Journal of Medicinal Chemistry

VOLUME 12, NO. 4 JULY 1969

Bridgehead Nitrogen Compounds as Potential Analgetics

A. H. BECKETT, R. G. LINGARD, AND A. E. E. THEOBALD[1]

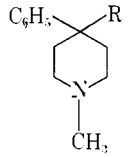
Department of Pharmacy, Chelsea College of Science and Technology, University of London, London SW 3, England

Received April 15, 1968
Revised Manuscript Received February 17, 1969

Some bridgehead nitrogen analogs of pethidine (Ia) and its reversed ester (Ib) were synthesized in order to obtain data on the importance of N-dealkylation and stereochemistry in the production of analgesia. The isomeric 7-acetoxy-7-phenylindolizidines (VIIa, VIIb) were prepared from the corresponding indolizidinol (VIa, VIb) and 2-acetoxy-2-phenylquinolizidine (XVb) from the quinolizidinol XIVb. Ethyl 2-phenylquinolizidine-2-carboxylate (XXIII) was synthesized from XVIII *via* XIX–XXIII; one isomer was isolated. Moderate to weak analgetic activity was shown by most compounds, the ester XXIII being the most potent, having about half the activity of pethidine.

Several theories on the mechanism of analgetic action have been advanced, especially with respect to N-dealkylation. Liver microsomal N-demethylase has been proposed as a model of the analgetic receptor,[2] some features of the latter having been deduced from a consideration of the structure–activity relationship of a number of methadone- and thiambutene-type analgetics,[3] in which the corresponding nor compound was thought to be the active drug. The concept of preliminary N-dealkylation has been questioned on the basis of results of kinetic[4,5] and incubation[6] studies. Furthermore, the bridgehead-nitrogen azamorphinans show considerable analgetic activity.[7]

In order to obtain further data on the importance of N-dealkylation in the analgetic response and the steric requirements of the analgetic receptor surface, some bridgehead-nitrogen analogs of pethidine (Ia) and its reversed ester (Ib) were synthesized, the compounds



Ia, R = CO_2Et
Ib, R = OCOEt

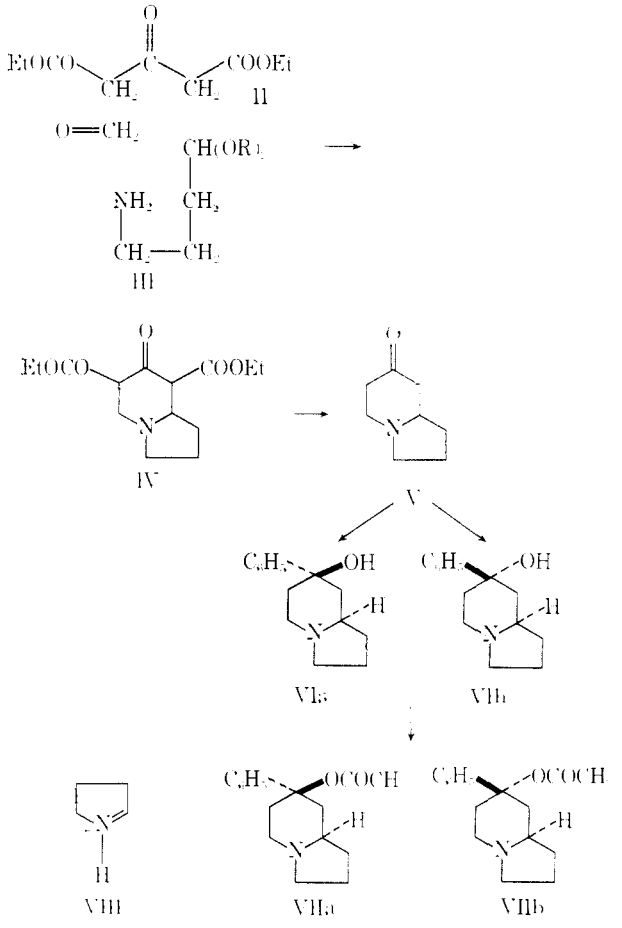
being 7-acetoxy-7-phenylindolizidine (VIIa and VIIb), 2-acetoxy-2-phenylquinolizidine (XVb), and ethyl 2-phenylquinolizidine-2-carboxylate (XXIII). The basicities of these compounds were similar to those of pethidine and its reversed ester, an important factor in determining distribution in body tissues.

N-Dealkylation, *i.e.*, ring fission, in these compounds should occur less readily than in pethidine on account of the bicyclic system. The most probable dealkylation mechanism involves preliminary hydroxylation on the alkyl carbon adjacent to N,[8] and this process would be greatly reduced by the steric hindrance imposed by the fused rings. The bridgehead analogs would be expected to show little, or no, activity on the N-dealkylation basis and might be analgetic antagonists. In addition, the fairly rigid azabicyclic system would permit the isolation of geometric isomers, and it was hoped that a comparison of activities of the isomers would clarify conformations adopted by flexible pethidine-like molecules at the analgetic receptor surface. Recent work on isomeric 1-methyl-4-phenyl-*trans*-decahydro-4-propionoxyquinolines has shown little difference in analgetic activity between isomers.[9]

The indolizidine derivatives were synthesized according to Scheme I. The intermediate ketone, indolizidin-7-one (V) was prepared by a modification of the method of Lions and Willison,[10] involving the condensation of γ-aminobutyraldehyde with diethyl acetonedicarboxylate (II) and formaldehyde in EtOH at pH 3. Although the mechanism of this condensation is not known, Mann and Smithies[11] suggested that γ-aminobutyraldehyde underwent spontaneous cyclization to the Δ^1-pyrroline VIII in biological systems. The product that we obtained by treating γ-aminobutyraldehyde diethyl acetal with HCl showed a distinct band at 1630 cm^{-1} in the ir spectrum, characteristic of the iminium group.[12,13] Potentiometric titration of γ-

