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HYPOHALITE-INDUCED OXIDATIVE DECARBOXYLATION OF α-AMINO ACIDS

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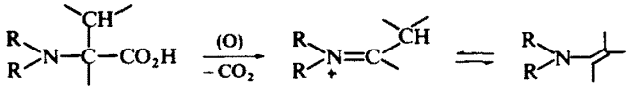
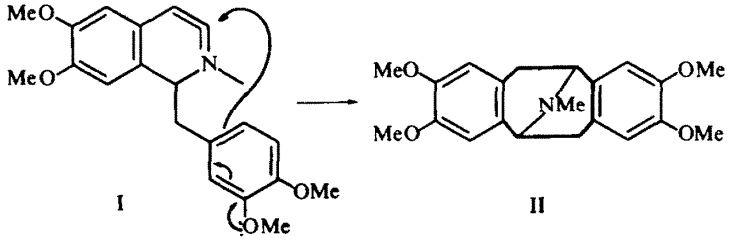
Abstract—As a model for certain *in vivo* alkaloid transformations and as a possible means for the preparation of specific enamines, the hypohalite-induced oxidative decarboxylation of various primary, secondary and tertiary α-amino acids was studied. The following reactions were observed: (1) N,N-dimethylglycine → N-chlorodimethylamine; (2) N-methyl-pipecolic acid → N-methyl-Δ^2-piperideine dimer (VIII); (3) quinolizidine-4-carboxylic acid (X) → $\Delta^{5,10}$ dehydroquinolizidine-4-carboxylic acid (IX); (4) 2-methyl-tryptophan (XVIII) → 4-acetylquinoline (XXV); (5) kynurenine (XXVI) → kynurine (XXVII); (6) 2.3,4,5-tetrahydro-β-carboline-4-carboxylic acid (XXIX, R = H) → norharman (XXXI); (7) 3-methyl-2.3,4,5-tetrahydro-β-carboline-4-carboxylic acid (XXIX, R = Me) → mono- and dichloro-3-methyliso-β-carbolines and a dichloro spiro lactam oxindole (XXXIII). The mechanisms of certain of these changes are discussed.

OXIDATIVE decarboxylation of α-amino acids is a well documented biochemical phenomenon which finds analogy in various non-enzymic chemical processes. The purpose of the present investigation was two-fold: (1) laboratory simulation of certain unusual biochemical reactions of this type, and (2) application of the reaction



to certain N,N-dialkyl α-amino acids, with a view toward selective generation of synthetically useful enamine functions in specific positions of given molecules.

Although biochemical oxidative decarboxylation of simple α-amino acids is securely established and need not concern us here, the operation of the degradation in more exotic natural product cases is less clearly defined and remains a subject for speculation and further experimentation. For example, the natural occurrence of N-methylpavine (II)[1] almost certainly requires the dihydroisoquinoline (I) as a



I II

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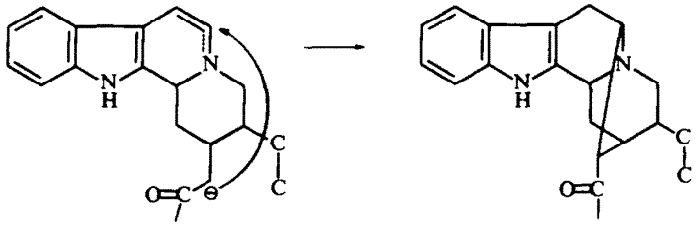
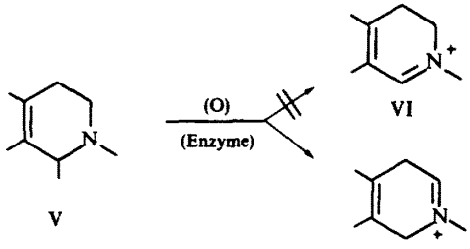
† Abstracted from the Ph.D. theses of V. B. Haarstad and R. L. Orvis, University of Wisconsin.



