oily product, which represented ethyl 2,3-*trans*-diphenyl-2,3-epoxypropionate, possessed bands in the infrared at 10.70 and 15.60 μ where the *cis*-diphenyl stereoisomer was transparent. Also, the *cis*-diphenyl stereoisomer, m.p. 58°, possessed a band at 7.96 μ where the oily stereoisomer was transparent.

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.97; H, 5.65.

2,3-*trans*-Diphenyl-2,3-epoxypropionic Acid.—A solution of 75 mg. of the oily glycidic ester obtained above (0.28 mmole) in 5.0 ml. of absolute ethanol was added to a sodium ethoxide solution prepared from 25 mg. (1.10 mmoles) of sodium, 5.0 ml. of absolute ethanol and 350 mg. of water. The mixture was allowed to stand at room temperature for 11 hours. It was then concentrated *in vacuo*, diluted with water and ether extracted. The aqueous phase was cooled in ice and carefully acidified with dilute hydrochloric acid and immediately ether extracted. The ether extract was washed free of acid and dried over Drierite and concentrated to afford 55 mg. of a solid melting at 90–92°. One crystallization from hexane–ether gave 32 mg. of acid, m.p. 96–98°. One further crystallization yielded material melting at 97.0–98.0° (reported[3] 100°).

Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 74.26, 75.62; H, 5.40, 4.89.

Acknowledgment.—Support of this research by the Office of Ordnance Research, U. S. Army, is gratefully acknowledged.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF KANSAS, LAWRENCE, KANS.]

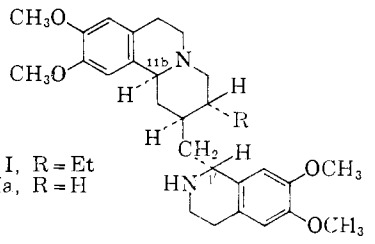
Synthetic Applications of Hexahydrogallic Acid. I. A New Route to Emetine[1]

BY ALBERT W. BURGSTAHLER AND ZOE J. BITHOS

RECEIVED MARCH 10, 1960

A synthetic route to the Ipecac alkaloid emetine (I) from hexahydrogallic acid and homoveratrylamine is described.

Primarily because of its powerful amoebicidal but undesirable toxic properties, emetine (I), the principal member of the Ipecac group of isoquinoline alkaloids, has long been a popular subject of extensive degradative, structural and synthetic studies.[2] Intensified considerably in recent years, these investigations have grown in importance and have now resulted in a number of independent total syntheses of emetine,[3] a significant partial synthesis,[4] and the complete elucidation of the stereochemistry and absolute configuration of the alkaloid.[5]



I, R = Et
Ia, R = H

In the present report, as part of a program concerned with synthetic applications of the hexahydrogallic acid obtained by catalytic hydrogenation of gallic acid,[6] a fundamentally new route to emetine is described.[1] This synthesis involves, as its key step, formation of the tricyclic lactam aldehyde IV by cyclodehydration of the β-substituted glutaraldehyde III, the latter, in turn, being obtained by periodate oxidation[7] of the homologated hexahydrogallic acid derivative II.[8]

A two-step hydrogenation of gallic acid, first with Raney nickel in aqueous base and then with platinum oxide in methanol, has been reported[6a] to furnish a homogeneous hexahydrogallic acid (VI) of m.p. 198° (uncor.) (203° cor.)[6b] in an over-all yield of 13 to 19%. In the present work, reduction of gallic acid under high pressure with 5% rhodium-on-alumina in ethanol has been found to afford this same product directly in yields of 45 to 50%. Like γ-pyrogallitol (*cis-cis*-1,2,3-cyclohexanetriol, V), which is the major product formed in the closely related hydrogenation of pyrogallol over the same catalyst (or over palladium or nickel),[9] this particu-

(1) Taken in part from the M.S. Thesis of Z.J.B., Univ. of Kansas, 1958. First reported in a Communication to the Editor, THIS JOURNAL, **81**, 503 (1959). A portion of this work was also presented before the Division of Organic Chemistry at the 133rd National Meeting of the American Chemical Society, San Francisco, Calif., April 13–18, 1958.

(2) For an excellent guide to much of the pertinent literature, *cf.* A. Brossi, H. Lindlar, M. Walter and O. Schnider, *Helv. Chim. Acta*, **41**, 119 (1958); see also papers cited in ref. 3 and 5.

(3) (a) R. P. Evstigneeva, R. S. Livshitz, L. I. Zakharkin, M. S. Bainova and N. A. Preobrazhensky, *Doklady Akad. Nauk, S.S.S.R.*, **75**, No. 4, 539 (1950), and later papers; (b) M. Barash and J. M. Osbond, *Chemistry & Industry*, 490 (1958); (c) A. R. Battersby and J. C. Turner, *ibid.*, 1324 (1958); (d) R. P. Evstigneeva and N. A. Preobrazhensky, *Tetrahedron*, **4**, 223 (1958); (e) A. Brossi, M. Baumann and O. Schnider, *Helv. Chim. Acta*, **42**, 1515 (1959); (f) A. Grüssner, E. Jaeger, J. Hellerbach and O. Schnider, *ibid.*, **42**, 2431 (1959); (g) M. Barash, J. M. Osbond and J. C. Wickens, *J. Chem. Soc.*, 3530 (1959); (h) A. R. Battersby and J. C. Turner, *ibid.*, 717 (1960).

(4) A. R. Battersby and B. J. T. Harper, *ibid.*, 1748 (1959).

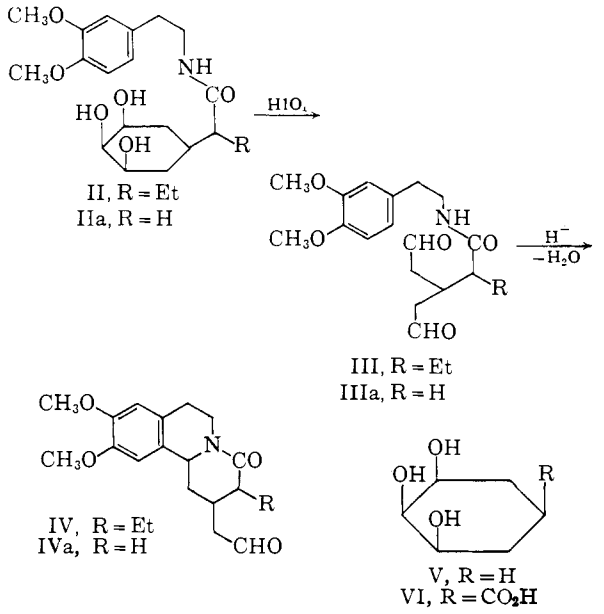
(5) (a) E. E. van Tamelen, P. E. Aldrich and J. B. Hester, THIS JOURNAL, **81**, 6214 (1959), (b) A. R. Battersby and S. Garratt, *J. Chem. Soc.*, 3512 (1959); (c) A. Brossi, A. Cohen, J. M. Osbond, P. Plattner, O. Schnider and J. C. Wickens, *ibid.*, 3630 (1959); (d) Y. Ban, M. Terashima and O. Yonemitsu, *Chemistry & Industry*, 568, 569 (1959).

(6) (a) W. Mayer, R. Bachmann and F. Kraus, *Ber.*, **88**, 316 (1955); (b) W. Mayer and L. Keller, *ibid.*, **92**, 213 (1959).

(7) The potential synthetic use of the hexahydrogallic acid structure as a source of a β-substituted glutaraldehyde intermediate was apparently first recognized by H. O. L. Fischer and G. Dangschat [*Helv. Chim. Acta*, **17**, 1200 (1934)] in connection with dihydroshikimic acid. A possible role of shikimic acid in the biosynthesis of emetine and related alkaloids has been amplified recently by E. Wenkert and N. V. Bringi, THIS JOURNAL, **81**, 1474 (1959). It also should be noted that use of a β-substituted glutaraldehyde in the synthesis of strychnine has been proposed by R. Robinson and J. E. Saxton, *J. Chem. Soc.*, 2596 (1953); *cf.* A. R. Katritzky, *ibid.*, 2581, 2586 (1955).

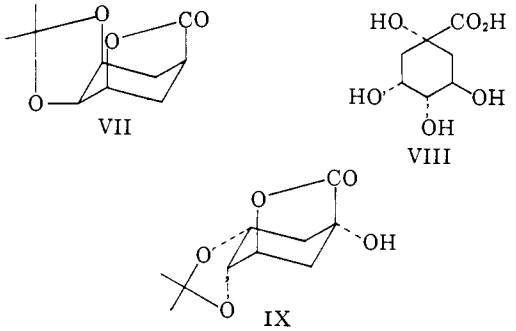
(8) A similar reaction sequence has also been applied in the total synthesis of yohimbine [E. E. van Tamelen, M. Shamma, A. W. Burgstahler, J. Wolinsky, R. Tamm and P. E. Aldrich, THIS JOURNAL, **80**, 5006 (1958)]. For a closely related cyclodehydration to form the erythrinane and erysotrine skeletons, *cf.* B. Belleau, *ibid.*, **75**, 5765 (1953); *Can. J. Chem.*, **35**, 651, 663 (1957); A. Mondon, *Angew. Chem.*, **68**, 578 (1956); *ibid.*, **70**, 406 (1958); also V. Boekelheide, *et al.*, THIS JOURNAL, **81**, 3955, 3959 (1959).