(1) Taken, in part, from the Ph.D. thesis (A. E. E. T.), 1966.
(2) J. Axelrod, *Science*, **124**, 263 (1956).
(3) A. H. Beckett, A. F. Casy, and N. J. Harper, *J. Pharm. Pharmacol.*, **8**, 874 (1956).
(4) E. L. Way and T. K. Adler, *Pharmacol. Rev.*, **12**, 383 (1960).
(5) C. Elison, H. W. Elliot, M. Look, and H. Rapoport, *J. Med. Chem.*, **6**, 237 (1963).
(6) C. Elison and H. W. Elliot, *Biochem. Pharmacol.*, **12**, 1363 (1963).
(7) H. Fujimora, N. Sugimoto, and G. Kayaski, *Japan. J. Pharmacol.*, **11**, 101 (1962).
(8) J. R. Gillette, J. V. Dingle, and B. B. Brodie, *Nature*, **181**, 898 (1958).
(9) E. E. Smissman and M. Steinman, *J. Med. Chem.*, **9**, 455 (1966).
(10) F. Lions and A. M. Willison, *J. Proc. Roy. Soc. N.S. Wales*, **73**, 240 (1940).
(11) P. J. G. Mann and W. R. Smithies, *Biochem. J.*, **61**, 89 (1955).
(12) N. J. Leonard and V. W. Gash, *J. Amer. Chem. Soc.*, **76**, 2781 (1954).
(13) N. J. Leonard, P. D. Thomas, and V. W. Gash, *ibid.*, **77**, 1552 (1955).

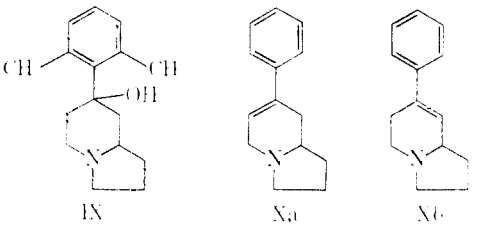
Scheme I



aminobutyraldehyde diethyl acetal with acid gave a pK_a of 10.45, but back-titration followed by titration with acid gave a reproducible pK_a of 7.00, while a similar series of titrations on 3,4-dihydroisoquinoline gave a reproducible pK_a of 6.94. This strongly suggests that γ-aminobutyraldehyde acetal, after initial hydrolysis, undergoes cyclization to the Δ^1-pyrroline VIII, which is the reactive intermediate in the condensation. Prolongation of the condensation reaction time to 5 days gave large amounts of crystalline material, identified as required keto ester IV. Decarboxylation of the keto ester in boiling dilute (1:1) HCl with a trace of zinc amalgam afforded the required amino ketone V in high yield.

The isolated indolizidin-7-one (V) darkened considerably within a few hours and was therefore treated with PhLi as rapidly as possible to give 7-phenylindolizidin-7-ol (VI). The mechanism of the nucleophilic addition of PhLi to carbonyl groups has been investigated;[14,15] such addition would occur to a greater extent on the less hindered side of the carbonyl C atom. Since the indolizidine system is predominantly *trans* (consisting of a *cis-trans* equilibrium mixture by inversion of the *nitrogen*), and kinetic control must operate because of the impossibility of equilibration, the predominant isomer would be that having an equatorial aryl group and axial lithium oxide, the preponderance depending on the bulk of the aryl group. Tlc on alumina indicated that two components were present in approximately equal amounts, although quantitative separation was not achieved.

Fractional crystallization of the reaction product from petroleum ether gave two components, 7(a)-phenylindolizidin-7(e)-ol (VIa, mp 121°) and 7(e)-phenylindolizidin-7(a)-ol (VIb, mp 112.5°). The structures assigned to these and other isomers have been established.[16] The most convenient method of separation was found to be the crystallization of VIa from a petroleum ether solution of the reaction product, followed by conversion of the residue to the hydrobromides. Treatment of the salts with boiling acetone left insoluble VIb as the hydrobromide. On cooling, a crystalline hydrobromide was deposited, and tlc of the regenerated base showed this to move faster than either isomer. The same compound was also produced on heating VIa in a mixture of HCl–AcOH, or by treatment of VIa·HBr with boiling acetone. The uv spectrum of this material showed a typical styrene absorption pattern which indicated that the material had been formed by dehydration of 7-phenylindolizidin-7-ol. Two structures are possible for this product, Xa and Xb, but gas chromatography gave a single peak. The nmr spectrum of the regenerated base showed a doublet at τ 4.1 (J = 6 cps) integrating for a single proton, indicating structure Xb.



Both indolizidine alcohols (VI) proved difficult to acetylate. Treatment with Ac_2O or AcCl in pyridine gave starting material or intractable tars. Treatment of the lithium oxide (the product from the addition of phenyllithium to indolizidin-7-one) with Ac_2O[15] gave a resin from which the desired esters could not be isolated, and VIa was unchanged by treatment with a mixture of AcOH and $HClO_4$. Acetylation of VIa was achieved in reasonable yield by heating a mixture of the amino-alcohol, isopropenyl acetate, and toluene-*p*-sulfonic acid,[17] giving 7(e)-acetoxy-7(a)-phenylindolizidine (VIIa), and VIb by the same procedure using either the free base or the hydrobromide to give 7(a)-acetoxy-7(e)-phenylindolizidine (VIIb).

The quinolizidine analog XV was prepared according to Scheme II. Quinolizidin-2-one (XIII) was prepared by the method of Rhodes and Soine,[18] using NaH in the cyclization. The amino ketone was treated with PhLi to give a mixture of two isomeric amino alcohols, 2(a)-phenylquinolizidin-2(e)-ol (XIVa) and 2(e)-phenylquinolizidin-2(a)-ol (XIVb). The factors determining the proportions of the two indolizidinol isomers will also apply here. Fractional crystallization of the reaction product from petroleum ether gave pure XIVa (mp 123.5°), but pure XIVb could not be isolated by crystallization. Chromatography of the reaction prod-

(14) C. G. Swain and L. Kent, *J. Amer. Chem. Soc.*, **72**, 518 (1950).

