 13) was accomplished by heating 1 g. of the acid with 6 cc. of acetic anhydride and 0.2 g. of fused sodium acetate for one hour on the steam-bath and treating the cooled solution with 1 g. of zinc dust. The yellow color was discharged in a few minutes and the mixture was then boiled briefly, diluted with acetic acid, filtered and treated with water. The product was caused to solidify by cooling and scratching, and initial crystallization from benzene containing a little ether gave 1.14 g. (82%) of product melting at 115–118°. Recrystallization from dilute alcohol afforded white microprisms.

From preparation of the **diazoketone** (No. 14), 4.78 g. of 9-(2-acetoxy-1,4-naphthoquinonyl-3)-pelargonic acid (No. 12) was converted to the acid chloride with 5 cc. of thionyl chloride at 60° as above and a solution of the chloride in dry ether was chilled to −10° and treated with a similarly chilled ethereal solution of 0.0256 mole of diazomethane prepared according to Arndt[10] and dried over solid potassium hydroxide and then sodium wire. Gas was evolved vigorously and after one-half hour at −10° the mixture was allowed to stand at room temperature for one-half hour, when the gas evolution had ceased and considerable yellow solid had separated. The mixture was concentrated at 0°, ligroin was added, and the oily yellow solid collected and triturated with 5 cc. of cold ether. The residual solid was suitable for use and melted at 74–78°; yield 2.92 g. (52%). A sample recrystallized five times from benzene–ligroin formed small yellow needles; it melted at 81.6–82.4° and began to decompose at 118–128°.

The **ketol VI** (No. 15) was prepared as above; yield from 500 mg. of diazoketone, 286 mg. (60%), m. p. 53–55°. The analytical sample formed rosets of tiny bright yellow needles (strong positive Fehling test). The yield of the corresponding **ketol acetate** (no. 16) from 148 mg. of diazoketone was 129 mg. (81%), m. p. 84–85.4° (light yellow rectangular plates).

**Anomalous Products.**—The anomalous substance No. 17 was prepared in the same way as the true diazoketone No. 14 except for the use of an alcohol- and water-containing diazoethane solution prepared in the usual manner from nitrosomethylurethan. The yield from 5.3 g. of acid was only 650 mg. The purified substance consisted of cream-colored granules. The non-reducing supposed ketol No. 18 likewise formed cream-colored granules; on acetylation it afforded a substance identical with the acetate, No. 19, resulting from the action of acetic acid on No. 17 (131 mg. from 221 mg.); the acetate formed rosets of cream-colored blades. A Rast molecular weight determination (E. Werble) gave the value 448 (calcd. 428). In absorption spectra the substances 18 and 19 are very similar to one another and show some similarity to the true ketols in the region 240–280 mμ but absorb more intensely in the region 330 mμ. Maxima were observed for No. 18 at the following wave lengths (and log $E$ values): 240 (4.4), 260 (4.15), 268 (4.1), 330 (3.9).

(10) Arndt, "Organic Syntheses," Coll. Vol. 11, 165 (1943).

## Summary

A carboxylated side chain is easily introduced at the free position of 2-methyl-1,4-naphthoquinone by alkylation with the peroxide derived from the half ester of a dibasic acid. Such naphthoquinonyl acids have been conjugated with sulfanilamides and also converted through diazoketones to naphthoquinonyl ketols possessing at least superficial structural relationships to cortical hormones and possibly to luciferin.

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[CONTRIBUTION FROM THE PURDUE RESEARCH FOUNDATION AND THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

# Aminoalkanol Derivatives of Benzo(f)chroman[1,2]

BY G. BRYANT BACHMAN AND HAROLD A. LEVINE

The antimalarial activity of compounds of the type RCHOH—$(CH_2)_nNR'_2$ (R = aryl, R′ = alkyl) suggested the preparation of related compounds in which the alcohol grouping is part of a ring system. Compounds of the 1-(α-naphthyl)-alkanolamine structure (X, XII, Fig. 1) in which the side-chain is linked to the beta position of the naphthalene nucleus by an oxygen atom, derivatives of benzo(f)chroman, seemed desirable compounds to prepare for comparison in view of the known high activity of the corresponding naphthalene derivatives.[3]

The synthetic methods usually employed in preparing compounds of the desired type start with a ketone which is brominated to form the alpha-bromoketone and then condensed with a secondary amine. The resulting α-dialkylaminoketone is reduced to the corresponding aminoalcohol. Alternatively the bromoketone may be converted to the corresponding bromohydrin by aluminum isopropoxide reduction and then condensed with a secondary amine.[4]

The parent ketone of this series, 1-benzo(f)-chromanone (I), has been prepared previously by the action of phosphorus pentoxide on β-(2-naphthoxy)-propionic acid.[5] A more convenient preparation was developed in this investigation. β-(2-Naphthoxy)-propionitrile,[6] from β-naphthol and acrylonitrile in the presence of Triton B,[6a] was cyclized by 85% sulfuric acid to give I in excellent yields. The same procedure applied to β-

(1) Based on the Ph.D. thesis of H. A. Levine, February, 1947.

(2) Read before the Medicinal Division of the American Chemical Society at the Atlantic City Meeting, April, 1947.

(3) Jacobs, Winstein, Ralls, Robson, Henderson, Akawie, Florsheim, Seymour and Seil, *J. Org. Chem.*, **11**, 21 (1946).

