[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Synthesis of 2-Hydroxymethylquinolizidine (*dl*-2-Lupinine)*

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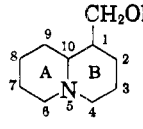
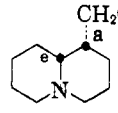
2-Hydroxymethylquinolizidine (*dl*-2-lupinine) has been synthesized by an unequivocal route starting with 2-carbethoxy-1-ketoquinolizidine.

It has been established that the product resulting from the reaction of ethoxymethyl α-picolyl ketone with acetic anhydride is 1-acetyl-3-ethoxypyrrocoline.

1-Hydroxymethylquinolizidine (I) is found in nature as the alkaloids (−)-lupinine (II)[3] and (+)-isolupinine [(+)-epilupinine] (III).[4] In lupinine, the hydrogens at C-1 and C-10 are in the *cis* relation, with the hydroxymethyl group axial to ring B in the chair conformation[5–12] and epimerizable[4,13–16] to the $C_{1,10}$-*trans* isomer with the hydroxymethyl group equatorial. Syntheses of *dl*-lupinine[8,17,18] and *dl*-epilupinine[17,18] have substantiated the structural assignments in these diastereomeric examples. Interest in the position isomers of the alkaloids (I) has led to the synthesis and characterization of the two racemates of 3-hydroxymethylquinolizidine (IV)[11,18–20] *dl*-3-lupinine (CH_2OH axial; CH_2OH α in the enantiomorphic representation where C_{10}-H is β) and *dl*-3-epilupinine (CH_2OH equatorial and β). A synthesis of '*dl*-2-lupinine" (V) has been reported by Winterfeld and Schneider,[21] but, as we have pointed out previously,[22] this synthesis was suspect since the deoxygenated compound related to the supposed "2-hydroxymethylquinolizidine" could not have been 2-methylquinolizidine. We have now devised a straightforward synthetic route to 2-hydroxymethylquinolizidine for the purpose of providing authentic material of structure V.



I



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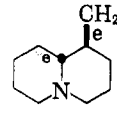

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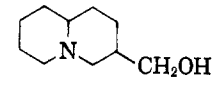
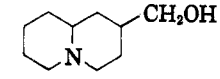


IV



V

The reduction of 2-carbethoxy-1-ketoquinolizidine (VI) with 2.2 equivalents of sodium borohydride furnished 2-carbethoxy-1-hydroxyquinolizidine (VII) in 89% yield. Dehydration of VII with sulfuric acid in glacial acetic acid, followed by a reesterification step led to 2-carbethoxy-Δ^1-dehydroquinolizidine, isolated as the hydrochloride (VIII), in 58% yield. Catalytic hydrogenation of VIII was followed by lithium aluminum hydride reduction of the intermediate 2-carbethoxyquinolizidine (hydrochloride) (IX). One racemate of 2-hydroxymethylquinolizidine (V) was obtained having the following properties: m.p. 74–76°; picrate, m.p. 144.5–145°; picrolonate, m.p. 171.5–173°; *p*-nitrobenzoate, m.p. 97–99° (picrate, m.p. 236.5–238°). The synthetic method was checked at the dehydration stage (VII → VIII) where, it might be argued, existed the possibility of rearrangement. Treatment of 2-carbethoxy-1-hydroxyquinolizidine (VII) with phosphorus oxychloride and pyridine,

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) Monsanto Chemical Co. Fellow, 1956–57.

(2) National Science Foundation Fellow, 1954–55.

(3) N. J. Leonard, "Lupin Alkaloids," in *The Alkaloids*, edited by R. H. F. Manske and H. L. Holmes, Vol. III, Academic Press, Inc., New York, N. Y., 1953.

(4) E. P. White, *New Zealand J. Sci. Technol.*, **33B**, 50 (1951).

(5) R. C. Cookson, *Chemistry & Industry*, 337 (1953).

(6) P. Karrer, F. Canal, K. Zohner, and R. Widmer, *Helv. Chim. Acta*, **11**, 1062 (1928).

(7) L. Marion, D. A. Ramsay, and R. N. Jones, *J. Am. Chem. Soc.*, **73**, 305 (1951).

(8) V. Boekelheide and J. P. Lodge, Jr., *J. Am. Chem. Soc.*, **73**, 3681 (1951).

(9) N. J. Leonard and B. L. Ryder, *J. Org. Chem.*, **18**, 598 (1953).

(10) F. Galinovsky, O. Vogl, and H. Nesvadba, *Monatsh.*, **85**, 1300 (1954).

(11) J. Ratuský, A. Reiser, and F. Šorm, *Chem. Listy*, **48**, 1794 (1954); *Collection Czechoslov. Chem. Communs.*, **20**, 798 (1955).

(12) If absolute configuration[5] and stereochemical analogy to the steroid conventions[11] are considered, in (−)-lupinine, the C_{10}—H is β and the C_1-CH_2OH is α.

(13) K. Winterfeld and F. W. Holschneider, *Ber.*, **64**, 137 (1931).

(14) C. Schöpf, E. Schmidt, and W. Braun, *Ber.*, **64**, 683 (1931).

(15) K. Krieg, Dissertation, Marburg, 1928.

(16) J. F. Couch, *J. Am. Chem. Soc.*, **56**, 2434 (1934).

(17) G. R. Clemo, W. McG. Morgan, and R. Raper, *J. Chem. Soc.*, 965 (1937); 1574 (1938).

