Tetrahedron, 1961, Vol. 14, pp. 54 to 75. Pergamon Press, Inc. Printed in Northern Ireland

THE STRUCTURE OF AJACONINE[1,2]

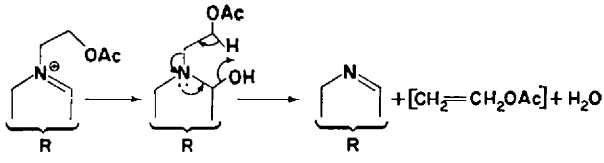
D. DVORNIK[3] and O. E. EDWARDS
Division of Pure Chemistry, National Research Council of Canada

(*Received* 29 *November* 1960)

THE alkaloid ajaconine was given its name by Keller and Völker[4] who found it among the bases extracted from *Delphinium ajacis* seeds. Hunter[5] confirmed its presence in this plant and prepared new derivatives. He also recognized its high basic strength. Goodson[6] assigned the correct empirical formula $C_{22}H_{33}O_3N$, and demonstrated the unsaturated character of the base. He was misled into suggesting the presence of an N-methyl group by the products of the Herzig–Meyer determination.

We have obtained the alkaloid from the strong base fraction from *Delphinium ajacis* seeds, and in addition as the major strong base from the seeds of *D. consolida* and a *Delphinium* hybrid. The physical constants, m.p. 167° and $[\alpha]_D$ −122° (*c*, 1·75 in ethanol) correspond closely to those reported by Goodson.[6] Its pK_a' was found to be 11·8 in 50 per cent aqueous methanol, and 11·3 in 80 per cent aqueous ethanol.

The presence of a carbinolamine–ether system N–C–OC in ajaconine was shown[2a] by the fact that it formed immonium salts (ν_{max} 1683 cm^{-1})[7] and that it was reduced by sodium borohydride to a dihydro base without loss of oxygen. The high pK_a' of the base was also consistent with this feature.[7c,8] The presence of three hydroxyl groups in the salts of ajaconine was shown by formation of a triacetyl derivative. The triacetoxy immonium chloride was converted by concentrated aqueous potassium hydroxide at 0°, with immediate extraction into carbon tetrachloride, into a triacetoxy carbinolamine. This base split when gently heated in solution into a small fragment (isolated as acetaldehyde *p*-nitrophenylhydrazone) and a diacetoxy azomethine (ν_{max} 1650 cm^{-1}) analyzing for $C_{24}H_{33}NO_4$. This reaction exactly parallels the fragmentation



Issued as N.R.C. No. 6252. Presented in part at the XXVI Congress of L'Association Canadienne Francaise pour l'Avancement des Sciences, Ottawa, November 2, 1958, as the Merck lecture of the Canadian Institute of Chemistry, June 14, 1960 [see *Chemistry in Canada* 13, 40 (1961)] and the diterpene symposium of the American Chemical Society, New York, September 14, 1960.

[1] Preliminary communications of some of this work have been published in [a] *Chem. & Ind.* 952 (1957); [b] *Proc. Chem. Soc.* 280 (1958); [c] *Ibid*, 305 (1958).

[2] National Research Council post-doctorate fellow. Present address: Research Laboratory, Ayerst, McKenna and Harrison, Montreal, Canada.

[4] O. Keller and O. Völker, *Arch. Pharm.* **251**, 207 (1913).

[5] M. V. Hunter, *Quart. J. Pharm.* **17**, 302 (1944).

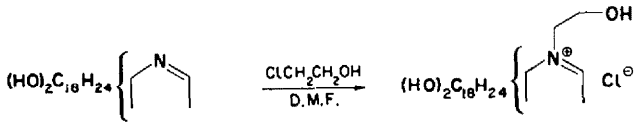
[6] J. A. Goodson, *J. Chem. Soc.* 245 (1945).

[7a] O. E. Edwards and T. Singh, *Canad. J. Chem.* **32**, 465 (1954); [b] B. Witkop and J. B. Patrick, *J. Amer. Chem. Soc.* **75**, 4474 (1953); [c] N. J. Leonard and V. W. Gash, *Ibid.* **76**, 2781 (1954).

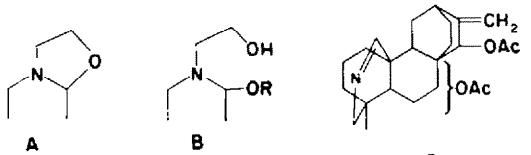
[8] O. E. Edwards, F. H. Clarke and B. Douglas, *Canad. J. Chem.* **32**, 235 (1954).

of the analogous derivative of atisine, and can be rationalized as above[9] (R = $(CH_3COO)_2C_{18}H_{24}$).

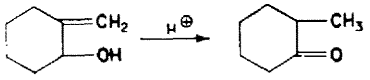
The acetoxy carbinolamines in both cases are soluble in hexane and carbon tetrachloride, hence are non-polar. In view of this and the ease of fragmentation in these solvents, we avoid more ionic forms of reaction mechanism. The presence of the N(β-oxyethyl) system was confirmed by partial synthesis of ajaconine hydrochloride from the azomethine diol obtained by hydrolysis of the above diacetate:



This parallels our earlier partial synthesis of atisine,[9] and completes the evidence for the presence of the systems A or B in ajaconine



This presence of an exocyclic methylene group in ajaconine was evident from the bands near 1665 cm^{-1} and 890 cm^{-1} in the infrared spectrum of ajaconine and its hydrochloride and various degradation products of the alkaloid. When dihydroajaconine was heated with *p*-toluenesulfonic acid in dioxane a product was formed in whose spectrum the above bands had disappeared and carbonyl absorption had appeared at 1705 cm^{-1}. This suggested that the exocyclic methylene was part of an allyl alcohol system in a six-membered or larger ring, which rearranged as shown.[10]



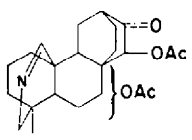
Thus the empirical formula, properties and chemistry of ajaconine were strikingly similar to those of atisine, and the possibility was entertained that ajaconine was a monohydroxyatisine. The identity of the skeletons of the two alkaloids was then proven by degrading ajaconine to a deoxygenated azomethine previously prepared from atisine.[9]

[9] D. Dvornik and O. E. Edwards, *Canad. J. Chem.* **35**, 860 (1957).

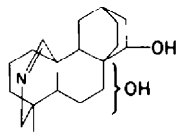
[10] This type of rearrangement was first observed for an atisine derivative by C. F. Huebner and W. A. Jacobs, *J. Biol. Chem.* **170**, 515 (1947); and later by C. Djerassi, A. E. Lippman, S. K. Figdor and J. Herran, *J. Amer. Chem. Soc.* **77**, 4801 (1955) with Garrya alkaloids. See also the model studies of Dreiding and Hartman, *J. Amer. Chem. Soc.* **78**, 1216 (1956).

[11] Since ajaconine proves to have the atisine skeleton, which we now conclude to be correctly represented by I (see below), this will be used for clarity of exposition from this point on. The numbering system used by us[9] conforms with the resin acid numbering and with the biosynthetic postulates for tetracarbocyclic diterpenes of Wenkert [*Chem. & Ind.* 282 (1955)] which have been established as essentially correct by A. J. Birch, R. W. Richards, H. Smith, A. Harris and W. B. Whalley, *Tetrahedron* **7**, 241 (1959).

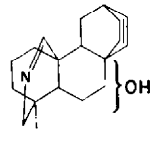
The above diacetoxyazomethine (I)[11] was oxidized with osmium tetroxide–periodate combination[12] to a ketol diacetate II. Wolff–Kishner reduction of this gave a mixture of the azomethine diol III and the monohydroxy compound IV.[13] Hydrogenation of the mixture over palladium on charcoal converted IV to V. The two components could then be separated by chromatography on alumina. Alternatively, the mixture of III and V arising from the hydrogenation was oxidized with chromic acid. This selectively converted the 8-hydroxyl to a carbonyl. Subsequent Wolff–Kishner reduction left substantially pure V. Sodium dichromate in acetic acid[14] converted V to the ketone VI which was then reduced to VII. This proved identical with the corresponding degradation product from atisine.[9]



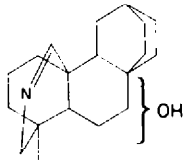
II



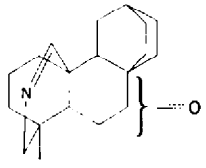
III



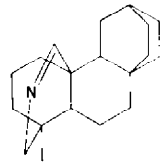
IV



V



VI



VII

The molecular rotation differences for comparable transformations of ajaconine and atisine were nearly identical (Table 1) suggesting that the location and configuration of the substituents on the bicycloöctane system were identical in the two bases.[2a] Fortunately the alkaloid atidine had just been described and the probability that it was a ketodihydroatisine recognized.[15] It seemed to us likely that its carbonyl oxygen and the unknown hydroxyl of ajaconine were on the same carbon. This was quickly proven correct by Pelletier[16], who converted atidine VIII by Wolff–Kishner reduction to dihydroatisine and by borohydride reduction to the dihydroatidine IX. The latter proved identical with the borohydride reduction product of ajaconine. Thus the location of the exocyclic methylene and the location and stereochemistry of the 8-hydroxyl are the same in ajaconine and atisine.

[12] R. Pappo, D. S. Allen, R. U. Lemieux and W. S. Johnson, *J. Org. Chem.* **21**, 478 (1956). The course of the osmium tetroxide oxidation of dihydroatisine and dihydroveatchine in which C-16 was oxidized rather than the exocyclic methylene [K. Wiesner, W. I. Taylor, S. K. Figdor, M. F. Bartlett, J. R. Armstrong and J. A. Edwards, *Chem. Ber.* **86**, 800 (1953); S. W. Pelletier and W. A. Jacobs, *J. Amer. Chem. Soc.* **78**, 4144 (1956)] we interpret as involving rapid co-ordination of one mole of osmium tetroxide with the unshared pair of electrons on the nitrogen. The reagent is then in a position to remove the proton on C-16 with the unshared pair on the nitrogen to give an immonium ion, but due to the large steric requirements of the complex does not appreciably attack the otherwise readily accessible exocyclic methylene group. In our experiments the unshared pair of electrons on the nitrogen was unavailable because of prior salt formation.

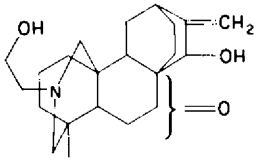
[13] The formation of olefins on Wolff–Kishner reduction of α-ketols has been thoroughly studied by R. B. Turner, R. Anliker, R. Hebling, J. Meier and H. Heusser, *Helv. Chim. Acta* **38**, 411 (1955). The olefin was isolated during the parallel work on atisine.[9]

[14] H. Heymann and L. F. Fieser, *J. Amer. Chem. Soc.* **73**, 5252 (1951).