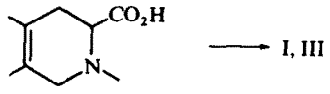
III IV

biochemical progenitor; and likewise, dihydro-β-carboline III suggests itself as an *in vivo* precursor of the sarpagine IV (and ajmaline) alkaloidal systems. Presumed



V VI I, III

intermediates I and II may derive by specific enzymatic dehydrogenation of the tetrahydroheterocyclic unit (V → I or II), in which case the *chemically* preferred oxidation to VI must be avoided. Alternatively, placement of the new imine–enamine double bond at the proper site can be achieved by less exceptional means if dependent upon oxidative decarboxylation of the corresponding α-amino acid VII, a reasonable species in a biochemical sequence. To the authors' knowledge, tracers experiments

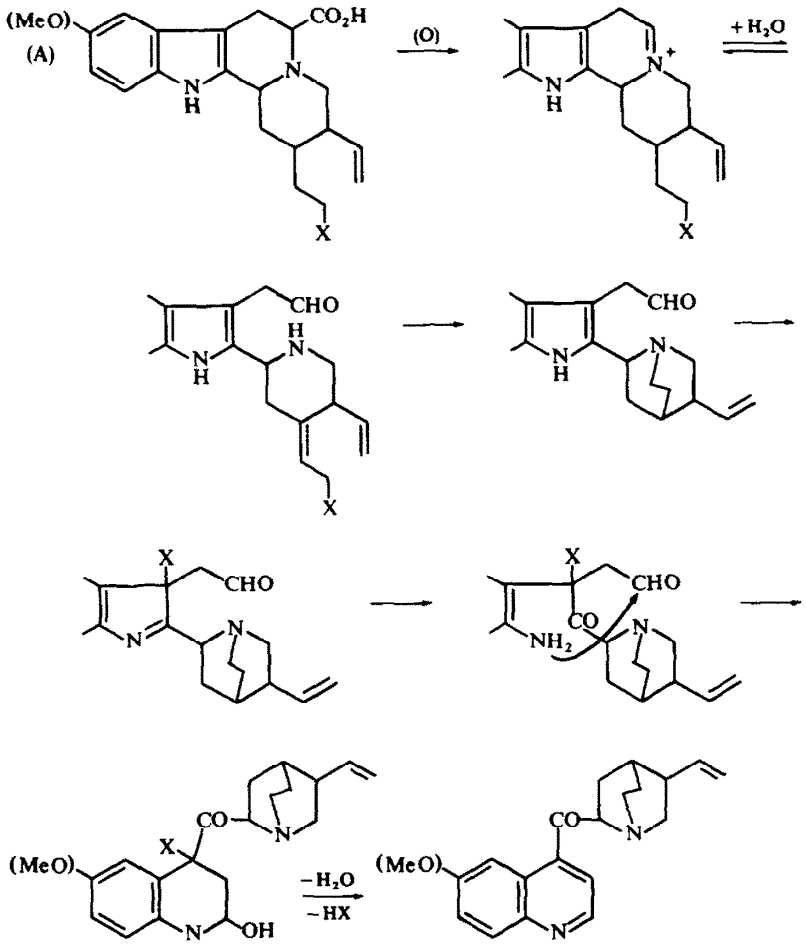


VII

have not ruled out this alternative, i.e. labelled tryptamine and 3,4-dioxygenated phenethylamine have not been tested for incorporation in the above or similar cases and found to be utilized.* In any event, an indolic amino acid of the type VII might serve as a useful intermediate in a total synthesis of the sarpagine–ajmaline type. provided that oxidative decarboxylation to the dihydro-β-carboline III could be achieved.

In a somewhat different instance, the quinine–cinchonine alkaloid system can be imagined to derive from the same type of polycyclic tetrahydro β-carboline carboxylic acid referred to above, but by a more involved oxidation pathway (A). Again, many

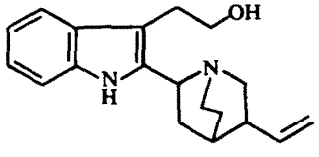
* [2-^{14}C] labelled tryptophan has been incorporated[2] but this type of result leaves open the question whether tryptamine is produced from it at an early stage and is utilized *per se*.



of the changes proposed represent reasonable organic chemical operations, and offer hope that similar reactions might be realized in the laboratory.*