(4) Winstein, Jacobs, Henderson and Florsheim, *ibid.*, **11**, 150 (1946).

(5) Chakravarti and Dutta, *J. Indian Chem. Soc.*, **16**, 639 (1939).

(6) This compound is claimed in French Patent 833,734 (1938), and Ufer, German Patent 670,357 (1939), but its physical constants are not reported.

(6a) Benzyltrimethylammonium hydroxide obtained from Rohm and Haas Company, Philadelphia. Other strong bases also function as catalyst for this addition.

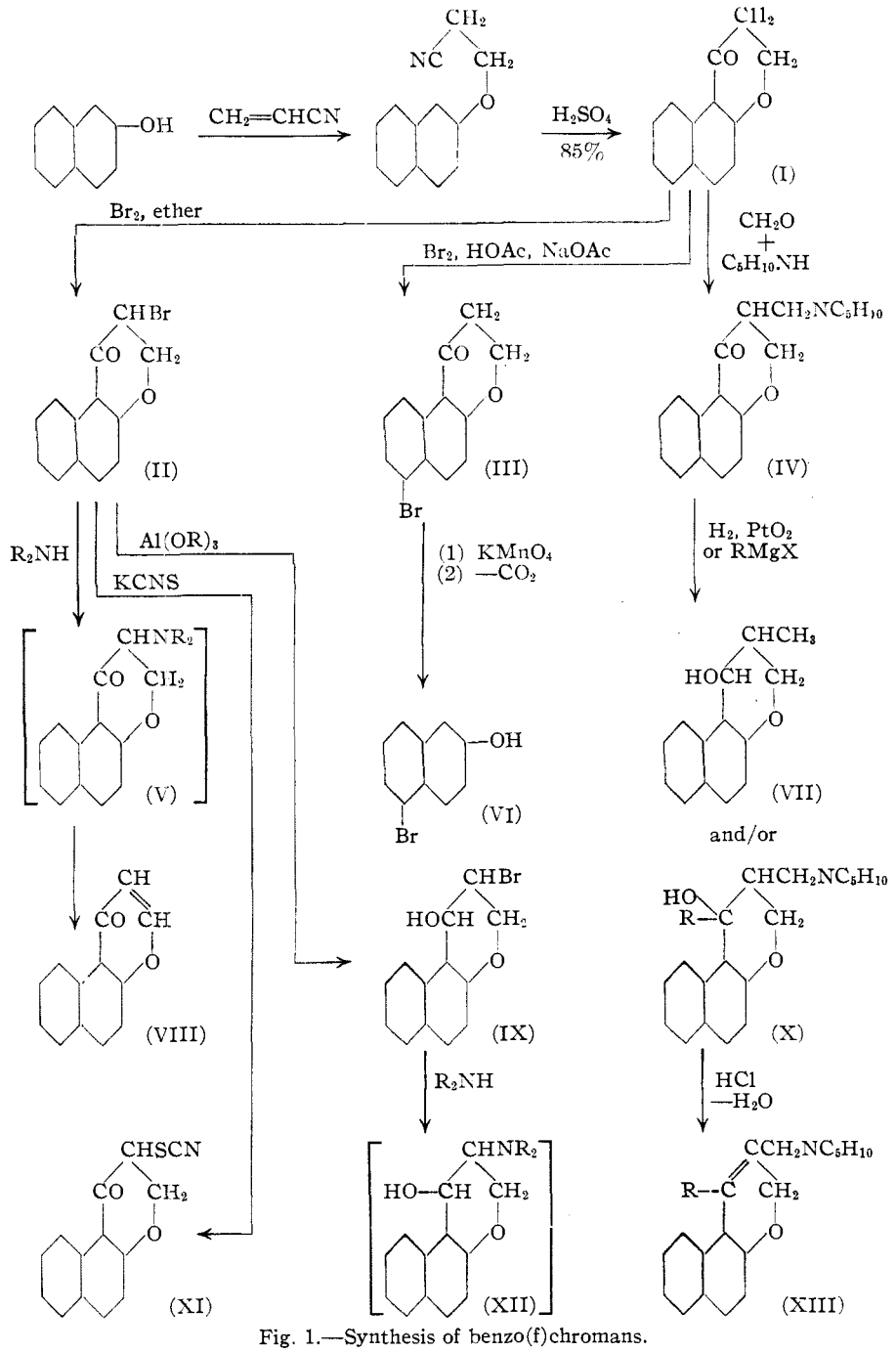


Fig. 1.—Synthesis of benzo(f)chromans.

naphthiol gave β-(2-naphtho)-propionitrile and 1-benzo(f)thiochromanone.[7]

Bromination of I in ether gave 2-bromo-1-benzo(f)chromanone (II). Bromination of I in acetic acid and subsequent treatment with sodium acetate gave an isomeric bromoketone (III) which was shown to be 7-bromo-1-benzo(f)-chromanone by oxidative degradation followed by decarboxylation to 5-bromo-2-naphthol (VI).

(7) Krollpfeiffer and Schultze, *Ber.*, **56**, 1819 (1923).

