[Contribution from the Chemistry Department of the University of Missouri]

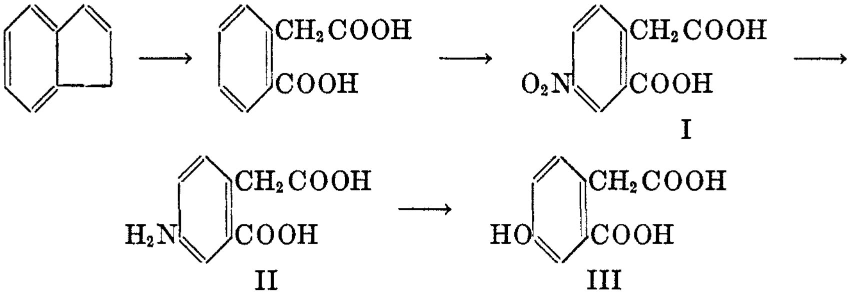
THE SYNTHESIS OF 7-METHOXY-1-ISOQUINOLONE[1]

HERBERT E. UNGNADE, DOROTHY V. NIGHTINGALE, and
HERBERT E. FRENCH

Received July 25, 1945

The synthesis of a series of compounds required 7-methoxy-1-isoquinolone for an intermediate. Its synthesis from indene is described in the following.

Indene was converted to 4-hydroxyhomophthalic acid through the following steps:



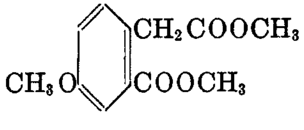
I

II

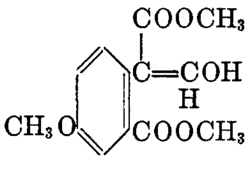
III

4-Nitrohomophthalic acid (I) (1) gave an average yield of 74% of the amino acid (II) when reduced with Raney nickel in methanol, at room temperature. Occasional runs, however, gave low yields without apparent reason. The hydroxy acid (III) was obtained in good yield by hydrolysis of the diazonium salt of (II). Its conversion to methyl 4-methoxyhomophthalate (IV) was accomplished either directly by methylating the hydroxy acid (III) with dimethyl sulfate or by way of 4-methoxyhomophthalic acid (V). The direct methylation and esterification (in one step) with dimethyl sulfate produced a good yield of (IV) in small runs, whereas larger amounts were best prepared by isolation of the methoxy acid (V) and subsequent esterification.

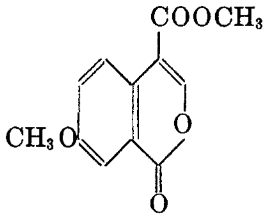
The hydroxymethylene ester (VI) resulted when methyl 4-methoxyhomophthalate (IV) was condensed with methyl formate according to the procedure of Diekmann and Meiser (2). Ring closure to the isocoumarin (VII) was readily effected by heating the ester (VI).



IV



VI

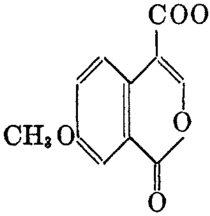


VII

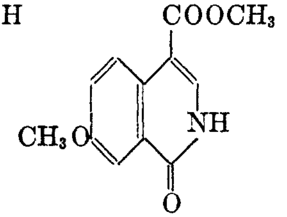
---

[1] The work described in this paper was done under a Contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Missouri.

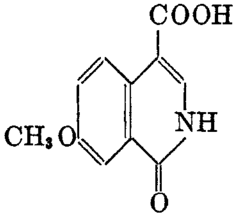
Methyl 7-methoxyisocoumarin-4-carboxylate (VII) was hydrolyzed to the corresponding acid (VIII) by refluxing with a mixture of hydrochloric acid and acetic acid. Either (VI) or (VII) reacted with concentrated aqueous ammonia in the cold or more rapidly on warming to give the isoquinolone ester (IX).



VIII



IX



X

When the isocoumarin acid (VIII) was heated with ammonia it gave a good yield of 7-methoxyisoquinolone (XI) instead of the expected acid (X). The isoquinolone acid (X) could be prepared by acid hydrolysis of the corresponding methyl ester (IX). Since this acid could not be decarboxylated by heating with ammonia it cannot be an intermediate in the formation of 7-methoxyisoquinolone (XI).

