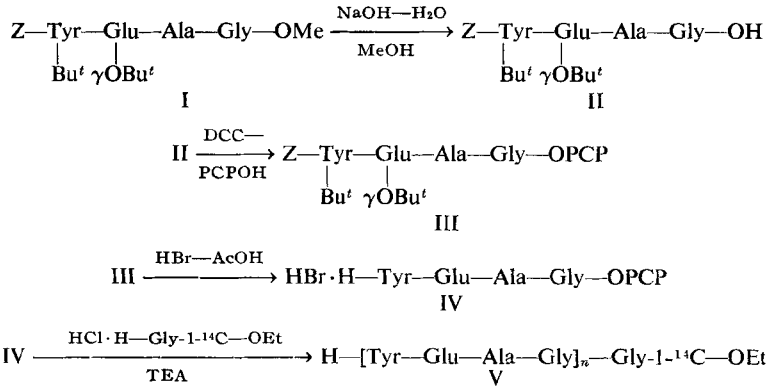

where DCC = dicyclohexylcarbodiimide, PCP = pentachlorophenyl, and TEA = triethylamine

Scheme I

Treatment of III with anhydrous hydrogen bromide in glacial acetic acid removed the *N*-carbobenzoxy and the *tert*-butyl protecting groups to yield the polymerizing unit, L-tyrosyl-L-glutamyl-L-alanylglycine pentachlorophenyl ester hydrobromide (IV), m.p. 180°, $[\alpha]_D^{28}$ − 3.3° (c 1.83 in dimethylformamide).

Anal.—Calcd. for $C_{25}H_{26}BrCl_5N_4O_8$: C, 39.1; H, 3.4; N, 7.3 Found: C, 39.1; H, 3.6; N, 7.6.

The polymerization of IV was conducted under dilute conditions in the presence of a preformed monomer glycine-1-^{14}C ethyl ester hydrochloride. This established polymerizing procedure has been shown to yield linear high molecular weight polypeptides (3–6) when the side groups are protected. In this case, the polymerizing unit (IV), dissolved in dimethyl sulfoxide, was added dropwise to a solution of glycine-1-^{14}C ethyl ester hydrochloride containing the total amount (3.5 equivalents) of triethylamine such that the final concentration of reactants was never more than 70 mmole/l. The polymerization was allowed to proceed for a week, after which the mixture was acidified and dialyzed extensively for 3 days. The precipitated polypeptide, poly-(L-tyrosyl-L-glutamyl-L-alanylglycyl)glycine-1-^{14}C ethyl ester (V), was collected by centrifugation, converted to its sodium salt, and dialyzed extensively for a week to remove all low molecular weight materials. This dialyzed polymer was lyophilized, converted to the free acid form by acidification, and again dialyzed to remove all traces of salt. Radioactive assay indicated 85% incorporation of the starting preformed monomer.

Anal.—Calcd. for $C_{19}H_{24}N_4O_7 \cdot \frac{1}{2}\ H_2O$: C, 53.15; H, 5.85; N, 13.05. Found: C, 52.8; H, 5.9; N, 13.0.

Filtration of the polymer through a calibrated column (7) of synthetic polysaccharide[1] (2.5 × 45 cm.), using a solution of 0.1 *M* NaCl–0.05 *M* $NaHCO_3$ buffer as eluent, indicated a molecular weight of at least 1 × 10^5.

To evaluate this method of preparing polypeptides with one that uses conventional protecting groups (3–6), a comparison was made of this polypeptide with that prepared using the *tert*-butyl ester for carboxyl protection (3). It was found that both polymers eluted from a column of the polysaccharide (2.5 × 45 cm.) in the same fractionation pattern, using a 0.1 *M* NaCl–0.05 *M* $NaHCO_3$ buffer as eluent. The two polymers were considered to be structurally identical since both materials were similarly antigenic in rabbits; each polypeptide crossreacted with the antibodies produced by the other, giving the same precipitin curve which was similar to that previously reported (8). From this evidence it was concluded that this method of carboxyl protection is compatible with the synthesis of linear high molecular weight polypeptides.

[1] Sephadex G-100.