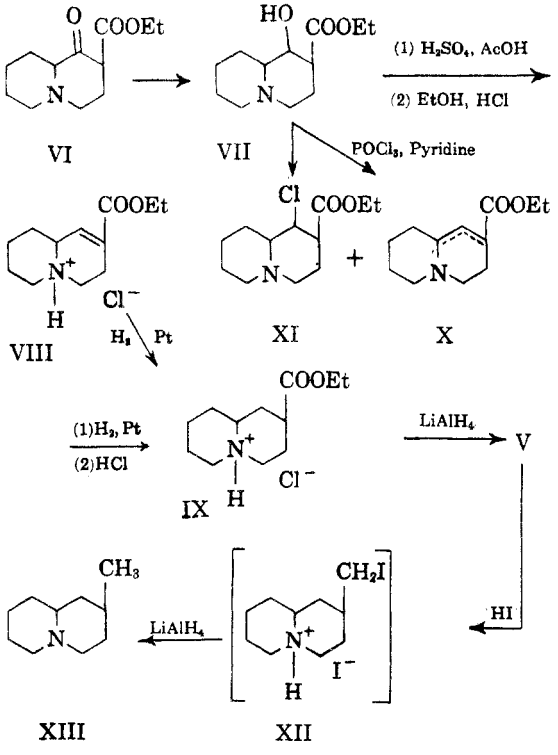
(18) J. Ratuský and F. Šorm, *Chem. Listy*, **47**, 1491 (1953); *Collection Czechoslov. Chem. Communs.*, **19**, 340 (1954).

(19) S. Ohki and K. Yamakawa, *Pharm. Bull. (Japan)*, **1**, 260 (1953).

(20) H. R. Lewis and C. W. Shoppee, *J. Chem. Soc.*, 313 (1956).

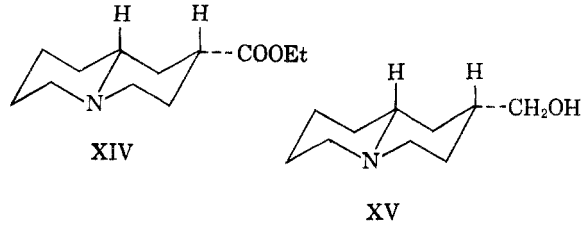
(21) K. Winterfeld and E. Schneider, *Ann.*, **581**, 66 (1953); *Naturwissenschaften*, **40**, 109 (1953).

(22) N. J. Leonard, R. W. Fulmer, and A. S. Hay, *J. Am. Chem. Soc.*, **78**, 3457 (1956).



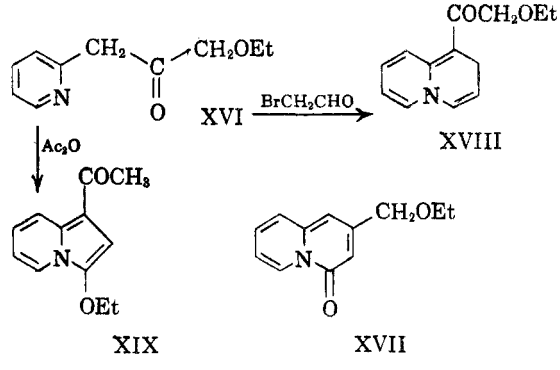
followed by hydrogenation with platinum of the unsaturated ester intermediate (X), produced the same saturated ester (IX) as obtained *via* the acid dehydration route. The chloro ester XI was a by-product.

The structure of our synthetic 2-hydroxymethylquinolizidine (V) was further confirmed by conversion to 2-methylquinolizidine (XIII) and direct comparison with samples of this compound prepared previously in our laboratory.[22] To accomplish this, the 2-hydroxymethylquinolizidine was heated under reflux with fuming hydriodic acid, and the resulting iodide hydriodide (XII) was reduced with lithium aluminum hydride to give an amine, isolated as the picrate (54% over-all yield), m.p. 150–151°, which was identical with the picrate of the predominant synthetic isomer (A)[22] of 2-methylquinolizidine (XIII). In the interest of determining which racemate of 2-hydroxymethylquinolizidine was represented by our synthetic product, we applied isomerizing conditions to the precursor 2-carbethoxyquinolizidine (available from IX). Under both acidic[23] and basic[24] epimerizing conditions (at C-2), over 60% of the original 2-carbethoxyquinolizidine was recovered, and no second racemate could be isolated in pure form. These findings indicate, in the light of parallel experiments in related series,[5,9,23] that the 2-carbethoxyquinolizidine at hand (hydrochloride, m.p. 202–203°) is the thermodynamically more stable isomer, with the C-2 and C-10 hydrogens *cis* and the carbethoxyl group equatorial (XIV, one enantiomorph represented). It follows that the 2-hydroxymethylquinolizidine which is obtained from XIV on lithium aluminum hydride reduction is of similar geometry (XV, one enantiomorph represented) and may be called *dl-2-lupinine* on the basis of nomenclature convention in this series,[11] wherein



the name "x-lupinine" (x = 2, 3, or 4) will be applied to the racemate having the CH_2OH *trans* with respect to the 10-hydrogen, and" x-epilupinine," to the racemate having the CH_2OH *cis* with respect to the 10β-hydrogen.[25]

Since our synthesis led to authentic 2-lupinine, the problem that remained was to determine at which point the synthetic route of Winterfeld and Schneider[21] was diverted from the same goal. The first step in their reaction sequence involved the condensation of ethoxymethyl α-picolyl ketone (XVI) with acetic anhydride in the presence of potassium acetate. The formation of "2-ethoxymethyl-4-quinolizone" ($C_{12}H_{13}NO_2$) (XVII) was postulated, in one rationalization,[21] as a Perkin-type condensation involving the carbonyl of XVI. It seemed more likely to us that XVI would be in-



volved as the active methylene component, and we found that the yellow $C_{12}H_{13}NO_2$ product, m.p. 65.5–66.5°, could be obtained in equivalent yield in the absence of potassium acetate. The acetic anhydride reaction thus becomes reminiscent of pyrrocoline syntheses of Tschitschibabin,[26] and more likely structures (XVIII, XIX), isomeric with XVII, can be postulated for the product of the condensation of ethoxymethyl α-picolyl ketone with acetic anhydride. One of these, 1-ethoxyace-

(23) K. Alder, M. Schumacher, and O. Wolff, *Ann.*, **570**, 230 (1950)

(24) C. Schöpf and O. Thomä, *Ann.*, **465**, 98 (1928).

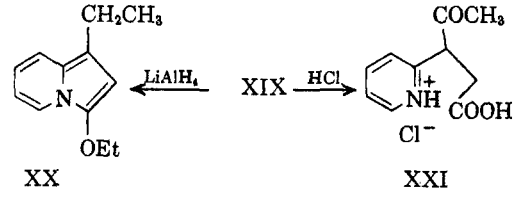
(25) It is perhaps significant that axial CH_2OH at C-1 or C-3 has only *one* 1:3-H interaction (both equatorial and axial isomers have been synthesized), whereas axial CH_2OH at C-2 has *two* 1:3-H interactions (only the equatorial isomer has been obtained thus far by synthesis).

