Anal. Calcd. for $C_{22}H_{20}O_5$: C, 72.53; H, 5.49. Found: C, 72.33; H, 5.75.

3-(α-Phenyl-β-acetylethyl)-4-hydroxycoumarin Benzoate.—To a solution of 10 g. of I in 40 ml. of dry pyridine was added 5.8 g. of benzoyl chloride at room temperature. Crystals formed immediately. After three hours the mixture was poured into 500 ml. of ice and water with stirring. The resulting solid was filtered and after four recrystallizations from acetone–water 4.4 g. of the desired product, m. p. 117–119°, was obtained.

Anal. Calcd. for $C_{26}H_{20}O_5$: C, 75.71; H, 4.89. Found: C, 75.41; H, 5.03.

The **p-nitrobenzoate** of I was prepared in a similar manner; yield 32%; m. p. 194–196°.

Anal. Calcd. for $C_{26}H_{19}O_7N$: C, 68.26; H, 4.19. Found: C, 68.05; H, 4.28.

Summary

1. Acetylation of the new anticoagulant rodenticide 3-(α-phenyl-β-acetylethyl)-4-hydroxycoumarin has yielded 3-(α-phenyl-β-acetylethyl)-4-hydroxycoumarin acetate, 2-methyl-2-acetoxy-4-phenyl-5-oxo-dihydropyrano(3,2-c)(1)benzopyran and 2-methyl-4-phenyl-5-oxo-γ-pyrano(3,2-c)(1)benzopyran.

2. The propionate, benzoate and *p*-nitrobenzoate esters have been prepared.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF MARYLAND]

Synthesis of Some Isoquinoline Derivatives Related to Podophyllotoxin

BY WILKINS REEVE AND WILLIAM M. EARECKSON, III[1]

A series of di- and tetrahydro-substituted isoquinolines, having certain of the structural features of podophyllotoxin, has been prepared in the hope some members might also possess the tumor-damaging properties of podophyllotoxin.

The amide (I) was prepared in 81% yield by treating homopiperonylamine with trimethoxybenzoyl chloride in benzene solution in the presence of calcium oxide. Under the usual Schotten–Baumann conditions, the amide is obtained in 65–70% yield. The cyclization of the amide to dihydroisoquinoline (II) was accomplished by the well-known Bischler–Napieralski reaction. Methylation of the dihydroisoquinoline (II) gave its methiodide (III), which on treatment with alkali was converted into a pseudo base. The structure assigned to this compound follows from the neutral character of the compound, its analysis, and the existence of a corresponding non-ionic cyanide (V) prepared from III by treatment with a sodium cyanide solution.

The tetrahydroisoquinoline (VI), prepared by the hydrogenation of II over Adams platinum oxide catalyst, could be methylated with methyl iodide to a mixture consisting of the hydroiodide of the starting material and VIII. However, the monomethyl derivative (VII) could be prepared in practically quantitative yield by the procedure of Clarke, *et al.*,[2] involving the refluxing of VI with formaldehyde and formic acid. Methylation of this with methyl iodide gave the pure quaternary salt (VIII).

The oxidation of all of the di- and tetrahydroisoquinoline compounds was studied in the hope a practical synthesis could be developed for 3′, 4′, 5′-trimethoxy-4,5-methylenedioxybenzophenone-2-carboxylic acid (IX), a compound which would be a valuable intermediate in the synthesis of podophyllotoxin. This compound has previously been obtained in small amounts by the oxidation of podophyllotoxin[3] and by the oxidation of a substituted phenyldihydronaphthalene.[4] Oxidation of the dihydroisoquinoline (II) with potassium permanganate in *t*-butyl alcohol–water mixture gave some of the keto acid (IX) but the main product was the completely aromatized isoquinoline (X). Oxidation of the latter gave negative results. The keto acid (IX) could also be obtained in small yield by the oxidation of compounds IV, VI and VII. Compound VIII was converted to the quaternary hydroxide which easily decomposed to an unsaturated compound. This, however, changed easily to a glassy product and oxidation was unsuccessful.

Experimental

All melting points are corrected. Analyses are by Mrs. Mary Aldridge and Mr. Byron Baer of this Laboratory.