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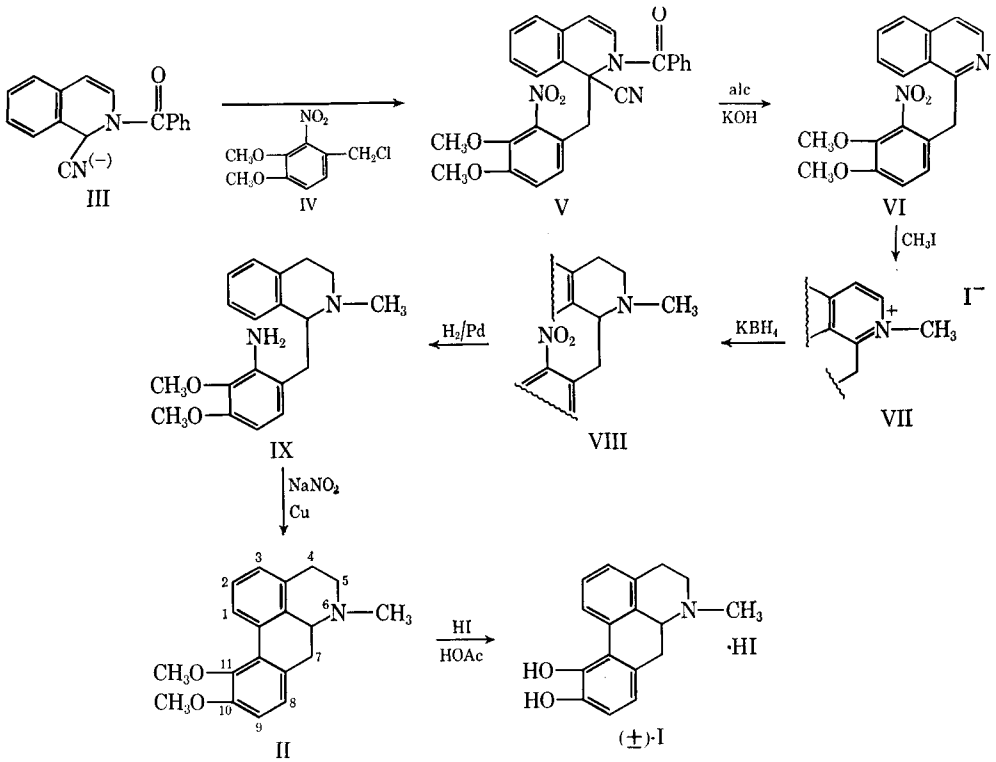
Aporphines V: Total Synthesis of (±)-Apomorphine

Keyphrases □ (±)-Apomorphine—total synthesis □ IR spectrophotometry—structure □ UV spectrophotometry—structure

Sir:

(−)-Apomorphine [(−)-I], the semisynthetic alkaloid obtained by vigorous treatment of morphine with strong mineral acids, has found medicinal application



Scheme I

as a powerful, centrally acting emetic and has been included in the official drug compendia of the United States (1) and is regulated by Federal Narcotic Laws (2). Apomorphine exerts a direct stimulating action on the vomiting center in the brain and thus initiates emesis (3). The biochemical mechanism of its action is not yet clearly understood.

The finding that subcutaneous administration of apomorphine to patients with selected neurologic disorders temporarily changed the neurologic manifestations in the same direction as with the administration of oral L-dopa has stimulated renewed interest in these catecholaminelike compounds (4).

We wish to report the first total synthesis of (±)-apomorphine [(±)-I] and to describe a versatile pathway with potential for the elaboration of structurally similar alkaloids. Although (±)-apomorphine has not been synthesized previously, the preparation of (±)-apomorphine dimethyl ether [(±)-II] has been the subject of considerable interest and was first successfully carried out by Späth and Hromatka (5) and subsequently by Hey and Palluel (6) and Sugasawa and Tachikawa (7). Their general methods were based on a Bischler–Napieralski cyclization of an *o*-nitrophenyl-*N*-phenylethylacetamide to a 3,4-dihydroisoquinoline derivative, which was subsequently transformed *via* the Pschorr procedure to apomorphine dimethyl ether. Several workers have found this sequence impracticable, since the Bischler–Napieralski cyclization is generally unsatisfactory (8) when the amide used lacks an activating substituent on the aromatic ring of the *N*-phenylethyl moiety. Our scheme (Scheme I) was based on the alkylation of the Reissert anion (III) with 2-nitro-3,4-dimethoxybenzyl chloride (IV) (9). A variety of 1-alkylisoquinolines has been prepared by this method (10). The standard procedure (11), in which phenyllithium is used to generate the anion in ether at −20°, gave a 35% yield of V, m.p. 208–209°, IR (KBr): $\nu_{max.}$ 2245 cm.$^{-1}$ (w), 1675 (s), 1640 (s), 1530 (s), 1375 (m); $\lambda_{max.}^{MeOH}$: 282 mμ (ε, 6100), 297 (ε, 6300), 316 (ε, 6100).

Anal.—Calcd. for $C_{26}H_{21}N_3O_5$: C, 68.56; H, 4.65; N, 9.23. Found: C, 68.57, H, 4.73, N, 9.22.

A procedure for the generation of the anion III employing sodium hydride in *N*,*N*-dimethylformamide at room temperature has recently been reported (12). Applying this modification to the synthesis of aporphines (13, 14), we obtained excellent yields of the desired isoquinoline (VI) without the isolation of V. The crude product (V) was hydrolyzed to furnish a 90% yield of VI (from III), m.p. 129–130°; $\lambda_{max.}^{MeOH}$: 261 mμ (ε, 6800), 272 (ε, 7200), 281 (ε, 5900), 308 (ε, 4400), 322 (ε, 5200).

Anal.—Calcd. for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.48; H, 4.88; N, 8.56,.