Development of a practical oxidative decarboxylation in the N,N-dialkyl α-amino acid series might provide, by reason of options in placement of the carboxyl function, a new method for the preparation of specific enamines, perhaps including less thermodynamically stable cases which would be unavailable by known routes, such as mercuric acetate oxidation of t-amines or interaction of sec-amines with aldehydes or ketones. As a case in point, the hypothetical intermediate III cannot be secured

* In previous interpretations of the quinine-cinchonine biosynthesis, the presumed quinuclidine aldehyde intermediate was considered to arise by oxidation of cinchonamine (i), followed by changes reproduced in scheme (A).[3] Tracer experiments have revealed that quinine arises in nature from DL-trytophan-2-^{14}C.



(i)

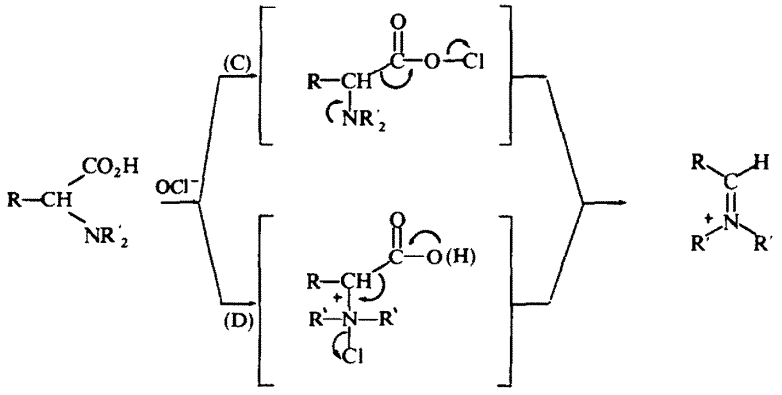
by direct laboratory oxidation of the substituted *tryptamine* V, since Δ^3-unsaturation results; however, oxidative decarboxylation of VII might lead to III.

Although various means for selective oxidative decarboxylation were considered and investigated, this publication deals only with the hypohalite method. Inorganic hypohalite had been used on various occasions for conversion of primary or secondary α-amino acids to aldehydes (B), but the degradation in the N,N-dialkyl series is

$$\text{R—CH(NH}_2\text{)—CO}_2\text{H} \quad \text{or} \quad \text{R—CH(NHR)CO}_2\text{H} \xrightarrow{\text{OCl}^-} \text{R—CHO} + \text{NH}_3 \text{ or } \text{RNH}_2 \qquad \text{(B)}$$

apparently unrecorded; in fact Gilman states[4] that "the presence of two alkyl groups on the nitrogen atom inhibits the action of hypochlorite".

In regard to mechanism, two logical courses are open, (C) and (D) below. In the present study, we have come upon no findings which permit an unambiguous choice

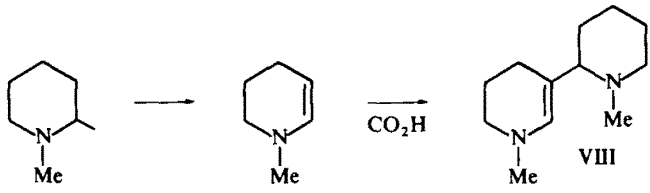


in the N,N-dialkyl series. However, results are more readily interpreted in terms of mode D; and by analogy with the primary and secondary amino cases, wherein N-chloramines are stated to be formed initially,[5] interpretation D will be used arbitrarily in the ensuing descriptions.

In the simplest case tested, one equivalent of hypochlorite was added to N,N-dimethylglycine in an acidity range of pH 1·5 to pH 6·3. Maximum decarboxylation occurred at pH 1·5 (45%) with a definite trend to a lower decarboxylation rate as the solution pH was increased. Although some dimethylamine was formed by hydrolysis of the intermediary Schiff base, rapid halogenation by unreacted hypochlorite caused its disappearance from the reaction mixture. Also, the fact that decarboxylation with one equivalent occurred only to the extent of 45% can be rationalized as a loss of the reagent in the halogenation of dimethylamine. Thus, in order to achieve complete decarboxylation, two equivalents of hypochlorite for each mole of amino acid were utilized in subsequent attempts. In the best of these cases a 96% yield of carbon dioxide was observed, and formaldehyde was found to be present in an 80% yield as determined by the method of Battersby.[6] The volatile chlorodimethylamine was isolated and its identity confirmed.

