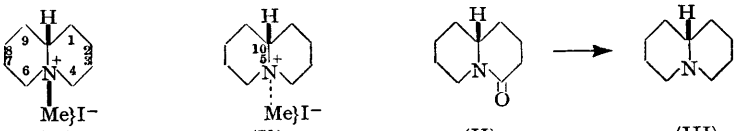
65. *Quinolizines and Quinolizidines. Part I. Reduction of 4-Oxoquinolizidines by Lithium Aluminium Hydride.*

By H. R. Lewis and C. W. Shoppee.

By the action of lithium aluminium hydride, 4-oxoquinolizidine (II) gives quinolizidine (III). Similarly, the (±)-3-ethoxycarbonyl-4-oxoquinolizidines (XII + XIII) give the (±)-3-hydroxymethylquinolizidines [(±)-3-lupinines] (XV + XVI), whilst (±)-1α-methoxycarbonylquinolizidine affords directly (±)-lupinine (as XXVI).

During 1953, in an attempt to isolate the *cis*- and the *trans*-quinolizidine methiodides (perhydropyridocoline methiodides) (cf. I*a* and *b*), and to examine their relative stabilities and ease of interconversion by racemisation at $N_{(5)}$, or at $C_{(10)}$,* as a result of activation † by the adjacent positive pole,[3] it was discovered that quinolizidine (III) could be obtained in 70% yield by the action of lithium aluminium hydride in ether or tetrahydrofuran on 4-oxoquinolizidine (II). Thyagarajan [4] states that 4-oxoquinolizidine is unaffected by lithium aluminium hydride, in contradiction of Clemo, Fox, and Raper [5] who, however, give no experimental detail.



(I*a*) (I*b*) (II) (III)

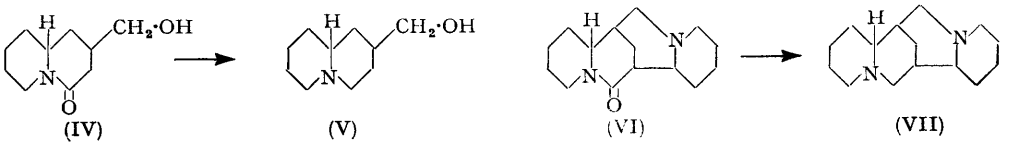
Similar reductions, that of (±)-2-hydroxymethyl-4-oxoquinolizidine (as IV) to (±)-2-lupinine (as V),[6] of (−)-oxosparteine (as VI) to (−)-sparteine (as VII),[7] and of 3-(1-methyl-2-piperidyl)-4-oxoquinolizidine [5] by lithium aluminium hydride, have been recorded, and

* These possibilities have independently been considered by Gellert,[1] who also envisaged the possibility of intermediate fission between the bridgehead carbon and the nitrogen atom followed by recyclization.

† Since this paper was written, an example has been provided by the smooth oxidation of quinolizidinium acetate with mercuric acetate to 2 : 3 : 6 : 7 : 8 : 9-hexahydroquinolizine by Leonard *et al.*[2]

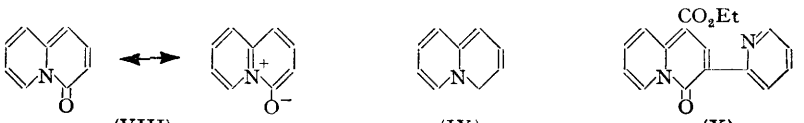
[1] Gellert, *Chem. and Ind.*, 1955, 983.
[2] Leonard, Hay, Fulmer, and Gash, *J. Amer. Chem. Soc.*, 1955, **77**, 439.
[3] Cf. Ingold and Rothstein, *J.*, 1929, 8, and later papers.
[4] Thyagarajan, *Chem. Rev.*, 1954, **54**, 1047.
[5] Clemo, Fox, and Raper, *J.*, 1954, 2693.
[6] Winterfeld and Schneider, *Annalen*, 1953, **581**, 66.
[7] Clemo, Raper, and Short, *Nature*, 1948, **162**, 286; *J.*, 1949, 663.

