tyrosyl-L-seryl-N$^{\epsilon}$-*t*-butyloxycarbonyl-L-lysine hydrazide (0.585 g, 72%): mp 186–188°; R_f 0.16.

Anal. Calcd for $C_{39}H_{57}N_7O_{12}$ (815.9): C, 57.41; H, 7.04; N, 12.02. Found: C, 57.17; H, 7.34; N, 12.17.

A number of attempts to secure pure tetrapeptide hydrazide from slightly impure tetrapeptide ester were unsuccessful; the tetrapeptide hydrazide was invariably obtained as a gel.

N-Benzyloxycarbonyl-L-tyrosyl-L-serylglycine Methyl Ester (XXIV).—A solution of sodium nitrite (0.210 g, 0.00305 mole) in water (3 ml) was added to a solution of N-benzyloxycarbonyl-L-tyrosyl-L-serine hydrazide (1.249 g, 0.003 mole) in acetic acid (18 ml), 2 *N* hydrochloric acid (12 ml), and water (10 ml) maintained at 0°. The resulting azide was precipitated with sodium chloride and extracted into three 10-ml portions of cold ethyl acetate. The combined extracts were washed free of acid with saturated sodium bicarbonate solution and dried (the drying agent was not removed until the coupling reaction was complete). A solution of glycine methyl ester, previously prepared by dissolving glycine methyl ester hydrochloride (0.414 g, 0.0033 mole) in dimethylformamide (30 ml) with warming, rapidly cooling the solution to 0°, and immediately adding triethylamine (0.46 ml, 0.0033 mole), was poured into the ethyl acetate solution of the azide. After 48 hr at 0°, the mixture was filtered, the solvents evaporated, and the residue dissolved in the minimum amount of hot 50% aqueous methanol. On cooling, the solution deposited almost colorless needles of N-benzyloxycarbonyl-L-tyrosyl-L-serylglycine methyl ester (1.005 g, 71%): mp 204–206°; $[\alpha]^{27}D$ −7.0° (*c* 1.0, dimethylformamide); R_f 0.19; ν_{max} 3400 very broad (OH), 2950 (CH), 1745 (methyl C=O), 1689 (urethane C=O), 1642 (amide I), 1512 (amide II), 1230 broad (OH), and 698 (Ph) cm^{-1}; λ_{max} 226, 257, 264, 268, 274, 277, and 284 mμ (ϵ 9760, 688, 1000, 1330, 1650, 1790, and 1380).

Anal. Calcd for $C_{23}H_{27}N_3O_8$ (473.5): C, 58.35; H, 5.75; N, 8.87. Found: C, 58.52; H, 5.69; N, 9.03.

The tripeptide was alternatively prepared by use of *t*-butyl nitrite, N-benzyloxycarbonyl-L-tyrosyl-L-serine hydrazide and glycine methyl ester hydrochloride (74%).

Registry No.—II, 1155-64-2; III, 2212-75-1; IV, 2212-76-2; VI, 2389-49-3; VII, 3252-80-0; IX, 3236-14-4; XII, 15376-59-7; XIV, 15523-36-1; XV, 15364-45-1; XVI, 2480-91-3; XVII, 15364-47-3; XVIII, 15364-48-4; XIX, 15523-37-2; XXII, 15364-49-5; XXIII, 15364-50-8; XXIV, 15364-51-9.