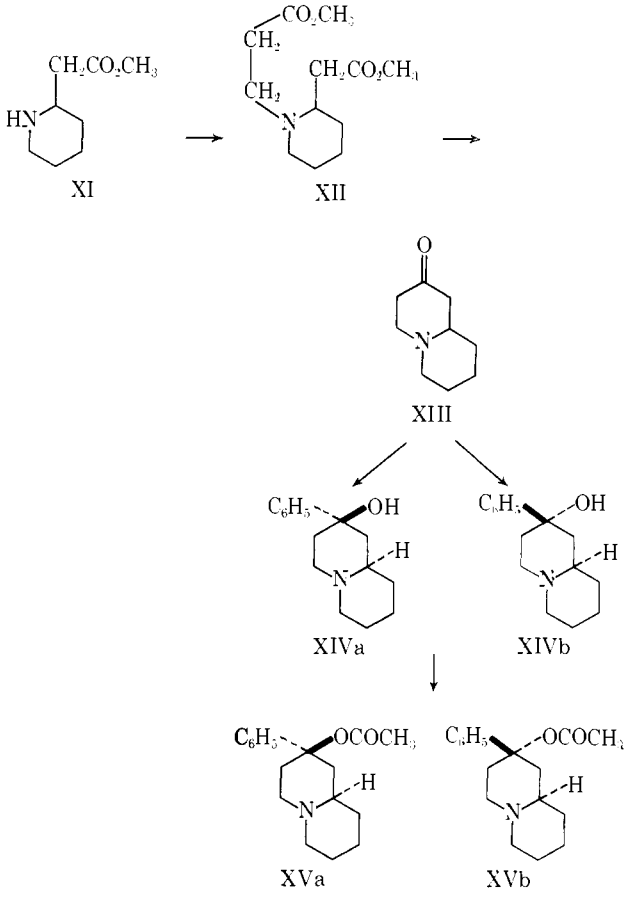
(15) N. J. Harper, A. H. Beckett, and A. D. J. Balon, *J. Chem. Soc.*, 2704 (1960).

(16) R. G. Lingard, A. H. Beckett, and A. E. E. Theobald, *J. Med. Chem.*, **12**, 569 (1969).

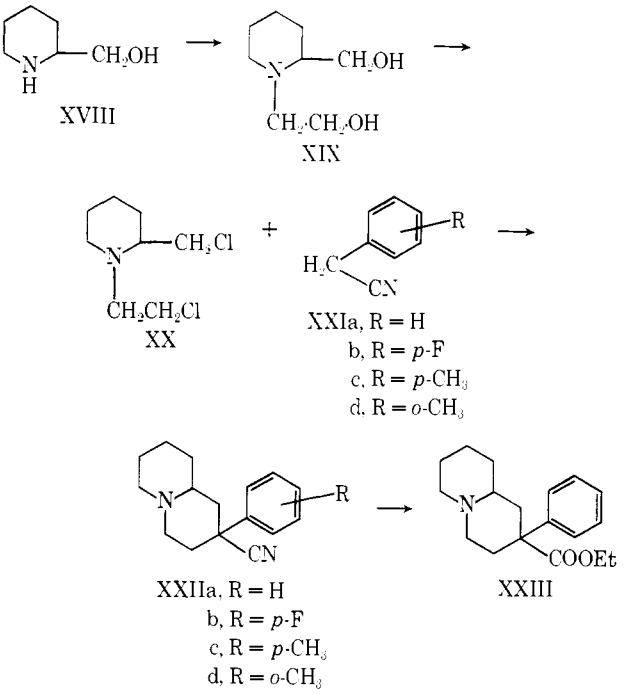
(17) R. N. Lacey, *Advan. Org. Chem.*, **2**, 213 (1960).

(18) H. J. Rhodes and T. O. Soine, *J. Amer. Pharm. Soc., Sci. Ed.*, **45**, 1956 (1956).

SCHEME II



SCHEME III



uct on an alumina column gave a quantitative separation of 46% XIVa (mp 123.5°) and 54% XIVb (mp 119°).

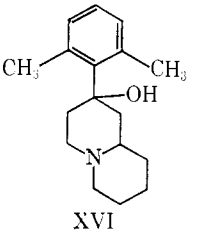
The behavior of the quinolizidine alcohols on attempted acetylation was similar to that encountered with the indolizidine alcohols. With isopropenyl acetate and toluene-*p*-sulfonic acid, XIVb underwent acetylation smoothly giving 2(a)-acetoxy-2(e)-phenylquinolizidine (XVb) whereas XIVa underwent partial elimination. The quinolizidine analog XXIII of pethidine was synthesized according to Scheme III. Piperidine-2-methanol was treated with β-chloroethanol or ethylene oxide to give the piperidinediol XIX, which was then converted to the corresponding dichloroamine XX. Aminoalkylation of $PhCH_2CN$ (XXIa) with the dichloroamine in DMF (NaH) gave 2-cyano-2-phenylquinolizidine (XXIIa). This compound, previously described,[19] was obtained almost quantitatively by our method, which is a modification of the procedure of Dahlbohm for norpethidine derivatives.[20] Under the conditions of the reaction, two isomeric nitriles would be predicted.

Tlc was used to separate two main components, but this could not be achieved quantitatively by column chromatography. Analytical separation of isomers was achieved by gas chromatography, the isomeric ratio being 32:60, but preparative gas chromatographic separation was unsatisfactory. Ethanolysis of the partially purified nitrile gave ethyl 2-phenylquinolizidine-2-carboxylate (XXIII) as one isomer, obtained pure in low yield by column chromatography.