Treatment of the base VI with methyl iodide gave the ammonium salt, m.p. 190–193°, in a quantitative yield (15). The methiodide VII was reduced with potassium borohydride to the tetrahydroisoquinoline VIII, m.p. 97–98.5°, in 80% yield (15). Reduction of the nitro compound VIII with palladium-on-charcoal and hydrogen gave 1-(2-amino-3,4-dimethoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (IX), m.p. 85–87.5°, in 80% yield; $\lambda_{max.}^{MeOH}$: 212 mμ (ε, 39,000), 265 (ε, 11,000), 272 (ε, 1400), 285 (ε, 1600). This compound was previously reported as a brown oil (5–7). It furnished a dipicrolonate, m.p. 191–192°, which did not depress the melting point of an authentic sample of the dipicrolonate, m.p. 189–190° (6). The amine IX was converted to (±)-apomorphine dimethyl ether [(±)-II] by modifications of procedures of Späth and Hromatka (5), copper powder being used as the coupling agent for the diazonium salt. (±)-II was isolated as an oil in 41%

yield after column chromatography. TLC (silica gel, chloroform) of this product showed only one component, and the R_f was identical with that of a sample of (−)-II prepared in 74% yield from (−)-I hydrochloride and diazomethane. The oily (±)-II was converted into a crystalline picrate, m.p. 187–189° dec., and a crystalline perchlorate, m.p. 263° dec.

The two preparations of apomorphine dimethyl ether [(−)-II and (±)-II] showed identical IR (film), UV, and NMR spectra; $\lambda_{max.}^{MeOH}$: 216 mμ (ε, 47,000), 269 (ε, 19,000), 306 s (ε, 2300); NMR ($CDCl_3$): 2.57 (3H, singlet), 2.66–3.37 (7H, multiplet), 3.73 (3H, singlet), 3.91 (3H, singlet), 6.91–7.18 (4H, multiplet), 8.28 (1H, doublet, J = 2 c.p.s.). (±)-Apomorphine dimethyl ether was converted to its hydroiodide salt with 57% hydriodic acid. Recrystallization from acetone–water yielded white needles, m.p. 279° dec.[1]

Anal.—Calcd. for $C_{19}H_{22}INO_2$: C, 53.91; H, 5.24; I, 29.98; N, 3.31. Found: C, 54.08; H, 5.40; I, 30.17; N, 3.13.

The demethylation of this hydroiodide proved an exceptionally facile reaction, considering the sensitivity of apomorphine to oxidizing agents as well as to acylating agents. The hydroiodide was heated with an equimolar mixture of 57% hydriodic acid and acetic anhydride at reflux for 1 hr. When the reaction mixture was diluted with ether, pure (±)-apomorphine hydroiodide was precipitated and isolated as a white crystalline powder, m.p. 282° dec.,[1] in 93% yield. This compound oxidized only slowly when stored in the cold under nitrogen. $\lambda_{max.}^{MeOH}$: 217 mμ (ε, 41,000), 273 (ε, 17,000), 309 (ε, 3300).

Anal.—Calcd. for $C_{17}H_{18}INO_2$: C, 51.66, H, 4.59, I, 32.11; N, 3.54. Found: C, 51.48; H, 4.69; I, 32.00; N, 3.40.

[1] Determined on a duPont differential thermal analyzer under nitrogen.

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BOOKS

REVIEWS

International Encyclopedia of Pharmacology and Therapeutics. Section 13, Volume 1-Anticholinesterase Agents. Edited by C. RADOUCO-THOMAS, Pergamon Press Ltd., Oxford, England, 1970. ix + 508 pp. 15.5 × 23.5 cm. Price $24.00.

The number of compounds that inhibit the class of enzymes known as cholinesterases has increased markedly in recent years. These compounds, which have had only limited applications in medical therapy and have few equals as investigational tools in pharmacology, are now important industrially as insecticides and militarily as the highly toxic "nerve gases," *e.g.*, sarin, soman, and tabun. Concurrently, large numbers of papers have been published dealing with chemical and biological aspects of these inhibitors and of the enzymes with which they react. Many reviews have subsequently appeared, of which the one edited by Koelle in 1963, *Cholinesterases and Anticholinesterase Agents*, may be the most extensive and most widely used.

The present volume of anticholinesterase agents for the most part covers the same literature as that of the review of Koelle and attempts to include most papers published through late 1968. The material is presented in two major subsections, with an introduction, titled "History of the Research With Anticholinesterase Agents," by Professor A. G. Karczmar, the Section Editor. This part considers in brief, historic detail the pharmacology of physostigmine, the concept of neurohumoral transmission, some novel aspects of the cholinergic system, organophosphorous inhibitors, early work on cholinesterases, the therapeutic uses of inhibitors of these enzymes, and some interesting points of disagreement among investigators of these areas.

Subsection I, titled "Reactions of Cholinesterases With Substrates, Inhibitors and Reactivators," compiled by Dr. Earl Usdin, comprises the major portion of the volume. The author states that a somewhat different point of view has guided this review: an intention not only to describe the reactions of cholinesterases with substrates, inhibitors, and reactivators, but to make known the differences and similarities among the reactions of these three classes of compounds. In this effort, reference has been made to the active