Apo-β-erythroidine (II) and Isoapo-β-erythroidine (III). A mixture of 118 mg of lactone XXX plus 69 mg of 5% palladium on barium sulfate in 70 ml of ethyl acetate was stirred at room temperature for 55 min under hydrogen at atmospheric pressure. After filtration, the filtrate was evaporated to a residue which was chromatographed on 14 g of Decalso (>150 mesh) with benzene and benzene–ether elution. Thin layer chromatographic analysis of the eluent showed only II, III, and XXX. This mixture was then purified by preparative thin layer chromatography on silica gel (benzene–acetone–acetic acid, 10:2:2.7). The bands corresponding to each compound were shaken with a mixture of 20 ml of aqueous bicarbonate (0.5 *M*) and 40 ml of ether. The mixture of silica gel in aqueous bicarbonate was extracted with two more 30-ml portions of ether, and the combined ether extracts were washed with three 10-ml portions of aqueous bicarbonate and 10 ml of water and dried. Evaporation of solvent gave 17 mg (14%) of apo-β-erythroidine[26] (II), 24 mg (20%) of isoapo-β-erythroidine (III), and 16 mg (13%) of recovered lactone XXX. Crystallization of II and III was achieved from acetone–water and ethanol–water, respectively. Apo-β-erythroidine had mp 128–129° (lit.[5a] 132–132.5°), $\nu_{max}^{CHCl_3}$ 1737 cm^{-1}, $\lambda_{max}^{C_2H_5OH}$ 345 mμ (ε 3500) and 240 mμ (ε 24,500).[27] Isoapo-β-erythroidine had mp 146–148° (lit.[5a] 146–147°), $\nu_{max}^{CHCl_3}$ 1705 cm^{-1}, $\lambda_{max}^{C_2H_5OH}$ 379 mμ (ε 6500), 288 (10,800), 253 (16,800).[27] In addition, both synthetic samples were shown to be pure and identical with authentic specimens[26] of apo-β-erythroidine (II) and isoapo-β-erythroidine (III) by thin layer chromatography.

1-Indolinebutyronitrile. Indoline (32 g) and 18.5 g of ω-bromobutyronitrile were heated at 75° for 2 hr under nitrogen. The reaction mixture was then taken up in a benzene–water mixture, and solid sodium bicarbonate was added until gas evolution ceased and the solid product had dissolved. The benzene layer was separated, and the aqueous solution was extracted with more benzene. The combined extracts were washed with water, dried, and evaporated to a residue which was fractionally distilled to give 15 g of indoline and 20.2 g (94%) of 1-indolinebutyronitrile, bp 128° (0.25 mm).

Anal. Calcd for $C_{12}H_{14}N_2$: C, 77.4; H, 7.5; N, 15.1. Found: C, 77.3; H, 7.7; N, 14.8.

7-Oxo-1,2,4,5,6,7-hexahydroazepino[3,2,1-*hi*]indole (IV). Eighteen grams of 1-indolinebutyronitrile and 15 g of potassium hydroxide were dissolved in 150 ml of 10% ethanol–water and refluxed for 7 hr under nitrogen. After cooling, the solution was washed with ether, and the pH was adjusted to 4.0. A second extraction with ether gave 21 g of 1-indolinebutyric acid which was not purified. Instead, 5 g of 1-indolinebutryic acid was treated with 150 g of polyphosphoric acid at 100° for 40 hr to give a 5–10% yield of ketone IV after distillation at 160° (5 mm): $\lambda_{max}^{C_2H_5OH}$ 376 mμ (ε 3000), 315 (830), 242 (12,600).

Anal. Calcd for $C_{10}H_{13}NO$: C, 77.0; H, 7.0; N, 7.5. Found: C, 76.7; H, 7.3; N, 7.2.

In addition, 70–80% of starting 1-indolinebutyric acid was recovered from the reaction mixture.