(9) W. R. Christian, C. J. Gogek and C. B. Purves, *Can. J. Chem.*, **29**, 911 (1951); *cf.* S. J. Angyal and D. J. McHugh, *J. Chem Soc.*, 3682 (1957).



lar stereoisomer of hexahydrogallic acid has also been demonstrated, both by Mayer and Keller[6b] and by ourselves, to have an all-*cis* configuration, as indicated in formula VI.

By reaction with acetone in the presence of an acid catalyst, VI is converted into a γ-lactone acetonide, VII,[6b,10] in the same manner that quinic acid (VIII) is transformed into the quinide acetonide IX.[11] Evidence for the all-*cis* nature of the



triol function in VI is provided by the *p*H change[12] of an aqueous solution of sodium periodate on admixture with a solution of the methyl ester of this acid. Just as with γ-pyrogallitol (V), there is a decided increase in acidity, due presumably to a peculiar "complexing" of the *cis-cis*-3,4,5-cyclohexanetriol system with periodate ion.[12] The methyl ester of quinic acid (VIII), which contains a *cis-trans*-3,4,5-triol grouping, does not exhibit this *p*H-lowering effect, nor do other cyclic *vic*-triols which are not all-*cis*.[12] Direct chemical proof of the all-*cis* character of the triol function in VI was obtained by Mayer and Keller,[6b] who, by using a sequence involving the Hunsdiecker reaction, succeeded in degrading VI to γ-pyrogallitol (V).

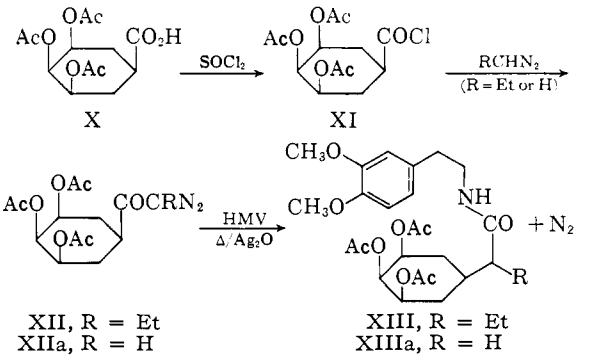
(10) We are indebted to Mrs. Shiu-shia (Hwang) Kung for the preparation of this derivative and several of its transformation products.

(11) H. O. L. Fischer, *Ber.*, **54**, 775 (1921); H. O. L. Fischer and G. Dangschat, *ibid.*, **65**, 1009 (1932).

(12) G. R. Barker and D. F. Shaw, *J. Chem. Soc.*, 584 (1959); G. R. Barker, *ibid.*, 624 (1960).

Finally, the nuclear magnetic resonance spectra[13] of the lactone acetonide VII and a derived tetrol are also in agreement with this stereochemical assignment (see Experimental).

For the preparation of the homologated hexahydrogallic acid derivatives II and IIa, the following reactions were employed. Hexahydrogallic acid



(VI) was converted to the crystalline triacetate X, m.p. 156–157°, by the action of acetic anhydride, as described by Mayer, *et al.*[6a] Treatment of X with thionyl chloride then provided the low-melting acid chloride XI, which, by reaction with 1-diazopropane, afforded the diazoketone XII, and, by reaction with diazomethane, the model diazoketone XIIa. The latter was obtained as a crystalline solid, m.p. 99–101°, but XII, like many substituted diazoketones,[14] remained a glass. When heated with silver oxide in 1,2-dimethoxyethane containing one molar equivalent of homoveratrylamine (HMV), these diazoketones underwent the desired Wolff rearrangement to give the corresponding amides XIII and XIIIa, respectively.[15] Again, in the model series (R = H) the product XIIIa was obtained crystalline, m.p. 126–127°, but in the ethyl series (XIII) it remained a glass. Selective hydrolysis of the ester functions in XIII and XIIIa afforded the crystalline triol amides II and IIa, m.p. 197–198° and 196–197°, respectively. In the model series the over-all yields of IIa from hexahydrogallic acid triacetate (X) ranged from 50 to 55%. In the R = ethyl series the best yields of II from X were about 20–25%. The infrared spectra (KBr) of II and IIa showed marked similarities and exhibited the expected intense amide carbonyl peak at 6.02 μ and broad –OH and –NH stretching in the 2.7–3.0 μ region.

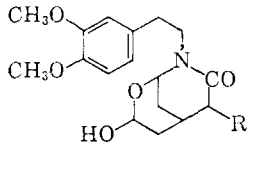
Cleavage of the triol function in II and IIa with periodic acid in aqueous 1,2-dimethoxyethane gave a mixture of what appeared to be mainly the lactol lactams XIV and XIVa (isolated in crystalline form in the case of the latter), along with the hydroxy lactam aldehydes XV and XVa. Each of these products had a characteristic δ-lactam absorption peak in the infrared at 6.09 μ (batho-

(13) We wish to express our appreciation to Dr. James N. Shoolery and his collaborators at the Varian Associates, Palo Alto, Calif., for these determinations and their interpretation.

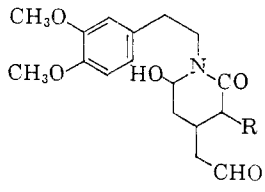
(14) A. L. Wilds and A. L. Meader, Jr., *J. Org. Chem.*, **13**, 763 (1948).

(15) There are numerous instances of the use of the Arndt–Eistert reaction in the synthesis of alkaloids and related products. *Inter alia*, *cf.* K. W. Bentley and S. F. Dyke, *Chemistry & Industry*, 1054 (1956), and references cited there; see also ref. 32 below.

chromic shift from the 6.02 μ band in the triol amides II and IIa, but only XV and XVa contained a 5.81 μ free-aldehyde carbonyl absorption band). From the spectra it also appeared that only relatively minor amounts of the free amide dialdehydes III and IIIa were present in the cleavage products as isolated.



XIV, R = Et
XIVa, R = H

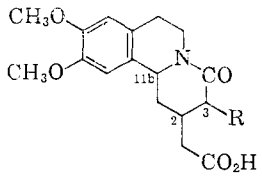


XV, R = Et
XVa, R = H

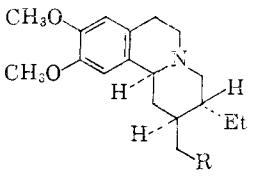
On treatment with warm, dilute phosphoric acid,[8] the cleavage-product mixtures readily underwent ring closure in a Pictet–Spengler type of cyclodehydration to give the tricyclic lactam aldehydes IV and IVa, which could not be obtained crystalline, but whose infrared spectra displayed the expected strong carbonyl absorption bands at 5.81 μ (aldehyde) and 6.17 μ (fused δ-lactam). From IVa a solid 2,4-dinitrophenylhydrazone, m.p. 208–210°, was deposited, but IV yielded only an oily derivative, thus indicating that it was probably a mixture of stereoisomers.

By oxidation with silver oxide in aqueous ethanol at *p*H 9–10, the preceding lactam aldehydes were converted to the corresponding crystalline lactam acids. In the model series (R = H) the yield of the lactam acid XVIa, m.p. 197–198°, was 65–70% over-all from the triol amide IIa. In the R = ethyl series, the total yield of solid acids from II was 55–60%, from which about 15% of the desired isomer (XVI, see below) of m.p. 190–191° could be separated by crystallization from acetone. Also isolated, in comparable or lower yields, were two additional isomeric lactam acids, XVIb, m.p. 223–225°, and XVIc, m.p. 201–202° (both acetone-insoluble).[15a]

Very recently, using an entirely different route, Grüssner, Jaeger, Hellerbach and Schnider[3f] have prepared the 191° lactam acid XVI and, in addition, have described its conversion to *dl*-emetine. These workers also obtained the 225° acid XVIb, which they reported to melt at 226–227°.[16] Moreover, they observed that the ethyl ester of the lower homolog of XVIb was epimerized during hydrolysis with base to form the lower homolog of XVI. Since the less stable ring junction of this type of benzoquinolizidine has been demonstrated to be unchanged by the action of hot potassium *t*-butoxide,[5b] it would seem most probable that the stereochemical difference between XVI and XVIb lies simply in the relative configurations of the acetic acid side chain in the two isomers (equatorial in XVI, as in emetine,[5] and axial in XVIb). However, in the absence of further evidence, this conclusion must be regarded as somewhat tentative, especially since epimerization at C-3 as well as at C-2 in the lower homolog of XVIb is also conceivable.



