Chemical and *X*-Ray Studies of a [1,4]Diazepino[7,1-*a*]isoquinolin-2-one, a Schmidt Reaction Product from 3-Ethyl-1,6,7,11b-tetrahydro-9,10-dimethoxy-4*H*-benzo[*a*]quinolizin-2(3*H*)-one

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The major and minor Schmidt reaction products from 3-ethyl-1,6,7,11b-tetrahydro-9,10-dimethoxy-4*H*-benzo[*a*]-quinolizin-2(3*H*)-one (I) are shown to be 4-ethyl-1,4,5,7,8,12b-hexahydro-10,11-dimethoxy[1,4]diazepino-[7,1-*a*]isoquinolin-2(3*H*)-one diastereoisomers, (II) and (III), respectively. Structure (II) has been confirmed for the major product by *X*-ray analysis of its hydrobromide which crystallises in the orthorhombic space group *Pbca* with $Z = 8$ in a unit cell of dimensions $a = 12{\cdot}412 \pm 0{\cdot}005$, $b = 20{\cdot}574 \pm 0{\cdot}010$, $c = 13{\cdot}657 \pm 0{\cdot}005$ Å; the structure was refined to R 0·078 for 1793 reflections measured by diffractometer. Conversion of the lactam (II) into its diastereoisomer (III) and into the diazacycloundecene (VIII) proceeds through a common intermediate (VI). Hydride reduction of the methiodide (IV) is followed by Hofmann elimination to give an enamine (XI), from which the tetrahydroisoquinolines (XII) and (XIII) are formed. Oxidation of either lactam (II) or (III) by mercuric acetate yields the didehydro- and tetradehydro-compounds (XV) and (XVI); these are hydrolysed rapidly by aqueous mineral acid with decarboxylation to a dihydroisoquinolinium salt (XX) and an isoquinolinium salt (XXI), respectively. The former cyclises in the presence of base to the imidazoisoquinoline (XXII).

BATTERSBY and his collaborators have shown [1] that application of the Schmidt reaction to the racemic tricyclic ketone (I) † gives a seven-membered lactam with the skeletal structure (II), in 77% yield, but they did not at that time investigate ‡ its stereochemical configuration. We have established unequivocally that its relative chirality at C-4 and C-12b is that shown in (II), and have also studied some aspects of the chemistry of this ring system.

In our experiments, addition of the ketone (I) [2] to a solution of hydrazoic acid in concentrated sulphuric acid at 0° gave the Battersby lactam (A) (90%), m.p. 193·5—195°, together with a minor product (B) (1·5%), m.p. 158—159°. That (B) is the diastereoisomer of (A) followed clearly from interconversions of the two compounds described in the following paragraphs, and so only their relative stereochemistry remained in question. The ^{1}H n.m.r. signal from the 12b-proton appeared at δ 3·92 for (A) but at 4·23 for (B), pointing [3] to *trans*- and *cis*-fused systems, respectively. A Dreiding model of the *trans*-fused system in which the seven-membered ring is in a chair conformation shows that an ethyl group at C-4 can only readily be accommodated in an equatorial alignment, and so (A) should be represented by formula (II). Product (B) would then have the relative chirality at C-4 and C-12b shown in (III); further, since the 12b-proton appears as a triplet ($J_{eq,ax}$, $J_{eq,eq}$) and not as a quartet, (B) must also have the conformation in which this angular proton, and consequently the ethyl group, are equatorial to the seven-membered ring. On the basis of these stereochemical assignments, it appears that only a small proportion of the starting ketone (I) had undergone inversion of configuration at C-3 before reaction with the hydrazoic acid. In support of this conclusion, when the Schmidt reaction was carried out by gradual addition of sodium azide to a solution of the ketone (I) in concentrated sulphuric acid, conditions which would permit the known acid-catalysed epimerisation [4] at C-3 to proceed further, the yield of the minor product (B) rose to 5%. That the Schmidt reaction proceeds only in the direction observed can be explained by the influence of the equatorial ethyl group in hindering the formation of an intermediate having the N_2^+ system *syn* to C-3; the sterically compatible *anti*-intermediate (a) leads *via* (b) to (c) as shown in Scheme 2.

The structural and configurational assignment § (II)

† In this paper, all compounds described are racemic; for diastereoisomers only one enantiomer is represented in the stereochemical formulae.

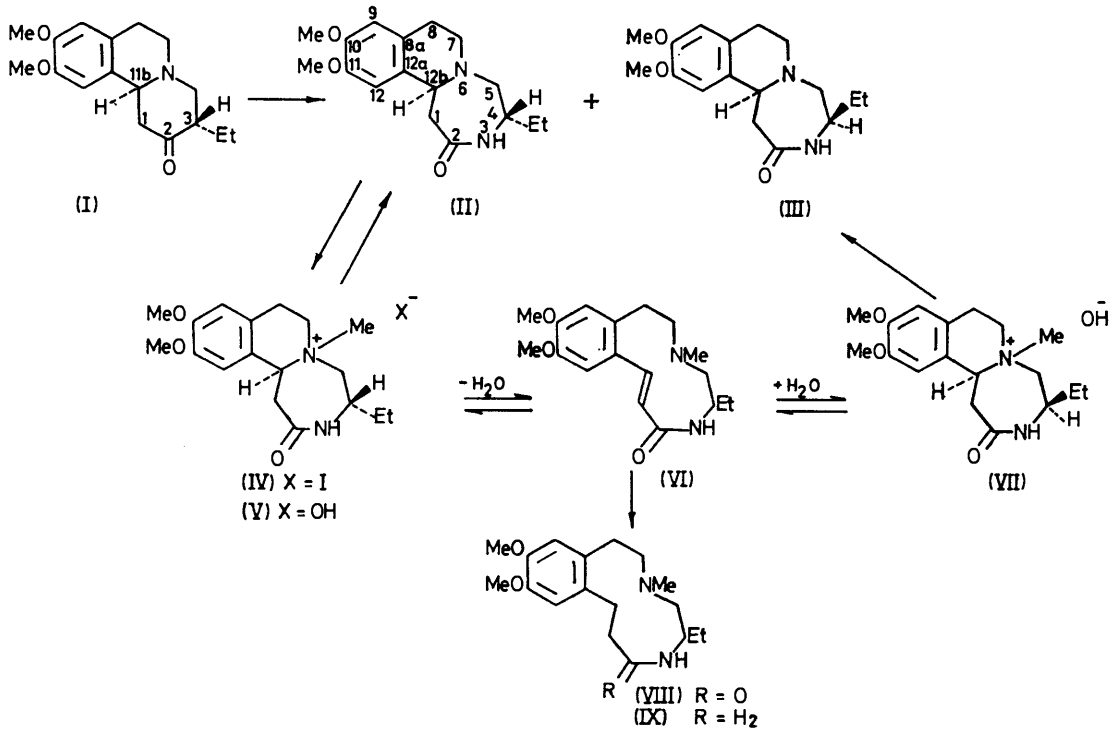
‡ Professor Battersby informs us that his more recent studies (paper in preparation) also show that structure (II) depicts its relative configuration.