Glycidic Ester XXII. To a solution of 84 mmoles of potassium *t*-butoxide in 10 ml of *t*-butyl alcohol was added 40 ml of benzene, and then 30 ml of solvent was distilled. After cooling, 1.5 g (80 mmoles) of azepinone XVII plus 1.08 g (84 mmoles) of ethyl chloroacetate in 10 ml of benzene were added. The resultant solution was stirred under nitrogen at room temperature for 2 hr and refluxed for 1 hr. The reaction mixture was then distributed between 250 ml of water and 100 ml of ether; the ether solution was washed with 15 25-ml portions of 0.2 *M* sodium hydroxide solution and two 50-ml portions of water, dried, and evaporated to a residue that was chromatographed on activity I neutral alumina. Elution with benzene and benzene–chloroform gave a residue that was dissolved in 2 ml of methanol and allowed to stand overnight at 0°. The 9 mg of crystalline material, mp 238–241°, that separated was removed by filtration and not further investigated. Evaporation of the filtrate gave 1.28 g (59%) of oily glycidic ester XXII, ν_{max} 1742 cm^{-1}.

Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.3; H, 7.0; N, 5.1; OC_2H_5, 16.5. Found: C, 70.3; H, 7.0; N, 5.2; OC_2H_5, 16.5.

(26) We have observed that apo-β-erythroidine is partially decomposed on silica gel using acetic acid as one of the developing solvents; hence, the true yield of II may be considerably higher than that isolated.

(27) (a) See ref 4a for the ultraviolet spectra of authentic II and III isolated from β-erythroidine. (b) In ref 9, the ultraviolet spectrum of II is reported to be slightly different from that reported in ref 4a and obtained by us for authentic apo-β-erythroidine; since no solvent is mentioned in ref 9, we presume a difference in solvent may be the explanation for the slight disagreement in reported spectra.

(28) Prepared[5a] from a sample of β-erythroidine hydrochloride kindly supplied by Dr. Karl Folkers.

Synthesis in the Emetine Series. XIII.[1] Structure and Synthesis of Psychotrine and 6′-O-Methyl-7′-desmethylpsychotrine

S. Teitel and A. Brossi

Contribution from the Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110. *Received May 19, 1966*

Abstract: The 6′ position for the free hydroxyl group in psychotrine (I) has been established by an unequivocal synthesis. The related 6′-O-methyl-7′-desmethylpsychotrine (XIII) has also been prepared. Acid hydrolysis of O-methylpsychotrine (II) gave a complex mixture containing both I and XIII.

The two phenolic Ipecac alkaloids psychotrine (I) and cephaeline (III) have been related to each other by reduction.[2] Their absolute configuration has been established since O-methylation yielded O-methylpsychotrine (II)[3] and emetine (IV),[2] respectively, two other Ipecac alkaloids of known absolute configuration.[4] However, the assignment of the free hydroxy group to the 6′ position in psychotrine (I) and cephaeline (III) has not been rigidly established since it is primarily based on the assumption by Brindley and Pyman[5] that the 6′-methoxyl in O-methylpsychotrine (II) is the most labile of the four methoxyls in the molecule and is preferentially cleaved on acid hydrolysis to give psychotrine (I) with a 6′-hydroxyl group. Pailer and Porschinski[6] lent support to this assumption when they subjected O-ethylcephaeline (V) to a lengthy degradation and obtained a semicarbazone which gave

(1) Paper XII: A. Brossi, H. Bruderer, M. DaPrada, F. A. Steiner, and A. Pletscher, *Arzneimittel-Forsch.*, **15**, 670 (1965).

(2) F. H. Carr and F. L. Pyman, *J. Chem. Soc.*, **105**, 1591 (1914).

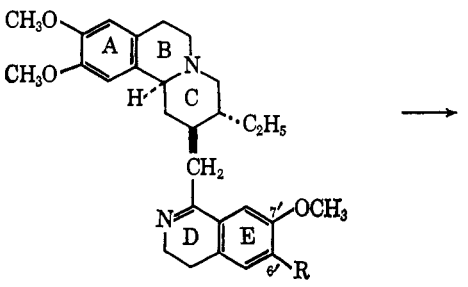
(3) F. L. Pyman, *ibid.*, **111**, 419 (1917).

