extracted with ether. The ether extract was washed with 0.1 *N* hydrochloric acid and saturated sodium bisulfite solution. The residue after removal of solvent was chromatographed on alumina. Elution with light petroleum gave 120 mg (65%) of a mixture of **1** and **2** in the ratio 84:16, respectively. Glpc separation ($^3/_8$ in. × 10 ft column packed with 20% FFAP on Chromosorb W, 150°) gave **1** as a colorless oil: ir 3060, 1650, 1370, 1358, and 805 cm^{-1}; nmr, δ 5.25 (1 H, multiplet, =C*H*), 1.70 (doublet overlying multiplet, J = 2 Hz, =CCH_3), 1.02 (3 H, singlet, CCH_3), and 0.9 ppm (6 H, multiplet, CH(CH_3)$_2$).

B. Acid-Catalyzed Isomerization of β-Bourbonene (2). A mixture of 130 mg (0.64 mmol) of synthetic **2** in 10 ml of 95% ethanol containing 2 drops of 10% hydrochloric acid was heated under reflux for 1 hr. The solution was made alkaline with 10% sodium bicarbonate solution and extracted with ether. The light brown, oily residue after removal of solvent was chromatographed on alumina, and elution with light petroleum gave 90 mg (69%) of virtually pure **1**. Glpc purification as described above gave synthetic **1**, identical with material prepared by method A. An exactly analogous reaction with natural **2** produced **1**, identical by ir, nmr, and mass spectra and glpc retention time with synthetic **1**, prepared by the two methods described above.

Acknowledgment. The authors are grateful to the Milton Fund of Harvard University, to the National Science Foundation, and to the donors of the Petroleum Research Fund for financial support.

Syntheses of *dl*-Lupinine and the Hydrolulolidine and Hydrojulolidine Ring Systems[1a]

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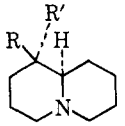
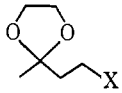
Contribution from the Department of Chemistry, Indiana University, Bloomington, Indiana 47401. *Received May 28, 1968*

Abstract: A method of quinolizidine and indolizidine synthesis is outlined. It is based on the acid-induced interaction of the α carbon of ketal functions of N-alkyl side chains of 3-acyl-2-piperideines with the piperideine α carbon. The syntheses of lupinine and related, but more complex, tricyclic alkaloid models by this method are developed.

During recent years we have been engaged in the development of a two-step synthesis of quinolizidines and indolizidines and its exploitation in the indole alkaloid field.[2] It is based on the conversion of 1-alkyl-3-acylpyridinium salts into 1-alkyl-3-acyl-2-piperideines on hydrogenation and acid-induced cyclization of the products.[3] The crucial second step depends on the presence of a nucleophilic moiety on the side chain radiating from the nitrogen site of the ring system and its intramolecular reaction with the nuclear aminocarbonium ion created by the action of acid. Since heretofore the nucleophilic units had been exclusively indole groups, it now became of interest to vary these substituents and thus to broaden the scope of alkaloid synthesis. Transient enols or enol ethers were chosen as possible nucleophilic alternates. A description of their employment in the preparation of the alkaloid lupinine (Ia) and hydrojulolidine and hydrolulolidine derivatives is presented herewith.



Ia, R = CH_2OH; R′ = H
b, R = H; R′ = CH_2OH



IIa, X = OH
b, X = OTs
c, X = $CH(CO_2Me)_2$
d, X = Br

Lupinine (Ia). The structural features of this simple alkaloid are ideally suited for construction by the aforementioned method of synthesis.[4] The spatial relationship of the oxygenated side chain to the nitrogen site suggests derivation of the substituted ring from a nicotinic acid system and the remaining four-carbon unit from a N-alkyl chain. The following reactions were modeled on this argument. Treatment of 4-hydroxy-2-butanone ethylene ketal (IIa)[5] with *p*-toluenesulfonyl chloride yielded labile sulfonate IIb whose alkylation of methyl nicotinate produced the salt IIIa.[6] Hydrogenation of the latter over palladium–charcoal[7] afforded the tetrahydropyridine IVa.

While it was predictable that IVa could be induced to form a bicyclic compound by ketal hydrolysis and intramolecular Mannich reaction, the concomitant liberation of a ketone group was an undesirable feature in connection with further chemical operations. Hence, it was important to transform IVa into a quinolizidine

(1) (a) This work was supported by the U. S. Department of Health, Education, and Welfare (Grant GM-11571); (b) Public Health Service Predoctoral Fellow, 1963–1966.

(2) E. Wenkert, K. G. Dave, C. T. Gnewuch, and P. W. Sprague, *J. Amer. Chem. Soc.*, **90**, 5251 (1968), and references therein.

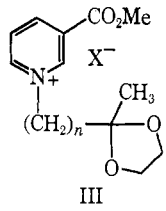
(3) For a general discussion of this method of synthesis, see E. Wenkert, *Accounts Chem. Res.*, **1**, 78 (1968).

(4) For previous syntheses of *dl*-lupinine see (a) G. R. Clemo, W. McG. Morgan, and R. Raper, *J. Chem. Soc.*, 965 (1937); (b) K. Winterfeld and H. von Cosel, *Arch. Pharm.*, 278, 70 (1940); (c) V. Boekelheide and J. P. Lodge, Jr., *J. Amer. Chem. Soc.*, 73, 3681 (1951); (d) V. Boekelheide, W. J. Linn, P. O'Grady, and M. Lamborg, *ibid.*, **75**, 3243 (1953); (e) J. Ratusky and F. Šorm, *Collect. Czech. Chem. Commun.*, **19**, 340 (1954); (f) H. R. Lewis and C. W. Shoppee, *J. Chem. Soc.*, 313 (1956); (g) E. E. van Tamelen and R. L. Foltz, *J. Amer. Chem. Soc.*, 82, 502 (1960); (h) F. Bohlmann and O. Schmidt, *Chem. Ber.*, **97**, 1354 (1964).

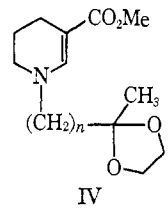
(5) L. Willimann and H. Schinz, *Helv. Chim. Acta*, **32**, 2151 (1949).

