The peracetylated glycoside was then converted by acetolysis into the peracetylated sugar. This was done by dissolving it at 0° in 5 ml. of acetic anhydride containing 0.1 ml. of concentrated sulfuric acid. After standing for 17 hr. at 24° the mixture was worked up according to standard procedure. The peracetyl amino sugar (188 mg.) obtained from the chloroform extracts did not crystallize. It was de-*O*-acetylated in 2 ml. of methanol containing 15 mg. of sodium methoxide (2 hr. at 0°). After dilution with methanol the solution was deionized with methanol-washed Amberlite IR-120(H^+), reconcentrated to a small volume, and the acetamido sugar IX was precipitated as an oil by the addition of excess ethyl acetate. It appeared chromatographically uniform[23] and was indistinguishable from authentic 3-acetamido-3-deoxy-D-galactose[12] (a), but well separated from 3-acetamido-3-deoxy-D-glucose[24] (b), 3-acetamido-3-deoxy-D-mannose[4] (c) and 3-acetamido-3-deoxy-D-gulose[11] (d). The ratios of migration were a:b:c:d = 0.96:1.00:1.10:1.13.

A small part of the oily acetamido sugar IX was crystallized from methanol–ethyl acetate and recrystallized from the same solvents; m.p. 168–169° dec., undepressed on admixture of authentic 3-acetamido-3-deoxy-D-galactose.

The main part of IX was hydrolyzed in 10 ml. of *N* hydrochloric acid at 100° for 90 minutes. The hydrolysate was treated with acid-washed charcoal and then brought to a sirup under several additions of water to remove the hydrochloric acid. Paper chromatography revealed the product to be inhomogeneous. The main spot, however, was identical in its R_{gm} value of 0.86 and in the shade of its ninhydrin color (brownish-gray, turning gray-violet) with the spot given by authentic 3-amino-3-deoxy-D-galactose hydrochloride (VIII). It was clearly distinct from the spots of the hydrochlorides of 3-amino-3-deoxy-D-glucose, -D-mannose, -D-talose and -D-allose[25] which travel with R_{gm} values, respectively, of 1.05, 1.13, 1.16 and 1.13. In addition there were present faint spots in the area of R_{gm} 1.05–1.16 and traces of streaking slow-moving impurities.

Degradation of 3-Amino-3-deoxy-α-D-talose Hydrochloride (X) to D-Lyxosamine Hydrochloride (XIII). N-Acetylation.—Pure aminotalose hydrochloride X (165 mg.) was N-acetylated in the presence of Dowex-1 (CO_3^{--})[26] according to the direction given for the N-acetylation of 3-amino-3-deoxy-D-glucose.[24] A dry, colorless, foamy product (161 mg.) was obtained that failed to crystallize; $[\alpha]^{20}_{D}$ +3° (*c* 1 in water). It was assigned formula XI.

Periodate Degradation.—A solution in 10 ml. of water of 142 mg. of the above acetamido sugar XI and 138 mg. of sodium metaperiodate was kept in the dark at 20°. After 30 minutes the solution had become yellow owing to the formation of free iodine. The reaction solution was therefore briefly agitated with one big crystal of sodium thiosulfate which was removed after the color had disappeared. Excess ethanol was then added to precipitate sodium iodate, the chilled mixture was filtered and the filtrate evaporated. An aqueous solution of the evaporation residue was further desalted by stirring with mixed Amberlites IR-120 (H^+) and CG-45(OH^-). The filtrate from the resins was heated for 30 minutes at 50° with 80 mg. of sodium bicarbonate, in order to hydrolyze formyl ester which may have been still present. Following deionization with IR-120(H^+) the solution was evaporated with several additions of ethanol. A colorless foam of N-acetyl-D-lyxosamine (XII) resulted weighing 104 mg. (85% of the theoretical) and showing $[\alpha]^{20}_{D}$ +19° (in water), in agreement with the literature.[13] Compound XII was chromatographically identical with authentic N-acetyl-D-lyxosamine[13] (a), but clearly distinct from specimens of N-acetyl-D-arabinosamine[4,13,24] (b) and N-acetyl-D-ribosamine[13] (c); ratios of migration, a:b:c = 1.33:1.18:1.43.

Like authentic N-acetyl-D-lyxosamine, and in contrast to the other N-acetyl-pentosamines, the product XII exhibited the Morgan–Elson color test *without heating* with sodium carbonate. This characteristic behavior is probably due to the presence in the equilibrium solution of sizable amounts of the furanose form.[13]

D-Lyxosamine Hydrochloride (XIII).—A solution of the N-acetate XII (100 mg.) in 10 ml. of 0.3 *N* hydrochloric acid was hydrolyzed for 2 hours on the steam-bath. The hydrolysate was neutralized with Amberlite CG-45 (OH^-), decolorized with charcoal, adjusted to *p*H 2 with dilute hydrochloric acid and evaporated to dryness. The solid obtained was not chromatographically pure; however, it gave a main spot identical with the one given by authentic D-lyxosamine hydrochloride.[13] The product was purified by precipitation with ethyl acetate from a solution in methanol–ethanol, the first flocculent parts of the precipitate being discarded. The solid was collected by centrifugation, then crystallized with some difficulty from methanol–ethanol when allowed to evaporate slowly on the air. The crystals (XIII) that were chromatographically pure, and an authentic specimen looked alike under the microscope, had the same R_f value, and gave almost superimposable infrared spectra. Especially characteristic for XIII was its complex mutarotation in half-saturated sodium borate solution. The curve given matched exactly the one determined by Kuhn and Baschang[13]; this distinguished XIII readily from D-ribosamine hydrochloride; $[\alpha]^{20}_{D}$ +5° (*t* = 0, extrapol.) → −18.6° (10 min.)→ −93.5° (90 min.)→ −68.0° (5 hr., final) (*c* 0.75 in half-saturated $Na_2B_4O_7$ solution).