§ This configuration has recently been assigned to a 3-methyl homologue by A. Buzas, F. Cossais, and J.-P. Jacquet (*Bull. Soc. chim. France*, 1972, 4397), who relied on Bohlmann absorption bands between 2700 and 2800 cm^{-1} (KBr dispersion) to demonstrate the presence of a *trans*-fused system. This parameter was of doubtful value for our lactams (A) and (B), however, since they had almost identical, weak absorption at 2700—2800 cm^{-1} in chloroform solution and, for a dispersion in potassium chloride, lactam (A) exhibited marked absorption only after the disc had been annealed.

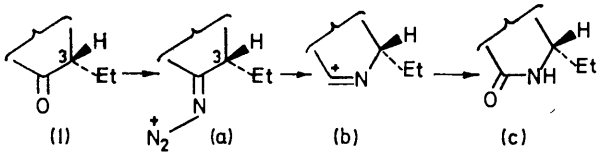
[1] A. R. Battersby, S. W. Breuer, and S. Garratt, *J. Chem. Soc.* (*C*), 1968, 2467.
[2] N. Whittaker, *J. Chem. Soc.* (*C*), 1969, 85.
[3] T. A. Crabb, R. F. Newton, and D. Jackson, *Chem. Rev.*, 1971, **71**, 109.
[4] H. T. Openshaw and N. Whittaker, *J. Chem. Soc.*, 1963, 1461; A. Brossi and O. Schnider, *Helv. Chim. Acta*, 1962, **45**, 1899.

for lactam (A) has now been confirmed by an *X*-ray crystal-structure analysis of its hydrobromide (see later).

In our studies of the chemistry of the lactam (II), ring-opening at the C(12b)–N(6) bond was first investigated. The methiodide (IV) was converted into the quaternary hydroxide (V) but this gave, on being heated at 180° under reduced pressure, not the expected [5] Hofmann-elimination product (VI), but a mixture of lactams (II) and (III). Formation of the latter was rationalised in terms of partial epimerisation at C-12b (with this racemic compound, equivalent to epimerisation at C-4) through the reversible formation of the ring-opened compound (VI), accompanied by de-quaternisation, as illustrated in Scheme 1. Support for the participation of the *seco*-structure (VI) in this transformation was afforded by u.v. absorption measurements (see Experimental section)



SCHEME 1



SCHEME 2

on the quaternary hydroxide (V) and by the demonstration that catalytic hydrogenation of (V) over platinum produced the eleven-membered lactam (VIII) in 88% yield. The latter is a representative of a novel ring system and, as expected [6] of a lactam of nine or more ring atoms, exhibited amide II absorption at 1552 cm^{-1}. Neither the quaternary iodide (IV) nor the corresponding chloride was susceptible to the catalytic hydrogenation conditions but treatment of the former in water with sodium amalgam also furnished the lactam (VIII). The yields of secondary amine resulting from reduction of the lactams (II) and (VIII) by sodium dihydrobis-(2-methoxyethoxy)aluminate contrasted markedly. The lactam (II) gave 90% of the diamine (II; CH_2 for CO) but the lactam (VIII) gave only 55% of the diamine (IX), owing perhaps, to some ring-cleavage of the initially produced eleven-membered carbinolamine.

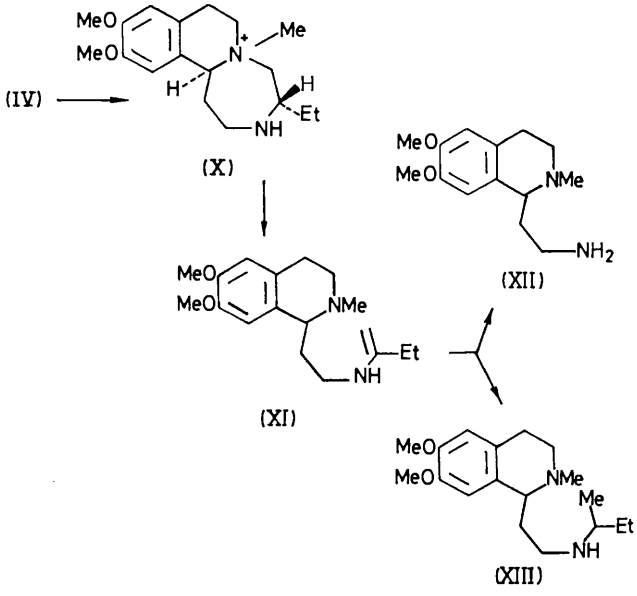
In the light of the above results, it seemed possible that treatment of the methiodide (IV) with sodium dihydrobis-(2-methoxyethoxy)aluminate might lead directly, through the *seco*-compound (VI), to the diamine (IX) or a didehydro-derivative of (IX). In the event, however, the reaction took a different course and gave principally the aminoethylisoquinoline (XII), together with some of its *N*-(2-butyl) derivative (XIII), the constitution of these products being elucidated principally through their ^1H n.m.r. spectra. It appears that the initial step (see Scheme 3) was reduction of the amide function to give compound (X), and was followed by Hofmann elimination to give the enamine (XI); a small proportion of the latter was then reduced to the 2-butyl derivative (XIII), the remainder undergoing hydrolysis to the aminoethyl compound (XII) during the subsequent work-up.