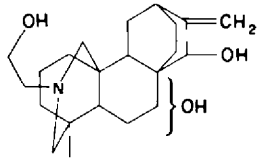
[15] S. W. Pelletier, *Chem. & Ind.* 1016 (1956).

[16] S. W. Pelletier, *Chem. & Ind.* 1670 (1957).

The extra oxygen of ajaconine thus presented the possibility of further testing of the postulated structure for atisine.[17] Hence there was double incentive for locating it and studying its environment. In order to do this we used a derivative containing no functional groups but the nitrogen and the undefined oxygen.

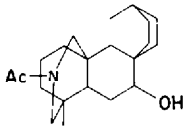


VIII

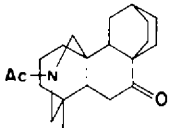


IX

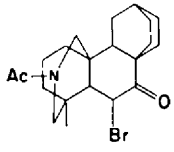
The azomethine alcohol V was reduced with sodium borohydride to the secondary-amino alcohol. This was acetylated and partially hydrolyzed to X. Sodium dichromate in acetic acid oxidized X to the corresponding ketone XI. When brominated in acetic acid in the presence of hydrogen bromide the ketone took up cleanly one mole of bromine to give the monobromo compound XII. The location of the substituents was



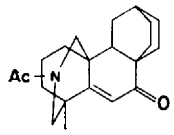
X



XI



XII



XIII

unequivocally shown by elimination of hydrogen bromide from XII to give the α–β unsaturated ketone XIII. The ultraviolet spectrum of XIII (λ_{max} 250 mμ) and the fact that its NMR spectrum contained a sharp one-hydrogen signal in the vinyl hydrogen region are consistent with it being a $\beta\beta$-disubstituted α–β unsaturated ketone with an exocyclic double bond.[18] Three one-hydrogen multiplets between 5·5 τ and

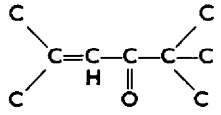
TABLE 1

Ajaconine derivatives	M_D	M_D	Atisine derivatives
C_{20} azomethine diol	−56°	−44°	C_{20} azomethine alcohol
C_{20} diacetoxyazomethine I	−306°	−205°	C_{20} acetoxyazomethine
C_{19} azomethine ketol diacetate II	−511°	−481°	C_{19} azomethine ketol acetate
C_{19} azomethine diol III	−128°	−139°	C_{19} azomethine alcohol
C_{19} azomethine alcohol V	−86°	−84°	C_{19} azomethine

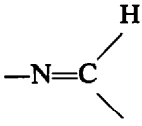
[17] K. Wiesner, R. Armstrong, M. F. Bartlett and J. A. Edwards, *Chem. & Ind.* 132 (1954). We considered that selenium dehydrogenation of a bridged skeleton at 340° could have rearranged a related skeleton into the observed phenanthrenes.

[18] L. F. Fieser and M. Fieser, *Steroids* p. 19. Reinhold, New York (1959).

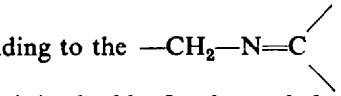
7·5 τ are very probably attributable to three of the four protons α to the nitrogen.[19] The remaining proton signal appears to be under the methyl band of the acetyl group. If this is correct, it substantiates the evidence from bromination that there is no hydrogen on the other carbon flanking the carbonyl. Hence we can write the environment of the ketone in XIII as



At this point it is desirable to survey the recent evidence bearing on the atisine-ajaconine skeleton. A reaction to be described below proves that C–17 is primary, and hence that the nitrogen is flanked by two such groups. In agreement with this, the N.M.R. spectrum of VII had an unsplit one-hydrogen signal at 2·3 τ corresponding to



(half-band width 7·4 cps) and a two-hydrogen doublet at 7·5 τ (separation 2·4 cps) corresponding to the



hydrogens. The broad azomethine hydrogen signal and the doublet for the methylene are probably caused by long range coupling. However these features prevent a positive conclusion that both carbons α to the nitrogen are attached to quaternary carbons. The methyl signal (9·17 τ) in this and other atisine and ajaconine derivatives is sharp, hence this group can definitely be placed on a quaternary carbon. The infrared spectra of the lactams oxoisoatisine[7a] and three described below, and the spectrum of a lactone derived from the hetero ring[20] showed that the smallest ring incorporating the nitrogen was at least six-membered. These facts are all reconcilable with Wiesner and colleagues' formulation of ring A and the hetero bridge. Indeed it is difficult to reconcile these and the dehydrogenations to 1-methyl-6-ethylphenanthrene[21] and 1-methyl-6-ethyl-3-azaphenanthrene[22] on any other basis.[23] By stepwise degradation of atisine followed by mild aromatization we had converted the bridged system carrying the allyl alcohol into a compound containing the 3,4 disubstituted phenol group XIV.[24] This proved unambiguously the presence

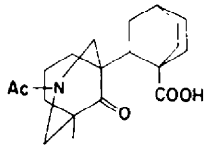
[19] Secondary and tertiary hydrogen attached to carbons adjacent to amide nitrogen and ketone carbonyls absorb in this range. See G.V.D. Tiers, Exploratory N.M.R. studies, Project 737602, Minnesota Mining and Manufacturing Co., St. Paul, Minn., U.S.A.

[20] O. E. Edwards and R. Howe, *Proc. Chem. Soc.* 62 (1959).

[21] W. A. Jacobs, *J. Org. Chem.* **16**, 1593 (1951).

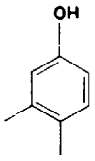
[22] D. M. Locke and S. W. Pelletier, *J. Amer. Chem. Soc.* **81**, 2246 (1959).

[23] We had hoped to provide direct evidence about the size of ring A by oxidation of the α-β unsaturated ketone XIII to the keto acid illustrated. The amorphous acid contained an extra oxygen however, and the attempt was abandoned.

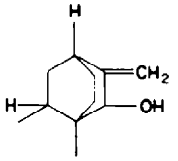


[24] D. Dvornik and O. E. Edwards, *Chem. & Ind.* 623 (1958).

and substitution of the bicycloöctane system to be as shown in XV. If the quaternary



XIV

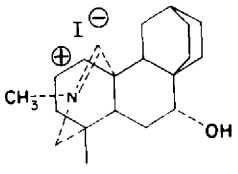


XV

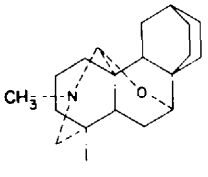
carbon adjacent to the carbonyl in XIII is the quaternary carbon of the bicycloöctane system, then the environment of the ketone fits perfectly the suggested atisine structure.

Thus despite the lack of rigorous proof, in view of the above evidence we now accept with confidence the suggested[17] atisine skeleton, and hence locate the extra oxygen of ajaconine on C–9. The evidence to be presented below unequivocally establishes the relative stereochemistry and fine structure of ajaconine. It also supports the absolute stereochemistry previously suggested for atisine.[24] In the subsequent exposition this absolute stereochemistry will be assumed for clarity.

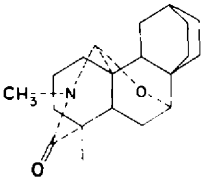
The configuration of the 9-oxygen was established as follows. Methyl iodide converted the azomethine alcohol V to the methiodide XVI. The base liberated from the salt by alkali proved to have no hydroxyl, and analysed correctly for the carbinolamine-ether XVII. Oxidation with permanganate converted this base to a lactam still containing the carbinolamine-ether bridge. Since in no case has it been possible to oxidize C–17 to a carbonyl with external reagents (see below) the lactam must be XVIII and the oxygen links C–9 and C–17. Thus the hydroxyl of V and hence the 9-oxygen of ajaconine is "*cis*" to the hetero bridge.



XVI

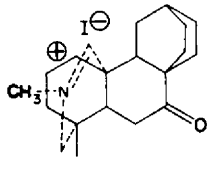


XVII

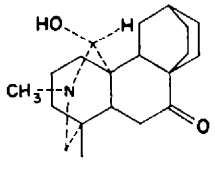


XVIII

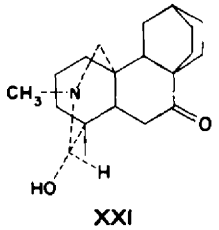
We next consider a unique internal hydride transfer reaction, which gave valuable information about ajaconine.[2b] The azomethine ketone VI was converted to the N-methyl immonium iodide XIX. This proved to be the salt of a very strong base, the carbinolamine XX (pK'_a 11·7). When XX was heated with sodium hydroxide in methanol two reactions took place. One was the isomerization to the isocarbinolamine



XIX



XX

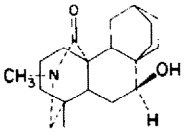


XXI

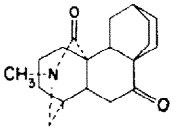
XXI, analogous to the isomerization of atisine to isoatisine. Base XXI had the weaker basicity (pK'_a 9·7) and shift of immonium ion absorption of its hydriodide (1702 cm^{-1} compared to 1688 cm^{-1} for XIX) characteristic of the iso-oxazolidines and carbinolamines.[9]

The second reaction produced an amide, which in view of its inertness to alkali at 200° was a lactam. Its structure was proven to be that shown in XXII in the following way. The hydroxyl configuration was "*trans*" to the hetero bridge since borohydride reduction of the ketone XXIII derived from it gave a high yield of the epimeric alcohol XXIV. Since borohydride reduction of 9-carbonyls in ajaconine derivatives such as VI and in atidine[16] gave back the original α-oriented hydroxyl[25] as major product, XXII must have a β-hydroxyl.

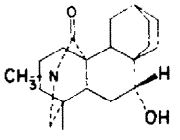
The location of the lactam carbonyl follows from the following evidence, Ketone XXIII was reduced by the Wolff–Kishner method. A lactam was produced which



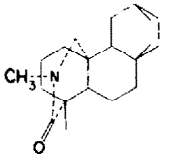
XXII



XXIII

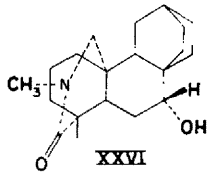


XXIV



XXV

proved different from XXV (prepared by oxidation of the corresponding tertiary amine from atisine).[26] Finally, the methiodide of base V was reduced with sodium borohydride. The acetate of the resulting tertiary-amino alcohol was oxidized to the lactam with Sarret's reagent.[27] Vigorous hydrolysis of the product gave the hydroxy lactam XXVI. This proved different from either of the epimeric hydroxylactams XXII and XXIV, thus the lactam carbonyl of XXII must be on C–17.