The next compound investigated was N-methylpipecolic acid, representative of a saturated cyclic α-amino acid. Many reactions were attempted using an aqueous solution of sodium hypochlorite in a pH range of 1 to 10. These investigations revealed

that maximum decarboxylation was achieved at pH 1·5 to pH 2·5, as evidenced by the optimum evolution of carbon dioxide and yield of 1,1′-dimethyl-Δ^2-tetrahydroanabasine (VIII).*† An increase in the reaction pH level (6 to 8) resulted in a sharp

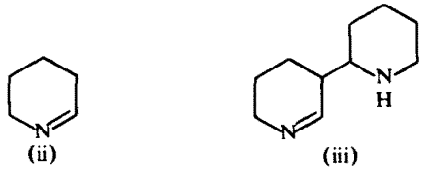


decrease of isolable product. At a lower pH the basic product exists in a protonated, iminium ion form, rendering the molecule less vulnerable to further reaction with any unreacted hypochlorite; whereas at higher pH levels further attack of the unprotonated form by the inhospitable hypochlorite reaction solution may become possible.

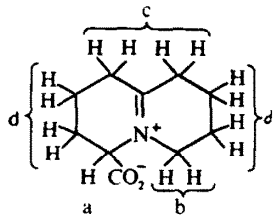
Initial attempts to decarboxylate oxidatively quinolizidine-4-carboxylic acid (prepared by the 6-step method of Maris and Hudlicky)[9] with one equivalent of hypochlorite at pH 2–9 resulted in the evolution of a negligible amount of carbon dioxide. Examination of the organic product indicated that the expected base, $\Delta^{5,10}$-dehydroquinolizidine, was not present, even in runs where the yield of carbon dioxide was increased by increasing the amounts of hypochlorite used. The aqueous reaction solution from a one equivalent attempt (pH 2) yielded a mixture of two components, one of which was identified as unreacted starting amino acid while the other was characterized as an enamine carboxylic acid, on the basis of the following evidence. The IR spectrum of the new substance exhibited bands at 5·99 and 6·18 μ. and the UV revealed absorption at 220 mμ (ε 2,345), typical of quinolizidine enamines.[10] Reduction of the enaminecarboxylic acid by catalytic means or with sodium borohydride yielded the original saturated amino acid. In D_2O, the NMR spectrum indicated that the compound had no protons in the vinyl region, and on this basis all possible structures except IX and IXa could be eliminated from further consideration. However, the spectrum did possess one proton at 5·65 τ (a), two protons at 6·3 τ (b), four protons at 7·85 τ (c) and eight protons at 8·2 τ (d). Structure IX was considered consistent with the NMR evidence, in that IXa should have displayed proton groupings at the above chemical shifts in the ratio 1 (a): 2 (b); 2 (c); 10 (d).

* It is interesting to note that the decarboxylation of N,N-dialkyl-α-amino acid-N-oxide to aldehyde, applied successfully by Sweenely and Horning[7] to the glycine case, in our hands failed to give Δ′-piperideine dimer when attempted on N-methylpipecolic acid. Material presumed to be the N-oxide of the latter gave rise to some formaldehyde and larger amounts of an unidentified, water-soluble mixture.

† B. Franck and D. Randau have reported[8] that lysine is converted by sodium hypochlorite to Δ′-



piperideine (ii) (4%), tetrahydroanabasine (iii) (4%), 2-piperidone (9%) and N-chloro-2-iminopiperidine (3%).