(4) A. R. Battersby, R. Binks, and C. G. Davidson, *ibid.*, 2704 (1959); A. R. Battersby and S. Garratt, *ibid.*, 3512 (1959).

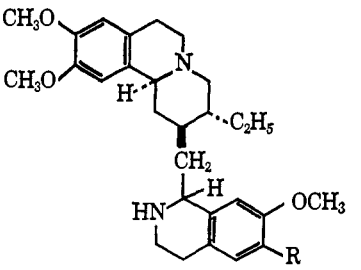
(5) W. H. Brindley and F. L. Pyman, *ibid.*, 1067 (1927).

(6) M. Pailer and K. Porschinski, *Monatsh. Chem.*, **80**, 101 (1949).

no melting point depression with a synthetic sample of 2-ethyl-4-ethoxy-5-methoxybenzaldehyde semicarbazone. However, the synthesis of the latter compound was ambiguous and required six recrystallizations to give a constant melting point.



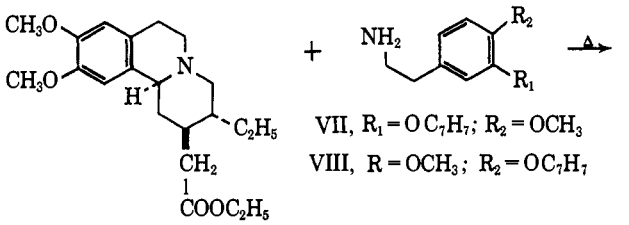
I, R = OH
II, R = OCH_3



III, R = OH
IV, R = OCH_3
V, R = OC_2H_5

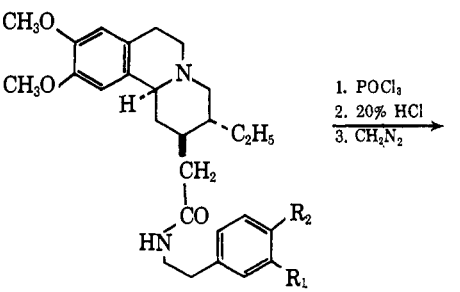
In contrast to the assumed[5] acid lability of the 6′-methoxyl in O-methylpsychotrine (II), recent studies[7] have shown that acid hydrolysis of 6,7-dimethoxy-substituted 1-methyl-3,4-dihydroquinolines caused preferential cleavage at the 7 position to give the corresponding 7-hydroxy derivatives. Further, the possibility existed that psychotrine (I) has a free hydroxyl group in ring A rather than ring E since there is at least one example of such an occurrence in nature.[8] In view of these considerations, it was of interest to rigidly establish the position of the hydroxyl group in I and III. This has now been accomplished by an unambiguous synthesis of psychotrine (I) and its 6′-O-methyl-7′-O-desmethyl isomer (XIII) which was needed for comparison purposes.

Condensation of the optically active tricyclic ester VI[9,10] with either 2-(3-benzyloxy-4-methoxyphenyl)-ethylamine (VII)[11] or 2-(4-benzyloxy-3-methoxyphenyl)-ethylamine (VIII)[12] gave the benzyl ether amides IX and X, respectively. Cyclization of the latter with phosphorus oxychloride afforded the corresponding benzyloxy-substituted 3,4-dihydroisoquinoline derivatives XI and XII which were debenzylated with 20% hydrochloric acid to give the phenolic bases I and XIII, respectively. Synthetic I was identical in all respects with natural psychotrine[10] which definitely confirmed Brindley and Pyman's assumption that the free hydroxyl group is in the 6′ position. Since psychotrine (I) has been related to cephaeline (III),[3] this also unequivocally established the 6′ position for the free hydroxyl group in the latter.[13] Synthetic I was readily distinguished by thin layer chromatography from its isomer (XIII). The latter was converted by treatment