(26) A. E. Tschitschibabin, *Ber.*, **60**, 1607 (1927).

tylpyrrocoline (XVIII), was made by the condensation of XVI with bromoacetaldehyde or, alternatively, with bromopyruvic acid, followed by a decarboxylation step. The yellow solid obtained, $C_{12}H_{13}NO_2$, m.p. 54–55°, was different from the acetic anhydride product.

The second possible pyrrocoline formulation, 1-acetyl-3-ethoxypyrrocoline (XIX), next received favorable consideration. The presence of a carbonyl group attached to a conjugated system was shown by the formation of a greenish black 2,4-dinitrophenylhydrazone. A monobenzylidene derivative was prepared readily under conditions commonly used with acetylpyrrocolines[27] and indicative of the —CH_2—CO— grouping. The fact that the ratio of the benzaldehyde moiety to the nitrogen-containing moiety in this condensation product is 1:1 instead of 1:2 as in the case of pyrrocoline itself[28] further suggested that the reactive 1- and 3-positions on the pyrrocoline nucleus were occupied. The spectral data on the $C_{12}H_{13}NO_2$ product can also be reconciled with structure XIX, but not with formula XVII. The appearance of the carbonyl infrared absorption band at 1645 cm.$^{-1}$ is comparable with the appearance of the C=O stretching maximum at 1635 cm.$^{-1}$ (with a shoulder at 1660 cm.$^{-1}$) in the infrared spectrum of 1,3-diacetylpyrrocoline. Carbonyl absorption in this range appears to be characteristic of a number of variously substituted indole carbonyl compounds as well.[29,30] The ultraviolet spectrum proved particularly useful in eliminating formula XVII, since the spectrum (principal maxima at 233, 332, and 369 mμ) of the $C_{12}H_{13}NO_2$ product was significantly different from that reported for 4-quinolizone.[8]

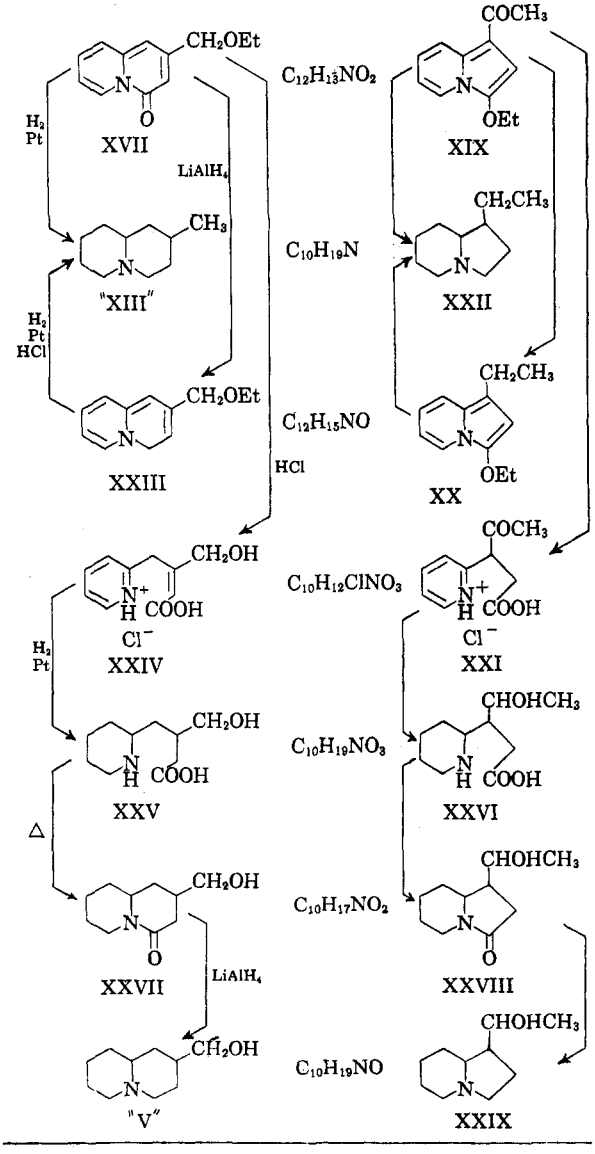
Further evidence strongly in favor of 1-acetyl-3-ethoxypyrrocoline (XIX) was found in the lithium aluminum hydride reduction product, 1-ethyl-3-ethoxypyrrocoline (XX), which had an ultraviolet spectrum closely resembling that reported for 1,3,5,7-tetramethylpyrrocoline.[31] Complete reduction by lithium aluminum hydride of a carbonyl group on the pyrrocoline nucleus to a methylene group has been observed in the case of 2,3-dimethyl-1-formylpyrrocoline,[32] and such reduction has also been observed in closely related compounds (indole-3-aldehyde, 3-acetylindole and 3-acetyl-2,4-dimethylpyrrole).[29,32,33] Cleavage and loss of ethoxyl from XIX was effected by hydrolysis with concentrated hydrochloric acid. The analysis (including the absence of ethoxyl, as determined by



Winterfeld and Schneider[21]) and infrared spectrum are compatible with the presently assigned structure, 3-(2′-pyridyl)-4-ketopentanoic acid hydrochloride (XXI), for the hydrolysis product.

