[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Total Synthesis of Oxygenated Lupin Alkaloids[1]

BY EUGENE E. VAN TAMELEN AND JOHN S. BARAN

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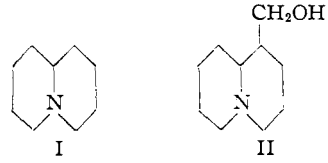
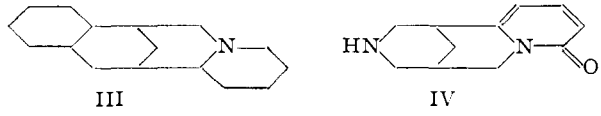
Details of the first total syntheses of various oxygenated lupin alkaloids, including cytisine, anagyrine and thermopsine, are described.

Collectively, the lupin alkaloids bear the quinolizidine ring (I) as a common structural unit, al-



I II

though, individually, members may differ with regard to such features as stereochemistry, oxidation state and number of additional rings. Thus, lupinine (II) represents the simplest, bicyclic type, the first in the family attained by synthesis.[2] The alkaloids[3,4] possessing the bridged, tetracyclic skeleton III contrasts with the lupinine case as well as that of cytisine (IV), an almost unique repre-

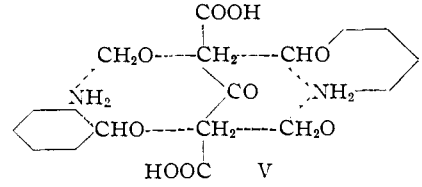


III IV

sentative of the tricyclic category. Synthesis of the saturated, oxygen-free tetracyclic system, has been reported[5]; on the other hand, laboratory duplication of tri- and tetracyclic oxygenated lupin alkaloids has not been achieved. This contribution is concerned with total syntheses of various members of this oxygenated class.

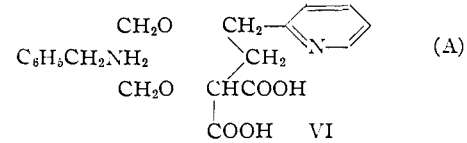
Synthesis of Cytisine.—Cytisine (ulexine, baptitoxine, sophorine), a bitter, powerfully poisonous base, was first isolated in 1865 and, since that time, has been identified as a constituent of many legumes. Chemical studies[3,4] carried out during the latter part of the nineteenth, and early part of the present century, led to a secure structural assignment in 1932 by Späth and Galinovsky[6] and by Ing.[7] Although there are to be found allusions to the cathartic and diuretic utility of cytisine, its general physiological properties[8] do not render it attractive for medicinal use.

Guided by the biogenetic schemes, *e. g.* V, promulgated by Robinson and others,[9,10] we initiated a



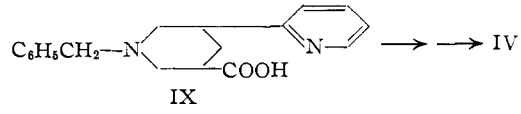
V

laboratory approach which, in the case of cytisine, involved the projected twofold Mannich condensation of benzylamine, formaldehyde and 2-(α-



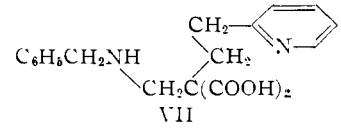
(A)

VI

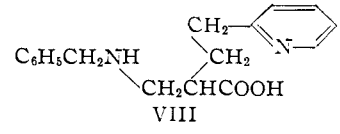


IX

pyridyl)-ethylmalonic acid (VI) (reaction A).[11] Continuation of the synthesis would involve (1) utilization of the remaining carboxyl for construction of the third ring, (2) oxidation to the pyridone system and (3) removal of the benzyl protecting group. When the reaction of the malonic acid VI, one mole of benzylamine and 2.2 moles of formaldehyde was carried out in dilute aqueous medium there was formed in good yield the mono-Mannich product VII. The corresponding monocarboxylic



VII



VIII

acid VIII could be obtained either by thermal decarboxylation of the malonic acid or by initially carrying out the condensation with prolonged heating and with benzylamine hydrochloride instead of the free base. Attempts to introduce a second methylene unit and thereby secure the desired bicyclic intermediate IX, were unsuccessful. These

(1) First reported in Communications to the Editor, THIS JOURNAL, **77**, 4944 (1955); **78**, 2913 (1956).

(2) G. R. Clemo, W. McG. Morgan and R. Raper, *J. Chem. Soc.*, 965 (1937).

(3) N. J. Leonard in Manske and Holmes, "The Alkaloids," Academic Press, Inc., New York, N. Y., 1953, Vol. III, pp. 120–199.

(4) F. Galinovsky, "Progress in the Chemistry of Natural Products," Springer-Verlag, Vienna, 1951, Vol. VIII, pp. 245–277.

(5) (a) N. J. Leonard and R. E. Beyler, THIS JOURNAL, **70**, 2299 (1948); (b) G. R. Clemo, R. Raper and W. S. Short, *Nature*, **162**, 268 (1948; (c) F. Sorm and B. Keil, *Collection Czechoslov. Chem. Commun.*, **13**, 554 (1948); F. Galinovsky and G. Kainz, *Monatsh.*, **80**, 112 (1949); (e) M. Carmack, B. Douglas, E. W. Martin and H. Suss, THIS JOURNAL, **77**, 4435 (1955).

(6) E. Späth and F. Galinovsky, *Ber.*, **65**, 1526 (1932).

(7) H. R. Ing, *J. Chem. Soc.*, 2778 (1932).

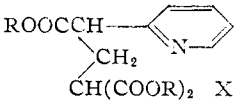
(8) T. A. Henry, "Plant Alkaloids," The Blakiston Co., Philadelphia, Pa., 1949, fourth edition, p. 153.

(9) R. Robinson, "The Structural Relations of Natural Products," Oxford University Press, London, 1955, p. 77.

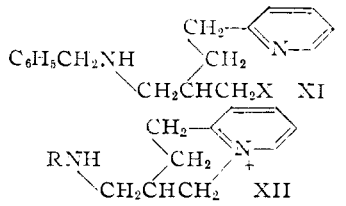
(10) The physiological-type synthesis claimed by E. Anet, G. K. Hughes and E. Ritchie, *Austr. J. Sci. Research, Ser. A*, **3**, 635 (1950), has been discredited by C. Shopf, G. Benz, F. Braun, H. Hinkel and R. Rokohl, *Angew. Chem.*, **65**, 161 (1953).

(11) W. von E. Doering and R. A. Weil, THIS JOURNAL, **69**, 2463 (1947).

attempts included the treatment with formaldehyde of the monocarboxylic acid VIII or its ester; the triester (X, R = C_2H_5) and the triacid (X, R

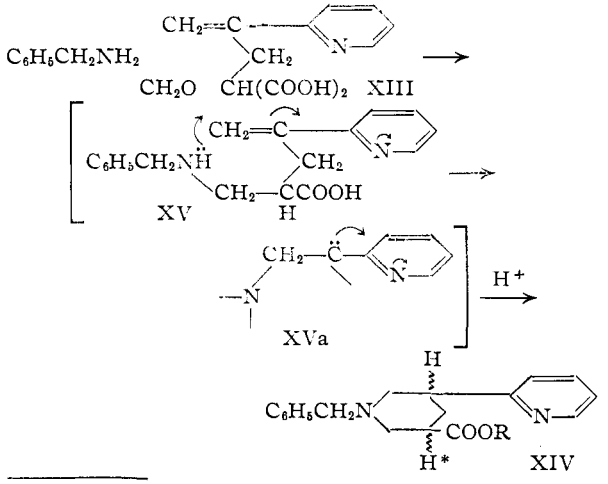


= H), which were available from an alternate approach (*vide infra*); the amino alcohol XI (X =



OH), obtained by lithium hydride reduction of the ethyl ester of VIII; and the quaternary salt XII (R = $C_6H_5CH_2$-), provided by cyclization of the primary bromide XI (X = Br) derived from the corresponding amino alcohol.

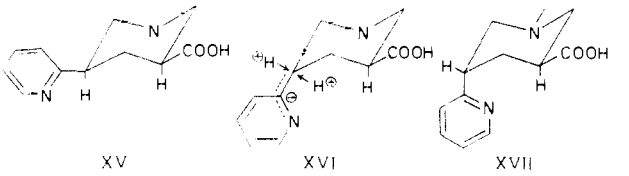
Although the plan to build up the bicyclic intermediate IX from 2-(α-pyridyl)-ethylmalonic acid had failed, we hoped to preserve the essence of the approach by utilizing instead 2-(α-pyridyl)-allylmalonic acid (XIII), which already possesses the methylene group which we failed to insert in our adherence to scheme (A). This acid seemed well suited for the kind of synthetic operation envisioned, in that the Mannich reaction would in this case be accompanied by the mechanistically sound conjugate addition of the benzylic nitrogen to the vinylpyridine system.[12] The diethyl ester of the starting material already had been described,[13] and can be prepared in reasonable yield by the reaction of sodiomalonic ester and 2-(α-pyridyl)-allylacetate, carried out in dimethylformamide–benzene. The diacid XIII was secured as a crystalline solid (m.p. 115° dec.); however, a dilute aqueous solution, obtained by addition of an amount of mineral acid *exactly* equivalent to the base used for saponification, was used for actual synthetic operations. Heating of the malonic acid solution with benzylamine and slightly more than one mole



of formaldehyde at 90–95° led to formation of 3-(α-pyridyl)-N-benzyl-piperidine-5-carboxylic acid, which was not isolated, but converted under Fischer conditions to the ethyl ester (XIV, R = C_2H_5), b.p. 183–185° (0.07 mm.). The over-all yield of this final product, based on the diethyl ester of XIII as the starting material, was 65%.

Although the reaction leading to the pyridylpiperidine VIII was not studied in detail, brief comment on its course seems in order. In carrying out the condensation, we observed that carbon dioxide was evolved rapidly during the initial stage of the heating period; on the other hand, the transformation of the vinylpyridine residue to the saturated pyridine system, as evidenced by ultraviolet assay during the course of the reaction, required about four hours for essential completion. Most simply interpreted, this behavior implies an initial Mannich condensation, affording XV, followed by the intramolecular conjugate addition which accomplishes ring closure. This view is supported by the relatively rapid rate of similar Mannich reactions (*e. g.*, VI → VII) and by the considerably more drastic conditions employed in the intermolecular addition of aliphatic amines to 2- or 4-vinylpyridine.[13,14]

A consequence of the step under discussion is the appearance in the intermediate XIV of two asymmetric centers, which were required to be *cis*, the more stable relationship (XV) as judged from the conformational point of view. The recent work of Zimmerman[15] on the stereochemical course of the ketonization of enols implies that the less stable,



XV XVI XVII

trans product XVII might, however, be the favored result in a kinetically controlled protonation (XVI) of the anion XVI, which is the immediate product arising in the ring closure step (XV). Fortunately, the outcome of the step is not critical insofar as the success of the synthesis is concerned, because XIV (R = C_2H_5) bearing a readily epimerizable H(*), permits independent, base-catalyzed equilibration and, consequently, predominance of the *cis* isomer. Experiments prompted by these considerations provided some information about the process XVI. After heating XIV (R = C_2H_5), the direct product of esterification, in refluxing ethanolic sodium ethoxide, we found the boiling point and refractive index virtually unchanged; however, in a succeeding step, where the tricyclic system is formed, the ester which had been subjected to the action of alcoholic base afforded yields approximately double those obtained from unequilibrated ester. Although the question of epimerization during the reaction which yields IX is left open, we conclude that a significant amount of the ester XIV (R = C_2H_5) is present as the *trans*

(12) A. H. Sommers, M. Freifelder, H. B. Wright and A. W. Weston, THIS JOURNAL, **75**, 57 (1953).