XXVI

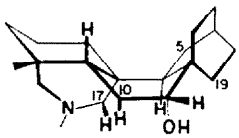
That XXII was formed by internal hydride transfer seemed likely because of the absence of any keto-lactam or carbinolamine–alcohol among the products. Experience with other diterpenoid alkaloids of the atisine[28] and Garrya[13] groups has been that even when C–17 was at an aldehyde oxidation level, oxidation to the 17-oxo compounds is extremely difficult. This is readily rationalized since the 17-hydrogen "*cis*" to the bicycloöctane system is inaccessible to external reagents. Similarly, the 9α-hydrogen of XXII could easily have been transferred from C–17, but is unlikely to have come from an external reagent since the α face of the carbonyl is hindered.

We thus conclude that XXII is formed by internal oxidation–reduction. The mechanism of its formation is discussed further below. Aside from the intrinsic interest

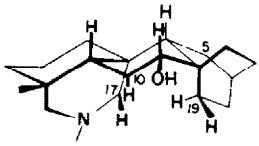
[25] We use α and β to designate orientation below and above the plane of projection respectively.
[26] We are grateful to Dr. R. Howe who carried out this experiment.
[27] G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarret, *J. Amer. Chem. Soc.* **75**, 422 (1953).
[28] S. W. Pelletier and W. A. Jacobs, *J. Amer. Chem. Soc.* **76**, 4496 (1954).

in the new type of hydride transfer reaction[29] these observations gave the first proof that C–17 in the atisine and garryine groups of alkaloids was primary.

With the skeleton and location of the substituents on a firm basis, it is possible to discuss the stereochemistry of ajaconine with confidence. The A:B fusion was proven by the formation of XVII, since the 9:17 oxide could not form in the *cis*-fused alternative. An anti coupling of rings A and C follows from the fact that the 9-hydroxyl in its original α-configuration is equatorial. The evidence for this is the high frequency of the C–O stretching absorption in XXIV (doublet at 1077 and 1082 cm^{-1}) and other 9-hydroxy compounds contrasted with the corresponding band at 1054 cm^{-1} in the β-hydroxy compound XXII. In addition the C–O stretching band of the acetoxy group in the acetate of X was a single sharp band at 1236 cm^{-1}.[30] A 9α-hydroxyl on a *trans–syn* skeleton would have to be axial as in XXVII since ring B would have to have a boat conformation, while on the *trans–anti* skeleton with ring B in a chair conformation (XXVIII) it would be equatorial as required.



XXVII



XXVIII

Two lines of evidence confirm this conclusion. The arguments advanced earlier[9] for the origin of the extremely high basic strength of atisine, based on the repulsive interaction of the 10:17:19 hydrogens when C–17 is tetrahedral, and the oxazolidine oxygen: C–5 hydrogen repulsion[31] are only valid if the skeleton is *trans–anti* fused. In the syn skeleton as in XXVII carbons 5 and 19 are remote from carbons 10 and 17. Secondly, the inertness of C–17 to external oxidizing agents discussed above cannot be accounted for on the basis of the *trans–syn* fusion.

With the *trans–anti* fusion proven[32] the arguments put forward[24] for the location of the ally alcohol system on the branch of the bicycloöctane "*trans*" to the hetero bridge are validated.

We are now in a position to consider the fine structure of ajaconine. Dihydroatisine XXIXa and dihydroajaconine XXIXb have comparable moderate rotations (M_D $-154°$ and $-150°$ respectively) hence the 9α hydroxyl contributes little to the rotation. Similarly the oxazolidine atisine XXX has M_D $-72°$. However all the compounds having a 9:17 carbinolamine-ether have large rotations.[33] Compound

[29] See N. C. Deno, H. J. Peterson and G. S. Saines, *Chem. Rev.* **60**, 7 (1960).

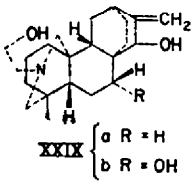
[30] R. N. Jones, P. Humphries, F. Herling and K. Dobriner, *J. Amer. Chem. Soc.* **73**, 3215 (1951); A. R. H. Cole, R. N. Jones and K. Dobriner, *Ibid.* **74**, 4571 (1952). The C—O stretching frequency of the alcohols is higher than normal, perhaps because of the extra rigidity of the bridged skeleton.

[31] N. J. Leonard, K. Conrow and R. R. Sauer, *J. Amer. Chem. Soc.* **80**, 5185 (1958) were the first to specify the 5-hydrogen vs. oxazolidine–oxygen interaction as a contributory factor to the anomalous basic strength of atisine. We simultaneously emphasized its importance as the driving force for the atisine to isoatisine conversion.[2d]

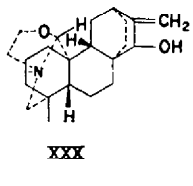
[32] J. Solo and S. W. Pelletier, *Chem. & Ind.* 1108 (1960) have recently presented similar arguments for the *trans–anti* stereochemistry based on our ajaconine work. We had earlier[2b,c] shown that the chemistry could be readily accounted for with this sterochemistry, but refrained from positive statement until the basic skeleton was more firmly established.

[33] The large rotational change is probably a result of the change in molecular shape as ring B changes from a chair to boat conformation. However the oxygen on C-17 in a configuration hitherto unknown for atisine derivatives might make a large rotatory contribution.

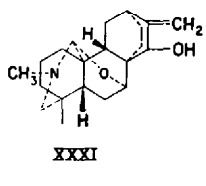
XVII had M_D −651°, and XXXI and the corresponding α–β unsaturated ketone XXXII had M_D −438° and −336° respectively. Since ajaconine has a rotation identical with that of XXXI (M_D − 439°) we conclude that it is not an oxazolidine but



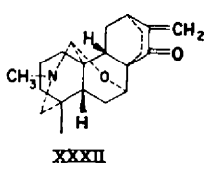
XXIX { a R = H; b R = OH



XXX

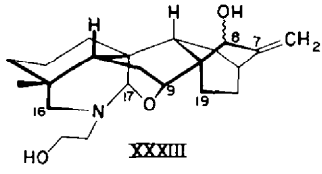


XXXI

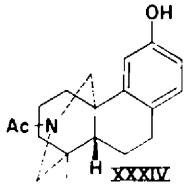


XXXII

is instead a 9:17 carbinolamine ether. Thus, in agreement with our earlier tentative assignment,[2c] ajaconine must be represented by XXXIII, with only the 8-hydroxyl configuration uncertain.



XXXIII



XXXIV

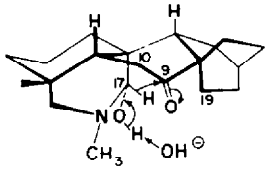
The absolute stereochemistry suggested for atisine[26] was based on the magnitude and sign of rotation of the phenol XXXIV (M_D −314°) derived from it, compared with the rotation of ferruginol (M_D +117°), methyl 6-hydroxydehydroabietate (M_D +234°) and podocarpic acid (M_{Hg} +396°). Support for this assignment comes from the occurrence of ajaconine in *Delphinium* species with the more complex diterpenoid alkaloid lycoctonine, for which the same absolute stereochemistry has been assigned using X-ray crystallography.[34] In addition the ketone XI has an O.R.D. curve with the first extremum (λ 308 mμ, α = +813°) of opposite sign and similar intensity to that of 7-ketocholestane,[35] and the ΔM_D on acetylation of alcohol X is of similar magnitude (−65°) and opposite sign to that for acetylation of 7β-hydroxycholestane (+36°).[36]

The ready formation of the oxide rings in ajaconine and in XVII requires that the boat conformation of ring B have similar energy to the chair conformation. This can only be true if C(17) or C(9) or both are trigonal, so that the bowsprit interactions are eliminated. Of course the bridging by oxygen serves the same purpose. We note that in the boat conformation of ring B the 10:17 interaction disappears, and the 17:19 interaction is reduced, facilitating approach to a transition state involving this conformation. A number of reactions of ajaconine derivatives which illustrate this further will now be described.

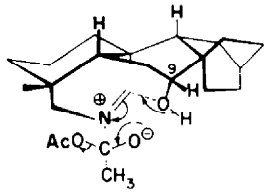
The internal hydride transfer reaction described above requires that ring B be a

[34] M. Przybylska and L. Marion, *Canad. J. Chem.* 37, 1843 (1959).
[35] C. Djerassi, *Optical Rotatory Dispersion* p. 51. McGraw-Hill, New York (1960). We cordially thank Dr. A. K. Bose for determining the O.R.D. spectrum
[36] Ref. 18, p. 253.

boat in the transition state, as illustrated in XXXV. Here the trigonal state of C-9 lowers the energy of the boat conformation.

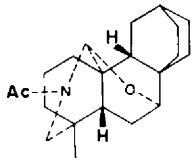


XXXV



XXXVI

A second illustration of the importance of the boat conformation of ring B in influencing the reactions of ajaconine derivatives comes from the acetylation of the azomethine alcohol V. The hydroxyl is predominantly equatorial in the ground state, as shown by the I.R. absorption cited above, and as expected is readily acetylated in most derivatives. Despite this V reacts readily at room temperature with acetic anhydride to give approximately equal quantities of the N-acetyl ether XXXVII and of the normal acetate. We consider that an acetic anhydride molecule approaching V co-ordinates with the unshared pair on nitrogen preferentially. Enough molecules have a boat conformation of ring B that the oxide formation (cf. XXXVI) competes with transfer of the acyl group to oxygen in the normal base-catalyzed esterification process, giving XXXVII.



XXXVII

Finally, the bromoketone XII has its ring B in a boat conformation in the ground state.[2b] This follows from the fact that the bromine is axial (infrared maximum normal at 1702 cm^{-1},[37] but U.V. maximum displaced[38] to 328 mμ). An axial 10α-bromo compound with ring B a chair is impossible, since even a hydrogen in that location is crowded (see above). Hence the bromine must be *trans* to the hetero bridge, and since it is axial ring B must be a boat[39] as illustrated in XXXVIII.