Since the intended synthesis of 2-lupinine by Winterfeld and Schneider[21] departed so early from the designed course, a number of revisions in structural assignments are required, as indicated in the accompanying table. The analyses, where previously supplied, are satisfactory for the new struc-

TABLE I

Structure Previously Assigned[21]	Molecular Formula	Revised Structure
		

(27) E. T. Borrows, D. O. Holland, and J. Kenyon, *J. Chem. Soc.*, 1069 (1946).
(28) M. Scholtz, *Ber.*, **45**, 734, 1718 (1912).
(29) W. P. Samuels, Ph.D. thesis, University of Illinois, 1955.
(30) L. M. Werbel, Ph.D. thesis, University of Illinois, 1957.
(31) J. E. Saxton, *J. Chem. Soc.*, 3239 (1951).
(32) E. D. Rossiter and J. E. Saxton, *J. Chem. Soc.*, 3654 (1953).
(33) A. Treibs and H. Scherer, *Ann.*, **577**, 139 (1952).

tures, since these are isomeric with the old. The "2-lupinane" of Winterfeld and Schneider is now logically represented as 1-ethyloctahydropyrrocoline (XXII) (We have been able to obtain only one racemate.), and the melting points of the picrate (146–147°) and picrolonate (184.5–185.5°) are close to those reported for the corresponding derivatives of "2-lupinane" (141° and 175–179°, respectively).[21] If the reaction sequence is followed formally to the concluding step (Table I), the logical structure to replace Winterfeld and Schneider's "2-lupinine" becomes 1-(1′-hydroxyethyl)-octahydropyrrocoline (XXIX). Furthermore, it is obvious that structural revisions will be necessary for the compounds which Winterfeld and Küllman[34] have reported originating with the reaction of phenyllithium with the compound now known to be XIX.

EXPERIMENTAL[35]

Sodium borohydride reduction of 2-carbethoxy-1-ketoquinolizidine. 2-Carbethoxy-1-hydroxyquinolizidine. To a solution of 10.0 ml. (10.9 g., 0.048 mole) of 2-carbethoxy-1-ketoquinolizidine[22] in 100 ml. of methanol, cooled with stirring in an ice bath, was added 1.0 g. (0.026 mole, 2.2 equiv.) of sodium borohydride in small portions during 10 min. Stirring was continued for 1.5 hr. before the mixture was poured into 200 ml. of ice water and extracted with chloroform. The residue from the combined chloroform extracts was distilled through a Holzman column. The distillation was complicated by the tendency of the material to superheat and also to solidify in the condenser. The yield of *2-carbethoxy-1-hydroxyquinolizidine* was 9.82 g. (89%), b.p. 102–106° (0.11 mm.), n_D^{25} 1.4933–1.4942 (supercooled liquid). The liquid soon solidified to a waxy solid, m.p. *ca.* 70°. The infrared spectrum of a crystal melt exhibited maxima at 3460 (O—H); 2945, 2870, 2810, 2760, 2680 (C—H); and 1735 cm.$^{-1}$ (ester C=O).

Anal. Calcd. for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.23; H, 9.24; N, 6.07.

In another reduction in which 4 moles (16 equiv.) of sodium borohydride were used per mole of 2-carbethoxy-1-ketoquinolizidine, the diol, *1-hydroxy-2-hydroxymethylquinolizidine*, was produced. This material was partially separated from the desired reduction product by distillation through a Holzman column. The highest boiling fraction solidified and was recrystallized from cyclohexane, m.p. 104–106°, selected infrared maxima (Nujol) at 3410, 3290, 3140 cm.$^{-1}$ (O—H).

Anal. Calcd. for $C_{10}H_{19}NO_2$: C, 64.82; H, 10.34; N, 7.56. Found: C, 64.83; H, 10.27; N, 7.30.

Sulfuric acid dehydration of 2-carbethoxy-1-hydroxyquinolizidine. 2-Carbethoxy-Δ^1-dehydroquinolizidine hydrochloride. To a solution of 9.67 g. (0.042 mole) of 2-carbethoxy-1-hydroxyquinolizidine in 10 ml. of glacial acetic acid was added 10 ml. of 36*N* sulfuric acid, and the mixture was maintained at 160° for 5 hr. The mixture was cooled and poured into 200 ml. of ice and water. Acetic acid was removed by extraction with ether. The aqueous solution was neutralized with potassium carbonate, and the potassium sulfate which separated was removed by filtration. The filtrate was evaporated to dryness under reduced pressure, absolute ethanol was added, and the mixture was again evaporated. An ethanolic solution of the residue was saturated with anhydrous hydrogen chloride and allowed to stand about 5 hr. After filtration, the filtrate was evaporated to dryness, and the residue eventually crystallized in a desiccator (see below). The solid filter cake was boiled in absolute ethanol, the potassium chloride was removed by filtration, and the filtrate was saturated with anhydrous hydrogen chloride. After standing a day, the same isolation procedure yielded a second crop of crystals. The total yield of 2-carbethoxy-Δ^1-dehydroquinolizidine hydrochloride was 6.02 g. (58%), m.p. 165–184°. Recrystallization from ethanol–ethyl acetate was a wasteful process but served to provide analytically pure material, m.p. 194–195°.

Anal. Calcd. for $C_{12}H_{20}ClNO_2$: C, 58.65; H, 8.20; N, 5.70. Found: C, 58.78; H, 8.45; N, 5.40.

The infrared spectrum (5% solution in chloroform) exhibited maxima at 2960 (C—H), 2300–2400 (amine salt), 1720 (α,β-unsaturated ester C=O) and 1670 cm.$^{-1}$ (C=C).

Hydrogenation of 2-carbethoxy-Δ^1-dehydroquinolizidine. 2-Carbethoxyquinolizidine hydrochloride. A solution of 1.73 g. (7.05 mmoles) of 2-carbethoxy-Δ^1-dehydroquinolizidine hydrochloride (m.p. 165–184°) in 100 ml. of absolute ethanol was hydrogenated at 3 atm. using 0.1 g. of platinum oxide. It was necessary to interrupt the hydrogenation frequently, filter the exhausted catalyst, and add fresh platinum oxide in order to realize the theoretical uptake. Removal of the catalyst and solvent yielded 0.76 g. (43%) of colorless crystals, m.p. 191–195°, which were recrystallized by dissolving in methylene chloride, adding ethyl acetate, and boiling until all the methylene chloride was removed. The analytical sample melted at 202–203°

Anal. Calcd. for $C_{12}H_{22}ClNO_2$: C, 58.17; H, 8.95; N, 5.65. Found: C, 58.53; H, 8.92; N, 5.78.

The infrared spectrum (5% solution in chloroform) showed maxima at 2960 (C—H), 2440 (amine salt), and 1735 cm.$^{-1}$ (ester C=O).