Several closely related cyanoquinolizidines were prepared to show the effect of aromatic nuclear substitution in controlling the isomeric ratio of the products. Gas chromatographic analysis showed that the isomeric ratio varied from 1:1 to 1:2 in the case of the unsubstituted and *para*-substituted compounds, 2-cyano-2-(*p*-fluorophenyl)quinolizidine (XXIIb) and 2-cyano-2-(*p*-tolyl)quinolizidine (XXIIc), while a single component was obtained with 2-cyano-2-(*o*-tolyl)quinolizidine (XXIId).

It is probable that the predominant isomer in the nitriles XXIIa, b, and c is that with the equatorial phenyl conformation.[21] Introduction of a moderately bulky *ortho* substituent, as in XXIId, should increase the proportion of the equatorial-substituted phenyl isomer.

The conformations of the indolizidine VII and quinolizidine XVb analogs of the reversed esters of pethidine were deduced from an examination and comparison of the ir and nmr spectroscopic properties of the isomeric tertiary alcohols VI and XIV and the aryl-substituted tertiary alcohols IX and XVI.[16] This



XVI

study indicated conclusively that the equatorial phenyl/axial hydroxyl conformation was possessed by the alcohols VIb and XIVb and, by inference, the equatorial

(19) K. Winterfeld, K. Küllmar, and W. Göbel, *Chem. Ber.*, **92**, 1510 (1959).

(20) R. Dahlbohm, B. Bjorkquist, and S. Ross, *Acta Chem. Scand.*, **17**, 227 (1963).

(21) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965.

phenyl/axial acetoxy conformation by the esters VIIb and XVb.

Pharmacology.—All the compounds described were screened for pharmacological activity by Dr. R. T. Brittain, Allen and Hanburys Ltd., Ware.

Preliminary tests for analgetic activity were determined in the mouse (Glaxo A2G strain) by the tail-clip test.[22] Analgetic antagonist activities were determined from the abilities of the various compounds to modify the action of morphine or codeine in the tail-clip test. Antitremorine activities in the mouse were determined from measurements of tremor and hypothermia.[23] A few compounds were also tested for oxytocic activity in isolated diestrus rat uterus, in view of their reasonably close structural similarity to some oxytocic sparteine derivatives.

In general, none of the compounds showed any marked pharmacological activity up to 100 mg/kg. A few derivatives (VIb, VIIa, b, Xb) showed a weak antitremorine action at an oral dose of 100 mg/kg, and one compound (Xb) exhibited a weak oxytocic action at a concentration of 100 mg/ml. Moderate to weak analgetic activity was shown by several compounds, but analgetic antagonism was not demonstrable. The highest analgetic activity was shown by the quinolizidine analog XXIII of pethidine, which was about half as active as pethidine itself. The conformation of this compound is uncertain, but is probably equatorial phenyl/axial ester as in pethidine.

Of the indolizidine analogs of pethidine reversed esters, the axial ester (VIIb) was more active than the equatorial ester (VIIa) and comparable in activity with 1-methyl-4-acetoxy-4-phenylpiperidine (which has about two-thirds the activity of pethidine[24]). The latter compound, being flexible, would adopt the axial ester conformation preferentially. The axial quinolizidine ester (XVb) was about as active as the corresponding indolizidine ester VIIb. The alcohols 7-(2,6-dimethylphenyl)indolizidin-2-ol (IX) and 2-(2,6-dimethylphenyl)quinolizidin-2-ol (XVI), in which the OH group is axial, were both about half as active as pethidine in the tail-clip test.

It has been postulated that a decisive factor in the mediation of the analgetic activity of pethidine and related compounds is the ease of N-dealkylation *in vivo*,[3] and the attenuation of such activity in replacing N-methyl by -ethyl and -isopropyl supports this view.[25] The indolizidines and quinolizidines should yield the N–H compound by ring cleavage less readily than the simple demethylation reported above, and might be expected to behave as analgetic antagonists rather than analgetics. The preliminary pharmacological data indicate weak analgetic activity in the tail-clip test with the axial ester being more active, and this may mean that N-dealkylation is not an essential feature for analgetic activity in all molecules. Further work is in progress to amplify these points.

Experimental Section[26]

γ-Aminobutyraldehyde Dimethyl Acetal (III, R = CH_3).—To a solution of β-cyanopropionaldehyde dimethyl acetal (79 g, 0.57 mole) in EtOH (1000 ml), Na in small lumps (70 g, 6.4 g-atoms) was added cautiously. When the initial vigorous reaction had subsided, the mixture was heated on a steam bath for 1 hr, then allowed to cool to room temperature. H_2O (200 ml) was then added cautiously and the mixture distilled through a short column until 700 ml of distillate had been collected. The residual liquor was then distilled under reduced pressure and this distillate was fractionated under reduced pressure to give 56 g (68%) of a colorless liquid, bp 73–76° (20 mm).

6,8-Dicarbethoxyindolizidin-7-one (IV).—A solution of γ-aminobutyraldehyde dimethyl acetal (16.1 g, 0.1 mole) in EtOH (200 ml) was neutralized to methyl orange with dilute (1:1) HCl. Immediately, formaldehyde solution (7.5 ml, 0.1 mole) and diethyl acetonedicarboxylate[27] (20.2 g, 0.1 mole) were added and the mixture was allowed to stand at room temperature for 5 days. The solution was neutralized with excess aqueous Na_2CO_3 and allowed to stand for 1 day further. The precipitate was filtered off and washed with EtOH (two 10-ml portions) and Et_2O (two 10-ml portions). Recrystallization from $CHCl_3$ gave 20.1 g (71%) of IV as needles, mp 92.5°. *Anal.* ($C_{14}H_{21}NO_5$) C, H, N.

Indolizidin-7-one (V).—A solution of 6,8-dicarbethoxyindolizidin-7-one (10 g, 0.035 mole) in dilute (1:1) HCl (100 ml) was heated under reflux in the presence of a trace of Zn/Hg for 2 hr. The cooled solution was made alkaline with NH_4OH and extracted with $CHCl_3$ (four 50-ml portions). The combined extracts were dried and evaporated under reduced pressure. Distillation of the residual oil gave V (3.73 g, 76%) as a colorless oil, bp 49–50° (0.06 mm), 98–102° (15 mm). Lions and Willison[10] reported bp 104–105° (18 mm).

