two weeks, the animals being weighed at frequent intervals. The results are given in Table I.

Summary

The 2-β-hydroxyethyl analog of quinacrine was synthesized and its chronic toxicity to white mice, as determined by the drug diet method, found to be one-third that of the parent drug.

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

Synthesis of Chromans from Phenols and from ortho-Hydroxy Aromatic Aldehydes[1,2]

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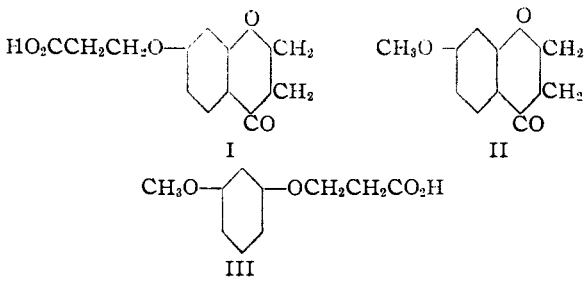
The success of the recently developed synthesis of benzo[f]chromanones by cyclization of β-naphthoxypropionitriles obtained from addition of β-naphthols to acrylonitrile[4] suggested a study of the application of this method to other phenols, especially those in the benzene series. From phenol itself 3-phenoxypropionitrile[5] was obtained in good yield, but a series of cyclization experiments gave only traces of impure ketonic material or no reaction. *p*-Nitrophenol and methyl salicylate did not add, and *o*- and *p*-chlorophenols added only slowly to acrylonitrile. Apparently, electron-withdrawing groups on the benzene nucleus hinder the addition. Even 6-bromo-2-naphthol gave poor yields (10%) of 3-(6′-bromo-2′-naphthoxy)-propionitrile. This cyclized satisfactorily, however, in the presence of sulfuric acid to 8-bromo-1-benzo[f]chromone.

The presence of electron-supplying groups on the benzene ring apparently increases the ease of addition of phenolic hydroxyl groups to acrylonitrile but does not necessarily increase the ease of cyclization of the product because of an increased tendency of such compounds to sulfonate. Resorcinol gives a dinitrile[5] in 40% yields, but treatment with cyclizing agents gives poor yields of a monocyclized product, 7-(2′-carboxy-ethoxy)-chromanone (I). Resorcinol monomethyl ether gives a nitrile in 76% yield. With 85% sulfuric acid this cyclizes to the expected 7-methoxy-chromanone (II),[6] while with 85% phosphoric acid the uncyclized 3-(3′-methoxyphenoxy)-propionic acid (III)[6] is obtained.

In all of these reactions sulfonation and phosphorylation led to considerable amounts of water-soluble, ether-insoluble products which were not investigated. The desired products were obtained in poor yields.

An alternative preparation of derivatives of chroman based on the addition of the hydroxyl group of salicylaldehyde to acrylonitrile followed by an aldol cyclization was also investigated.



When salicylaldehyde was heated in an excess of acrylonitrile in the presence of dimethylbenzyl-cetyl-ammonium hydroxide (Triton B) as a catalyst, reaction proceeded to only a limited extent. Three crystalline products were isolated from the alkali-insoluble fraction of the reaction mixture in yields of 1–2%. These compounds were identified by qualitative tests and analytical data as 2-(β-cyanoethoxy)-benzaldehyde (IV), 3-cyano-4-chromanol (V), and 3-cyano-1,2-benzopyran (VI). Attempts to increase the yield of V by the use of other condensation catalysts were unsuccessful. When the condensation was carried out at 100° with Triton B as a catalyst, there was a marked increase in the amount of alkali-insoluble product, but pure V could not be isolated. 3-Aminomethyl-4-chromanol (VII) was prepared by reduction of V in acetic anhydride with platinum oxide catalyst,[7] followed by hydrolysis with methanolic sodium hydroxide.