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[23] Aniline hydrogen phthalate spray; since acetamido sugars are not very perceptible to this indicator, small amounts of accompanying isomers may have escaped detection.

[24] H. H. Baer, *J. Am. Chem. Soc.*, **83**, 1882 (1961).

[25] Obtained by acid hydrolysis from 3-amino-3-deoxy-1,2;-5,6-diisopropylidene-α-D-allose (m.p. 92–94°) kindly supplied by Dr. D. H. Ball, Natick, Mass. *Cf.* R. U. Lemieux and P. Chu, *J. Am. Chem. Soc.*, **80**, 4745 (1958).

[26] S. Roseman and J. Ludowieg, *ibid.*, **76**, 301 (1954).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF IRWIN, NEISLER & CO., DECATUR, ILL.]

Stereospecific Syntheses of 2-Arylethyl-5-acyloxy-6-alkoxy-*cis*-octahydroisoindole Derivatives. The Stereochemical Course of the Epoxidation of *cis*-Δ⁴-Tetrahydrophthalic Anhydride

BY ALLAN P. GRAY, DONALD E. HEITMEIER AND HAROLD KRAUS

RECEIVED AUGUST 23, 1961

Evidence has been adduced indicating that epoxidation of *cis*-Δ⁴-tetrahydrophthalic anhydride affords exclusively the β-epoxy derivative, and epoxidation of N-phenethyl-*cis*-Δ⁴-tetrahydrophthalimide gives predominantly the β-epoxide accompanied by a lesser amount of the α-isomer. These results have been interpreted as supporting the half-boat conformation (D) for both the anhydride and the imide. The epoxides have been converted, by stereospecific processes, to a series of 2-phenethyl-, 2-naphthylethyl- and 2-indolylethyl-5-acyloxy-6-alkoxy-*cis*-octahydroisoindole derivatives which have been examined for "reserpine-like" pharmacological activities.

A host of compounds more or less emulating structural features of the reserpine molecule[1] has been synthesized[2] in recent years. The present report is concerned with a stereospecific synthesis of a group of *cis*-octahydroisoindole derivatives,

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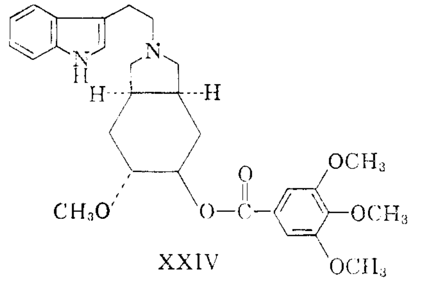
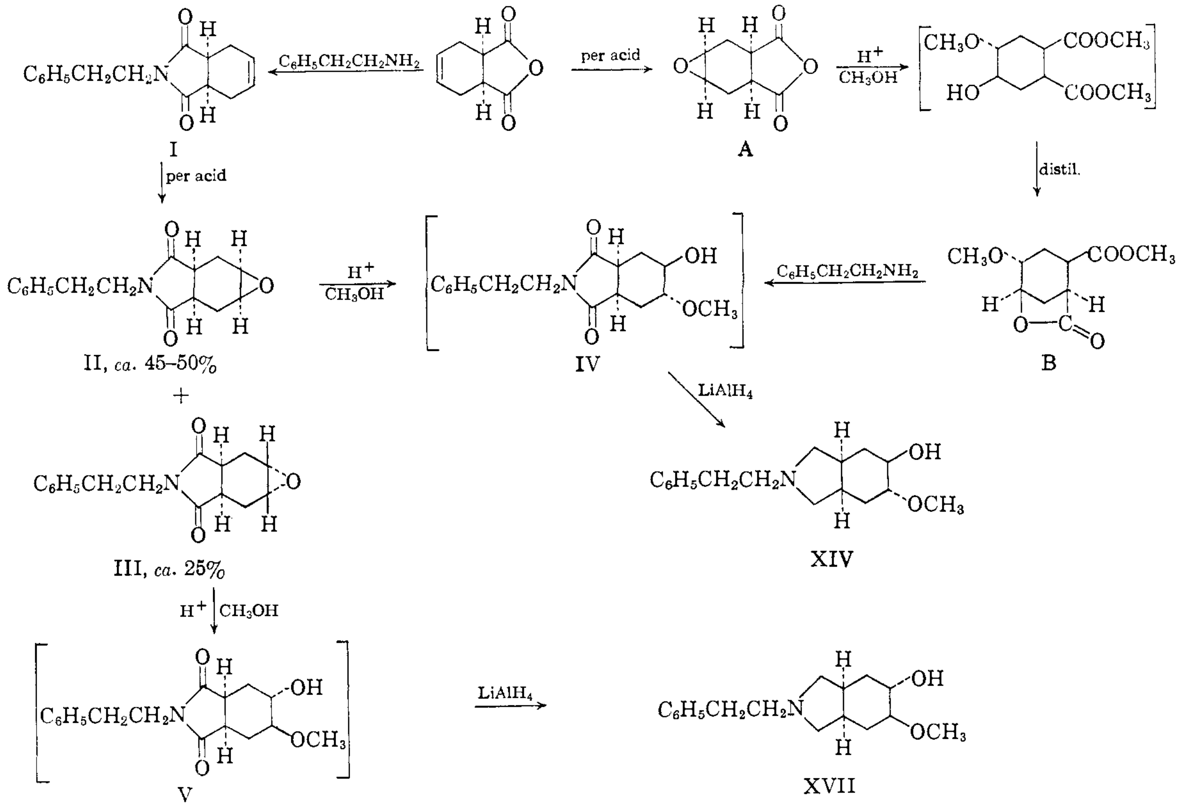
[1] For the definitive discussion of the structure and stereochemistry of reserpine, see P. E. Aldrich, *et al.*, *J. Am. Chem. Soc.*, **81**, 2481 (1959).