When the lactam (II) was oxidised with an excess of

[5] *Cf.* L. A. Paquette and L. D. Wise, *J. Org. Chem.*, 1965, **30**, 228.

[6] L. J. Bellamy, ' Advances in Infrared Group Frequencies,' Methuen, London, 1968, p. 285.

mercuric acetate in refluxing aqueous acetic acid, the acetate (XIV) of the pale yellow anhydro-base (XV) crystallised in 64% yield from the demercurated reaction liquid; the liquors, on basification, afforded the yellow-brown anhydro-base (XVI) in 22% yield. The structures of these didehydro- and tetradehydro-products were clearly delineated on the basis of their u.v. and ^{1}H n.m.r. spectra; in each case, the vinylic proton at C-1 was exchangeable by deuterium oxide owing to equilibration of the compounds with their respective cations (XIV) and (XIX). The salt (XIV) was inert to the conditions of oxidation and hence the tetradehydro-compound must have arisen through a different intermediate. It is suggested (Scheme 4) that a mixture of quaternary compounds (XIV) and (XVII) was first formed and that the latter, through its equilibrium with the anhydro-base (XVIII), underwent further oxidation to the fully



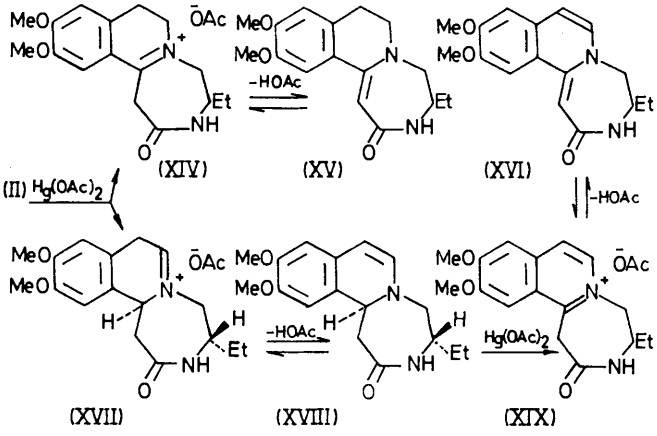
SCHEME 3

aromatic isoquinolinium salt (XIX), the cation of the tetradehydro-product (XVI) isolated. A similar mechanism was advanced [7] to account for a by-product formed in the oxidation of a 1,2,3,4-tetrahydroisoquinoline Mannich base. The tetradehydro-product was, interestingly, formed in excess of the didehydro-product on oxidation of the *cis*-fused lactam (III) by mercuric acetate. It was also shown, by t.l.c., that both oxidation products are formed, presumably by a hydride transfer [8] mechanism, on prolonged heating of the lactam (II) with carbon tetrachloride in a sealed tube at 100°. Catalytic hydrogenation of the quaternary salt (XIV) gave a mixture in which the *cis*-fused lactam (III) predominated over the *trans*-fused lactam (II).

[7] H. T. Openshaw and N. Whittaker, *J. Chem. Soc.*, 1963, 1449.

[8] *Cf.* A. V. El'tsov, *J. Org. Chem. U.S.S.R.*, 1965, **1**, 1121; R. K. Grantham, O. Meth-Cohn, and M. A. Naqui, *J. Chem. Soc.* (*C*), 1969, 1438.

The amide bond in both the quaternary species (XIV) and (XIX) was labile even to cold aqueous 0·5N-mineral acid, and at 100° rapid hydrolysis was accompanied by

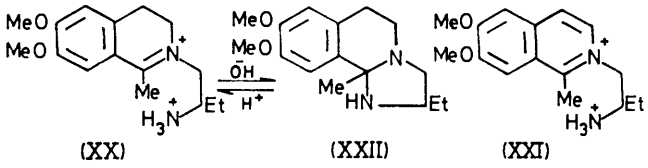


SCHEME 4

spontaneous decarboxylation [9] of the resulting 1-carboxymethylisoquinolinium salts, with formation of the 3,4-dihydroisoquinolinium salt (XX) and the isoquinolinium salt (XXI), respectively. The 3,4-dihydro-compound was converted by aqueous alkali into a colourless, ether-soluble gum for which the structure (XXII) was indicated by its spectroscopic properties. Treatment of this imidazoisoquinoline with mineral acid immediately regenerated the dihydroisoquinolinium ion. Predictably, the isoquinolinium salt (XXI) did not cyclise analogously in the presence of aqueous alkali since, in this case, cyclisation would have involved loss of the considerable energy of aromatisation.

X-*Ray Crystal Structure Analysis of Lactam* (*A*) *Hydrobromide*.—The structure was solved from diffractometer data by the heavy-atom method, and refined by least-squares and difference-Fourier methods to R 7·8%, with anisotropic temperature factors, and including hydrogen atoms.

The structural and configurational assignment (II) for lactam (A) was thus confirmed. A general view of the



SCHEME 5

molecule is shown in Figure 1 and detailed bond lengths and angles in Figure 2. All bond lengths and angles are as expected. The benzene ring was found to be essen-

[9] J. M. Osbond, *J. Chem. Soc.*, 1951, 3464; S. G. Agbalyan, A. O. Nshanyan, and L. A. Nersesyan, *Izvest. Akad. Nauk Armyan S.S.R. khim. Nauk*, 1963, **16** (1), 77.

tially planar (χ^2 0·99). The six-membered tetrahydropyridine ring adopts the half-chair conformation with