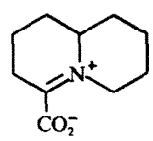


IX

NMR of Quinolizidine-4-carboxylic acid hydrobromide

τ value	No. of protons
6·21	(multiplet) 2 (a')
6·88	(multiplet) 2 (b')
8·15	(multiplet) 12

Water line visible at 5·25 τ



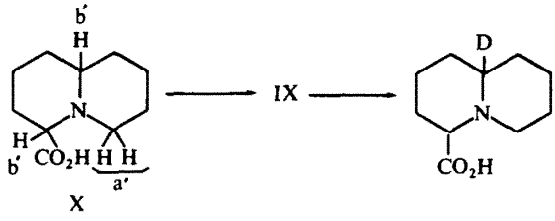
IXa

NMR of 10-Deuteroquinolizidine-4-carboxylic acid

τ value	No. of protons
6·36	(multiplet) 2 (a')
7·00	(multiplet) 1 (b')
8·15	(multiplet) 12

Water line visible at 5·30 τ

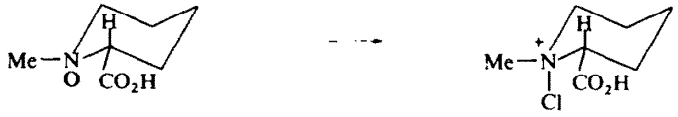
In order to interpret the NMR data, the enaminecarboxylic acid was reduced with sodium borodeuteride and the spectrum of the deuterated amino acid was then compared with that of the original quinolizidine-4-carboxylic acid. The deuterated acid lacked one proton in the 7·0 τ region which was present in the original saturated amino acid, thus permitting the assignment X.



X

The stereochemistry of the starting amino acid, quinolizidine-4-carboxylic acid, was elucidated by conversion to the methyl ester, equilibration by refluxing with sodium methoxide and then hydrolysis to the (stable) amino acid form. This treatment yielded the original amino acid in high yield, suggesting that the original synthesis[9] had yielded the product with the more stable, equatorial ester function.

Aside from representing a different mode of action of hypochlorite on an N,N-dialkylamino acid, the quinolizidine carboxylic acid case permits certain tentative conclusions regarding the oxidative decarboxylation mechanism. First of all, the conversion to iminium zwitterion IX *without* decarboxylation almost certainly depends on preliminary N-halogenation. It seems more likely, then, that attack by halogen on nitrogen (mechanism D) is also involved in cases which ultimately follow the decarboxylation course, and therefore formation of acyl hypochlorite (mechanism C) is not an integral feature of the reaction. Furthermore, because of the ready conformational inversion of nitrogen, it would appear that, if mechanism C were normally operative, all α-amino acids should eliminate *with* decarboxylation, and this is not the case. Secondly, comment may be made on the stereoelectronics of the two contrasting examples. If the N-chlorination process involved the more stable conformation of N-methylpipecolic acid, cation XI should result. However, if *trans*,



XI

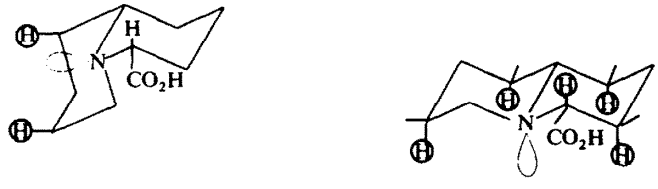
coplanar arrangement of participating substituents is needed for the decarboxylative elimination, structure XI would not serve. Assuming the above, stereoisomer XII is required; and it can best arise by equatorial attack of the halogen source on

XII

conformation XIII followed by conformational inversion of the intermediate di-equatorial product XIV. Presumably, process XIII → XIV is preferred over others

XIII XIV

because of steric considerations. In the quinolizidine carboxylic acid case, apparently the steric advantage (two axial hydrogen interactions) offered by inverted conformation XV is not sufficient to outweigh reaction of the more stable *trans* quinolizidine



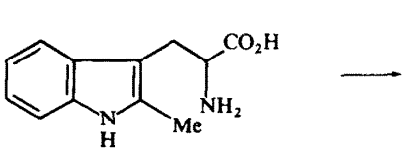
XV XVI

ring conformation (XVI) (four axial hydrogen interferences). Thus, isomer XVII is formed which, not being well set up conformationally for decarboxylation, suffers simple *trans* elimination by removal of adjacent proton, apparently that one at C-10.*

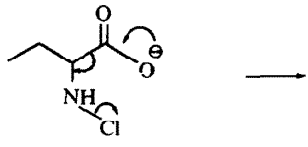
* Although presented as a *direct* elimination to a product by loss of 10-hydrogen, formation of IX could be imagined to involve initial conversion to IXa, followed by isomerization to observed final product.