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Derivatives of Morphine. V.[1] The Structure of Anhydrometathebainol

ULLI EISNER AND ULRICH WEISS

Laboratory of Physical Biology, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland 20014

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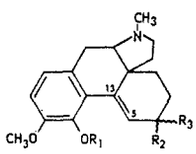
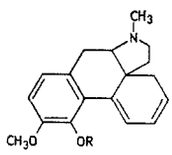
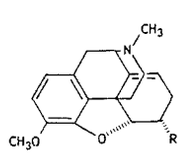
During their investigation of metathebainone (I), Small and Meitzner[2] described the preparation of "anhydrometathebainol" by dehydration of metathebainol (II) with ethanolic KOH at 160°. The authors were not able to assign a structure to the product, although they considered formula III, resulting from straightforward dehydration of II. However, they discarded III on the grounds that the dihydro derivative, obtained by catalytic hydrogenation,[3] seemed to be different from dihydrodesoxymetacodeine, the product of Wolff–Kishner reduction of I. The latter was assumed to be V and should hence be identical with dihydro-III. On this basis they concluded that "the formation of anhydrometathebainol has involved a deeper-seated structural change then mere dehydration."



I, R_1 = H; R_2R_3 = O
II, R_1 = R_2 = H; R_3 = OH
IV, R_1 = Ac; R_2 = OAc; R_3 = H
V, R_1 = R_2 = R_3 = H
VI, R_1 = Ac; R_2 = R_3 = H



III, R = H
VII, R = Ac



VIII, R = OH
IX, R = H

We were interested in the possibility of such a rearrangement and have reinvestigated this work in order to establish the structures of anhydrometathebainol and of the related dihydro derivatives. Metathebainol (II) was prepared either by catalytic hydrogenation[2] or, more conveniently, by borohydride reduction of metathebainone (I). In our hands the former procedure was erratic and gave mixtures, possibly containing products of hydrogenolysis which were not further investigated. Borohydride reduction resulted in a mixture of epimers which could be used directly for the subsequent step. The same crystalline diacetate (IV) was obtained from both preparations.

Dehydration of metathebainol by the method of Small and Meitzner[2] or by a slightly modified procedure gave crude anhydrometathebainol which could not be purified by crystallization. The melting points of this and of the other free phenols in this series were low and indefinite due to variable solvation and were therefore not suitable for characterization. Acetylation of anhydrometathebainol furnished the acetate, which could be purified readily and was identical with an authentic specimen.[2] The nmr spectrum showed a complex multiplet (3 H) in the olefinic region (δ 5.5–6.3), which was resolved into three distinct multiplets (one proton each), centered at δ 6.1, 5.92, and 5.67, on a 100-Mc instrument. The long-wavelength band in the uv region (see Experimental Section) showed a bathochromic shift (~18 mμ) with respect to metathebainol diacetate (IV) and to dihydroanhydrometathebainol acetate (see below). The strong negative circular dichroism ($\Delta\epsilon_{286-288}$ −11.3) and optical rotatory dispersion (complex negative effect, first extremum at 313 mμ, [Φ] −19,700°) are compatible with the presence of an inherently dissymmetric chromophore such as the nonplanar phenylbutadiene system. The above evidence is consistent with structure III for anhydrometathebainol which is further corroborated by the study of the dihydro derivative.

Catalytic hydrogenation of anhydrometathebainol acetate resulted in the uptake of 1 mol of hydrogen. The dihydro derivative was found to be identical with the product obtained on acetylation of dihydrodeoxymetacodeine (V), prepared[2] by Wolff–Kishner reduction of I. The structure of this was confirmed by spectroscopic data (see Experimental Section), which are consistent with VI. Of particular interest in the nmr

(1) Part IV: U. Weiss and S. J. Daum, *J. Med. Chem.*, **8**, 123 (1965).
(2) L. F. Small and E. Meitzner, *J. Amer. Chem. Soc.*, **55**, 4602 (1933).
(3) Throughout the metathebainone series, $\Delta^{8(13)}$ is relatively inert to catalytic hydrogenation.

spectrum is the resemblance of the olefinic region (triplet due to one proton centered at δ 6.0 for V and 5.8 for VI) to that of neopine (VIII) (triplet, δ 5.5; actually, the X part of a deceptively simple ABX system[4]) and deoxycodeine D (IX)[5] (triplet, δ 5.65).

It is thus clear that anhydrometathebainol possesses the expected structure III and that the earlier observations on the nonidentity of dihydroanhydrometathebainol and dihydrodesoxymetacodeine were erroneous.