The reaction of II with diethylamine under a nitrogen atmosphere led to the formation of a highly unstable aminoketone (V). Attempts to isolate this material were unsuccessful; instead, its decomposition products, diethylamine and 1-benzo(f)-chromone (VIII), were obtained. Aluminum isopropoxide reduction of the crude aminoketone failed; acetone was not liberated during the reaction. Catalytic hydrogenations with platinum oxide or palladium–charcoal catalysts were likewise unsuccessful. Absorption of hydrogen was slow and incomplete; only traces of non-volatile, basic material were isolated.

Bromination of VIII in carbon disulfide followed by boiling in methanol gave 2-bromo - 1 - benzo(f)-chromone. This reacted with diethylamine to form an unstable analytically impure amine, presumably 2-diethylamino-1 - benzo(f)chromone. It gave diethylamine on hydrogenation and its hydrochloride decomposed on standing in the air.

Nitrosation of I gave a red oil which could not be crystallized or otherwise purified. Catalytic hydrogenation also cleaved this product and the desired 2-amino-1-benzo(f)chromanol was not obtained.

The failure of the aminoketone method prompted an investigation of the condensation of amines with the bromohydrin, 2-bromo-1-benzo-(f)-chromanol (IX), prepared by aluminum isopropoxide reduction of II. Condensation of IX with secondary amines under the conditions recommended by Winstein and Jacobs[4] led to ex-

tensive decomposition. The desired aminoalcohol was probably formed but the principal products were the secondary amine hydrobromide and a red-brown tar. The small amounts of base-soluble material found in the reaction mixtures indicated that a naphthol had been regenerated by ring-cleavage. When the condensation was carried out at lower temperatures, part of the starting material was recovered, but the desired aminoalcohols could not be isolated.

In the light of these results, it was felt that a direct proof of the α-bromoketonic structure of II by formation of a thiazole ring would be desirable. Condensation of II with thiourea[8] led to the formation of a red tar from which a pure material was not isolated even with the aid of chromatographic techniques. An alternative preparation of aminothiazoles, ring-closure of an α-thiocyanoketone by the action of ammonia,[9] was also explored. The thiocyanoketone (XI) was prepared in good yield by the reaction of II with potassium thiocyanate in absolute ethanol, but the action of ammonia on XI resulted in the formation of a dark tar from which an aminothiazole could not be isolated. In spite of the failure of these ring closures it is felt that the bromine is probably alpha rather than beta to the carbonyl group.

The Mannich reaction affords a convenient synthesis of aminoketones. Harradence and coworkers[10] report the preparation of Mannich ketones derived from chromanone itself. The corresponding reaction of 1-benzo(f)chromanone with piperidine hydrochloride and formaldehyde proceeds smoothly to give 2-piperidinomethyl-1-benzo(f)chromanone (IV). The homologs from dimethyl and diethyl amines were also prepared. The aminoalcohols derived from IV are characterized by the unusual ease with which they dehydrate. Reduction gave an oily mixture which probably contained some of the desired secondary alcohols (X, R is H), but which yielded only a chromene on attempted purification *via* acid salts. Reaction with Grignard reagents gave tertiary alcohols (X, R is alkyl) which lost water spontaneously on neutralization with hydrogen chloride.

Catalytic hydrogenation of IV was accompanied by hydrogenolysis of the piperidine moiety and the consequent formation of 2-methyl-1-benzo(f)chromanol (VII). Neither the free base nor the hydrochloride of the aminoalcohol could be crystallized. The crude liquid hydrochloride dehydrated when heated in acetone to form crystalline 2-piperidonomethyl-3-benzo(f)chromene hydrochloride (XIII, R is H). The addition of Grignard reagents, prepared from methyl iodide and ethyl bromide, to IV gave the corresponding aminoalcohols. The free base of the 1-ethyl compound was isolated as a crystalline solid. The 1-methyl compound could not be crystallized but was isolated as the hydrochloride of the dehydration product.

(8) Trauman, *Ann.*, **249**, 10 (1888).

(9) Hantzsch, *Ber.*, **61**, 1776 (1929).

(10) Harradence, Hughes and Lions, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 273 (1938).

**Pharmacological Testing.**—The following compounds were tested as antimalarials and found inactive: benzo(f)chromanone (I), the two 2-piperidinomethyl-3-benzo(f)chromene hydrochlorides (XIII, R is $CH_3$ and $C_2H_5$) 2-piperidinomethyl-1-benzo(f)chromanone hydrochloride (IV), 2-dimethylamino-1-benzo(f)chromanone hydrochloride, 2-diethylamino-1-benzo(f)chromanone hydrochloride, the analytically impure 2-diethylamino-1-benzo(f)chromone hydrochloride, and 1-ethyl-2-piperidinomethyl-1-benzo(f)chromanol acetate. It may be concluded that the antimalarial activity of 1-naphthyl-2-dialkylaminoethanols is probably lost when the ethanol group is cyclized with the naphthalene ring to form a benzo(f)chroman. The 2-dialkylaminomethyl-1-benzo(f)chromanols desired to test this relationship more perfectly could not be prepared in a pure form because of the ease with which they dehydrated, but the compounds synthesized and tested were so closely related in structure to the desired compounds and were so devoid of antimalarial activity that further investigation of this field would seem to be unpromising.

**Acknowledgment.**—The authors are indebted to Eli Lilly and Company and to the Purdue Research Foundation for financial support of this investigation.