N-(3,4,5-Trimethoxybenzoyl)-homopiperonylamine (I).—This was prepared by the method of Slotta and Haberland[5] by mixing 102 g. (0.616 mole) of homopiperonylamine[6] dissolved in 600 ml. of dry benzene with 142 g. (0.616 mole) of trimethylgalloyl chloride[7] also dissolved in 600 ml. of dry benzene. The thick pasty mass was stirred mechanically, and 55 g. of calcium oxide, ground to pass a 150-mesh sieve, was added over a 90-minute period. The temperature was maintained at 75–80°. The reaction mixture was filtered hot, the filtrate cooled, the amide (53 g., m. p. 133.5–135.5°) filtered off, and the filtrate concentrated to 100 ml. to yield another 18.5 g. of amide. The insoluble material from the reaction mixture was ex-

(1) du Pont Fellow in Chemistry, 1949–1950.

(2) H. T. Clarke, H. B. Gillespie and S. Z. Weishaus, THIS JOURNAL, **55**, 4576 (1933).

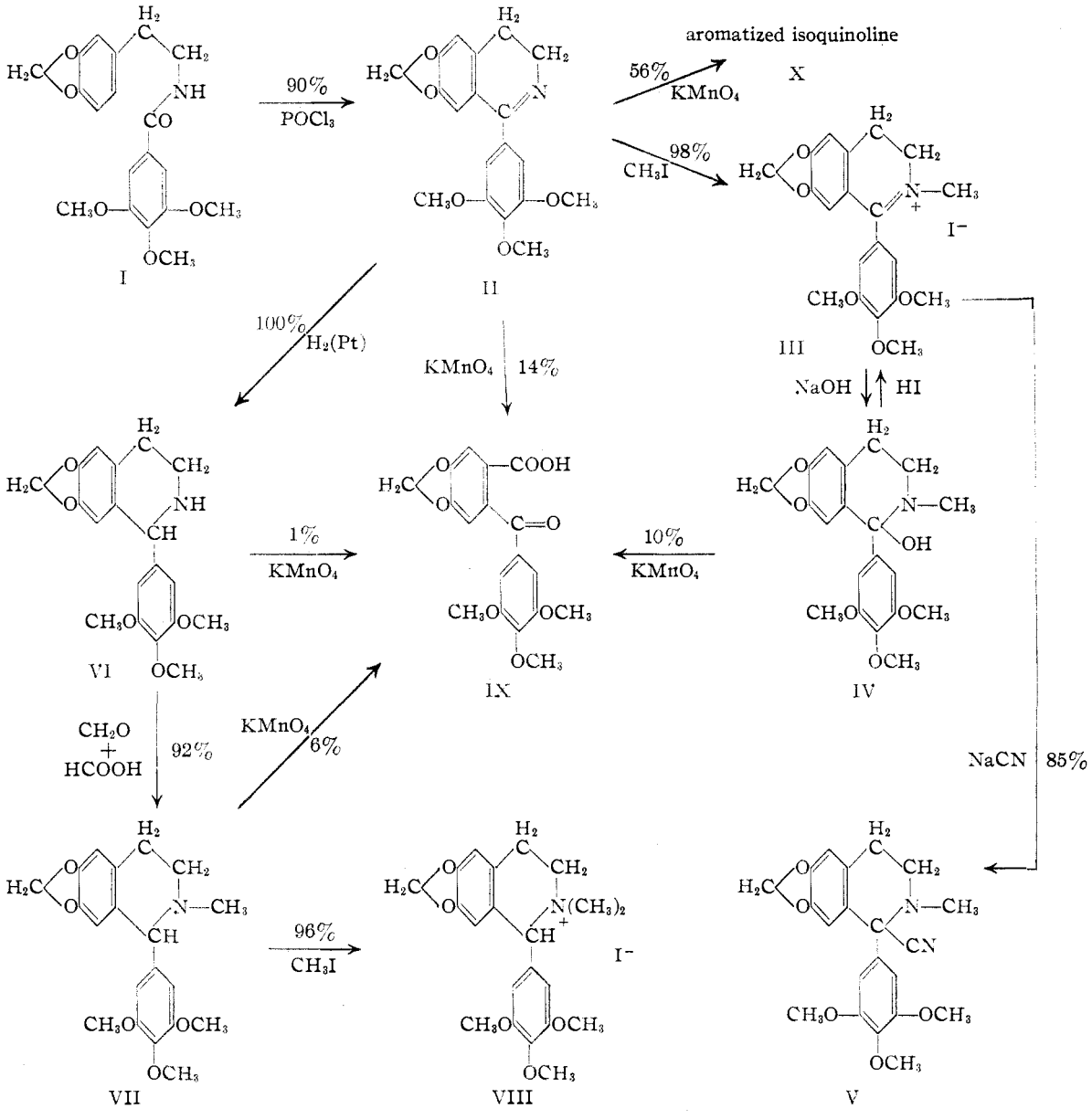
(3) E. Spath, F. Wessely and E. Nadler, *Ber.*, **66**, 125 (1933).