A second synthesis of derivatives of chroman from salicylaldehyde was also developed. The base catalyzed addition of salicylaldehyde to an aliphatic primary nitroölefin followed by an aldol-type of cyclization gives both the nitroalcohol (VIII) and the nitroölefin (IX) of the expected structures. β-Chloronitroparaffins prepared according to the method of Riley[8] were used as sources of the nitroölefins. The two reactions may be accomplished in one step by condensing the chloronitroparaffin with the sodium salt of salicylaldehyde. Of the three chloronitroparaffins tried, 2-chloro-1-nitroethane, 1-chloro-2-nitropropane and 2-chloro-1-nitropropane, only the last gave the desired products. The others gave polymeric material. This result was not unexpected since the intermediate nitroölefins of the type

(1) From the Ph.D. thesis of H. A. Levine, Purdue University, February, 1947.

(2) The assistance of Mr. A. Karler in many of these experiments is gratefully acknowledged.

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(4) Bachman and Levine, THIS JOURNAL, **69**, 2341 (1947).

(5) Cook and Reed, *J. Chem. Soc.*, 920 (1945).

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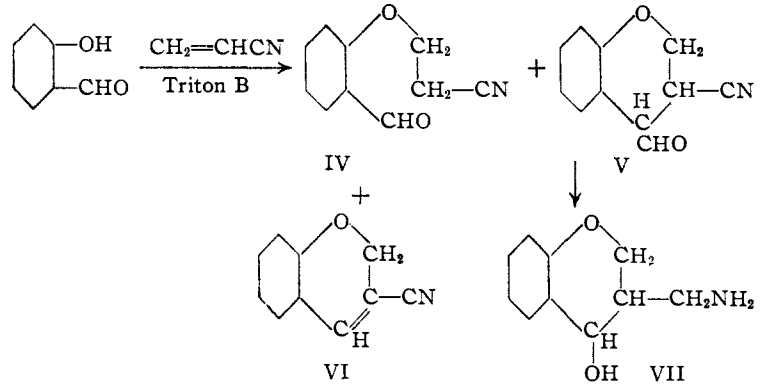
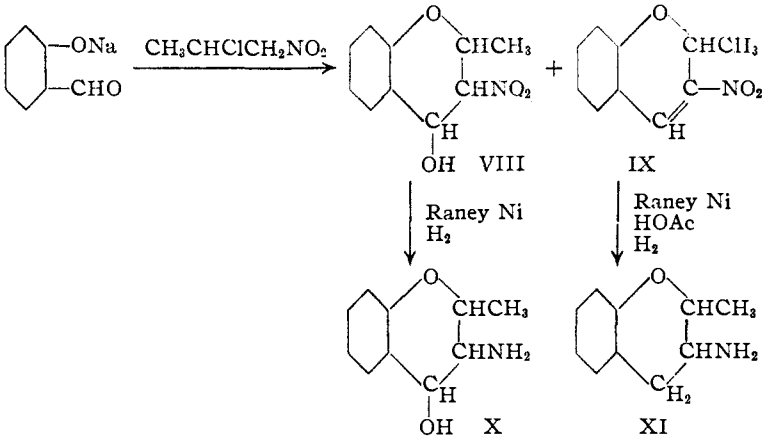
(7) Carothers and Jones, THIS JOURNAL, **47**, 3051 (1925).

(8) McBee and Riley, U. S. Patent 2,337,912 (Dec. 28, 1943).



$R-C(NO_2)=CH_2$ have been reported to polymerize very readily.[9] Since 3-aminochromans structurally resemble known sympathomimetic phenylethylamine derivatives,[10] VIII and IX were converted to the corresponding amines for testing. Catalytic hydrogenation of 2-methyl-3-nitro-4-chromanol (VIII) proceeds smoothly to give the corresponding amino alcohol (X). The preparation of



2-methyl-3-aminochroman (XI) proved to be more difficult. Reduction of IX to the oxime catalytically,[11] or with iron filings and hydrochloric acid,[11] was unsuccessful. Tarry products were obtained. However catalytic hydrogenation with Raney nickel gave the desired amine in low yield.