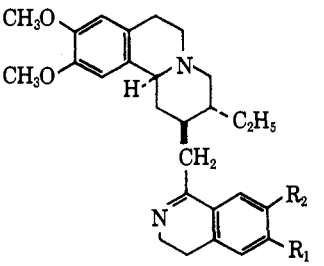


VII, $R_1 = OC_7H_7$; $R_2 = OCH_3$
VIII, $R = OCH_3$; $R_2 = OC_7H_7$

VI



IX, $R_1 = OC_7H_7$; $R_2 = OCH_3$
X, $R_1 = OCH_3$; $R_2 = OC_7H_7$



XI, $R_1 = OC_7H_7$; $R_2 = OCH_3$ (*via* 1)
XII, $R_1 = OCH_3$; $R_2 = OC_7H_7$ (*via* 1)
I, $R_1 = OH$; $R_2 = OCH_3$ (*via* 1 and 2)
XIII, $R_1 = OCH_3$; $R_2 = OH$ (*via* 1 and 2)
II, $R_1 = R_2 = OCH_3$ (*via* 1, 2, and 3)

(7) A. Brossi, M. Baumann, and R. Borer, *Monatsh. Chem.* **96**, 25 (1965); A. Brossi and R. Borer, *ibid.*, **96**, 1409 (1965); H. Bruderer and A. Brossi, *Helv. Chim. Acta*, **48**, 1945 (1965).

(8) Pailer and Porschinski's degradation of O-ethylcephaeline (ref 6) located the free hydroxyl group of cephaeline at the 6′ position. Their work is in accord with the definitive work of Battersby and Oppenshaw [A. R. Battersby and H. T. Oppenshaw, *J. Chem. Soc.*, S59 (1949)] on the exhaustive methylation of emetine, and hence cephaeline cannot have a free hydroxyl group in ring A. However, a ring A hydroxylated analog of the chemically related alkaloid tubulosin has recently been isolated: A. Poplak, E. Haack, and H. Springler, *Tetrahedron Letters*, 10, 1081 (1966). In view of this, it is not unlikely that similarly constituted minor Ipecac alkaloids might also be found.

(9) H. T. Openshaw and N. Whittaker, *J. Chem. Soc.*, 1461 (1963).

(10) We are grateful to Drs. Openshaw and Whittaker of the Wellcome Research Laboratories, Beckenham, England, for a generous supply of the optically active ester VI as well as samples of natural psychotrine (I) and natural O-methylpsychotrine (II).

(11) M. Tomita and H. Yamaguchi, *J. Pharm. Soc. Japan*, 72, 1219 (1952).

(12) J. M. Babbitt and T. Chase, *J. Org. Chem.*, **24**, 1107 (1959).

(13) Very recently, C. Szántay, L. Töke, and P. Kolonitis, *J. Org. Chem.*, **31**, 1447 (1966), reported on a total synthesis of racemic cephaeline. Their synthetic material was reported to be identical with the natural alkaloid based on the ultraviolet spectrum (no details) and the R_f value. This synthesis has been achieved by condensation of racemic protoemetine with 3-hydroxy-4-methoxyphenethylamine in a Pictet–Spengler type of reaction. This is therefore further proof for the 6′ position of the free phenolic hydroxy group in cephaeline, and therefore psychotrine.

with diazomethane into O-methylpsychotrine (II) which was identical with the nautral alkaloid.[10]

The procedure of Brindley and Pyman[5] for the hydrolysis of O-methylpsychotrine (II) with hydrochloric acid at 170° was repeated and the reaction mixture analyzed by thin layer chromatography using psychotrine (I), O-methylpsychotrine (II), and 6′-O-methyl-7′-desmethylpsychotrine (XIII) as comparison samples. As expected, the hydrolysis gave a rather complex mixture containing I and XIII, as well as II and at least six other components. It is evident that, in contrast to Brindley and Pyman's[5] postulation, selective cleavage of the methoxyl groups does not take place.