XVI, R = Et (m.p. 190–191°)
XVIa, R = H (m.p. 197–198°)
XVIb, R = Et (m.p. 223–225°)
XVIc, R = Et (m.p. 201–202°)



XVII, R = CH_3
XVIIa, R = CHO

On the basis of experiments described in the next three paragraphs it was recognized early in the course of the present work that the 191° lactam acid XVI possessed the desired emetine stereochemistry. It is to be noted therefore that the cyclization reaction which produced its precursor thus gave rise to the more stable of the two possible configurations at C-11b in the quinolizidine ring junction. In the recent yohimbine synthesis,[8] which involved a similar cyclodehydration step, the less stable arrangement at the analogous center was the predominant stereochemical outcome. The somewhat greater reactivity of an indole ring, as compared to a dimethoxyphenyl ring, toward electrophilic attack probably accounts, at least in part, for this difference in stereochemistry of ring closure. A similar relationship of ring activity to product stereochemistry has also been observed in aromatic cyclodehydrations leading to the formation of octahydrophenanthrenes.[17]

Selective reduction of the methyl ester, m.p. 53–54°, of the 191° lactam acid XVI with lithium borohydride, followed by *O*-tosylation and then reductive removal of both the tosylate and the lactam grouping, led to the formation of the corresponding *trans*-diethyl tricyclic base XVII, which was characterized as its hydrochloride, m.p. 247–248°.[5a] Infrared and mixed m.p. comparison of the latter with an authentic sample[18] confirmed this configurational assignment. The same sequence with the 225° lactam acid XVIb afforded an isomeric tricyclic base hydrochloride of m.p. 213–215°. The similar transformation of XVIc has not been investigated.

Alternatively, Raney nickel desulfurization of the ethylene thioacetal of the lactam aldehyde mixture IV, and then reduction of the lactam function with lithium aluminum hydride, resulted in the formation of a basic product from which the same hydrochloride (m.p. and mixed m.p. 247–248°) of the *trans*-diethyl tricyclic base XVII was readily isolated in about 15% over-all yield. Similarly, reduction of the lactam function in IV with the aldehyde grouping protected as its ethylene glycol acetal, followed by Wolff–Kishner reduction of the regenerated aldehyde[19] also afforded this same base, although in slightly lower yield.

(15a) Owing to incomplete purification of earlier samples, slightly lower melting points for acids XVIb and XVIc were recorded in our preliminary communication (*cf.* ref. 1).

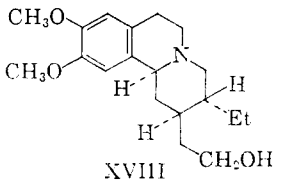
(16) Through the courtesy of Dr. O. Schnider in sending us samples of this acid and its methyl ester, the identity of the two preparations of XVIb has now been confirmed by direct comparison.

(17) *Cf.* R. A. Barnes and A. D. Olin, THIS JOURNAL, **78**, 3830 (1956), and earlier papers cited there.

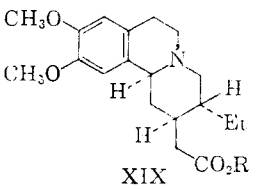
(18) Kindly supplied by Professor E. E. van Tamelen; see ref. 5a.

(19) This material corresponds to the structure of protoemetine (XVIIa), but without the stereochemical homogeneity of the latter;

To provide further evidence for the emetine stereochemistry of XVI, the methyl ester of this acid was reduced with lithium aluminum hydride to furnish the corresponding tricyclic amino alcohol XVIII. This proved, on the basis of indistinguishable infrared spectra and an undepressed perchlorate mixed m.p. of 178–181°,[3h] to be identical with material prepared by reduction of authentic samples of the tricyclic amino ester XIX (R = Me or Et), whose conversion to emetine has already been recorded.[3,5,20] The corresponding amino alcohols derived from the isomeric acids XVIb and XVIc had infrared spectra which differed significantly from that of XVIII.

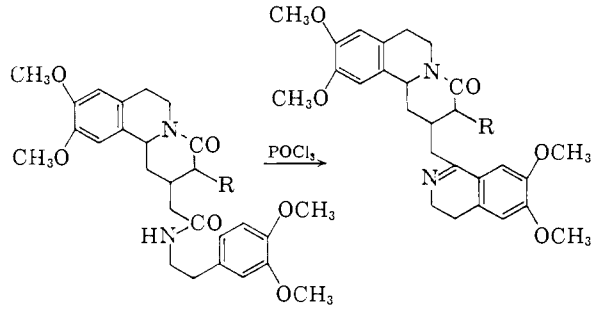


XVIII



XIX

The final stages of the synthesis, involving attachment of a tetrahydroisoquinoline nucleus to the benzoquinolizidine system, proved to be somewhat troublesome, since the remaining intermediates could not be obtained crystalline. Formation of the lactam amides XX,[3f] XXa and XXb,[3f] by condensation of homoveratrylamine with the methyl esters of the corresponding lactam acids XVI, XVIa and XVIb, respectively, was readily achieved, but these products, although they gave correct elemental analyses, could not be obtained crystalline, even after extensive chromatographic purification and evaporative distillation. Since spectrally identical substances were obtained by reaction of homoveratrylamine with the corresponding lactam acid chlorides,[3f] interference of the lactam function in the reaction of the ester grouping with homoveratrylamine does not appear to have occurred.



XX, R = Et
XXa, R = H
XXb, R = Et

XXI, R = Et
XXIa, R = H
XXIb, R = Et

Bischler–Napieralski ring closure at this stage offered the advantage of giving rise to unsaturated lactam bases (XXI, XXIa and XXIb) capable of being separated easily from unchanged (neutral) starting materials and other non-basic by-products by simple extraction procedures. Although XXI, XXIa and XXIb were not crystalline, their characteristic infrared spectra[19] confirmed the assigned constitutions. The action of lithium aluminum hydride in a mixture of ether and 1,2-dimethoxyethane proved to be an efficient means to effect simultaneous reduction of both the lactam and imine functions in these dehydro bases. From the reduction of XXI a mixture of racemic emetine (I and its mirror image) and racemic isoemetine (I and its mirror image, with C-1′ inverted) was isolated as the mixed bis-hydrochloride. *dl*-Emetine was then separated through its oxalate salt, m.p. 159–161°.[3f] Since the resolution of *dl*-emetine has already been recorded,[3a,d,e,g] this work thus constitutes a new synthetic route to the alkaloid.

Applied to XXIb, the above reduction procedure afforded what appeared to be an essentially homogeneous product, which is a diastereoisomer of *dl*-emetine.[3f] In the model series, XXIa was converted to a product having the desethylemetine structure[21] (Ia, but with undefined stereochemistry); this material was characterized in part by several solid derivatives.

As an alternative route to emetine, reduction of the lactam function in the 191° lactam acid XVI by sodium in alcohol,[22] or, more satisfactorily, by high pressure hydrogenation over Adkins copper chromium oxide catalyst,[23] was explored. The acid-soluble product was esterified with ethanol or methanol and then purified by chromatography on neutral alumina to give the previously reported[3] tricyclic amino ester XIX (R = Et or Me), whose conversion to emetine has already been described[3] and confirmed.[5a]

Acknowledgments.—We are grateful to the University of Kansas for a grant from the General Research Fund; to the National Science Foundation for financial support in the later stages of this work (NSF-G7287); and to the National Institutes of Health for a summer research appointment. We also wish to express our appreciation to Drs. A. R. Battersby, O. Schnider and E. E. van Tamelen for providing comparison samples and spectra and to the Eli Lilly Co. for supplying homoveratrylamine.

Experimental[24]

Hexahydrogallic Acid (VI).—Hydrogenation of 50 g. (0.266 mole) of recrystallized, reagent-grade gallic acid monohydrate in 250 ml. of 95% ethanol with 8 g. of 5% rhodium-on-alumina catalyst[25] at 70–75° under a pressure of

cf. A. R. Battersby, G. C. Davidson and B. J. T. Harper, *J. Chem. Soc.*, 1744 (1959); also ref. 4.

(20) The coöperation of Drs. A. R. Battersby and E. E. van Tamelen in providing comparison samples and spectra of synthetic XVIII and XIX is gratefully acknowledged.

(21) *Cf.* M. Barash and J. M. Osbond, *J. Chem. Soc.*, 2157 (1959); also ref 32.

(22) *Cf.* the conversion of 4-aza-3-cholestanone to 4-azacholestane reported by C. C. Bolt, *Rec. trav. chim.*, **57**, 905 (1938). In the present instance demethoxylation appeared to be a competing process; see ref. 5a, footnote 15.

(23) H. Adkins in R. Adams, "Organic Reactions," Vol. VIII, John Wiley and Sons, Inc., New York, N. Y., 1954, Chap. 1; *cf.* J. C. Sauer and H. Adkins, THIS JOURNAL, **60**, 402 (1938).