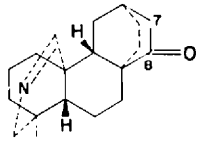
The bromoketone is the product of bromination under thermodynamic control.[39b,40] (HBr catalyst in acetic acid). If the hydrogen bromide is omitted the uptake of bromine is two moles. The reason for this behavior seems to be the bad steric situation of a second bromine replacing the 10-hydrogen in XL due to the 1,3 interaction with the methyl group. This must raise the oxidation potential of the dibromo

[37] R. N. Jones, D. A. Ramsay, F. Herling and K. Dobriner, *J. Amer. Chem. Soc.* **74**, 2828 (1952).
[38] R. C. Cookson, *J. Chem. Soc.* 282 (1954).
[39] Other examples of bromocyclohexanones in boat conformation have been reported. *cf.* [a] C. Djerassi, N. Finch and R. Mauli, *J. Amer. Chem. Soc.* **81**, 4997 (1959); [b] D. H. R. Barton, D. A. Lewis and J. F. McGhie, *J. Chem. Soc.* 2907 (1957).
[40] E. J. Corey, *Experientia* **9**, 329 (1953).

compound to the point where it oxidizes HBr when this is in high enough concentration relative to the bromine present.

The bromine of the monobromoketone is under considerable compression from the three axial hydrogens and the one branch of the bicycloöctane system. This and the true *cis* relation of the ajacent hydrogen must be the cause of the very facile pyrolysis of the compound. When the amorphous bromocompound was heated for 2 hr at 100° in vacuo it was transformed in good yield to the hydrobromide of the α–β unsaturated ketone XIII. This proves to be the best way to prepare the latter, since the lithium chloride in dimethylformamide dehydrobromination[41] procedure gave as much as 60 per cent of an intriguing side reaction described below. Unfortunately, the sensitivity of the bromocompound made its use in the determination of the absolute configuration of ajaconine by application of the octant rule hazardous.

The major byproduct of the lithium chloride catalyzed dehydrobromination of XII was a base analyzing correctly for $C_{19}H_{27}ON$, showing no evidence of conjugation in its ultraviolet absorption, and having ν_{max} 1696 cm^{-1} (isolated ketone). The most likely structure seemed to be XXXIX. This was proven correct by reduction of the α-aminoketone system with zinc and acetic anhydride, the product being the N-acetyl ketone XI. (It is interesting to note that an N:C–10 bridge has been postulated for hypognavin by Sakai[42].) Since the unshared electron pair on the amide nitrogen is



XXXVIII

normally not available due to the amide resonance, we consider that the process is most likely a concerted one with chloride ions or a lithium chloride molecule attracted to the amide dipole releasing the nitrogen electrons for the SN_2 displacement.

As expected from the exposed nature of the unshared pair on the nitrogen of XXXIX it reacted rapidly with methyl iodide. The amorphous base produced by the action of sodium methoxide in methanol on this methiodide contained none of the expected α–β unsaturated ketone according to the infrared spectrum.

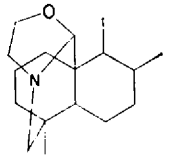
Atisine and ajaconine derivatives present a unique opportunity for the study of the effect of distant polar functions on the basic strength of nitrogen. For example, carbonyls on C–8 and C–9 reduce the basicity of the nitrogen in XL and VI by 0·75 and 1·0 pK_a' units relative to the azomethine VII, respectively. The case of XL represents interaction at a distance of near 5·5 A. We hope to correlate data from these and the more complex diterpenoid alkaloids in a later paper.

In recent years there has been much interest in *trans*-spatial effects on ultraviolet spectra.[43] Two noteworthy examples were found in this work. The long wavelength carbonyl bands of XL[9] and XXIII had intensities of 101 and 99 respectively, three to

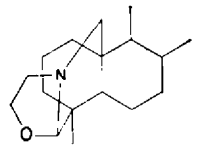
[41] R. P. Holysz, *J. Amer. Chem. Soc.* **75**, 4432 (1953).
[42] S. Sakai, *Chem. & Pharm. Bull.* **7**, 55 (1959) .
[43] O. E. Edwards and L. Marion, *Canad. J. Chem.* **32**, 195 (1954); A. Marchant and A. R. Pinder, *J. Chem. Soc.* 327 (1956); E. R. H. Jones, G. H. Mansfield and M. C. Whiting, *Ibid.* 4073 (1956); R. C. Cookson and N. S. Wariyar, *Ibid.* 2302 (1956).

five times that of isolated ketones. These must be effects of the C=N and lactam carbonyl dipoles on the $n \rightarrow \pi^*$ transition probability.

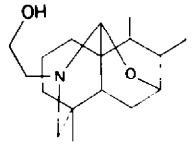
Oxazolidines or carbinolamines with the oxygen on C–17 in the atisine, ajaconine and garrya alkaloid series (type XLI) rearrange on heating with alkali in high yield to the isomeric compounds with the oxygen on C–16 (type XLII). However, attempts to rearrange ajaconine itself gave a mixture, and the N-methyl 9,17-ethers XXXI and XVII failed to isomerize. We hence concluded[2c] that the driving force for the rearrangement is absent in the internal carbinolamine ethers (type XLIII). Inspection of Courtauld models showed that the only major interaction relieved in going from XLI to XLII was that between the 17-oxygen and the nearest hydrogen on C–5. This



XXXIX



XL



XLI

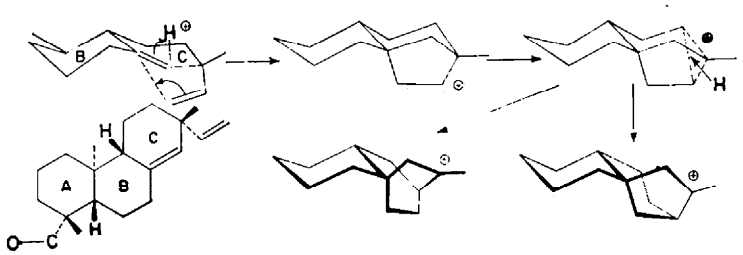
destabilizing factor is absent in the 9:17 ethers. The internal carbinolamine ethers lack the 10:17:19 hydrogen interactions present in XLI and XLII and the interactions of the free hydroxyethyl chain with the ring A hydrogens is probably less than that of the oxazolidines. In addition an entropy factor must favor the internal ether over the oxazolidines. It is thus not surprising that the 9:17 ethers are the more stable of the states represented by XLI to XLIII.

The driving force for the atisine to isoatisine,[44] veatchine to garryine[45] and cauachichicine to isocauachicine[10b] conversions must then, in view of their common stereochemistry,[46] be the above 17-oxygen: 5-hydrogen repulsion.[31,47]

It is interesting that despite the relatively stable character of the internal carbinolamine ethers, the salts of ajaconine and XVII are immonium salts. This would seem to be largely a reflection of the intrinsic stability of the imine and immonium states of nitrogen. For example, there is no evidence for the existence of enamines with secondary nitrogen[48] in the absence of other unsaturation, and tertiary enamines are very strong bases.[49]

Finally, the above structural and stereochemical conclusions relative to atisine and ajaconine confirm the structure and relative stereochemistry assigned to the garrya alkaloids[50] since Pelletier has interrelated the two groups,[32,46] and now enable absolute stereochemistry to be assigned to these also. It is interesting to note that the biosynthetic postulate of Wenkert[11] predicts that the two groups of alkaloids would have the same stereochemistry about their bicycloöctane systems:

[44] W. A. Jacobs and L. C. Craig, *J. Biol. Chem.* **147**, 567 (1943).
[45] K. Wiesner, S. K. Figdor, M. F. Bartlett and D. R. Henderson, *Canad. J. Chem.* **30**, 608 (1952).
[46] S. W. Pelletier, *J. Amer. Chem. Soc.* **82**, 2398 (1960).
[47] *Note added in proof:* We are unable to agree with the recent conformational arguments of Solo and Pelletier [*Proc. Chem. Soc.* 14 (1961)], and consider that the ready rearrangement of XX and one other N-methyl 17-hydroxy compound (unpublished work) to the 16-hydroxy compounds invalidates their explanation of the rearrangement.
[48] B. Witkop, *J. Amer. Chem. Soc.* **76**, 5597 (1954).
[49] R. Adams and J. E. Mahan, *J. Amer. Chem. Soc.* **64**, 2588 (1942).
[50] K. Wiesner and J. A. Edwards, *Experimentia* **15**, 255 (1955).



XLII XLIII XLIV

They would appear then to have a common origin in a diterpene XLIV bearing a mirror image relation to l-epipimaric acid.[51]

EXPERIMENTAL

Unless otherwise stated ultraviolet absorption spectra were determined in 95% ethanol, infrared spectra as Nujol mulls, and rotations in absolute ethanol. The pK'_a values are the pH's at half titration under the described conditions. Alumina was Woelm brand neutral alumina deactivated where necessary. The cited activities are on the Brockmann scale.[52] Wolff–Kishner reductions were carried out using the Huang-Minlon procedure.[53] Melting points were determined on a Kofler hot stage.

Ajaconine

The bases were extracted by 5% acetic acid[54] from the whole seeds of *D. consolida* and *D. Ajacis*, and from a hybrid which gave a similar alkaloid pattern to that of *D. consolida*. A strong base–weak base separation was effected by adjusting the acid solution to pH 8, extracting with chloroform to remove weaker bases, then making the solution strongly basic (pH > 10) and again extracting with chloroform. The pale yellow strong-base fraction crystallized from concentrated ether solution or from aqueous methanol. The yield of ajaconine was in each case of the order of 0·04%. After recrystallization to a constant melting point of 167° it had $[\alpha]_D$ −122° (C, 1·75), M_D −439°. Its pK'_a in 50% aqueous methanol was 11·8 and in 80% aqueous ethanol 11·3. Its infrared spectrum had bands at 3100, 1665 and 889 cm^{-1} (>C=CH$_2$); 3380 and 3300 cm^{-1} (OH).

Ajaconine triacetate hydrochloride

A methanol solution of ajaconine was carefully neutralized with a dilute methanol solution of hydrochloric acid. The resulting salt would not crystallize. It was then acetylated by dissolving in acetic anhydride and heating on a water bath for 3 hr. The reagent was removed under reduced pressure. The residue was dissolved in ethyl acetate and again taken to dryness under reduced pressure. When this was repeated using acetone as solvent a foam was produced which was dried at 100° under 1×10^{-3} mm pressure.

(Found: Acetyl 24·30%. Calc. for $C_{28}H_{40}ClNO_6$; 3-acetyl groups, 24·75%).

It had I.R. max at 1735 cm^{-1} (OAc) and at 1667 cm^{-1} (>C=N<⊕) All attempts to crystallize this salt were unsuccessful.