[2] *E.g.*, see M. A. Karim, W. H. Linnell and L. K. Sharp, *J. Pharm. Pharmacol.*, **12**, 74 (1960), and the many references cited therein.

the relationship of which to reserpine is suggested in the formulation of the closest analog in the series, 2-(3-indolylethyl)-5β-(3,4,5-trimethoxybenzoxy)-6α-methoxy-*cis*-octahydroisoindole (XXIV).[3] In connection with this work the stereochemical course of the epoxidation of *cis*-Δ^4-tetrahydrophthalic anhydride has been examined.



XXIV



cis-Δ^4-Tetrahydrophthalic anhydride has been epoxidized with peracetic acid,[4] but the stereochemistry of the derived 4,5-epoxy compound was not elaborated. We have effected the epoxidation with perbenzoic as well as with peracetic acid and have obtained the same epoxide as the only isolable product in roughly 50% yield with either reagent. The product is considered to be the 4,5β-epoxy derivative A.

Subjection of A to boiling methanol containing a few drops of sulfuric acid afforded a thick oil presumed to be a methoxy dimethyl ester derivative, inasmuch as on attempted vacuum distillation methanol was evolved and the carbomethoxy lactone B was obtained. The infrared spectrum of B, C=O stretching bands at 1740 cm.$^{-1}$ (5.75μ) (ester) and at 1785 cm.$^{-1}$ (5.60μ) (5-membered lactone),[5] no O—H stretching band present, confirms the gross structural assignment for the compound. The obvious explanation for lactone formation is, of course, that epoxidation had yielded the β-epoxide A which had undergone methanolysis in the usual way[6] to give the indicated product with the hydroxy and carbomethoxy groups on the same side of the cyclohexane ring. Formation of a lactone from the α-epoxide would necessitate either that: (a) the *cis*-diester had rearranged to the *trans* isomer under the methanolysis conditions (which is unlikely in view of the stability of esters of *cis*-hexahydrophthalic acid in boiling acidic alcohol,[7] but certainly not impossible since the 4,5-substituents could have affected configurational relationships); or (b) methanolysis had opened the anhydride ring first and this was followed by backside attack of the carboxylic acid group on the epoxide (which is unattractive for a number of reasons, not the least of which being that the product should then have been a hydroxy rather than a methoxy lactone). In any event, heating B with phenethylamine at a

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[3] The α,β stereochemical designations are patterned after the now widely adopted steroid convention. See L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd Edition, Reinhold Publ. Corp., New York, N. Y., 1949, p. 93.

[4] J. E. Gill and J. Munro, *J. Chem. Soc.*, 4630 (1952).

[5] L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 1954, pp. 159, 160; see also P. Wilder, Jr., and A. Winston, *J. Am. Chem. Soc.*, **77**, 5598 (1955); H. K. Hall, Jr., and R. Zbinden, *ibid.*, **80**, 6428 (1958).

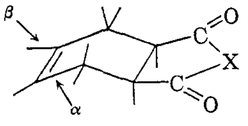
[6] *E.g.*, see S. Winstein and R. B. Henderson, *ibid.*, **65**, 2196 (1943).

[7] W. Hückel and E. Goth, *Ber.*, **58**, 447 (1925); L. Bauer and C. N. V. Nambury, *J. Org. Chem.*, **26**, 1106 (1961).

bath temperature *ca.* 175° afforded a hexahydrophthalimide, formulated as IV, which was not isolated but reduced directly with lithium aluminum hydride to an octahydroisoindole, XIV. Since *cis*-hexahydrophthalimides are known to be more stable than the *trans*-isomers and *trans*-imides rearrange to *cis* under the conditions used for imide formation,[8] and since isomerization should not occur in the course of lithium aluminum hydride reduction, both IV and XIV almost certainly have *cis* ring junctures as indicated.

Additional information relating to the configurational assignments derives from investigation of an alternative synthetic route. Reaction of *cis*-Δ^4-tetrahydrophthalic anhydride with phenethylamine provided a tetrahydrophthalimide which must have retained the *cis* configuration as represented in I.[9] Epoxidation of I, with either peracetic or perbenzoic acid, gave two epoxides, II (crystalline solid) and III (barely solid at room temperature), which were isolated in about 45–50% and 25% yields, respectively. Methanolysis of the major product, II, afforded a methoxy-hydroxy imide which was shown to be IV by its reduction to XIV, identical with the product derived from A. Subjecting III to the same reaction sequence provided an isomeric octahydroisoindole derivative, XVII. The fact that XIV is produced from II as well as from A strongly suggests that both epoxides have the β-configuration. Other processes leading to the same octahydroisoindole isomer from the corresponding α-epoxides require a minimum of two coincidental isomerizations; *e.g.*, the α-isomer of A would have to isomerize α-*cis* to *trans* and back to α-*cis* in being converted to XVII. On this basis III, the epoxyhexahydrophthalimide obtained from I in smaller yield, would be the α-epoxide.