EXPERIMENTAL[2]

4-Nitrohomophthalic acid (I). The best yields of 4-nitrohomophthalic acid were obtained by nitration of homophthalic acid with fuming nitric acid (3). Homophthalic acid (150 g.), prepared according to Whitmore and Cooney (1) was added in small amounts with stirring to 480 cc. of fuming nitric acid (*d* 1.5) contained in an ice-bath at such a rate that the temperature did not rise above 22°. After standing one and one-half hours at room temperature, 480 g. of crushed ice was added with stirring at such a rate that the temperature did not exceed 25°. The precipitate was filtered with suction, washed thoroughly with water, and air dried. The yield was 60%, m.p. 222–225° (dec.).

4-Aminohomophthalic acid (II). The nitro acid (40 g.) was dissolved in 200 cc.of methanol and reduced with 15 g. of Raney nickel at room temperature under an initial pressure of 1800 lbs. The reaction mixture containing the crystalline amino acid was filtered. The amino acid was separated from the nickel by repeated extractions with boiling water. It crystallized on cooling. The filtrate was concentrated until no further amino acid separated on standing for several days. The compound did not melt below 300°, yield 74–86%.

Anal. Calc'd for $C_9H_9NO_4$: C, 55.38; H, 4.61.
Found:[3] C, 55.30; H, 4.89.

4-Hydroxyhomophthalic acid (III). The amino acid (100 g.) was dissolved in a hot solution of 100 cc. of concentrated sulfuric acid and 150 cc. of water. When solution was complete 460 cc. of water was added and the mixture cooled to 0°. A solution of 36 g. of sodium nitrite in 84 cc. of water was added through a dropping-funnel at such a rate that the temperature did not rise above 5°.

The cold diazonium solution was added slowly to a vigorously boiling solution of 300 cc. of concentrated sulfuric acid and 250 cc. of water. After the reaction was complete the solution was cooled in ice-water. The precipitated hydroxy acid was filtered with suction, transferred to a beaker, and washed with 300 cc. of water in order to remove adhering sul-

---

[2] Analyses by Lois May, Columbia University, Margaret Ledyard and Winifred Cameron, Northwestern University Microanalytical Laboratory.

[3] Corrected for a small amount of ash.

furic acid. The dry acid weighed 83.5 g. (83%). It melted at 214–215° (dec.) after crystallization from 87% formic acid but could not be obtained analytically pure.

4-Methoxyhomophthalic acid (*V*). 4-Hydroxyhomophthalic acid (93 g., 0.5 mole) was dissolved in 600 cc. of 10% aqueous sodium hydroxide (1.5 moles). To this solution was added with stirring 189 g. (150 cc., 1.5 moles) of dimethyl sulfate, and the mixture allowed to stand overnight. Solid material dissolved upon addition of 50 cc. of 10% sodium hydroxide solution (with stirring). Another portion of dimethyl sulfate (50 cc.) was added which caused more solid to separate. Excess sodium hydroxide (1500 cc. of 10% solution) was then added and the mixture refluxed for seven hours. After cooling, the mixture was carefully acidified with concentrated sulfuric acid. A crystalline precipitate separated immediately and was filtered with suction. The product was washed with 100 cc. of water and dried, yield 75.5 g. After crystallizing from water the acid melted at 185–186°.

Anal. Calc'd for $C_{10}H_{10}O_6$: C, 57.14; H, 4.76.
Found: C, 57.20; H, 5.11.

Methyl 4-methoxyhomophthalate (*IV*). 4-Hydroxyhomophthalic acid (14 g., 0.07 mole) was dissolved in a solution of 8.4 g. (0.21 mole) of sodium hydroxide in 28 cc. of water. To the cooled solution was added 27 g. (0.21 mole) of dimethyl sulfate. After the exothermic reaction had subsided, the mixture was diluted with 50 cc. of water and brought to boiling. The product was extracted with ether, and the ether solution washed with sodium bicarbonate and water, dried over magnesium sulfate, and distilled. The residual oil (7 g., 41%) was sublimed from a molecular still at 110° (1×10^{-6} mm.). The distillate solidified on standing, m.p. 53–54°.

Anal. Calc'd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.88.
Found: C, 60.69; H, 6.06.