XVII

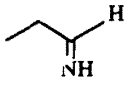
In connection with the previously described scheme for the biochemical conversion of the indole alkaloid to the quinine alkaloid system, consideration was given to the possibility of achieving the laboratory conversion of a representative 3-indolyl acetaldehyde to a 4-acylquinoline, by means of steps which would parallel the cited changes (sequence A). Inspection of the literature revealed that a simple case, 2-methyl-3-indolylacetaldehyde (XXI), might be prepared by controlled oxidation of 2-methyl tryptophan (XVIII) with sodium hypochlorite, presumably by way of operation XVIII → XIX → XX → XXI. This method brought to mind the possibility of carrying out with this same reagent, not only conversion XVIII → → XXI, but the sequence XXI → → XXV as well, the sought-for parallel to the biosynthetic speculation. Accordingly, 2-methyltryptophan was warmed (50°) for a short time



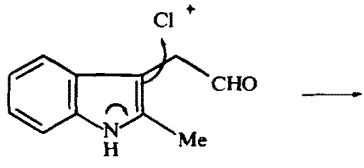
XVIII



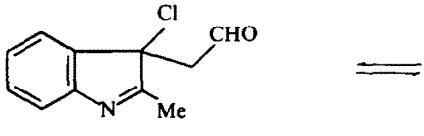
XIX



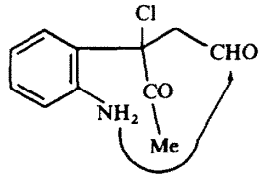
XX



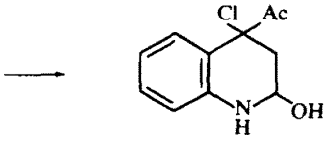
XXI



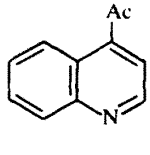
XXII



XXIII



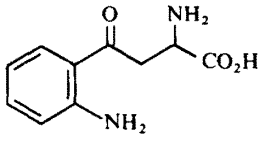
XXIV



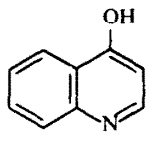
XXV

with *two* equivalents of alkaline hypochlorite, under which conditions 4-acetylquinoline (XXV) was produced in approximately 20% yield. This over-all transformation must proceed through the individual stages just suggested (or by means of very similar processes) and must then involve at least seven distinct, consecutive chemical steps.*†

Another, better known example of tryptophan metabolism is conversion to kynurenine (XXVI) and thence to kynurine (4-quinolinol, XXVII).[14] Of the various



XXVI



XXVII

imaginable pathways from kynurenine to the quinoline, that featuring the formyl ketone is most closely related to the type of chemical change under discussion. Despite the unstable character of the intermediate type XXVIII apparently involved,

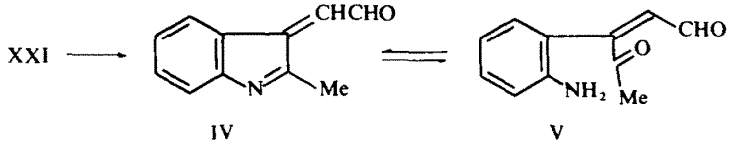
XXVIII

sodium hypohalite does effect direct conversion of the amino acid XXVI to 4-quinolinol. On the basis of spectral observations, no kynurenic acid (4-hydroxyquinolinic acid) was formed in the process.

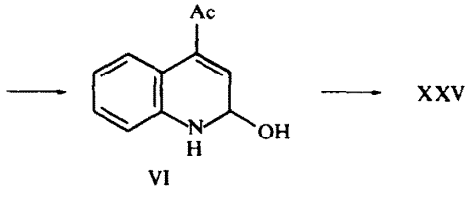
Within the tetrahydro-β-carboline category, both the secondary XXIX (R = H) and the tertiary XXIX (R = Me) amino acids were subjected to the action of alkaline

* The 2-methyltryptophan → 4-acetylquinoline conversion was first reported by van Tamelen and Haarstad[12]

† Certain alternative possibilities (e.g., the change XXI → IV → V → VI → XXV) are equally reasonable and have not been excluded experimentally.