Dihydroajaconine

To a solution of 105 mg (0·292 mmole) of ajaconine in 10 ml of 80% aqueous methanol was added 189 mg of sodium borohydride. After it had been left at room temperature for 1·5 hr the clear solution was evaporated to dryness *in vacuo*, water added and the base extracted with chloroform. Evaporation of the solvent gave a quantitative yield of a white froth, which crystallized as a monohydrate from aqueous acetone, m.p. 99–101°; $[\alpha]_D^{20}$ −39 ± 1° (*c*, 1·04), M_D −150, pK'_a 7·7 (in 90% ethanol titrated with 0·049 N *p*-toluenesulfonic acid in 80% ethanol). The sample for analysis was air-dried at

[51] A. K. Bose, *Chem. & Ind.* 1104 (1960).
[52] H. Brockman and H. Schodder, *Chem. Ber.* **74**, 73 (1941).
[53] Huang-Minlon, *J. Amer. Chem. Soc.* **68**, 2487 (1946).
[54] We are indebted to Prof. R. C. Cookson who suggested this technique.

room temperature. (Found: C, 69·60; H, 9·67. Calc. for $C_{22}H_{30}O_6N{\cdot}H_2O$ (379·52): C, 69·62; H, 9·83%). I.R. max 3350 cm^{-1} (OH); 1795 cm^{-1}, 1652 cm^{-1}, 895 cm^{-1} (>C=CH_2).

Dihydroajaconine triacetate

A solution of 116 mg (0·306 mmole) of dihydroajaconine monohydrate in 10 ml of 1:1 acetic anhydride–pyridine mixture was left for 19 hr at room temperature. The solution was evaporated to dryness under reduced pressure and the residue distributed between ether and an aqueous sodium hydrogen carbonate solution. Evaporation of the solvent left a quantitative yield of a white froth which eventually crystallized from n-pentane. After two recrystallizations from aqueous acetone the product melted at 133–135°; $[\alpha]_D^{20}$ $-92 \pm 2°$ (*c*, 1·11); M_D $-448 \pm 9°$. (Found: C, 69·11; H, 8·35. Calc. for $C_{28}H_{41}O_6N$ (487·62): C, 68·96; H, 8·48). I.R. max 1738, 1728, 1246 cm^{-1} (OAc); 1656 cm^{-1} 893 cm^{-1} (>C=CH_2).

Isomerization of dihydroajaconine

A solution of 41·5 mg (0·11 mmole) of dihydroajaconine monohydrate in 10 ml of dioxane was warmed over refluxing benzene for 14·5 hr with 207 mg (1·2 mmole) of *p*-toluenesulfonic acid in an atmosphere of nitrogen. The solution was evaporated to dryness *in vacuo* and the residue distributed between 3 N aqueous sodium carbonate solution and ether. Evaporation of the solvent left a quantitative yield of a faintly yellow oil, which failed to crystallize. I.R. max (chloroform) 3550 cm^{-1}, 3450 cm^{-1} (OH) 1705 cm^{-1} (six-membered or larger ring ketone).

Diacetoxy C_{20}-azomethine I

A solution of 8·96 g of ajaconine in 52 ml of methanol was cooled in an ice bath, then carefully neutralized using 1 N hydrochloric acid. The solution was evaporated to dryness under reduced pressure, giving a white froth. This was dissolved by warming with 45 ml of pyridine, and 45 ml of acetic anhydride added to the solution. After 16·5 hr at room temperature this solution was taken to dryness under reduced pressure. The residue was dissolved in 25 ml of 0·02 N hydrochloric acid, and neutral material removed by two ether extractions. The aqueous layer was then cooled to ca. 5°, emulsified with 20 ml of carbon tetrachloride using a mechanical agitator, and ca. 30 ml of ice-cold 50% potassium hydroxide solution added quickly. After 30 sec the agitation was stopped, the layers separated, and the aqueous layer washed twice with fresh carbon tetrachloride. The combined carbon tetrachloride extracts were dried briefly over anhydrous sodium sulfate, filtered through celite, then slowly concentrated by boiling in an open erlenmeyer flask. After 50 min a concentrated brown solution remained. This was taken to dryness under reduced pressure, sodium carbonate solution added, and the products extracted into ether. The ether solution was extracted twice with 20 cm^3 volumes of 3 N sulfuric acid. The acid solution was back-washed with ether, then the combined ether layers washed with water. When dried and evaporated the ether yielded 530 mg of neutral product which crystallized spontaneously. The acid solution and water wash were made alkaline with sodium carbonate and the liberated base extracted into ether. When evaporated the ether left a yellow, mainly crystalline residue. This was heated with hexane, leaving a reddish brown amorphous residue. The hexane solution contained 8·7 g of crude C_{20} azomethine diacetate. This was adsorbed on 56 g of neutral alumina, activity 1. Hexane, benzene, benzene–ether mixtures and ether eluted 5·9 g (59%) of quite pure diacetate, m.p. 145°. Two recrystallizations from hexane gave a product with m.p. 148° and $[\alpha]_D^{25}$ $-77°$ (*c*, 1·06), M_D $-306°$. A sample sublimed at 147°, 5×10^{-4} mm melted at 152–154°. (Found: C, 72·35; H, 8·48. Calc. for $C_{24}H_{33}O_4N$ (399·51): C, 72·15; H, 8·33%). I.R. max 1737 cm^{-1} (OAc), 1650 cm^{-1} (C=N) and 907 cm^{-1} (>C=CH_2).

In a comparable run using 889 mg of ajaconine the carbon tetrachloride distillate was collected and emulsified with a solution of *p*-nitrophenylhydrazine in 20% solution of acetic acid in water. The precipitate was collected and combined with the solid recovered from the carbon tetrachloride. This was dissolved in chloroform, washed with 3 N hydrochloric acid followed by water. The neutral residue from evaporation of the chloroform was recrystallized from aqueous ethanol giving 167 mg of yellow needles m.p. 115–126°. This was adsorbed on 20 times its weight of neutral alumina, activity 1.

Benzene and 20% ether in benzene eluted 163 mg (38%) of golden yellow solid, which when crystallized from ether–pentane mixture melted at 127–131°. This did not depress the m.p. of authentic acetaldehyde p-nitrophenylhydrazone (m.p. 127–130°).

C_{20}-azomethine diol and its methiodide

A solution of 107 mg (0·268 mmole) of the C_{20}-azomethine diacetate in 10 ml 70% aqueous methanol containing 447 mg of potassium hydroxide was refluxed for 35 min. The clear solution was evaporated to dryness under reduced pressure, water added and the base extracted with chloroform. The residue after removal of solvent was recrystallized from chloroform-n-hexane, giving a quantitative yield (84 mg) of a crystalline product, m.p. 207–209°; $[\alpha]_D^{25}$ $-18 \pm 1°$ (*c*, 1·80 in absolute ethanol), M_D $-56 \pm 3°$. The sample for analysis was sublimed at 160–180°/0·5 μ. (Found: C, 76·02; H, 9·16. Calc. for $C_{20}H_{29}O_2N$ (315·44): C, 76·15; H, 9·27%). I.R. max (chloroform) 3570 cm^{-1}, 3400 cm^{-1} (OH); 1650 cm^{-1} (>C=N); 897 cm^{-1} (>C=CH_2). The *methiodide* of the base was prepared in 75% yield by reaction with methyl iodide in acetone. m.p. 220° $[\alpha]_D^{25}$ $-16°$, M_D $-71°$; pK_a' 10·5 (dissolved in 95% ethanol, titrated with 0·05 N NaOH in 50% aqueous ethanol). I.R. max 1684 cm^{-1} (>C=N⊕).

Synthetic ajaconine

A solution of 53 mg (0·168 mmole) of the C_{20}-azomethine diol and 0·5 ml of 2-chloroethanol in 4 ml of dimethylformamide was warmed for 24 hr over refluxing benzene. After cooling the solution was evaporated to dryness under reduced pressure, water added, the solution made alkaline and the base extracted with chloroform. Evaporation of the solvent gave 53·5 mg (87% of theory) of a residue which crystallized spontaneously on being sprayed with ether. The product had $[\alpha]_D^{21}$ $-117 \pm 6°$ (*c*, 0·65 in abs. ethanol) and showed no melting point depression with a sample of ajaconine.

Diacetoxyazomethine ketone II

Diacetoxyazomethine I (320 mg, 0·8 mmole) was dissolved in 3·5 ml of 80% aqueous acetic acid. To this was added a solution of 172 mg (0·676 mmole) of osmium tetroxide in 3·5 ml of the same solvent. The solution slowly turned to dark reddish-brown. After one hour at room temperature a solution (heated to dissolve, then cooled) of 571 mg (1·94 mmole) of sodium paraperiodate in 13 ml of 80% acetic acid was added. The color soon began to fade. The solution was left at room temperature for 4 hr at the end of which it was nearly colorless and a crystalline precipitate had formed. The solution was cooled, filtered, and the crystals washed with methanol. The filtrates were taken to dryness under reduced pressure, and the product distributed between chloroform and dilute sodium carbonate solution. The chloroform solution gave 257 mg of white froth. This was adsorbed from benzene onto 2·6 g of neutral alumina, activity 1 (Brockmann). Three 25 ml portions of benzene eluted 187 mg, which after one recrystallization from acetone–ether and two from acetone–hexane melted at 250°. It had $[\alpha]_D^{21}$ $-127°$ (*c*, 1·14). (Found: C, 68·91; H, 7·70. Calc. for $C_{23}H_{31}NO_3$: C, 68·80; H, 7·78%). I.R. max 1755, 1731 cm^{-1} (OAc, C=O) and 1652 cm^{-1} (C=N).

C_{19}-azomethine diol III

The hydrazone was formed from 131 mg (0·326 mmole) of diacetoxyazomethine ketone II using 1·5 ml of 95% hydrazine in 2 ml of triethylene glycol. The solution was heated to 155°, then 1 g of potassium hydroxide added gradually. The bath temperature was raised to 205° and kept there for 4 hr. The reaction mixture was cooled, diluted with water and extracted 3 times with chloroform. The chloroform was back washed 3 times with water. It contained 86 mg of product which crystallized spontaneously. This was adsorbed on 4·3 g of alumina, activity 2. Benzene, ether, and methanol in ether eluted 75 mg. All the fractions when crystallized from acetone gave 39 mg of lovely needles of the azomethine diol III m.p. 225°. The melting point did not change on further recrystallization. It had $[\alpha]_D$ $-42°$ (*c*, 0·95), M_D $-128°$; I.R. max 3420, 3330, 3160 cm^{-1} (OH), 1657 cm^{-1} (C=N). (Found: C, 75·17; H, 9·20. Calc. for $C_{19}H_{29}NO_2$ (303·43): C, 75·20; H, 9·63%). The mixture of azomethine alcohol, unsaturated azomethine alcohol, and diol in the mother liquors was best treated as described below to obtain pure V.