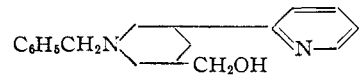
(13) F. Bohlmann, N. Ottawa and R. Keller, *Ann.*, **587**, 162 (1954).

(14) G. Magnus and R. Levine, THIS JOURNAL, **78**, 4127 (1956); H. Reich and R. Levine, *ibid.*, **77**, 5434 (1955).

(15) H. E. Zimmerman, *J. Org. Chem.*, **20**, 549 (1955).

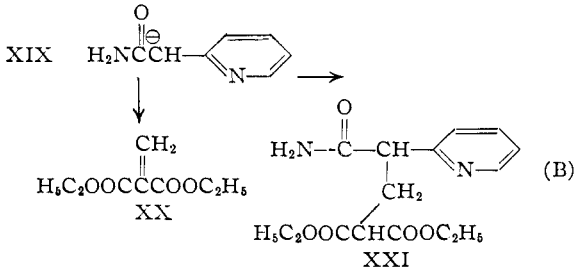
form XVII, thereby indicative of equatorial protonation—extensive, if not exclusive.

Lithium aluminum hydride reduction of the bicyclic intermediate XIX (R = C_2H_5) afforded a nearly quantitative yield of the expected alcohol XVIII, the first of the intermediates comprising the projected sequence leading to the tricyclic system of cytisine.



XVIII

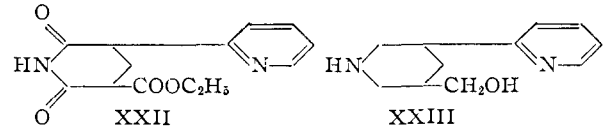
We now divert attention from the above approach to a second one (B), which also features the acquisition of the intermediary aminoalcohol XVIII. Inception of the project involved the addi-



XXI

tion of α-pyridylacetamide (XIX) to methylene malonic ester XX. Although no clean-cut product was obtained when this type of reaction was attempted with an alkaline catalyst,[16] it was found that *the desired addition proceeded, without added catalyst, on brief refluxing of the components in ethanol.* Doubtless, the pyridine nitrogen acts as a built-in, basic catalyst, of an activity order appropriate for bringing about a smooth addition reaction.[17]

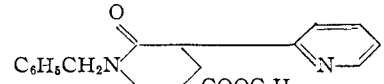
Ring closure of the amide diester XX to the glutarimide XXII was indicated as the next logical



XXII XXIII

move. Sodium ethoxide in refluxing ethanol produced an 89% yield of the imide, m.p. 137–138°, which could be prepared more expeditiously from the starting pyridylacetamide without isolation of the intermediate addition product XXI.

Hydride reduction of the glutarimide XXII to XXIII failed, seemingly because of the several active hydrogens in XXII, or in a partial reduction product derived therefrom. Temporary blocking of an acidic function, an obvious device which might allow normal reduction, was effected by subjecting the sodium salt of the carboethoxyglutarimide to the action of benzyl chloride in dimethylformamide. Prolonged treatment of the crude alkylation mixture with lithium aluminum hydride in refluxing ether produced a mixture from which separated a 14% yield of a crystalline solid;

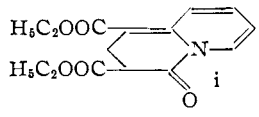


XXIV

analysis indicated it to be one of the several possible dibenzyl substitution products. Distillation of the product remaining after removal of the dibenzylated fraction provided a 29% yield of the liquid N-benzylaminoalcohol XVIII, derived from the mono-N-benzylglutarimide XXIV. The infrared spectrum of this material was indistinguishable from that of material secured by the route A, described earlier; moreover, the alcohol produced by the glutarimide reduction gave rise to various transformation products (*vide infra*) identical with those obtainable from aminoalcohol originating from the alternate source.[18,19]

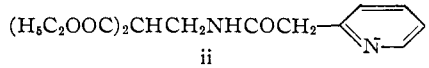
Although the key intermediate the N-benzylaminoalcohol XVIII was now accessible by two routes, it should be emphasized that the preparation

(16) R. Adams and S. Miyano, THIS JOURNAL, **76**, 3168 (1954), reported that ethyl α-pyridyl acetate and methylene malonic ester yield, in the presence of sodium ethoxide, the addition-cyclization product (i).



i

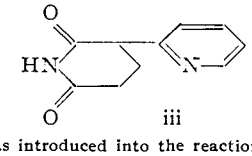
(17) Treatment of this amide diester with aqueous ammonia led to the triamide XXIb, independently secured by amination of the triester XXIa obtained by addition of ethyl pyridylacetate to methylene malonic ester. This result at this stage excluded the alternate structure ii for the α-pyridylacetamide-methylene malonic ester addition product.



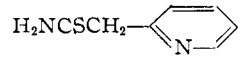
ii

(18) An attempt to obtain the N-benzylglutarimide XXIV *via* addition of N-benzyl-α-pyridylacetamide to methylenemalonic ester, failed.

(19) Other attempts to reduce the carboethoxyimide to the piperidine alcohol XVIII were made. Copper chromite-catalyzed hydrogenolysis (J. H. Paden and H. Adkins, THIS JOURNAL, **58**, 2487 (1936); H. Adkins and H. Billica, *ibid.*, **70**, 3121 (1948)) proved unsuccessful in that, although two moles of hydrogen were absorbed, only the decarboethoxylated product iii could be isolated. A thioamide function

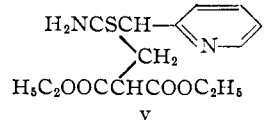


iii

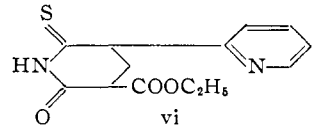


iv

was introduced into the reaction series by converting α-pyridylacetamide to the thioamide iv through treatment with phosphorus pentasulfide in refluxing toluene (yield 15–20%). Addition of this anionic agent to methylene malonic ester proceeded smoothly, affording the thioamide diester v, which readily cyclized, on treatment with ethanolic base, to the yellow-orange, crystalline thioimide vi. Desulfurization of this imide gave a mixture of products, from which there could be isolated a 23% yield of a colorless crystalline product, m.p. 140.4–141.5°, possessing the formula $C_{13}H_{14}N_2O_3$. The analytical results required the simple loss of an -SH unit and thereby implied the presence of a new double bond. The unsaturation revealed itself in the

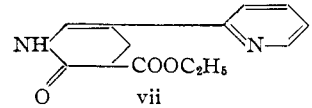


v



vi

ultraviolet, where its conjugation with the pyridine ring was indicated by absorption at 307 mμ (ε 17,500). We therefore consider the desulfurization product to possess structure vii. Further reduction

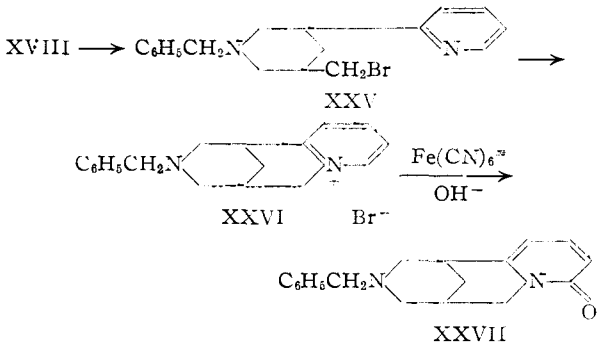


vii

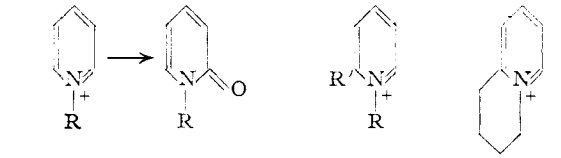
of vii seemed feasible; however, efforts along these lines were unattractive, and the sequence involving thioamides was abandoned.

which utilizes the Mannich-ring closure step was the more satisfactory, with respect to operational facility and over-all yield.

The sequence of steps designed to lead from the piperidine alcohol to the cytisine system is encompassed by the formulas XXV-XXVII. Although

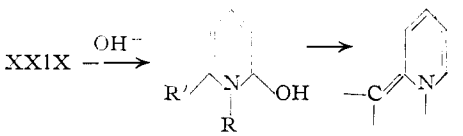


the conversion of the aminoalcohol to the corresponding bromide XXV and the quaternization of the latter seemed secure, oxidation of the salt XXVI to the pyridone XXVII was suspect. Preparation of pyridones by alkaline ferricyanide oxidation of quaternary salts (XXVIII) derived from pyridine itself is well known,[20] yet the operation cannot be applied to α-alkylpyridinium salts (XXIX) or to the simplest member (XXX) of the tetrahydroquinolizinium salt class[13] to which the tri-



XXVIII XXIX XXX

cyclic intermediate XXVI also belongs. Reflection on the nature of the structures involved leads to the conclusion that attachment of hydroxyl to a pyridinium salt followed by oxidation, observed with the simplest type XXVIII, is not the only path-



XXXI

way open to the 2-alkyl type, which can instead eliminate to the anhydro base XXXI; ensuing oxidation may then proceed abnormally, and the expected α-alkyl-α'-pyridone is not formed. Turning to the item of particular interest, we see that, on account of the restrictions explicit in Bredt's rule, *the tricyclic cation XXVI is not convertible to an anhydro base.* Consequently, it may be concluded, insofar as oxidation of pyridinium salts to pyridones is concerned, that the case for which model experiments portended failure is in fact the very case with the structural feature allowing success.

Turning again to the account of the experimental, refluxing of the aminoalcohol XVIII with 48% aqueous hydrobromic acid resulted in formation of the bromide XXV; the free base was not isolated, but cyclized, on brief heating in benzene, to the crystalline quaternary bromide. When aminoalcohol secured by hydride reduction of unepimerized ester (XIV, R = C_2H_5) was used in this step, the over-all yield amounted to 25%; on the other hand, base treatment of the ester preliminary to the same series of operations raised the over-all yield to 56%. Oxidation of the tricyclic salt, carried out with alkaline ferricyanide in aqueous solution at approximately 100°, produced N-benzyl-*dl*-cytisine (XXVII), m.p. 137.5–139.0°. The identity of the synthetic product was demonstrated by infrared spectral comparison with N-benzyl-l-cytisine, obtained by direct alkylation of the alkaloid with benzyl chloride.

In order to complete the synthesis there remained, apart from the resolution, the requirement of removing the benzyl group from the N-benzylated base. After satisfying ourselves that the reductive cleavage could not be managed readily by a catalytic process, we resorted to constant-boiling hydriodic acid, using the conditions prescribed by Marion[21] for regeneration of cytisine from various N-alkylated products. This last operation afforded a 53% yield of *dl*-cytisine, m.p. 146–147°, which was purified by sublimation, followed by recrystallization from acetone–ether. The infrared spectra of the synthetic and the natural bases, both in chloroform solution, were indistinguishable.