7-Phenylindolizidin-7-ol (VI).—A solution of indolizidin-7-one (20 g, 0.14 mole) in dry Et_2O (200 ml) was added dropwise to a stirred solution of excess PhLi in dry Et_2O over a period of 2 hr. The mixture was heated under reflux for a further 2 hr, cooled, and poured onto crushed ice (500 g). It was acidified with dilute (1:1) HCl and the phases were separated. The aqueous phase was made alkaline with aqueous NaOH and the liberated base was extracted with Et_2O (three 50-ml portions). The combined extracts were dried, decolorized with charcoal (5 g), and evaporated under reduced pressure to give 30 g (98%) of the mixed isomers as a pale brown crystalline mass.

Separation of Isomers of 7-Phenylindolizidin-7-ol (VI). A. Tlc.—Chromatography of the reaction product on alumina (Merck, tlc grade, 0.25-mm layer) using Et_2O as solvent gave two spots, R_f 0.53 and 0.36.

B. Adsorption Chromatography.—The crude reaction product (1.5 g) was chromatographed on an alumina column (Spence, grade 0, 25 × 2 cm), eluting successively with Me_2CO, $CHCl_3$, and MeOH, to give a single fraction (0.58 g, mp 109–112°) which showed a single component on tlc. Recrystallization of 100 mg of this fraction from petroleum ether (bp 60–80°) gave 50 mg of VIb as needles, mp 112.5°. *Anal.* ($C_{14}H_{19}NO$) C, H, N.

C. Fractional Crystallization of the Bases.—The crude reaction product (20 g) was dissolved in the minimum of boiling petroleum ether (100 ml) and allowed to stand for 12 hr. The precipitate was collected and redissolved in boiling petroleum ether and allowed to stand, when a crop of prisms separated (2.5 g, mp 122°). A further two crops of crystals were obtained (5.0 g, mp 90–94°; 2.2 g, mp 90–94°) which could not be purified further by fractional crystallization. Recrystallization of the first crop from petroleum ether gave 2.0 g (10%) of VIa as prisms, mp 123°. *Anal.* ($C_{14}H_{19}NO$) C, H, N.

D. Combined Fractional Crystallization of Bases and Hydrobromides.—The crude reaction product (7.5 g) was dissolved in boiling petroleum ether (100 ml) and the solution was seeded with a crystal of VIa and allowed to stand for 4 hr. The crystals were filtered off and washed with petroleum ether to give 1.5 g of VIa as off-white prisms. Subsequent crystal crops showed two spots on tlc. These and the mother liquor were combined and evapo-

(22) C. Bianchi and J. Franceschini, *Brit. J. Pharmacol. Chemotherapy*, **9**, 280 (1954).

(23) P. S. J. Spencer, *ibid.*, **25**, 79 (1965).

(24) A. U. K. Foster and A. J. Carman, *J. Pharmacol. Exptl. Therap.*, **91**, 195 (1947).

(25) O. J. Braenden, N. B. Eddy, and H. Halbach, *Bull. World Health Organ.*, **13**, 937 (1955).

(26) All melting points were determined in a capillary tube and are corrected. Ir spectra were recorded on a Unicam S.P. 200 spectrophotometer as paraffin mulls or liquid films unless otherwise stated. Uv spectra were recorded on a Unicam S.P. 800 spectrophotometer and potentiometric titrations were performed using a Pye Dynacap pH meter. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(27) R. Adams and H. M. Chiles, "Organic Syntheses," Coll. Vol. I, H. Gilman and A. M. Blatt, Ed., Chapman and Hall, London, 1941, p 237.

rated to dryness, and the residue was dissolved in dry Et_2O (250 ml). Dry HBr was passed through the stirred Et_2O solution until precipitation was complete. The suspension of hydrobromides was quickly filtered and washed with dry Et_2O. Acetone (250 ml) was added, and the mixture was heated on a steam bath for 10 min. The insoluble material was filtered off (1.6 g) and tlc of the regenerated base showed a single component. Recrystallization of 100 mg of the material from Me_2CO gave 50 mg (8%) of VIb·HBr, mp 220.5° *Anal.* ($C_{14}H_{20}BrNO$) C, H, N. The remainder of the Me_2CO-insoluble hydrobromide was dissolved in H_2O (10 ml) and made alkaline with NH_4OH. The base was extracted with Et_2O (three 5-ml portions) and the combined extracts were dried and evaporated under reduced pressure. Crystallization of the gummy residue from petroleum ether gave 0.8 g of VIb as needles, mp 112.5°.

7-Acetoxy-7-phenylindolizidine (VIIa).—A mixture of 7-phenylindolizidin-7-ol (VIa, 1.0 g, 0.046 mole), toluene-*p*-sulfonic acid (50 mg), and isopropenyl acetate (20 ml) was heated under reflux for 5 hr. The solution was cooled, diluted with dry Et_2O until slightly opalescent, and allowed to stand at 5° overnight. The gummy precipitate was filtered off and recrystallized from EtOH–Et_2O to give 0.71 g (59%) of VIIa, mp 167°. *Anal.* ($C_{23}H_{29}NO_5S$) C, H, N.

7-Acetoxy-7-phenylindolizidine (VIIb).—A mixture of 7-phenylindolizidin-7-ol hydrobromide (VIb) (2.0 g, 0.065 mole), toluene-*p*-sulfonic acid (50 mg), and isopropenyl acetate (40 ml) was heated under reflux for 6 hr. The solvent was evaporated under reduced pressure and the residue crystallized from EtOH–Et_2O. Recrystallization from *i*-PrOH gave 1.3 g (59%) of VIIb, mp 165°. *Anal.* ($C_{16}H_{12}BrNO_2$) C, H, N.