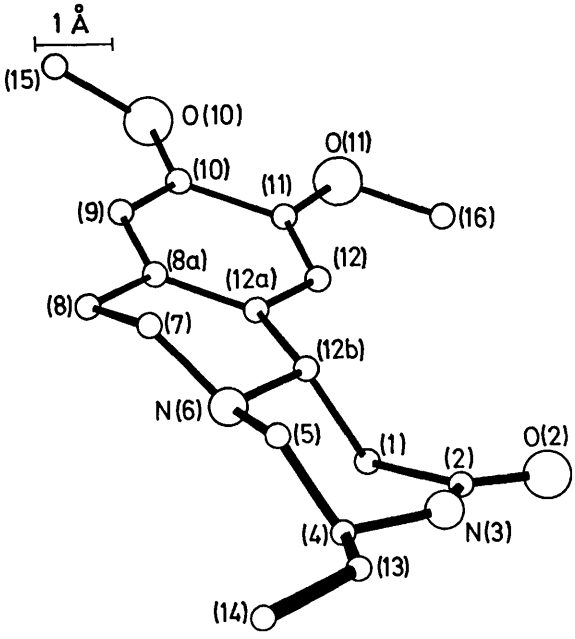


FIGURE 1 The perspective drawing of lactam (A) (as the hydrobromide), showing the crystallographic numbering scheme

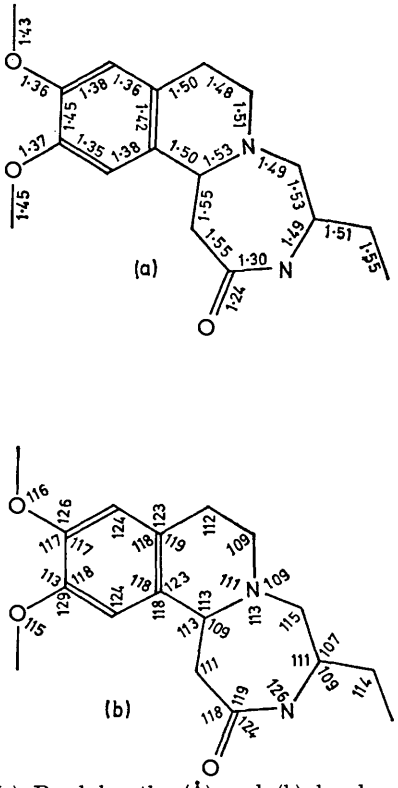


FIGURE 2 (a) Bond lengths (Å) and (b) bond angles (°) for lactam (A) (as the hydrobromide). Mean standard deviations are 0·02 Å and 2·0°

C(7) significantly (0·6 Å) above the plane of the benzene ring and N(6) slightly (0·15 Å) below the plane. The seven-membered ring is in a ' chair ' conformation with atoms N(3), C(1)—(4) coplanar and the remaining atoms in an approximately parallel plane 1·1 Å away. The seven-membered ring is *trans*-fused to the tetrahydropyridine ring, with the N(6)–C(5) and C(12b)–C(1) bonds equatorial to the six-membered ring. The ethyl group at C(4) is also equatorially disposed, and C(14) is closer to H(4) than to N(3) or C(5). The hydrogen on N(3) was located and found to be approximately in the C(2), N(3), C(4) plane.

EXPERIMENTAL

I.r. spectra were measured for potassium chloride dispersions. The ^{1}H n.m.r. spectra were determined for solutions in deuteriochloroform with tetramethylsilane as internal reference, by use of a Varian HA-100 spectrometer.

*4-Ethyl-*1,4,5,7,8,12b-*hexahydro-*10,11-*dimethoxy*[1,4]*diazepino*[7,1-a]*isoquinolin-*2(3H)-*one* (II) *and* (III).—(i) Stirred concentrated sulphuric acid (150 ml) was maintained at 0° during the addition in portions, over 30 min, of sodium azide (18 g, 1·5 mol) and subsequent dropwise addition, over 1·5 h, of the racemic tricyclic ketone [2] (I) (50 g) in chloroform (60 ml). The mixture was poured onto ice, diluted with water to *ca.* 4 l, and basified with potassium hydroxide; the precipitated solid was extracted into chloroform (2 × 1 l) and the extract was washed with water, dried (Na_2SO_4), and evaporated. Crystallisation of the residue from ethanol (400 ml) gave solvated crystals, concentration of the liquors also affording more pure compound; the combined product was freed from alcohol of crystallisation at 90°, to leave 47 g (90%), m.p. 193·5—195° (lit.,[1] 190—192°), of t.l.c.-pure (SiO_2; $CHCl_3$–MeOH, 10 : 1) lactam (II) (Found: C, 67·0; H, 8·05; N, 9·2. Calc. for $C_{17}H_{24}N_2O_3$: C, 67·1; H, 7·95; N, 9·2%), δ 3·92br (1H, d, 12b-H) and 3·63 (1H, m, 4-H), *m/e* 304 (M^+). Its *hydrobromide* (from aqueous acetone) had m.p. 220° (efferv.) (Found: C, 53·15; H, 6·65; Br, 20·35; N, 7·25. $C_{17}H_{25}BrN_2O_3$ requires C, 53·0; H, 6·55; Br, 20·8; N, 7·25%). The alcoholic liquors were concentrated to 25 ml, acidified with concentrated aqueous hydrogen bromide, and diluted with ether (10 ml), and the resulting crystals were recrystallised from alcohol to give pure lactam (III) hydrobromide (1·03 g, 1·5%), m.p. 236° (efferv.); addition of ether to the derived (aq. KOH–CH_2Cl_2) base yielded needles of the *lactam* (III), m.p. 158—159° (Found: C, 67·2; H, 8·2; N, 9·0%), δ 4·23 (1H, t, 12b-H) and 3·48 (1H, m, 4-H).

(ii) When the same quantities of reactants were added to the sulphuric acid in the reverse order, 41·43 g (79%) of lactam (II) and 3·47 g (5·2%) of lactam (III) hydrobromide were isolated.

