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Reisert Compound Studies. VII. The Synthesis of Calycotomine (1)

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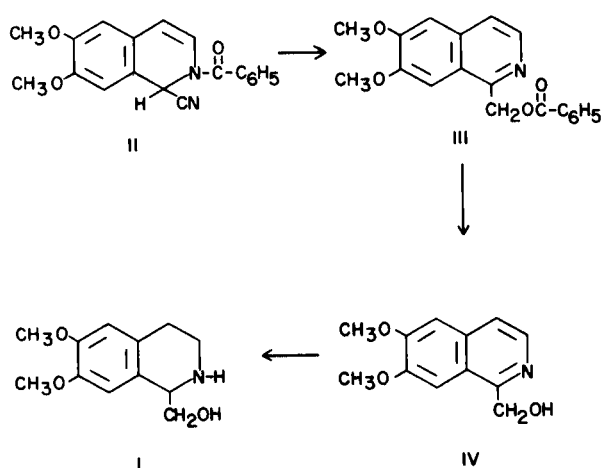
The alkaloid calycotomine has been synthesized in 44% overall yield by use of the Reisert compound of 6,7-dimethoxyisoquinoline.

The alkaloid calycotomine (I) has been isolated from several plants (3,4) in both the optically active and *d,l*-forms. Several syntheses of the racemic alkaloid have been reported (5-8).

In view of the ability of Reisert compounds to condense with aldehydes (9,10) and the previous utilization of these intermediates for alkaloid syntheses (11,12), it appeared likely that calycotomine could be easily synthesized by a similar method employing 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinolalidonitrile (II) as the key intermediate.

The requisite starting material, 6,7-dimethoxyisoquinoline, was synthesized both by the Pomeranz-Fritsch cyclization of veratrylidene aminoacetal using a modification of a previously reported procedure (11) and by the Bischler-Napieralski cyclization of β -(3,4-dimethoxyphenyl)ethylamine followed by dehydrogenation as reported earlier (11). The Reisert compound II was prepared from 6,7-dimethoxyisoquinoline, benzoyl chloride and potassium cyanide by the methylene chloride method (13). The yield of usable material (76%) was a vast improvement over the 31% previously reported using the aqueous method (11).

The lithium salt of II, prepared by treatment of II with phenyllithium, was treated at -50° with gaseous formaldehyde (14). The desired product, 1-(6,7-dimethoxyisoquinolyl)carbinyl benzoate (III), was isolated in 77% yield as its hydrochloride. Hydrolysis of III in aqueous ethanolic potassium hydroxide yielded 1-(6,7-dimethoxyisoquinolyl)carbinol (IV) in 94% yield.



Catalytic reduction of the hydrochloride salt of IV in ethanol-water resulted in a near quantitative yield of calycotomine I. The overall yield of calycotomine by this six step sequence is 44% as compared to 20% (5), 18% (6), 5% (7), and 8% (8) in previous syntheses. In each case β -(3,4-dimethoxyphenyl)ethylamine was the starting material. Thus, the synthesis of calycotomine via the Reisert compound II provides the most attractive route to this alkaloid and illustrates the general synthetic utility of this interesting class of compounds.

EXPERIMENTAL (16)

6,7-Dimethoxy-3,4-dihydroisoquinoline.

This compound was prepared in 97% yield from β -(3,4-dimethoxyphenyl)ethylamine by the method of Popp and McEwen (11).

6,7-Dimethoxyisoquinoline.

(a) This compound was prepared in 82% yield by dehydrogenation of the 3,4-dihydro compounds as reported (11). (b) Aminoacetal and veratraldehyde gave veratrylideneaminoacetal in quantitative yield by the method of Forsyth *et al.* (17). To a mixture of 225 g. of polyphosphoric acid and 2 ml. of phosphorus oxychloride maintained at $23-27^\circ$ was added with stirring 29.0 g. (0.103 mole) of the acetal over a period of 1.5 hrs. Then 5 ml. of additional phosphorus oxychloride was added and the mixture stirred 2.5 hrs. at $23-27^\circ$. After pouring on ice, filtering, washing with 25 ml. of ether, making the mixture basic with sodium hydroxide, extraction with chloroform and removal of the chloroform a dark residue remained. Extraction of this residue with ether gave 13.1 g. (67%) of 6,7-dimethoxyisoquinoline. Picrate, m.p. $221-223^\circ$.

2-Benzoyl-6,7-dimethoxy-1,2-dihydroisoquinolalidonitrile (II).

Using the method of Popp and Blount (13) 4.55 g. (0.024 mole) of crude 6,7-dimethoxyisoquinoline and 4.70 g. (0.072 mole) of potassium cyanide in 50 ml. of methylene chloride and 12 ml. of water were treated with 5.6 ml. (0.048 mole) of benzoyl chloride to give a 76% yield of II, m.p. $159-162^\circ$.

1-(6,7-Dimethoxyisoquinolyl)carbinyl Benzoate (III).