Resolution was accomplished by working with *d*-camphor-10-sulfonic acid as the resolving agent. Crystallization of the salt by addition of acetone to equimolar amounts of the components dissolved in methanol resulted in complete resolution, as evidenced by the identity of the isolated product, m.p. 283–285°, with the *d*-camphor-10-sulfonate of natural cytisine. Further, the base regenerated from the salt obtained in the resolution possessed a melting point, 154.5–155.5°, and rotation, $[\alpha]^{22}D$ −188.5° (water), substantially identical with those recorded for natural cytisine. The mixed melting point determination of the resolved synthetic base and the natural base (m.p. 154.5–155.5°) showed no depression, and the infrared spectra measured on samples dissolved in chloroform were identical.

Two alkaloids which have been demonstrated to be simple N-alkyl derivatives of cytisine are caulophylline (N-methylcytisine)[22] and rhombifoline (N-butenylcytisine).[21] The first has been detected in a fair number of *Leguminosae*, while the second has been isolated from only one plant, *Thermopsis rhombifolia* (Nutt). Richards; both have been obtained from natural cytisine by appropriate N-alkylation.[21,23] With the parent now accessible by total synthesis, these two substances may therefore be regarded similarly.

Synthesis of Oxygenated Tetracyclic Lupin Alkaloids.—Of the great variety of lupin alkaloids the *tetracyclic* bases are the more numerous and, therefore, more representative. The reported syn-

(20) *e.g.*, R. A. Prill and S. M. McElvain, Gilman's "Organic Syntheses," John Wiley and Sons, New York, N. Y., 1943, Coll. Vol. II, p. 419.

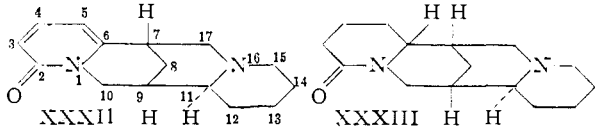
(21) W. F. Cockburn and L. Marion, *Can. J. Chem.*, **30**, 92 (1952).

(22) J. U. Lloyd, *Proc. Am. Pharm. Assoc.*, **41**, 115 (1893); F. B. Power and A. H. Salway, *J. Chem. Soc.*, **103**, 191 (1913).

(23) A. Partheil, *Ber.*, **24**, 635 (1891).

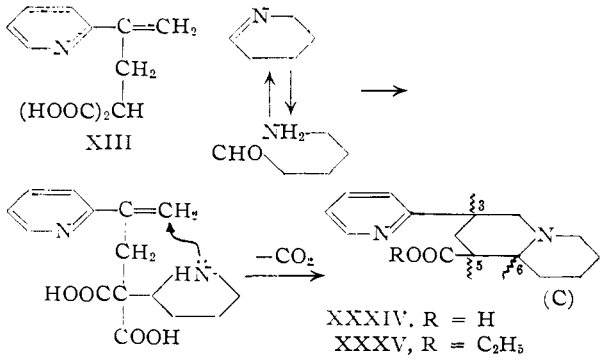
theses of the sparteine system are simple and effective; however, because of the particular symmetry properties of the oxygen-free system, synthetic techniques can be employed which are not amenable to the oxygenated class. It appeared that the first of the two cytisine approaches described above might be modified so as to allow an entry into the oxygenated tetracyclic group, and the account below is concerned with details of such attempts.

l-Anagyrine, at times referred to as monolupine, rhombinine or alkaloid III, is a distillable oil first



XXXII XXXIII

isolated by Partheil and Spasski[24] from *Anagyris foetida*, and since detected in many other lupin alkaloid sources. The efforts of Galinovsky, Ing, Clemo, Rydon and others resulted in the acceptance of structure XXXII, a ring homolog of cytisine, which substance anagyrine markedly resembles. Lupanine, appearing variously as the *d*-, *l*- or *dl*-forms, also gained the attention of numerous investigators; and clear recognition of its structural nature (XXXIII) resulted from the work of Clemo[25,26] and Ing.[27]



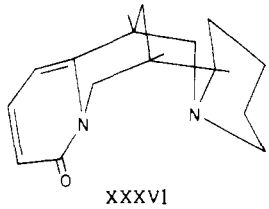
XIII XXXIV, R = H
XXXV, R = C_2H_5

Initiation of the anagyrine synthesis involves the Mannich reaction between 2-(α-pyridyl)-allylmalonic acid (XIII) and 5-aminovaleraldehyde, accompanied by cyclization to 3-(α-pyridyl)-quinolizidine-1-carboxylic acid (XXXIV) (sequence C). In practice, an aqueous alcoholic solution of the unsaturated pyridylmalonic acid and the solid trimer of Δ^1-piperidine was heated on a steam-bath; isolation of the acidic material was followed, without purification, by esterification under Fischer conditions, fractional distillation of the resulting product affording the liquid ethyl ester XXXV of the acid XXXIV. Thus, by putting to use two readily available starting materials, it was possible to assemble, in a single laboratory operation, a suitably oxidized tricyclic intermediate possessing the entire carbon–nitrogen skeleton of the tetracyclic lupin system.

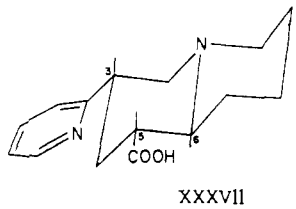
During the course of the multiple operations described above there arise three asymmetric centers.

(24) A. Partheil and L. Spasski, *Apoth. Z.*, **10**, 903 (1895).
(25) G. R. Clemo and G. C. Leitch, *J. Chem. Soc.*, 1811 (1928).
(26) G. R. Clemo, R. Raper and Ch. Tenniswood, *ibid.*, 429 (1931).
(27) H. R. Ing, *ibid.*, 504 (1933).

In addition to the obvious fact that the bridged system of anagyrine requires that the potential bridgehead hydrogens be *cis*, we note that the hydrogen at position-11 is *trans* to that at the bridgehead, as depicted by the conformational expression XXXVI.



XXXVI

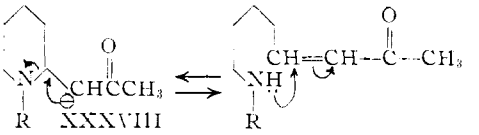


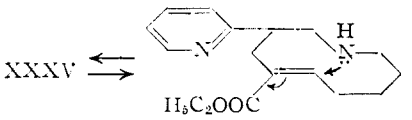
XXXVII

A noteworthy feature of the molecular system is the axial 11,12-bond, one of three axial attachments to ring C. In operating within the tetracyclic framework, production of the more stable, equatorial arrangement at C-11 (for example, conversion of sparteine to α-isosparteine[28] or the catalytic reduction of anagyrine to lupanine[27]) is commonly effected; on the other hand, generation of an axial linkage has not been realized, and therefore provision for the required stereochemistry at C-11 of anagyrine should be made before the bridged system is locked in place. The all-axial status of ring C in the bridged system corresponds to the conformationally inverted form of an all-equatorial system, and thus, in order to achieve the less stable stereochemical arrangement present in anagyrine, there is required simply the most stable, all-equatorial form XXXVII of intermediate XXXV. However, consideration of the chemical changes during which the three asymmetric centers in the tricyclic intermediate IX are created, force the conclusion that dependable stereochemical predictions are not possible. In the first place, a choice between the *erythro* and *threo* forms for the monocarboxylic acid XXXIV which results from the decarboxylation step is difficult. Secondly, as pointed out earlier, the nature of the proton transfer to the penultimate product in sequence C, the α-pyridyl anion, is uncertain. Fortunately there can be brought to use a mechanistic device which, in effect, allows equilibration of all the asymmetric centers in XXXV, and therefore ensures acquisition of the required stereochemical isomer. That treatment of the ester with anhydrous alcoholic alkoxide will effect at C-5 conversion to the anion and thus to the more stable configuration, is well precedented and requires no further comment. Whether such a process can be brought into operation at the similarly activated C-3 position is less certain—there is evidence that abstraction of a proton from an α-pyridylmethine carbon under these conditions is a relatively slow process.[29] Nevertheless, direct equilibration at a second asymmetric center seems likely. Galinovsky and co-workers[30] have demonstrated that *d*-isopelletierine or N-methyl-*d*-isopelletierine (XXXVIII), although stable in acidic media, suffers fairly

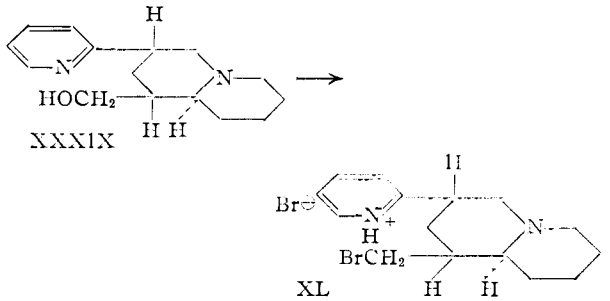
(28) K. Winterfeld and C. Rauch, *Arch. Pharmaz. Ber. dtsch. pharmaz. Ges.*, 272, 273 (1934).
(29) W. v. E. Doering and V. Z. Pasternak, THIS JOURNAL, **72**, 143 (1950).
(30) F. Galinovsky, G. Bianchetti and O. Vogl, *Monatsh.*, **84**, 1221 (1953).

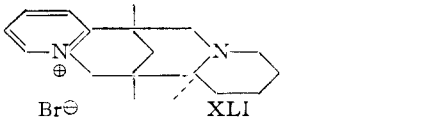
rapid racemization in weakly basic aqueous solution at room temperature or below; the change was considered as due to a β-elimination–addition process which momentarily destroys the asymmetric center. Accordingly, the action of refluxing anhydrous alcoholic base would be expected to induce in XXXV temporary elimination to a 10-membered heterocyclic ring and lead, therefore, ultimately to the required all-equatorial isomer XXXVII.[31]





In order to prepare for conversion to the tetracyclic stage, the equilibrated pyridyl ester was reduced by means of lithium aluminum hydride to the primary alcohol XXXIX, a high-boiling liquid obtained in essentially quantitative yield. Heating of the alcohol in refluxing 48% hydrobromic acid resulted in conversion to the hydrobromide XL of the corresponding bromide, which was not isolated but was used immediately for the cyclization step. The free base obtained by benzene extraction after basification of the medium used to prepare the salt was heated briefly in the extraction solvent; ring closure afforded the crystalline tetracyclic pyridinium salt XLI. The final step in the synthesis,

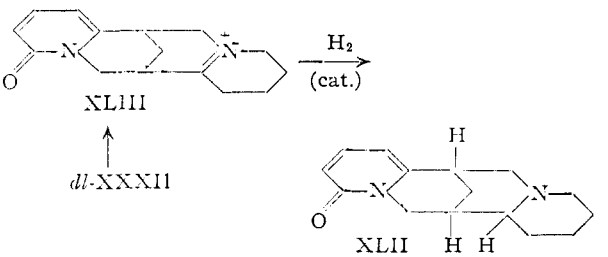




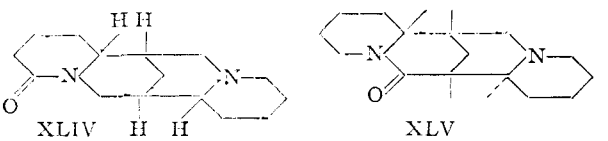
oxidation of the pyridinium to the pyridone ring, was accomplished by heating with aqueous alkaline potassium ferricyanide; the liquid product was converted to the crystalline perchlorate and purified in that state. The free base, obtained by regeneration from the highly purified salt (m.p. 315°) and then distilled, exhibited a complex infrared spectrum which was identical in every detail with that of *l*-anagyrine, the authentic liquid specimen[24] being obtained in a comparable fashion from its pure perchlorate (m.p. 315°).[32] Since we gained no evidence for the formation of diastereoisomers after the step involving equilibration of the tricyclic ester XI, we regard this total synthesis as stereoselective.