(24) Melting points were determined in capillary tubes or, where indicated, on a microscope hot-stage, and are corrected. Unless specified otherwise, infrared spectra were measured in chloroform solution on a Perkin–Elmer, model 21, recording spectrophotometer. Analytical samples were dried *in vacuo* at 80° or at a temperature 30° below their melting points, whichever was lower. Analyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and by the Analytical Service Laboratory at the National Institutes of Health, Bethesda, Md., under the direction of Dr. William C. Alford.

(25) Obtained from Baker and Co., Inc., 113 Astor St., Newark 5, N. J.

2500 p.s.i. required 4 to 8 hr. for completion, depending on the activity of the catalyst. After filtration and thorough washing of the recovered catalyst with hot water to remove partially crystallized product, the colorless filtrate[26] was concentrated rapidly on the steam-bath under reduced pressure until crystallization began or was readily induced by the addition of ethyl acetate to the viscous residue. After crystallization had proceeded for several hours at 0° the product VI was collected and washed with 100 ml. of cold 3:1 ethyl acetate–absolute ethanol and finally with 100 ml. of low boiling (40–60°) petroleum ether. When dry, the product weighed 21–24 g. (45–51%) and melted at 196–199°. Small additional amounts (1–3 g.) of this same material could usually be obtained by further concentration of the mother liquors. Recrystallization was most conveniently accomplished from a mixture of ethanol and ethyl acetate or acetone containing a small amount of water. The yield of recrystallized VI was 19–21 g. (40–45%), m.p. 199–200° (lit.[6a] 198°), hot-stage m.p. 200–202° (lit.[6b] 203°).

The methyl ester of this acid, prepared by the action of diazomethane in aqueous ethanol–ether, crystallized from ethanol–ether as matted clusters which melted at 132–133°, as recorded by Mayer, *et al.*[6a] When 200 mg. (1 mmole) of this ester was added to 60 ml. of 0.005 *M* sodium periodate adjusted to *p*H 8.0 with sodium hydroxide,[12] the *p*H of the solution changed rapidly to 6.5.

When water or dioxane was used as solvent, or when other catalysts, such as palladium- or ruthenium-on-carbon, were tried, the hydrogenation of gallic acid gave comparatively poor yields of the above acid. On several occasions variation in the yield of product with rhodium-on-alumina as the catalyst in the reduction could be traced to differences in the activity of different batches of catalyst.

γ-Pyrogallitol (V).—The hydrogenation of 40 g. (0.317 mole) of reagent-grade pyrogallol with 5 g. of 5% rhodium-on-alumina in 200 ml. of 95% ethanol at 55–60° under 3000 p.s.i. appeared to be complete in about 20 min. After removal of the catalyst by filtration and concentration of the filtrate at reduced pressure, there was obtained, by crystallization from ethanol–acetone, 26 g. (62% yield) of slightly impure γ-pyrogallitol (V), m.p. 143–147°. Recrystallization from alcohol–acetone afforded 20 g. (48%) of the pure substance, m.p. 147.5–148° (lit.[9] 148°).

Lactone Acetonide VII of Hexahydrogallic Acid.[10]—A suspension of 5.0 g. (0.0284 mole) of hexahydrogallic acid (VI) and 2 g. of *p*-toluenesulfonic acid in a mixture of 200 ml. of acetone and 200 ml. of petroleum ether (b.p. 50–60°) was refluxed in an apparatus equipped with a water take-off. After 24 hr. the mixture had become homogeneous. It was then cooled, and basic lead carbonate was added, with stirring, until the *p*H of an aliquot in water was about 8. After filtration of the solids the solution was concentrated and the residue crystallized from acetone–petroleum ether (b.p. 40–60°) to yield 4.2 g. (75%) of the **lactone acetonide VII**, m.p. 170–172°, λ_{max} 5.65 μ (γ-lactone). Recrystallization from the same solvent pair afforded large, flattened prisms, m.p. 172–173° (lit.[6b] 171°). The n.m.r. spectrum[13] showed axial-equatorial proton spin–spin coupling (4 peaks in the region 238 to 246 c.p.s., with tetramethylsilane serving as an internal reference) of a type attributable to the interaction of an axial with two adjacent equatorial protons, each being attached to an oxygen-bearing carbon atom, as in VII.

Anal. Calcd. for $C_{10}H_{14}O_4$ (198.2): C, 60.59; H, 7.12. Found: C, 60.75; H, 6.88.

For reduction, a portion of the above product was refluxed for 1 hr. with a lithium aluminum hydride in ether–1,2-dimethoxyethane (1:1). After dropwise addition of saturated aqueous sodium sulfate and then introduction of anhydrous sodium sulfate and more ether, the mixture was filtered and the solvents evaporated under reduced pressure. The solid tetrol monoacetonide (**3,4-isopropylidene-3,4,5-trihydroxycyclohexylcarbinol**) which resulted was conveniently recrystallized from absolute ethanol; m.p. 111–112°.

Anal. Calcd. for $C_{10}H_{18}O_4$ (202.2): C, 59.38; H, 8.97. Found: C, 59.20; H, 8.85.

(26) In the event of incomplete reduction this filtrate gradually turned dark and gave a positive ferric chloride test for gallic acid; however, this circumstance ordinarily did not interfere with the isolation of the product.

Brief warming of the preceding compound in 95% ethanol containing a few drops of dilute hydrochloric acid, followed by rapid concentration of the solution *in vacuo*, furnished the free tetrol (**3,4,5-trihydroxycyclohexylcarbinol**), m.p. 193–194°. Recrystallized from dilute ethanol, this substance melted at 194–195°. It also gave the *p*H-lowering effect with periodate ion[12] noted above for the methyl ester of hexahydrogallic acid. The pattern of peaks in the n.m.r. spectrum[13] at 42 to 69 c.p.s. from the HDO resonance indicated the presence of an axial proton at C-3 and at C-5 and an equatorial one at C-4, as would be expected of an all-*cis* structure with the ring in the more stable of the two possible chair conformations.

Anal. Calcd. for $C_7H_{14}O_4$ (162.2): C, 51.84; H, 8.70. Found: C, 51.66; H, 8.87.

Hexahydrogallic Acid Triacetate (X).—This derivative was prepared essentially in the manner described by Mayer, *et al.*[6a] From 10 g. (0.057 mole) of hexahydrogallic acid, m.p. 198–199°, there was obtained 15–17 g. of crude product, m.p. 152–154°. Recrystallization from 50 ml. of hot acetone–ethyl acetate (added first) and 50 ml. of petroleum ether (b.p. 60–70°, added second) yielded 13.5–14.5 g. (78–84%) of the pure triacetyl derivative X as shiny plates, m.p. 156–157° (lit.[6a] 152–153°).

The methyl ester (diazomethane) crystallized from methanol–petroleum ether (b.p. 40–60°) as large, jagged prisms, m.p. 91–92°.

Anal. Calcd. for $C_{14}H_{20}O_8$ (316.3): C, 53.16; H, 6.37. Found: C, 53.26; H, 6.29.

Sequence to the Triol Amides II and IIa. A. Preparation of the Diazoketones XII and XIIa.—Reaction of 10 g. (0.033 mole) of the above triacetyl derivative X of hexahydrogallic acid, m.p. 156–157°, with 10 ml. of freshly distilled thionyl chloride in 20 ml. of dry benzene at 70° for 1 hr., followed by several successive codistillations with benzene *in vacuo* to remove excess thionyl chloride, afforded the corresponding acid chloride XI as a colorless oil (crystalline at 0°). This, without further purification, was added dropwise, in benzene, to a well-stirred, dry solution of 4.2 g. (0.1 mole) of diazomethane in ether previously cooled to −5° and maintained at −5 to 0° throughout the addition. After 24 hr. at this temperature the reaction mixture was stripped of solvent and excess diazomethane under aspirator vacuum at 30–40° (bath temperature). The resulting light yellow residue was then taken up in benzene–petroleum ether (b.p. 40–60°) and the solution chilled to −10°. **The diazoketone XIIa** deposited as large, light yellow prisms, m.p. 96–99° dec., yield 10.2 g. (94%). Recrystallization afforded 9.5 g. (89%) of purified product, m.p. 99–101° dec.; λ_{max} 4.7, 5.77 and 6.15 μ.

Anal. Calcd. for $C_{14}H_{18}O_7N_2$ (326.3): C, 51.53; H, 5.56. Found: C, 51.72; H, 5.86.

On occasion, when the diazomethane solution apparently was not dried sufficiently, a small deposit of the colorless **anhydride of hexahydrogallic acid triacetate** slowly formed during the 24-hour reaction period. Recrystallization of this product from benzene–petroleum ether (b.p. 40–60°), gave large needle clusters, m.p. 180–181°; λ_{max} 5.5(s) and 5.8(vs) μ.

Anal. Calcd. for $C_{26}H_{34}O_{15}$ (586.5): C, 53.24; H, 5.84. Found: C, 53.26; H, 5.96.