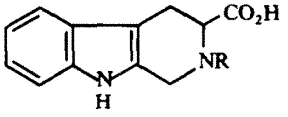


IV V

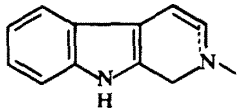


VI

hypochlorite. In neither instance, and under no conditions investigated, could there be isolated the simple oxidative decarboxylation product, the dihydro-β-carboline XXX; although it seems likely that in all cases, the enamine may have been formed as

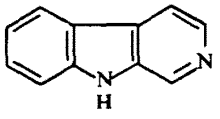


XXIX

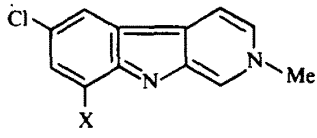


XXX

an unstable, easily oxidized intermediate. The secondary amino acid merely generated in poor yield norharman XXXI, probably arising by facile halogenation-elimination of dihydro-β-carboline. Likewise, the N-Me variant was prone to over-oxidation.



XXXI

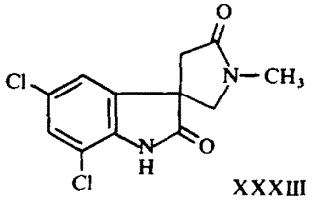


XXXII

and the action of hypohalite was complex. When a large excess (10 equivalents) of reagent was employed, a 70% yield of carbon dioxide was observed. A mixture of basic nitrogenous products was recovered; and by application of TLC on alumina, the product was purified and fractionated into three main products. Two of these fractions were yellow (R_f 0·25 and R_f 0·65), both exhibiting IR and UV spectra which were very similar to those of 3-methylnorharman. An elemental analysis of a picrate indicated that this product with the lower R_f value was a monochloro-3-methylnorharman. The NMR spectrum of the compound had three protons at 5·87 τ (N-Me) and a group of approximately 6 aromatic protons at 2·44 τ, which finding lent additional weight to the monochloro assignment. Similarly, the second yellow compound was characterized as a dichloro-3-methylnorharman by an elemental analysis, infrared, ultraviolet and NMR spectra. Hydrogenolysis of the monochloro- and dichloro-3-methylnorharmans with 30% palladium-on-carbon in each case yielded 3-methylnorharman.

By analogy with other examples of electrophilic substitution, halogenation presumably occurs first in the 5-position and is followed by additional attack at the 7-position. On this basis, the structures for the chlorinated norharman products have been tentatively assigned as XXXII (X = H) and XXXII (X = Cl); however, no additional experiments were performed to confirm the assignment.

The third, colorless product isolated from the ten equivalent reaction has been assigned the dichlorodilactam structure XXXIII based upon the following evidence.