The apparently exclusive attack of per acid on the double bond from the side of the anhydride ring, and predominantly from the side of the imide ring of I warrants examination. Henbest and coworkers found that 2-cyclohexenols are epoxidized by perbenzoic acid to β-epoxy derivatives, the hydroxyl group apparently participating intramolecularly in the reaction,[10] but that 3-cyclohexenemethanol and, strikingly, methyl 3-cyclohexenecarboxylate are converted to α-epoxy derivatives.[11] The course of the latter reactions was tentatively attributed to steric effects.[11] It may be noted that the outcome of the present epoxidations was unaffected by an increase in size of the per acid from peracetic to perbenzoic. Since this change included a change in solvent from acetic acid to chloroform, the fact that only a single epoxide was obtained from the anhydride cannot plausibly be ascribed to a special instability of the other isomer. Formation of a significant amount of α-epoxide from I, on the other hand, might be attributed to steric hindrance to approach from the β-side offered by the bulky phenethyl group. Explanation for the contrast in behavior between methyl 3-cyclohexenecarboxylate,[11] on the one hand, and *cis*-Δ^4-tetrahydrophthalic anhydride and I, on the other, must lie in conformational differences. Thus, the most stable conformation of the former is a half-chair form, whereas the latter, fused ring systems should be at lowest energy in a half-boat form. Buckles has suggested that this should be somewhat as represented by D.[12] The puckered ring of conformation D should hinder per acid attack from the α-direction, thus favoring β-attack. It is worth noting that D is reminiscent of the conformation of the rigid system, *exo*-*cis*-3,6-endomethylene-Δ^4-tetrahydrophthalic anhydride, which has been shown to undergo epoxidation from the β-side to give the equivalent *exo*-epoxy derivative.[13] Consequently, the evidence gleaned from these epoxidation studies offers support for the suggested conformation D.



D

Naphthylethyl and indolylethyl analogs of XIV were prepared as indicated in the tables and in the Experimental section. These *cis*-octahydroisoindole derivatives were acylated and the ester derivatives examined for pharmacological activity. They were found to possess distinct, albeit relatively weak, "reserpine-like" hypotensive and central depressant activity. The indole derivatives appeared to resemble reserpine most closely in the profile of their biological actions.[14,14a]

Experimental[15]

4,5β-Epoxy-*cis*-hexahydrophthalic Anhydride (A).—Epoxidation of *cis*-Δ^4-tetrahydrophthalic anhydride[16] with peracetic acid[4] afforded 49% of A, m.p. 203–205°.

With Perbenzoic Acid.—To 250 ml. of cold chloroform containing 0.11 mole of perbenzoic acid[17] was added 18.5 g. (0.12 mole) of the tetrahydrophthalic anhydride. The solution was stored in the refrigerator for 3 days, and the crystalline precipitate which had formed was collected and recrystallized from ethyl acetate to give 10.2 g. (55%) of A, m.p. 202–204°; a mixture m.p. with the product obtained using peracetic acid was not depressed. The original chloroform mother liquor was washed with 5% sodium carbonate solution, dried and evaporated to leave only a trace of residual material. Recrystallization of this provided *ca.* 0.2 g. more of A, m.p. 202–204°.

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[8] W. Hückel and H. Müller, *Ber.*, **64**, 1981 (1931); B. Bailey, R. D. Haworth and J. McKenna, *J. Chem. Soc.*, 967 (1954).

[9] See H. R. Snyder and G. I. Poos, *J. Am. Chem. Soc.*, **72**, 4104 (1950).

[10] H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1958 (1957).

[11] H. B. Henbest and B. Nicholls, *ibid.*, 221 (1959).

[12] R. E. Buckles, *Chem. Revs.*, **57**, 643 (1957).

[13] J. A. Berson and S. Suzuki, *J. Am. Chem. Soc.*, **80**, 4341 (1958).

[14] We are indebted to Dr. T. B. O'Dell and associates for the biological information.

[14a] H. B. Henbest and co-workers, *Tetrahedron Letters*, 398 (1961), recently reported evidence that electrostatic effects, exerted across space, tend to direct epoxidation *trans* to a polar substituent (*e. g.*, a cyano group). It would appear in the present instance that steric influences prevail over dipole interactions.

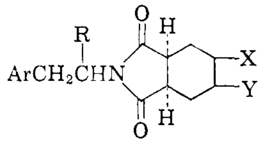
[15] Microanalyses were performed by the Clark Microanalytical Laboratories, Urbana, Ill., and by the Micro-Tech Laboratories, Skokie, Ill. Infrared spectra were determined in KBr disks by the Sadtler Research Laboratories, Philadelphia, Pa. Melting points are corrected for stem exposure.

[16] Yields were substantially improved by recrystallizing Eastman Kodak Co., practical grade, material prior to use.

[17] G. Braun, "Organic Syntheses," Coll. Vol. I, 2nd edition, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 431.

TABLE I

cis-HYDROPHTHALIMIDES

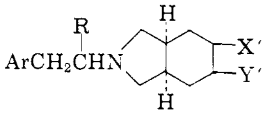


	Ar	R	X, Y	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
I	Phenyl	H	$\Delta^{4,5}$	90–92	$C_{16}H_{17}NO_2$	75.28	75.28	6.71	6.81
II	Phenyl	H	β-Epoxy[a]	157–158	$C_{16}H_{17}NO_3$	70.84	70.78	6.32	6.37
III	Phenyl	H	α-Epoxy[b]	[c]	$C_{16}H_{17}NO_3$	70.84	70.85	6.32	5.97
IV	Phenyl	H	β-OH, α-OCH_3	[d]					
V	Phenyl	H	α-OH, β-OCH_3	[d]					
VI	Phenyl	CH_3	$\Delta^{4,5}$	69–70[e]	$C_{17}H_{19}NO_2$	75.80	75.82	7.11	7.13
VII	Phenyl	CH_3	β-Epoxy	169–170[f]	$C_{17}H_{19}NO_3$	71.56	71.74	6.71	6.71
VIII	Phenyl	CH_3	α-Epoxy	[d]					
IX	Phenyl	CH_3	β-OH, α-OCH_3	[d]					
X	Phenyl	CH_3	α-OH, β-OCH_3	[d]					
XI	3-Indolyl	H	β-OH, α-OCH_3	128–130	$C_{19}H_{22}N_2O_4$	66.65	66.62	6.48	6.67
XII	3-Indolyl	H	β-OH, α-OC_2H_5	[d]					
XIII	1-Naphthyl	H	β-OH, α-OCH_3	[d]					

[a] Epoxide value, by calcium chloride–hydrochloric acid method, 82.5% of theoretical. [b] Epoxide value, 91.5%. [c] Low melting solid. [d] Thick oil. [e] Obtained from *d*-amphetamine; $[\alpha]^{25}D$ +67.0° (*c* 1.00 in chloroform.) [f] $[\alpha]^{25}D$ +80.0° (chloroform).