7-(2,6-Dimethylphenyl)indolizidin-7-ol (IX).—A solution of indolizidin-7-one (1.5 g, 0.011 mole) in dry Et_2O (10 ml) was added dropwise to a stirred solution of excess 2,6-$Me_2C_6H_3Li$ in dry Et_2O (40 ml). The mixture was heated under reflux for 2 hr, cooled, and poured into 20 ml of ice–water. It was acidified and the aqueous layer was washed with Et_2O (two 5-ml portions) and made alkaline. The precipitated oil was extracted with Et_2O (three 20-ml portions) and the combined extracts were dried and evaporated to give a viscous oil (1.6 g). Crystallization from petroleum ether gave 0.7 g (27%) of IX, mp 97–98°. *Anal.* ($C_{16}H_{23}NO$) C, H, N.

7-Phenylhexahydroindolizine (X). A.—A solution of 7-phenylindolizidin-7-ol (VIa) (1.0 g, 0.046 mole) in a mixture of HCl (3 ml) and AcOH (5 ml) was heated under reflux for 8 hr. The solution was evaporated under reduced pressure and the residue was dissolved in H_2O (10 ml). The aqueous solution was made alkaline and the free base was extracted with Et_2O (three 10-ml portions). The combined extracts were dried, and dry HBr was passed through the solution until precipitation was complete. Crystallization of the crude precipitate from Me_2CO–EtOH gave 0.57 g (44%) of X, mp 197°. *Anal.* ($C_{14}H_{18}NBr$) C, H, N.

B.—Dry HBr was passed through a solution of 7-phenylindolizidin-7-ol (VIa) (2.0 g, 0.092 mole) in Me_2CO (100 ml) until precipitation was complete. The precipitate was filtered off quickly, washed (Me_2CO), and dissolved in 200 ml of boiling Me_2CO. The solution was allowed to cool and the crystalline deposit was recrystallized from Me_2CO to give 0.47 g (20%) of X, mp 198°. Gas chromatography of the bases regenerated from both samples of their hydrobromides both showed a single component of retention time 4 min (Perkin-Elmer F-11 chromatograph, flame ionization detector; 1-m column of KOH 5% and Carbowax 20M, 2% on Chromosorb G at 207°; gases, N_2, 20; H_2, 15; and air, 25 psi).

Methyl Piperidyl-2-acetate (XI).—A solution of methyl pyridine-2-acetate (30 g, 0.2 mole) in a mixture of 6 *N* HCl (50 ml) and MeOH (300 ml) was hydrogenated using PtO_2 (0.3 g) at room temperature and atmospheric pressure. The solution was evaporated under reduced pressure and the solid white residue was triturated with NH_4OH (100 ml). The alkaline solution was extracted with Et_2O (six 50-ml portions) and the combined extracts were dried and evaporated. Distillation of the residual oil under reduced pressure gave XI (22 g, 68%) as an oil: bp 101–102° (5 mm); ν_{max} 3400 (NH), 1730 cm^{-1} (CO ester).

1-Carbomethoxyethyl-2-carbomethoxymethylpiperidine (XII). A.—The method of Clemo, *et al.*,[28] was modified in that $CaCO_3$ was employed in place of $BaCO_3$, giving a 45% yield of XII as a pale yellow oil, bp 174–178° (17 mm), lit.[28] bp 170–175° (1.0 mm).

(28) G. R. Clemo, T. P. Metcalf and R. Raper, *J. Chem. Soc.*, 1429 (1936).

B.—A solution of methyl acrylate (2.6 g, 0.03 mole) in absolute EtOH (5 ml) was added slowly to a solution of methyl 2-piperidylacetate (4.0 g, 0.025 mole) in absolute EtOH (5 ml). The mixture was allowed to stand for 8 days when the solvent was evaporated under reduced pressure. Distillation of the residual oil gave XII (5.0 g, 82%) as a pale yellow oil, bp 129–131° (0.5 mm).

Quinolizidin-2-one (XIII).—Dry xylene (80 ml) was placed in a dry 700-ml wide-mouthed reaction vessel. The apparatus was thoroughly flushed with dry N_2 and the xylene was heated to 130°. NaH (6.7 g of a 50% w/w dispersion in mineral oil, 0.14 mole) was cautiously added in small portions and the hot suspension was stirred for 30 min. A solution of XII (31.7 g, 0.13 mole) in dry xylene (120 ml) was added dropwise over a period of 2 hr. The stirred mixture was heated for a further 1.5 hr, allowed to cool, and finally chilled in ice. The N_2 flow was stopped and ice-cold HCl (23 ml) was added slowly over a period of 15 min. Stirring was continued for a further 30 min when the phases were separated. The xylene was extracted with two further 25-ml portions of HCl, followed by H_2O (25 ml). The combined aqueous solutions were heated under reflux for 2.5 hr, when H_2O was evaporated under reduced pressure. The solid residue was triturated with 50% aqueous KOH (20 ml) and the base was extracted with Et_2O (four 5-ml portions) followed by $CHCl_3$ (two 50-ml portions). The extracts were washed with saturated aqueous NaCl, combined, dried, and evaporated. Distillation of the residual brown oil under reduced pressure gave quinolizidin-2-one (XIII, 10.9 g, 55%) as a pale yellow oil, bp 115–116° (15 mm), lit.[18] bp 115° (16.5 mm); picrate, mp 206°, lit.[18] mp 209°; ν_{max} 2700–2800 (*trans*-quinolizidine), 1710 cm^{-1} (CO).