quantitative reduction of a 6 : 7-dihydro-4-oxoquinolizine derivative by lithium aluminium hydride in refluxing tetrahydrofuran has been observed by Swan.[8]



(IV) (V) (VI) (VII)

In contrast to these reductions, it has been reported by Boekelheide and Lodge [9] that 4-oxoquinolizine (VIII) cannot be reduced to quinolizine (IX) by the use of lithium aluminium hydride. This may be due to the aromatic nature of 4-oxoquinolizine, although a derivative of 4-oxoquinolizine, 1-ethoxycarbonyl-4-oxo-3-2′-pyridylquinolizine (X), has been hydrogenated over copper chromite at 250°/300—350 atm. to a mixture of (±)-sparteine and (±)-*iso*sparteine (as VII).[10]



(VIII) (IX) (X)

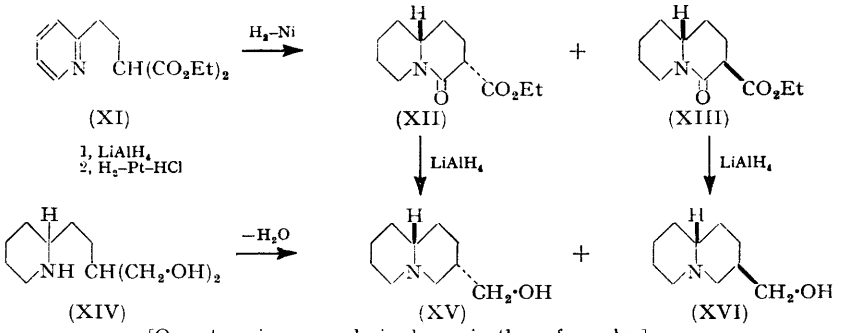
In view of our successful reduction of 4-oxoquinolizidine (II) with lithium aluminium hydride, it was decided to attempt a similar reduction of (±)-3-ethoxycarbonyl-4-oxoquinolizidine (XII + XIII) because Boekelheide and Rothchild [11] have stated that reduction with lithium aluminium hydride in ether gives only 4-oxoquinolizidine (II), and this is quoted in " Organic Reactions," Vol. VI, p. 477. 2-(3 : 3-Diethoxycarbonylpropyl)-pyridine (XI) was hydrogenated with Raney nickel at 145°/200 atm. to a mixture of the two racemates, one form of each of which is represented by [XII; 3-CO_2Et (axial)] and [XIII; 3-CO_2Et (equatorial)]. These compounds are not true β-keto-esters because the presence of the tertiary nitrogen atom adjacent to the 4-carbonyl group, $>N\overset{\curvearrowright}{-}C\cdot CH\cdot CO_2Et$ (with $\curvearrowleft O$), hinders enolisation of the hydrogen atom attached to $C_{(3)}$; thus no colour is developed with ferric chloride, and inversion at $C_{(3)}$ in (XII) to give the more thermodynamically stable isomeride (XIII) does not occur. Reduction with lithium aluminium hydride gave in 70% yield a mixture of (±)-*trans*-3-lupinine (as XV), a structural isomer of the naturally occurring alkaloid (−)-lupinine, and of (±)-*cis*-3-lupinine (as XVI). The product was very difficult to crystallise, but was obtained crystalline in part by repeated distillation in a high vacuum. The m. p. (56—58°) corresponds with that of the crystalline material prepared [12] from 2-(3 : 3-diethoxycarbonylpropyl)pyridine (XI) by reduction with lithium aluminium hydride to the corresponding glycol, hydrogenation to 2-(3 : 3-bishydroxymethyl)piperidine (XIV), and dehydration, or conversion into the dibromide and treatment with sodium acetate.