(4) R. D. Haworth and T. Richardson, *J. Chem. Soc.*, 348 (1936). The preparation of this keto acid has also been briefly described by W. J. Gensler and C. M. Samour in a Communication to the Editor (THIS JOURNAL, **72**, 3318 (1950), submitted May 27, 1950) in which they claim priority on the synthesis of this compound. They apparently were unaware of the successful synthesis of the keto acid and its methyl ester by R. D. Haworth and T. Richardson in 1936.

(5) K. H. Slotta and G. Haberland, *Angew. Chem.*, **46**, 766 (1933).

(6) W. Reeve and W. M. Eareckson, THIS JOURNAL, **72**, 3299 (1950).

(7) M. Asano and K. Yamaguti, *J. Pharm. Soc. Japan*, **60**, 105 (1940).



tracted with 1500 ml. of boiling 95% ethanol and filtered hot. On cooling the filtrate, 61.5 g. of amide was obtained, and on concentrating the mother liquors (final volume, 150 ml.), 43 g. more was separated. The total yield was 176 g., m. p. 130–135°, 80%. Two recrystallizations from 95% ethanol gave a pure white sample, m. p. 135.5–136°. *Anal.* Calcd. for $C_{19}H_{21}O_6N$: C, 63.50; H, 5.89; N, 3.90; OCH_3, 25.92. Found: C, 63.68; H, 5.97; N, 4.01; OCH_3, 25.86.

Shaking homopiperonylamine with trimethylgalloyl chloride in 15% sodium hydroxide according to the usual Schotten–Baumann conditions gave 65–70% yields of the amide.

1-(3,4,5-Trimethoxyphenyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline (II) was prepared by refluxing for three hours a mixture consisting of 180 g. (0.5 mole) of the amide (I) and 400 ml. (4.3 moles) of phosphorus oxychloride dissolved in 1000 ml. of dry toluene. The cooled reaction mixture was poured into 2 l. of petroleum ether (b. p. 60–80°), allowed to stand for 30 minutes, the petroleum ether decanted, and the gummy solid heated with 500 ml. of 95% ethanol. Most of the solid dissolved; on cooling, 169 g. (90%) of the hydrochloride of II was obtained as a bright yellow powder, m. p. 234–236° (dec.). Three grams more was obtained by concentrating the mother liquor and diluting it with ether.

The salt was converted to the free base by treatment with alkali, and recrystallized from ethanol–water. The white solid melted at 159.5–160°. *Anal.* Calcd. for $C_{19}H_{19}O_5N$: C, 66.83; H, 5.61; N, 4.10; OCH_3, 27.27. Found: C, 66.95; H, 5.75; N, 4.18; OCH_3, 27.01.

An analytical sample of the **hydrochloride** was prepared by treating an ether solution of the free base with dry hydrogen chloride. The bright yellow solid was recrystallized from ethanol–ether, m. p. 235.5–236° (dec.). *Anal.* Calcd. for $C_{19}H_{20}O_5NCl$: C, 60.41; H, 5.34; N, 3.71; OCH_3, 24.65. Found: C, 60.71; H, 5.49; N, 3.75; OCH_3, 24.68.