Lithium aluminum hydride reduction of 2-carbethoxyquinolizidine hydrochloride. 2-Hydroxymethylquinolizidine. 2-Carbethoxyquinolizidine hydrochloride (4.19 g., 0.017 mole) was added as a solid during 10 min. to a stirred suspension of 1.93 g. (0.05 mole) of lithium aluminum hydride in 125 ml. of dry tetrahydrofuran. After 1.5 hr., the excess hydride was destroyed, 10 ml. of water was added, and the tetrahydrofuran was removed with a current of steam until the vapor temperature reached 99°. The organic base was extracted from the cooled residue with ether and isolated in the usual manner. Purification by distillation in high vacuum yielded 2.58 g. (90%) of viscous, colorless oil, n_D^{22} 1.5053–1.5066 (supercooled liquid), which could be crystallized from pentane, colorless prisms, m.p. 74–76°.

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.28. Found: C, 71.27; H, 11.16; N, 8.28.

The infrared spectrum (crystal melt) exhibited a band at 3180–3380 (O—H) and maxima at 2809, 2830, 2780, 2740, and 2680 cm.$^{-1}$ (C—H).

The *picrate* of this racemate of 2-hydroxymethylquinolizidine crystallized from methanol as yellow needles, m.p. 144.5–145°.

Anal. Calcd. for $C_{16}H_{22}N_4O_8$: C, 48.24; H, 5.57; N, 14.06. Found: C, 48.07; H, 5.72; N, 13.69.

The *picrolonate* was prepared in methanol and was recrystallized from ethyl acetate containing a trace of methanol, light yellow prisms, m.p. 171.5–173°.

Anal. Calcd. for $C_{20}H_{27}N_5O_6$: C, 55.42; H, 6.28; N, 16.16. Found: C, 55.88; H, 6.03; N, 15.93.

A small sample of the base was boiled with an equivalent of *p*-nitrobenzoyl chloride in benzene for 2.5 hr. Ether and

(34) K. Winterfeld and K. Küllman, *Arch. Pharm.*, **289**, 272 (1956).

(35) All melting points are corrected. We are indebted to Mrs. Esther Fett, Mrs. Lucy Chang, Mrs. R. Maria Benassi, Miss Claire Higham and Mr. Jozsef Nemeth for microanalyses, to Mrs. Louise Griffing and Mr. James Brader for determination of the infrared absorption spectra, and to Mr. Mou-shu Chao for determination of the ultraviolet absorption spectra. (Cyclohexane was used as the solvent for the ultraviolet spectra.)

10% aqueous sodium hydroxide solution were added, and the mixture was shaken. The ether layer was divided into 2 portions. The first portion was evaporated to dryness, and the *p-nitrobenzoate* was recrystallized once from aqueous methanol and several times from hexane, colorless leaflets, m.p. 97–99°.

Anal. Calcd. for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.97; N, 8.80. Found: C, 64.95; H, 7.01; N, 8.77.

To the second portion of the ethereal solution was added methanolic picric acid. After recrystallization from a large volume of 95% ethanol, the picrate of the *p-nitrobenzoate* was obtained as yellow prisms, m.p. 236.5–238°.

Anal. Calcd. for $C_{23}H_{25}N_5O_{11}$: C, 50.46; H, 4.60; N, 12.79. Found: C, 50.95; H, 4.54; N, 12.61.

Conversion of 2-hydroxymethylquinolizidine to 2-methylquinolizidine. The racemate of 2-hydroxymethylquinolizidine described above (0.52 g., 3.08 mmoles) was heated under reflux overnight with 15 ml. of fuming hydriodic acid. The mixture was evaporated to dryness *in vacuo*, and acetone was used to collect the crystals on a sintered glass funnel, yield 0.99 g. (79%), m.p. 241–250° after darkening at 170°. The infrared spectrum was consistent with the formulation of this material as the hydriodide of 2-iodomethylquinolizidine. The only absorption bands above 1500 cm.$^{-1}$ occurred at 2560, 2710, 2840, and 2910 cm.$^{-1}$

The crude iodide hydriodide was added to a suspension of 0.50 g. of lithium aluminum hydride in 80 ml. of tetrahydrofuran which had been freshly distilled from lithium aluminum hydride. After 2 hr. at reflux temperature the excess hydride was destroyed with ethyl acetate, and water and finally dilute hydrochloric acid were added. The tetrahydrofuran was removed by steam distillation. The mixture was rendered strongly alkaline and extracted with ether. Methanolic picric acid was added to the ethereal solution, and concentration produced yellow needles which were recrystallized from absolute ethanol, yield 0.51 g. (54% over-all yield), m.p. and mixture m.p. with authentic 2-methylquinolizidine (isomer A) picrate,[22] 150–151°.

The infrared spectra (5% solution in acetonitrile) of this picrate of 2-methylquinolizidine and of 2-methylquinolizidine (isomer A) picrate[22] [as well as that of 2-methylquinolizidine (isomer B) picrate[22] in acetonitrile!] were indistinguishable.

Attempted epimerization of 2-carbethoxyquinolizidine. An attempt at isomerization at C-2 of the 2-carbethoxyquinolizidine with sodium ethoxide in refluxing ethanol resulted in recovery of over 60% of the original racemate, as the hydrochloride. A similar result was obtained from an attempted isomerization of 2-carbethoxyquinolizidine with concentrated hydrochloric acid in a sealed tube at 150° for 6 hr.

On the assumption that the mother liquors remaining after isolation of the unique 2-carbethoxyquinolizidine hydrochloride from the attempted isomerizations might contain the epimeric racemate, the following additional reaction sequence was employed. The residue from evaporation of the mother liquors was reduced with lithium aluminum hydride, and the supposed mixture of racemates of 2-hydroxymethylquinolizidine was chromatographed on alumina. A material, the picrate of which was much lower melting than that observed earlier, was obtained, but recrystallization failed to narrow the melting range (107–115°, cloudy melt; clear at 122°).

Anal. Calcd. for $C_{16}H_{22}N_4O_8$: C, 48.24; H, 5.57. Found: C, 48.34; H, 5.54.