C_{19}-azomethine alcohol V *and its methiodide*

Crude product from Wolff–Kishner reduction of the diacetoxy azomethine ketone II was hydrogenated over palladium (uptake approximately 20 mole%). The resulting mixture of C_{19}-alcohol and diol (approx. 350 mg) was oxidized overnight with chromium trioxide in acetic acid (1.5 atom equiv of oxygen). The product was reduced by the Wolff–Kishner method, giving 300 mg of product. This was chromatographed on 6·4 g of neutral alumina, activity 2. Forty ml of 50% hexane-benzene eluted 104 mg of quite pure C_{19}-azomethine. Sixty ml of the same solvent and 30 ml of benzene eluted 42 mg of mixture. Benzene and 20% ether in benzene eluted 80 mg of crude C_{19} azomethine alcohol V. The remaining 43 mg of eluate was amorphous.

After recrystallization from acetone-hexane and aqueous acetone V melted at 252°, $[\alpha]_D^{25}$ −30° (*c*, 1·0), M_D −86°. I.R. max 3160, 1084 cm^{-1} (OH), 1659 cm^{-1} (C=N). (Found: C, 79·56; H, 10·05. Calc. for $C_{19}H_{29}ON$ (287·43). C, 79·39; H, 10·17%). The *methiodide* formed readily when methyl iodide was added to an acetone solution of the base. It melted at 275°. (Found: C, 55·78; H, 7·49. Calc. for $C_{20}H_{32}ION$: C, 55·94; H, 7·51%). I.R. max 1672 cm^{-1}  .

Chromic acid oxidation of III *(C_{19}-azomethine ketol)*

To a solution of 128 mg (0·42 mmole of III) in 1 ml of acetic acid was added a solution of 34 mg (0·34 mmole) of chromium trioxide in 2 ml of 90% acetic acid. This was left for 15 hr at room temperature. After addition of around 50 mg of sodium bisulfite the solution was evaporated under reduced pressure. The residue was taken up in 9 ml of 1:1 concentrated ammonia-water, and the product extracted into chloroform. After one recrystallization from acetone–hexane it melted at 211°. Three more crystallizations from the same solvent mixture raised the m.p. to 210–212·5°. I.R. max 3120, 1083, 1075 cm^{-1} (OH), 1723 cm^{-1} (C=O), 1660 cm^{-1} (C=N). (Found : C, 75·98; H, 8·90. Calc. for $C_{19}H_{27}O_2N$ (301·41): C, 75·71; H, 9·03%).

Wolff-Kishner reduction of the C_{19}-azomethine ketol

The hydrazone was formed from the above ketol using 1·5 ml of 95% hydrazine in 1·5 ml of triethylene glycol. After 1 hr at 155°, 1 g of potassium hydroxide was slowly added. The temperature was raised to 200° and maintained there for 4 hr. The solution was cooled, diluted with water and extracted with chloroform. The chloroform was back washed with water. The product (83 mg of white solid) crystallized readily from acetone. It had m.p. 251°, $[\alpha]_D$ −30° (*c*, 1·0), and proved identical in all respects with the C_{19}-azomethine alcohol V.

N-*acetyl carbinolamine-ether* XXVI

The mixture from hydrogenation of the product from Wolff–Kishner reduction of II (see preceding section) (2·28 g) was dissolved in acetic anhydride and left for 20 hr at room temperature. The reagent was removed under reduced pressure, and the residue hydrolyzed by 1½ hr reflux with potassium hydroxide in methanol. The product was separated by distribution between methylene chloride and 3 N sulfuric acid, into 1·08 g of basic and 1·35 g of neutral materials. The base was partially separated by chromatography on a 15-fold ratio of alumina into III and V.

The neutral fraction was adsorbed from benzene onto a 20-fold ratio of alumina of activity 2. Benzene, benzene–ether mixtures and ether eluted 811 mg of XXVI. After recrystallization from pentane this melted at 144°. I.R. max 1647 cm^{-1} (N-acetyl), 1025, 1017 cm^{-1} (ether). (Found: C, 76·73, H, 9·31. Calc. for $C_{21}H_{31}NO_3$: C, 76·55; H, 9·48%).

N-*acetyl carbinolamine ether from* III

A 2% methanol in ether mixture eluted a further 590 mg from the above chromatogram. After four recrystallizations from acetone this melted at 224°. (Found: C, 72·87; H, 8·96. Calc. for $C_{21}H_{31}NO_3$: C, 73·00 H, 9·05%).

Hydrolysis of XXVI

A solution of 537 mg of N-acetyl carbinolamine-ether XXVI in 5 ml of triethylene glycol containing 800 mg of potassium hydroxide and 3 drops of 95% hydrazine was heated in a bath at 195° for 7·5 hr. The product yielded 343 mg of pure starting material and 190 mg of azomethine alcohol V.

After two recrystallizations from acetone and one from methanol-acetone V separated as hexagonal plates, m.p. 252° identical with the sample described above.

C_{19}-azomethine ketone VI *and its methiodide*

To a solution of 83·5 mg (0·29 mmole) of the C_{19}-azomethine alcohol V in 1 ml of glacial acetic acid a solution of 39 mg (0·13 mmole) (34% excess over one atom of oxygen) of finely powdered sodium dichromate dihydrate in 2·5 ml of glacial acetic acid was added. After standing for 65 min at room temperature, the solution was chilled and the excess of the oxidizing agent destroyed by introducing sulfur dioxide. The green solution was evaporated to dryness under reduced pressure and the residue distributed between 10 ml of aqueous ammonia (1:1) and ether. The ethereal solution was washed with 6 N aqueous sulfuric acid and water, and the acidic washings basified. The mixture was then extracted with methylene chloride. Removal of the solvent gave 69 mg (83% of theory) of a n-pentane soluble product, which after being recrystallized from aqueous acetone melted at 123–125·5°; $[\alpha]_D^{25}$ +5 ± 1° (*c*, 1·15, in absolute ethanol); M_D +14·5 ± 3°. pK_a': 4·3 (in 95% ethanol titrated with 0·05 N *p*-toluene sulfonic acid in 80% ethanol). (Found: C, 79·81; H, 9·36; Calc. for $C_{19}H_{27}ON$ (285·41): C, 79·95; H, 9·54%). I.R. max 1708 cm^{-1} (six or larger ring ketone); 1656 cm^{-1} (>C=N); 1425 cm^{-1} (methylene α to six or larger ring ketone); λ_{max} 245 mμ (log ε 1·94) (C=N), and a shoulder with log ε 1·64 mμ at 280 mμ (>C=O) (95% ethanol).

A crystalline *methiodide*, m.p. greater than 355°, was formed quickly when excess methyl iodide was added to an acetone solution of the base. I.R. max 1706 cm^{-1} (C=O), 1688 cm^{-1} (>C=N⊕); pK_a' 11·7 (95% ethanol solution titrated with 0·05 N sodium hydroxide). (Found: C, 56·29; H, 7·11. Calc. for $C_{30}H_{30}INO$ (427·37): C, 56·20; H, 7·08%).

Wolff–Kishner reduction of the C_{19}-azomethine ketone VI

A solution of 51·5 mg (0·18 mmole) of the C_{19}-azomethine ketone in 1·5 ml of triethylene glycol and 1·0 ml of hydrazine (95%) was immersed in a preheated bath at 110° and the temperature gradually raised to 160°. Approx. 550 mg of potassium hydroxide were added and the mixture heated at 200 ± 5° for 3 hr. After cooling water was added and the mixture extracted with methylene chloride. Evaporation of the solvent gave 36·5 mg (74·5%) of an oil which after being dissolved in n-pentane was adsorbed on a column of neutral aluminum oxide (1:25, activity 1). The material eluted with ether crystallized spontaneously. On recrystallization from aqueous acetone the product melted at 110–112·5°; $[\alpha]_D^{25}$: −28 ± 2° (*c*, 0·71, in absolute ethanol). The sample for analysis was sublimed at 100° at 0·5 μ. (Found: C, 84·15; H, 10·61. Calc. for $C_{19}H_{29}N$ (271·43): C, 84·07; H, 10·77%). The product was identical with the C_{19}-azomethine base obtained from atisine (mixed m.p. and I.R. spectrum). Its NMR spectrum (60 mc, 22% solution in carbon tetrachloride with 2·5% tetramethylsilane as internal reference) had signals at 2·3τ (half band-width 7·4 cps, one hydrogen) 7·5τ (doublet separated by 2·4 cps, two hydrogens), 9·17τ (sharp, three hydrogens).

Sodium borohydride reduction of the C_{19}-azomethine alcohol V

To a solution of 60 mg (0·21 mmole) of the C_{19}-azomethine alcohol in 7 ml 80% aqueous methanol 100 mg of sodium borohydride was added. After being kept for 1½ hr at room temperature and 15 min on a water bath of 70°C, the solution was evaporated to dryness under reduced pressure. Water was added and the base extracted with methylene chloride. Evaporation of the solvent left 60 mg of the crude dihydro-derivative. After four recrystallizations from acetone–water it melted at 189–190°. $[\alpha]_D^{25}$: −31 ± 3° (*c*, 0·71), M_D −90 ± 5°. (Found: C, 79·01; H, 10·68. Calc. for $C_{19}H_{31}ON$ (289·45): C, 78·84; H, 10·80%). I.R. max 3140 cm^{-1} (OH); 3350 cm^{-1} (NH).

N-*acetyl* C_{19} *alcohol* X

A solution of 57 mg (0·2 mmole) of the C_{19}-secondary amino alcohol in 10 ml of a mixture of pyridine and acetic anhydride (1:1) was refluxed for 30 min. The residue obtained on evaporation to dryness under reduced pressure was dissolved in ether, filtered from some amorphous precipitate, and washed with 3 N aqueous hydrochloric acid and water respectively. Evaporation of the solvent gave 72 mg (98%) of the crude faintly yellow, oily O,N-diacetate. This was then refluxed for 30 min with

10 ml of 70% aqueous methanol containing 0·5% of potassium hydroxide. The methanol was removed under reduced pressure, water added and the solution extracted with methylene chloride. Removal of the solvent gave 56 mg (87%) of an oily product which crystallized on being sprayed with ether. After being recrystallized from acetone/n-hexane then from aqueous acetone, the product melted at 228°; $[\alpha]_D$ −44 ± 2° (*c*, 0·93); M_D −146 ± 7°. (Found: C, 76·53; H, 9·74. Calc. for $C_{21}H_{33}O_2N$ (331·48): C, 76·09; H, 10·03%). I.R. max 3362 cm^{-1} (OH); 1615 cm^{-1} (amide). A solution of 39 mg of X in 2 ml of triethylene glycol containing 1 g of potassium hydroxide and 2 drops of hydrazine was heated in a bath at 190° for 1 hr. The product consisted of 11 mg of unchanged X (28%) and 26 mg of crystalline secondary amine.