Ethyl 4-methoxyhomophthalate. Esterification of 4-methoxyhomophthalic acid (26 g., 0.12 mole) with 44 cc. of absolute ethyl alcohol, 90 cc. of benzene, and 16 g. of concentrated sulfuric acid gave 15 g. (45%) of ester and 11.0 g. of solid material soluble in carbonate solution (m.p. 95–97°). The ester was distilled from a molecular still at 110° (1×10^{-6} mm.). It did not solidify.

Anal. Calc'd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.76.
Found: C, 63.15; H, 7.07.

Methyl 7-methox yisocoumarin-4-carboxylate (*VII*). Methyl 4-methoxyhomophthalate (22 g.) and methyl formate (8 g.) were added to 2.3 g. of sodium wire in 100 cc. of dry ether. The reaction mixture was allowed to stand for twenty-nine hours at room temperature. The mixture was decomposed with water, the aqueous layer washed with ether and acidified with hydrochloric acid. The ether extract of this solution gave 8 g. of a viscous oil, the hydroxymethylene ester (VI). When heated on a water-bath it was isomerized to the isocoumarin ester which melted at 124–125° after crystallization from methyl alcohol.

Anal. Calc'd for $C_{12}H_{10}O_5$: C, 61.53; H, 4.26.
Found: C, 61.67; H, 4.56.

7-Methoxyisocoumarin-4-carboxylic acid (*VIII*). The above methyl ester (1.3 g.) was refluxed for two hours with a mixture of 30 cc. of concentrated hydrochloric acid and 20 cc. of acetic acid. A solid separated on cooling. It was crystallized from acetic acid, m.p. 254.5–255°, yield 0.56 g.

Anal. Calc'd for $C_{11}H_8O_5$: C, 60.00; H, 3.63.
Found: C, 60.24; H, 3.86.

Methyl 7-methoxy-1-isoquinolone-4-carboxylate (*IX*). Methyl 7-methoxyisocoumarin-4-carboxylate (8 g.) was stirred with 300 cc. of concentrated ammonia, warmed, and allowed to stand overnight. The insoluble product was filtered with suction and dried, yield 2 g. After crystallizing from methyl alcohol the ester melted at 223–223.5°.

Anal. Calc'd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.76.
Found: C, 61.51; H, 4.32.

7-Methoxy-1-isoquinolone-4-carboxylic acid (*X*). A mixture of methyl 7-methoxyisoquinolone-4-carboxylate (0.6 g.), hydrochloric acid (15 cc.), and acetic acid (10 cc.) was refluxed for one-half hour. An insoluble precipitate separated during this period. It was filtered, washed, and dried at 100°, yield, 0.43 g., m.p. 345° (dec.). The acid crystallized poorly from acetic acid, a little better after addition of water.

Anal. Calc'd for $C_{11}H_9NO_4$: C, 60.27; H, 4.11; N, 6.39.
Found: C, 60.41; H, 4.35; N, 6.45.

7-Methoxy-1-isoquinolone (XI). 7-Methoxyisocoumarin-4-carboxylic acid (0.28 g.) was refluxed for one hour with 15 cc. of concentrated ammonia, and the mixture allowed to stand overnight. The insoluble precipitate of isoquinolone was filtered and dried, yield 0.15 g., m.p. 206.5–207.5°. After crystallization from benzene it melted at 207–207.5°.

Anal. Calc'd for $C_{10}H_9NO_2$: C, 68.56; H, 5.14; N, 8.00.
Found: C, 68.49; H, 5.16; N, 7.92.

The filtrate gave a trace of the acid (X) upon acidification with hydrochloric acid.

Acknowledgment. The authors wish to thank the University Research Council, University of Missouri, for a grant for the purchase of equipment used in this investigation.

SUMMARY

7-Methoxyisoquinolone has been prepared from homophthalic acid in eight steps.

COLUMBIA, MO.

REFERENCES

(1) WHITMORE AND COONEY, *J. Am. Chem. Soc.*, **66**, 1239 (1944).
(2) DIEKMANN AND MEISER, *Ber.*, **41**, 3253 (1908).
(3) INGOLD AND PIGGOTT, *J. Chem. Soc.*, **123**, 1497 (1923).