2-Phenylquinolizidin-2-ol (XIV).—A solution of amino ketone XIII (10.9 g, 0.071 mole) in dry Et_2O (100 ml) was added dropwise to a stirred solution of excess PhLi in dry Et_2O (150 ml). The solution was heated under reflux for 1 hr, cooled, and poured onto crushed ice (250 g). The mixture was acidified with dilute (1:1) HCl and the Et_2O layer was washed with dilute (1:1) HCl (two 25-ml portions). The combined aqueous solutions were made alkaline and the oil was extracted with Et_2O (three 50-ml portions). The combined extracts were dried and evaporated to give 14.8 g (90%) of a pale yellow glassy solid. The ir spectrum (CS_2) showed ν_{max} 3500 (bonded OH), 2700–2800 (*trans*-quinolizidine), 700 cm^{-1} (phenyl). Tlc on alumina (Merck, tlc, 0.25-mm layer) showed two components present in approximately equal amounts.

Separation of the Isomers of 2-Phenylquinolizidin-2-ol. A.—The crude reaction product (14.8 g) was dissolved in boiling petroleum ether (100 ml) and allowed to stand for 2 days when 13.3 g of crystalline material (mp 93–96°) was deposited. This was redissolved in boiling petroleum ether (300 ml) and allowed to stand for 2 hr. The crystals were filtered off and washed with petroleum ether (two 5-ml portions) to give a white solid (0.23 g, mp 120.5–121°). Tlc showed a single component. A further crop of crystals (mp 121–122°) was obtained and the two crystal fractions were combined and recrystallized from petroleum ether to give 1.2 g (8%) of XIVa, mp 123°. *Anal.* ($C_{15}H_{21}NO$) C, H, N.

B.—The crude reaction product (1.7 g) was chromatographed on an alumina column (Spence, grade H, 12 × 2.5 cm). Elution with Et_2O gave 0.57 g (53.6%) of one component, while continued elution with EtOH gave 0.49 g (46.3%) of a second component. Recrystallization of the first component from petroleum ether gave 0.43 g (43%) of XIVb, mp 119°. *Anal.* ($C_{15}H_{21}NO$) C, H, N.

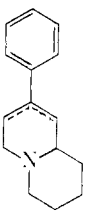
Recrystallization of the second component from petroleum ether gave 0.4 g (40%) of XIVa, mp 122.5°, mmp 123° with XIVa from A.

A similar experiment using 6.0 g of the crude reaction product, chromatographed on a 15 × 4 cm column, gave 3.3 g of XIVb (55%) and 2.5 g of XIVa (42%).

2-Acetoxy-2-phenylquinolizidin-2-ol (XVb).—A mixture of the alcohol XIVb (0.5 g, 0.002 mole), toluene-*p*-sulfonic acid (0.6 g), and isopropenyl acetate (10 ml) was heated under reflux. The mixture was cooled and the insoluble material was filtered off and washed with Et_2O (two 2-ml portions) to give a pale pink powder (0.8 g), mp 192°. A further 0.1 g of material was obtained on dilution of the filtrate with Et_2O. Recrystallization of the combined crystal crops from absolute EtOH gave 0.5 g (56%) of XVb as the toluene-*p*-sulfonate, mp 192°. *Anal.* ($C_{24}H_{31}NO_5S$) C, H, N.

Attempted Acetylation of 2-Phenylquinolizidin-2-ol (XIVa).—A

mixture of the alcohol XIVa (0.5 g, 0.002 mole), toluene-*p*-sulfonic acid (0.6 g), and isopropenyl acetate (10 ml) was heated under reflux for 4 hr. The mixture was cooled and diluted with Et_2O to give a dark oily precipitate which solidified on trituration with dry Et_2O. Recrystallization from EtOH–Et_2O gave white prisms (0.1 g), mp 155°. Further recrystallization from *i*-PrOH gave 0.08 g (11%) of XVII as the toluene-*p*-sulfonate: mp 165°; $\lambda_{max}^{H_2O}$ 217 mμ (ε 19,300), 224 (18,300), 244 (13,500). *Anal.* ($C_{22}H_{25}NO_3S$) C, H, N.



XVII

2-(2,6-Dimethylphenyl)quinolizidin-2-ol (XVI).—A solution of the amino ketone XIII (2.0 g, 0.013 mole) in dry Et_2O (50 ml) was added dropwise to a stirred solution of excess 2,6-Me_2PhLi in dry Et_2O (150 ml). The mixture was heated under reflux for 3 hr, cooled, and poured into ice–water (100 ml). The product was acidified with dilute (1:1) HCl and the aqueous phase was made alkaline with NH_4OH, then extracted with Et_2O (two 50-ml portions) followed by $CHCl_3$ (two 50-ml portions). The combined extracts were dried and evaporated. Chromatography of the residue on alumina (Spence, grade H, 25 × 2 cm) and elution with Et_2O gave 2.2 g of a crystalline solid; recrystallization from petroleum ether gave 1.25 g (37%) of XVI, mp 135°. *Anal.* ($C_{17}H_{25}NO$) C, H, N.

Piperidine-2-methanol (XVIII).—A solution of pyridine-2-methanol (20 g, 0.17 mole) in a mixture of 6 *N* HCl (35 ml) and MeOH (200 ml) was hydrogenated using PtO_2 (0.2 g) at room temperature and atmospheric pressure. The solution was filtered and evaporated, and the residue was made alkaline, then saturated with NaCl. The base was extracted with Et_2O (five 50-ml portions) and the combined extracts were dried and evaporated under reduced pressure to give XVIII (20 g, 95%) as a pale yellow oil which solidified on standing, mp 72°, lit.[29] mp 67–69°.

1-(2-Hydroxyethyl)-2-hydroxymethylpiperidine (XIX).—To a cold solution of XVIII (55 g, 0.48 mole) in absolute EtOH (250 ml) was added a cold solution of ethylene oxide (22.4 g, 0.51 mole) in absolute EtOH (250 ml). The mixture was allowed to stand at 5° for 12 days, then at room temperature for a further day. The solvent was evaporated under reduced pressure and distillation of the residual oil *in vacuo* gave XIX (63 g, 96%) as a clear, viscous oil, bp 136° (2 mm), lit.[30] bp 130–140° (1.0–1.5 mm).