The analysis was correct for a picrate of 2-hydroxymethylquinolizidine, so the material was assumed to be a mixture of the two racemates. The mixture was converted to 2-methylquinolizidine *via* the iodide hydriodide as before, but only the familiar isomer A of 2-methylquinolizidine was isolated (12%). Thus, while some of the other racemate of 2-hydroxymethylquinolizidine was probably present in the hydride reduction mixture just described, it was not properly characterized, nor was its presence proved unequivocally.

Phosphorus oxychloride dehydration of 2-carbethoxy-1-hydroxyquinolizidine. A solution of 15.47 g. (0.068 mole) of 2-carbethoxy-1-hydroxyquinolizidine in 93 ml. of pyridine maintained under nitrogen was cooled in ice while 9.3 ml. (*ca.* 0.1 mole) of phosphorus oxychloride was added dropwise with stirring. When the addition was complete, the mixture was stirred at 25° under nitrogen for 48 hr. and then poured into cold 10% aqueous sodium hydroxide solution and extracted with chloroform. The mixture recovered from the chloroform was distilled, b.p. 83–95° (0.06 mm.), n_D^{25} 1.4985–1.4929, weight 9.03 g. The infrared spectrum exhibited maxima at 1715 (α,β-unsaturated ester C=O), 1740 (ester C=O), 1685 (C=C), and a series in the C—H stretching region: 2930, 2850, 2800, and 2755 cm.$^{-1}$

Hydrogenation of the phosphorus oxychloride dehydration product. The distilled dehydration product (11.27 g.) dissolved in 75 ml. of glacial acetic acid was hydrogenated at 3 atm. using platinum oxide. About one third of the theoretical amount of hydrogen was absorbed. Replacing the catalyst with a fresh quantity did not bring about further hydrogen uptake. The mixture was filtered, 12*N* hydrochloric acid was added to the filtrate, and the resulting solution was evaporated to dryness under reduced pressure. The oil was caused to crystallize by the addition of toluene, which was then removed at reduced pressure. The residue was recrystallized from methylene chloride–ethyl acetate as colorless crystals, m.p. 195–198°, yield 5.1 g. (38%), indentified by mixture m.p. and infrared spectrum as the same *2-carbethoxyquinolizidine hydrochloride* which was obtained earlier.

The combined mother liquors would neither crystallize nor absorb additional hydrogen under the conditions described above. Redistillation of the base liberated from these mother liquors followed by chromatography on acid-washed alumina yielded a pure substance which was isolated as the hydrochloride. The structure assigned to this product is *2-carbethoxy-1-chloroquinolizidine hydrochloride*, m.p. 136–137°, weight 1.75 g. The infrared spectrum (5% solution in chloroform) showed maxima at 1739 (ester C=O), 2300–2400 (amine salt), and 2960, 2935 and 2860 cm.$^{-1}$ (C—H).

Anal. Calcd. for $C_{12}H_{21}Cl_2NO_2$: C, 51.07; H, 7.50; N, 4.96. Found: C, 51.02; H, 7.50; N, 4.96.

Reduction of 2-carbethoxy-1-chloroquinolizidine to 2-hydroxymethylquinolizidine. 2-Carbethoxy-1-chloroquinolizidine hydrochloride (1.06 g., 3.75 mmoles) was added as a solid to 0.42 g. of lithium aluminum hydride suspended in 35 ml. of tetrahydrofuran which had just been distilled from lithium aluminum hydride. The mixture was heated under reflux for 14 hr., the hydride was destroyed, and concentrated aqueous sodium hydroxide solution was added. The base was extracted with ether and converted to the picrate, yellow needles from methanol–ethyl acetate, mixture m.p. with 2-hydroxymethylquinolizidine picrate (m.p. 144.5–145°), 147.5–151°, identical infrared spectra in acetonitrile solution.

1-Ethyl-1-hydroxyoctahydropyrrocoline. To the Grignard reagent prepared from 18.7 g. (0.12 mole) of ethyl iodide and 2.9 g. (0.12 g.-atom) of magnesium in 100 ml. of absolute ether was added a solution of 10.3 g. (0.074 mole) of 1-ketooctahydropyrrocoline[36] in 35 ml. of anhydrous ether. The reaction mixture was stirred under reflux for 3 hr. after addition of the ketone was completed. The mixture was treated with aqueous sodium hydroxide solution, and the product was obtained from the ether extracts, b.p. 80–82° (0.9 mm.) [reported[37] 85–87° (1 mm.)], $n_D^{23.5}$ 1.4887, yield 6.16 g. (30%).

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.94; H, 11.31; N, 8.28. Found: C, 71.06; H, 11.46; N, 8.08.

1-Ethyloctahydropyrrocoline. To a cooled solution of 12 g. of phosphorus pentoxide in 25 ml. of 85% phosphoric acid

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(37) G. R. Clemo and T. P. Metcalfe, *J. Chem. Soc.*, 1518 (1937).

was added 6.0 g. (0.035 mole) of 1-ethyl-1-hydroxyoctahydropyrrocoline. The reaction mixture was gradually raised to 145° and maintained there for 3 hr. The dehydro amine was isolated *via* basification and ether extraction. The crude product of the dehydration was dissolved in 50 ml. of absolute ethanol and hydrogenated at 25° and 3 atm., using Raney nickel catalyst, in 50 min. The solvent was removed by concentration *in vacuo*, and the residue was distilled through a micro spinning band column. Six fractions were collected arbitrarily: the first four had constant refractive index, n_D^{24} 1.4729; the fifth, 1.4740; the sixth, 1.4904. The first four fractions appeared to consist of only one racemate of 1-ethyloctahydropyrrocoline, the sixth fraction was unreacted 1-ethyl-1-hydroxyoctahydropyrrocoline and the fifth fraction appeared to be a mixture of these two compounds. Attempts to isolate a second picrate from the mother liquors of the fractions one through four were unsuccessful. An analytical sample of *1-ethyloctahydropyrrocoline* was prepared by regeneration from the analytically pure picrate of m.p. 146–147°.