The diazoketone produced by reaction of the acid chloride XI with a threefold excess of 1-diazopropane[14,27] in ether at 0° for 48 hr. was a deep yellow oil which could not be obtained crystalline but did have the expected infrared absorption at 4.8(s), 5.76(vs) and 6.18(s) μ.

B. Formation of the Triacetoxy Amides XIII and XIIIa.—By means of a systematic variation of the reaction temperature, the period of heating, the ratio of homoveratrylamine to diazoketone, the quantity of solvent, and the amount of silver oxide, the following procedure, which is typical, was found to give optimum yields in the homologation step.

To a solution of 5.0 g. (15.3 mmoles) of the model series diazoketone XIIa, m.p. 99–101° dec., in 50 ml. of 1,2-dimethoxyethane (redistilled from lithium aluminum hydride, b.p. 83–84° (745 mm.)), an equimolar quantity (2.80 g.)

(27) The use of petroleum ether (b.p. 40–45°) as the solvent in the nitrosation of ethyl N-propylurethan was found to improve the yield in the preparation of 1-diazopropane; *cf.* F. W. Bollinger, F. N. Hayes and S. Siegel, THIS JOURNAL, **72**, 5592 (1950).

of freshly distilled homoveratrylamine, b.p. 110–112° (0.1 mm.), was added. A reflux condenser connected to an azotometer was attached to the flask, and the mixture was heated to 65°. Over a period of 45 min., 1 to 2 g. of freshly precipitated silver oxide was added in small portions, with occasional swirling of the flask. A vigorous evolution of nitrogen occurred, and, after an additional 20 min., was essentially complete (95% of theory). The bath temperature was then raised to 105° and the mixture allowed to reflux for 5 to 6 hr. At the end of this period the colloidal silver and silver oxide had become largely coagulated, and the solution had acquired a bright yellow color. The hot mixture was filtered through Celite, the flask rinsed with chloroform, and the filtrate evaporated under reduced pressure to remove most of the solvent. The tan residue was taken up immediately in 100 ml. of chloroform and extracted twice with 20-ml. portions of cold 5% hydrochloric acid and once with 10% sodium bicarbonate solution. The chloroform layer was dried briefly over anhydrous magnesium sulfate, filtered and evaporated on the steam-bath. The viscous residue was then dissolved in 20 ml. of hot acetone to which dry ether was added until cloudiness appeared. The triacetoxy amide **XIIIa** slowly crystallized at 0° as fine clusters, m.p. 120–124°, yield 6.82 g. (93%). Recrystallization from the same solvent pair provided 6.18 g. (84%) of colorless product, m.p. 124–125°. The analytical sample melted at 125–126°, λ_{max} 5.77(vs) and 6.05(s) μ.

Anal. Calcd. for $C_{24}H_{33}O_9N$ (479.5): C, 60.11; H, 6.94; N, 2.92. Found: C, 60.29; H, 6.81; N, 2.97.

Application of the same procedure to the liquid diazoketone XII obtained *via* the acid chloride XI from 10 g. (0.033 mole) of hexahydrogallic acid triacetate (X) failed to yield a crystalline product. The infrared spectrum of the crude material isolated as above indicated the presence of the desired amide (λ_{max} 5.77 and 6.05 μ). Chromatography on a 35 × 250 mm. column of Woelm, activity grade 1, non-alkaline alumina separated a fragrant, oily impurity (no 6.05 μ band) by elution with benzene. The partially purified amide **XIII** (strong infrared bands at 5.77 and 6.05 μ) was eluted as a viscous, tan oil with 1:1 benzene–chloroform. It could not be obtained crystalline, even after further chromatography.

Selective Hydrolysis of XIII and XIIIa to the Triol Amides II and IIa.—A solution of 2.50 g. (5.22 mmoles) of the triacetoxy amide XIIIa, m.p. 124–125°, in 50 ml. of dilute ethanol was mixed with 4 g. of potassium carbonate in 20 ml. of water. By the addition of more water or alcohol, as required, a single phase was produced, and the solution was allowed to stand overnight at 45–50°, or for several days at room temperature (23°). It was then carefully neutralized with dilute hydrochloric acid until *p*H 5 was reached. After concentration of the solution to near dryness on the steam-bath under aspirator vacuum, 100 ml. of absolute ethanol was added to the semi-solid residue, and the resulting mixture digested on the steam-bath for 10 min. The insoluble material was collected by filtration, redigested with additional ethanol, and the same process (*i.e.*, evaporation to dryness and digestion with ethanol) was repeated twice more with the combined filtrates. Finally, the combined organic material was dissolved in the minimum quantity of refluxing 95% ethanol, and an equal volume (*ca.* 20 ml.) of hot ethyl acetate was added. The model triol amide IIa crystallized rapidly as small, colorless needle clusters, m.p. 191–194°, after having been dried at 70°; yield 1.71 g. (93%). Recrystallization of this material from the same solvent pair afforded 1.60 g. (87% yield) of purified product, m.p. 196–197°, λ_{max}^{KBr} 2.9 and 6.07 μ.

Anal. Calcd. for $C_{18}H_{27}O_6N$ (353.4): C, 61.17; H, 7.70; N, 3.96. Found: C, 61.40; H, 7.87; N, 3.82.

The chromatographed triacetoxy amide XIII from the preceding homologation step was similarly treated with 8 g. of potassium carbonate in dilute ethanol solution. Isolation of the product in the manner just described for the model series afforded the **triol amide II** as fine, colorless clusters, m.p. 194–196°, which, however, crystallized much more slowly. Recrystallization from ethanol raised the m.p. to 197–198°. The yield was somewhat variable, but in the better runs it ranged from 2.7 to 3.1 g. (21 to 25% overall from 10.0. of hexahydrogallic acid triacetate). The infrared spectrum (KBr pellet) showed the characteristic amide carbonyl peak at 6.08(vs) and associated hydroxyl at 2.9(s) μ.

Anal. Calcd. for $C_{20}H_{31}O_6N$ (381.5): C, 62.97; H, 8.19; N, 3.67. Found: C, 62.82; H, 8.24; N, 3.43.

Acetylation of this compound with acetic anhydride under a variety of conditions failed to yield a crystalline product.

Conversion of the Triol Amides to the Lactam Acids. A. Formation of the Lactol Lactams XIV and XIVa.—Two grams (5.66 mmoles) of the model triol amide IIa, m.p. 195–197°, was dissolved in 30 ml. of a 1:1 mixture of dimethoxyethane and water with the aid of slight warming. The solution was cooled to 10°, and 4.0 g. of periodic acid in 8 ml. of water was added to it, with stirring, whereupon a light yellow coloration appeared momentarily. After the solution had stood for 0.5 hr. at 15–20° it was evaporated to a volume of 15 ml. under reduced pressure with the bath temperature kept below 30°. The remaining solution was then extracted five times with 25-ml. portions of chloroform. The combined chloroform fractions were washed with 20 ml. of 10% sodium bicarbonate solution. After brief contact with anhydrous magnesium sulfate, they were evaporated on the water-bath (40°) under reduced pressure. The nearly colorless residue was taken up in a few ml. of ethanol–petroleum ether (b.p. 40–60°), and colorless prisms of the lactol lactam **XIVa**, m.p. 116–118°, slowly deposited at 0°; yield 0.93 g. (51%). Recrystallized from the same solvent pair, these melted at 120–121°; λ_{max} 2.9(w) and 6.09(s) μ; no absorption at 3.7 or 5.8 μ.

Anal. Calcd. for $C_{17}H_{23}O_5N$ (321.4): C, 63.53; H, 7.21; N, 4.36. Found: C, 63.59; H, 7.12; N, 4.61.

The mother liquors from the above material yielded 0.65 g. of non-crystalline residue, whose infrared spectrum [λ_{max} 2.9(w), 3.7(w), 5.8(s) and 6.1(s) μ] and behavior in the next step indicated that it was probably the corresponding hydroxy lactam aldehyde XVa. No particular attempt was made to characterize this material.

From the periodic acid cleavage of 1.0 g. (2.63 mmoles) of the triol amide II, m.p. 196–198°, there was obtained, by the same procedure, a light yellow, oily product (0.85 g.), whose infrared spectrum had peaks at 2.9(w), 3.7(w), 5.8(m) and 6.09(s) μ, indicating that it was probably a mixture of the derived lactol lactam XIV and the hydroxy lactam aldehyde XV.

B. Cyclization of the Periodate Cleavage Products to the Tricyclic Lactam Aldehydes IV and IVa.—The total crude product from the cleavage of 2.0 g. of the model triol amide IIa was dissolved in 10 ml. of 1,2-dimethoxyethane. To this solution 6 ml. of 85% phosphoric acid–water (1:1) was added, and the mixture was heated at 75–80° for 0.5 hr. During this period the color of the mixture gradually turned to deep orange. After evaporation of the dimethoxyethane under reduced pressure, the mixture was diluted with 25 ml. of water and extracted five times with 25-ml. portions of chloroform. The combined chloroform layers were then washed with 10% sodium bicarbonate solution until the washings were basic to methyl red. Most of the colored by-products were removed by this operation. Finally, the chloroform solution was dried with anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to furnish an oily, light tan residue, whose infrared spectrum [λ_{max} 5.80(s) and 6.17(vs) μ; no absorption at 6.09 μ] was in agreement with the assigned structure, **4-oxo-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[a]quinolizine-2-acetaldehyde (IVa)**.