## Experimental

All melting points are corrected.

β-(2-Naphthoxy)-propionitrile.—A mixture of 1100 g. of acrylonitrile (20.8 mole), 800 g. of 2-naphthol (5.4 mole) and 75 ml. of 40% Triton B[6a] was heated at reflux for eighteen hours and then allowed to stand overnight. The crystalline precipitate was filtered from the dark mother liquors, washed with 1 liter of 2.5% sodium hydroxide and 2 liters of water, and air-dried. A pale-yellow crystalline material, 593 g., m. p. 105–106°, was obtained.

The material precipitated on acidifying the washing was combined with the dark filtrate, returned to the reaction flask, and heated at reflux for twenty hours. The crystalline precipitate obtained on cooling was filtered off, washed with 500 ml. of 2.5% sodium hydroxide and two 500-ml. portions of water and air-dried. A yellow crystalline material, 297 g., m. p. 103–105°, resulted. A third crop of nitrile, 44.5 g., m. p. 103–105°, was obtained by heating the filtrate combined with the material precipitated on acidification of the washings for an additional sixteen hours; total yield 844.5 g., 79.2%. Pure β-(2-naphthoxy)-propionitrile, recrystallized from acetone, is a colorless solid, m. p. 105.5–107.0°.

*Anal.* Calcd. for $C_{13}H_{11}NO$: N, 7.11. Found: N, 7.16, 7.34.

β-(2-Naphthio)-propionitrile.—To a stirred, externally cooled mixture of twelve drops of 40% Triton B[6a] and 32 g. of acrylonitrile (0.60 mole), 24 g. of 2-naphthiol (0.15 mole) was added in small portions during twenty minutes. The reaction mixture was then kept at 65° for one hour. It was diluted with 500 ml. of ether, 5 ml. of glacial acetic acid was added to neutralize the catalyst, and the precipitated polymer was filtered off. The filtrate was evaporated and distilled at 2 mm. to give 29.4 g. of colorless β-(2-naphthio)-propionitrile, b. p. 178–179°; yield 92%.

*Anal.* Calcd. for $C_{13}H_{11}NS$: C, 73.20; H, 5.20. Found: C, 73.19, 73.23; H, 5.29, 5.21.

**1-Benzo(f)chromanone (I).**—Two hundred grams of crude β-(2-naphthoxy)-propionitrile was added to 2 liters of vigorously stirred 85% sulfuric acid. The reaction mixture was stirred for two hours and then poured with stirring upon 3 kg. of ice. The light purple material which precipitated on standing overnight was filtered off and washed with 500 ml. of 5% sodium hydroxide and 1500 ml. of water. The crude, dry ketone weighed 146 g., m. p. 49–50°. A second crop of ketone, 29 g., m. p. 49–49.5°, was obtained from the filtrate on standing. Yield was 87.5%. Pure 1-benzo(f)chromanone, recrystallized from benzene–ligroin (b. p. 90–100°), is an almost colorless solid, m. p. 50–51°. Chakravarti and Dutta[5] report this compound as a yellow oil.

*Anal.* Calcd. for $C_{13}H_{10}O_2$: C, 78.70; H, 5.05. Found: C, 78.71, 78.76; H, 5.08, 5.02.

The 2,4-dinitrophenylhydrazone is a brilliant scarlet compound, m. p. 312°.

**1-Benzo(f)thiochromanone.**—A mixture of 10.6 g. of β-(2-naphthio)-propionitrile (0.05 mole) and 100 g. of 85% sulfuric acid was stirred for two hours. The milky suspension first formed gave way to a deep red solution with a green fluorescence. The reaction mixture was poured into 800 ml. of water, allowed to stand overnight, and filtered. The residue was triturated with 100 ml. of 5% sodium hydroxide, filtered and washed with water. A yellow solid, 9.3 g., m. p. 60–65° was obtained. Recrystallization from 100 ml. of methanol gave 4.6 g. of yellow needles, m. p. 67–68°; yield 43.2%. The melting point was unaffected by recrystallization. Krollpfeiffer and Schultze[7] report a m. p. of 68–69°.

**2-Bromo-1-benzo(f)chromanone (II).**—A solution of 80 g. of crude 1-benzo(f)chromanone (I) (0.4 mole) in 500 ml. of U. S. P. ether was heated to reflux in a 1-liter three-necked flask equipped with a mercury-sealed Hershberg stirrer, a dropping funnel and a reflux condenser, and 65 g. of bromine (0.4 mole) was added dropwise during forty-five minutes. The refluxing mixture was stirred for an additional three hours and then allowed to stand overnight. Filtration gave 71 g. of a greenish solid, Crop 1, m. p. 111–113°. The filtrate was evaporated to dryness and the residue was recrystallized from 300 ml. of isopropanol to give Crop 2. Recrystallization of Crop 1 from 350 ml. of isopropanol gave 63.8 g. of yellow crystals, m. p. 112.5–114.0°. Crop 2 was recrystallized from the crystallization mother liquors of Crop 1 to give 22.0 g. of bromoketone, m. p. 111–113°; total yield 85.5 g., 76.5%. Bromination in anhydrous ether gave a lower yield (46.8%) of bromoketone.

Pure 2-bromo-1-benzo(f)chromanone, recrystallized from isopropanol, is a pale-yellow solid, m. p. 113.5–114.0°.