Anal. Calcd. for $C_{10}H_{19}N$: C, 78.36; H, 12.50; N, 9.14. Found: C, 78.53; H, 12.73; N, 9.17.

The *picrate* crystallized from ethanol as small yellow needles, m.p. 146–147° (reported[37] 134°).

Anal. Calcd. for $C_{16}H_{22}N_4O_7$: C, 50.25; H, 5.70; N, 14.66. Found: C, 50.54; H, 5.77; N, 14.60.

The *picrolonate* was formed in acetone and recrystallized from ethanol as yellow prisms, m.p. 184.5–185.5° (reported[37] 176°).

Anal. Calcd. for $C_{20}H_{27}N_5O_5$: C, 57.54; H, 6.52; N, 16.78 Found: C, 57.62; H, 6.48; N, 17.02.

1,3-Diacetylpyrrocoline. The procedure was that of Scholtz[28] and Tschitschibabin,[26,38] involving the heating of α-picoline with acetic anhydride in a sealed tube at 220–230°, m.p. 174.5–176°, colorless needles from water. The infrared spectrum (5% solution in chloroform) showed carbonyl absorption at 1630 cm.$^{-1}$ (with a shoulder at 1660) and C—H absorption at 3020 (m) and 3140 cm.$^{-1}$ (w). The ultraviolet spectrum exhibited the following maxima: 226 mμ (log ε 4.11), 254 (4.44), 279 (4.06), 289 (4.23), 335 (4.29), and 345 (4.39). Infection points were observed at 249 (4.35) and 269 (3.77) and minima at 232 (4.06), 263 (3.65), 283 (4.01), 299 (3.71), and 345 (4.18).

Pyrrocoline was obtained from the 1,3-diacetylpyrrocoline by hydrochloric acid hydrolysis with heating,[38] m.p. 72–73°. Attempted reaction of pyrrocoline with ethoxyacetic anhydride in a sealed tube at 230° failed to yield any 1,3-di(ethoxyacetyl)pyrrocoline.

Ethoxymethyl α-picolyl ketone. This compound was prepared by the method of Winterfeld and Schneider[21] from α-picolyllithium and ethyl ethoxyacetate, b.p. 104–106° (0.3 mm.), yield 53%; *picrate*, m.p. 118.5–119° as reported,[21] yellow needles from ethanol.

Anal. Calcd. for $C_{16}H_{16}N_4O_9$: C, 47.06; H, 3.92; N, 13.72. Found: C, 47.40; H, 3.93; N, 14.14.

1-Ethoxyacetylpyrrocoline. The cyclization method of Tschitschibabin[26] was employed, using equimolar quantities of ethoxymethyl α-picolyl ketone and bromoacetylaldehyde,[39,40] but 1-ethoxyacetylpyrrocoline was obtained in only microscopic yield as a pale yellow solid, m.p. 52–53°. The substance showed the usual green fluorescence of a pyrrocoline in solution. It was made more efficiently from bromopyruvic acid. The condensation followed the general conditions of Borrows and Holland.[41]

To a solution of 7.5 g. (0.042 mole) of ethoxymethyl α-picolyl ketone in 200 ml. of absolute ethanol was added 7.0 g. (0.042 mole) of freshly prepared bromopyruvic acid.[42,43] The mixture was warmed on the steam bath for 3 hr. and and then allowed to stand at 25°. The solid that separated was recrystallized from ethanol as light yellow needles, m.p. 175–176° (dec.), yield 4.0 g. (39%) of *1-ethoxyacetylpyrrocoline-2-carboxylic acid.*

Anal. Calcd. for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.42; H, 5.34; N, 5.75.

The decarboxylation of this intermediate (0.5 g.) was effected by heating with 0.09 g. of copper bronze catalyst and 4 ml. of freshly distilled quinoline for 30 min. Ether (50 ml.) was then added to the cooled mixture. The ethereal solution was filtered, the ether was evaporated, and the quinoline was distilled. The residue was dissolved in hexane (with a few drops of ethyl acetate) and chromatographed on alumina. From the benzene elution fraction was obtained a brown residue upon removal of the solvent. It was recrystallized, with decolorization, from hexane containing a few drops of ethyl acetate, yielding 200 mg. of *1-ethoxyacetylpyrrocoline*, light yellow prisms, m.p. 54–55°. There was no significant depression of melting point when this product was mixed with that obtained using bromoacetaldehyde.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 71.10; H, 6.28; N, 7.12.

Reaction of ethoxymethyl α-picolyl ketone with acetic anhydride. 1-Acetyl-3-ethoxypyrrocoline. The combination of ethoxymethyl α-picolyl ketone, acetic anhydride, and dry potassium acetate followed the directions of Winterfeld and Schneider,[21] and the product was purified by recrystallization from hexane to yield light yellow needles, m.p. 65.5–66.5° (reported[21] 64.5°), yield 34%. In solution the compound exhibited blue fluorescence.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45. Found: C, 70.46; H, 6.54.

The same compound was obtained when potassium acetate was omitted from the reaction mixture. Thus, a mixture of 9.3 g. (0.052 mole) of ethoxymethyl α-picolyl ketone and 20 ml. (0.21 mole) of acetic anhydride was heated under reflux at 140° for 2 hr. Acetic anhydride was removed at aspirator pressure, and the product was collected at 145–160° (0.2–0.3 mm.), yield 4.0 g. (38%). It solidified after distillation and was recrystallized from hexane, light yellow needles, m.p. 65.5–66.5°, identical with the compound obtained following the earlier reaction conditions.

The infrared spectrum (5% solution in carbon tetrachloride) showed a large number of sharp peaks in the fingerprint region. A carbonyl stretching band appeared at 1645 cm.$^{-1}$ and C—H stretching bands at 3005, 2950, and 2900 cm.$^{-1}$ The ultraviolet spectrum exhibited maxima at 233 mμ (log ε 4.42), 256 (3.62), 265 (3.65), 275 (3.52), ~322 (3.93), 332 (3.94), and 369 (3.87). Minima appeared at 253 (3.61), 260 (3.60), 272 (3.47), 283 (3.09), and 345 (3.76). No pure product could be isolated when 1-acetyl-3-ethoxypyrrocoline was heated with ethoxyacetic anhydride in a sealed tube.