Since lupanine has been secured by catalytic reduction of anagyrine, the synthesis described above also embraces, in a formal sense, the structure of the former alkaloid.

It was apparent that by building upon the foundation of total synthesis now established certain other minor quinolizidine alkaloids should be attainable without great difficulty. One such case is represented by thermopsine. This alkaloid, isolated as the *d*-form from *Lupinus* genera and as the *l*-form from *Thermopsis* genera,[2] was demonstrated by Marion and Leonard to possess the tetracyclic pyridone structure XLII, *i.e.*, diastereoisomeric with anagyrine.[33] Partial synthesis of thermopsine had not been reported, although the conversion from anagyrine seemed feasible. Accordingly, synthetic anagyrine was treated with a hot solution of mercuric acetate in acetic acid so as to destroy by dehydrogenation the permutable asymmetric center. The intermediary product, presumably an imino salt of structure XLIII, was hydrogenated with the aid of 6% palladium-on-strontium carbonate. The reduction, which was unsatisfactory in the sense that a mixture of product and starting material resulted, led in small yield to a crystalline base which after fractional sublimation melted at 170–172°. *dl*-Thermopsine, obtained by mixing equal parts of *d*- and *l*-thermopsine from natural sources, was available and a mixed melting point with this "natural" material (m.p. 171–173°) showed no depression. In addition, the infrared spectra of the two samples in chloroform solution were indistinguishable. *dl*-Thermopsine has been obtained therefore by total synthesis.



α-Isolupanine (XLIV), occurring naturally in *Lupinus cadatus* Kellogg and *Lupinus sericeus* R. Br., has been secured by partial synthesis in two ways: (i) catalytic reduction of *l*-thermopsine and (ii) the mercuric acetate dehydrogenation, followed by catalytic reduction, of *d*-lupanine.[33] Thus this all-*cis* tetracyclic pyridone falls within the scope of the synthetic operations described above.



(31) These postulates were supported collectively by the decided shift in refractive index on subjecting analytically pure ester, obtained directly by Fischer esterification of the acid XXXIV, to the action of alcoholic sodium ethoxide and recovery of ester in nearly quantitative yield.

(32) L. Marion and S. W. Fenton, *J. Org. Chem.*, **13**, 780 (1948).

(33) L. Marion and N. J. Leonard, *Can. J. Chem.*, **29**, 355 (1951).

Since the reports of the work described above first appeared other results falling in this area have been disclosed. Bohlmann and his co-workers[34] as well as Govindachari and associates[35] have announced total syntheses of cytisine; and Clemo, Raper and Seaton[36] have completed a synthesis of lupanine. In addition, the Bohlmann group has attained the aphylline structure XLV.[37,38]

Acknowledgment.—This research was supported by grants from the Research Committee of the Graduate School, University of Wisconsin, and by the National Science Foundation (G 1240). The authors are indebted to Professor Marion, who kindly supplied samples of cytisine, anagyrine and the optical antipodes of thermopsine; to Professor Galinovsky, who generously provided cytisine; and to Mr. Thomas Katz, for technical assistance.

Experimental

All melting points are corrected; all boiling points are uncorrected. The infrared spectra were taken on a Baird infrared recording spectrophotometer (model B). All ultraviolet spectra were taken on a Cary recording spectrophotometer (model 11 MS) in 95% ethanol using a 1-cm. cell.

3-(2-Pyridyl)-1,1,3-propanetricarboxylic Acid Triethylester (XXIa).—A solution of 7.5 g. of freshly distilled methylene malonic ester[39] (44 mmol.), b.p. 209–214°, in 10 ml. of absolute ethanol was added with stirring to a solution of 14 g. (85 mmol.) of ethyl 2-pyridylacetate[40] in 10 ml. of absolute ethanol. The temperature of the mixture rose slowly to 61° and dropped. The solution was allowed to stand for 22 hours. Distillation of the solution *in vacuo* gave 9.1 g. of ethyl 3-pyridylacetate, b.p. 82–85° (0.6 mm.), and 8.4 g. of an orange liquid, b.p. 167–169° (0.2 mm.), $n^{25}D$ 1.4815, in a 94% yield, based on recovered ethyl 2-pyridylacetate.

Anal. Calcd. for $C_{17}H_{23}O_6N$: C, 60.53; H, 6.83. Found: C, 60.10; H, 6.82.

3-(2-Pyridyl)-1,1,3-propanetricarboxamide (XXIb).—One gram (2.96 mmol.) of the triester, was shaken occasionally with 45 ml. of concentrated aqueous ammonia for two days. The crystals which separated were filtered, washed with water and a few ml. of ethanol, and recrystallized from water to give 300 mg. of colorless crystals, m.p. 251–252°, yield 31%.

Anal. Calcd. for $C_{11}H_{14}O_3N_4$: C, 52.79; H, 5.64. Found: C, 52.54; H, 5.46.

2-Pyridylacetamide.—Forty-one grams of ethyl-2-pyridylacetate (0.248 mole) was mixed with 100 ml. of concentrated aqueous ammonia and was allowed to stand two days with occasional shaking. The aqueous ammonia was removed *in vacuo*, leaving a residue which crystallized on cooling. The crude material, when recrystallized from absolute ethanol, yielded 22.8 g. of colorless needles, m.p. 119–120°. Concentration and cooling of the mother liquors yielded an additional 2.3 g. of product, m.p. 118–120°. The total yield was 75%.

Anal. Calcd. for $C_7H_8ON_2$: C, 61.75; H, 5.95. Found: C, 62.06; H, 6.19.

α-Carbethoxy-γ-(2-pyridyl)-glutaramic Acid, Ethyl Ester (XXI).—To a solution of 22 g. (0.162 mole) of 2-pyridylacetamide in 150 ml. of absolute ethanol at room temperature was added with stirring 22.5 g. (0.131 mole) of freshly distilled methylene malonic ester, b.p. 209–214°. After the solution was allowed to stand for one hour it was refluxed for two hours and cooled overnight. The product which crystallized was filtered, washed with cold absolute ethanol, and dried. It weighed 26.6 g., m.p. 102–106° (66% yield). After recrystallization from absolute ethanol the product melted at 105–106°.

Anal. Calcd. for $C_{16}H_{20}O_6N_2$: C, 58.4; H, 6.56. Found: C, 58.15; H, 6.57.

α-Carbethoxy-γ-(2-pyridyl)-glutarimide (XXII).—A solution of 3.08 g. (10 mmol.) of XXI in 25 ml. of absolute ethanol was added with stirring to a solution of 230 mg. (10 mmol.) of sodium dissolved in 10 ml. of absolute ethanol. After this mixture was refluxed with stirring for 45 minutes (a salt began to precipitate after 5 minutes) and cooled, it was acidified with glacial acetic acid. The solvent was removed *in vacuo* and the residue extracted with 100 ml. of chloroform. The chloroform solution was washed with water, dried over anhydrous sodium sulfate and freed of solvent *in vacuo*. When the residue was recrystallized from ethanol, 2.3 g. of a colorless, crystalline product, m.p. 133–138°, was collected in 89% yield. Recrystallization from ethanol yielded crystals melting at 137–138°.

Anal. Calcd. for $C_{13}H_{14}O_4N_2$: C, 59.5; H, 5.39. Found: C, 59.65; H, 5.81.

The above glutarimide was also prepared directly from 2-pyridylacetamide as follows: To a solution of 25 g. (0.185 mole) of 2-pyridylacetamide in 200 ml. of absolute ethanol was added with stirring 26.6 g. (0.152 mole) of freshly distilled methylene malonic ester. After standing for 45 minutes, the solution was refluxed for 1.5 hours. Then a solution of 3.5 g. (0.152 mole) of sodium in 100 ml. of absolute ethanol was added with stirring. After refluxing the solution for 1.25 hours, it was made just acid with 12 *N* hydrochloric acid (or excess glacial acetic acid). The sodium chloride was filtered off. The filtrate, which was concentrated to 180 ml., was cooled overnight at 0°. The crystals which deposited were filtered, washed with cold ethanol, and dried. The product weighed 12.8 g., m.p. 131–138°. The mother liquors were concentrated and cooled; the combined second and third crop of crystals, m.p. 131–137°, weighed 3.8 g. Recrystallization of the combined crops from absolute ethanol gave 12.5 g. of XXII, m.p. 137–138° (30% yield).

When either XXI or XXIa was treated with concentrated aqueous ammonia for 1 hour, over a 50% yield of the triamide XXIb crystallized from the aqueous ammonia solution in very pure form, m.p. 251–252°. The mixed melting point with triamide obtained from the triester XXI gave no depression.

α-2-Pyridylglutarimide.—To 500 mg. (1.6 mmol.) of XXII was added 10 ml. of di-*n*-butyl Cellosolve, b.p. 170–200°. The mixture was refluxed for 18 hours, cooled and filtered. The solvent was removed *in vacuo*. The oily residue, which was recrystallized from chloroform–ether, yielded 150 mg. of crude crystalline material, m.p. 130–140°. Recrystallization from ethanol after treatment with Norit yielded colorless crystals, m.p. 140–142°, yield 49%.

Anal. Calcd. for $C_{10}H_{10}O_2N_2$: C, 63.1; H, 5.30. Found: C, 63.29; H, 5.59.

It was found that when XXII was refluxed with lower boiling inert solvents, *e.g.*, di-*n*-butyl ether, α-2-pyridylglutarimide was isolated, as described above, in lower yields. However, the period of reflux had to be extended up to a week. Heating XXII in water or acetic anhydride over extended periods yielded only intractable materials.

α-2-Pyridylglutarimide. By Attempted Reduction of XXII with Hydrogen Over Copper Chromite.—A solution of 5.12 g. (0.0195 mole) of XXII in 38 ml. of absolute ethanol, to

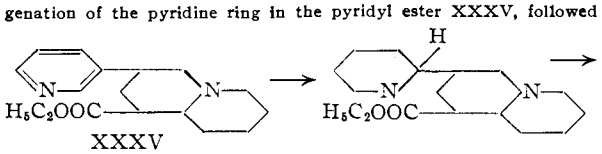
(34) F. Bohlmann, A. English, N. Ottawa, H. Sander and W. Weise, *Angew. Chem.*, **67**, 708 (1955); *Chem. Ber.*, **89**, 792 (1956).

(35) T. R. Govindachari, S. Rajadurai, M. Subramanian and B. S. Thyagarajan, *J. Chem. Soc.*, 3839 (1957).

(36) G. R. Clemo, R. Raper and J. C. Seaton, *ibid.*, 3390 (1956).

(37) F. Bohlmann, W. Weise, H. Sander, H.-G. Hanke and E. Winterfeldt, *Chem. Ber.*, **90**, 653 (1957).

(38) Our efforts to synthesize aphylline involved catalytic hydrogenation of the pyridine ring in the pyridyl ester XXXV, followed



XXXV

by ring closure to the lactam structure. The sequence produced a complex mixture from which could be separated with difficulty: (1) a substance appearing to be the C-6 epimer of aphylline (results obtained by A. Lourie in this Laboratory), and (2) a lactam which, although insufficiently studied and characterized, seemingly was identical in the infrared with a small sample of aphylline provided by Professor Galinovsky.

(39) G. B. Bachmann and H. A. Tanner, *J. Org. Chem.*, **4**, 493 (1939).