*Anal.* Calcd. for $C_{13}H_9O_2Br$: Br, 28.84. Found: Br, 28.98, 28.96.

**7-Bromo-1-benzo(f)chromanone (III).**—A solution of 8.0 g. of bromine (0.05 mole) in 50 ml. of acetic acid was slowly added to 10 g. of 1-benzo(f)chromanone (0.05 mole) dissolved in an equal volume of acetic acid. A red crystalline material precipitated which rapidly dissolved when 4.1 g. of anhydrous sodium acetate (0.05 mole) was added. The clear red solution was poured into 150 ml. of water and allowed to stand. The precipitated solid was filtered off, washed with water, and crystallized from 50 ml. of absolute ethanol. Tan needles, 5.5 g., m. p. 123–125°, were obtained; yield 39.8%. Recrystallization from ethanol gave almost colorless needles, m. p. 125–126°.

*Anal.* Calcd. for $C_{13}H_9O_2Br$: C, 56.34; H, 3.25. Found: C, 56.68; H, 3.38.

One gram of this material was oxidized with an excess of alkaline permanganate solution. Ether extraction of the oxidation mixture gave a colorless acid, m. p. 161–165°. On heating this acid in a sublimation apparatus at 5 mm., carbon dioxide was evolved and a crystalline sublimate, m. p. 104–105°, which contained halogen and had a phenolic odor was obtained. 5(8)β-Bromo-2-naphthol, m. p. 105°, was prepared from 5(8)β-bromo-2-nitronaphthalene by von Braun.[11] Recently, Hodgson[12] showed by independent synthesis that von Braun's bromonitronaphthalene is 5-bromo-2-nitronaphthalene. Thus, the isomeric bromoketone prepared in this work is 7-bromo-1-benzo(f)chromanone.

**Reaction of II with Diethylamine.**—These experiments were carried out in anhydrous dioxan under a nitrogen atmosphere at 14–15° for sixteen to twenty hours. Two moles of amine were used per mole of bromoketone. Filtration gave diethylammonium bromide in yields of 90–95%. (a) Addition of an equivalent of hydrogen chloride dissolved in anhydrous dioxan to the filtrate precipitated a yellow powder, melting range 100–195°, partially soluble in water. Attempted purification of this material led to the isolation of diethylammonium chloride and 1-benzo(f)-chromone (VIII). (b) Evaporation of the filtrate left a brown oil. Crystallization of this material from methanol gave VIII. Vacuum distillation resulted in the same product. (c) Catalytic hydrogenation of the filtrate with platinum oxide catalyst proceeded slowly. The absorption of hydrogen was incomplete (0.28 mole per mole of ketone). Only traces of a 5% hydrochloric acid-soluble oil were isolated from the reduction mixture. (d) The filtrate was evaporated under reduced pressure and the residue was dissolved in anhydrous isopropanol. An excess of freshly prepared 1 *N* isopropanolic aluminum isopropoxide was added and the mixture was heated at reflux for forty-five minutes. It was then slowly distilled over a period of four hours. No acetone was detected in the distillate.

**2-Bromo-3-ethoxy-1-benzo(f)chromanone.**—A solution of 8.2 of bromine (0.051 mole) in 25 ml. of chloroform was added to 10 g. of 1-benzo(f)chromone (0.051 mole) dissolved in 25 ml. of the same solvent. After standing overnight the reaction mixture was filtered. An orange crystalline material, 9.1 g., m. p. 170–171°, was obtained. It dissolved in 40 ml. of hot absolute ethanol to form a yellow solution. On cooling, the solution deposited 2.3 g. of a crystalline solid, m. p. 110–112°. Recrystallization from methanol gave 1.4 g. of colorless crystals, m. p. 113.5–114.5°. Yield was 8.6%.

*Anal.* Calcd. for $C_{15}H_{13}O_3Br$: C, 56.08; H, 4.05. Found: C, 56.14, 55.99; H, 4.09, 3.97.

**2-Bromo-1-benzo(f)chromone.**—A suspension of 50 g. of 1-benzo(f)chromone (0.253 mole) in 250 ml. of carbon disulfide was cautiously heated in a 500-cc. suction flask to complete solution, and 41.0 g. of bromine (0.253 mole) was then added dropwise over a period of twenty minutes. The mixture was allowed to stand two and one-half hours at room temperature. Fifty ml. of methanol was then added, the air in the vessel displaced by carbon dioxide, and the mixture heated to reflux for five minutes. The oil which remained after evaporation *in vacuo* was recrystallized from 50 ml. of butanol to give a solid contaminated with an oil. The oil was removed by washing with methanol. Two more recrystallizations from isopropanol gave 21.0 g. (30.1% yield) of pale yellow crystals, m. p. 119.5–120.0°.

*Anal.* Calcd. for $C_{13}H_7O_2Br$: C, 56.73; H, 2.55; Br, 29.06. Found: C, 56.70, 56.84; H, 2.59, 2.49; Br, 28.89, 29.01.

