Synthesis of Calycotomine and Its Analogs[1]

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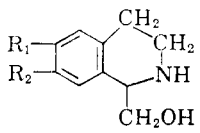
An attempt by White[2] to synthesize (±)-calycotomine (I), an isoquinoline alkaloid of *Calycotome* species (Fam. *Leguminosae*) from homoveratrylamine and glycolic aldehyde, under "Phytochemical conditions" met with failure. The present authors have reinvestigated the matter and eventually effected the syntheses of calycotomine (I) and its analogs—*viz.*, 6,7-demethylcalycotomine (Ib) and 3-carboxy-6,7-demethylcalycotomine.



(I). $R_1 = R_2 = -OCH_3$
(Ia). $R_1 = OH$; $R_2 = -OCH_3$
(Ib). $R_1 = R_2 = -OH$

A survey of the literature[3] on phytochemical synthesis of isoquinoline derivatives has revealed that strong activation of the benzene ring at the point of ring closure in β-phenylethylamines is necessary. Hence, homoisovanillylamine was chosen instead of homoveratrylamine as the starting material for the synthesis of (±)-calycotomine.

Homoisovanillylamine hydrochloride[4] was condensed (*p*H, 4.5–5.0) with glycolic aldehyde at 30° according to the method of Beke[5] *et al.* to afford 6-demethylcalycotomine (Ia) (yield, 65–70%). The latter on methylation with diazomethane furnished the desired base (racemic; over-all yield, 45–50%).

6,7-Demethylcalycotomine hydrochloride[6] (Ib) was prepared by the condensation of 3,4-dihydroxy-β-phenylethylamine hydrochloride (obtained by demethylating homoveratrylamine with concentrated hydrochloric acid) with glycolic aldehyde.

6,7-Demethyl-3-carboxy-calycotomine was prepared from DOPA hydrochloride, m.p. 246°, and glycolic aldehyde in a similar way. Attempts to remove carboxyl from this compound by enzymes at room temperature to prepare 6,7-demethylcalycotomine failed, although smooth decarboxylation of the compound proceeded at elevated temperature. Further studies on decarboxylation of this analog under mild conditions are being continued.

Both homopiperonylamine hydrochloride (the free base being prepared by reducing 3,4-methylenedioxy-β-nitrostyrene with lithium aluminum hydride) and homoveratrylamine hydrochloride failed to react with glycolic aldehyde to produce the desired isoquinoline derivatives.

EXPERIMENTAL[7]

3-Hydroxy-4-methoxyphenylethylamine.[4] Homoveratrylamine (22.0 g., 0.35 mole) was added in a thin stream to liquid ammonia (300 ml.) in which sodium (8.73 g., 1.14 mole) has been dissolved. The resulting mixture was allowed to stand for 6 hr. until it reached room temperature (30°). The mixture was then decomposed by cautious addition of ice chips. It was then extracted with ether (2 × 50 ml.) to remove unchanged homoveratrylamine, and the aqueous phase was aerated to remove excess of ammonia. The solution was made acidic with acetic acid while cooling. After ether extraction, the acid layer was treated with excess sodium bicarbonate and the amine thus released was extracted with *n*-butyl alcohol (3 × 100 ml.). The butyl alcohol extract (150 ml.), dried over anhydrous sodium sulfate, was treated with ethereal hydrochloric acid gas. The crystalline hydrochloride (18.0 g.) thus formed was recrystallized from a mixture of absolute alcohol and dry ether in shining needles, m.p. 203–204°.

Anal. Calcd. for $C_9H_{14}NO_2Cl$: N, 6.88. Found: N, 6.37.