Experimental Section[14]

N-(3-Benzyloxy-4-methoxyphenethyl)-3-ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2H-benzo[*a*]quinolizine-2-acetamide (IX). A mixture of 2.5 g (6.9 mmoles) of (−)-3-ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2H-benzo[*a*]quinolizine-2-acetic acid ethyl ester (VI)[9,10] and 3.88 g (16 mmoles) of 2-(3-benzyloxy-4-methoxyphenyl)ethylamine (VII)[11] was heated at 180° under nitrogen for 18 hr, triturated with ether, and filtered. The solids were dissolved in ethanol and treated with activated carbon, and the filtrate was evaporated. The residue was crystallized from an alcohol–water mixture to give 2 g (50%) of IX, mp 160–161°. An analytical sample prepared from ether–petroleum ether (bp 30–60°) exhibited mp 160–161°; ν_{max}^{KBr} 3300 (NH), 1645 (amide I), 1520 (amide II), 1265 and 1240 (ether), and a complex band at 1020 cm^{-1}; tlc (system B), single spot at R_f 0.65.

Anal. Calcd for $C_{35}H_{44}N_2O_5$: C, 73.40; H, 7.74. Found: C, 73.71; H, 7.98.

N-(4-Benzyloxy-3-methoxyphenethyl)-3-ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2H-benzo[*a*]quinolizine-2-acetamide (X). A mixture of 2.15 g (5.95 mmoles) of VI and 3.34 g (13.8 mmoles) of 2-(4-benzyloxy-3-methoxyphenyl)ethylamine (VIII)[12] was heated at 180° under nitrogen for 18 hr, cooled, and crystallized from benzene to give 1.35 g (64%)[15] of X, mp 178–180°. An analytical sample prepared from methanol exhibited mp 179–181°; ν_{max}^{KBr} 3290 (NH), 1635 (amide I), 1515 (amide II), 1265 and 1235 (ether), and a doublet at 1035 and 1010 cm^{-1}; tlc (system B), single spot at R_f 0.5.

Anal. Calcd for $C_{35}H_{44}N_2O_5$: C, 73.40; H, 7.74. Found: C, 73.20; H, 7.64.

2-(6-Benzyloxy-3,4-dihydro-7-methoxy-1-isoquinolinylmethyl)-3-ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2H-benzo[*a*]quinolizine (XI). A mixture of 900 mg (1.56 mmoles) of IX and 0.43 ml of phosphorus oxychloride in 18 ml of dry benzene was refluxed for 1 hr, poured onto ice–water, and rendered alkaline with sodium hydroxide. The mixture was extracted with ethyl acetate (three 15-ml portions). The ethyl acetate extracts were combined, washed, dried, stirred with 10 g of Woelm neutral alumina for 30 min, and filtered. The filtrate was evaporated to give 503 mg (58%) of XI as a pale yellow oil; tlc (system A), main spot at R_f 0.7 with a trace at the point of application. An aliquot was treated in ethanol with excess oxalic acid dihydrate to give the crystalline dioxalate of XI which upon recrystallization from methanol exhibited mp 201–203°; tlc (system A), single spot at R_f 0.7; no amide band in the infrared; $\lambda_{max}^{H_2O}$ 241 mμ (ε 19,000), 289 (8000), 306 (9600), 355 (9500); $\lambda_{max}^{0.1NHCl}$ 241 mμ (ε 19,000), 289 (8600), 306 (10,000), 355 (9500); nmr: phenyl group at δ 7.42, four aromatic protons at δ 6.60, 6.72, 7.23, and 7.42, $-OCH_2$ at δ 5.25, three OCH_3 groups at δ 3.67, 3.73, and 3.88.

Anal. Calcd for $C_{35}H_{42}N_2O_4 \cdot 2C_2H_2O_4$: C, 63.74; H, 6.31. Found: C, 63.88; H, 6.40.