Experimental Section

Melting points were determined on a Kofler block. Ultraviolet spectra were determined in ethanol on a Cary 14 spectrophotometer, infrared spectra in chloroform solution on a Beckman IR7 spectrophotometer, and nmr spectra in deuteriochloroform on a Varian A60 or HA100 instrument. The optical rotatory dispersion was measured on a Cary 60 spectropolarimeter, the circular dichroism on the Jouan dichrograph of the University of Strasbourg.

Metathebainol (II). **A.** Metathebainone (2.99 g) dissolved in a minimum of ethanol was treated with 0.1 *N* HCl (100 ml) and Adams catalyst (50 mg). The mixture was hydrogenated at 46 psi for 18 hr, filtered, basified with ammonia and extracted with chloroform. Evaporation of the extracts afforded an oil which crystallized on contact with methanol. Crystallization from methanol afforded metathebainol (1.93 g, 64%), mp 76–80° (lit.[2] mp 87–88° for chloroform solvate, 92–93° for methanol solvate); no carbonyl stretching appeared in the infrared spectrum. In another experiment, hydrogenation was continued for 12 hr and gave crystalline metathebainol, contaminated with starting material, in 27% yield.

B. Metathebainone (3.0 g) in ethanol (35 ml) was treated with sodium borohydride (1.75 g) portionwise with stirring for 30 min. Stirring was continued for 6 hr, acetone was added to decompose excess borohydride, the solution was poured into water, acidified with acetic acid, and basified with ammonia. Extraction with chloroform afforded an oil (2.97 g) which did not crystallize, but was sufficiently pure for the next step. Its infrared spectrum was essentially identical with that of the product from the previous preparation.

Metathebainol diacetate (IV) was prepared from metathebainol by the method of Small and Meitzner:[2] mp 137–138° (lit.[2] mp 140°); λ_{max} 291, 242, 214 mμ (ϵ 2900, 11,000, 27,200).

Anhydrometathebainol (III).—The base was prepared by the method of Small and Meitzner.[2] Alternatively, II (1.0 g) and potassium hydroxide (0.25 g) in ethylene glycol (6.5 ml) were heated at 160° for 4 hr. The reaction mixture was worked up in the usual way, affording III as a crystalline solid (0.27 g) after crystallization from methanol, indefinite mp 70–100° (lit.[2] mp 106–107°). Thin layer chromatography on silica gel using cyclohexane–diethylamine (9:1) as eluent showed the presence of some impurities. Purification of the product by preparative thin layer chromatography in the same solvent system gave a sample mp 112–115° (softens at 70°) after crystallization from methanol.

Acetylanhydrometathebainol (VII) could not be prepared by the published method.[2] It was obtained by acetylation of crude III with pyridine–acetic anhydride at room temperature for 5 days. It had mp 174–176° after crystallization from methanol (lit.[2] mp 166°); uv bands were at λ_{max} 307 mμ (ϵ 13,800), 245 (infl) (46,000), 225 (infl) (11,300), 211 (20,000). Circular dichroism showed a broad, evidently complex, negative band, between ~240 and 340 mμ, with maximum, $\Delta\epsilon$ −11.3, at 281–288 mμ. Optical rotatory dispersion in methanol (*c* 0.04) showed $[\Phi]_{325}$ −18,100° (sh), $[\Phi]_{313}$ −19,700°, $[\Phi]_{297}$ ±0°, $[\Phi]_{\sim 270-260}$ +38,000°, $[\Phi]_{248}$ +45,900° $[\Phi]_{230}$ +3600°, $[\Phi]_{220}$ *ca.* +17,000°. The identity with an authentic sample prepared by Small and Meitzner was established by mixture melting point determination and comparison of infrared spectra.