Pharmacological Testing.—The aminochromans tested as sympathomimetics showed no pressor activity (VII), slight pressor activity (XI) or slight depressor activity (X). In addition X showed no antimalarial, slight antihistaminic, and no analgesic action.

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(9) Wieland and Sakellarios, *Ber.*, **52**, 898 (1919).
(10) Hartung, *Ind. Eng. Chem.*, **37**, 126 (1945).
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Experimental

Reactions of Acrylonitrile with Phenols.—The phenol (0.25 mole) was refluxed with acrylonitrile (2–4 moles) and *Triton B* (dimethylbenzylacetylammonium hydroxide) (2–5 ml.) for about twenty hours. The reaction mixture was diluted with two volumes of a solvent (ether or chloroform), filtered, and washed successively with several portions of 5% aqueous sodium hydroxide, dilute hydrochloric acid and then water. Evaporation of the solvent and distillation or recrystallization of the residue gave the desired product. The yields and physical properties are as follows: (a) 3-phenoxypropionitrile,[5] 67.5%, m. p. 59–60° from benzene–petroleum ether (reported,[5] 70%, m. p. 61–62°); (b) 3-(7′-bromo-2′-naphthoxy)-propionitrile, 10%, m. p. 120° from ethanol. *Anal.* Calcd. for $C_{13}H_{10}NOBr$: N, 5.07. Found: N, 5.03, 4.98. (c) 1,3-Di-(2′-cyanoethoxy)-benzene, 40%, m. p. 110–111° (reported,[5] 53%, m. p. 112°). (d) 3-(3′-methoxyphenoxy)-propionitrile 76.5%, b. p. 145–146° (3 mm.), m. p. 29.5–30.5°. *Anal.* Calcd. for $C_{10}H_{11}NO_2$: C, 67.77; H, 6.26; N, 7.91. Found: C, 67.75, 67.89; H, 6.18, 6.12; N, 8.00, 7.73.

Cyclizations of 3-Aryloxypropionitriles.—No success attended efforts to cyclize 3-phenoxypropionitrile with concd. or 85% sulfuric acid, 85% phosphoric acid, stannic chloride, phosphorus oxychloride, or acetic anhydride and sodium acetate at various temperatures. Either no reaction occurred or water-soluble, ether-insoluble products were formed. The remaining nitriles were treated as follows: 3-(7′-bromo-2′-naphthoxy)-propionitrile, 17.0 g., was mixed with 200 ml. of 85% sulfuric acid, stirred till dissolved, and poured into 2 liters of ice and water. The yellowish-white solid was recrystallized from 50% aqueous ethanol; yield 13.6 g., 80%, m. p. 123°, of 8-bromo-1-benzo(f)-chromanone.

Anal. Calcd. for $C_{13}H_9O_2Br$: Br, 28.48. Found: Br, 28.96, 28.98.

1,3-Di-(2′-cyanoethoxy)-benzene, 5 g., and 85% sulfuric acid, 25 ml., were mixed and stirred at room temperature for three hours, poured into 200 ml. of water and let stand five days. The precipitated solid, collected and recrystallized from water, gave tan needles, 0.7 g. (12.8%) m. p. 171–173°. They were soluble in dilute solutions of sodium bicarbonate and gave a positive ketone test with 2,4-dinitrophenylhydrazine. The analytical data indicate the product to be 7-(2′-carboxyethoxy)-chromanone (I).

Anal. Calcd. for $C_{12}H_{12}O_5$: C, 61.01; H, 5.12. Found: C, 60.92, 60.86; H, 5.17, 5.21.

3-(3′-Methoxyphenoxy)-propionitrile, 5 g., and 85% sulfuric acid, 25 ml. were mixed and stirred at room temperature for three hours and then heated on a steam-bath for one hour. The cooled mixture was poured into 200 ml. of water and extracted with ether. The ether extract was evaporated and the oily residue was recrystallized from water. The product, 7-methoxychromanone (II), was obtained in 0.1 g. yield (2%) as colorless needles m. p. 52–54° (reported,[6] m. p. 50–56°, yield 18–40%).