(6) The sulfonic ester IIb is an interesting variant of methyl vinyl ketone as a reactive intermediate in organochemical synthesis and can be used for C-alkylation. The preparation of IIc by the alkylation of dimethyl malonate is described in the Experimental Section. Recently the ketal bromide IId[5] was utilized in related fashion [G. Stork and R. Borch, *J. Amer. Chem. Soc.*, **86**, 935 (1964); G. Stork, *Pure Appl. Chem.*, **9**, 131 (1964)].

(7) E. Wenkert, K. G. Dave, F. Haglid, R. G. Lewis, T. Oishi, R. V. Stevens, and M. Terashima, *J. Org. Chem.*, **33**, 747 (1968).



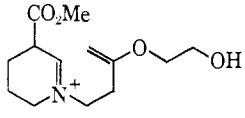
III



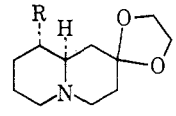
IV

a, $n = 2$
b, $n = 3$
c, $n = 4$

keeping the ketal function intact. It was assumed that a carbon–carbon bond-forming reaction could be modeled after the acid-catalyzed halogenation of ketals which has been proposed to proceed *via* a transient enol ether intermediate.[8] On the supposition of potential intermediacy of V the ketal IVa was exposed to various nonhydroxylic acid media. On treatment with *p*-toluenesulfonic acid in benzene IVa was converted into a quinolizidine derivative, while treatment with anhydrous ethereal hydrogen chloride yielded a mixture of the latter and its stereoisomer.[9] Base-catalyzed equilibration of the mixture gave a single isomer identical with the cyclization product from the *p*-toluenesulfonic acid treatment. The stereochemistry of this compound hence was that depicted in VIa. Lithium aluminum hydride reduction of the bicyclic ester produced the amino alcohol VIb whose hydrolysis with aqueous acid and Wolff–Kishner reduction led to *dl*-epilupinine (Ib). Similar reduction of the isomer mixture, hydrolysis, and further reduction yielded Ib and *dl*-lupinine (Ia) in *ca.* 3:1 ratio.

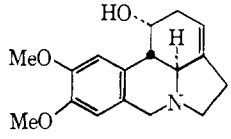


V

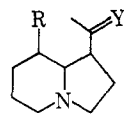


VIa, R = CO_2Me
b, R = CH_2OH

Hydrolulolidine Derivatives. The fundamental principles upon which the above lupinine synthesis was based seemed applicable to the construction of more complex ring systems. One under early consideration was that of the lycorinoid *Amaryllidaceae* alkaloids, *e.g.*, pluviine (VII). The following discussion describes a facile synthesis of the nonaromatic portion of these plant products.

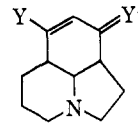


VII

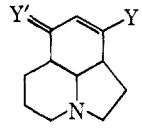


VIIIa, R = CO_2Me; Y = O
b, R = $CH(OCH_2)_2$, Y = $(OCH_2)_2$

Methyl nicotinate was alkylated with 5-bromo-2-pentanone ethylene ketal[5,10] and the resultant salt IIIb hydrogenated.[7] Exposure of the product, tetrahydropyridine IVb, to anhydrous ethereal hydrogen chloride led to the keto ester VIIIa.[11] Deketalation appeared to have occurred on work-up. Dieckmann condensation of VIIIa gave a diketone whose treatment with methanolic acid produced a single enol ether of structure IXa or Xa. Its reduction with lithium aluminum hydride yielded an alcohol (IXb or Xb) which could be transformed into the unsaturated ketone IXc or Xc on acid hydrolysis. Hydrogenation of the latter led to an amino ketone (XIa or b).

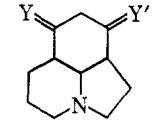


IX

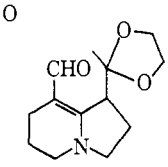


X

a, Y = OMe; Y′ = O
b, Y = OMe; Y′ = HOH
c, Y = H; Y′ = O



XIa, Y = O; Y′ = H_2
b, Y = H_2, Y′ = O



XII

In view of the ambiguities associated with the structures of the tricyclic compounds correlation with substances of established constitution appeared desirable. As a consequence, syntheses of ketone IXc and its dihydro derivative XIb by unambiguous means were undertaken. Nicotinaldehyde was alkylated with 5-bromo-2-pentanone ethylene ketal and the salt hydrogenated. The resultant tetrahydropyridine XII was impervious to or fully decomposed in a variety of acid treatments in analogy with previous experience on vinylogous amides derived from aldehydes or ketones (in contrast to esters) which are known to form stable conjugate acids.[2,7] Thus special conditions had to be found for the cyclization of XII, for example, ones which would overcome an unfavorable equilibrium between the starting piperideine and desired indolizidine. Success finally was achieved upon the acid-catalyzed interaction of XII with ethylene glycol. The reaction yielded ketal acetal VIIIb. Acid-induced hydrolysis of VIIIb and aldolization–dehydration produced the unsaturated ketone IXc, and hydrogenation thereof led to the hydrolulolidone XIb. Neither of the tricyclic ketones was identical with its analog derived from methyl nicotinate (*vide supra*).

Since the dissimilarity of the two series could be ascribed to positional isomerism or stereoisomerism, the stereochemistry of the substances had to be simplified. For this reason it was decided to dehydrogenate representative members of the two series of compounds. The tricyclic α,β-unsaturated ketones from methyl nicotinate as well as from nicotinaldehyde, *i.e.*, IXc, were treated with trimethyl orthoformate and acid to form enol ethers or ketals and the intermediates dehydrogenated over palladium–charcoal in xylene solution. Each ketone thereby was converted to a

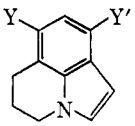
(8) M. E. Wall and H. W. Jones, *J. Amer. Chem. Soc.*, **79**, 3222 (1957), and references therein; A. Marquet, M. Dvolaitzky, H. B. Kagan, L. Mamlock, C. Ouannes, and J. Jacques, *Bull. Soc. Chim. Fr.*, 1822 (1961); A. Marquet and J. Jacques, *ibid.*, 90 (1962); P. E. Eaton, *J. Amer. Chem. Soc.*, **84**, 2344 (1962); E. W. Garbisch, Jr., *J. Org. Chem.*, **30**, 2109 (1965).