TABLE II

cis-OCTAHYDROISOINDOLES



	Ar	R	X', Y'	Salt	M.p., °C.[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Halogen, %[b] Calcd.	Halogen, %[b] Found
XIV	Phenyl	H	β-OH, α-OCH_3	..	[c]	$C_{17}H_{25}NO_2$					5.09	5.03
				HCl	158–160	$C_{17}H_{26}ClNO_2$	65.48	65.62	8.40	8.01	11.37	11.38
				CH_3I	136–137	$C_{18}H_{28}INO_2$	51.81	52.23	6.76	6.80	30.41	30.19
XV	Phenyl	H	β-TMB,[d] α-OCH_3	HCl[e]	157–158	$C_{27}H_{36}ClNO_6$	64.07	64.16	7.17	7.50	7.01	7.21
				CH_3Br	92–93	$C_{28}H_{38}BrNO_6$	59.57	59.27	6.78	6.70	14.16	14.58
XVI	Phenyl	H	β-$C_2H_5NHCO_2$–, α-OCH_3	..	64–67	$C_{20}H_{30}N_2O_3$					4.05	3.92
				HCl	64–67	$C_{20}H_{31}ClN_2O_3$	62.73	63.17	8.16	8.69	9.26	9.16
XVII	Phenyl	H	α-OH, β-OCH_3	..	[f]	$C_{17}H_{25}NO_2$					5.09	5.03
				HCl	165–166	$C_{17}H_{26}ClNO_2$	65.48	65.73	8.40	8.31	11.37	11.41
XVIII	Phenyl	H	α-TMB,[d] β-OCH_3	HCl[e]	174	$C_{27}H_{36}ClNO_6$	64.07	63.72	7.17	7.20	7.01	7.49
XIX	Phenyl	CH_3	β-OH, α-OCH_3	..	[g]	$C_{18}H_{27}NO_2$					4.84	4.80
				HCl	83–85[h]	$C_{18}H_{28}ClNO_2$	66.33	66.92	8.66	8.41	10.88	10.91
XX	Phenyl	CH_3	β-TMB,[d] α-OCH_3	..	87–89	$C_{28}H_{37}NO_6$					2.90	2.89
				HCl	126–128	$C_{28}H_{38}ClNO_6$	64.66	64.83	7.36	7.37	6.82	6.82
XXI	Phenyl	CH_3	α-OH, β-OCH_3	..	[i]	$C_{18}H_{27}NO_2$					4.84	4.74
				HCl	66–84[j]	$C_{18}H_{28}ClNO_2$	66.33	66.07	8.66	8.88	10.88	10.69
XXII	Phenyl	CH_3	α-TMB,[d] β-OCH_3	HCl[e]	168–171	$C_{28}H_{38}ClNO_6$	64.66	64.71	7.36	7.28	6.82	6.82
XXIII	3-Indolyl	H	β-OH, α-OCH_3	..	94–96	$C_{19}H_{26}N_2O_2$					4.46	4.17
				HCl	98–99[k]	$C_{19}H_{27}ClN_2O_2$	65.03	64.78	7.76	7.98	10.11	9.60
XXIV	3-Indolyl	H	β-TMB,[d] α-OCH_3	HCl[e]	198–199.5	$C_{29}H_{37}ClN_2O_6$	63.90	64.18	6.84	6.79	6.51	6.31
				HCl[l]	125–126[m]	$C_{30.5}H_{41}ClN_2O_{6.5}$	63.69	63.88	7.19	7.13	6.17	6.06
XXV	3-Indolyl	H	β-$C_2H_5CO_2$–, α-OCH_3	HCl[e]	158–163	$C_{22}H_{31}ClN_2O_3$	64.93	65.10	7.68	7.69	8.71	8.55
XXVI	3-Indolyl	H	β-$C_6H_5CH_2CO_2$–, α-OCH_3	HCl[e]	76[n]	$C_{27}H_{33}ClN_2O_3$	69.14	69.24	7.09	6.80	7.56	7.12
XXVII	3-Indolyl	H	β-OH, α-OC_2H_5	HCl[c]	116–117	$C_{20}H_{29}ClN_2O_2$	65.83	66.13	8.01	7.72	9.71	9.60
XXVIII	3-Indolyl	H	β-$C_6H_{11}CO_2$–,[o] α-OC_2H_5	HCl[e]	176–178	$C_{27}H_{39}ClN_2O_3$	68.25	68.60	8.27	8.11	7.46	7.57
XXIX	1-Naphthyl	H	β-OH, α-OCH_3	..	[p]	$C_{21}H_{27}NO_2$					4.30	4.29
				HCl	55–60[q]	$C_{21}H_{28}ClNO_2$	69.70	69.12	7.80	7.51	9.80	9.73
XXX	1-Naphthyl	H	β-TMB,[d] α-OCH_3	HCl[e]	229–231	$C_{31}H_{38}ClNO_6$	66.94	66.54	6.88	6.79	6.37	6.36
XXXI	1-Naphthyl	H	β-$C_2H_6CO_2$–, α-OCH_3	HCl[e]	138–145	$C_{24}H_{32}ClNO_3$	69.00	69.10	7.72	7.66	8.47	8.46