The 2,4-dinitrophenylhydrazone crystallized from ethanol as deep yellow prisms, m.p. 208–210° dec.

Anal. Calcd. for $C_{23}H_{25}O_7N_5$ (483.5): C, 57.13; H, 5.21. Found: C, 57.38; H, 5.43.

The product from the cyclization of the cleavage product in the series R = ethyl, **3-ethyl-4-oxo-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[a]quinolizine-2-acetaldehyde (IV)**, was also obtained as a liquid, with strong infrared absorption at 5.80 and 6.17 μ, but none at 6.09 μ. The oily 2,4-dinitrophenylhydrazone and semicarbazone derivatives deposited readily, but did not show any tendency to crystallize.

C. Oxidation of the Lactam Aldehydes IV and IVa to the Corresponding Lactam Acids.—A solution of the model lactam aldehyde IVa [obtained from the cleavage and cyclization of 1.15 g. (3.25 mmoles) of the model triol amide IIa, m.p. 194–196°] in 60 ml. of 95% ethanol was mixed with 15 ml. of 30% aqueous silver nitrate. A 10% aqueous sodium hydroxide solution was then added, drop-

wise, with good stirring, until *p*H 9.5 was reached. The temperature of the mixture was gradually raised to 55–60°, and additional amounts of base were occasionally introduced in order to maintain the *p*H at 9.5. After 4 hr. the still-warm mixture was filtered through Celite, the filter-cake washed with 50 ml. of hot 50% ethanol, and the combined filtrates concentrated *in vacuo* to a volume of 30 ml. This residue was extracted with two 25-ml. portions of benzene, acidified with cold 6*N* hydrochloric acid to *p*H 2 (transient red color), and then re-extracted rapidly with five 25-ml. portions of chloroform. The combined chloroform layers were washed with two 10-ml. portions of water and dried briefly over anhydrous magnesium sulfate. After filtration and concentration of the chloroform solution under reduced pressure, a pale yellow oil was obtained which rapidly gave a granular crystalline deposit upon digestion with 10 ml. of acetone and a few ml. of petroleum ether (b.p. 60–70°). Crystallization appeared to be complete after 2 hr. at −20°, and the product, m.p. 190–194°, was collected and washed with cold acetone–petroleum ether (b.p. 40–60°); yield 0.72 g. (71% over-all from the triol amide IIa). Concentration of the mother liquors from the filtration furnished an additional 25 mg. of this same product. There was no evidence of a second isomer. Recrystallization of the combined material from benzene–ethanol–petroleum ether (b.p. 60–80°) gave 0.67 g. (66%) of nearly colorless **4-oxo-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[a]quinolizine-2-acetic acid (XVIa)**, m.p. 195–196°. The analytical sample, after several further crystallizations from the same solvent combination, had m.p. 197–198°; λ_{max}^{KB} 2.9 (m), 5.8 (s) and 6.18 (vs) μ.

Anal. Calcd. for $C_{17}H_{21}O_5N$ (319.4): C, 63.93; H, 6.63; N, 4.39. Found: C, 63.96; H, 6.85; N, 4.05.

Oxidation of the lactam aldehyde IVa to the above acid could also be accomplished by the action of dilute aqueous potassium permanganate in acetone or by peracetic acid (one equivalent), but the yields in both instances were distinctly inferior (*ca.* 20–40%).

Esterification of 1.0 g. (3.14 mmoles) of XVIa, m.p. 195–196°, in benzene–methanol by the action of ethereal diazomethane furnished the corresponding lactam methyl ester, **methyl 4-oxo-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[a]quinolizine-2-acetate**, which crystallized as fine prism clusters from methanol–ether when the solution was cooled to −10° but remelted at room temperature; λ_{max} 5.77(s) and 6.17(vs) μ. Subsequently, a more stable crystalline modification (jagged prisms) was obtained which was recrystallized readily from methanol–ether at 0°; m.p. 121–123°, yield 0.86 g. (82%).

Anal. Calcd. for $C_{18}H_{23}O_5N$ (333.4): C, 64.85; H, 6.95; N, 4.20. Found: C, 65.04; H, 6.97; N, 4.15.

Application of the foregoing silver oxide oxidation procedure to the lactam aldehyde mixture IV derived from 1.0 g. (2.62 mmoles) of II, m.p. 196–197°, similarly furnished a pale yellow oil which gradually gave a granular crystalline deposit upon digestion with 8 ml. of acetone. After the crystallization had proceeded for 20 min. at room temperature (23°), the solids were collected by filtration, washed with acetone, and the filtrate reconcentrated and taken up in 10 ml. of acetone–petroleum ether (b.p. 40–60°) and cooled to −15°. The weight of the first crop ranged from 220 to 280 mg. (24 to 30%) and consisted mostly of the highest melting lactam acid XVIb, mixed with varying amounts of the intermediate melting isomer XVIc (both comparatively insoluble in acetone). From the lower temperature crystallization, a second crop was collected, which weighed 180 to 260 mg. (20 to 28% yield) and appeared to be a mixture of the lowest melting lactam acid XVI (needles, fairly soluble in warm acetone) and the intermediate melting isomer XVIc.

Separation of the three isomeric lactam acids was conveniently accomplished by digestion of the mixtures with acetone, causing the lowest melting acid to go into solution and leaving the two higher melting acids largely undissolved. Several crystallizations of this acetone-soluble isomer from acetone–petroleum ether (60–70°) gave well-formed needle clusters of **3-ethyl-4-oxo-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[a]quinolizine-2-acetic acid (XVI)**, m.p. 190–191° (hot-stage), raised from 170–185°, yield 80–120 mg. (9–13%).

Anal. Calcd. for $C_{19}H_{25}O_5N$ (347.4): C, 65.69; H, 7.25; N, 4.03. Found: C, 65.60; H, 7.19; N, 4.04.

Esterification of this acid with diazomethane in ether–benzene furnished the corresponding methyl ester, **methyl 3-ethyl-4-oxo-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[a]quinolizine-2-acetate**, which crystallized initially with considerable difficulty from ether–methanol as colorless, slightly elongated prisms, m.p. 53–54°.

Anal. Calcd. for $C_{20}H_{27}O_5N$ (361.4): C, 66.46; H, 7.53; N, 3.88. Found: C, 66.60; H, 7.44; N, 3.97.

The highest melting lactam acid **XVIb** was obtained as fine, colorless granules, m.p. 223–225° (hot-stage) (lit.[3f] m.p. 226–227°), after several recrystallizations of the first, acetone-insoluble fraction from ethanol–benzene–acetone; yield 140–180 mg. (15–20%).

Anal. Found: C, 65.89; H, 7.49; N, 4.26.

A mixed m.p. of this acid with a sample generously supplied by Dr. O. Schnider,[3f,16] m.p. 222–225° (hot-stage), was undepressed.

The methyl ester (diazomethane) crystallized from methanol–ether as irregular prisms, m.p. 140–142° (soft. 138°).

Anal. Found: C, 66.16; H, 7.25; N, 4.44.

A mixed m.p. of this ester with a sample furnished by Dr. O. Schnider, m.p. 139–141° (hot-stage), was also undepressed. The infrared spectra likewise were identical [λ_{max} 5.76(s) and 6.17(vs) μ].

From the crystallization mother liquors of the preceding two acids the intermediate melting isomer **XVIc** was obtained as colorless, fine prisms, m.p. 201–202° (hot-stage), unchanged by further recrystallization from benzene–methanol; yield 40–60 mg. (4–7%).

Anal. Found: C, 65.98; H, 7.17; N, 3.91.

A mixed m.p. of this acid with the 191° acid XVI was depressed to 155–165°. With the 225° acid XVIb the mixed m.p. was 193–200°.

The methyl ester of XVIc (diazomethane) crystallized from methanol–ether as jagged prisms, m.p. 94–95° (soft. 92°). The infrared spectrum of this ester was very similar to that of the methyl ester of the 225° lactam acid XVIb.

Anal. Found: C, 66.21; H, 7.65; N, 4.05.