*4-Ethyl-*1,2,3,4,5,7,8,12b-*octahydro-*10,11-*dimethoxy-*2-*oxo-*[1,4]*diazepino*[7,1-a]*isoquinoline Methiodide* (IV).—The lactam (II) (10 g) was stirred with acetone (150 ml) and methyl iodide (15 ml) under reflux for 1 h and, after cooling, the resulting hygroscopic crystals were collected and washed with acetone, to give the *methiodide trihydrate* (16·2 g, 98·5%), m.p. 203° (efferv.) (Found: C, 43·2; H, 6·5; I, 25·45; N, 5·45; loss on drying at 100°, 10·85. $C_{18}H_{27}IN_2O_3$, $3H_2O$ requires C, 43·2; H, 6·65; I, 25·4; N, 5·6; H_2O, 10·8%). It is sparingly soluble in cold water.

The Quarternary Hydroxide (V) *and its Pyrolysis.*—The methiodide (IV) trihydrate (10 g) was stirred with Amberlite

400 (OH^- form) (20 ml) in degassed water (40 ml) until the crystals had dissolved and the mixture was then poured onto a prepared column of the resin (*ca.* 400 ml). Elution with degassed water (2 l) and evaporation of the eluate at 12 mmHg (nitrogen) pressure left the crude syrupy quaternary hydroxide (V); $\lambda_{max.}$ 318 nm (ε 1140) in methanol, intensified on addition of sodium hydroxide, indicative of the presence of a component with a conjugated veratrole chromophore. When the syrup was heated at 12 mmHg (nitrogen) pressure, while the bath temperature was raised from 150 to 185° during 1·5 h, methanol was evolved, and crystallisation of the residual gum from alcohol (20 ml) yielded lactam (II) (1·13 g), m.p. and mixed m.p. 193—195°. The material recovered from the alcoholic liquors was subjected to column chromatography on alumina; product eluted by methylene chloride and 1 : 1 methylene chloride–chloroform was converted in ethanol–ether into a hydrobromide which, on recrystallisation (H_2O–EtOH), gave the lactam (III) hydrobromide (0·74 g), m.p. 240° (efferv.). This afforded the lactam (III) (0·55 g), m.p. and mixed m.p. 158—159°.

5-*Ethyl*-1,2,3,4,5,6,8,9-*octahydro*-11,12-*dimethoxy*-3-*methyl*-3,6-*benzodiazacycloundecin*-7-*one* (VIII).—(*a*) A suspension of the methiodide (IV) trihydrate (2 g) and Amberlite 400 (Cl^- form, 5 ml) in water (25 ml) was stirred until the crystals had dissolved and the solution was poured through a column of the resin, with water as eluant. The syrupy methochloride recovered from the eluate was shaken with platinum oxide (0·25 g) in methanol (25 ml) and water (2 ml) under hydrogen; absorption ceased after 10 min, when conversion into platinum was complete but, on addition of a solution of sodium hydroxide (0·7 g) in water (3 ml), absorption of 1 mol. equiv. of hydrogen (96 ml at 26° and 763 mmHg) took place during 3·5 h. After filtration, water (50 ml) was added, the methanol was evaporated off *in vacuo*, and the product was extracted into methylene chloride. The extract was washed with water, dried (Na_2SO_4), concentrated to small bulk, and poured through a column of activated alumina (10 g) (elution with methylene chloride followed by methylene chloride–chloroform). Removal of the solvent from the combined eluate and crystallisation of the residual solid from benzene afforded the solvated (9% benzene) *benzodiazacycloundecine* (VIII) (1·24 g, 88%), m.p. 156·5—157·5° [Found (material dried at 100°): C, 67·45; H, 8·85; N, 8·85. $C_{18}H_{28}N_2O_3$ requires C, 67·45; H, 8·8; N, 8·75%], *m/e* 320 (M^+), $\nu_{max.}$ 1646 (amide I) and 1552 cm^{-1} (amide II), δ 2·9—2·4 (10H, 5 × CH_2). Its *hydrobromide*, m.p. 253—255° (Found: C, 53·95; H, 7·35; Br, 19·75; N, 6·9. $C_{18}H_{29}BrN_2O_3$ requires C, 53·85; H, 7·3; Br, 19·95; N, 7·0%), and *methiodide*, m.p. 275° (efferv.) (Found: C, 49·15; H, 6·8; I, 27·6; N, 5·9. $C_{19}H_{31}IN_2O_3$ requires C, 49·35; H, 6·75; I, 27·5; N, 6·05%), were obtained from solutions of the base in hot acetone.

(*b*) Sodium amalgam (3% Na; 20 g) and the methiodide (IV) trihydrate (2 g) were stirred in water (50 ml) at 50° until the crystals had dissolved, then at ambient temperature for 2 days. More amalgam (10 g) was added and, after 18 h, the resulting solid was extracted into chloroform. The solution was washed with water, dried (Na_2SO_4), and evaporated, and the residual gum was digested with ether to give the lactam (VIII) (0·67 g, 52%), m.p. and mixed m.p. 156—157·5°.

Reductions with Sodium Dihydrobis-(2-*methoxyethoxy*)-*aluminate*.—(a) *Lactam* (II). A suspension of the lactam (5 g) in dry tetrahydrofuran (15 ml) under dry nitrogen was treated during 5 min with the dihydroaluminate [15 ml of a 70% solution (Vitride) in benzene] and the resulting solution was refluxed for 4 h. After decomposition of the excess of reagent with water (100 ml), with cooling, and addition of aqueous 40% potassium hydroxide (15 ml), the product was extracted into benzene (2 × 100 ml) and the benzene solution was washed with water, dried (Na_2SO_4), and evaporated. A solution of the residual gum in ethanol (15 ml) was acidified with concentrated aqueous hydrogen bromide and diluted with acetone (75 ml). After 1 h, the resulting suspension of crystals was treated with more acetone (75 ml), kept for 1 h, and filtered, to give 7·45 g of material, m.p. 197° (efferv.). Addition of acetone (200 ml) to a solution of the crystals in water (12 ml) gave 4-*ethyl*-1,2,3,4,5,7,8,12b-*octahydro*-10,11-*dimethoxy*[1,4]*diazepino*[7,1-a]*isoquinoline* (II; CH_2 for CO) *dihydrobromide acetone solvate* (7·02 g), m.p. 203° (efferv.) (Found: C, 47·05; H, 6·85; Br, 31·0; N, 5·35; loss on drying at 140°, 11·3. $C_{17}H_{28}Br_2N_2O_2,CH_3COCH_3$ requires C, 47·05; H, 6·7; Br, 31·35; N, 5·5; acetone 11·35%). The presence of acetone of crystallisation was first established by i.r. spectroscopy (KCl disc); on dissolution of the crystals in water, acetone was immediately liberated. The derived base (II; CH_2 for CO) gave *m/e* 290 (M^+).

