5-Hydroxy-6-benzylaminoethyl-4,7-dimethylcoumarin. This substance was obtained in 85% yield by hydrolysis of 5,6-(3′ - benzyl - 4′ - dihydro) - *m* - oxazino - 4,7 - dimethylcoumarin. Since it was sparingly soluble in most solvents, it was purified by repeated washings with ethanol, m.p. 152°.

Anal. Calcd. for $C_{19}H_{20}NO_3Cl$: N, 4.0. Found: N, 3.7.

The free base was recrystallized from aqueous methanol, m.p. 138–140°.

Anal. Calcd. for $C_{19}H_{19}NO_3$: N, 4.5. Found: N, 4.3.

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A Synthesis of (±)-Isocorydine

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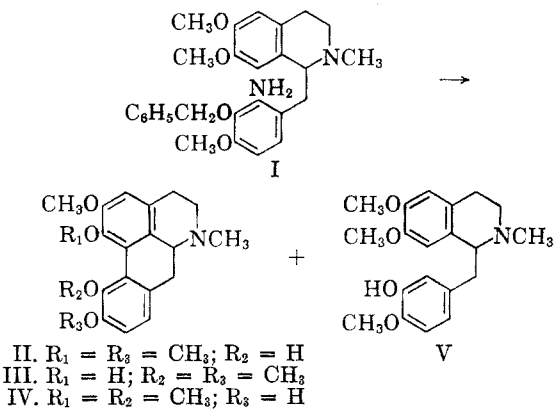
By keeping the diazonium salts of certain substituted 2′-aminobenzyl-*N*-methyltetrahydroisoquinolines in solution for a certain time and then adding catalytic copper and heating, Hey and co-workers[1] used successfully the Pschorr reaction for the synthesis of phenolic aporphine alkaloids. Difficulties were encountered by Hey and Palluel[1b] in a tentative synthesis of (±)-isocorydine (II); they could only isolate the hydrochloride of a base different from the desired alkaloid.

The successful synthesis by the same method of the closely related alkaloid (±)-corydine (III)[1b] and of 3-hydroxy-4,5,6-trimethoxyaporphine (pseudocorydine) (IV),[2] a base that has not been found in nature, induced us to reinvestigate the synthesis of (±)-isocorydine (II) by this method.

While this work was in progress, Kikkawa[3] published a synthesis of (±)-isocorydine in which the acid solution of the diazonium salt, after standing, was boiled without addition of copper, for a short time.

We found that (±)-isocorydine (II) is formed and can be isolated under the same conditions employed for the synthesis of (±)-corydine (III)[1b] and (±)-pseudocorydine (IV).[2] The yield is very poor (0.82% as hydrochloride) for the picrolonate of the benzyloxy-*N*-methylisoquinoline base (I). The benzylisoquinoline alkaloid, (±)-laudanidine (V), is produced in larger amounts (2.3% yield), and two other contaminating bases were also present. Separation



II. $R_1 = R_3 = CH_3$; $R_2 = H$
III. $R_1 = H$; $R_2 = R_3 = CH_3$
IV. $R_1 = R_2 = CH_3$; $R_3 = H$

of the four bases could only be effected by column chromatography.

The method employed by Kikkawa[3] gave a larger yield of the (±)-isocorydine (II) than of (±)-laudanidine (V) and also a third basic substance.

A similar increase in yield of the aporphine base (±)-corydine when changing from copper decomposition to simple heating has been described by Amurugan, Govindachari, Nagarajan, and Rao.[4]

EXPERIMENTAL

Melting points are not corrected. Descending paper chromatography on Whatman No. 1 was employed. Mobile phase was the upper layer of a mixture of methyl isobutyl ketone with a sodium acetate–acetic acid buffer of *p*H 5.6 (1:1). Dragendorff reagent was used for developing the alkaloidal spots.