The structure of our reduction product was confirmed by preparation of a methiodide, picrate, and 3 : 5-dinitrobenzoate, and by oxidation with chromium trioxide to an acid, characterised as the methyl ester. Winterfeld and Heinen [12] state that in their preparation " the formation of the two diastereoisomeric forms of (±)-3-lupinine did not occur." The presence in our reduction product of both (±)-*trans*-3-lupinine (as XV) and (±)-*cis*-3-lupinine (as XVI) is suggested by the infrared absorption spectrum in dilute solution; this shows peaks at 3620 and 3400 $cm.^{-1}$ corresponding with non-bonded and hydrogen-bonded O–H stretching vibrations, the latter being due to an intramolecular O–H←N≤ bond

[8] Swan, *J.*, 1949, 1720.
[9] Boekelheide and Lodge, *J. Amer. Chem. Soc.*, 1951, **73**, 3681.
[10] Leonard and Beyler, *ibid.*, 1948, **70**, 2298.
[11] Boekelheide and Rothchild, *ibid.*, 1949, **71**, 879.
[12] Winterfeld and Heinen, *Annalen*, 1953, **578**, 171; 1951, **573**, 85.

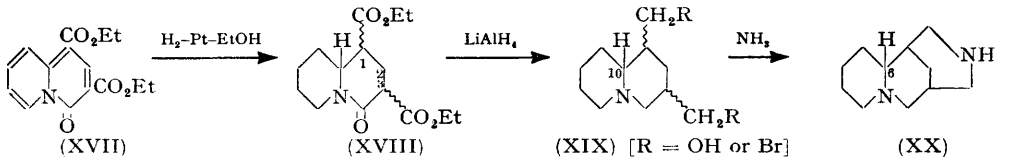
which appears to be possible only if the 3-hydroxymethyl group has the axial configuration (XV).[13] *

The absence of enolisation in the system $>N\cdot CO\cdot\overset{|}{C}H\cdot CO_2Et$, suggested above, finds

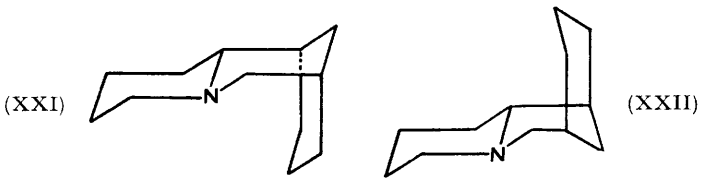


[One stereoisomer only is shown in these formulæ.]

support in the recent synthesis, which also involves reduction of a 4-oxoquinolizidine with lithium aluminium hydride, of (±)-deoxytetrahydrocytisine (XX) by Galinovsky, Vogl, and Moroz : [14] †



In substance (XX), the $-CH_2\cdot NH\cdot CH_2-$ bridge must for steric reasons be attached to the quinolizidine nucleus by bonds which are *cis* to each other; this bridge may be *cis* or *trans* relative to the bridgehead hydrogen atom at position 10 of the quinolizidine nucleus, here position 6 of the tricyclic system. Thus there will be two racemic forms, namely, (*a*) the "*trans*"-form of which one stereoisomer is shown in (XXI), containing three chair conformations, and (*b*) the "*cis*"-form of which one stereoisomer is shown in (XXII), containing



one boat and two chair conformations. Galinovsky *et al.* assumed that their product (XX) contained both racemates, and they describe "the separation of the racemates by means of the dipicrate," although in fact only one crystalline dipicrate was obtained. Predominant or exclusive *cis*-addition of hydrogen in the catalytic reduction of 1 : 3-diethoxycarbonyl-4-oxoquinolizine (XVII) would lead to a single racemate [as XVIII;

* [*Added, December 21st*, 1955.] Ratusky *et al.*[13a] prepared the 3-lupinines by another method and separated (±)-*trans*-3-lupinine, m. p. 59° (as XV), from (±)*cis*-3-lupinine, m. p. 30° (as XVI), by chromatography. They assigned configuration on the basis of dipole moments.

† [*Added, December 21st*, 1955.] Boekelheide *et al.*[14a] quote a personal communication from Dr. L. Marrian recording the successful reduction of (±)-3-ethoxycarbonyl-4-oxoquinolizidine with lithium aluminium hydride which they have confirmed, without giving experimental details.

[13] Cf. Marion, Ramsay, and R. N. Jones, *J. Amer. Chem. Soc.*, 1951, **73**, 305.