**Reaction of 2-Bromo-1-benzo(f)chromone with Diethylamine.**—A mixture of 12.4 g. of 2-bromo-1-benzo(f)-chromone (0.045 mole), 8.76 g. of diethylamine (0.12 mole), and 50 ml. of absolute ethanol was allowed to stand overnight. The clear red solution was evaporated *in vacuo*. The red residue was extracted with 150 ml. of benzene. The benzene solution precipitated a bulky yellow solid when shaken with 350 ml. of 3% aqueous hydrochloric acid. This material was filtered, washed with benzene and 3% acid successively, and dried *in vacuo*. Recrystallization from methanol–anhydrous ether gave 11.0 g. of yellow needles, m. p. 170–180°. A second recrystallization from this solvent pair gave 10.5 g., m. p.

(11) von Braun, Hahn and Seeman, *Ber.*, **55**, 1697 (1922).

(12) Hodgson and Turner, *J. Chem. Soc.*, 381 (1943).

204–206° (dec.). Further recrystallization did not change the melting point. The analytical data for this compound did not correspond exactly to the expected structural formula. Recrystallization from ethanol–isopropyl ether did not effect further purification. Since the purified material darkened on standing, it is probable that the incorrect analytical data were due to partial decomposition before analysis.

*Anal.* Calcd. for $C_{17}H_{18}NO_2Cl$: C, 67.22; H, 5.96; N, 4.61; Cl, 11.67. Found: C, 65.52, 65.41; H, 5.59, 5.66; N, 4.64, 4.55; Cl, 11.72, 11.87.

A solution of the compound in ethanol was hydrogenated with platinum oxide as a catalyst. Approximately the theoretical absorption of hydrogen occurred. The only basic material found in the reduction mixture was diethylamine.

**3-Bromo-1-benzo(f)chromanol (IX).**—A mixture of 27.7 g. of 2-bromo-1-benzo(f)chromanone (II) (0.10 mole), 102 g. of freshly distilled aluminum isopropoxide (0.50 mole) and 400 ml. of anhydrous isopropanol was heated at reflux for twenty-five minutes and then quickly cooled. The clear yellow solution was poured with stirring into 300 ml. of 6 *N* hydrochloric acid and allowed to stand overnight. The precipitate was filtered off and washed with two 100-ml. portions of 3 *N* hydrochloric acid followed by 400 ml. of water. A colorless, finely crystalline material which decomposed between 130 and 145° when heated in a capillary melting point tube was obtained. The true melting point was determined by observing the lowest temperature at which liquefaction occurred without decomposition within fifteen seconds after the capillary was inserted in the melting point bath. The melting point thus determined was 167–168°. Yield was 18.5 g., 66.7%. Pure 2-bromo-1-benzo(f)chromanol, recrystallized from benzene was obtained as colorless needles, m. p. 168–169°.

*Anal.* Calcd. for $C_{13}H_{11}O_2Br$: C, 55.90; H, 3.94; Br, 28.64. Found: C, 55.90, 55.98; H, 4.13, 4.00; Br, 28.57, 28.45.

**Condensation of IX with Secondary Amines.**—A number of amines (dimethyl, diethyl and dibutyl amines and piperidine) were condensed with IX. A typical experiment with dimethylamine will illustrate the nature of the reaction products.

A mixture of 5.5 g. of IX (0.02 mole), 5.1 g. of dimethylamine (0.09 mole), and 20 ml. of absolute ethanol was heated in a Carius tube at 113–118° for sixteen hours. The resulting red-brown reaction mixture was evaporated on a steam-bath under reduced pressure. Extraction of the brown tarry residue with boiling benzene left a crystalline solid identified as dimethylammonium bromide.

Addition of hydrogen chloride to the benzene extract precipitated a small amount of a dark oil. Fractional precipitation of this oil from ethanol–anhydrous ether gave a red tar which partially crystallized on long standing. The crystals were insoluble in water but soluble in 5% sodium hydroxide and contained halogen. Evidently ring cleavage had occurred.

**2-Thiocyano-1-benzo(f)chromanone (XI).**—A mixture of 5.5 g. of 2-bromo-1-benzo(f)chromanone (0.02 mole), 9.7 g. of anhydrous potassium thiocyanate (0.10 mole) and 50 ml. of absolute ethanol was heated to reflux for thirty minutes and then allowed to stand for two days. Filtration followed by successive washings with 50 ml. of ethanol and 150 ml. of water gave 4.2 g. of colorless, crystalline XI, m. p. 121–122°; yield 82.3%.

*Anal.* Calcd. for $C_{14}H_9NO_2S$: C, 65.87; H, 3.55; N, 5.49. Found: C, 65.73, 65.82; H, 3.56, 3.62; N, 5.59, 5.51.

**2-Piperidinomethyl-1-benzo(f)chromanone (IV).**—A mixture of 12.3 g. of piperidine hydrochloride (0.1 mole), 23.8 g. of 1-benzo(f)chromanone (0.12 mole), 4.5 g. of paraformaldehyde (0.15 mole), 0.25 ml. of concentrated hydrochloric acid, and 50 ml. of absolute ethanol was heated to reflux. After two hours, 3.0 g. of paraformaldehyde (0.1 mole) was added and heating was continued for eighteen hours. The hot mixture was poured into 250 ml. of water and extracted with two 50-ml. portions of ether. The aqueous solution was made basic, allowed to stand until precipitation was complete, and filtered. Recrystallization from 500 ml. of methanol gave 19.5 g. of colorless needles, m. p. 82–83°; yield 66.2%. The hydrochloride of IV, recrystallized from ethanol melted at 174–176°, resolidified and remelted at 224–227°.