[a] The salts melt with decomposition. [b] Ionic halogen by potentiometric titration, or (bases) basic nitrogen by acetous-perchloric titration. [c] Thick oil, b.p. 164–168° (0.5 mm.), $n^{25}D$ 1.5397. [d] TMB = 3,4,5-trimethoxybenzoxy. [e] The base was obtained as an oil which did not crystallize. [f] Thick oil, b.p. 165–170° (0.3 mm.), $n^{25}D$ 1.5400. [g] Thick oil, b.p. 171–177° (0.4 mm.). [h] $[\alpha]^{24}D$ +14.0° (*c* 1.00 in ethanol). [i] Thick oil, b.p. 163–175° (0. 4 mm.). [j] Very hygroscopic; $[\alpha]^{24}D$ +14.0° (ethanol). [k] Melted with preliminary shrinking and gas evolution. [l] Hemi-isopropyl alcoholate of the hydrochloride; loss in weight on drying at 110° (*in vacuo*) 7.0%; calcd. 5.2%. [m] Melted with gas evolution, then resolidified and melted again at 198–200°. [n] With considerable gas evolution. [o] $C_6H_{11}CO_2$– = cyclohexanecarboxy. [p] Thick oil, b.p. 175–210° (0.1 mm.). [q] Hygroscopic, melted to a glass.

2β-Carbomethoxy-5β-hydroxy-4α-methoxycyclohexanecarboxylic Acid γ-Lactone (B).—A mixture of 48.0 g. (0.28 mole) of A and 300 ml. of absolute methanol containing 5 drops of concentrated sulfuric acid was boiled under reflux on a steam-bath for 6 hours, by which time all of the anhydride had dissolved. The solution was concentrated *in vacuo* to about half its volume, stirred with sufficient calcium carbonate to neutralize the acid, filtered and lyophilized, the last traces of solvent methanol being removed at 0.5 mm. from the residual thick oil. The bath temperature was then gradually raised to *ca.* 190° at which point vaporized material (methanol) was collected in the Dry Ice trap and the product began to distil as a colorless oil, 33.3 g. (54%), b.p. 150–152° (0.3 mm.), n^{28}D 1.4778.

Anal. Calcd. for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.29; H, 6.65.

2β-Carbethoxy-5β-hydroxy-4α-ethoxycyclohexanecarboxylic Acid γ-Lactone (C).—A similar reaction of A with boiling ethanol yielded 42% of C as a colorless oil, distilling over the range 121–142° (0.5 mm.), n^{25}D 1.4650.

Anal. Calcd. for $C_{12}H_{18}O_5$: C, 59.50; H, 7.49; sapon. equiv., 121.1. Found: C, 59.05; H, 7.61; sapon. equiv., 119.5.

Hexahydrophthalimides by Reaction of γ-Lactones with Arylethylamines. N-(3-Indolylethyl)-4β-hydroxy-5α-methoxy-*cis*-hexahydrophthalimide (XI).—An intimate mixture of 50.0 g. (0.31 mole) of tryptamine[18] and 75.0 g. (0.35 mole) of γ-lactone B was heated under a slow stream of nitrogen in an oil-bath at a temperature of 145° for 6 hours. The dark melt bubbled gently during the heating period and solidified to a glass on cooling. A chloroform solution of the glass was washed with 5% hydrochloric acid, extracted with 5% sodium hydroxide solution and finally washed with water. Drying of the chloroform layer over sodium sulfate and dilution with petroleum ether (b.p. 60–70°) yielded 66.5 g. (63%) of tan crystals, m.p. 125–129° after preliminary softening at 110°. Recrystallization from chloroform–petroleum ether afforded XI as colorless crystals, m.p. 128–130°.

Compounds IV, XII and XIII were also prepared in this way.

Tetrahydrophthalimides. N-Phenethyl-*cis*-Δ⁴-tetrahydrophthalimide (I).—A mixture of 50.0 g. (0.33 mole) of *cis*-Δ⁴-tetrahydrophthalic anhydride and 40.0 g. (0.33 mole) of phenethylamine was heated in an oil-bath at a bath temperature of 175° for 4 hours, toward the end of which period the temperature was gradually raised to 200°. The cooled melt was crystallized from ethanol to give 72.9 g. (87%) of I in the form of colorless needles, m.p. 90–92°.

Epoxidation of Tetrahydrophthalimides. N-Phenethyl-4,5β-epoxy-*cis*-hexahydrophthalimide (II) and N-Phenethyl-4,5α-epoxy-*cis*-hexahydrophthalimide (III).—To 950 ml. of an ice-cold chloroform solution containing 0.28 mole of perbenzoic acid was added a solution of 70.0 g. (0.27 mole) of I in 150 ml. of chloroform. The solution was stored in the refrigerator for 48 hours, washed with aqueous sodium carbonate and then with water. Drying and removal of the chloroform and crystallization of the residue from benzene yielded 35.0 g. (48%) of II as colorless needles, m.p. 157–158°.

Evaporation of the benzene mother liquors to dryness afforded 20 g. (27%) of III as a thick yellow oil which crystallized out of benzene–petroleum ether as a low melting solid.

Comparable yields of II (46%) and III (20%) were obtained when Compound I was epoxidized in chloroform solution with commercial (Becco) 40% peracetic acid; the 1% of sulfuric acid this contains was neutralized by the prior addition of sodium acetate.

Peracetic acid epoxidation of VI gave similar results: 47% of **N-α-methylphenethyl-4,5β-epoxy-*cis*-hexahydrophthalimide** (VII) and 27% of **N-α-methylphenethyl-4,5α-epoxy-*cis*-hexahydrophthalimide** (VIII).

Methanolysis of Epoxyhexahydrophthalimides. N-Phenethyl-4β-hydroxy-5α-methoxy-*cis*-hexahydrophthalimide (IV).—A mixture of 35.0 g. (0.13 mole) of II and 300 ml. of methanol containing a few drops of concentrated sulfuric acid was heated under reflux on a steam-bath for 4 hours. The cooled solution was treated with calcium carbonate, filtered and evaporated to yield 33 g. of IV as a thick yellow oil which could not be crystallized.

Similar methanolyses of III, VII and VIII, respectively, provided V, IX and X.