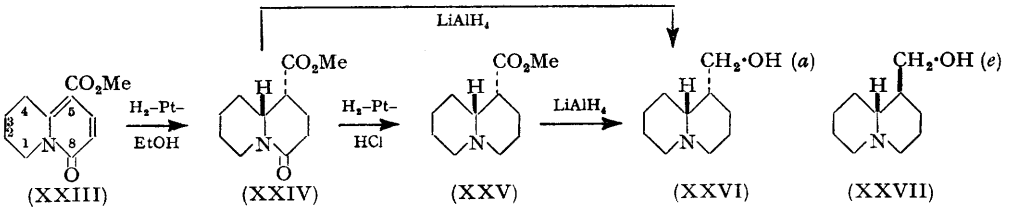
[13a] Ratusky and Šorm, *Coll. Czech. Chem. Comm.*, 1954, **19**, 340; Ratusky, Reiser and Šorm, *ibid.*, 1955, **20**, 798.

[14] Galinovsky, Vogl, and Moroz, *Monatsh.*, 1952, **83**, 246.

[14a] Boekelheide, Linn, O'Grady, and Lamborg, *J. Amer. Chem. Soc.*, 1953, **75**, 3244.

1α : 3α–CO_2Et (diaxial)] in which enolisation and inversion to the more thermodynamically stable equatorial configuration at position 3 do not occur; clearly, the primary alcohol or alkyl bromide groups (XIX : R = OH or Br) must be *cis*-related for cyclisation, and appear to possess the diaxial α-configuration (cf. XXI).

Finally, we have examined the reduction of (±)-1α-methoxycarbonyl-4-oxoquinolizidine (as XXIV) with lithium aluminium hydride. Boekelheide and Lodge [9] synthesised (±)-lupinine (as XXVI) by hydrogenation of 1 : 2 : 3 : 4-tetrahydro-5-methoxycarbonyl-8-oxoquinolizine (XXIII) with platinum–ethanol to the octahydro-ester, ensuring *cis*-addition of hydrogen at the 10 : 5 : 6 : 7-double-bond system, and thus producing (±)-1α-methoxycarbonyl-4-oxoquinolizidine (as XXIV); the cyclic amide grouping of (XXIV) was then reduced, not with lithium aluminium hydride, but by hydrogenation with platinum in aqueous hydrochloric acid to give (±)-1α-methoxycarbonylquinolizidine (as XXV), subsequently reduced by lithium aluminium hydride to (±)-lupinine (as XXVI). We find that (±)-1α-methoxycarbonyl-4-oxoquinolizidine (as XXIV) can be converted directly into (±)-lupinine (as XXVI) by reduction with lithium aluminium hydride in ether.



Boekeheide and Lodge's synthesis confirms the view that the 1-hydroxymethyl group in (±)-lupinine has the axial α-conformation, as had previously been deduced by Cookson [15] from the infrared absorption spectrum determined in dilute chloroform solution by Marion, Ramsay, and R. N. Jones.[13] Cookson also deduced that the absolute configuration of (−)-lupinine is correctly given by (XXVI) from its conversion by Karrer, Canal, Zohner, and Widner [16] into a 4-methylnonane, $[\alpha]_D$ −1·3°, corresponding with optically pure 4-methylnonane (*A*), $[\alpha]_D$ −1·7°. This assignment is confirmed by examination of the infrared spectrum in dilute carbon disulphide solution of (+)-*epi*lupinine, the absolute configuration of which is represented by (XXVII), in which interaction between the equatorial 1β-hydroxymethyl group and the nitrogen atom is sterically impossible. A specimen of this naturally occurring alkaloid,[17] most kindly made available by Dr. Crow, showed an intermolecular hydrogen-bonded hydroxyl band at ~3400—3200 cm.$^{-1}$, which vanished on dilution, leaving the free hydroxyl band at ~3650 cm.$^{-1}$. The configurations (XXVI, XXVII) are consistent with the reported conversion of (−)-lupinine (XXVI) into (+)-*epi*lupinine (XXVII) by sodium in boiling benzene.[18]

C_5H_{11}
H—C—Me,
(*A*) C_3H_7

Experimental

For general experimental directions see *J.*, 1955, 2876. The infrared spectrum was determined in CS_2 on a Perkin-Elmer double-beam instrument.