1-(3,4,5-Trimethoxyphenyl)-2-methyl-6,7-methylenedioxy-3,4-dihydroisoquinolinium iodide (III) was prepared by dissolving 21.7 g. (0.064 mole) of the above free base (II) and 15 g. (0.11 mole) methyl iodide in 500 ml. of

dry benzene and allowing to stand overnight. Twenty-six grams of a yellow precipitate was obtained. Another 4 g. was obtained by allowing the mother liquor to stand four days. The product melted at 222–223° (dec.); total yield 98%. *Anal.* Calcd. for $C_{20}H_{22}O_5NI$: C, 49.70; H, 4.59; N, 2.90; OCH_3, 19.26; I, 26.26. Found: C, 49.96; H, 4.81; N, 2.98; OCH_3, 19.28; I, 26.02.

Attempts to methylate II with dimethyl sulfate gave a less pure product.

Treatment of the methiodide (III), dissolved or suspended in water, with excess sodium hydroxide solution gave the **pseudo base** (IV), a white solid melting at 146–147° after recrystallizing from warm benzene. *Anal.* Calcd. for $C_{20}H_{23}O_5N$: C, 64.33; H, 6.21; OCH_3, 24.93. Found: C, 64.52; H, 6.53; OCH_3, 24.82. Attempts to treat the pseudo base with 2,4-dinitrophenylhydrazine, aniline and acetone to form the corresponding carbonyl derivatives were unsuccessful.

1-(3,4,5-Trimethoxyphenyl)-1-cyano-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (V) was prepared by treating 0.5 g. of III, dissolved in 50 ml. of water, with a water solution containing 2 g. of sodium cyanide. A white precipitate (0.4 g.) formed which melted at 133–133.5° after two recrystallizations from 60% ethanol. The pseudo cyanide is readily soluble in benzene. *Anal.* Calcd. for $C_{21}H_{22}O_5N_2$: C, 65.96; H, 5.80; N, 7.33; OCH_3, 24.35. Found: C, 66.15; H, 6.04; N, 7.50; OCH_3, 24.24.

1-(3,4,5-Trimethoxyphenyl)-6,7-methylenedioxy-1,2,-3,4-tetrahydroisoquinoline (VI) was prepared by hydrogenating 34.1 g. (0.1 mole) of II in 100 ml. of glacial acetic acid at room temperature and atmospheric pressure over Adams platinum oxide catalyst. Two hours were required for the yellow color of the solution to be discharged. The colorless solution was diluted with 600 ml. of water and neutralized with concd. ammonium hydroxide. A gummy mass (34.6 g., 100% yield) separated which solidified as the solution cooled. Two recrystallizations from ethanol gave fine white needles m. p. 97–98.5°. Passing dry hydrogen chloride into an ether solution of the base precipitated the **hydrochloride**, m. p. 242–242.5° (dec.). A sample for analysis was recrystallized from ethanol, and melted 0.5° higher. *Anal.* Calcd. for $C_{19}H_{22}O_5NCl$: C, 60.09; H, 5.84; N, 3.69; OCH_3, 24.51. Found: C, 60.09; H, 6.00; N, 3.44; OCH_3, 24.62.

The benzoyl derivative was prepared by the same procedure as used in the preparation of I except the benzene solution was washed with acid and base and evaporated to yield the crude benzoate. Three recrystallizations gave a white product, m. p. 124.5–125°. The yield was 70% after one recrystallization. *Anal.* Calcd. for $C_{26}H_{25}O_6N$: C, 69.78; H, 5.63; N, 3.13; OCH_3, 20.80. Found: C, 70.01; H, 5.70; N, 3.19; OCH_3, 20.81.

1-(3,4,5-Trimethoxyphenyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (VII) was prepared by treating 31.2 g. (0.091 mole) of VI with 53 ml. of 90% formic acid and 21 ml. of a 35% formaldehyde solution. The mixture was maintained at 50–60° for 12 hours while carbon dioxide bubbled off, and then refluxed for four hours. The solution was diluted with 600 ml. of water and neutralized with ammonium hydroxide. The light tan precipitate (29.9 g., 92%) was recrystallized from ethanol giving white needles, m. p. 133–134°. *Anal.* Calcd. for $C_{20}H_{23}O_5N$: C, 67.20; H, 6.49; N, 3.92; OCH_3, 26.04. Found: C, 67.20; H, 6.50; N, 4.14; OCH_3, 25.91.