(9) Two closely related reactions of ketals have been reported: an intramolecular reaction of the Michael type [K. J. Clark, G. I. Fray, R. H. Jaeger, and R. Robinson, *Tetrahedron*, **6**, 217 (1959); G. W. K. Cavill and F. B. Whitfield, *Aust. J. Chem.*, **17**, 1260 (1964)] and α-acylations [R. D. Youssefyeh, *J. Amer. Chem. Soc.*, **85**, 3901 (1963); *Tetrahedron Lett.*, 2161 (1964)].

(10) C. A. Grob and R. Moesch, *Helv. Chim. Acta*, **42**, 728 (1959).

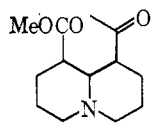
(11) None of the structural formulas in the hydrolulolidine section are intended to reveal stereochemical details.

unique methoxytrimethyleneindole. Since the one based on nicotinaldehyde had to possess structure XIIIb, the isomer derived from methyl nicotinate was XIIIa. It now was possible to assign structures to the progenitors of the latter indole. The product of Dieckmann condensation of the indolizidine VIIIa and etherification is IXa, its dihydro derivative IXb, the latter's hydrolysis product Xc, and its hydrogenation product XIa. Upon completion of the elucidation of the structures of all hydrololidones it was clear that the pluviine-like alkaloid model Xc had been synthesized in five facile steps from methyl nicotinate.

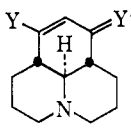


XIIIa, Y = OMe; Y′ = H
b, Y = H; Y′ = OMe

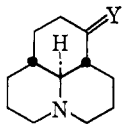
Hydrojulolidine Derivatives. Since the hydrojulolidone equivalent of XIb represents the basic ring skeleton of a large group of *Lycopodium* alkaloids and its construction by the by now well-founded procedure was within easy reach, its synthesis was investigated. Methyl nicotinate was alkylated with 6-bromo-2-hexanone ethylene ketal, prepared by the ketalation of the known keto bromide,[12] and the salt IIIc hydrogenated.[7] Cyclization of the piperideine IVc under the influence of acid and deketalation, probably on work-up, yielded the quinolizidine XIV. Without investigation of its stereochemistry the bicyclic compound was transformed into the tricycle XVa on successive treatments with base and methanolic acid. Lithium aluminum hydride reduction of XVa gave the alcohol XVb, whose acid hydrolysis yielded the unsaturated ketone XVc. Hydrogenation of the latter led to the perhydrojulolidone XVIa.



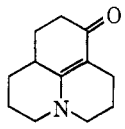
XIV



XVa, Y = OMe; Y′ = O
b, Y = OMe; Y′ = HOH
c, Y = H; Y′ = O



XVIa, Y = O
b, Y = α-H, β-OH
c, Y = α-H, β-OTs
d, Y = H_2



XVII

Palladium-catalyzed dehydrogenation of XVIa to the known vinylogous amide XVII[4h,13] proved the gross structure of the hydrojulolidone.[14] On the assumption of the Dieckmann cyclization having engendered equilibration at all bridgehead centers compounds XV and XVI were considered to possess the all-*trans* configuration. The first, albeit negative, clue regarding the stereochemistry of these substances came from a comparison of XVIa with its all-*cis* stereoisomer,[4h,15] mp 46.5–47.5°. They were found to be different. Final and direct proof of stereochemistry could be obtained by deoxygenation of XVIa. Wolff–Kishner reduction *via* its semicarbazone or sodium borohydride reduction, tosylation of the alcohol XVIb, and lithium aluminum hydride reduction led to the perhydrojulolidine with an all-*trans* backbone (XVId).[16–18]

Experimental Section

Melting points were determined on a Reichert micro hot stage and are uncorrected. Unless otherwise stated, proton magnetic resonance spectra of deuteriochloroform solutions with tetramethylsilane acting as internal standard were recorded on a Varian A-60 spectrometer. Neutral alumina of activity IV was used for chromatography. Silica gel G was used for thin layer chromatography.

3-Ketobutyl *p*-Toluenesulfonate Ethylene Ketal (IIb). *p*-Toluenesulfonyl chloride, 10.0 g, was added to an ice-cold solution of 6.5 g of alcohol IIa[5] in 20 ml of pyridine and the mixture left standing at 10° for 12 hr. It then was poured onto ice and extracted with ether. The extract was washed with water and sodium bicarbonate solution and then concentrated to a volume of *ca.* 30 ml at room temperature. Toluene was added and the solution evaporated on a steam bath at *ca.* 20-mm pressure to a volume of *ca.* 30 ml. This process was repeated several times until all ether and traces of pyridine had been removed. Thereafter the product IIb was kept in 100 ml of toluene and used in this form for N-alkylation. (The instability of IIb made its always being kept in solution of paramount importance.)

Dimethyl 3-Ketobutylmalonate Ethylene Ketal (IIc). A solution of IIb (from 6.5 g of IIa and 10.0 g of *p*-toluenesulfonyl chloride) in 40 ml of dioxane (prepared by the above prescription except for dioxane substituting toluene) was added dropwise to a suspension of the potassium salt of dimethyl malonate (from 2.0 g of potassium and 6.5 g of dimethyl malonate) in 50 ml of dioxane at room temperature and the mixture refluxed with stirring for 18 hr. The precipitate was filtered and washed with dioxane and the combined filtrates were evaporated under vacuum. The ether extract of the residue was washed with 5% sodium hydroxide solution and with water and evaporated. Distillation of the residual oil, 8.5 g, gave liquid diester IIc, bp 142–144° (1.0 mm), infrared spectrum (neat), C=O 5.77 μ (s).

Anal. Calcd for $C_{11}H_{18}O_6$: C, 53.65; H, 7.37. Found: C, 53.55; H, 7.18.

Hydrolysis of IIc by standard means yielded δ-ketocaproic acid, mp and mmp 168° (lit.[19] mp 168°).