(b) *Lactam* (VIII). Reduction of the solvated (benzene) lactam (1 g) in tetrahydrofuran (2 ml) with Vitride (2 ml), as in (a), afforded a base which was converted in ethanol into a dihydrobromide (0·75 g), m.p. 246° (efferv.). Recrystallisation (MeOH) gave prisms (0·61 g), m.p. 220° (efferv.), of solvated (MeOH) 5-*ethyl*-2,3,4,5,6,7,8,9-*octahydro*-11,12-*dimethoxy*-3-*methyl*-1H-3,6-*benzodiazacycloundecine* (IX) *dihydrobromide* [Found (material dried at 120°): C, 45·8; H, 7·05; Br, 33·85; N, 5·85. $C_{18}H_{32}Br_2N_2O_2$ requires C, 46·15; H, 6·9; Br, 34·2; N, 6·0%]. The derived base gave *m/e* 306·2298 (M^+; $C_{18}H_{30}N_2O_2$ requires *M*, 306·2307).

(c) *The methiodide* (IV). The methiodide (IV) trihydrate (5 g) was dried in a current of nitrogen at 125°, stirred in tetrahydrofuran (15 ml) under dry nitrogen, treated dropwise with Vitride (20 ml), and refluxed for 2·5 h. After addition of aqueous potassium hydroxide, the product was extracted into chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated. The residual gum was a mixture of one major and three minor components (t.l.c. on SiO_2 in 1 : 1 $Me_2N{\cdot}CHO$–MeOH or Al_2O_3 in 40 : 1 $CHCl_3$–MeOH). It afforded a dihydrobromide (1·74 g), m.p. 248° (efferv.), from ethanol (30 ml); recrystallisation by concentration of a solution in hot methanol gave solvated 1-(2-*aminoethyl*)-1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-2-*methylisoquinoline* (XII) *dihydrobromide* (1·17 g), m.p. 267° (efferv.) (Found: C, 40·45; H, 5·9; Br, 38·15; N, 6·6; loss on drying at 100°, 1·9. $C_{14}H_{24}Br_2N_2O_2,0{\cdot}25CH_3OH$ requires C, 40·7; H, 6·0; Br, 38·1; N, 6·65; MeOH, 1·9%), $\nu_{max.}$ 2950 ($-\overset{+}{N}H_3$), 2700 and 2630 cm^{-1} ($-\overset{+}{N}H<$). The derived base (XII) gave *m/e* 250 (M^+) and 206 (M — $CH_2{\cdot}CH_2{\cdot}NH_2$, base peak), δ 3·51 (1H, t, 1-H), 3·2—2·6 (6H, 3 × CH_2), 2·2br (2H, exch. D_2O, NH_2), and 1·92 (2H, q, CH_2 β to NH_2).

The mixture of bases recovered from the alcoholic liquors was chromatographed on alumina (40 g) in benzene (elution with methylene chloride and with chloroform). The material recovered from the chloroform eluate was purified by extraction into ether and further chromatography (Al_2O_3). Treatment with hydrogen chloride in acetone then afforded 1,2,3,4-*tetrahydro*-6,7-*dimethoxy*-2-*methyl*-1-[2-(1-*methylpropylamino*)*ethyl*]*isoquinoline* (XIII) *dihydrochloride*

(25 mg) (Found: C, 55·25; H, 8·35; Cl, 17·7; N, 7·15. $C_{18}H_{32}Cl_2N_2O_2,\frac{2}{3}H_2O$ requires C, 55·25; H, 8·55; Cl, 18·15; N, 7·15%). The derived base (XIII) gave *m/e* 306·2302 (M^+; $C_{18}H_{30}N_2O_2$ requires *M*, 306·2307) and 206·1183 (M^+ — side chain, base peak; $C_{12}H_{16}NO_2$ requires 206·1182), δ 3·51 (1H, t, 1-H), 1·01 (3H, 2 close doublets of unequal intensity arising from 2 racemates, $CH_3{\cdot}CH<$) and 0·97 (3H, t, $CH_3{\cdot}CH_2$).