Quinolizidine (III).—(*a*) A solution of lithium aluminium hydride (1 g.) in ether (30 c.c.) was prepared by stirring and refluxing for 2 hr. in a 3-necked flask equipped with an efficient reflux condenser fitted with a calcium chloride tube. The middle neck was equipped with a stirrer (fitted with nichrome wire links) connected through a single-surface condenser to a metal stirrer-head and overhead electric motor. This arrangement obviated the use of the rather inconvenient mercury-seal apparatus. To this solution was added tetrahydrofuran (200 c.c.; purified by distillation over sodium) and the mixture stirred and refluxed for 10 min. 4-Oxoquinolizidine [11] (II) (2·3 g.), dissolved in purified tetrahydrofuran (100 c.c.), was added slowly

[15] Cookson, *Chem. and Ind.*, 1953, 337.
[16] Karrer, Canal, Zohner, and Widner, *Helv. Chim. Acta*, 1928, **11**, 1062.
[17] Crow and Riggs, *Austral. J. Chem.*, 1955, **8**, 136.
[18] Krieg, Diss., Marburg, 1928; cf. Clemo and Rudinger, *J.*, 1951, 2714.

with stirring and the mixture stirred and refluxed for 2 hr. Most of the ether and tetrahydrofuran were removed in a vacuum, and water added cautiously to the residue, which was then made strongly alkaline with 2N-potassium hydroxide. The mixture was extracted thrice with ether, and the combined ethereal extracts were dried and evaporated. The residue (1·7 g.) was distilled to give quinolizidine, b. p. 162°/24 mm. (1·45 g., 69%), identified as the hydrochloride, m. p. 260°, picrate, m. p. 199—200° (Galinovsky and Stern [19] give m. p. 199—200°), and methiodide, m. p. 331—332° (decomp.) (lit.,[19] m. p. 333° (decomp.)].

(*b*) A solution of 4-oxoquinolizidine (2·9 g.) in dry ether (40 c.c.) was added dropwise with stirring to a solution of lithium aluminium hydride (1·2 g.) in ether (60 c.c.) prepared as above, and the mixture set aside and then refluxed for 2½ hr. Water was added dropwise with stirring, and the alumina filtered off and washed with ether. The filtrate was made strongly alkaline with 2N-potassium hydroxide and extracted thrice with ether. The combined ethereal extracts were dried and evaporated, to give an almost colourless residue of quinolizidine (2·0 g., 76%) (picrate, m. p. 197—198°).

(±)-3-*Hydroxymethylquinolizidine* [(±)-3-*Lupinine*] (XV + XVI).—(*a*) A solution of (±)-3-ethoxycarbonyl-4-oxoquinolizidine [11] (XII + XIII) (4·6 g., giving no colour with ferric chloride) in purified tetrahydrofuran (280 c.c.) was added dropwise with stirring to a solution of lithium aluminium hydride (2·0 g.) in ether (500 c.c.) prepared as above. Ether was removed until the vapour temperature reached 62°, and the residual solution was refluxed for 3 hr. After cooling, water was added and the mixture kept overnight. The liquid was decanted and the alumina was washed with ether. The washings and solution were evaporated in a vacuum to small bulk and extracted thrice with ether, the combined ethereal extracts dried and evaporated, and the residue was distilled, to give (±)-3-hydroxymethylquinolizidine, b. p. 97°/0·15 mm. (2·7 g., 70%) (Found: C, 69·3; H, 11·1; N, 8·05. Calc. for $C_{10}H_{19}ON$: C, 71·0; H, 11·2; N, 8·3%). It was very difficult to obtain the product crystalline with a sharp m. p., since it is very soluble both in organic solvents and in water; repeated distillation at 97°/0·15 mm. finally gave crystals, m. p. 57—58°.