N-Alkylpyridinium Salts. A solution of 6.8 g of methyl nicotinate in 20 ml of toluene was added to the standard toluene solution of sulfonate IIb (*vide supra*) and the mixture refluxed with stirring under nitrogen for 48 hr. The solvent was decanted from the oil which had separated and the residue washed with anhydrous ether and dried under vacuum. The oily product IIIa (X = OTs), 20.8 g, was used for the next reaction without further purification.

A solution of 5.0 g of methyl nicotinate in 10.0 g of 4-ketopentyl bromide ethylene ketal[5,10] was heated at 60° with stirring under nitrogen for 24 hr. The thick paste was washed several times with anhydrous ether and dried under vacuum. The oily product IIIb (X = Br), 13.5 g, was hydrogenated without further purification.

A solution of 57.0 g of 5-ketohexyl bromide,[12] 10 mg of *p*-toluenesulfonic acid, and 20.5 g of ethylene glycol in 400 ml of benzene was refluxed for 18 hr under azeotropic removal of water. Then benzene

(12) E. P. Anderson, J. V. Crawford, and M. L. Sherrill, *J. Amer. Chem. Soc.*, 68, 1294 (1946).

(13) Z. Valenta, P. Deslongchamps, P. Ellison, and K. Wiesner, *ibid.*, 86, 2533 (1964).

(14) The authors are indebted to Professors Bohlmann and Wiesner for gifts of samples of XVII.

(15) A kind gift of a sample of this compound by Professor Bohlmann permitted this comparison.

(16) (a) M. Protiva and V. Prelog, *Helv. Chim. Acta*, 32, 621 (1949); (b) N. J. Leonard and W. J. Middleton, *J. Amer. Chem. Soc.*, 74, 5114 (1952); (c) F. Bohlmann and C. Arndt, *Chem. Ber.*, 91, 2167 (1958); (d) L. Mandell, B. A. Hall, and K. P. Singh, *J. Org. Chem.*, 29, 3067 (1964).

(17) Gifts of samples of this compound kindly supplied by Professors Leonard and Mandell are acknowledged gratefully.

(18) An abbreviated description of the elaboration of the unsaturated ketone XVc on route to the *Lycopodium* alkaloids can be found in ref 3.

(19) W. H. Bentley and W. H. Perkin, *J. Chem. Soc.*, 69, 1510 (1896).

was removed by slow atmospheric distillation and finally completely under reduced pressure. Distillation of the residue gave 63.0 g of 5-ketohexyl bromide ethylene ketal: bp 65–67° (0.5 mm); pmr spectrum, three-proton singlet 1.30 (Me), two-proton triplet 3.40 (J = 7.0 cps) (bromomethylene), four-proton singlet 3.92 ppm (oxymethylenes).

Anal. Calcd for $C_8H_{15}O_2Br$: C, 43.06; H, 6.77. Found: C, 43.11; H, 6.88.

A solution of 13.7 g of methyl nicotinate in 22.3 g of 5-ketohexyl bromide ethylene ketal was heated at 65° with stirring under nitrogen for 24 hr. The viscous mass was washed several times with anhydrous ether and dried under vacuum. The oily product IIIc (X = Br), 34.6 g, was used in the next reaction without further purification.

A solution of 10.0 g of nicotinaldehyde in 20.0 g of 4-ketopentyl bromide ethylene ketal[5,10] was heated at 60° with stirring under nitrogen for 24 hr. The oil was washed with anhydrous ether and dried under vacuum. The oily product, 27.2 g, was hydrogenated without further purification.

Tetrahydropyridines. A mixture of 26.4 g of IIIa (X = OTs), 8 ml of triethylamine, and 4.0 g of 10% palladium–charcoal in 70 ml of methanol was hydrogenated at room temperature and at a pressure of 45 psi. Upon cessation of hydrogen uptake the catalyst was filtered and the filtrate evaporated. A methylene chloride solution of the residue was washed successively with ice-cold water, ice-cold 5% hydrochloric acid, saturated brine solution, and saturated sodium bicarbonate solution, dried over anhydrous potassium carbonate, and evaporated. A benzene solution of the residue was passed through a short alumina column and evaporated. For further reactions the product, 7.52 g, was distilled at 125–130° (bath temperature) (0.05 mm). Chromatography on silica gel (elution with chloroform) and rechromatography on alumina (elution with benzene) gave an analytically pure sample of liquid IVa: ir (CCl_4), C=O 5.96 (s), 6.20 (s), 6.24 μ (s); uv (95% EtOH) λ_{max} 295 mμ (log ϵ 4.22); pmr, three-proton singlets 1.31 (CMe), 3.63 (OMe), four-proton singlet 3.92 (oxymethylenes), one-proton singlet 7.31 ppm (olefinic H).

Anal. Calcd for $C_{13}H_{21}O_4N$: C, 61.15; H, 8.29; N, 5.49. Found: C, 60.96; H, 8.19; N, 5.41.

The following procedure was identical for all bromide salts. A mixture of 34.6 g of IIIb (X = Br), 10 ml of triethylamine, and 6.5 g of 10% palladium–charcoal in 80 ml of methanol was hydrogenated at room temperature and at a pressure of 45 psi. After the cessation of hydrogen uptake the catalyst was filtered and the filtrate evaporated. Benzene was added and the mixture taken to dryness in order to remove all traces of methanol. Further addition of benzene resulted in the precipitation of triethylamine hydrobromide which was filtered. The filtrate was passed through a short alumina column and then distilled. The fraction of bp 195–210° (0.05 mm), 10.6 g, was used for further reactions. The analytical sample of IVb was prepared by chromatography of a benzene solution on alumina and a chloroform solution on silica gel. Thin layer chromatography of the purified material on silica gel (19:1 chloroform–methanol) revealed a single spot. The spectra for liquid IVb were: ir (neat), C=O 5.95 (s), 6.18 (s), 6.24 μ (s); uv (MeOH) λ_{max} 296 mμ (log ϵ 4.20); pmr, three-proton singlets 1.31 (CMe), 3.66 (OMe), four-proton singlet 3.95 (oxymethylenes), one-proton singlet 7.35 ppm (olefinic H).

Anal. Calcd for $C_{14}H_{23}O_4N$: C, 62.23; H, 8.61; N, 5.20. Found: C, 62.47; H, 8.63; N, 5.51.