The hydrochloride was prepared by passing dry hydrogen chloride into an ether solution of the free base, m. p. 240–241° (dec.) after two recrystallizations from ethanol. *Anal.* Calcd. for $C_{20}H_{24}O_5NCl$: C, 60.99; H, 6.14; N, 3.56; OCH_3, 23.63. Found: C, 60.94; H, 6.30; N, 3.84; OCH_3, 23.61.

1-(3,4,5-Trimethoxyphenyl)-2,2-dimethyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinolinium iodide (VIII) was prepared by dissolving 8.0 g. (0.0224 mole) of VII and 6.0 g. (0.042 mole) methyl iodide in 400 ml. dry benzene and allowing to stand 18 hr. A white solid (10.7 g., 96%) was obtained, m. p. 233–234° (dec.). Material recrystallized from ethanol had the same m. p. *Anal.* Calcd. for $C_{21}H_{26}O_5NI$: C, 50.50; H, 5.25; N, 2.80; OCH_3, 18.64. Found: C, 50.48; H, 5.23; N, 3.01; OCH_3, 18.70.

The quaternary hydroxide was prepared by treating a solution of the iodide with the equivalent amount of thallous hydroxide solution. The strongly basic solution changed to a neutral, highly unsaturated solution after standing a day. Evaporation of the solution yielded a clear, colorless, glass-like material. Oxidation with potassium permanganate solution gave little or none of the keto acid (IX).

3′,4′,5′-Trimethoxy-4,5-methylenedioxybenzophenone-2-carboxylic Acid (IX). **A. From II.**—Refluxing 6.2 g. of II with 11 g. of potassium permanganate in 300 ml. of 1:1 *t*-butyl alcohol–water solvent for 18 hr. yielded 3.5 g. of **1-(3,4,5-trimethoxyphenyl)-6,7-methylenedioxyisoquinoline** (X), m. p. 112–115°, and 1.1 g. of the crude keto acid (IX). *Anal.* for the isoquinoline **hydrochloride**, m. p. 252–253° (dec.). Calcd. for $C_{19}H_{18}O_5NCl$: C, 60.73; H, 4.83; N, 3.73; OCH_3, 24.78. Found: C, 60.94; H, 5.07; N, 3.89; OCH_3, 24.74. After two recrystallizations from aqueous methanol, 0.9 g. of the keto acid (IX) was obtained, m. p. 215–216°. Reported m. p. 214–216°.[3,4] *Anal.* Calcd. for $C_{18}H_{16}O_8$: C, 60.00; H, 4.48; OCH_3, 25.84. Found: C, 60.24; H, 4.78; OCH_3, 25.78.

Repetition of the above, but at room temperature, gave an increased yield of the isoquinoline and none of the keto acid. The use of chromic acid in acetic acid, lead tetraacetate in acetic acid, and nitric acid with vanadium pentoxide as oxidizing agents was unsuccessful.

B. From IV.—Four grams of the pseudo base (IV) was refluxed with 8 g. of potassium permanganate in 1:1 *t*-butyl alcohol–water solution for 18 hr. The yield of recrystallized keto acid was 0.4 g., m. p. 214–216°.

C. From VI.—Three grams of VI on refluxing with potassium permanganate solution as described in part A gave a few milligrams of the keto acid and 1 g. of the dihydroisoquinoline (II). A similar oxidation of the benzoyl derivative was unsuccessful.

D. From VII.—Oxidation as in part A, but at room temperature, gave 0.36 g. of crude keto acid from 5.5 g. of VII.

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Summary

The preparation of 1-(3,4,5-trimethoxyphenyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline (II) and of a series of methylated and hydrogenated derivatives is described. 3′,4′,5′-Trimethoxy-4,5-methylenedioxybenzophenone-2-carboxylic acid (IX) has been prepared by the oxidation of several of these products.

COLLEGE PARK, MD. RECEIVED MAY 22, 1950