Oxidations with Mercuric Acetate.—(*a*) The lactam (II) (20 g) was heated with mercuric acetate (88 g, 4·2 mol. equiv.) in aqueous 10% acetic acid (400 ml) under reflux for 10 min; the mixture was then diluted with aqueous 10% acetic acid (200 ml), heated on a steam-bath, saturated with hydrogen sulphide, cooled, and filtered (Hyflo). The filtrate was concentrated *in vacuo* to 150 ml and set aside at room temperature, then during 3 days at 0°, to yield pale cream prisms (15·3 g, 64%), m.p. 143—145°, of the *acetate* (XIV) (Found: C, 62·9; H, 7·25; N, 7·65. $C_{19}H_{26}N_2O_5$ requires C, 62·95; H, 7·25; N, 7·75%), $\lambda_{max.}$ (N-HOAc) 248, 315, and 362 nm (ε 15,100, 10,100, and 10,900). Treatment of (XIV) with aqueous potassium hydroxide gave an anhydro-base which was extracted into chloroform; evaporation of the chloroform and treatment of the base with ether afforded crystals, m.p. 171—172°, of 4-*ethyl*-4,5,7,8-*tetrahydro*-10,11-*dimethoxy*[1,4]*diazepino*[7,1-a]*isoquinolin*-2(3H)-one (XV) (Found: C, 67·25; H, 7·35; N, 9·1. $C_{17}H_{22}N_2O_3$ requires C, 67·55; H, 7·35; N, 9·25%), $\lambda_{max.}$ (ethanolic 0·001N-NaOH) 231, 275, and 333 nm (ε 23,200, 5340, and 18,000), δ 6·92br (1H, exch. D_2O, NH) and 5·33 (1H, d, *J* 2 Hz, decoupled by irradiation at NH, slow exch. with D_2O, 1-H). The liquors from the filtration of the acetate (XIV) were basified with aqueous potassium hydroxide. The liberated base was extracted into chloroform, and the extract was washed with water, dried (Na_2SO_4), and evaporated. The residual solid was crystallised from ethanol (50 ml) to give yellow-brown needles (4·36 g, 22%), m.p. 224—225°, of solvated 4-*ethyl*-4,5-*dihydro*-10,11-*dimethoxy*[1,4]*diazepino*-[7,1-a]*isoquinolin*-2(3H)-*one* (XVI); a recrystallised sample had m.p. 226—227° [Found (material dried at 100°): C, 67·95; H, 6·8; N, 9·2. $C_{17}H_{20}N_2O_3$ requires C, 68·0; H, 6·7; N, 9·35%], δ 7·12br (1H, exch. D_2O, NH), 6·61 and 6·12 (2H, both d, coupled to each other, *J* 7 Hz, 7-H and 8-H), and 5·61br (1H, s, exch. D_2O, 1-H), $\lambda_{max.}$ (ethanolic 0·001N-NaOH) 236, 262infl, 271, 284, 292, 340infl, 378infl, 395, and 413 nm (ε 35,200, 14,200, 14,800, 15,700, 18,200, 5690, 11,600, 15,700, and 12,400). In ethanolic N-HOAc it showed $\lambda_{max.}$ 261, 323, 395, and 413 nm (ε 52,700, 10,300, 1170, and 1070), indicative of *ca.* 92% protonation to the salt (XIX) in this medium on the basis of the absorption spectrum of compound (XXI) (see below). The alcoholic liquors from (XVI) gave, on similar work-up, a further 0·71 g (3%) of compound (XIV) and 0·65 g (3%) of compound (XVI).

(*b*) Oxidation of the lactam (III) (0·5 g) with mercuric acetate, as in (*a*), afforded the acetate (XIV) (183 mg, 31%) and compound (XVI) (200 mg, 41%).

Lactams (II) *and* (III) *from the Acetate* (XIV).—The acetate (1 g) was shaken with platinum oxide (100 mg) in methanol (20 ml) containing acetic acid (0·5 ml) under hydrogen [uptake 86 ml (26° and 765 mmHg) during 20 min]. The catalyst was collected and washed with methanol and chloroform, the combined filtrate was evaporated *in vacuo*, and a solution of the residue in chloroform was washed with aqueous potassium hydroxide, then with water, and dried (Na_2SO_4). The residual mixed bases were separated, as before, to give the lactam (II) (0·29 g) and the lactam (III) hydrobromide (0·50 g).

2-(2-*Aminobutyl*)-3,4-*dihydro*-6,7-*dimethoxy*-1-*methyliso-quinolinium Bromide Hydrobromide* (XX).—A solution of the acetate (XIV) (4·78 g) in aqueous 0·5N-HCl (240 ml) was heated under reflux for 70 min, evolution of carbon dioxide being monitored by absorption in aqueous barium hydroxide. The cooled (0°) solution was basified with aqueous potassium hydroxide, the product was extracted into chloroform (150 ml), and the extract was washed with water, dried (Na_2SO_4), and evaporated. A solution of the residual gum in ethanol (75 ml) was acidified with concentrated aqueous hydrogen bromide, seeded, and diluted with ether (100 ml) during 1 h. The resulting suspension of yellow crystals was kept for 3 days and filtered, to give the *bromide hydrobromide* (XX) (5·75 g), m.p. 235° (efferv.) (Found: C, 43·8; H, 6·0; Br, 36·25; N, 6·2. $C_{16}H_{26}Br_2N_2O_2$ requires C, 43·85; H, 6·0; Br, 36·55; N, 6·4%), $\lambda_{max.}$ (0·001N-HCl) 246, 309, and 362 nm (ε 15,500, 10,500, and 10,500). Treatment of this salt with aqueous potassium hydroxide liberated 2-*ethyl*-1,2,3,5,6,10b-*hexahydro*-8,9-*dimethoxy*-10b-*methylimidazo*-[2,1-a]*isoquinoline* (XXII), which was extracted into chloroform and recovered therefrom as a gum, $\lambda_{max.}$ (0·1 N-NaOH) 282 nm (ε 3600), *m/e* 276 (M^+) and 261 (*M* — angular Me, base peak), δ 2·26br (1H, exch. D_2O, NH) and 1·52 (3H, s, angular CH_3).

2-(2-*Aminobutyl*)-6,7-*dimethoxy*-1-*methylisoquinolinium Chloride Hydrochloride* (XXI).—A solution of compound (XVI) (1 g) in 0·5N-HCl (50 ml) was heated under reflux for 70 min; the water was evaporated off *in vacuo* and the residual mixture of gum and crystals was treated with ethanol and set aside at 0° to give crystals (0·96 g), m.p. 245° (efferv.), of the *chloride hydrochloride monohydrate* (XXI) (Found: C, 52·5; H, 7·0; Cl, 19·6; N, 7·6; loss on drying at 120°, 5·3. $C_{16}H_{24}Cl_2N_2O_2,H_2O$ requires C, 52·6; H, 7·15; Cl, 19·45; N, 7·65; H_2O, 4·95%), $\lambda_{max.}$ (0·001N-HCl) 255, 316, and 329infl nm (ε 56,000, 12,100, and 8950), $\lambda_{max.}$ (0·1N-NaOH) 254, 311, and 328infl nm (ε 57,000, 10,000, and 6760).

Crystal Structure Determination.—The hydrobromide of lactam (A) was recrystallised from methanol, and oscillation and Weissenberg photographs were taken about the *a* axis to establish unit-cell dimensions and space group. For intensity measurement a crystal of dimensions *ca.* 0·6 × 0·4 × 0·2 mm was mounted about the *a* axis on a Hilger and Watts four-circle diffractometer. Unit cell dimensions were refined by a least-squares fit on the diffractometer. With Mo-K_α radiation, intensity data were collected for $2\theta \leqslant 50°$ by use of an ω—2θ scan. Reflections with $I < 3\sigma(I)$ were considered unobserved, leaving 1793 independent observed reflections which were used in the subsequent refinement. No absorption corrections were made. Data reduction and subsequent crystallographic calculations were performed using the '*X*-ray '70' system of programs.[10] Atomic scattering factors were taken from ref. 11.