A mixture of 36.6 g of IIIc (X = Br), 15 ml of triethylamine, and 4.0 g of 10% palladium–charcoal in 100 ml of methanol was hydrogenated according to the above procedure and worked up in the same manner. Crude product, 14.2 g, was obtained which yielded pure liquid IVc; spectra: ir (CCl_4), C=O 5.91 (s), 6.15 (s), 6.23 μ (s); pmr, three-proton singlets 1.29 (CMe), 3.62 (OMe), four-proton singlet 3.92 (oxymethylenes), one-proton singlet 7.34 ppm (olefinic H).

Anal. Calcd for $C_{15}H_{25}O_4N$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.66; H, 8.74; N, 5.11.

A mixture of 27.0 g of N-(4-ketopentyl)nicotinaldehyde ethylene ketal bromide, 13 ml of triethylamine, and 4.5 g of 10% palladium–charcoal in 75 ml of methanol was hydrogenated as above. Purification of crude product, 6.4 g, yielded liquid XII: ir (neat), C=O, C=C 6.26 μ (s); pmr, three-proton singlet 1.31 (Me), four-proton singlet 3.95 (oxymethylenes), one-proton singlets 6.92 (olefinic H), 8.82 (aldehydic H).

Anal. Calcd for $C_{13}H_{21}O_3N$: C, 65.24; H, 8.85; N, 5.85. Found: C, 65.12; H, 8.66; N, 5.72.

Acid-Catalyzed Cyclizations. A solution of 1.25 g of IVa and 1.20 g of anhydrous p-toluenesulfonic acid in 125 ml of anhydrous benzene was refluxed under nitrogen for 12 hr. The cooled mixture was passed slowly into a stirring suspension of excess sodium bicarbonate in methylene chloride. The inorganic salts were filtered and washed with methylene chloride. The combined filtrates were dried over anhydrous potassium carbonate and evaporated. The residue, still containing p-toluenesulfonic acid salts, was extracted with ether. The extract was washed with ice-cold 5% sodium hydroxide and water and dried over potassium carbonate. Evaporation yielded an oil whose chromatography on silica gel and elution with 19:1 chloroform–methanol produced 0.89 g of an oil whose distillation led to liquid VIa: ir (neat), C=O 5.79 μ (s); one spot on tlc (19:1 chloroform–methanol); picrate, mp 206–207°, crystallized from methanol.

Anal. Calcd for $C_{19}H_{24}O_{10}N_4$: C, 48.72; H, 5.16; N, 11.96. Found: C, 48.61; H, 4.98; N, 11.78.

A solution of 2.30 g of IVa in 50 ml of anhydrous ether was saturated with hydrogen chloride gas and left stirring at room temperature for 12 hr. Methylene chloride, 200 ml, and solid sodium bicarbonate were added, the salts filtered and washed with methylene chloride, and the combined filtrates evaporated. A methylene chloride extract of the residue was washed with 5% sodium hydroxide, dried over potassium carbonate, and evaporated. Chromatography as above yielded 0.18 g of starting material and 1.88 g of product whose distillation led to a liquid mixture of VIa and its stereoisomer: ir (neat), C=O 5.79 μ (s); two spots on tlc (19:1 chloroform–methanol).

Anal. Calcd for $C_{13}H_{21}O_4N$: C, 61.15; H, 8.29; N, 5.49. Found: C, 61.19; H, 8.54; N, 5.51.

Isomerization of 500 mg of the mixture in 20 ml of methanol in the presence of 20 mg of sodium methoxide at room temperature for 12 hr yielded 410 mg of VIa, picrate mp 206–207°.

The reaction and work-up of a solution of 6.0 g of IVb in 400 ml of dry ether saturated with hydrogen chloride gas followed those of IVa. The product, 3.6 g, crystallized on standing. Recrystallization from hexane gave colorless needles of VIIIa: mp 61–62°; ir (Nujol), C=O 5.78 (s), 5.90 μ (s); pmr, three-proton singlets 2.16 (CMe), 3.57 ppm (OMe).

Anal. Calcd for $C_{12}H_{13}O_3N$: C, 63.97; H, 8.50; N, 6.22. Found: C, 64.24; H, 8.61; N, 6.23.

Crystallization from methanol gave VIIIa picrate, mp 178–179°.

Anal. Calcd for $C_{18}H_{22}O_{10}N_4$: C, 47.58; H, 4.88; N, 12.33. Found: C, 47.77; H, 5.03; N, 12.40.

The reaction and work-up of a solution of 12.4 g of IVc in 700 ml of dry ether saturated with hydrogen chloride gas were carried out according to the above directions. Distillation gave 7.2 g of product which crystallized on long standing. Recrystallization from hexane yielded XIV: mp 61–62°; ir (Nujol), C=O 5.79 (s), 5.90 μ (s); pmr, three-proton singlets 2.13 (CMe), 3.57 ppm (OMe); picrate mp 210–212°, crystallized from methanol.

Anal. Calcd for $C_{19}H_{24}O_{10}N_4$: C, 48.72; H, 5.16; N, 11.96. Found: C, 48.71; H, 5.15; N, 11.91.

A solution of 4.0 g of XII, 3.0 g of p-toluenesulfonic acid, and 3 ml of ethylene glycol in 330 ml of toluene was slowly distilled with constant replenishment of toluene. After 30 hr it was concentrated nearly to dryness, taken up in methylene chloride, and treated with solid sodium bicarbonate. The inorganic salts were filtered, the filtrate was evaporated, and the residue was extracted with hexane. The extract was passed through a short alumina column and evaporated. The oil, 3.7 g, could not be induced to crystallize. Distillation gave acetal ketal VIIIb: bp 117–118° (0.5 mm); pmr, three-proton singlet 1.31 (Me), four-proton multiplet 3.86 (acetal oxymethylenes), four-proton singlet 3.95 (ketal oxymethylenes), one-proton doublet 5.11 ppm (J = 3.0 cps) (acetal methine).

Anal. Calcd for $C_{15}H_{25}O_4N$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.73; H, 8.81; N, 4.70.