(*b*) (Cf. Boekelheide and Rothchild.[11]) A solution of (±)-3-ethoxycarbonyl-4-oxoquinolizidine (5 g.) in dry ether (30 c.c.) was added to one of lithium aluminium hydride (2·1 g.) in ether (150 c.c.) (prepared as above) and refluxed for 1 hr.; working up as in (*a*) gave (±)-3-hydroxymethylquinolizidine (0·6 g., 17·6%), b. p. 138°/mm.

(*c*) (±)-3-Ethoxycarbonyl-4-oxoquinolizidine (4·4 g.) in dry ether (125 c.c.) was added to lithium aluminium hydride (2·2 g.) in ether (150 c.c.) (prepared as above) at 0°, and the whole left overnight, then refluxed for 3 hr. Ethanol (25 c.c.) and then water (10 c.c.) were added dropwise with stirring at 0°. The alumina was filtered off and extracted thrice with hot ethanol. The combined ethanolic solutions were evaporated and made acid to Congo-red with 5N-hydrochloric acid. The aqueous solution was extracted twice with ether, made strongly alkaline with 2N-potassium hydroxide, and extracted four times with ether. The ethereal extracts were dried and evaporated. The residue (2·7 g.) was distilled, to give (±)-3-hydroxymethylquinolizidine (2·4 g., 73%), b. p. 98°/0·15 mm.

Preparation (*a*) gave a methiodide, white needles, m. p. 249—250° after recrystallisation from ethanol (Found: C, 42·3; H, 7·3; N, 4·35; I, 40·3. Calc. for $C_{11}H_{22}ONI$: C, 42·4; H, 7·1; N, 4·5; I, 40·8%). Preparations (*b*) and (*c*) gave this methiodide, m. p. and mixed m. p. 244—246° [with methiodide of (*a*)].

Preparation (*a*) gave a picrate, m. p. 126—127°, after recrystallisation from ethanol (Found: C, 48·27; H, 5·4; N, 16·4. Calc. for $C_{16}H_{22}O_8N_4$: C, 48·24; H, 5·5; N, 14·0%). Preparations (*a*), (*b*), and (*c*) reacted vigorously with acetyl chloride, hydrogen chloride being evolved.

Winterfeld and Heinen [12] gave the following m. p.s: (±)-3-hydroxymethylquinolizidine, m. p. 57·5—58° (b. p. 60—80°/0·010 mm.); picrate, m. p. 140—141·5°; methiodide, m. p. 254—256° (decomp.)].

(±)-3-*Quinolizidylmethyl* 3 : 5-*Dinitrobenzoate*.—(±)-3-Hydroxymethylquinolizidine 204 mg.) was heated under reflux with 3 : 5-dinitrobenzoyl chloride (180 mg.) in benzene (20 c.c.) for 2 hr. and left overnight at 15°. A small amount of a cream-coloured precipitate (probably the hydrochloride of the dinitrobenzoate) was filtered off and washed with benzene; the filtrate was shaken with 4N-sodium hydroxide (10 c.c.), then with water (10 c.c.). After drying, the benzene was removed in a vacuum, and ethanol (1·5 c.c.) added to the residue; after cooling at 0° for 2 hr., the product was filtered off and dried; recrystallisation from ethanol gave (±)-3-*quinolizidylmethyl* 3 : 5-*dinitrobenzoate*, m. p. 108—109° [Found (after drying at 60°/0·02 mm. for 2 hr.): C, 56·1; H, 5·6; N, 11·8. $C_{17}H_{21}O_6N_3$ requires C, 56·2; H, 5·8; N, 11·6%].

[19] Galinovsky and Stern, *Ber.*, 1943, **76**, 1034.

