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CLEAVAGE STUDIES ON PHTHALIDEISOQUINOLINES

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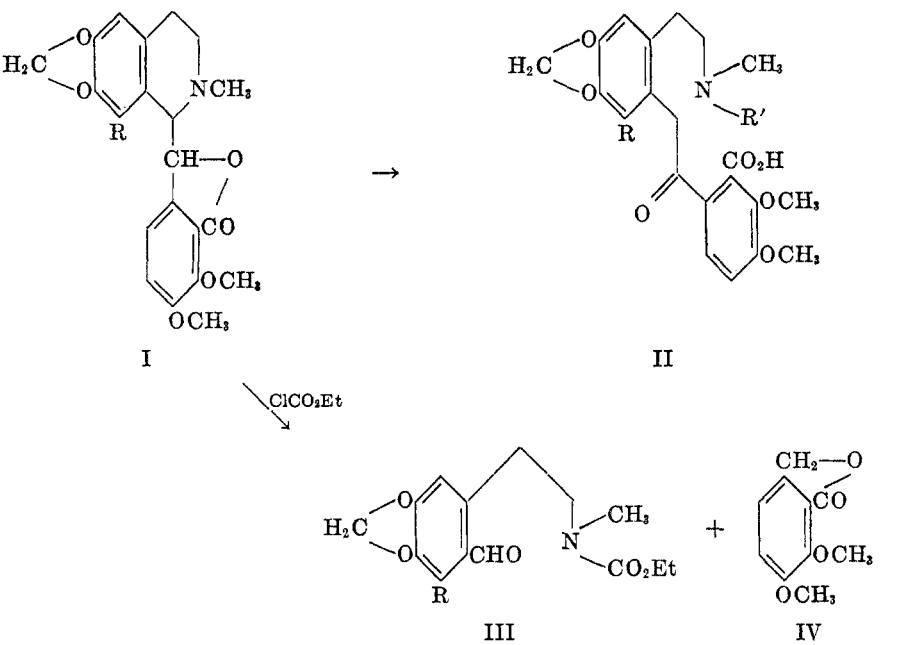
The conversion of phthalideisoquinoline alkaloids to the nornarceine-type of compound (II, R′ = H) has been accomplished by several methods (1, 2) which are relatively inefficient. Since analogs of nornarceine (II, R = OCH_3, R′ = H) were required as intermediates in this laboratory, a study of preparative methods was undertaken. Cleavage of narcotine (I, R = OCH_3) by dilute acetic acid (1) afforded only 10% of nornarceine. Application of this reaction to (+)-corlumine yielded the unchanged alkaloid along with a minute quantity of crystalline material melting at 181–186° which was insufficient for further investigation.



Attempts to prepare N-benzoylnornarceine (3) (II, R = OCH_3, R′ = COC_6H_5) by the action of benzoyl chloride on narcotine invariably yielded unchanged starting material. The analytical data and melting point reported (3) correspond as well to narcotine as to the product claimed. Dr. Major has kindly repeated his experiments and confirmed the observation that narcotine is not cleaved by benzoyl chloride (4). Benzoyl bromide, 3,5-dinitrobenzoyl chloride, anisoyl chloride, and acetic anhydride also failed to affect narcotine, hydrastine, and

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(+)-corlumine. However, nitro-(±)-corlumine (5) was cleaved by benzoyl chloride, as indicated by the isolation of 4-nitro-6,7-methylenedioxyphthalide.

Cleavage of phthalideisoquinolines was effected by ethyl chloroformate, but in an undesired fashion. The action of ethyl chloroformate upon hydrastine (I, R = H) under Schotten-Baumann conditions (6) afforded meconin (IV) and N-carbethoxyhydrastinine (III, R = H). Similarly, meconin (IV) and N-carbethoxycotarnine (III, R = OCH_3) were formed from narcotine (I, R = OCH_3). N-Carbethoxycotarnine was also prepared from cotarnine chloride by the action of ethyl chloroformate. The reaction failed with (+)-corlumine. 2,4-Dinitrophenylhydrazones of the N-carbethoxy derivatives were prepared and characterized. The urethans were resistant to hydrolysis by aqueous-methanolic sodium hydroxide.

A single application of the cyanogen bromide reaction (7) to the cleavage of narcotine failed to yield isolable products.

Narcotine benzylchloride and benzyliodide were prepared and subjected to Hofmann degradation under various conditions. The action of methanolic potassium hydroxide on narcotine benzyliodide yielded a white, crystalline solid, m.p. 207–210° dec., which possessed the properties and analytical composition to be expected of N-benzylnornarceine dihydrate (II, R = OCH_3, R′ = $CH_2C_6H_5$). Its infrared spectrum agrees with the structure decided upon. The principal spectral bands corresponded to a carboxylic acid (5.81 and 3.72 microns), a ketone (5.95 microns), an amino acid (4.33 microns), and a phenyl group (6.1–6.4 microns). Several attempts to debenzylate the compound catalytically (palladium-charcoal, three atmospheres of hydrogen, room temperature, in ethanol, and in acetic acid containing perchloric acid) were unsuccessful.