Acetate of X

Pure X was acetylated using 1:1 acetic anhydride-pyridine mixture at 80° for 5 hr. The reagents were removed under reduced pressure. The residue was taken up in methylene chloride and this solution washed with dilute sulfuric acid and sodium carbonate solution. The neutral product melted at 144–146° before and after recrystallization from a hexane-pentane mixture. $[\alpha]_D^{25}$ −57° (*c*, 1·54), M_D −211°. (Found: C, 73·27; H, 9·28. Calc. for $C_{23}H_{35}O_3N$: C, 73·95; H, 9·45%).

N-*acetyl* C_{19} *ketone* XI

To a solution of 32 mg (0·097 mmole) of the N-acetyl C_{19}-alcohol in 1 ml of glacial acetic acid a solution of 12 mg (0·04 mmole) (39% excess over one atom of oxygen) of finely powdered sodium dichromate dihydrate in 4 ml of glacial acetic acid was added. After standing at room temperature for 1 hr, the solution was chilled and the excess of the oxidizing agent destroyed by introducing sulfur dioxide. The green solution was evaporated to dryness under reduced pressure. The residue was distributed between aqueous ammonia (1:1) and ether. Evaporation of the solvent gave 32 mg of a product which after two crystallizations from methylene chloride/n-hexane and one from aqueous acetone had m.p. 188·5–191·5°; $[\alpha]_D^{25}$ −28 ± 1° (*c*, 0·83 in absolute ethanol); M_D −92 ± 3°. (Found: C, 76·63; H, 9·36. Calc. for $C_{21}H_{31}O_2N$ (329·47): C, 76·55; H, 9·48%). I.R. max.: 1698 cm^{-1} (six-membered or larger ring ketone); 1629 cm^{-1} (amide); 1432 cm^{-1} (methylene α to a ketone).

N-*acetyl bromoketone* XII

N-acetyl C_{19}-ketone XI (10·6 mg) was dissolved in 5 ml of a solution of bromine in acetic acid containing hydrogen bromide (stock solution, 94 mg bromine, 0·1 ml of 20% hydrogen bromide in acetic acid, in 20 ml of dry acetic acid). At intervals 1 ml aliquots of the solution were added to aqueous potassium iodide solution and the liberated iodine titrated with 0·02 N sodium thiosulfate. The titre was compared with that corresponding to 1 ml of stock solution determined immediately after each unknown. The molar uptake was 1·0 (2·5 hr), 1·0 (5 hr) and 0·90 (23 hr). In a comparable run without the hydrogen bromide the molar uptake was 1·08 in 3·5 hr and 1·91 in 51 hr.

In a preparative run 56 mg of the N-acetyl ketone was dissolved in 5 ml of stock solution (679 mg of bromine, 0·4 ml of 20% hydrogen bromide in acetic acid in 20 ml of acetic acid).[55] After 17 hr at room temperature in the dark a little solid sodium carbonate was added to neutralize the hydrogen bromide, then the excess bromine and acetic acid were removed under reduced pressure (gentle heating). The residue was dissolved in methylene chloride and dilute sodium carbonate solution. The methylene chloride layer yielded 86 mg of pale yellow bromoketone. This could not be induced to crystallize. (Found: C, 63·63; H, 7·72. Calc. for $C_{21}H_{30}BrNO_3$: C, 61·76; H, 7·40%).

Dehydrobromination of XII

(a) Bromoketone XII (86 mg) was dissolved in 5 ml of dry dimethylformamide and 51 mg of dry lithium chloride added. The mixture was held at 100° for 4 hr, the solvent removed under reduced pressure and the product separated into neutral and basic compounds by distribution between methylene chloride and 6 N sulfuric acid. The 27 mg of neutral product crystallized spontaneously. On recrystallization from acetone–hexane 13 mg m.p. 212° was obtained. The mother liquors gave less pure crystals of the same substance. This proved identical with the α-β unsaturated ketone described below. The 40 mg of base also crystallized spontaneously.

(b) The bromoketone from 60 mg of N-acetyl ketone was dissolved in 6 ml of dimethylformamide and 31 mg of lithium chloride and 60 mg of lithium carbonate added. After 5 hr at 105° the solvent

[55] If more hydrogen bromide was used an oily precipitate formed rapidly.

was removed under reduced pressure and the residue treated as in (a). Forty-five milligrams of neutral product and 16 mg of hexacyclic base were obtained. The neutral fraction crystallized readily giving 29 mg of crude α-β unsaturated ketone.

(c) Amorphous bromoketone XII (48 mg) was maintained at 100° under 0·1 mm pressure for 2 hr. The light brown amorphous product had intense infrared absorption at 1640 cm^{-1} but only a very small peak at 1700 cm^{-1} which might be unchanged bromoketone. By distribution between methylene chloride and 3 N sulfuric acid it was separated in to 43 mg of neutral and 6 mg of basic products. The latter crystallized spontaneously and proved identical with the hexacyclic base described below. The neutral product after one recrystallization melted at 205° and showed no melting point depression with the neutral products from (a) and (b).

N-acetyl α-β unsaturated ketone XIII

The melting point was raised to 211° by chromatography on alumina (25-fold, activity 2), followed by two recrystallizations from acetone; $[\alpha]_D$ +45° (*c*, 0·45); λ_{max} 250 mμ (ε 9300), 329 mμ (ε 96); I.R. max 1664 cm^{-1} (conjugated ketone), 1644 cm^{-1} (amide). (Found: C, 76·88; H, 8·83. Calc. for $C_{21}H_{29}NO_2$ (327·45): C, 77·02; H, 8·93%).

Oxidation of XIII

The α-β unsaturated ketone was inert to osmium tetroxide in ether. A solution of 43 mg of XIII in 5 ml of acetone, 0·05 ml of acetic acid and 0·5 ml of water reduced 50 mg of potassium permanganate in 2 hr, but extra permanganate persisted unchanged. The manganese dioxide was removed by filtration, the acetone evaporated, and the product separated into a trace of acidic material and 54 mg of yellow neutral gum. The latter was dissolved in 10 ml of a saturated solution of lead tetracetate in acetic acid and 1 ml of water, and left for 115 hr at room temperature in the dark. The product was separated into 20 mg of neutral and 21 mg of acid material. The neutral material had lactone character, being opened to an acid in methanolic alkali. This had a different infrared spectrum from the acid produced directly. The latter would not crystallize.

Combined acid fractions from several permanganate-lead tetraacetate oxidation (48 mg) were dissolved in acetic acid (4 ml) and oxidized by shaking for 24 hr with suspended sodium bismuthate (100 mg). After the addition of a drop of phosphoric acid the mixture was filtered and the acetic acid removed under reduced pressure. The product was separated into 6 mg of neutral and 38 mg of acid materials. The latter would not crystallize, but now had a much altered infrared spectrum. The sodium bismuthate oxidation was repeated, 5 mg of neutral product and 26 mg of acid being obtained. The latter had I.R. max 1705, 1745 cm^{-1} (ketone and carboxyl), 1625 cm^{-1} (lactam). Its sodium salt had I.R. max. 1710 cm^{-1} (ketone) and 1635 cm^{-1} (amide). The recovered acid was converted to its methyl ester (CH_3N_2), which was distilled at 150°, 5 × 10^{-4} mm. (Found: C, 66·54; H, 7·84; Calc. for $C_{21}H_{31}O_5N$: C, 66·82; H, 7·84%).

Hexacyclic base XLI

The crystalline base from the above dehydrobrominations when recrystallized twice from hexane had m.p. 141°, and pK_a' 5·6 (95% ethanol). (Found: C, 80·43; H, 9·49. Calc. for $C_{19}H_{27}NO$: C, 79·95; H, 9·54). Its ultraviolet spectrum had λ_{max} 307 mμ (ε 51) and its infrared spectrum had ν_{max} 1696 cm^{-1} (ketone) but no NH absorption.

A solution of 15 mg of the base in 1 ml of acetic anhydride and 0·5 ml of acetic acid was maintained at 100° for 1·5 hr while a total of 160 mg of zinc dust was added in small portions. The mixture was left overnight at room temperature, then taken to dryness under reduced pressure. The residue was extracted with methylene chloride, and the combined solutions extracted with 6 N sulfuric acid. The 22 mg of neutral material left in the methylene chloride crystallized readily from acetone–hexane giving 16 mg m.p. 191°. This did not depress the melting point of the original N-acetyl ketone XI.

Hexacyclic base methiodide

When 0·25 ml of methyl iodide was added to a solution of 42 mg of the base in 0·5 ml of acetone and 3 ml of ether a precipitate formed nearly instantly. After three hours in the dark the solid was collected, giving 63 mg m.p. 296°. After two recrystallizations from methanol–acetone mixtures its m.p. was 291–293°. (Found: C, 56·49; H, 7·07. Calc. for $C_{20}H_{30}INO$: C, 56·20; H, 7·08%).

Hoffmann degradation of the methiodide (55 mg) by 4 hr heating with potassium hydroxide in aqueous methanol gave 33 mg (92%) of a hexane-soluble oil. The non-crystalline perchlorate of the base had an ultraviolet spectrum having only weak end absorption and a low intensity peak at 275 mμ (carbofiyl).

N-*methyl carbinolamine ether* XXXI

The methiodide of the C_{20}-azomethine diol (220 mg) was dissolved in 5 ml of water, the solution cooled to 0° and 10 ml of methylene chloride added. The two layers were mechanically interdispersed and ice cold 50% potassium hydroxide added. The layers were separated and the aqueous layer extracted twice more with methylene chloride. The organic layers yielded 118 mg of colorless oil (74%). This was dissolved in pentane and filtered from 4 mg of amorphous material. The residual oil had $[\alpha]_D$ −133° (*c*, 1·07). Its pK_a' was 10·6 (in 95% ethanol titrated with 0·05 N *p*-toluenesulfonic acid in 50% ethanol). The oil was distilled *in vacuo*. (Found: C, 76·68; H, 9·48. Calc. for $C_{21}H_{31}O_2N$ (329·47): C, 76·55; H, 9·48%).

Attempted isomerization of XXXI

A solution of 113 mg of the base in 10 ml of methanol containing 0·8 g of potassium hydroxide was refluxed in a nitrogen atmosphere for 3 hr. The recovered oily base had $[\alpha]_D^{26}$ −131° (*c*, 0·9), pK_a' 10·5 (same solvents as above) and its infrared spectrum was identical with the starting material.