Lupinine (Ia) and Epilupinine (Ib). A solution of ester VIa, 500 mg, in 20 ml of ether was added dropwise to a suspension of 200 mg of lithium aluminum hydride in 40 ml of ether and the mixture stirred for 6 hr. It then was treated with sodium sulfate decahydrate and filtered. The precipitated salts were washed with ethyl acetate; the combined filtrate was dried over anhydrous potassium carbonate and evaporated. Crystallization of the residual oil from ether yielded 480 mg of alcohol VIb, mp 114–115°. A solution of the latter in 20 ml of 20% sulfuric acid was left standing at room temperature for 12 hr. It then was passed slowly into a suspension of sodium bicarbonate in 60 ml of methylene chloride. The two-phase mixture was separated and the aqueous solution extracted with ethylene chloride. The combined organic solutions were dried

over potassium carbonate and evaporated. An ether extract of the residue was washed with 5% sodium hydroxide and water and evaporated. A solution of the residual oil, 360 mg, 1.4 ml of 98% hydrazine, and 850 mg of potassium hydroxide in 6 ml of ethylene glycol was heated slowly to 180°. The mixture was refluxed under nitrogen for 12 hr, then cooled and acidified with 5% hydrochloric acid. The solvents were removed under high vacuum and the residue was treated with ammonium hydroxide and extracted (liquid–liquid) with chloroform. The extract was evaporated and the residual oil chromatographed on alumina and eluted with methylene chloride. Evaporation yielded 170 mg of *dl*-epilupinine (Ib): infrared spectrum identical with that of an authentic sample [(KBr) OH 3.20 μ (m, broad)]; methiodide, mp 248–249° (lit.[4a] mp 248–249°), crystallized from methanol.

Anal. Calcd for $C_{11}H_{22}ONI$: C, 42.44; H, 7.07; N, 4.50. Found: C, 42.38; H, 7.26; N, 4.42.

The identical procedure was used for the reduction, hydrolysis, and further reduction of the mixture of VIa and its stereoisomer. Starting material, 1.40 g, was converted to a mixture of amino alcohols whose chromatography yielded 180 mg of Ia (elution with cyclohexane) and 550 mg of Ib (elution with methylene chloride). Crystallization of the product from hexane produced *dl*-lupinine: mp 63–64° (lit.[4a] mp 61°); infrared spectrum identical with that of an authentic specimen; methiodide, mp 298–301° dec, crystallized from methanol.

Anal. Calcd for $C_{11}H_{22}ONI$: C, 42.44; H, 7.07; N, 4.50. Found: C, 42.26; H, 7.14; N, 4.65.

Base-Catalyzed Cyclizations. A solution of 2.27 g of VIIIa and potassium *t*-butoxide (from 800 mg of potassium) in 50 ml of *t*-butyl alcohol was refluxed with stirring under nitrogen for 12 hr. The mixture was stripped of solvent under vacuum, methanol added, and the solution saturated with hydrogen chloride gas and left standing for 48 hr. It then was evaporated and the residue extracted with methylene chloride. The extract was treated with solid sodium bicarbonate and the inorganic salts were filtered. The filtrate was taken to dryness and a benzene solution of the residue passed through a short alumina column. The product, 1.20 g, was crystallized from hexane yielding colorless needles of IXa: mp 122–123°; ir (Nujol), C=O, C=C 6.09 (s), 6.25 μ (s); pmr, three-proton singlet 3.68 (Me), one-proton broad singlet 5.32 ppm (olefinic H).

Anal. Calcd for $C_{12}H_{17}O_2N$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.61; H, 8.38; N, 6.99.

A reaction of 18.69 g of XIV and potassium *t*-butoxide (from 5.8 g of potassium) in 450 ml of *t*-butyl alcohol was carried out and worked up according to the above procedure. Crystallization of the product from hexane yielded 9.23 g of XVa: mp 89–91°; ir (Nujol), C=O, C=C 6.11 (s), 6.25 μ (s); pmr, three-proton singlet 3.72 (Me), one-proton doublet 5.38 ppm (J = 2.5 cps) (olefinic H).

Anal. Calcd for $C_{13}H_{19}O_2N$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.47; H, 8.46; N, 6.32.

Allyl Alcohols. A suspension of 500 mg of lithium aluminum hydride and 1.00 g of IXa in 90 ml of dry ether was kept at room temperature under nitrogen for 6 hr. Sodium sulfate decahydrate was added, the mixture filtered, and the precipitate washed with ethyl acetate. The combined filtrates were evaporated. Crystallization of the residue from hexane gave 930 mg of IXb: mp 117–118°; ir (Nujol), OH 3.15 (m), C=C 6.01 μ (s); pmr, three-proton singlet 3.53 (Me), one-proton doublet of triplets 4.35 (J = 2 cps), 4.50 (J = 2 cps) (hydroxymethine), one-proton broad singlet 4.62 ppm (olefinic H).

Anal. Calcd for $C_{12}H_{19}O_2N$: C, 68.86; H, 9.15; N, 6.69. Found: C, 68.73; H, 9.10; N, 6.80.

An identical reaction and work-up of 570 mg of XVa and 98 mg of lithium aluminum hydride in 70 ml of ether led to 565 mg of product whose crystallization from hexane gave alcohol XVb: mp 157–158°; ir (CCl_4), OH 2.80 (w), C=C 6.05 μ (s); pmr, three-proton singlet 3.50 (Me), one-proton multiplet 3.90 (hydroxymethine), one-proton triplet 4.56 ppm (J = 2.5 cps) (olefinic H).

Anal. Calcd for $C_{13}H_{21}O_2N$: C, 69.92; H, 9.47; N, 6.27. Found: C, 69.94; H, 9.44; N, 6.19.

Unsaturated Ketones. A solution of 700 mg of IXb in 5 ml of methanol and 10 ml of 10% sulfuric acid was stirred at room temperature for 4 hr. It then was poured slowly into a stirring mixture of 30 ml of 10% sodium hydroxide and 50 ml of methylene chloride. The aqueous solution was separated and extracted with methylene chloride. The combined organic solutions were dried over potassium carbonate and evaporated. This yielded 480 mg of liquid Xc: ir (neat), C=O 5.99 μ (s); pmr, one-proton pair of doublets 5.99 (J = 2.5, 10.0 cps) (olefinic α-H), one-proton pair of triplets 6.61 ppm (J = 2.5, 10.0 cps) (olefinic β-H); picrate, mp 177–179° dec, crystallized from methanol.