Crystal data. $C_{17}H_{24}N_2O_3,HBr$, $M = 385·3$. Orthorhombic, $a = 12·412 \pm 0·005$, $b = 20·574 \pm 0·010$, $c = 13·657 \pm 0·005$Å, $U = 3487·5$ Å^3, $D_m = 1·46$, $Z = 8$, $D_c = 1·47$, $F(000) = 1600$. Space group *Pbca* from systematic absences: $0kl$ when $k = 2n + 1$, $h0l$ when $l = 2n + 1$,

[10] '*X*-Ray '67' system of programs, J. M. Stewart, University of Maryland Technical Report TR 67 58, 1967, revised 1970, eds. J. M. Stewart, F. A. Kundell, and J. C. Baldwin.

[11] 'International Tables for *X*-Ray Crystallography,' vol. III, Kynoch Press, Birmingham, 1962.

Atomic co-ordinates, with standard deviations indicated in parentheses

Atom	*x/a*	*y/b*	*z/c*
Br	0·1246(1)	0·1753(1)	0·0717(1)
C(1)	0·2944(10)	0·1422(7)	0·3056(9)
C(2)	0·2698(10)	0·1869(7)	0·3944(9)
N(3)	0·2420(9)	0·2470(6)	0·3780(7)
C(4)	0·2198(10)	0·2768(7)	0·2806(9)
C(5)	0·3225(11)	0·2798(7)	0·2188(9)
N(6)	0·3558(8)	0·2171(5)	0·1727(7)
C(7)	0·4428(11)	0·2310(7)	0·0978(9)
C(8)	0·4640(11)	0·1714(7)	0·0401(9)
C(8a)	0·4966(10)	0·1156(7)	0·1039(9)
C(9)	0·5617(11)	0·0670(7)	0·0724(11)
C(10)	0·5948(11)	0·0155(7)	0·1295(10)
C(11)	0·5551(11)	0·0136(7)	0·2297(10)
C(12)	0·4896(11)	0·0617(6)	0·2604(9)
C(12a)	0·4571(10)	0·1126(6)	0·2018(9)
C(12b)	0·3938(10)	0·1669(6)	0·2478(8)
O(2)	0·2781(8)	0·1631(5)	0·4772(6)
C(13)	0·1825(12)	0·3459(7)	0·2959(9)
C(14)	0·1314(15)	0·3774(8)	0·2034(11)
O(10)	0·6597(9)	−0·0342(5)	0·1009(8)
C(15)	0·7195(12)	−0·0246(9)	0·0124(13)
O(11)	0·5932(8)	−0·0385(5)	0·2812(7)
C(16)	0·5547(15)	−0·0436(9)	0·3808(11)
H(1A)	0·3096	0·0928	0·3307
H(1B)	0·2252	0·1408	0·2561
H(3)	0·2000	0·2617	0·4300
H(4)	0·1607	0·2460	0·2430
H(5A)	0·3878	0·2971	0·2663
H(5B)	0·3109	0·3163	0·1616
H(6)	0·2855	0·1968	0·1373
H(7A)	0·5162	0·2462	0·1352
H(7B)	0·4169	0·2705	0·0503
H(8A)	0·5264	0·1816	−0·0123
H(8B)	0·3901	0·1591	0·0016
H(9)	0·5891	0·0681	−0·0037
H(12)	0·4611	0·0607	0·3364
H(12b)	0·4488	0·1901	0·2989
H(13A)	0·2515	0·3751	0·3175
H(13B)	0·1236	0·3470	0·3546
H(14A)	0·0639	0·3483	0·1825
H(14B)	0·1917	0·3767	0·1450
H(14C)	0·1056	0·4233	0·2150
H(15A)	0·7694	−0·0600	−0·0125
H(15B)	0·7696	0·0190	0·0213
H(15C)	0·6626	−0·0147	−0·0470
H(16A)	0·5833	−0·0817	0·4225
H(16B)	0·5758	0·0006	0·4192
H(16C)	0·4675	−0·0480	0·3788

*hk*0 when $h = 2n + 1$. Mo-K_α radiation, $\lambda = 0{\cdot}7107$ Å; μ(Mo-K_α) = 25·2 cm^{-1}.

The atomic co-ordinates of the bromine atom were found from an unsharpened Patterson synthesis. A three-dimensional Fourier summation, based on the heavy-atom phases, revealed the positions of the remaining 22 non-hydrogen atoms.

Initially four cycles of block-diagonal least-squares refinement of atomic positions and isotropic temperature factors were carried out with all the data and unit weights. After the fourth cycle the value of the agreement factor R was 0·14 and in subsequent refinement the atomic temperature factors were allowed to vary anisotropically. Two further cycles reduced R to 0·085. A difference-Fourier synthesis was then calculated and revealed the approximate positions of all hydrogen atoms. The hydrogen atom positions were then calculated accurately from bond length and angle considerations and included in the structure-factor calculations. Analysis of the agreement between F_c and F_o showed no very significant variation between different ranges of F_o so that unit weights were retained. Four final rounds of least-squares refinement, including but not refining the hydrogen atoms, reduced R to 0·078, after a total of 10 cycles, the largest parameter shifts being then of the order of $0{\cdot}2\sigma$, indicating that the refinement had converged.* The accuracy of the structure was confirmed by computing a final difference map which showed no peaks or depressions $>0{\cdot}4$ eÅ^{-3}. Final atomic co-ordinates are listed in the Table.

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* Observed and calculated structure factors are listed in Supplementary Publication No. SUP 20829 (10 pp., 1 microfiche). See Notice to Authors No. 7 in *J.C.S. Dalton*, 1972, Index issue.