2-(7-Benzyloxy-3,4-dihydro-6-methoxy-1-isoquinolinylmethyl)-3-ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2H-benzo[*a*]quinolizine (XII). A mixture of 1.35 g (2.36 mmoles) of X and 0.66 ml of phosphorus oxychloride in 28 ml of dry benzene was refluxed 1 hr, cooled, poured into ice–water, treated with 10% sodium hydroxide to pH 10, and extracted into ethyl acetate (three 20-ml portions). The ethyl acetate extracts were combined, washed, dried, and evaporated to give 1.29 g of a brown gum which was crystallized from an ethanol–water mixture to give 0.85 g (65%) of XII, mp 99–101°. An analytical specimen, prepared from ethanol–water, exhibited mp 102–104°; no amide band in the infrared; tlc (system A), single spot at R_f 0.4; tlc (system B), single spot at R_f 0.95; $\lambda_{max}^{i\text{-PrOH}}$ 218 mμ (ε 32,800), 280 (10,300), 306 (5940); $\lambda_{max}^{0.1NHCl}$ 243 mμ (ε 20,170), 288 (7570), 305 (9110), 351 (8000); nmr: phenyl group at δ 7.37, four aromatic singlets at δ 6.45, 6.62, 6.93, and 7.17, $-OCH_2$ at δ 5.13, three OCH_3 groups at δ 3.62, 3.70, and 3.85.

Anal. Calcd for $C_{35}H_{42}N_2O_4$: C, 75.78; H, 7.63. Found: C, 75.74; H, 7.73.

Psychotrine (I). A solution of 400 mg (0.72 mmoles) of XI in 2 ml of 20% hydrochloric acid was heated at steam bath temperature for 1 hr, cooled to 4°, treated with concentrated ammonium hydroxide to pH 10, and extracted with 20 ml of ethyl acetate. The extract was washed, dried, and evaporated. The residue was crystallized twice from a mixture of acetone–water to give 144 mg (43%) of psychotrine (I) as pale yellow crystals identical with natural psychotrine:[10] mp 117–120°,[16] no mixture melting point depression; tlc (system A), single spot at R_f 0.35 (two-dimensional chromatography of a mixture of synthetic and natural substances gave a single spot at R_f 0.34); $\nu_{max}^{CHCl_3}$ 3530 cm^{-1} (OH) and multiple bands centered at 1300 and 1260 cm^{-1}; $\lambda_{max}^{0.1NHCl}$ 240 mμ (ε 13,900), 288 (5700), 306 (6250), 356 (6800); nmr: two aromatic singlets at δ 6.45 and 7.02, two aromatic protons as singlet at δ 6.58, three OCH_3 groups at δ 3.62, 3.68, and 3.77. Optical rotations were for synthetic I;[17] $[\alpha]^{20}D$ +68.4°, $[\alpha]_{576}^{20}$ +73.8°, $[\alpha]_{546}^{20}$ +90.3°, $[\alpha]_{436}^{20}$ +91.4° (unstable), $[\alpha]_{365}^{20}$ 0° (*c* 1.0, ethanol); for natural I:[17] $[\alpha]^{20}D$ +73.1°, $[\alpha]_{576}^{20}$ +78.4°, $[\alpha]_{546}^{20}$ +96.1°, $[\alpha]_{436}^{20}$ +99.1° (unstable), $[\alpha]_{365}^{20}$ 0° (*c* 1.0, ethanol). A mass spectrum for synthetic I gave a molecular weight observed at 464 (calculated 464.6); major fragments were observed at *m/e* 273, 272, 244, 199, 190.

Anal. Calcd for $C_{26}H_{36}N_2O_4$: C, 72.39; H, 7.81. Found: C, 72.45; H, 7.60.

6′-O-Methyl-7′-desmethylpsychotrine (XIII). A solution of 755 mg (1.36 mmoles) of X in a mixture of 2 ml of concentrated hydrochloric acid and 1.6 ml of water was heated at 100° for 1 hr, cooled, adjusted to pH 10 with concentrated ammonium hydroxide, and extracted with ethyl acetate (three 10-ml portions). The ethyl acetate extracts were combined, washed, dried, and evaporated. The residue was crystallized from an ethanol–acetone–petroleum–ether mixture to give 330 mg (53%) of XIII, mp 191–193°. An analytical specimen, prepared by recrystallization from ether, exhibited mp 194–195°; $\nu_{max}^{CHCl_3}$ 3530 (OH), multiple bands centered at 1275 (C=O bonding) cm^{-1}; tlc (system A), single spot at R_f 0.7; $\lambda_{max}^{0.1NHCl}$ 240 mμ (ε 17,000), 288 (7500), 304 (9200), 357 (7900); nmr: four aromatic singlets at δ 5.60, 6.55, 6.78, and 6.98, three OCH_3 groups at δ 3.63, 3.68, and 3.82; $[\alpha]^{20}D$ +47.1°, $[\alpha]_{576}^{20}$ +50.0°, $[\alpha]_{546}^{20}$ +58.0°, $[\alpha]_{436}^{20}$ +58.0°, $[\alpha]_{365}^{20}$ +57.9° (*c* 2.0, ethanol). The mass spectrum gave a molecular weight observed at 464 (calculated 464.6); major fragments were observed at *m/e* 273, 272, 244, 191, 190, 176.