Anal. Calcd for $C_{17}H_{18}O_8N_4$: C, 50.24; H, 4.47; N, 13.79. Found: C, 50.12; H, 4.28; N, 13.68.

An identical reaction and work-up of 1.00 g of XVb in 30 ml of 10% sulfuric acid solution led to 820 mg of liquid XV: ir (CCl_4) C=O 5.98 μ (s); pmr, one-proton pairs of doublets 5.93 (J = 10.0, 2.5 cps) (olefinic α-H), 6.61 ppm (J = 10.0, 2.5 cps) (olefinic β-H); picrate, mp 224–230° dec, crystallized from methanol.

Anal. Calcd for $C_{18}H_{20}O_8N_4$: C, 51.43; H, 4.80; N, 13.33. Found: C, 51.60; H, 4.69; N, 13.27.

A solution of 1.00 g of VIIIb in 10 ml of 70% sulfuric acid was stirred at room temperature for 12 hr. It then was mixed with methylene chloride and solid carbonate added slowly. The inorganic salts were filtered and the filtrate was dried over anhydrous potassium carbonate. This procedure was repeated several times. Thereafter the solvent was evaporated and the residual oil chromatographed on alumina. Elution with benzene–hexane gave 380 mg of IXc as low-melting solid: ir (CCl_4), C=O 5.90 μ (s); pmr, one-proton pairs of doublets 5.95 (J = 10.0, 2.5 cps) (olefinic α-H), 6.69 ppm (J = 10.0, 2.5 cps) (olefinic β-H); picrate, mp 199–201°, crystallized from methanol.

Anal. Calcd for $C_{17}H_{18}O_8N_4$: C, 50.24; H, 4.47; N, 13.79. Found: C, 50.34; H, 4.40; N, 13.74.

Hydrololidones and Hydrojulolidone. A mixture of 180 mg of Xc and 50 mg of 10% prereduced palladium–charcoal in 15 ml of ethyl acetate was hydrogenated at room temperature and atmospheric pressure. The catalyst was filtered and the filtrate evaporated yielding 165 mg of low-melting XIa: ir (CCl_4), C=O 5.82 μ (s); picrate, mp 207–209°, crystallized from methanol.

Anal. Calcd for $C_{17}H_{20}O_8N_4$: C, 50.00; H, 4.94; N, 13.72. Found: C, 49.99; H, 5.01; N, 13.53.

Similar hydrogenation of 180 mg of IXc yielded 170 mg of XIb, mp 66–67°: ir (Nujol), C=O 5.81 μ (s); picrate, mp 211–212°, crystallized from methanol.

Anal. Calcd for $C_{17}H_{20}O_8N_4$: C, 50.00; H, 4.94; N, 13.72. Found: C, 50.12; H, 4.83; N, 13.61.

Similar hydrogenation of 144 mg of XVc led to 139 mg of XVIa, mp 56–57°: ir (CCl_4), C=O 5.82 μ (s), nonidentical with the spectrum of the all-*cis* isomer.[4h,15]

Anal. Calcd for $C_{12}H_{19}ON$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.76; H, 9.95; N, 7.27.

Dehydrogenations. A solution of 400 mg of Xc and 500 mg of *p*-toluenesulfonic acid in 4 ml of methyl orthoformate was stirred for 12 hr. It was poured slowly into a suspension of sodium bicarbonate in methylene chloride. The inorganic salts were filtered and washed with methylene chloride. Evaporation of the combined solutions left a residue whose extract with chloroform was washed with ice-cold 5% sodium hydroxide and water and dried over potassium carbonate. The solution was evaporated, the residue taken up in 10 ml of xylene, 100 mg of 10% palladium–charcoal added, and the mixture refluxed under nitrogen for 24 hr. The catalyst was filtered and the filtrate evaporated. Chromatography of the residue on alumina and elution with hexane yielded 85 mg of oily indole XIIIa: ir (CCl_4), C=C 6.15 μ (m); uv (MeOH), λ_{max} 220 mμ (log ϵ 4.58), 280 (3.79), 290 (3.80); pmr, two-proton multiplets 2.82 (benzylic Hs), 3.80 (aminomethylene), three-proton singlet 3.75 (OMe), two-proton pairs of doublets 6.29 (J = 3.0 cps), 6.80 (J = 3.0 cps) (indole H's), 6.67 (J = 10.0 cps), 7.30 ppm (J = 10.0 cps) (benzene H's); picrate, mp 234–235° dec, recrystallized from methanol.

Anal. Calcd for $C_{18}H_{16}O_8N_4$: C, 51.92; H, 3.87; N, 13.46. Found: C, 51.71; H, 4.11; N, 13.67.

The unsaturated ketone IXc, 400 mg, was exposed to the same reaction sequence and led to 82 mg of XIIIb: mp 79–81°; ir (Nujol), C=C 6.25 μ (w); uv (MeOH), λ_{max} 222 mμ (log ϵ 4.57), 270 (3.79), 287 (3.78), 298 (3.78); pmr, two-proton triplets 2.83 (J = 7.0 cps) (benzylic H's), 3.94 (J = 7.0 cps) (aminomethylene), three-proton singlet 3.84 (OMe), two-proton pairs of doublets 6.32 (J = 8.0 cps), 6.72 (J = 8.0 cps) (benzene H's), 6.47 (J = 3.0 cps), 6.83 ppm (J = 3.0 cps) (indole H's); picrate, mp 242–243° dec, crystallized from methanol.

Anal. Calcd for $C_{18}H_{16}O_8N_4$: C, 51.92; H, 3.87; N, 13.46. Found: C, 51.69; H, 3.61; N, 13.22.

A mixture of 200 mg of XVIa and 100 mg of 10% palladium–charcoal in 10 ml of xylene was refluxed with stirring under nitrogen for 24 hr. The catalyst was filtered and washed with ethanol. The combined solutions were taken to dryness under vacuum; the residue was exposed to thick layer chromatography on silica gel G. With the use of a 19:1 chloroform–methanol solvent system the

product was isolated from the fast-moving bands. Sublimation of the eluate, 15 mg, yielded XVII: ir (Nujol), C=O, C=C 6.11 μ (s). The ultraviolet spectrum and tlc behavior were identical with those of an authentic sample.[4h,13,14]

trans,trans-**Hexahydrojulolidine (XVId).** A. Ketone XVIa, 200 mg, was converted to its semicarbazone in the usual manner. Crystallization from methanol afforded 152 mg of colorless needles of semicarbazone: mp 236–237°; ir (Nujol), NH 2.82 (w), 3.00 (w), 3.18 (m), C=O 5.86 μ (s).