*Anal.* Calcd. for $C_{19}H_{21}NO_2 \cdot HCl$: C, 68.79; H, 6.64. Found: C, 68.84, 68.70; H, 6.67, 6.73.

**2-Dimethylaminomethyl-1-benzo(f)chromanone.**—A mixture of 8.4 g. (0.08 mole) of dimethylamine hydrochloride, 20 g. (0.072 mole) of 1-benzo(f)chromanone, 9.2 g. (0.307 mole) of paraformaldehyde, 2 ml. of concentrated hydrochloric acid and 200 ml. of water was heated fourteen days on a steam cone. The ether extract of the cooled solution was dried and evaporated. The residue was recrystallized from ethanol–isopropyl ether to white plates, m. p. 171–172°. The picrate melts at 215–216°.

*Anal.* Calcd. for $C_{16}H_{18}NO_2Cl$: N, 4.80. Found: N, 4.75, 4.67.

**2-Diethylaminomethyl-1-benzo(f)chromanone.**—The preparation followed the procedure for the dimethyl homolog. The picrate melts at 186–187°, the hydrochloride at 165–166°.

*Anal.* Calcd. for $C_{18}H_{22}NO_2Cl$: Cl, 11.08. Found: Cl, 11.10, 11.12.

**Catalytic Reduction of IV.**—A mixture of 15.0 g. of IV, 100 ml. of absolute ethanol and 0.3 g. of platinum oxide catalyst was subjected to catalytic hydrogenation. The theoretical pressure drop occurred during five hours. After filtration of the catalyst, the reduction mixture was distilled at 25 mm. from a water-bath. From the distillate 1.2 g. of piperidine hydrochloride was obtained (20% deamination). The residual oil could not be crystallized. Accordingly, it was dissolved in ether and extracted with dilute hydrochloride acid. The ether solution, A, was saved. Addition of an excess of concentrated ammonium hydroxide precipitated a brown oil which could not be crystallized. Addition of hydrogen chloride to an ether solution of this material precipitated an oil which could not be crystallized from the usual solvents. On heating this oil in acetone, 6.47 g. of a colorless solid, m. p. 182–185°, was obtained. Two recrystallizations from acetone gave 5.40 g. of 2-piperidinomethyl-3-benzo(f)chromene (XIII, R is H) hydrochloride, m. p. 193–195°; yield 32%.

*Anal.* Calcd. for $C_{19}H_{21}NO \cdot HCl$: C, 72.27; H, 7.02; N, 4.44. Found: C, 71.90, 71.91; H, 7.10, 7.24; N, 4.45, 4.38.

A crystalline solid was obtained from the ether solution of acid-insoluble material, A. Recrystallization from ligroin (b. p. 90–100°) gave 2-methyl-1-benzo(f)chromanol (VII) as colorless needles, m. p. 122.0–123.5°.

*Anal.* Calcd. for $C_{14}H_{14}O_2$: C, 78.49; H, 6.51. Found: C, 78.41, 78.31; H, 6.60, 6.67.

**1-Ethyl-2-piperidinomethyl-1-benzo(f)chromanol (X, R is $C_2H_5$).**—The reaction was carried out under a nitrogen atmosphere in an all-glass apparatus equipped with an efficient stirrer. The Grignard reagent was prepared from 12.2 g. of magnesium turnings (0.5 mole) and 54.5 g. of ethyl bromide (0.5 mole) in 50 ml. of anhydrous ether. A solution of 29.5 g. of IV (0.1 mole) in 100 ml. of anhydrous benzene was added to the stirred mixture during ten minutes. Stirring was continued at room temperature for thirty minutes and then at reflux for one hour. A saturated solution of ammonium chloride (200 ml.) was added slowly. The grey emulsion which resulted was filtered. The filtrate was separated and the aqueous layer extracted with ether. The combined organic extracts were dried, filtered, and evaporated at reduced pressure to give 36 g. of a yellow oil. Crystallization of this oil from 40 ml. of absolute ethanol gave 14.5 g. of solid, m. p. 136–138°. Recrystallization from methanol gave the chromanol as colorless needles, m. p. 139–140°; yield 44.5%.

*Anal.* Calcd. for $C_{21}H_{27}NO_2$: C, 77.50; H, 8.37; N, 4.27. Found: C, 77.30, 77.46; H, 8.46, 8.38; N, 4.36, 4.29.

**1-Ethyl-2-piperidinomethyl-3-benzo(f)chromene (XIII, R is $C_2H_5$).**—Exactly 0.01 mole of ethanolic hydrogen chloride was added gradually to a solution of 0.01 mole of the chromanol in butyl ether. A yellow oil precipitated which slowly crystallized to colorless crystals, m. p. 230–233°. Recrystallization from methanol gave pure 1-ethyl-2-piperidinomethyl-3-benzo(f)chromene hydrochloride, m. p. 244–245°. The free base, recrystallized from ethanol, melted at 89.0–89.5°.

*Anal.* Calcd. for $C_{21}H_{25}NO\cdot HCl$: C, 73.32; H, 7.62; Cl, 10.31. Found: C, 73.14, 73.27; H, 7.70, 7.75; Cl, 10.33, 10.22.