3-Benzyloxy-4-methoxy-2-nitrophenylacetic acid. To 10 g. of 3-hydroxy-4-methoxy-2-nitrophenylacetic acid, dissolved in 10 ml. of ethanol-water (1:1), 50 ml. of benzyl chloride was added and refluxed for 3.5 hr. with good agitation. After boiling, 150 ml. of water was added and the mixture distilled with steam until all the unchanged benzyl chloride was eliminated. The crude benzyl ester of the acid remained in the flask as a heavy oil, and was hydrolyzed by boiling for 30 min. with 200 ml. of water and 160 ml. of 5*N* sodium hydroxide. By acidification the free acid precipitated in crystalline condition. After good cooling, 11.5 g. (82%) of pale yellow needles were collected, m.p. 140–145°. Recrystallized several times from ethanol, it melted 145–146°.

Anal. Calcd. for $C_{16}H_{15}NO_6$: C, 60.56; H, 4.77; N, 4.42. Found: C, 60.42; H, 4.55; N, 4.60.

3′-Benzyloxy-4′-methoxy-2′-nitrophenyl-N-2-(3,4-dimethoxyphenyl)ethyl-acetamide. This compound was prepared by condensing in the usual way[2]—the chloride of the former acid with 3,4-dimethoxyphenylethylamine. The chloride was prepared by reaction with thionyl chloride and employed without further purification. Long, almost white needles, m.p. 108–109°, were obtained.

Anal.: Calcd. for $C_{26}H_{28}N_2O_7$: C, 64.99; H, 5.87; N, 5.83. Found: C, 64.55; H, 5.65; N, 5.41.

Hey and Palluel[1b] gave a m.p. 45–46° for this compound, containing one mole of water. Recrystallization of the high-melting amide from 80% methanol gave a product, m.p. 48–50°.

Pschorr reaction with 1-(2′-amino-3′-benzyloxy-4′-methoxybenzyl)-N-methyl-6,7-dimethoxytetrahydroisoquinoline (I). The picrolonate of this isoquinoline was prepared from the former amide according to Hey and Palluel.[1b] One gram of the picrolonate was suspended in 5 ml. of methanol, and 5 ml.

(1) (a) D. H. Hey and L. C. Lobo, *J. Chem. Soc.*, 2246 (1954); (b) D. H. Hey and A. L. Palluel, *J. Chem. Soc.*, 2926 (1957).

(2) B. Frydman, R. Bendisch, J. Comín, and V. Deulofeu, *J. Org. Chem.*, **25**, 100 (1960).

(3) I. Kikkawa, *J. Pharm. Soc.*, **78**, 1006 (1958); *Chem. Abstr.*, **53**, 3260 (1959).

(4) N. Amurugan, T. R. Govindachari, K. Nagarajan, and U. R. Rao, *Chem. Ber.*, **91**, 40 (1958).

of methanol containing 1 ml. of concd. sulfuric acid was added with good agitation to avoid any rise of temperature. The insoluble picrolonic acid was filtered. The methanolic solution of the base was cooled to 0°, and 150 mg. of sodium nitrite, dissolved in 10 ml. of methanol, was slowly added. After leaving overnight at 5°, 300 mg. of catalytic copper powder were added when a fast evolution of nitrogen took place. After 1 hr. the suspension was boiled for 30 min., the copper filtered, one volume of water added, and the acidic solution extracted with ether, the extract being discarded. It was then made alkaline with concd. ammonia and extracted again with ether until a negative Mayer reaction was obtained.

The ether extract containing the basic substances was evaporated, and the well dried residue (355 mg.) was dissolved in the minimum amount of benzene and submitted to chromatography on a column of 23 g. of alumina (Woelm, grade III). The elution was carried out with benzene containing increasing amounts of ethanol. With benzene–0.2% ethanol, the initial fractions eluted contained a substance giving a positive alkaloid reaction, with R_f 0.59 and a green fluorescence in the ultraviolet. In the medium fractions another basic product with R_f 0.32 and violet fluorescence was detected, and in the last fractions, a substance also with R_f 0.32 but with a pale blue fluorescence was present. By increasing the concentration of ethanol to 0.4% and then to 1%, elution of the same substances went on, until another one with R_f 0.07 and green fluorescence appeared in the last collected fractions.

Only the fractions containing the products with R_f 0.32 and a violet fluorescence and with R_f 0.07 were worked, as a preliminary hydrolysis with acid showed on paper chromatography that they were related to (±)-isocorydine and (±)-laudanidine.