Lithium Aluminum Hydride Reduction of Hexahydrophthalimides.—All of the 5-hydroxy-6-alkoxyoctahydroisoindoles listed in Table II were prepared by this process which is illustrated by the following examples.

A. **2-Phenethyl-5β-hydroxy-6α-methoxy-*cis*-octahydroisoindole (XIV).**—To a slurry of 19.0 g. (0.5 mole) of lithium aluminum hydride in 500 ml. of anhydrous ether was added, dropwise with stirring, a solution of 42.0 g. (0.14 mole) of IV in 100 ml. of dry ethylene glycol dimethyl ether. Stirring was continued and the reaction mixture was heated at reflux for 11 hours. Ethyl acetate was added to the ice-cold mixture followed by 100 ml. of water to hydrolyze the aluminum complexes. The filtered ethereal solution was extracted with aqueous acid, the acid extract was made alkaline and the precipitate taken into ether. Drying and removal of the ether left an oil which was distilled to give 27 g. (70%) of XIV, b.p. 164–168° (0.5 mm.), n^{25}D 1.5397.

The hydrochloride salt of XIV, recrystallized from isopropyl alcohol–ethyl acetate, formed colorless pellets, m.p. 158–160°.

XIV picrate, recrystallized from ethanol, melted at 168–169°.

XIV methiodide showed m.p. 136–137° after recrystallization from isopropyl alcohol–ethyl acetate.

Corresponding salts of XIV obtained by reduction of IV derived (a) from the γ-lactone B and (b) from the β-epoxyhexahydrophthalimide (II) showed identical melting points. Melting points of mixtures were not depressed.

B. **2-Phenethyl-5α-hydroxy-6β-methoxy-*cis*-octahydroisoindole (XVII).**—In essentially the same way, lithium aluminum hydride reduction of V afforded 56% of XVII, b.p. 165–170° (0.3 mm.), n^{25}D 1.5400.

XVII hydrochloride melted at 165–166° after recrystallization from isopropyl alcohol–ethyl acetate. The melting point of a mixture with XIV hydrochloride was depressed to 131–143°.

XVII picrate, recrystallized from methanol–ethanol, showed m.p. 158–160°. Admixture with XIV picrate depressed the melting point to 148–159°.

C. **2-(3-Indolylethyl)-5β-hydroxy-6α-methoxy-*cis*-octahydroisoindole (XXIII).**—To a slurry of 20.9 g. (0.55 mole) of lithium aluminum hydride in a mixture of 750 ml. of ether and 750 ml. of ethylene glycol dimethyl ether was added, dropwise with stirring, a solution of 52.0 g. (0.15 mole) of XI in 500 ml. of warm glycol diether. The reaction mixture was heated under reflux for 10 hours. Ethyl acetate, water and then 1700 ml. of 5% hydrochloric acid were successively added to the ice-cold reaction mixture. The aqueous acid layer was separated, washed with ether, treated with 280 g. of sodium potassium tartrate (Rochelle salt), made alkaline and extracted with ether. Drying and removal of the ether left a thick oil which partially crystallized from aqueous isopropyl alcohol. The mixture of crystals and oil was treated with charcoal in a 2% hydrochloric acid solution. The acid solution was neutralized with concentrated ammonia to precipitate an oil which crystallized on standing. Recrystallization from aqueous isopropyl alcohol afforded 28.3 g. (60%) of product, m.p. 89–95°. After another recrystallization from aqueous ethanol XXIII showed m.p. 94–96°.

Ester Derivatives.—For the most part the esters listed in Table II were prepared by treatment of the 5-hydroxy-6-alkoxyoctahydroisoindoles with appropriate acid chlorides.

A. **2-Phenethyl-5β-(3,4,5-trimethoxybenzoxy)-6α-methoxy-*cis*-octahydroisoindole (XV).**—To an ice-cold solution of 11.0 g. (0.04 mole) of XIV in 250 ml. of dry pyridine was added, portionwise with stirring, 28.0 g. (0.12 mole) of 3,4,5-trimethoxybenzoyl chloride. After it had stood for 3 days at room temperature, the dark red solution was poured on cracked ice and acidified with 10% hydrochloric acid. The precipitated trimethoxybenzoic anhydride was filtered off and the filtrate was washed with ether, cooled in an ice-bath, made alkaline with solid potassium carbonate and extracted with ether. Drying and removal of the ether left an oil which failed to crystallize. Treatment of an ether solution of the oil with ethereal hydrogen chloride precipitated the salt. Recrystallization from acetone–

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[18] Conveniently prepared in good yield by the method of J. Thesing and F. Schülde, *Chem. Ber.*, **85**, 324 (1952), as modified by G. Stork and R. K. Hill, *J. Am. Chem. Soc.*, **79**, 498 (1957).

ether (with charcoal) yielded 9.5 g. (48%) of the **hydrochloride salt of XV** as colorless crystals, m.p. 157–158°.

B. 2-Phenethyl-5α-(3,4,5-trimethoxybenzoxy)-6β-methoxy-*cis*-octahydroisoindole (XVIII).—A similar treatment of XVII with trimethoxybenzoyl chloride afforded **XVIII hydrochloride**, m.p. 174° after recrystallization from acetone–ether. The melting point of a mixture of the hydrochloride salts of XV and XVIII was depressed to 135–143°.