(40) R. B. Woodward and E. C. Kornfeld, *Org. Syntheses*, **29**, 44 (1949).

which 7.7 g. of copper chromite catalyst had been added, was hydrogenated in a 97-ml. steel bomb at 300 atm. of hydrogen. At temperatures above 180°, 0.039 mole of hydrogen was absorbed rapidly, and the hydrogenation essentially stopped, although the temperature was raised to 250° and kept there indefinitely. The cooled hydrogenation mixture was filtered and the catalyst washed with ethanol. The solution was concentrated and, upon cooling, 2.0 g. of crystalline product, m.p. 137–140°, deposited. The yield was 49%. Recrystallization of the crude product yielded crystals melting at 140–142°. A mixed melting point with XXII was 115–120°; a mixed melting point with material obtained previously gave no depression.

(2-Pyridyl)-thioacetamide.—A pulverized mixture of 1.36 g. (10 mmol.) of 2-pyridylacetamide, 1.11 g. (5 mmol.) of phosphorus pentasulfide and 1.11 g. (11.1 mmol.) of potassium sulfide were added to 100 ml. of toluene in a 250-ml. erlenmeyer flask. The mixture was spread out at the bottom of the flask and refluxed for two hours. The hot toluene was decanted from the melt and cooled at 0°. The product which crystallized was filtered; it weighed 320 mg., m.p. 88–92° (15–20% yield). The crude product was dissolved in hot benzene, and the solution treated with Norit, filtered, and cooled. Colorless crystals, m.p. 92°, deposited. The thioamide decomposed on standing (over a period of several weeks).

Anal. Calcd. for $C_7H_8SN_2$: C, 55.2; H, 5.28. Found: C, 55.27; H, 5.14.

(2,2-Dicarbethoxyethyl)-α-(2-pyridyl)-thioacetamide (XLVI).—To a solution of 370 mg. (2.43 mmol.) of 2-pyridylthioacetamide in 8 ml. of absolute ethanol was added 410 mg. (2.43 mmol.) of freshly distilled methylenemalonic ester. After the solution remained at 25° for 15 minutes, it was refluxed for 15 minutes and cooled to −10°. Crystallization was induced by scratching the flask. The colorless crystals which deposited were filtered, washed with a few milliliters of ethanol, and dried. The product, m.p. 122–124°, weighed 550 mg. (70% yield). Recrystallization from absolute ethanol yielded crystals, m.p. 124.5–125.5°.

Anal. Calcd. for $C_{15}H_{20}O_4N_2S$: C, 55.7; H, 6.22. Found: C, 55.47; H, 6.17.

α-Carbethoxy-γ-(2-pyridyl)-thioglutarimide (XLVII).—To a solution of 490 mg. (11 mmol.) of sodium methoxide in 10 ml. of absolute ethanol was added a hot solution of 2.95 g. (10.6 mmol.) of XLVI in absolute ethanol. The mixture was refluxed for 3 minutes and allowed to stand 10 minutes. Then 0.6 ml. of glacial acetic acid was added, and the solution was cooled. Water was added and the aqueous mixture was extracted with three 30-cc. portions of chloroform. The chloroform solution was separated, dried over anhydrous sodium sulfate and evaporated. When the residue was recrystallized from ethanol, yellow-orange crystals separated, m.p. 176–177°, and weighed 1.5 g. (58% yield). Recrystallization from ethanol yielded crystals, m.p. 177–178°. An infrared spectrum in chloroform indicated major peaks at 5.80, 5.93 and 6.16 μ.

Anal. Calcd. for $C_{13}H_{14}O_3N_2S$: C, 56.2; H, 5.07. Found: C, 56.1; H, 5.07.

3-Carbethoxy-5-(2-pyridyl)-3,4-dihydropyridone.—To a solution of 1 g. (3.62 mmol.) of XLVII in 25 ml. of absolute ethanol was added 5 g. of freshly prepared Raney nickel.[41] The mixture was refluxed with stirring for 0.5 hour, cooled, and filtered. The Raney nickel was refluxed with 15 ml. of absolute ethanol and filtered. The combined filtrates were freed of solvent, and the residue was dissolved in hot benzene. After the benzene solution was filtered, 200 mg. of greenish crystals, m.p. 200–210°, was collected and discarded. The benzene filtrate was concentrated and cooled for several hours. A colorless crystalline product, m.p. 120–124°, weighing 250 mg., deposited. Recrystallization of the crude product from ethanol–benzene gave colorless crystals, m.p. 140.5–141.5°, weighing 200 mg. (23% yield). An ultraviolet spectrum in 95% ethanol showed a λ_{max} at 307 mμ (ε 17,500). An infrared spectrum in chloroform indicated peaks at 5.80, 5.93 and 6.09 μ.

Anal. Calcd. for $C_{13}H_{14}O_3N_2$: C, 63.4; H, 5.68. Found: C, 63.66; H, 5.75.

Condensation of Sodium α-Carbethoxy-γ-(2-pyridyl)-glutarimide with Benzyl Chloride.—A solution of 14.2 g. (0.542 mole) of XXII in 75 ml. of absolute ethanol was added to a solution of 1.24 g. (0.542 mole) of sodium in 40 ml. of absolute ethanol. The mixture was refluxed for 45 minutes and a salt precipitated. The mixture was cooled and filtered rapidly. The salt was washed with 30 ml. of absolute ethanol followed by 50 ml. of absolute ether. The salt, after it was dried at 80° for 15 minutes, weighed 14.1 g. (0.05 mole, 91% yield). The salt and 6.48 g. (0.50 mole) of benzyl chloride were dissolved in 90 ml. of N,N-dimethylformamide. The solution was stirred at 105–130° for 1 hour and then steam distilled until no chloride ion could be detected in a sample of the aqueous distillate when tested with alcoholic silver nitrate solution. The aqueous mixture was transferred into a separatory funnel with 200 ml. of chloroform. The chloroform solution was washed with 20 ml. of 5% sodium bicarbonate, four 30-ml. portions of water, separated, and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*. The residue, a yellow, very viscous oil, weighed 17.4 g.

N-Benzyl-α-(2-pyridyl)-γ-carbamidoglutaramide or N-Benzyl-α-carbamido-γ-(2-pyridyl)-glutaramide.—To 2.25 g. of the viscous oil obtained in the preceding experiment was added 100 ml. of concentrated aqueous ammonia and enough methanol to give a clear solution. The mixture was allowed to stand for 4 days. The solvent was removed *in vacuo*, and the residue recrystallized from 8 ml. of absolute ethanol. Four crops of crystals, all melting at 207–209° and weighing 500 mg., were recovered. Recrystallization from absolute ethanol yielded colorless crystals, m.p. 216–219°. An infrared spectrum in a Nujol mull indicated peaks at 3.04, 3.26, 5.92 and 6.07 μ.

Anal. Calcd. for $C_{18}H_{20}O_3N_4$: C, 63.5; H, 5.92. Found: C, 63.41; H, 5.92.

N-Benzyl-3-hydroxymethyl-5-(2-pyridyl)-piperidine (XVIII).—To a slurry of 2.0 g. (0.053 mole) of lithium aluminum hydride in 200 ml. of absolute ether, was added over one hour a solution of 6.1 g. of the viscous oil (obtained in the alkylation of the glutarimide XXII, with benzyl chloride) in 100 ml. of absolute ether. The reaction mixture was refluxed with stirring for an additional two days. It was decomposed by adding dropwise 1.5 ml. of water, 2 ml. of 20% sodium hydroxide and 7 ml. of water with vigorous stirring. The ether solution was filtered and the collected alumina washed twice with refluxing ether. The ether fractions were combined and the ether removed. The residue, on standing for one day, crystallized partially. The semicrystalline mixture was triturated with ether, filtered, and the precipitate washed with ether–petroleum ether. Concentration and cooling of the filtrate yielded an additional amount of product to give a total amount of 930 mg. of dialkylation product, m.p. 146–147° (14% yield).

Anal. Calcd. for $C_{25}H_{28}ON_2$: C, 80.60; H, 7.54; N, 7.53. Found: C, 80.52; H, 7.51; N, 7.69.

The residue from the above crystallization yielded 4.80 g. of a very viscous oil. One gram of the viscous oil on distillation *in vacuo* yielded 0.80 g. of a light yellow, viscous liquid, b.p. 190–199° (0.1 mm.). The distillate crystallized partially. The crystalline solid was separated by dissolving the partially crystalline oil in a minimum amount of ether and centrifuging. The supernatant ether solution was separated and distilled *in vacuo* to give 300 mg. of a straw-colored, viscous oil, b.p. 196–197° (0.1 mm.), whose infrared spectrum in chloroform solution was indistinguishable from that of N-benzyl-3-hydroxymethyl-5-(2-pyridyl)-piperidine prepared by an alternate route. The over-all yield of this amino alcohol from sodium α-carbethoxy-γ-(2-pyridyl)-glutarimide was 29%. When the 300 mg. of the amino alcohol was refluxed with 48% hydrobromic acid according to the procedure below, 25 mg. of a colorless, crystalline solid, m.p. 170.5–171.5°, was isolated. A mixed melting point with authentic XXVI gave no depression.

N-Benzyl-2-pyridylacetamide.—To 20.8 g. (0.126 mole) of ethyl 2-pyridylacetate was added 19.3 g. of benzylamine. The mixture was kept at 175° for 5 hours and then distilled *in vacuo* until the temperature of the distillate reached 116° at 0.3 mm. On cooling, the residue crystallized. The crude product was dissolved in ether–petroleum ether (b.p. 60–69°) and treated with Norit. When the solution was filtered and cooled, 8.2 g. of colorless needles, m.p. 75–77° (28% yield), were collected. Recrystallization from ether–petroleum ether raised the melting point to 76.5–77.5°.

Anal. Calcd. for $C_{14}H_{14}ON_2$: C, 74.3; H, 6.23. Found: C, 74.15; H, 5.89.

(41) H. Adkins and A. A. Pavlic, THIS JOURNAL, **68**, 1471 (1946).

α-Carboxy-α-(N-benzylaminomethyl)-γ-(2-pyridyl)-butyric Acid (VII).—To a solution of 1.8 g. (8.63 mmol.) of VI and 0.92 g. (8.6 mmol.) of benzylamine in 66% aqueous ethanol was added 1.75 g. (20.1 mmol.) of 37% aqueous formaldehyde solution. The mixture was warmed on a steam-bath and after several minutes crystals precipitated. The precipitate was filtered, washed with cold ethanol, and dried at 70°. The product weighed 2.15 g. (76% yield) and decomposed at 138° with evolution of a gas. For the preparation of an analytical sample, the product was merely washed with ethanol and dried at 70° (0.1 mm.).

Anal. Calcd. for $C_{18}H_{20}O_4N_2$: C, 65.86; H, 6.11. Found: C, 65.6; H, 6.13.

α-(N-Benzylaminomethyl)-γ-(2-pyridyl)-butyric Acid (VIII).—When 450 mg. (1.37 mmol.) of VII was pyrolyzed at 160° until evolution of gas was complete, and benzene was added to the melt, a colorless product weighing 100 mg. (25% yield), m.p. 175–185°, crystallized. Recrystallization from benzene–ethanol raised the melting point to 183–184°.

Anal. Calcd. for $C_{17}H_{20}O_2N_2$: C, 71.80; H, 7.09; N, 9.94. Found: C, 71.41; H, 7.34; N, 9.94.