It has been reported (8) that tertiary amino acids of suitable configuration can be converted to lactams by the action of thionyl chloride with concomitant loss of alkyl halide. Application of this reaction to narceine employing thionyl chloride, oxalyl chloride, and phosphorus pentachloride failed to yield well-defined products exclusive of starting material.

The usual method of converting narcotine to narceine (9) failed when applied to (+)-corlumine.

EXPERIMENTAL[3]

N-Carbethoxyhydrastinine (III, R = H). A solution of 5 g. of hydrastine in 100 ml. of chloroform was stirred during the addition of 2.6 g. of ethyl chloroformate and a solution of 1.44 g. of sodium hydroxide in 10 ml. of water. Two similar treatments of the chloroform solution with ethyl chloroformate and sodium hydroxide solution followed at one-hour intervals. After another hour, the chloroform layer was washed with 20% hydrochloric acid, dried, and concentrated to yield a yellow oil which would not crystallize. Distillation at 145° (bath)/1 μ yielded a solid which melted at 101° after decolorization and recrystallization three times from dilute methanol. This compound was shown to be meconin (IV) [melting point (10) and mixture melting point]. N-Carbethoxyhydrastinine was obtained as impure crystals, m.p. 72–74°, which were converted to the *2,4-dinitrophenylhydrazone*, deep-red crystals, m.p. 218–219°, after recrystallization from ethyl acetate.

[3] Microanalyses by Galbraith Laboratories, Knoxville, Tennessee. Melting points were obtained on a calibrated apparatus.

Anal. Calc'd for $C_{20}H_{21}N_5O_3$: C, 52.28; H, 4.61; N, 15.25.
Found: C, 52.17; H, 4.55; N, 15.32.

N-Carbethoxycotarnine (III, R = OCH_3). In a similar fashion narcotine afforded meconin and N-carbethoxycotarnine. The latter crystallized from dilute methanol in long white needles, m.p. 104°. Its structure was corroborated by the infrared spectrum.

Anal. Calc'd for $C_{15}H_{19}NO_6$: C, 58.24; H, 6.19; N, 4.53.
Found: C, 58.35, 58.32; H, 6.47, 6.33; N, 4.70, 4.52.

The *2,4-dinitrophenylhydrazone* crystallized from ethyl acetate in clusters of long, orange-red needles, which melted at 185–187°, resolidified, and melted again at 200–201°.

Anal. Calc'd for $C_{21}H_{23}N_5O_9$: C, 51.53; H, 4.74; N, 14.31.
Found: C, 51.41; H, 4.72; N, 14.23.

Cotarnine chloride (1 g.) was converted by the action of sodium hydroxide to cotarnine which melted at 122–123° dec. after recrystallization from benzene. The cotarnine was dissolved in chloroform and treated with ethyl chloroformate under conditions already described. The N-carbethoxycotarnine thus formed was recrystallized from dilute methanol and melted at 103.5–104°, either alone or in admixture with the sample prepared from narcotine. The 2,4-dinitrophenylhydrazones were also identical.

Narcotine benzyliodide. To 3 g. of narcotine dissolved in hot dry acetone was added 1.65 g. of benzyl iodide (11), and the solution was heated to boiling and allowed to cool for one hour. The yellow needles (4.06 g., 89%) were recrystallized from absolute ethanol and melted at 154–156°. The formation of the quaternary salt proceeded less efficiently in benzene.

Anal. Calc'd for $C_{29}H_{30}INO_7$: C, 55.16; H, 4.79; N, 2.22.
Found: C, 55.12; H, 4.80; N. 2.21.

N-Benzylnornarceine (II, R = OCH_3, R′ = $CH_2C_6H_5$). Narcotine benzyliodide (3 g.), 10 ml. of methanol, and 12 ml. of 25% methanolic potassium hydroxide were refluxed for 90 minutes, most of the methanol was removed by distillation, and 12 ml. of water was added to the mixture. After cooling, the solution was neutralized with acetic acid and extracted with chloroform. Concentration of the chloroform yielded a tan solid which after decolorization and recrystallization from dilute methanol was obtained as white needles, m.p. 207–210° dec. In a large scale preparation a 72% yield was obtained.

Anal. Calc'd for $C_{29}H_{31}NO_8 \cdot 2H_2O$: C, 62.47; H, 6.33; N, 2.51.
Found: C, 62.13; H, 6.19; N, 2.56.

SUMMARY

1. Phthalideisoquinolines are cleaved by ethyl chloroformate, forming a phthalide and the N-carbethoxy derivative of the pseudobase corresponding to the isoquinoline portion of the original molecule.

2. The reported formation of benzoylnornarceine from narcotine has been found to be in error.

3. Hofmann degradation of narcotine benzyliodide yielded N-benzylnornarceine in excellent yield. The product could not be debenzylated with palladium-charcoal in absolute ethanol.

4. Corlumine could not be cleaved by ethyl chloroformate or Hofmann degradation.

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