Anal. Calcd for $C_{26}H_{36}N_2O_4$: C, 72.39; H, 7.81; N, 5.99. Found (average of eight determinations): C, 72.59; H, 8.12; N, 6.05.

O-Methylpsychotrine (II) Derived from 6′-O-Methyl-7′-desmethylpsychotrine (XIII). A solution of 100 mg of XIII in 10 ml of methanol containing an excess of diazomethane in ether[16] was stored at 4° for 2 hr and then at room temperature for 20 hr. The volatiles were evaporated at 35° in a stream of nitrogen, and the residue was extracted with ether (two 10-ml portions). The ether extract was evaporated to give 80 mg of a yellow oil which was dissolved in 1.8 ml of ethanol and added to a solution of 50 mg of

(14) All melting points (corrected) were taken in open capillary tubes in a Thomas-Hoover melting point apparatus. Infrared spectra were determined with a Beckman IR-5 infrared spectrophotometer and ultraviolet spectra were measured with a Cary Model 14M spectrophotometer. The nmr spectra were obtained in DMSO-d_6 with a Varian A-60 spectrometer using tetramethylsilane as an internal standard. The mass spectra were run on a CEC 21-110 spectrometer. All thin layer chromatography employed silica gel G plates developed for 15 cm with either system A (benzene–methanol–concentrated ammonium hydroxide, 70:30:1) or system B (chloroform–methylene chloride–ethyl acetate–methanol–concentrated ammonium hydroxide, 30:70:30:5:1) and detected with Dragendorff's reagent.

(15) Based on the recovery of 0.8 g of VI by chromatography of the mother liquors over Woelm Grade I basic alumina.

(16) The melting point for natural psychotrine is 122° with sintering at 115°; see ref 5.

(17) O. Hesse, *Ann. Chem.*, 405, 36 (1914); $[\alpha]^{15}D$ +69.3° (*c* 2% of tetrahydrate, ethanol).

(18) Freshly prepared from 2 g of nitrosomethylurea according to the procedure of F. Arndt "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p 165.

oxalic acid dihydrate in 1 ml of ethanol. The mixture was centrifuged, and the precipitate washed with ethanol (two 1-ml portions) and crystallized from methanol (7 ml) to give 72 mg of II as white needles identical with the crystalline dihydrogen oxalate, prepared as above from natural[10] O-methylpsychotrine: mp 161–163° (effervescence),[19] no mixture melting point depression; tlc (system A), single spot at R_f 0.88 for both synthetic and natural II; optical rotation for synthetic II: $[\alpha]^{20}D$ +39.8°, $[\alpha]^{20}_{576}$ +42.1°, $[\alpha]^{20}_{546}$ +50.0°, $[\alpha]^{20}_{436}$ +133.0°, $[\alpha]^{20}_{365}$ +133.0° (*c* 2, H_2O); optical rotation for natural II:[19] $[\alpha]^{20}D$ +37.3°, $[\alpha]^{20}_{576}$ +39.7, $[\alpha]^{20}_{546}$ +47.6°, $[\alpha]^{20}_{436}$ +130.1°, $[\alpha]^{20}_{365}$ +130.1° (*c* 2, H_2O).