C. 2-(3-Indolylethyl)-5β-(3,4,5-trimethoxybenzoxy)-6α-methoxy-*cis*-octahydroisoindole (XXIV).—A solution of 40.0 g. (0.13 mole) of XXIII in 300 ml. of dry pyridine, cooled in an ice-bath, was treated with 90 g. (0.4 mole) of 3,4,5-trimethoxybenzoyl chloride. The solution was allowed to warm to room temperature and then stored in the dark for 5 days. The solution was poured on a slurry of cracked ice and 10% hydrochloric acid solution and the resultant mixture thoroughly washed with ethyl acetate to remove trimethoxybenzoic anhydride. The remaining aqueous acid layer was cooled in ice, made alkaline with solid potassium carbonate and extracted with ether. Drying and removal of the ether left a red resin that was dissolved in ethyl acetate and shaken with a 3% hydrochloric acid solution to precipitate the crude hydrochloride salt of the product as a red oil, not soluble in either layer. The red oil was washed with fresh solvent and crystallized (with charcoal) from isopropyl alcohol–ether to yield 32.1 g. of crystalline material, m.p. 119–125° (with gas evolution). Recrystallization from isopropyl alcohol–ether and then from acetone–ether afforded 17.5 g. of the anhydrous **hydrochloride salt of XXIV** as colorless crystals, m.p. 198–199.5° (gas evolution).

Dilution of the isopropyl alcohol mother liquors with more ether precipitated 12.6 g. of crystals which analyzed as the **hemi-isopropyl alcoholate of XXIV hydrochloride**, m.p. (gas evolution) 125–126°, followed by resolidification and remelting at 198–200°. The alcoholate could be converted to the anhydrous salt by treatment with hot isopropyl alcohol or hot acetone. The combined yield of analytically pure material was 42%.

D. 2-Phenethyl-5β-(N-ethylcarbamyloxy)-6α-methoxy-*cis*-octahydroisoindole (XVI).—A mixture of 7.0 g. (0.025 mole) of XIV and 3 ml. of ethyl isocyanate was heated on a steam-bath for 45 minutes. The reaction mixture was taken up in benzene and the solution was evaporated under reduced pressure to a thick oil. Crystallization of this from petroleum ether (b.p. 60–70°) afforded 6.9 g. (80%) of XVI, m.p. 64–67°.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IOWA STATE UNIVERSITY, AMES, IOWA]

Synthesis of Olivacine[1]

BY ERNEST WENKERT AND K. G. DAVE

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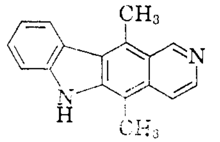
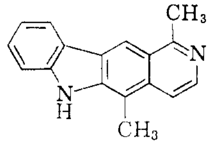
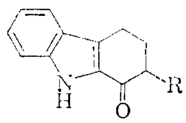
A synthesis of the indole alkaloid olivacine is described.

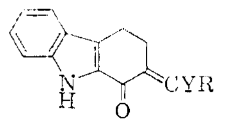
The year 1959 witnessed the completion of the structure elucidation of an array of indole alkaloids one of whose common features was their lack of structural correspondence with the well-known natural bases of the yohimbine–ajmalicine–corynantheine and strychnos types. It was of interest to synthesize some of these compounds in order to corroborate their structures as well as study their chemistry. The first alkaloid chosen was olivacine, a $C_{17}H_{14}N_2$ base, which had been isolated recently from four sources, *Aspidosperma olivaceum* Müll. Arg.,[2a] *Aspidosperma longepetiolatum* Kuhlm.,[2b] *Aspidosperma australe* Müll. Arg.[2c] and *Tabernaemontana psychotrifolia*,[2d] and a comparison of whose basicity, spectral properties and possible biosynthesis with those of ellipticine, an isomeric alkaloid of structure I,[3] had led Marini-Bettolo and Schmutz to suggest II as its structure.[4,5]


I


II

The ketotetrahydrocarbazole IIIa appeared to be the most likely candidate as starting material for the synthesis of the pyridocarbazole system. It could be converted to its hydroxymethylene (IVa) and ethoxalyl (IVb) derivatives by sodium ethoxide-induced acylation with ethyl formate and ethyl oxalate, respectively. Transformations of the two compounds to further useful intermediates were carried out in parallel investigations.


IIIa, R = H
b, R = CH_2CO_2Et
c, R = CH_2CO_2H


IVa, R = H, Y = OH
b, R = CO_2Et, Y = OH
c, R = CO_2Et, Y = OAc
d, R = CO_2Et, Y = H
e, R = H, Y = OAc
f, R = H, Y = O*i*-Pro

Acetylation of the ethoxalyl derivative IVb led to the diester IVc, which afforded the ketoester IVd on partial hydrogenation over palladium–charcoal. Zinc–acetic acid reduction of either ester IVc or IVd led to the saturated ketoester IIIb. Methyllithium addition to the latter or to its acid IIIc yielded two products both of which seemed to have suffered dehydration, presumably

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[1] This work was presented for the first time at the International Symposium on the Chemistry of Natural Products, under the auspices of the Section of Organic Chemistry of the International Union of Pure and Applied Chemistry, Melbourne, Canberra and Sydney, Australia, August 15–25, 1960. It was supported by U. S. Army Chemical Corps contract DA18-108-405-CML-269.

[2] (a) J. Schmutz and F. Hunziker, *Pharm. Acta Helv.*, **33**, 341 (1958); (b) G. B. Marini-Bettolo, *Ann. Chim.*, **49**, 869 (1959); (c) M. A. Ondetti and V. Deulofeu, *Tetrahedron Letters*, No. **7**, 1 (1959); (d) M. Gorman, N. Neuss, N. J. Cone and J. A. Deyrup, *J. Am. Chem. Soc.*, **82**, 1142 (1960).

[3] R. B. Woodward, G. A. Iacobucci and F. A. Hochstein, *ibid.*, **81**, 4434 (1959).

[4] G. B. Marini-Bettolo and J. Schmutz, *Helv. Chim. Acta*, **42**, 2146 (1959).

[5] Just prior to completion of our work there appeared a synthesis of olivacine (II) by J. Schmutz and H. Wittwer [*ibid.*, **43**, 793 (1960)]. While this constituted a rigorous proof of the structure of the alkaloid, our work was continued, since it involved a route of synthesis quite dissimilar from that of the Swiss workers.