Condensation of 3-hydroxy-4-methoxyphenylethylamine hydrochloride with glycolic aldehyde. A solution of homoisovanillylamine hydrochloride (0.9 g.) and glycolic aldehyde (0.4 g.) in water (10 ml.) was adjusted to *p*H 4.5–5.0 and allowed to stand at 30° for 3 days. The reaction product was then made basic with sodium carbonate and extracted with chloroform. The chloroform extract (4 × 20 ml.) of the base was worked up in the usual way and upon concentration it deposited 6-demethylcalycotomine (Ia). On repeated crystallizations from the same solvent, colorless rods (0.6 g., 65% yield), m.p. 198–200° dec. were obtained.

Anal. Calcd. for $C_{11}H_{15}NO_3$: C, 63.16; H, 7.18; N, 6.69; $-OCH_3$, 14.83. Found: C, 62.89; H, 6.89; N, 6 71; $-OCH_3$, 14.59.

dl-Calycotomine. 6-Demethylcalycotomine (0.6 g.) dissolved in dry ether (50 ml.) was added slowly to dry ethereal diazomethane liberated from nitrosomethylurea (4 g.) and allowed to stand at 25–26° for overnight. The solvent was then removed *in vacuo* and the residue (0.5 g.) was dissolved in hydrochloric acid (*4N*, 20 ml.) and extracted with ether (3 × 25 ml.). The acidic aqueous solution was basified with aqueous sodium hydroxide (10%, 45 ml.) and extracted with chloroform (3 × 50 ml.). The latter was worked up as above (*vide supra*) and was evaporated to dryness *in vacuo*. The residue (0.3 g.) was subsequently crystallized in colorless matted needles, m.p. 134° (yield, 45–50%) from a mixture of ethyl acetate and petroleum ether (b.p. 40–60°) in the proportion (1:1). The latter did not depress the melting point of an authentic sample of *dl*-calycotomine λ_{max}^{alc} 240 (log ε, 3.48) and 290 mμ (log ε, 3.66).

Anal. Calcd. for $C_{12}H_{17}NO_3$: C, 64.57; H, 7.62; N, 6.28; $-OCH_3$, 27.80. Found: C, 64.39; H, 7.38; N, 6.28; $-OCH_3$, 28.01.

Calycotomine hydrochloride. Dry ethereal hydrogen chloride (10 ml.) was added to calycotomine (0.2 g.) dissolved in

(1) For preliminary communications describing this work see A. Chatterjee and N. Adityachaudhury, *Sci. & Cult.*, **25**, 389 (1959); *Naturwiss.*, **47**, 207 (1960).

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(7) Melting points are uncorrected. Microanalyses were carried out by W. Manser, E. T. H., Zürich.

dry ether (10 ml.) in the cold, the hydrochloride of the base (0.15 g.) separated immediately. The latter was crystallized from a mixture of absolute alcohol and dry ether in colorless rods, m.p. 195–196°. Synthetic calycotomine hydrochloride caused no depression in melting point on admixture with an authentic sample of (±)-calycotomine hydrochloride, and their infrared spectra (Nujol) were found to be identical and superimposable.

Anal. Calcd. for $C_{12}H_{18}NO_3Cl$: C, 55.49; H, 6.93; N, 5.40; —OCH_3, 23.89. Found: C, 55.72; H, 7.12; N, 5.51; —OCH_3, 24.01.

3,4-Dihydroxy-β-phenylethylamine hydrochloride. Homoveratrylamine (5.0 g.) was heated with concentrated hydrochloric acid (8 ml.) in a sealed tube at 160–170° for 8 hr. when complete demethylation occurred. After cooling in an ice bath, the whole solution solidified. The base hydrochloride (4.0 g.) thus obtained was crystallized from acetone containing a little water in fine silky needles, m.p. 241° (yield, 80%).

Anal. Calcd. for $C_8H_{12}O_2NCl$: N, 7.38. Found: N, 7.45.