The product when 85% phosphoric acid was used instead of 85% sulfuric acid was 3-(3′-methoxyphenoxy)-propionic acid[6] (III). The ether extract of the reaction mixture was itself extracted with 5% aqueous sodium hydroxide. This latter extract was acidified and the solid precipitate was recrystallized from water (Norit decolorization). The product, 1.4 g. (25.3% yield), was obtained as colorless plates, m. p. 80–82° (reported[6] m. p. 81–83°, 15% yield).

Reaction of Acrylonitrile with Salicylaldehyde.—A mixture of 61 g. of salicylaldehyde (0.5 mole), 133 g. of acrylonitrile (2.5 mole), and 5 ml. of 40% Triton B was heated at reflux for thirty hours, cooled, poured into a mixture of 40 ml. of concd. hydrochloric acid and 500 ml. of ether, and filtered. The ether layer was extracted with three 200-ml. portions of 5% sodium hydroxide, dried, and evaporated under vacuum to yield 16.0 g. of at an oil. Fractional precipitation from benzene by the addition of petroleum ether (b. p. 90–100°) gave 2.0 g. of a crystalline solid. Recrystallization from benzene gave 1.7 g. (2% yield) of 3-cyano-4-chromanol (V), m. p. 141–142.5°.

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18. Found: C, 68.58, 68.52; H, 5.18, 5.25.

The crystallization mother liquors were evaporated and distilled. Fraction I, b. p. 105–137°, 2.9 g., partially crystallized on cooling to give 1.0 g. (1.3% yield) of 3-cyano-1,2-benzopyran (VI), colorless plates (from methanol), m. p. 48–49°.

Anal. Calcd. for $C_{10}H_7NO$: N, 8.81. Found: N, 8.84, 8.96.

Fraction II, b. p. (2 mm.) 137–170°, 5.5 g., partially crystallized on cooling to give 1.2 g. (1.3% yield) of 2-(2′-cyanoethoxy)-benzaldehyde (IV), m. p. 73–75° (from benzene).

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18. Found: C, 68.69, 68.56; H, 5.12, 5.17.

3-Aminomethyl-4-chromanol (VII) Hydrochloride.—A mixture of 7.0 g. of 3-cyano-4-chromanol (V), 50 ml. of acetic anhydride, and 0.3 g. of platinum oxide catalyst was hydrogenated for nine hours, filtered, and vacuum-evaporated to yield 9.0 g. of the diacetylated amino alcohol, m. p. 160–165°. Eight grams of this material in 50 ml. of methanol and 100 ml. of 15% sodium hydroxide was heated at reflux for twenty-four hours. The hydrolysis mixture was extracted with ether. Addition of anhydrous hydrogen chloride to the dried ether extract followed by recrystallization of the solid product from ethanol–butyl ether gave 4.0 g. (52% yield) of VII hydrochloride, m. p. 175–176° (d).

Anal. Calcd. for $C_{10}H_{13}NO_2 \cdot HCl$: C, 55.68; H, 6.54. Found: C, 55.88, 55.77; H, 6.64, 6.61.

Reaction of 2-Chloro-1-nitropropane with Salicylaldehyde.—A solution of 1 mole of sodium ethoxide in 500 ml. of absolute ethanol was added to a cooled, stirred mixture of 122 g. of salicylaldehyde (1 mole) and 100 ml. of absolute ethanol. The stirred suspension was kept at 10° while 123.5 g. of 2-chloro-1-nitropropane (1 mole) was added dropwise during one hour. The yellow reaction mixture was stirred for five hours at 5–10° and then overnight at room temperature, filtered, and the filtrate evaporated under vacuum. The residual oil partially solidified on cooling. Filtration followed by washing with 500 ml. of 1:4 ethylene dichloride-petroleum ether (b. p. 90–100°) gave 65.0 g. of Solid A, m. p. 98–100°. The filtrate and washings were evaporated and distilled at 3 mm. The fraction of b. p. 135–145° was recrystallized from 75 ml. of methanol; yield 29.5 g. of yellow crystals, m. p. 72–75° Solid B, Crop 1.