Acetyldihydroanhydrometathebainol (VI).—A solution of VII (0.425 g) in ethanol (20 ml) was shaken in an atmosphere of hydrogen in the presence of Adams catalyst (50 mg). Hydrogen uptake (35 ml; theoretical uptake for 1 mol = 32 ml) was complete in less than 1 hr. The solution was filtered and the filtrate was evaporated to dryness. The residual solid (0.44 g) was crystallized three times from hexane and had mp 115.5–116°. The solution of the compound in concentrated hydrochloric acid does not show the blue halochromism of II, III, and IV even on heating. Uv absorptions were at λ_{max} 288 mμ (ϵ 4000), 243 (10,400), 215 (29,900).

Anal. Calcd for $C_{20}H_{25}NO_3$; C, 73.24; H, 7.66; N, 4.17%. Found: C, 73.37; H, 7.70; N, 4.28%.

Wolff-Kishner Reduction of Metathebainone.—The preparation was carried out by the method of Small and Meitzner,[2] affording a crystalline solid, mp 51–69° (lit.[2] mp 72°), which rapidly darkened on exposure to air. It could be purified by preparative thin layer chromatography on silica gel using cyclohexane–diethylamine (9:1) as eluent and had mp 40–70° after crystallization from methanol. On standing over calcium chloride the solvent-free base was obtained as a glass. Acetylation with acetic anhydride in pyridine at room temperature for 2 days afforded the acetyl derivative, mp 114–115°, after crystallization from hexane. It was identical in every respect (mixture melting point determination and infrared spectrum) with VII.

Registry No.—III, 15448-36-9; VI, 15448-37-0; VII, 15448-38-1; morphine, 57-27-2.

Acknowledgment.—We are indebted to Drs. E. L. May and L. J. Sargent of this institute for kindly supplying a sample of acetylanhydrometathebainol originally prepared by Small and Meitzner, to Dr. E. Lustig, of the Food and Drug Administration, Washington, D. C., for measurement of the 100-Mc spectrum, to Mrs. K. Warren, National Heart Institute, for measurement of infrared spectra, and to Professor Guy Ourisson, Strasbourg, for measurement of the circular dichroism.

(4) T. Rüll, *Bull. Soc. Chim. Fr.*, 586 (1963).

(5) U. Weiss, unpublished results.

Synthesis of Murrayanine[1]

D. P. CHAKRABORTY AND B. K. CHOWDHURY

Bose Institute, Calcutta 9, India

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In a previous communication, the structure of murrayanine, $C_{14}H_{11}NO_2$, mp 168°, a simple carbazole derivative isolated from the stem bark of *Murraya koenigii* Spreng., was proposed as 1-methoxy-3-formylcarbazole (I) by Chakraborty, Barman, and Bose.[2a] From the spectral evidences (uv, ir, nmr) and the results of reactions, it was shown that murrayanine could be formulated either as 1-methoxy-3-formylcarbazole (I) or as 1-methoxy-6-formylcarbazole (II). The assignment of the formyl group at position 3 of the carbazole nucleus was made on the basis of nmr data of murrayanine. We, therefore, sought a confirmation of the previously proposed structure by synthesis. The present report relates to the synthesis of murrayanine and the preparation of compounds (VII and VIII) from natural murrayanine. The intermediate

(1) When this synthesis was complete we received a personal communication from Dr. D. J. Crum informing us that he has also synthesized murrayanine. Since then we came across his communication (*Chem. Commun.*, 417, 1966) which shows that his method and approach are different from ours. A short communication on our results appeared in *Sci. Cult.* (Calcutta), **32**, 590 (1966). The paper was presented at the Joint Convention of the Chemical Research Committee, C. S. I. R., and the Society of Biological Chemists of India, held at Delhi on Dec 25–27, 1966.

(2) (a) D. P. Chakraborty, B. K. Barman, and P. K. Bose, *Tetrahedron*, **21**, 681 (1965); (b) B. H. Brown and P. G. Philpott, *J. Chem. Soc.*, 7185 (1965), and references therein.