The decarboxylated acid VIII also could be prepared directly by the following procedure. To a solution of 2.5 g. (11.2 mmol.) of VI and 1.6 g. (11.2 mmol.) of benzylamine hydrochloride, m.p. 256°, in 50 ml. of water was added 1.22 g. (15 mmol.) of 37% aqueous formaldehyde. During the first few minutes of heating on a steam-bath, a crystalline precipitate appeared and dissolved on further heating. The heating was continued overnight, and then 1.12 g. of solid potassium bicarbonate was added gradually with stirring to the warm solution. On cooling, the product crystallized, was filtered, washed with cold water, and dried. The yield was 2.05 g. (72%), m.p. 183–184°. A mixed melting point with VIII gave no depression.

Ethyl α-(N-Benzylaminomethyl)-γ-(2-pyridyl)-butyrate.—Twenty-seven and two-tenths grams (0.96 mole) of VIII was dissolved in one liter of absolute ethanol saturated with anhydrous hydrogen chloride. After allowing the solution to stand for 2 days, the solvent was removed *in vacuo*. The residue was dissolved in 100 ml. of water, and the aqueous solution was made strongly basic to litmus with 3 *N* sodium hydroxide. The turbid mixture was extracted with three 100-ml. portions of chloroform. The combined extracts were dried over anhydrous sodium sulfate, the chloroform was removed *in vacuo* and the residual oil distilled. The ester distilled at 150–160° (0.1 mm.), $n^{25}D$ 1.5362, and weighed 26.3 g. (85% yield).

Anal. Calcd. for $C_{19}H_{24}O_2N_2$: C, 73.04; H, 7.74. Found: C, 72.75; H, 7.41.

3-(N-Benzylaminomethyl)-1,2,3,4-tetrahydroquinolizinium Bromide Hydrobromide (XII).—A solution of 26.3 g. (0.0843 mole) of the ethyl ester of VIII in 150 ml. of absolute ether was added dropwise with stirring to a slurry of 3.2 g. (0.084 mole) of lithium aluminum hydride in 200 ml. of absolute ether. The reduction mixture was decomposed, with vigorous stirring, by careful addition of 2.5 ml. of water, 3.4 ml. of 20% sodium hydroxide and 11.8 ml. of water. The granular alumina was filtered and washed thoroughly with refluxing ether. The ether filtrates were combined and the solvent removed completely *in vacuo;* the crude amino alcohol, 22 g. (100% yield), remained. This was dissolved in a mixture of 90 g. of 48% hydrobromic acid and 30 g. of concentrated sulfuric acid and the resulting solution refluxed for 3 hours. The hydrobromic acid was removed *in vacuo* and the residue dissolved in about 7.5 ml. of water. The aqueous solution was cooled to 5° and poured into a separatory funnel together with 150 ml. of benzene. Then 4 *N* sodium hydroxide was added until the solution was basic to phenolphthalein. During the addition of base the solution was kept cold by the addition of small amounts of ice. When the neutral point was being reached, an oil was precipitated which was immediately extracted into benzene by shaking. After the solution was basic to phenolphthalein, the initial benzene layer was separated and the aqueous layer extracted with three 75-ml. portions of benzene. The cold benzene extracts were shaken with anhydrous sodium sulfate for 3 minutes, after which the benzene was decanted and refluxed for 1 hour. Then the benzene was decanted from the oil which deposited during reflux, and the oil was dissolved in 40 ml. of absolute ethanol. To this solution 13 g. of 48% hydrobromic acid was added, and when the solution was cooled to 0°, a crystalline solid separated. The product was filtered, washed with cold absolute ethanol, and dried. The product weighed 17.7 g., m.p. 228–230°. An additional 3.7 g. of product was collected by concentrating and cooling the mother liquors. The total yield of product based on the ester was 65%. An analytical sample prepared by recrystallization of the crude product from absolute ethanol melted at 229–230°. An ultraviolet spectrum in 95% ethanol indicated a λ_{max} at 267 mμ (ε 6100). An infrared spectrum in a Nujol mull indicated peaks at 6.15 and 6.34 μ.

Anal. Calcd. for $C_{17}H_{22}N_2Br_2$: C, 49.30; H, 5.36. Found: C, 49.56; H, 5.35.

Debenzylation and Conversion to 3-Aminomethyl-1,2,3,4-tetrahydroquinolizinium Bromide Hydrobromide.—A solution of 6.48 g. (0.020 mole) of the ethyl ester of VIII in 30 ml. of absolute ethanol was shaken at 23° in a steel bomb with 2 g. of 10% palladium-on-charcoal at 245 lb. of hydrogen. After the absorption of the required amount of hydrogen (about 20 hours), the hydrogenation mixture was filtered, freed of solvent, and distilled *in vacuo*. The table summarizes the data on the distillation.

Fraction	B.p., °C. (0.4 mm.)	Wt., g.	$n^{25}D$	Infrared spectra of liquid film
1	115–125	0.4	1.4921	No benzyl group
2	125–142	2.0	1.5008	No benzyl group
3	140–142	0.4	1.5075	No benzyl group
4	142–144	.4	1.5108	Small amt. of benzyl present
5	144–200	.8	1.5238	Benzyl group present

Fractions 1, 2 and 3 obtained above were dissolved in absolute ether and the solution added over 1 hour to a slurry of 0.76 g. of lithium aluminum hydride in 100 ml. of absolute ether. The mixture was refluxed for an additional 0.5 hour and decomposed as outlined in other reductions. The alumina was filtered, washed with warm ether, and the ether filtrates distilled to leave the crude amino alcohol. The table summarizes the data obtained on the distillation of the crude amino alcohol.

Fraction	B.p., °C. (0.4 mm.)	Wt., g.	$n^{25}D$	Infrared spectrum of liquid film
1	130–140	0.15	1.5165	
2	140–158	.63	1.5259	Indistinguishable; no peaks
3	158–165	.50	1.5359	characteristic of benzyl
4	162–165	.10	1.5371	or carbonyl group

To fractions 3 and 4 of the debenzylated amino alcohol was added a mixture of 2 ml. of 48% hydrobromic acid and 1 ml. of concentrated sulfuric acid. The resulting solution was refluxed for 3 hours and worked up according to the procedure outlined for the conversion of XVIII. In this manner 350 mg. of colorless, crystalline material, m.p. 257–258°, was isolated. The over-all yield was 5.4%; ultraviolet spectrum: λ_{max} 268 mμ; infrared spectrum in Nujol mull: peaks at 6.15 and 6.32 μ.

Anal. Calcd. for $C_{10}H_{16}N_2Br_2$: C, 37.0; H, 4.94 Found: C, 36.70; H, 5.05.

Diethyl 2-(2-Pyridyl)-allylmalonate.—To a slurry of 10.5 g. (0.438 mole) of sodium hydride in a solution of 50 ml. of benzene and 50 ml. of dimethylformamide was added over 1 hour with cooling 96 g. (0.60 mole) of malonic ester. The resulting solution was poured rapidly into a dropping funnel and added dropwise with stirring over a period of 1.5 hours to a solution of 72 g. (0.40 mole) of allyl 2-(2-pyridyl)-acetate[13] in 50 ml. of dimethylformamide and 25 ml. of benzene at reflux. The usual precautions for protecting the reaction from moisture were taken. After the mixture was refluxed for an additional 1.75 hours and cooled, 35 ml. of glacial acetic acid was added dropwise and carefully with stirring. The mixture was then poured into 300 g. of ice and 85 ml. of concentrated hydrochloric acid. The aqueous mixture was extracted with 150 ml. of benzene, the benzene layer separated and extracted once with 60 ml. of 3 *N* hydrochloric acid. The aqueous acid layers were combined, made basic with 135 ml. of 10 *N* sodium hydroxide, and extracted

with 200-ml. and two 100-ml. portions of ether. The ether extracts were combined and dried over anhydrous sodium sulfate. When the solvent was removed *in vacuo* the residue on distillation gave 27 ml. of a forerun, b.p. 40–140° (0.7–0.5 mm.), and 57 g. (52% yield) of product, b.p. 148–160° (0.5 mm.).

2-(2-Pyridyl)-allylmalonic Acid (XIII).—To 5.0 g. (18 mmol.) of diethyl 2-(2-pyridyl)-allylmalonate was added 9.55 ml. of 4.18 *N* sodium hydroxide. The mixture was refluxed until a clear solution was obtained (about 2 hours), cooled, and extracted with 20 ml. of chloroform. With cooling the aqueous solution was neutralized with 11.42 ml. of 3.50 *N* hydrochloric acid. The water was removed completely *in vacuo*, and the residue dissolved in absolute ethanol. The precipitated sodium chloride was filtered, and the filtrate freed of solvent *in vacuo*. The residue was dissolved in absolute ethanol and benzene and filtered to remove last traces of sodium chloride. After the filtrate was freed completely of solvent *in vacuo* and 200 mg. of the residue was triturated with ether and absolute ethanol, 50 mg. of a colorless, crystalline material, m.p. 115° dec., separated. Recrystallization from absolute ethanol–ether yielded crystals, m.p. 115° (with evolution of gas).

Anal. Calcd. for $C_{11}H_{11}O_4N$: C, 59.7; H, 4.98. Found: C, 59.66; H, 4.98.

N-Benzyl-3-carbethoxy-5-(2-pyridyl)-piperidine (XIV, R = C_2H_5).—Forty-one grams (0.148 mole) of diethyl 2-(2-pyridyl)-allylmalonate was saponified with 100 ml. of 3.20 *N* sodium hydroxide (about 2.5 hours under vigorous reflux). The saponification mixture was cooled and, while the solution was kept at 0° by the addition of small amounts of ice, 128 ml. of 2.50 *N* hydrochloric acid was added. To this solution 13.6 g. (0.163 mole) of 36% aqueous formaldehyde, 15.8 g. (0.148 mole) of benzylamine and enough ethanol to make the solution clear were added. This mixture was heated on a steam-bath overnight. It was distilled at atmospheric pressure until 140 ml. of water was collected, then cooled and extracted with 75 ml. of ether. The ether extract was discarded and the aqueous solution extracted continuously for 20 hours with chloroform. The chloroform extract was freed of solvent and the residue dissolved in 1.5 liters of absolute ethanol saturated with anhydrous hydrogen chloride. After the solution was allowed to stand for two days, the solvent was removed *in vacuo*. The sirup was dissolved in 50 ml. of water and ice added. This solution was made basic with 3 *N* sodium hydroxide and the turbid mixture extracted with four 150-ml. portions of ether. The ester extracts were dried over anhydrous sodium sulfate; the ether was removed, and the residual liquid distilled to give 31.3 g. (65% yield) of a light yellow liquid, b.p. 183–185° (0.07 mm.), $n^{25}D$ 1.5510–1.5520.

Anal. Calcd. for $C_{20}H_{24}O_2N_2$: C, 74.04; H, 7.46. Found: C, 74.45; H, 7.84.

3-Carbethoxy-5-(2-pyridyl)-piperidine.—A solution of 1.86 g. (5.73 mmol.) of ester XIV in 20 ml. of absolute ethanol was shaken with 1.8 g. of 10% palladium-on-charcoal at 110 lb. of hydrogen. After the absorption of 1.06 equivalents of hydrogen (about 10 hours), the hydrogenation mixture was filtered, the catalyst washed with ethanol. The filtrate was freed of solvent and the residual liquid distilled to give 1.0 g. (75% yield) of a colorless liquid, b.p. 149–152° (0.4 mm.), $n^{25}D$ 1.5183.