(±)-3-*Carboxyquinolizidine*.—(±)-3-Hydroxymethylquinolizidine (1·21 g.) in sulphuric acid (435 mg.) and water (2·5 c.c.) was mixed with chromium trioxide (1·2 g.) in sulphuric acid (1·74 g.) and water (25 c.c.) at 15°, kept for 1 hr. at 15°, and heated on the water-bath for a further 45 min. Sulphur dioxide was then passed into the solution, which was heated to the b. p. and made alkaline to litmus with aqueous ammonia; excess of ammonia was boiled off, and chromic hydroxide filtered off, and washed twice with boiled water. The combined filtrates were evaporated in a vacuum, and the residue was extracted with boiling ethanol. Evaporation of the extract in a vacuum gave a brown gum, which was suspended in dry acetone and stirred whilst absolute ethanol was added dropwise. In this way, (±)-3-*carboxyquinolizidine* was obtained as an almost colourless powder (A) (50 mg.; m. p. 197—199°), which was purified by sublimation at 110°/0·01 mm. to give amorphous material, m. p. 206° (rapid heating; with slower heating, sintering takes place over a wide range of temperature, although the final m. p. is the same). On account of the extremely hygroscopic nature of this material [cf. lupinic acid (1-carboxyquinolizidine)[20]] a satisfactory analysis could only be obtained after drying at 40°/0·02 mm. (Found: C, 65·3; H, 9·3; N, 7·3. $C_{10}H_{17}O_2N$ requires C, 65·6; H, 9·3; N, 7·6%).

(±)-3-*Methoxycarbonylquinolizidine*.—The filtrate from (A) above was evaporated under reduced pressure, the residue, after drying at 40°/0·02 mm., was dissolved in methanol, and the solution saturated with dry hydrogen chloride and refluxed for 45 min. After evaporation in a vacuum, a little water was added, and the solution made alkaline with potassium carbonate and extracted with ether. The ethereal extract was dried and evaporated, and the residue distilled, to yield (±)-3-*methoxycarbonylquinolizidine*, b. p. 85°/0·6 mm. [795 mg.; 57%, based on (±)-3-hydroxymethylquinolizidine)] (Found: C, 67·2; H, 8·8; N, 7·2. $C_{11}H_{19}O_2N$ requires C, 67·0; H, 9·6; N, 7·1%).

This ester (404 mg.) was refluxed with methyl iodide (1·15 g.) in dry methanol (8 c.c.) for 1 hr. The *methiodide* (525 mg., 76%) was precipitated with ether (m. p. 177—179°, with sintering from 169°) and refluxed in dry acetone (30 c.c.) for 15 min. The undissolved material (m. p. 220°) was filtered off and recrystallised from ether–ethanol, the m. p. rising to 230° (Found: C, 42·8; H, 6·3; N, 4·3. $C_{12}H_{22}O_2NI$ requires C, 42·5; H, 6·5; N, 4·1%). This methiodide was crystalline.

The acetone solution was concentrated and kept at 0° for 3 hr. The resulting precipitate was filtered off (m. p. 187—188°) and recrystallised from dry acetone. The m. p. of this amorphous material was thereby unaltered (Found: C, 42·4; H, 6·5; N, 3·8%).

A mixture of the two methiodides gave a double m. p. 187—189° and 202—207°.

(±)-*Lupinine* (XXVI).—A solution of (±)-1α-methoxycarbonyl-4-oxoquinolizidine[9] (XXIV) (450 mg.) in dry ether (12 c.c.) was added dropwise with stirring to one of lithium aluminium hydride (300 mg.) in ether (20 c.c.) (prepared as above), and the mixture left overnight, then refluxed for 2 hr. Water was added dropwise with stirring, and the alumina filtered off and extracted thrice with hot ethanol. The combined ethanolic solutions were evaporated and made acid to Congo-red with 5N-hydrochloric acid. The aqueous solution was extracted twice with ether, made strongly alkaline with 2N-potassium hydroxide, and extracted thrice with ether. The combined ethereal extracts were dried, and evaporated, leaving a residue (180 mg., 50%) of (±)-lupinine. A methiodide was obtained, having m. p. 288—289° (decomp.) after recrystallisation from absolute ethanol [Boekelheide and Lodge[9] give m. p. 298—301° (decomp.); Clemo, Morgan, and Raper[21] give m. p. 303° (decomp.).] (Found: C, 42·4; H, 7·0; N, 4·8. Calc. for $C_{11}H_{22}ONI$: C, 42·4; H, 7·1; N, 4·5%).

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[20] Willstätter and Fourneau, *Ber.*, 1902, **35**, 1914.
[21] Clemo, Morgan, and Raper, *J.*, 1937, 965; 1938, 1574.