Stereochemical Correlations. A. *trans*-2,3-Diethyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[a]quinolizine (XVII).—1.—Reaction of 100 mg. of the methyl ester of the 191° lactam acid XVI with 100 mg. of lithium borohydride in 50 ml. of ether–1,2-dimethoxyethane (1:1) at 30° for 1 hr., followed by the addition of water and dilute hydrochloric acid and isolation of the neutral product by extraction with chloroform, afforded the corresponding lactam carbinol [λ_{max} 2.9(w) and 6.17(vs) μ; no absorption in the 5.7–5.8 μ region], which was converted to the tosylate derivative essentially by the procedure described by van Tamelen, Aldrich and Hester[5a] for the related uncyclized piperidone. Reaction of the lactam tosylate with lithium aluminum hydride in refluxing ether–1,2-dimethoxyethane, or with thiourea,[5a] followed by treatment with Raney nickel in refluxing ethanol,[5a] furnished *ca.* 20–30 mg. of a basic product which was purified by chromatography on alumina (elution with 3:1 chloroform–benzene). On treatment with hydrogen chloride in ether–ethyl acetate, this material deposited the **hydrochloride of *trans*-2,3-diethyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[a]quinolizine (XVII)**, as fine prisms, m.p. 243–247°, yield 15–20 mg. (16–21%). Recrystallization from the same solvent pair raised the m.p. to 247–248°.[5a]

Anal. Calcd. for $C_{19}H_{29}O_2N\cdot HCl$ (339.9): C, 67.13; H, 8.90. Found: C, 67.14; H, 8.99.

A mixed m.p. of this derivative with a sample furnished by Professor van Tamelen,[5a] m.p. 247–248°, was undepressed. The richly detailed infrared spectra of the two specimens (as KBr pellets) were also indistinguishable.

Application of the same sequence to the methyl ester of the 225° lactam acid XVIb furnished an **isomeric hydrochloride**, m.p. 213–215°, after recrystallization from ethyl acetate. The infrared spectrum (KBr) of this derivative differed considerably from that of the preceding material.

Anal. Found: C, 66.95; H, 9.02.

2.—Formation of the ethylene thioacetal of the crude lactam aldehyde prepared from 300 mg. of the triol amide II was achieved by the boron trifluoride etherate method.[28]

(28) L. F. Fieser, THIS JOURNAL, **76**, 1945 (1954).

The crude thioacetal was reductively desulfurized by the action of Raney nickel in refluxing ethanol, and the product (λ_{max} 6.17μ) submitted to the action of lithium aluminum hydride in 50 ml. of refluxing ether–1,2-dimethoxyethane (1:1). From the basic product of this reaction 40 mg. (15% over-all yield) of the hydrochloride of the *trans*-diethyl tricyclic base XVII, m.p. and mixed m.p. 247–248°, was isolated.

3.—Conversion of the crude lactam aldehyde IV (from 300 mg. of the triol amide II) to the corresponding acetal derived from ethylene glycol was performed by the *p*-toluenesulfonic acid–toluene procedure. Treatment of the product (λ_{max} 6.17 μ; no absorption at 3.7 or 5.8 μ) with lithium aluminum hydride in ether gave an oily base (no band at 6.17 μ). This was allowed to stand for 1 hr. with warm, dilute hydrochloric acid, the solution was cooled and made alkaline with sodium bicarbonate, and the desired tricyclic aldehyde base (XVIIa plus stereoisomers) [λ_{max} 3.7(w) and 5.81(s) μ] was recovered as an oil by extraction with chloroform. When this material was submitted to the Huang-Minlon modification of the Wolff–Kishner reduction,[29] 28 mg. (10% yield) of the hydrochloride, m.p. 246–248°, of the *trans*-diethyl tricyclic base XVII was obtained.

B. *trans*-2-(ω-Hydroxyethyl)-3-ethyl-9,10-dimethoxy-1,2,-3,4,6,7-hexahydro-11b*H*-benzo[a]quinolizine (XVIII).—Reduction of 400 mg. of the methyl ester of the 191° lactam acid XVI with 250 mg. of lithium aluminum hydride in 40 ml. of ether–1,2-dimethoxyethane (1:1) gave, after hydrolysis of the reaction mixture with Rochelle salts solution and extraction of the product with ether, 340 mg. of the crude tricyclic amino alcohol XVIII. This was purified by evaporative distillation, b.p. (bath temp.) 170–180° (0.004 mm.), but it did not crystallize. Its perchlorate, however, deposited as fine prisms from cold ethanol which were recrystallized from ethanol–ethyl acetate; m.p. 178–181° (soft. 175°).[3h]

Anal. Calcd. for $C_{19}H_{29}O_3N\cdot HClO_4$ (419.9): C, 54.34; H, 7.20; N, 3.34. Found: C, 54.45; H, 7.41; N, 3.25.

A mixed m.p. of the above salt with a sample kindly supplied by Dr. A. R. Battersby[20] from the emetine synthesis intermediate XIX (R = Et)[3c,h] showed no depression. Likewise, the infrared spectra of the free amino alcohols[20] were found to be identical. The hydrochloride crystallized from ethanol–ethyl acetate as fine plates, m.p. 243–244°, as reported.[5a]

The infrared spectrum of the amino alcohol similarly derived from the methyl ester of the 225° lactam acid XVIb was distinctly different from that of the above material, especially in the 9–11 μ region, as was also that derived from the methyl ester of the 202° lactam acid XVIc.

Sequence to *dl*-Emetine. A. Formation of the Lactam Amides XX, XXa and XXb.—To 0.50 g. (1.48 mmoles) of the methyl ester of the model lactam acid XVIa 1.0 ml. of freshly distilled homoveratrylamine was added, and the mixture heated under a slow stream of nitrogen at 205–210° for 0.5 hr. At the end of this time the ester band at 5.77 μ in the infrared had disappeared completely (reaction incomplete after 15 min.). The mixture was then dissolved in 50 ml. of chloroform and the resulting solution washed two times with 20-ml. portions of 2*N* hydrochloric acid and then once with 20 ml. of 10% sodium hydroxide solution. The chloroform layer was dried over anhydrous magnesium sulfate, filtered, and the solvent evaporated. The nearly colorless, viscous residue (0.7 g.), which could not be obtained crystalline, even after extensive chromatography on alumina, had the expected intense carbonyl peaks at 6.02 (amide) and 6.17 μ (δ-lactam), corresponding to the lactam amide XXa. An analytical sample prepared by evaporative distillation was a glass, b.p. (bath temp.) 210° (0.0005 mm.).

Anal. Calcd. for $C_{27}H_{34}O_6N_2$ (482.6): C, 67.20; H, 7.10; N, 5.81. Found: C, 66.88; H, 7.26; N, 6.03.

The preparation of the lactam amide XX from the methyl ester of the 191° lactam acid XVI was similarly achieved. It also was a glass, b.p. (bath temp.) 210° (0.0004 mm.); λ_{max} 6.02(s) and 6.17(vs) μ.

Anal. Calcd. for $C_{29}H_{38}O_6N_2$ (510.6): C, 68.21; H, 7.50; N, 5.49. Found: C, 68.35; H, 7.58; N, 5.31.

In the 225° lactam acid series (XVIb) the corresponding lactam amide XXb was evaporatively distilled under the same conditions and crystallized partially on standing, m.p. 63–65°; λ_{max} 6.02(s) and 6.18(vs) μ.

Anal. Found: C, 68.10; H, 7.48; N, 5.22; OCH_3, 23.7 (theory 24.3).

These lactam amides could also be obtained by reaction of excess homoveratrylamine in benzene with the corresponding acid chlorides. However, since the reaction of thionyl or oxalyl chloride with the lactam acids was attended by considerable darkening and by-product formation, the preparation of the acid chlorides was best achieved by the action of oxalyl chloride on the dry sodium salts of the acids.

B. Bischler–Napieralski Ring Closure of the Lactam Amides.—The crude lactam amides (0.5 g.) from the preceding step were each dissolved in 10 ml. of a mixture of alcohol-free chloroform and toluene (1:1), 0.15 ml. of freshly distilled phosphorus oxychloride was added, and the mixture heated under nitrogen at 85° (bath temperature) for 1 hr. The reaction mixture was then cooled in an ice-bath, diluted with 40 ml. of chloroform, and shaken vigorously with 25 ml. of 5% sodium hydroxide containing a small amount of crushed ice. The extraction was repeated, and the combined chloroform layers were dried and evaporated under reduced pressure. The infrared spectra of the crude product retained strong lactam absorption at 6.17 μ, but the amide band of the precursor at 6.02 μ had completely disappeared; in addition, two sharp bands at 6.24 and 6.43 μ, characteristic of a 3,4-dihydroisoquinoline,[19] were present.

Partial purification of this material was achieved in the following manner. To the crude product 50 ml. of 2 *N* hydrochloric acid was added, and the well-stirred mixture extracted twice with 50 ml. of benzene–ethyl acetate (1:1). The aqueous phase was then cooled in an ice-bath, and cold 10% potassium hydroxide was then added until the mixture was strongly basic. The oily dehydro base (XXI, XXIa or XXIb) was then isolated by extraction with chloroform, but it could not be obtained crystalline in any of the three cases. No attempt, however, was made to characterize it in the form of salts.