Anal. Calcd. for $C_{13}H_{18}O_2N_2$: C, 66.64; H, 7.74. Found: C, 66.64; H, 8.04.

N-Benzyl-3-hydroxymethyl-5-(2-pyridyl)-piperidine (XVIII).—A solution of 31.3 g. (0.097 mole) of the ethyl ester XIV in 150 ml. of anhydrous ether was added dropwise to a slurry of 6 g. (0.158 mole) of lithium aluminum hydride in 400 ml. of anhydrous ether. The mixture was decomposed by adding dropwise with vigorous stirring 4.7 ml. of water, 6.3 ml. of 20% sodium hydroxide and 22 ml. of water. The ether solution was filtered and the collected alumina washed with 200 ml. of refluxing ether for 0.5 hour. The ether filtrates were combined and freed of solvent. The residue was distilled *in vacuo* using an air condenser to give 27.8 g. (99% yield) of a straw colored, very viscous liquid, b.p. 194–196° (0.1 mm.).

Anal. Calcd. for $C_{18}H_{22}ON_2$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.78; H, 8.24; N, 9.84.

Conversion of N-Benzyl-3-hydroxymethyl-5-(2-pyridyl)-piperidine to XXVI.—A solution of XVIII in 125 ml. of 48% hydrobromic acid was refluxed for 18 hours. The aqueous acid was removed *in vacuo* and the residue dissolved in a mixture of 50 ml. of water and 20 g. of ice. This aqueous solution was placed in a separatory funnel, and 10 ml. of 4 *N* sodium hydroxide and 100 ml. of benzene were added and shaken. The aqueous basic solution was extracted twice more with 50-ml. portions of benzene. The combined benzene extracts were dried over anhydrous sodium sulfate for 5 minutes, and the benzene decanted and refluxed for 0.5 hour. The benzene was decanted from the oil which deposited, and the oil crystallized upon cooling. The cream-colored crystalline solid was broken up, washed onto a filter funnel with benzene, washed with anhydrous ether, and dried at 110° for 15 minutes. The crystalline product weighed 1.28 g. (25% yield), m.p. 166–169°. When recrystallized from acetone, after treatment with Norit, the colorless crystals melted at 170.5–171.5°. An ultraviolet spectrum in 95% ethanol indicated a λ_{max} at 267 mμ (ε 5100). An infrared spectrum in chloroform indicated peaks at 6.15 and 6.32 μ.

Anal. Calcd. for $C_{18}H_{21}N_2Br$: C, 62.6; H, 6.29; N, 8.23. Found: C, 62.80; H, 6.15; N, 8.12.

Epimerization of Ethyl Ester XIV.—To a solution of 370 mg. (16.4 mmol.) in 40 ml. of absolute ethanol was added a solution of 5.00 g. of ester, $n^{25}D$ 1.5510–1.5520, obtained previously. The mixture was refluxed for 1 hour and acidified with glacial acetic acid. The ethanol was removed *in vacuo* and the residue dissolved in ether. The ether solution was washed with aqueous sodium carbonate, water and dried over anhydrous sodium sulfate. The ether was removed and the residue distilled to give 4.22 g. (85% yield) of a light yellow liquid, b.p. 193–194° (0.3 mm.), $n^{25}D$ 1.5509–1.5518.

Reduction of Epimerized Ester with Lithium Aluminum Hydride and Conversion of the Product to XXVI.—When 4.07 g. (12.5 mmol.) of epimerized ester was reduced with 0.94 g. of lithium aluminum hydride in ether according to the previously outlined procedure, 3.49 g. (99% yield) of the amino alcohol XVIII was recovered. When this amino alcohol was refluxed with 48% hydrobromic acid for 18 hours and worked up exactly according to the procedure for the identical conversion described above, 2.37 g. (56% yield) of XXVI, m.p. 167–169°, was recovered.

***dl*-N-Benzylcytisine (XXVII).**—To a solution of 1 g. (2.9 mmol.) of XXVI in 50 ml. of water was added 8 g. of solid sodium hydroxide and 8 g. of solid potassium ferricyanide. The mixture was swirled until the solids dissolved. A yellow precipitate appeared and was dissolved by the further addition of 100 ml. of water. The solution was warmed on a steam-bath for 15 minutes, and then an additional 4 g. of sodium hydroxide and 4 g. of potassium ferricyanide were added. After the mixture was heated on a steam-bath overnight and cooled, it was extracted with a 100-ml. and three 50-ml. portions of ether. The ether extracts were dried over anhydrous sodium sulfate; the ether was evaporated, and the residue upon scratching crystallized to give 300 mg. of product, m.p. 128–136°. Recrystallization of the crude product from ether–petroleum ether (b.p. 60–68°) gave 186 mg. (22% yield) of colorless crystals, m.p. 137.5–139°. The infrared spectra in chloroform and carbon disulfide solution of the product and N-benzylcytisine obtained by the alkylation of the natural base were indistinguishable.

Anal. Calcd. for $C_{18}H_{20}ON_2$: C, 77.11; H, 7.19. Found: C, 77.16; H, 7.22.

N-Benzylcytisine.—To a solution of 300 mg. (1.58 mmol.) of cytisine in 25 ml. of acetone (previously dried over anhydrous potassium carbonate) was added 400 mg. of potassium carbonate. To this mixture at reflux, a solution of 207 mg. (1.64 mmol.) of benzyl chloride in 25 ml. of acetone was added with stirring over a period of 1 hour. After the mixture was refluxed with stirring for an additional 1.5 days, it was filtered and solvent distilled off. The crystalline residue was extracted with two 25-ml. portions of hot ether, the ether was evaporated, and the residue recrystallized from petroleum ether (b.p. 60–68°)–ether to yield 222 mg. (50% yield) of colorless crystals, m.p. 142–144°.

Anal. Calcd. for $C_{18}H_{20}ON_2$: C, 77.11; H, 7.19. Found: C, 77.23; H, 7.39.

***dl*-Cytisine.**—Two hundred and eighty milligrams (1 mmol.) of *dl*-N-benzylcytisine was placed in a 50-ml. round-

bottomed flask along with 790 mg. of phenol as solvent and heated on a steam-bath to give a homogeneous solution. After cooling, 6.8 ml. of freshly distilled constant boiling hydriodic acid was added followed by 110 mg. of ammonium iodide and 13 drops of 5% auric chloride solution. A stream of nitrogen was passed through and the temperature slowly raised to 150° and held there for 0.5 hour to drive off the excess hydriodic acid and phenol. The temperature then was raised rather quickly to 225° and held there for 5 minutes to decompose the hydriodide. After cooling, the solid residue was thoroughly triturated with hot dilute hydrochloric acid and ether. Almost the entire residue dissolved by this treatment. The aqueous acid layer was separated and washed with ether. The combined ether extracts were washed once with dilute hydrochloric acid, and the combined aqueous acid extracts made strongly alkaline with 3 *N* sodium hydroxide. The basic solution was extracted with four 50-ml. portions of methylene chloride, which were combined, dried over anhydrous potassium carbonate, and freed of solvent. The residue was sublimed at 0.1 mm. to give 105 mg. of crystalline material, m.p. 133–147°. Recrystallization from acetone–ether yielded 100 mg. (53% yield) of *dl*-cytisine, m.p. 146–147°. The infrared spectra of the synthetic and natural base in chloroform solution were indistinguishable.

Anal. Calcd. for $C_{11}H_{14}ON_2$: C, 69.5; H, 7.37. Found: C, 69.53; H, 7.46.

Cytisine *d*-Camphor-10-sulfonate.—To a mixture of 46.4 mg. (0.2 mmol.) of *d*-camphor-10-sulfonic acid and 38 mg. (0.20 mmol.) of cytisine in a 15-ml. centrifuge tube was added the minimum amount of methanol to give a solution. This solution was diluted with 3 ml. of acetone, cooled, and the tube scratched. The crystalline product which separated was recrystallized from methanol–acetone to give 64 mg. (76% yield) of colorless needles, $[\alpha]^{22}D$ −43.8° (ethyl alcohol), m.p. 283–285°, softening at 175–180°.

Anal. Calcd for $C_{21}H_{30}O_5N_2S$: C, 59.7; H, 7.12. Found: C, 59.44; H, 7.22.

Resolution of *dl*-Cytisine.—To 18.8 mg. (0.1 mmol.) of *dl*-cytisine and 23 mg. (0.1 mmol.) of *d*-camphor-10-sulfonic acid in a 5-ml. centrifuge tube was added 0.2 ml. of methanol. After the mixture was completely dissolved, 2 ml. of acetone was added, and the solution was seeded with a crystal of previously obtained authentic cytisine *d*-camphor-10-sulfonate. Upon cooling the solution for 1.5 days, the crystals which deposited were centrifuged, washed twice with acetone, and dried. The colorless needles, m.p. 283–285°, $[\alpha]^{22}D$ −44.2° (ethyl alcohol), weighed 8 mg. (40% yield). A mixed melting point with cytisine *d*-camphor-10-sulfonate obtained from the natural base gave no depression. The infrared spectra of the synthetic and authentic cytisine *d*-camphor-10-sulfonates in a Nujol mull were identical.

The salt was dissolved in dilute aqueous base, and the solution extracted thrice with 20-ml. portions of methylene chloride. The organic layer was separated and dried over anhydrous potassium carbonate. When the solvent was removed and the residue sublimed at 0.1 mm., 2 mg. of colorless crystals, m.p. 154.5–155.5°, $[\alpha]^{22}D$ −118.5° (water), was obtained. A mixed melting point with *dl*-cytisine was 138–144°. A mixed melting point with cytisine obtained from natural sources, m.p. 154.5–155.5°, was 154.5–155.5°.

3-(2-Pyridyl)-5-carboethoxyquinolizidine (XXXIV).—Twenty-seven and seven-tenths grams (0.1 mole) of allyl-2-(2-pyridyl)-malonic ester was saponified with 59.12 ml. of 3.75 *N* sodium hydroxide for 2.33 hours at vigorous reflux (all of the insoluble ester should be completely dissolved after about 2.0 hours). Then the saponification mixture was cooled to 0° and acidified with 59.12 ml. of 3.75 *N* hydrochloric acid at 0°. To this aqueous solution was added a solution of 9.13 g. (0.11 mole) of α-tripiperideine, m.p. 55–61°,[42] in 125 ml. of 95% ethanol. The mixture was then heated on a steam-bath for 24 hours, cooled, and extracted with three 50-ml. portions of chloroform in order to remove the excess α-tripiperidineine.[43] The aqueous solution was freed completely of solvent *in vacuo* and the residue leached with hot absolute ethanol. The ethanolic solution was filtered from the sodium chloride and solvent distilled *in vacuo*. The sirupy residue was dissolved in 1 liter of absolute ethanol which had been saturated with dry hydrogen chloride, and the solution allowed to stand two days at room temperature. The solvent then was removed *in vacuo* and the residue dissolved in 75 ml. of water and 25 g. of ice. The aqueous solution was made strongly basic with 4 *N* sodium hydroxide and extracted with five 50-ml. portions of chloroform. The chloroform solution was dried over anhydrous sodium sulfate, freed of solvent *in vacuo*, and the residue distilled at 0.1 mm. The data on the distillation are

Fraction	B.p., °C., (0.4 mm.)	Weight, g.	$n^{25}D$	λ_{max}, ethanol, mμ
1	80–115	1.10	1.5103	.....
2	115–145	0.95	1.5163	234, 261, 271
3	145–155	0.50	1.5181	234, 261
4	155–159	1.09	1.5202	234, 261
5	159–161	1.17	1.5225	... 261
6	161–166	1.40	1.5242	... 261
7	166–167	1.49	1.5268	... 261
8	166–167	1.75	1.5284	... 261

Fractions 4–8 were combined to give 6.90 g. of product (24%).