**1-Methyl-2-piperidinomethyl-3-benzo(f)chromene.**—The Grignard reagent was prepared from 17.0 g. of methyl iodide (0.12 mole) and 2.92 g. of magnesium turnings (0.12 mole). A solution of 17.8 g. of IV (0.06 mole) in 100 ml. of anhydrous ether was added during one hour to the stirred reaction mixture. It was then heated at reflux for an additional thirty minutes. An excess of saturated aqueous ammonium chloride was added carefully and the reaction mixture was extracted with four 100-ml. portions of ether. Evaporation of the dried ether extracts gave 15.5 g. of a brown oil which could not be crystallized. It was dissolved in methanol and added to a solution of hydrogen chloride in anhydrous ether. On standing a colorless crystalline material, m. p. 237–239°, was obtained. Recrystallization from methanol–water (3:1) gave 4.7 g. of the chromene hydrochloride, m. p. 249–250°; yield 22.6%.

*Anal.* Calcd. for $C_{20}H_{23}NO\cdot HCl$: C, 72.85; H, 7.28; N, 4.25; Cl, 10.76. Found: C, 72.78, 72.67; H, 7.35, 7.30; N, 4.11, 4.22; Cl, 10.85, 10.76.

## Summary

1-Benzo(f)chromanone and 1-benzo(f)thiochromanone have been prepared by an improved method. The former has been converted into various hydroxylamino derivatives and related compounds for testing as antimalarials.

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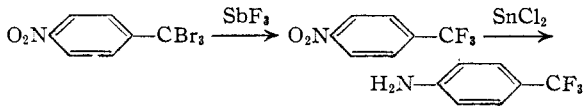
[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

# Ortho and Para Substituted Derivatives of Benzotrifluoride

BY REUBEN G. JONES

The ordinary substitution reactions such as nitration[1] and halogenation[2,3] take place exclusively in the meta position of benzotrifluoride. Thus, the readily obtained meta-substituted derivatives have been rather extensively investigated while the ortho- and para-substituted derivatives of benzotrifluoride are relatively unknown.

In connection with an investigation of the physiological properties of compounds containing the trifluoromethyl ($CF_3$-) group, a need arose for a number of derivatives of benzotrifluoride with substituents in the ortho and para positions. The most convenient approach to the synthesis of a variety of ortho- and para-substituted benzotrifluorides appeared to be through the corresponding amino compounds. The known *o*-aminobenzotrifluoride was prepared by modifications of the method of Rouche.[4] *p*-Aminobenzotrifluoride was obtained by the following sequence of reactions




By the well known diazonium transformations, the amino compounds were converted to the phenols, fluorides, chlorides, bromides and iodides presented in Table I.

TABLE I

ORTHO AND PARA SUBSTITUTED BENZOTRIFLUORIDES

| Substituent | Yield, % | B. p., °C.[a] | Mm. | $n^{25}D$ | $d^{25}_{25}$ | Analyses, % Calcd. C | Calcd. H | Found C | Found H |
|---|---|---|---|---|---|---|---|---|---|
| *o*-OH[b] | 68 | 147 –148 | 760 | | | 51.86 | 3.11 | 51.65 | 3.28 |
| *p*-OH[c] | 80 | 71.5–72 | 8 | | | 51.86 | 3.11 | 51.96 | 3.45 |
| *o*-F | 83 | 114.5 | 750 | 1.4040 | 1.293 | 51.23 | 2.46 | 50.96 | 2.65 |
| *o*-Cl[6] | 80 | 148.5–149 | 760 | 1.4533 | 1.356 | 46.56 | 2.23 | 46.64 | 2.39 |
| *o*-Br | 88 | 167.5–168 | 745 | 1.4805 | 1.656 | 37.36 | 1.79 | 37.37 | 1.96 |
| *p*-Br | 85 | 160 –160.5 | 745 | 1.4710 | 1.614 | 37.36 | 1.79 | 37.25 | 1.76 |
| *o*-I | 78 | 197.5–198 | 750 | 1.5258 | 1.896 | 30.91 | 1.48 | 31.36 | 1.54 |
| *p*-I[d] | 90 | 185.5–186 | 745 | 1.5158 | 1.851 | 30.91 | 1.48 | 30.93 | 2.10 |

[a] Corrected. [b] Melting point 45.5–46°. [c] Melting point 46.5–47°. [d] Melting point 17–17.5°.

Nitration of *m*-iodobenzotrifluoride[5] produced a mixture from which the solid 2-nitro-5-iodobenzotrifluoride (57.5% yield) readily was separated. This compound was identified by comparison with a sample made from 2-nitro-5-aminobenzotrifluoride through the Sandmeyer reaction. The

(1) Swarts, *Bull. sci. acad. roy. Belg.*, **6**, 389 (1920) [*Chem. Zentr.*, **92**, 11, 32 (1921)].

(2) Simons and Ramler, THIS JOURNAL, **65**, 389 (1943).

(3) Wertyporoch, *Ann.*, **493**, 153 (1932).

(4) Rouche, *Bull. sci. acad. roy. Belg.*, **13**, 346 (1927); [*Chem. Zentr.*, **98**, 11, 1817 (1927)].

(5) Finger and Kolinowski, *Trans. Illinois State Acad. Sci.*, **37**, 66 (1944) [*C. A.*, **39**, 1146 (1945)].