C. Reduction of the Dehydro Base Lactams.—Reduction of XXa to the *rac*-desethylemetine structure (2-[6′,7′-dimethoxy-1′,2′,3′,4′-tetrahydroisoquinolinyl-(1′)-methyl]-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[a]-quinolizine) was performed as follows. The product (0.35 g.) from the preceding step in the series R = H (XXa) was dissolved in 10 ml. of 1,2-dimethoxyethane and the solution added, over a period of several minutes, to 0.5 g. of lithium aluminum hydride in 30 ml. of dry ether and 1,2-dimethoxyethane (1:1). The resulting suspension was stirred at reflux for 0.5 hr., cooled in an ice-bath, and the excess reagent destroyed by the dropwise addition of ethyl acetate in ether. After concentration on the steam-bath under reduced pressure, the mixture was diluted with 50 ml. of chloroform, and then extracted with two 25-ml. portions of cold 15% potassium hydroxide solution. The chloroform layer was washed with 25 ml. of water, dried briefly over anhydrous magnesium sulfate, and evaporated under reduced pressure. Chromatographic purification of the pale yellow residue on a 1.5 × 8 cm. column of basic Woelm alumina (activity grade 1) gave a fraction eluted with benzene–chloroform (1:1), which appeared to consist mainly of the desired product. Its infrared spectrum was strikingly similar to that of a sample of (−)-emetine (I) prepared from the emetine hydrochloride supplied by the Inland Alkaloid Co.[30] By evaporative distillation an analytical sample was obtained, b.p. (bath temp.) 190–195° (0.0004 mm.), which slowly set to a semi-crystalline glass, m.p. 75–80°.

Anal. Calcd. for $C_{27}H_{36}O_4N_2$ (452.6): C, 71.65; H, 8.02; N, 6.19. Found: C, 71.60; H, 8.12; N, 5.78.

The tan chloroplatinate, m.p. 243–247° dec., deposited readily from a solution of the base in 5 *N* hydrochloric acid upon the addition of chloroplatinic acid in water. Pailer, *et al.*,[31] report a m.p. of 243° dec. for this derivative of a synthetic desethylemetine.

The bis-picrolonate, precipitated as a fine yellow powder from ethanol–ethyl acetate, melted at 179–182° dec.

(29) Huang-Minlon, THIS JOURNAL, **68**, 2487 (1946); *cf.* ref. 5b

(30) We are deeply grateful to Professor W. E. McEwen of this Department for a generous gift of this material.

(31) M. Pailer, K. Schneglberger and W. Reifschneider, *Monatsh.*, **83**, 513 (1952).

Anal. Calcd. for $C_{27}H_{36}O_4N_2 \cdot C_{20}H_{16}O_{10}N_8$ (980.97): C, 57.54; H, 5.34; N, 14.28. Found: C, 57.45; H, 5.59; N, 14.25.

In a similar manner the reduction of 0.50 g. of the dehydro base lactam XXI was also performed. The product (410 mg.) appeared to be a mixture of *dl*-emetine and *dl*-isoemetine. It gave 230 mg. of a hydrochloride which melted over the range 225–238° dec. after several crystallizations from ethanol–ethyl acetate. By treatment with ammonia this derivative yielded 120 mg. of an amorphous base, m.p. 60–68°, in which the presence of *dl*-emetine was readily demonstrated by the infrared spectrum and also by the formation of its oxalate, m.p. 159–161°, after recrystallization from methanol–ether.[3f]

From the reduction of 0.65 g. of the dehydro base lactam XXIb was obtained 0.35 g. of a hydrochloride, m.p. 236–240° dec. after recrystallization from ethanol–ethyl acetate, as reported.[3f] The infrared spectrum of the regenerated free base was very similar to that of (−)-emetine; however, it also contained a number of small but distinct differences.

Formation of the Tricyclic Ester Base XIX from the 191° Lactam Acid XVI. A.—To 35 ml. of refluxing absolute ethanol containing 200 mg. of the lactam acid XVI, 3 g. of sodium was added, in small pieces. After the reaction was complete the mixture was concentrated *in vacuo*, acidified with dilute hydrochloric acid, and extracted with three 25-ml. portions of benzene–ether (1:1). The aqueous phase was evaporated to dryness under reduced pressure, and 50 ml. of absolute ethanol was added. The solution was filtered, saturated with hydrogen chloride at 20°, and allowed to stand overnight at this temperature. After evaporation of the solvent under reduced pressure the residue was treated with 20 ml. of 5% aqueous ammonia and re-extracted with chloroform. Evaporation of the chloroform furnished 45 mg. of an ester (λ_{max} 5.77 μ; no lactam absorption) which was purified by chromatography on neutral alumina (Woelm, activity grade 1) and then treated with anhydrous hydrogen chloride in ethanol–ether. The resulting hydrochloride (12 mg.), m.p. 192–194°[3d] after recrystallization from ethanol–ethyl acetate, crystallized with some difficulty. The regenerated free ester (XIX, R = Et) was evaporatively distilled, b.p. (bath temp.) 145–150° (0.0004 mm.), and then crystallized from petroleum ether (b.p. 40–60°) as fine needles, m.p. 65–66° (hot-stage) (lit.[3c,h] 66–66.5°). The perchlorate crystallized from ethanol–ether in stout needles, m.p. 145–146°[3h] (raised to 167–169° after being dried *in vacuo* at 80°). A mixed m.p. of this derivative with an authentic specimen graciously provided by Dr. A. R. Battersby[3h,20] was undepressed.

The corresponding methyl ester (XIX, R = Me), m.p. 78–97°[5a] (hydrochloride m.p. 204–206°[5a]), could also be obtained from the reduction product in similar fashion. The infrared spectrum of this ester and that of an authentic sample kindly supplied by Professor E. E. van Tamelen[5a,20] were identical.

B.—Alternatively, and somewhat more satisfactorily, the lactam function in XVI could be reduced at high pressure (4500 p.s.i.) and elevated temperature (230°) with Adkins copper chromium oxide catalyst[23] in freshly purified dioxane. By this means, the hydrogenation of 100 mg. of XVI in a 20-ml. micro glass liner with 80 mg. of high-activity catalyst[23] in 5 ml. of dioxane afforded, after esterification of the basic product with ethanol and chromatography on alumina, 21 mg. of the hydrochloride of XIX (R = Et), m.p. 192–194°. The regenerated ester had m.p. and mixed m.p. 65–66° with the preceding preparation, and the infrared spectra were also identical.

CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY, UNIVERSITY OF NORTH CAROLINA, CHAPEL HILL, N. C.]

The Pyrolysis of 2-(N-β-Acyloxyethylanilino)-4,6-dialkoxy-*s*-triazines[1]

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The pyrolysis of 2-(N-β-acyloxyethylanilino)-4,6-dialkoxy-*s*-triazines proceeds smoothly, in the absence of solvent, giving high yields of 2-N-vinylanilino-4-hydroxy-6-alkoxy-*s*-triazines and the corresponding alkyl ester. Pyrolysis of the triazines in the presence of added anions and decomposition of carbonyl oxygen-18 labeled 2-(N-β-acetoxyethylanilino)-4,6-dimethoxy-*s*-triazine indicates the reaction involves the formation of a free acid anion. The unusual ease of pyrolysis, 250°, suggests the formation of the acid anion may proceed by an intramolecular process involving a nitrogen atom of the triazine ring. A mechanism compatible with the observed experimental results is proposed.

Numerous examples in the literature describe the pyrolytic decomposition of esters containing a β-hydrogen in the alkyl portion of the molecule. The accepted interpretation[4] of the process depicts the formation of the observed reaction products, an acid and an olefin, by a cyclic transition state. Schaefer, *et al.*,[5] however, have described the pyrolysis of several esters which did not yield the expected products. For example, pyrolysis of 2-(N-β-acetoxyethylanilino)-4,6-diethoxy-*s*-triazine (Ib) at 250°, resulted in the formation of ethyl acetate (IIIb) and a product assigned as 2-N-vinylanilino-4-hydroxy-6-ethoxy-*s*-triazine (IIb). Likewise, pyrolytic decomposition of the dimethoxy-*s*-triazine acetate (Ia) was reported to yield IIa and presumably IIIa, although the latter ester was not characterized. In contrast 2,4,6-tris-(N-β-acetoxyethylanilino)-*s*-triazine was stable when heated to 350° alone or in the presence of 2,4,6-trimethoxy-*s*-triazine. These observations led to the suggestion[5] that the products were produced by an unknown type of intramolecular decomposition. The present report concerns a more detailed study of these interesting results in an effort to clarify the course of the pyrolysis reaction.

The dialkoxy-*s*-triazine esters (Ia–d) were prepared in good yield using cyanuric chloride and N-phenylethanolamine[6] as starting materials. Etherification of the resulting 2-(N-β-hydroxyethylanilino)-4,6-dichloro-*s*-triazine with the appropriate alcohol in base afforded the 2-(N-β-hydroxyethylanilino)-4,6-dialkoxy-*s*-triazines which were esterified with the desired acid chloride in pyridine solution.

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(3) Abstracted from the Ph.D. Dissertation of Mr. Jerome Hollander, January, 1960.

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