1-(2-Chloroethyl)-2-chloromethylpiperidine (XX).—A solution of redistilled $SOCl_2$ (143 g, 1.2 moles) in dry $CHCl_3$ (500 ml) was added slowly to a stirred solution of the amino alcohol XIX (63 g, 0.4 mole) in pyridine (5 ml) and dry $CHCl_3$ (500 ml). The stirred solution was heated under reflux for 4 hr and cooled, and the $CHCl_3$ was evaporated under reduced pressure. C_6H_6 (50 ml) was added to the residue and evaporated under reduced pressure to remove the last traces of $SOCl_2$. The residue was dissolved in ice–water (150 ml) and made alkaline with chilled NH_4OH. The base was extracted with Et_2O (four 50-ml portions), and the combined extracts were dried and then evaporated under reduced pressure. Distillation of the residual oil *in vacuo* gave XX (58 g, 74%) as a pungent, colorless oil, bp 85–87° (0.05 mm). The picrate crystallized from EtOH as needles, mp 96–97°, lit.[19] bp 74–75° (0.7 mm), picrate mp 92–95°.

2-Cyano-2-phenylquinolizidine (XXIIa).—To a vigorously stirred cold (5°) solution of XX (18.0 g, 0.09 mole) and $PhCH_2CN$ (16.5 g, 0.14 mole) in dry DMF (500 ml) was added NaH (20.2 g of a 50% w/w dispersion in mineral oil, 0.42 mole) in small portions, taking care to keep the reaction mixture below 10° until H_2 evolution ceased. The mixture was then allowed to warm to room temperature and finally heated on a steam bath for 2 hr. The cooled mixture was poured onto crushed ice (500 g) and diluted with 2 l. of H_2O and the oil was extracted with $CHCl_3$ (three 200-ml portions). The combined $CHCl_3$ solutions were reextracted with HCl (three 50-ml portions). The acid extracts were diluted with H_2O (200 ml), made alkaline, and extracted with Et_2O (three 50-ml portions). The combined extracts were dried and evaporated to give a viscous brown oil: (20 g, 91%); $\nu_{max}^{CCl_4}$ 2700–2800 (*trans*-quinolizidine), 2200 (CN), 700 cm^{-1} (Ph). Tlc showed two components, but these could not be separated on alumina or silica columns.

The oil (5 g) was dissolved in EtOH (20 ml) and excess saturated EtOH–picric acid added. Recrystallization from EtOH gave 2.3 g (5.4%) of XXIIa picrate, mp 235°. *Anal.* ($C_{22}H_{23}O_7N_5$)C, H, N.

The following compounds were prepared by a similar route.

2-Cyano-2-(*p*-fluorophenyl)quinolizidine (XXIIb) was prepared from *p*-fluorophenylacetonitrile (XXIb, 10 g, 0.074 mole), giving 6.3 g of a pale brown oil which contained two components by tlc on alumina. The oil was dissolved in EtOH (20 ml) and excess saturated ethanolic picric acid was added. Recrystallization from EtOH gave 4.4 g (14.2%) of XXIIb picrate, mp 212°. *Anal.* ($C_{22}H_{22}FN_5O_7$)C, H, N.

2-Cyano-2-(*p*-tolyl)quinolizidine (XXIIc) was prepared from *p*-tolylacetonitrile (XXIc, 10 g, 0.076 mole) giving 10.7 g of a brown oil. Recrystallization of the picrate from EtOH gave 5.2 g (17%) of XXIIc picrate, mp 187°. *Anal.* ($C_{23}H_{25}N_5O_7$) C, H, N.

2-Cyano-2-(*o*-tolyl)quinolizidine (XXIId) was prepared from *o*-tolylacetonitrile (XXId, 10 g, 0.076 mole) giving 10.7 g of a brown oil. Recrystallization of the picrate from EtOH gave 5.4 g (17.5%) of XXIId picrate, mp 152°. *Anal.* ($C_{23}H_{25}N_5O_7$) C, H.

Gas Chromatography of Cyanoquinolizidines.—The crude products from the above reactions were examined for the presence of isomers on a Perkin-Elmer F11 gas chromatograph using a 1-m column of Chromosorb G (80–100 mesh, acid-washed) coated with KOH (5%) and Carbowax 20M (2%) at 200° (gas pressures: N_2, 15; H_2, 15; air, 20 psi). Samples of approximately 10 mg were dissolved in dry Et_2O (1 ml) and 3–5-μl aliquots were injected into the column. The retention times and relative areas were XXIIa (5.7, 7.6; 32:68), XXIIb (5.3, 6.2; 39:61), XXIIc (7.8, 9.2; 43:57), XXIId (8.8; 100).

Ethyl 2-Phenylquinolizidin-2-carboxylate (XXIII).—A mixture of 2-cyano-2-phenylquinolizidine (XXIIa, 1.0 g, 0.0042 mole), H_2SO_4 (4 ml), and absolute EtOH (6 ml) was heated on a steam bath for 8 hr. The EtOH was evaporated under reduced pressure and the oily residue was diluted with ice–water (20 ml). The cooled solution was made alkaline and the base was extracted with C_6H_6 (three 15-ml portions). The combined extracts were evaporated to give 0.9 g of a dark oil. This was dissolved in Me_2CO (3 ml) and chromatographed on a silica gel column (20 × 2 cm) eluting with Me_2CO and collecting 25-ml fractions. Fractions 5–6 were combined and evaporated to give a crystalline solid (0.25 g). Recrystallization from aqueous EtOH gave 0.069 g (5%) of XXIII, mp 67°. *Anal.* ($C_{18}H_{25}NO_2$) C, H, N.

(29) F. F. Blicke and C. Y. Lu, *J. Amer. Chem. Soc.*, **77**, 29 (1955).

(30) O. M. Friedman, H. Sommer, and E. Boger, *ibid.*, **82**, 5202 (1960).