Anal. Calcd. for $C_{17}H_{24}O_2N_2$: C, 70.80; H, 8.39. Found: C, 70.77; H, 8.16.

Epimerization of 3-(2-Pyridyl)-5-carboethoxyquinolizidine.—To 0.53 g. (23.2 mmol.) of freshly cut sodium dissolved in 50 ml. of absolute ethanol was added a solution of 6.68 g. (23.2 mmol.) of 3-(2-pyridyl)-5-carboethoxyquinolizidine, b.p. 155–167° (0.4 mm.), in 25 ml. of absolute ethanol. The solution was refluxed for 1 hour taking the usual precautions of keeping the apparatus free from external moisture, cooled, and carefully acidified with excess glacial acetic acid. Then enough water was added to dissolve the precipitated sodium acetate, and the aqueous ethanolic solution was freed of solvent *in vacuo*. The residue was dissolved completely in a mixture of 150 ml. of ether and 50 ml. of water and placed in a separatory funnel. The aqueous portion was separated, and the ether solution washed with saturated aqueous sodium carbonate solution. The ether solution was separated, dried over anhydrous sodium sulfate, freed of solvent, and the residual oil distilled to give an almost colorless oil, b.p. 145–166° (0.4 mm.), $n^{25}D$ 1.5238–1.5255, λ_{max} only at 261 μ. The yield totaled 5.76 g. (85%).

3-(2-Pyridyl)-5-hydroxymethylquinolizidine (XXXIX).—A solution of 4.92 g. (17.1 mol.) of epimerized 3-(2-pyridyl)-5-carboethoxyquinolizidine, b.p. 145–166° (0.4 mm.), in 100 ml. of anhydrous ether was added with stirring over 15 minutes to a slurry of 0.90 g. (23.6 mmol.) of lithium aluminum hydride in 150 ml. of anhydrous ether. After the mixture was refluxed for an additional 15 min., 1.3 ml. of water, 1 ml. of 20% sodium hydroxide and 3.6 ml. of water were added successively with vigorous stirring. After the mixture was stirred for 15 min. at reflux, the alumina was allowed to settle and was filtered. The alumina was washed twice for 0.3 hr. with 100-ml. portions of refluxing methylene chloride. The combined filtrates were freed of solvent *in vacuo* and the residue distilled to give 3.93 g. (94%) of a colorless, extremely viscous liquid, b.p. 180–187° (0.3 mm.).

Anal. Calcd. for $C_{15}H_{22}ON_2$: C, 73.13; H, 9.00. Found: C, 72.62; H, 8.99.

The amino alcohol from the above hydride reduction need not be distilled after removing all the volatile solvent, but can be used directly in the next step.

Treatment of 3-(2-Pyridyl)-5-hydroxymethylquinolizidine with 48% Hydrobromic Acid and Conversion to the Tetracyclic Quaternary Salt XLI).—Four grams (16.3 mmol.) of 3-(2-pyridyl)-5-hydroxymethylquinolizidine was dissolved

(42) C. Schöpf, A. Komzak, F. Brauh and E. Jacobi, *Ann.*, **559**, 1 (1948).

(43) The reaction can be followed by taking the ultraviolet spectrum of a drop of the reaction mixture in ethanol at different times. In the beginning only the peaks at 234 and 271 μ, which are characteristic of the vinylpyridine residue, appear. As the reaction proceeds the optical density of the peak at 234 μ diminishes and the peak at 261 μ, characteristic of saturated 2-alkylpyridines, appears. At the end of the reaction the optical density of the two peaks at 234 and 261 μ are about equal.

in 75 ml. of 48% hydrobromic acid and refluxed for 20 hours. The acid solution was freed completely of solvent *in vacuo*, and the residue was dissolved in 25 cc. of water, cooled to 5°, and transferred with 50 ml. of benzene to a separatory funnel. The following steps were carried out as quickly as possible to prevent too much quaternization in aqueous solution. To the cold mixture in the separatory funnel was added 20 ml. of 3 *N* sodium hydroxide. The mixture was shaken vigorously and the benzene layer separated. The aqueous portion then was extracted with two 50-ml. portions of benzene. The benzene extracts were combined, dried over anhydrous sodium sulfate for several minutes with swirling, and the benzene solution decanted into another flask. The benzene solution was refluxed for 45 minutes during which time a crystalline solid precipitated. The mixture was filtered, and the crystalline solid was recrystallized from acetone to give 1.10 g. (21% yield) of colorless crystals, m.p. 209–215°. Recrystallization from acetone (Norit) yielded material of m.p. 214–216°. The crude material, m.p. 209–215°, can be used for the oxidation to anagyrine.

Anal. Calcd. for $C_{15}H_{21}N_2Br$: C, 58.25; H, 6.85. Found: C, 58.35; H, 7.06.

dl-Anagyrine.—To a solution of 356 mg. (1.15 mmol.) of the tetracyclic quaternary salt XLI in 2 ml. of water was added a solution of 600 mg. of sodium hydroxide and 800 mg. (2.35 mmol.) of potassium ferricyanide in 4 ml. of water. The cloudy mixture was heated on a steam-bath and diluted with water until the total volume of solution was about 8.5 ml., at which point the solution became almost clear again. The solution was heated on the steam-bath (vessel should be stoppered to prevent evaporation of solvent) for one day, cooled and extracted with five 15-ml. portions of benzene. The combined benzene extracts were dried over anhydrous sodium sulfate, freed of solvent *in vacuo*, and the residue distilled in a 10 mm. diameter glass tube (sealed at one end), by heating in an appropriate aluminum block, to give 114 mg. (41%) of *dl*-anagyrine, b.p. 170–175° (0.1 mm.) a light yellow glass at room temperature.

A freshly prepared sample, 114 mg. (0.47 mmol.), was dissolved in 5 ml. of methanol and neutralized with 4.63 ml. of 0.101 *N* perchloric acid. The solution was evaporated to dryness, and the crystalline residue recrystallized from absolute methanol to give 114 mg. (81%) of colorless, cottony needles, m.p. 315°.

Anal. Calcd. for $C_{15}H_{21}O_5N_2Cl$: C, 52.25; H, 6.14. Found: C, 52.29; H, 6.12.

A sample of *dl*-anagyrine regenerated from pure *dl*-anagyrine perchlorate was distilled for analysis to give a colorless glass, b.p. 170° (0.1 mm.). The infrared spectra in carbon disulfide solution, and ultraviolet spectra in 95% ethanol, of *dl*-anagyrine and authentic *l*-anagyrine were indistinguishable.

dl-Thermopsine.—Thirty-five mg. (0.143 mmol.) of *dl*-anagyrine (regenerated from its perchlorate) was dissolved in 5 ml. of 5% aqueous acetic acid. To the solution in a 15-ml. graduated centrifuge tube was added 365 mg. (1.14 mmol.) of mercuric acetate. After the mercuric acetate dissolved, a slow, fine stream of nitrogen was passed through the solution, and the solution was heated on a steam-bath for two hours. The volume of solvent was kept constant by the addition of 5% acetic acid. After heating, the solution was cooled to 0° and the precipitated mercurous acetate (100 mg.) was centrifuged. The aqueous solution was then saturated with hydrogen sulfide, 5 drops of concentrated hydrochloric acid and 3 drops of concentrated sulfuric acid were added to the mixture, and the mixture was heated on a steam-bath until the mercuric sulfide coagulated. Then the mercuric sulfide was centrifuged, and the clear aqueous layer was evaporated to dryness *in vacuo*. The residue was dissolved in water and the solution made basic. Since the dehydrogenation product is unstable, the basic solution was rapidly extracted with four 15-ml. portions of chloroform, which were subsequently dried over anhydrous sodium sulfate for several minutes. The chloroform solution was filtered, evaporated under a stream of nitrogen, and 10 ml. of absolute methanol was added to the residue. The methanolic solution was shaken with two 50-mg. portions of Raney nickel, filtered, and hydrogenated over 30 mg. of 6% palladium-on-strontium carbonate at 1 atmosphere of hydrogen for 5 minutes. The hydrogenation mixture was filtered, the solvent evaporated completely, and the residue (31.5 mg.) was chromatographed on a column of 400 mg. of silicic acid in chloroform (ratio of height to width of column was 3:1). The mixture was placed on the column with 5 drops of chloroform solution and eluted with 1% methanol in chloroform. A band which immediately separated with 1% methanol in chloroform was collected and the residue obtained after evaporation of solvent was sublimed at 0.1 mm. to give 6 mg. of an oil, b.p. 150–170° (1 mm.). On scratching, the oil crystallized to material melting at 155–165°. The solid was recrystallized from a very small amount of acetone–ether and resublimed to give an oily solid, m.p. 160–168°. This solid was washed in the sublimation tube with a little ether and then resublimed to give 2 mg. of *dl*-thermopsine, m.p. 170–172°. A mixed m.p. with authentic *dl*-thermopsine was 170–172°. The infrared spectra in carbon disulfide solution, and the ultraviolet spectra in 95% ethanol of synthetic and authentic samples of *dl*-thermopsine were identical.

MADISON, WISC.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF DELAWARE]

Observations on the Mechanism of Addition Reactions of Olefins; Criteria for Mechanism in Mixed Aqueous Solvents

BY HAROLD KWART AND LEWIS B. WEISFELD[1]

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The rate of racemization of optically active 3-*p*-menthene has been found to be equal to the rate of addition to the double bond in highly acidic aqueous alcoholic solutions. These results are consistent with the hydration mechanism proposed by Taft and co-workers[2] and exclude a reaction sequence in which a carbonium ion is formed in a preliminary proton equilibrium step. The addition rates are well correlated by the activity postulate and the acidity scale suggested by Grunwald and co-workers.[7,9,10] This latter observation has been interpreted to establish a reaction mechanism whereby a π-complex is formed in a primary proton equilibrium followed by a rate-determining transition to carbonium ion with the exclusion of solvent from the major transition state. The acetoxylation of 3-*p*-menthene in glacial acetic acid with trifluoroacetic acid as catalyst is found to be mechanistically analogous to the hydration–etherification reaction. Criteria are developed for kinetic analysis of lyonium ion catalyzed reactions in other than purely aqueous media.

Introduction

A series of experiments reported by Taft and co-workers[2] constitute the most recent and most informative studies on the detailed mechanism of H^+ addition reactions of common olefinic substances.

(1) E. I. du Pont de Nemours, Fellow 1955–1956.

(2) (a) R. W. Taft, Jr., THIS JOURNAL, **74**, 5372 (1952); (b) J. B. Levy, R. W. Taft, Jr., and L. P. Hammett, *ibid.*, **75**, 1253 (1953); (c) R. W. Taft, Jr., Abstracts of Papers, 125th Meeting A.C.S., Kansas City, Mo., March, 1954, p. 12P; (d) R. W. Taft, Jr., E. L. Purlee, P. Riesz and C. A. DeFasio, THIS JOURNAL, **77**, 1584 (1955); (e) P. Riesz, R. W. Taft, Jr., and R. H. Boyd, *ibid.*, **79**, 3724 (1957).