Synthesis of 6,7-demethylcalycotomine. 3,4-Dihydroxy-β-phenylethylamine hydrochloride (1.0 g.) and glycolic aldehyde (0.6 g.) dissolved in water (10 ml.) were adjusted to *p*H 3–4 and kept for 3 days at 25–26°. The mixture was concentrated *in vacuo* and the crystals (0.85 g.) which separated were crystallized from a mixture of alcohol and acetone (1:1) in shining colorless needles, m.p. 208–209° dec. (yield, 70–75%). It showed λ_{max}^{alc} in the ultraviolet region at 288 mμ (log ε, 3.57).

Anal. Calcd. for $C_{10}H_{13}NO_3$, HCl: C, 51.83; H, 6.05; N, 6.05. Found: C, 51.77; H, 6.01; N, 6.03.

Synthesis of 3-carboxy-6,7-demethylcalycotomine. DOPA hydrochloride was prepared by adding dry ethereal hydrogen chloride (10 ml.) to DOPA (0.2 g.) dissolved in ether. It crystallized from dry methanol in plates, m.p. 246° dec. (yield, 0.18 g.). An aqueous solution (5 ml.) of DOPA hydrochloride (0.15 g.) was condensed with glycolic aldehyde (0.08 g.) at *p*H 4–5 and allowed to stand at 25–26° for 3 days. On concentrating the solution, 3-carboxydemethylcalycotomine crystallized in fine needles (yield, 0.1 g.) which were insoluble in alcohol, acetone, chloroform, ethyl acetate, and benzene. The compound crystallized from water, m.p. 281–282° dec. 3-Carboxydemethylcalycotomine showed λ_{max}^{alc} in the ulraviolet region at 280 mμ (log ε, 3.54).

Anal. Calcd. for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.44; N, 5.85. Found: C, 55.01; H, 5.43; N, 5.82.

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Synthesis of 8-Halogenoflavones[1]

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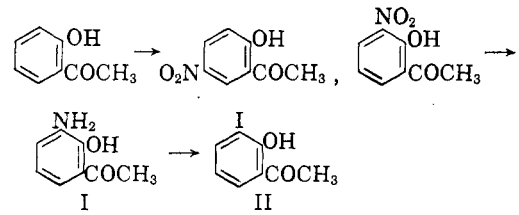
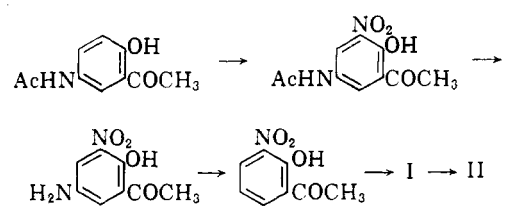
No work on 8-halogenoflavones and related compounds except on 8-chloroflavone,[4] 8-bromo-5,7-dimethoxy-, and 5,7,4′-trimethoxyflavone,[5] has previously been reported. In continuing the studies of 6-[6] and 7-halogenoflavones,[7] 8-bromoflavone was prepared in good yield applying the procedure of Ruhemann. 8-Fluoro- and 8-iodoflavone, -flavanone, -flavonol, and the 4′-methoxy compounds, including the corresponding chalcones, were prepared by the usual way,[6,7] starting from 3-fluoro- and 3-iodo-2-hydroxyacetophenone, respectively.

3-Fluoro-2-hydroxyacetophenone was prepared by the Fries rearrangement of *o*-fluorophenyl acetate. Attempts to synthesize 2-hydroxy-3-iodo-, bromo-, and chloroacetophenone by this method were unsuccessful,[8] producing 2,4-diiodophenol[9] or 3-halogeno-4-hydroxyacetophenone[8] and nearly none of the expected product. The synthesis of 2-hydroxy-3-iodoacetophenone was accomplished by two routes: (a) nitration of *o*-hydroxyacetophenone as described in previous papers on the synthesis of 6-halogenoflavones,[6,10]



and (b) nitration of 5-acetamino-2-hydroxyacetophenone,[11] followed by diazotization and reduction[12] as shown in the accompanying equation.



3-Fluoro- and 3-iodo-2-hydroxyacetophenone were condensed smoothly with benzaldehyde or anis-

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