Solid A was dissolved in 500 ml. of hot acetic acid, refluxed for thirty minutes, poured into 1500 ml. of water, filtered, and the solid recrystallized from 1 l. of 1:4 ethylene dichloride–petroleum ether (90–100°); yield, 22.4 g. (10.7%) of pure 2-methyl-3-nitro-4-chromanol (VIII), m. p. 135–137°.

Anal. Calcd. for $C_{10}H_{11}NO_4$: C, 57.44; H, 5.26; N, 6.70. Found: C, 57.57, 57.48; H, 5.37, 5.32; N, 6.79, 6.71.

The dilute acetic acid mother liquors were evaporated to 1 liter, cooled and filtered. The yellow residue was combined with the methanol filtrates from Solid B, Crop 1. Evaporation followed by rectification gave an orange oil, b. p. 120–123° (2 mm.). This material was crystallized from 50 ml. of methanol to give 38.0 g. of yellow crystals, m. p. 72–75°; Solid B, Crop 2; total yield 77.5 g. (35.2%). Pure 2-methyl-3-nitro-1,2-benzopyran (IX), m. p. 75.0–75.5°, was obtained by recrystallization from methanol.

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.85; H, 4.71; N, 7.33. Found: C, 62.63, 62.69; H, 4.79, 4.71; N, 7.48, 7.40.

2-Methyl-3-amino-4-chromanol (X).—A mixture of 18.2 g. of 2-methyl-3-nitro-4-chromanol (VIII), 200 ml. of absolute ethanol, and 5 g. of Raney nickel catalyst was hydrogenated under a pressure of 1400 lb. for seven hours at 40–50°. Recovery of the product and recrystallization from 475 ml. of benzene gave 7.5 g. of colorless needles, m. p. 155–159°. The benzene mother liquors were extracted with four 50-ml. portions of 5% hydrochloric acid. Addition of an excess of sodium hydroxide to this extract gave 4.2 g. of a tan solid, m. p. 146–156°. This material was recrystallized from benzene, combined with the first crop of crystals, and recrystallized again. A total of 9.9 g. (63.6% yield) of pure 2-methyl-3-amino-4-chromanol, m. p. 158–159°, was obtained. Which of the several possible racemic pairs this represents was not determined.

Addition of isopropyl ether to a solution of 2-methyl-3-amino-4-chromanol in methanolic hydrogen chloride precipitated the crystalline hydrochloride, m. p. 229–230°.

Anal. Calcd. for $C_{10}H_{13}NO_2 \cdot HCl$: N, 6.50. Found: N, 6.67, 6.71.

2-Methyl-3-aminochroman (XI).—A mixture of 19.1 g. (0.1 mole) of 2-methyl-3-nitro-1,2-benzopyran (IX), 6.0 g. of acetic acid (0.1 mole), 75 ml. of methanol, and 5 g. of Raney nickel catalyst was hydrogenated at 1400 lb. pressure, first at 40–50° then at 90–100°, filtered, treated with 9 ml. of concd. hydrochloric acid, and evaporated under vacuum. The residue was successively extracted with 125 ml. of water and 100 ml. of 5% hydrochloric acid. The extracts were made basic and extracted with benzene. The red benzene extracts were dried over potassium hydroxide and evaporated. Vacuum distillation of the dark residual oil gave 3.9 g. of a colorless liquid, b. p. 101–105° (4 mm.).

The crude hydrochloride of this product was recrystallized from isopropyl alcohol–isopropyl ether and then twice from purified nitromethane to obtain colorless needles, m. p. 216.0–217.5°.

Anal. Calcd. for $C_{10}H_{13}NO \cdot HCl$: N, 7.02. Found: N, 7.22, 7.28.

Summary

New syntheses of chroman derivatives based on the cyclizations of phenol–acrylonitrile addition products and salicylaldehyde–nitroölefin addition products have been investigated.

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