α-β *unsaturated ketone* XXXII

Active manganese dioxide[56] (1·36 g) was suspended for 4·5 hr in a solution of 92 mg of XXXI in ethanol-free chloroform. The solid was removed by filtration. The filtrate and washings contained 73 mg (80%) of crystalline solid. This was recrystallized once from acetone, giving prismatic needles m.p. 146–148°. This was sublimed for analysis. It had $[\alpha]_D^{25}$ −102°(*c*, 0·97), M_D −336°; I.R. max 1706 cm^{-1} (α-β unsaturated ketone), 1635 and 875 cm^{-1} (>C=CH$_2$) and 1044 cm^{-1} (C—O—C); λ'_{max} 222 mμ (ε 6840), 334 mμ (ε 102). (Found: C, 77·29; H, 8·78. Calc. for $C_{21}H_{29}NO_2$ (327·45): C, 77·02; H, 8·93%).

Carbinolamine ether XVII

The methiodide of V (42 mg) was dissolved in 3 ml of hot water, the solution cooled to 10° and cold aqueous potassium hydroxide added. The base was quickly extracted into methylene chloride, giving 27 mg of hexane soluble crystalline product. After one recrystallization from hexane this melted at 155°. It did not depress the melting point of the product from attempted alkali-catalyzed isomerization of the carbinolamine ether (see below).

Attempted isomerization of XVII

The methiodide of V (256 mg) was dissolved in 10 ml of methanol containing 0·49 g of potassium hydroxide. The solution was refluxed for 3 hr under nitrogen. The product was separated into 3 mg of neutral and 160 mg of benzene-extractable base (83%). The base was converted to its hydriodide m.p. 275°. After two recrystallizations from methanol–ethyl acetate it melted at 277°; $[\alpha]_D$ −35° (*c*, 1·04), M_D −150°. (Found: C, 56·36, H, 7·45. Calc. for $C_{20}H_{32}INO$ (429·39): C, 55·94; H, 7·51). I.R. max 3440 cm^{-1} (OH) and 1685 cm^{-1} (>C=N$^{\oplus}$<).

The base liberated from this salt was hexane soluble. It crystallized from hexane as prisms, m.p. 155°, $[\alpha]_D$ −216° (*c*, 0·74), M_D −651°. Its infrared spectrum had no bands in the hydroxyl or carbonyl regions. (Found: C, 79·82; H, 10·43; Calc. for $C_{20}H_{31}NO$ (301·46): C, 79·67; H, 10·37%).

Action of alkali on methiodide XIX

A solution of 197 mg of the methiodide and 362 mg of potassium hydroxide in 10 ml of methanol was refluxed under nitrogen for 3 hr. The methanol was removed under reduced pressure, and the product distributed between ether and 6 N sulfuric acid. The base recovered from the acid solutions was neutralized with hydriodic acid in methanol, giving 55 mg of the crystalline hydriodide of XXI.

[56] J. Attenburow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jensen and T. Walker, *J. Chem. Soc.* 1094 (1952). F. Sondheimer, O. Manura, M. Urquiza and G. Rosenkranz, *J. Amer. Chem. Soc.* 77, 4145 (1955).

The ether layers yielded 80 mg of neutral product which crystallized spontaneously. After one recrystallization from acetone 55 mg of pure lactam alcohol XXII was obtained.

Hydriodide of XXI

This crystallized as silky needles from methanol-ethyl acetate mixtures. It melted rather indefinitely around 328°. (Found: C, 56·38; H, 7·09. Calc. for $C_{20}H_{30}ION$ (427·37): C, 56·20; H, 7·08%). I.R. max 3480 cm^{-1} (OH), 1700 cm^{-1} (C=O) and 1685 cm^{-1} .

Lactam alcohol XXII

After recrystallization from acetone–hexane this melted at 244°, $[\alpha]_D$ −4°(*c*, 1·05), M_D −12°. I.R. max 3380, 1054 cm^{-1} (OH) and 1620 cm^{-1}. (Found: C, 75·48; H, 9·70. Calc. for $C_{20}H_{31}NO_2$ (317·46): C, 75·67; H, 9·84%).

Lactam ketone XXIII

A solution of 15 mg (0·050 mmole) of sodium dichromate in 5 ml of acetic acid was added to a solution of 44 mg (0·139 mmole) of lactam alcohol XXII in 2 ml of acetic acid. The mixture was left for 2 hr at room temperature, then excess dichromate reduced with sulfur dioxide. The acetic acid was removed under reduced pressure, and the residue taken up in ether and dilute ammonia solution. The ether extracted 45 mg of colorless oil which was hexane soluble. A filtered hexane solution was taken to dryness and the residue crystallized from pentane. It had m.p. 112°; $[\alpha]_D^{26}$ −3·5° (*c*, 1·73), M_D −11°; I.R. max 1706 cm^{-1} (ketone) and 1650 cm^{-1} (lactam); λ_{max} 280 mμ (ε 99). (Found: C, 76·00; H, 9·16. Calc. for $C_{20}H_{29}NO_2$ (315·44): C, 76·15; H, 9·27%).

α-Hydroxy lactam XXIV

Lactam ketone XXIII (23 mg) was dissolved in 7 ml of 90% aqueous methanol and 26 mg of sodium borohydride added. After 1 hr at room temperature the bulk of the solvent was removed on the steam bath and replaced by water. A crystalline solid separated. Yield 20 mg (85%), m.p. after one recrystallization from acetone–hexane 203°. A mixture of this with the *β*-hydroxy lactam XXII melted between 200 and 215°. It had $[\alpha]_D$ −41° (*c*, 0·66), M_D −130°. I.R. max 3405, 1082, 1077 cm^{-1} (OH), 1620 cm^{-1} (lactam). (Found: C, 75·83; H, 9·68. Calc. for $C_{20}H_{31}NO_2$ (317·46): C, 75·67; H, 9·84%)

Wolff–Kishner reduction of XXIII

Thirty eight mg of lactam ketone XXIII was dissolved in 1·4 ml of triethylene glycol and 1 ml of 95% hydrazine. The solution was heated under reflux in a bath maintained at 150° for 30 min. Potassium hydroxide (0·57 g) was cautiously added, the bath temperature raised to 220° and kept there for 3·5 hr. The reaction mixture was diluted with water and the product extracted into chloroform. The residue from evaporation of the chloroform was dissolved in ether and the solution washed twice with 6 N sulfuric acid and once with water. The ether solution yielded 32 mg of product of which 29 mg was pentane soluble. This was adsorbed from pentane onto 0·6 g of alumina, activity 3. Pentane (150 ml) eluted 22 mg of crystalline solid. This was recrystallized from aqueous acetone giving needles, m.p. 128°. It was sublimed at 125°, 6 × 10^{-4} mm. It had $[\alpha]_D^{26}$ −36° (*c*, 0·61), M_D −108°; I.R. max 1642 cm^{-1} (amide). (Found: C, 79·58; H, 10·24. Calc. for $C_{20}H_{31}NO$ (301·46): 79·67; H, 10·37%).

Hydroxy lactam XXVI

The methiodide prepared from 94 mg (0·327 mmole) of C_{19}-azomethine alcohol V was left for 1 hr with 202 mg of sodium borohydride in 10 ml of 80% aqueous methanol. The 100 mg of oily product was acetylated by 30 min heating at 100° with 10 ml of 1:1 acetic anhydride–pyridine. The product was 112 mg of pale yellow oil with I.R. max (CS_2), 1738 cm^{-1} (OAc). This was left for 15 hr with 324 mg of chromium trioxide in 5 ml of pyridine. The excess oxidizing agent was reduced with sulfur dioxide and the solution then taken to dryness under reduced pressure. Aqueous ammonia was added and the product extracted into ether. The ether layers were washed with 6 N sulfuric acid and water. The ether retained 90 mg (78%) of pentane soluble oil. This was hydrolyzed by refluxing with potassium hydroxide in aqueous methanol. The 72 mg of crystalline neutral product was recrystallized

five times from acetone–hexane. It had m.p. 216·5°, $[\alpha]_D^{24}$ −56° (*c*, 0·57), M_D −178°. A mixture with hydroxy lactam XXIV melted over a wide range starting at 163°. I.R. max 3322, 1090, 1080 cm^{-1} (OH), 1618 cm^{-1} (lactam). (Found: C, 75·78; H, 9·70. Calc. for $C_{20}H_{31}NO_2$ (317·46): C, 75·67; H, 9·84%). The compound was recovered quantitatively after 4 hr refluxing under nitrogen with a 20% solution of potassium hydroxide in 50% aqueous ethanol.

Lactam XXV[26]

The methiodide of VII (from 150 mg of the base) was dissolved in 10 ml of 80% methanol, 130 mg of sodium borohydride added, and the solution left at room temperature for three hours. The solvent was evaporated, dilute sodium carbonate solution added and the product extracted into ether. The 153 mg of product after four recrystallizations from acetone melted at 60° and had $[\alpha]_D$ −71° (*c*, 0.93). (Found: C, 83·74; H, 11·36. Calc. for $C_{20}H_{33}N$: C, 83·56; H, 11·57%).

The above N-methyl base (35 mg) was dissolved in 2 ml of pyridine, and the solution added to a mixture of chromium trioxide (55 mg) and 2 ml of pyridine. After 20 hr at room temperature sulfur dioxide was bubbled into the cooled solution. The pyridine was removed under reduced pressure, dilute hydrochloric acid added, and the neutral product extracted into ether. The ether was washed with water, dried and evaporated. The 22 mg of product crystallized readily. The product from two runs was combined (51 mg) and adsorbed from hexane onto 1·5 g of alumina, grade 4. Thirty milliliters of hexane eluted 31 mg, which after two recrystallizations from pentane had m.p. 136°, $[\alpha]_D$ −57° (*c*, 0·69). I.R. max 1650 cm^{-1} (lactam). (Found: C, 79·91; H, 10·20. Calc. for $C_{20}H_{31}NO$: C, 79·67; H, 10·37%). The lactam was recovered quantitatively after 2 hr at 200° under Wolff-Kishner conditions.

Acknowledgements—We are grateful to Mr. A. Knoll for isolation of the ajaconine and Mr. M. Lesage for its characterization and for valuable technical assistance; to Mr. R. Lauzon for the infrared spectra and Mr. H. Seguin for the microanalyses. We are indebted to Mr. J. Nicolson, Dr. F. A. L. Anet and Dr. H. J. Bernstein for the NMR spectra, and to the latter for advice on interpretation; and to Dr. A. K. Bose for the rotatory dispersion curve.