Anal. Calcd for $C_{13}H_{22}ON_4$: C, 62.37; H, 8.89; N, 22.38. Found: C, 61.89; H, 8.83; N, 22.25.

A solution of 500 mg of potassium hydroxide in 5 ml of ethylene glycol was concentrated by distillation to half its volume. The semicarbazone, 160 mg, was added and the solution refluxed for 4 hr. The cooled solution was acidified with 5% hydrochloric acid and all solvents were removed under vacuum. The residue was made basic by the addition of ammonium hydroxide and extracted with chloroform. The extract was dried over anhydrous potassium carbonate and evaporated. The oily residue was converted into a picrate. Crystallization from methanol yielded 78 mg of XVId·picrate, mp, mmp 182° (lit.[16b,d] mp 184°);[17] the infrared spectrum was identical with that of an authentic sample.[17]

B. Sodium borohydride, 200 mg, was added in several portions to a stirring solution of 200 mg of ketone XVIa in 5 ml of methanol. Thereafter the solvent was removed under vacuum and water added to the residue. The aqueous solution was extracted with ether and the extract dried over sodium sulfate and evaporated. Crystallization of the solid residue, 200 mg, from hexane yielded alcohol XVIb, mp 114–116°.

Anal. Calcd for $C_{12}H_{21}ON$: C, 73.79; H, 10.84. Found: C, 74.03; H, 10.76.

A solution of 200 mg of the alcohol and 100 mg of freshly crystallized *p*-toluenesulfonyl chloride in 2 ml of pyridine was left standing at 10° for 12 hr. Chloroform, 20 ml, and excess solid sodium bicarbonate were added and the inorganic salts filtered. The filtrate was washed with ice–water and ice-cold 5% sodium hydroxide solution and dried over potassium carbonate. Solvent removal yielded an oily residue whose last traces of pyridine were removed by distillation of added toluene. Crystallization of the residue from benzene yielded 160 mg of tosylate XVIc: mp 169–171°; ir (Nujol), C=C 6.27 μ (w); pmr, three-proton singlet 2.41 (Me), one-proton multiplets 3.45, 4.12 (aminomethine, tosyloxymethine), AB pair of doublets 7.27 (J = 8.0 cps), 7.75 (J = 8.0 cps) (aromatic H's).

Anal. Calcd for $C_{19}H_{27}O_3NS$: N, 4.01. Found: 3.86.

A suspension of 200 mg of lithium aluminum hydride and 150 mg of the tosylate in 20 ml of tetrahydrofuran was left stirring at room temperature for 12 hr. Sodium sulfate decahydrate was added and the inorganic salts were filtered and washed with ethyl acetate. The combined filtrates were evaporated and the residual oil was transformed into its picrate. Crystallization of the latter from methanol yielded 108 mg of the derivative of XVId, mp, mmp 184°, identical in all respects with an authentic specimen.

Halomethyl–Metal Compounds. XIX. Further Studies of the Aryl(bromodichloromethyl)mercury–Olefin Reaction[1]

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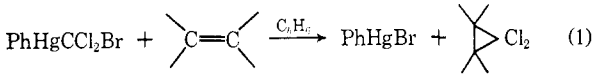
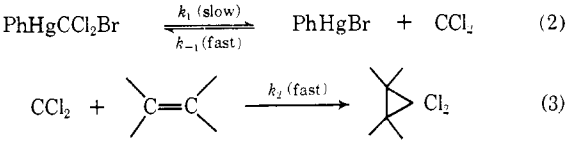
Abstract: Kinetic studies of the reactions of substituted aryl(bromodichloromethyl)mercury compounds, *p*-$ZC_6H_4HgCCl_2Br$ (Z = H, Cl, F, Me, MeO), with $Me_2C{=}CMeEt$ in benzene solution at 39.0° showed that the rate of CCl_2 extrusion from these mercurials differs only slightly as a function of Z. This insensitivity to electronic factors is taken as evidence in support of a concerted CCl_2 extrusion process proceeding *via* the cyclic transition state I. A study of reactions in which two different substituted styrenes were allowed to compete for a deficiency of phenyl(bromodichloromethyl)mercury-derived dichlorocarbene gave the following relative rate constants: *p*-$CH_3C_6H_4CH{=}CH_2$, 1.52; $C_6H_5CH{=}CH_2$, 1.00; *p*-$FC_6H_4CH{=}CH_2$, 0.961; *p*-$ClC_6H_4CH{=}CH_2$, 0.839; *m*-$CF_3C_6H_4CH{=}CH_2$, 0.453. These data correlate well with the Hammett equation and give ρ −0.619 ± 0.045 using σ^+ constants. The addition of CCl_2 to the olefinic C=C bond thus appears to be a concerted, electrophilic addition in which the transition state is but slightly polar, as shown in II.

A recent kinetic study of the reaction of phenyl(bromodichloromethyl)mercury with olefins, which gives *gem*-dichlorocyclopropanes in high yield[4] (eq 1), showed that a free carbene mechanism as indicated



(1)

in eq 2 and 3 was operative.[5] However, a more detailed understanding of the individual steps of this reaction sequence seemed desirable. This report concerns further studies of the mercurial decomposition step



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(*i.e.*, the factors which influence k_1) and the CCl_2 + olefin reaction step (k_2).

The Mercurial Decomposition Step. In our previous study it was found that the rate of *gem*-dichlorocyclopropane formation in the $PhHgCCl_2Br$–$Me_2C{=}CMeEt$ reaction was independent of the initial olefin concentration and first order in mercurial concentration.[5] In the case of this olefin, which was the most reactive (in such reactions) of a series examined in competition studies,[6] it appears that k_2 is much larger than k_{-1}, so that the rate expression (eq 4) for the eq 2–3 reaction

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