The *2,4-dinitrophenylhydrazone* was prepared by dissolving 0.1 g. of 1-acetyl-3-ethoxypyrrocoline in 4 ml. of absolute ethanol and adding a solution containing 0.2 g. of 2,4-dinitrophenylhydrazine. The solid which formed within 3 hr. was collected and recrystallized twice from pyridine and once from a large volume of ethyl acetate to give a mat of black needles with a greenish cast, m.p. 238–239°.

Anal. Calcd. for $C_{18}H_{17}N_5O_5$: C, 56.39; H, 4.47; N, 18.28. Found: C, 56.48; H, 4.31; N, 18.30.

The *benzylidene* derivative was made from 0.1 g. of 1-acetyl-3-ethoxypyrrocoline, 0.2 ml. of benzaldehyde and

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(40) E. N. Stepanov, N. Preobrashenski, and M. Schtschukina, *Ber.*, **58**, 1718 (1925); **59**, 2533 (1926).

(41) E. T. Borrows and D. O. Holland, *J. Chem. Soc.*, 673 (1947).

(42) J. Wegman and H. Dahn, *Helv. Chim. Acta*, **29**, 415 (1946).

(43) D. B. Sprinson and E. Chargaff, *J. Biol. Chem.*, **164**, 417 (1946).

one pellet of potassium hydroxide in 5 ml. of absolute ethanol. After 42 hr. at 25°, the mixture was cooled in ice and scratched to induce crystallization of the product. After one recrystallization from aqueous ethanol, the orange prisms melted at 125–126°.

Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 78.33; H, 5.74; N, 4.81. Found: C, 78.56; H, 5.88; N, 4.72.

Lithium aluminum hydride reduction of 1-acetyl-3-ethoxypyrrocoline. 1-Ethyl-3-ethoxypyrrocoline. A solution of 2.8 g. (13 mmoles) of 1-acetyl-3-ethoxypyrrocoline in 70 ml. of anhydrous ether was added to a suspension of 0.57 g. (15 mmoles) of lithium aluminum hydride in 50 ml. of ether. The mixture was heated at the reflux temperature for 2.5 hr., the excess hydride was destroyed cautiously with water, and the mixture was steam distilled. About 800 ml. of distillate was collected before the yellow oil stopped distilling. The layers of the distillate were separated, the aqueous layer was extracted with ether, and the organic extracts were combined, dried, and the ether was removed. The residue was distilled through a Holzman column at 147.5–152° (13 mm.) as an orange mobile liquid, yield 1.80 g. (75%).

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.46; H, 8.24; N, 8.06.

The infrared spectrum (liquid film) confirmed the complete reduction of the carbonyl function (disappearance of the band at 1645 $cm.^{-1}$ present in the spectrum of 1-acetyl-3-ethoxypyrrocoline); C—H stretching bands appeared at 3100, 2980, 2940, and 2680 $cm.^{-1}$ The ultraviolet spectrum exhibited maxima at 241 mμ (log ε 4.30), 285 (3.50), 296 (3.50), and 382 (3.17) and a well defined minimum at 291 (3.40). The other minima were broad, located approximately at 275 and 315 mμ.

Hydrolysis of 1-acetyl-3-ethoxypyrrocoline. 3-(2′-Pyridyl)-4-ketopentanoic acid hydrochloride. A solution of 0.5 g. of 1-acetyl-3-ethoxypyrrocoline and 1.0 ml. of 12*N* hydrochloric acid was warmed on the steam bath for 2 hr. The mixture was placed in a vacuum desiccator over potassium hydroxide. Crystals soon formed, which were hygroscopic, but washing with boiling chloroform removed this property, m.p. 158–167° [reported[21] 156° (dec.)].

Anal. Calcd. for $C_{10}H_{12}ClNO_3$: C, 52.20; H, 5.27; N, 6.10. Found: C, 52.21; H, 5.33; N, 6.02.

The infrared spectrum (Nujol) indicated the presence of ketone (1710 $cm.^{-1}$) and acid (1725) carbonyls, amine salt (2550), and the pyridinium grouping (1635). Additional bands were present at 1830, 1890, 1955, and 2015 $cm.^{-1}$

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Preparation of the Pyridalacetones and the Inductive Effect of Nitrogen on the Dehydration of the Intermediate Aldols*[1]

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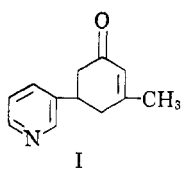
The *trans*-isomers of 2-, 3-, and 4-pyridalacetone have been prepared by two synthetic approaches. The tendency for an olefin-forming elimination by the intermediate ethyl 3-hydroxy-3-pyridyl-2-acetopropionates and the 4-hydroxy-4-pyridyl-2-butanones increases as the position of substitution on the pyridine ring is changed from 2 to 3 to 4, which suggests that the inductive effect of the nitrogen plays an important role in the chemistry of these compounds.

The preparation of the pyridalacetones, which was first attempted by application of the procedures described for benzalacetone[2] and the pyridine analogs of chalcone,[3] was unsuccessful. Acid catalyzed condensations using hydrogen chloride[4] and boron fluoride[5] did not yield the desired products. In order to learn more about the properties of the pyridalacetones so that the more direct synthesis route from the pyridine aldehydes and acetone could be effected, the pyridalacetones were prepared from the ethyl pyridalacetoacetates. The synthesis was first attempted with pyridine-3-aldehyde by the method of Knoevenagel,[6] but it became apparent that even at the low temperature (−20°) or during subsequent steps a large amount of Michael addition of acetoacetic ester to ethyl 2-(3′-pyridal)acetoacetate (VII) was taking place, since distillation after the decarboxylation step yielded a 3-methyl-5-(3′-pyridyl)-Δ^2-cyclohexenone (I). (The position of the double



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bond has not been definitely fixed in the cyclohexenone ring. It may have migrated to the Δ^5 position.) In order to avoid this side reaction, the condensation was run in an ether solution. In this manner the product crystallized as it was formed, and the ethyl 2-pyridalacetoacetates were obtained relatively free from acetoacetic ester.

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