(±)-*Isocorydine hydrochloride.* Evaporation of the fractions containing the product with R_f 0.32 with violet fluorescence yielded 13 mg. of a crude product, that was boiled for 40 min. with 1 ml. of 20% hydrochloric acid. After cooling, the solution was extracted with ethyl ether, made basic with ammonia, and extracted again with ether. The ether extract gave on evaporation an oily residue of 7.5 mg. Seventy-five milligrams of this crude residue, obtained from several preparations totaling 10 g. of the picrolonate, was dissolved in benzene and chromatographed employing a column of 8 g. of alumina. After washing the column with benzene, it was eluted with benzene–0.1% ethanol. All fractions containing the substance giving R_f 0.32 and violet fluorescence were united and evaporated. The dried residue (35 mg.) was dissolved in absolute ether and hydrogen chloride passed through the solution. A white solid precipitated, that was centrifuged, dried, dissolved in warm absolute ethanol, and ether added to turbidity. By staying at 0° overnight, crystals were formed that were collected had a m.p. 211–212° (35 mg.).

Recrystallization from absolute ethanol–ether, gave small prisms, m.p. 211–212° (Vacuum) λ_{max} 220 mμ (log ε 4.65); 267 mμ (4.18); 303 mμ (3.81). The ultraviolet spectrum and the usual color reactions were identical to those obtained with (−)-isocorydine hydrochloride, m.p. 215–218°.

Anal. Calcd. for $C_{20}H_{23}NO_4 \cdot HCl$: C, 63.57; H, 6.40; N, 3.71; Cl, 9.39. Found: C, 63.69; H, 6.46; N, 3.61; Cl, 9.67.

(±)-*Isocorydine* (II). A solution of 30 mg. of the former hydrochloride in 2 ml. of water was made alkaline with sodium hydrogen carbonate solution and extracted with ether, until the Mayer reaction was negative. The ethereal extract was well dried, and the ether evaporated off. The oily residue crystallized when a small amount of absolute ether was added. After recrystallization from acetone–absolute ether, a m.p. of 150–152° was obtained; λ_{max} 267 mμ (log ε 4.10), 302 mμ (3.58) (Ethanol) [identical with the ultraviolet spectrum of a sample of natural (±)-isocorydine]. The infrared spectra in chloroform were also identical except for a shoulder at 8.25 μ in the spectrum of the racemic compound. The m.p. of (±)-isocorydine is in agreement with that given by Kikkawa (m.p. 151–152°). Go[5] gave a m.p. 185° for a (±)-isocorydine that he prepared by racemization of the natural base.

(±) *Laudanidine* (*Laudanine*) (V). The fractions containing the substance with R_f 0.07 were united and evaporated giving 130 mg. of an oily residue that was boiled for 40 min. with 10 ml. of 20% hydrochloric acid. The acidic solution was extracted with ether, made alkaline with ammonia, and exhaustively extracted with ether. This ethereal solution was evaporated and the residue (51 mg.) dissolved in 0.5 methanol. By staying at 5° (±)-laudanidine crystallized; that recrystallized from methanol gave 7 mg. of prisms m.p. 164–165°, λ_{max} 284 mμ (log ε 3.78) giving no depression in m.p. with an authentic sample of (±)-laudanidine (m.p. 163–164°).

When the eluted fractions containing the substance with R_f 0.07 from several preparations representing in total 10 g. of picrolonate were worked as described, 90 mg. of (±)-laudanidine, m.p. 163–165°, were obtained.

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Reactions of 1-Diazo-3-(*o*-nitrophenyl)-acetone[1]

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The reaction of *o*-nitro-ω-diazoacetophenone (I) with glacial acetic acid involves ring closure, with formation of *N*-hydroxyisatin (IV).[2] There appears to be no direct evidence for the mechanism of this interesting transformation, but it seems likely that the initial stage is cyclization to a six-membered intermediate (II) which is followed by deprotonation and cleavage to *o*-nitrosophenylglyoxal (III) and finally recyclization to IV. With this possible path in mind the similar treatment of 1-diazo-3-(*o*-nitrophenyl)acetone (V) with acetic acid was examined to see whether a corresponding ring closure to 1,3-dihydroxycarbostyril (VI) would occur, presumably *via* a seven-membered intermediate.

The diazo ketone was prepared in the usual way from *o*-nitrophenylacetyl chloride. This acid chlo-

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