Hydrolysis of O-Methylpsychotrine According to Brindley and Pyman.[5] To 239 mg (0.5 mmole) of natural[10] O-methylpsychotrine in 0.0275 ml (0.5 mmole) of concentrated sulfuric acid and 0.063 ml of water[20] was added 0.049 ml (0.0585 mmole) of concentrated hydrochloric acid, and the mixture was heated in a sealed tube at 170° for 6 hr. The yellow solution was diluted with water (2 ml), concentrated ammonium hydroxide (2 ml) was added, and the precipitate was filtered to give 107 mg of crude as a yellow amorphous solid. Tlc (system A) showed a complex mixture containing nine distinct spots; three of these were individually removed from the plate and separately rechromatographed on plates with pure synthetic samples and thus identified as O-methylpsychotrine (II), psychotrine (I), and 6′-O-methyl-7′-desmethylpsychotrine (XIII), respectively. To a 40-mg aliquot of the above crude isolate dissolved in ethanol (3.5 ml) was added excess oxalic acid dihydrate. The precipitate was removed by filtration and crystallized from methanol to give 28 mg, mp 128–138°, with the same complex mixture on tlc as exhibited by the initial crude isolate.

(19) Reference 9: mp 161–163°, $[\alpha]^{23}D$ +41° (*c* 2.0, H_2O), for dihydrogen oxalate of natural O-methylpsychotrine.

(20) Brindley and Pyman[5] used O-methylpsychotrine sulfate heptahydrate for their hydrolysis experiment.

Acknowledgment. We are indebted to Dr. A. Steyermark and his staff for the microanalyses, to Dr. T. Williams, Dr. V. Toome, and Mr. S. Traiman for the determination of the nmr, ultraviolet, and infrared spectra, and to Dr. F. Vane and Dr. P. Bommer for the interpretation of the mass spectra. We also thank Mr. J. Van Burik for technical assistance.

Accelerated Polymerization of N-Carboxyamino Acid Anhydrides in Frozen Dioxane[1]

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Abstract: Polymerization of the N-carboxyamino acid anhydrides (NCA's) of phenylglycine, phenylsarcosine, glycine, and several alicyclic amino acids was studied in liquid and frozen dioxane in the presence and absence of added initiator. Rates of NCA reaction were at least 10 times as high in frozen solutions between +5 and −26° as in liquid systems. Solubility, infrared, and end-group analyses confirmed the formation of polyamino acids. The NCA solubilities, the inverse relationship between concentration and the fraction of NCA molecules reacting, and the apparent absence of adventitious catalysts suggest the possible importance of juxtaposition and alignment in the frozen matrix.

Polymerization of N-carboxyamino acid anhydrides (4-substituted 2,5-oxazolidinediones, NCA's) has added much to our understanding of protein configuration.[2] The reactions are carried out in bulk at elevated temperatures or, more frequently, in inert solvents in the presence of initiators. The possibility of a new approach to the synthesis of polyamino acids from NCA's was suggested by the rate increases observed on carrying out a number of bimolecular reactions in frozen solutions[3–5] and by the synthesis in ice of poly-6-aminopenicillanic acid.[6] This paper reports a study of the polymerization of several NCA's in frozen dioxane solutions. These represent NCA's which polymerize readily in the presence of an initiator and a less thoroughly studied group whose members show unusual stability.

Experimental Section

Most of the experiments were carried out with no addition of an initiator. It was therefore important for quantitative reproducibility to avoid the adventitious introduction of initiators with the anhydride or solvent. The anhydrides were synthesized, recrystallized, and analyzed as described previously.[7,8] The *p*-dioxane used was Matheson Coleman and Bell Spectroquality with an analysis of 99+% and an infrared spectrum showing no bands near 3300 cm^{-1}. A new bottle, generally from the same lot, was opened for each experiment; our determination showed a sharp freezing point at 11.8°, the same value as that reported by Grubb and Osthoff[9] and by Teague and Felsing.[10]

In one of the runs described below, initial freezing was carried out in a Dry Ice–acetone bath, and the tubes were then transferred to various constant-temperature chambers. In all other runs at temperatures below the freezing point, the solutions were initially frozen rapidly in an ice–salt mixture at −11°. (With the NCA of 1-aminocyclobutanecarboxylic acid, rate constants at −11°

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