To a solution of 12.0 g. (0.0375 mole) of crude II in 400 ml. of dioxane and 160 ml. of anhydrous ether at -50° was added, under a nitrogen atmosphere, an ethereal solution of phenyl lithium from 4.0 ml. (0.0382 mole) of bromobenzene. To the resultant deep burgundy solution maintained at -45 to -50° was added gaseous formaldehyde prepared by heating a stirred solution of paraformaldehyde in mineral oil at about 160° . The formaldehyde was passed through the solution on a stream of nitrogen for about 15 min. The resultant yellow suspension was stirred for 1 hr. at -20° under a nitrogen atmosphere and allowed to rise to ambient temperature over 5 hrs. The mixture was diluted with ether, washed with water and extracted with 10% hydrochloric acid (5 x 25 ml.). On cooling these extracts 6.55 g. of 1-(6,7-dimethoxyisoquinolyl)carbinyl benzoate hydrochloride hydrate was obtained. Recrystallization from ethanol-ethyl acetate gave a solid, m.p. $182.5-184^\circ$.

Anal. Calcd. for $C_{19}H_{17}NO_4 \cdot HCl \cdot H_2O$: C, 60.40; H, 5.34; N, 3.71; Cl, 9.39. Found: C, 60.78; H, 5.31; N, 3.47; Cl, 9.46.

Treatment of the hydrochloride hydrate with warm 5% sodium hydroxide gave III, m.p. $125-127^\circ$ (from ethanol-water).

Anal. Calcd. for $C_{19}H_{17}NO_4$: C, 70.57; H, 5.30; N, 4.33. Found: C, 70.39; H, 5.34; N, 4.18.

The ether solution from the original reaction mixture gave on evaporation 4.80 g. of unreacted II. The yield of III based on unrecovered starting material was thus 77%.

1-(6,7-Dimethoxyisoquinolyl)carbinol (IV).

A solution of 5.80 g. (0.0153 mole) of 1-(6,7-dimethoxyisoquinolyl)-carbinyl benzoate hydrochloride hydrate and 5.5 g. of potassium hydroxide in 85 ml. of ethanol and 14 ml. of water was refluxed for 13 hrs. After removal of most of the ethanol the mixture was diluted with water, cooled, and extracted with chloroform. Concentration of the dried chloroform extract gave 3.15 g. (94%) of solid, m.p. 130°. Recrystallization from benzene-hexane and then carbon tetrachloride-hexane gave fluffly needles, m.p. 132-134°.

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.74; H, 5.88; N, 6.24.

Treatment of IV with alcoholic picric acid gave the picrate, m.p. 189.5-191.5° (from ethanol).

Anal. Calcd. for $C_{18}H_{19}N_4O_{10}$: C, 48.22; H, 3.60; N, 12.50. Found: C, 48.38; H, 3.61; N, 12.30.

When an aqueous ethanolic solution of the free base was treated with the calculated amount of concentrated hydrochloric acid and taken to dryness, the salt was isolated, m.p. 194.8-195.1° (from ethanol-benzene).

Anal. Calcd. for $C_{12}H_{13}NO_3 \cdot HCl \cdot 1.5 H_2O$: C, 50.97; H, 6.06; N, 4.96; Cl, 12.54. Found: C, 50.96; H, 5.87; N, 5.08; Cl, 12.82.

After drying over phosphorus pentoxide at 140° *in vacuo* the hydrochloride had a melting point of 219.5-220°.

Anal. Calcd. for $C_{12}H_{13}NO_3 \cdot HCl$: C, 56.36; H, 5.52; N, 5.48. Found: C, 56.28; H, 5.51; N, 5.40.

Calycotomine (I).

A mixture of 0.85 g. (0.0003 mole) of 1-(6,7-dimethoxyisoquinolyl)-carbinol hydrochloride hydrate, 0.2 g. of platinum oxide, 150 ml. of ethanol and 40 ml. of water was subjected to an initial hydrogen pressure of 50.0 p.s.i.g. at about 45° for 20 hrs. During this time the theoretical amount of hydrogen was absorbed. After filtration, concentration of the solution gave 0.78 g. (100%) of solid, m.p. 135-137° (from benzene). Reported, m.p. 139-141 (3), 135-136 (5), 132-134 (6), 134-135 (7), and 134° (8).

The picrate was prepared from ethanolic picric acid, m.p. 201-202° (from ethanol). Reported, m.p. 203-204° (7).

Anal. Calcd. for $C_{18}H_{20}N_4O_{10}$: C, 47.79; H, 4.46; N, 12.39. Found: C, 47.68; H, 4.39; N, 12.21.

The hydrochloride was prepared, m.p. 196.7-198° (from benzene-methanol). Reported, m.p. 195-196° (7,8). This hydrochloride did not depress the melting point of an authentic sample of *dl*-calycotomine hydrochloride (18) and had an identical infrared spectra with the sample.

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Received November 28, 1964

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