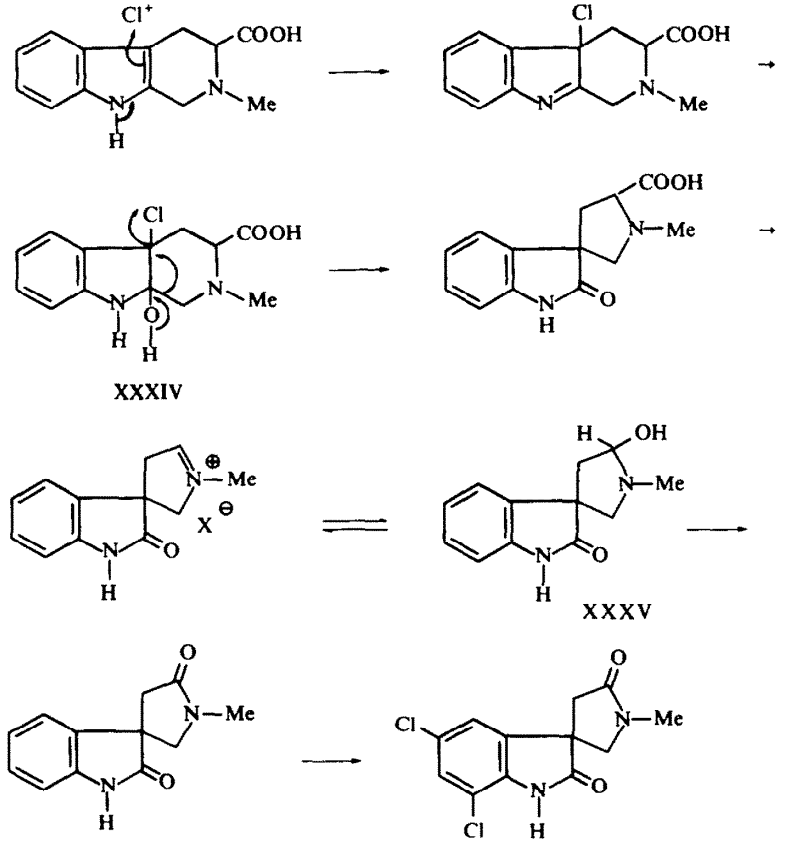


XXXIII

An elemental analysis was consistent with the assigned molecular formula of $C_{12}H_{10}N_2Cl_2O_2$, and the infrared spectrum had peaks at 5·77 μ (oxindole) and 5·90 μ (5-membered lactam). Absorption at 257 mμ in the UV was also consistent with the absorption reported for other spiro-oxindoles. Furthermore, the NMR spectrum was in agreement with the spiro-oxindole structure. Two distinctive AB quartets, one at 6·77 τ, 6·34 τ of J_{AB} 10 c/s and another at 7·61 τ, 7·11 τ with J_{AB} 17 c/s were indicative of two methylene groups which were rigidly held in the conformation of the spiro arrangement. Three additional protons in a singlet at 7·16 (N-Me) and three other protons in a multiplet (aromatic and oxindole N-H) were also observed in the NMR spectrum.

A mechanistic pathway for the formation of the oxindole-lactam can be formulated in terms of the following sequence (E). Attack by chloronium ion at the β-position of the indole moiety can be presumed to occur in addition to the anticipated halogenation, β-elimination and decarboxylation of the amino acid function. A hydrated form XXXIV of the imine can undergo a 1,2-shift with expulsion of chloride ion to yield the spiro system. The proposed mechanistic sequence also involves oxidation of the hydrated enamine XXXV to a lactam system; chlorination in the aromatic nucleus completes formation of the lactam-oxindole XXXIII. The exact sequence of steps as outlined above is merely a proposed stepwise transformation, and the actual sequence of events could be different.

(E)



XXXIV

XXXV

With one equivalent of hypochlorite and at pH 2, decarboxylation of amino acid to the extent of 6·4% was observed. 3-Methylnorharman was isolated in a 5% yield along with lesser quantities of the monochloro- and the dichloro-3-methylnorharman. Thus, oxidative decarboxylation probably occurs first; but annular halogenation and aromatization are competitive with the initial reaction and preclude any selectivity in the hypohalite degradation.

EXPERIMENTAL

General information. M.ps were taken using evacuated and sealed Pyrex capillary tubes in a Hershberg apparatus or were taken on a hot stage. All m.ps were not corrected further. All b.ps are uncorrected.

Analyses were performed by the Huffman Microanalytical Laboratories, Wheatridge, Colorado, the Spang Microanalytical Laboratory, Ann Arbor, Michigan and by Micro-Tech Laboratories, Skokie, Illinois.

IR spectra were taken on a Perkin–Elmer Infracord spectrophotometer and on a Baird double-beam self recording spectrophotometer. All UV spectra were taken on a Cary recording spectrophotometer (Model 11MS). The NMR spectra were determined using a Varian A-60 NMR spectrophotometer.

The reaction apparatus. The reaction apparatus employed in all oxidative decarboxylations consisted of a 3-necked flask fitted with a N_2 bubbler inlet tube, dropping funnel, gas outlet tube and magnetic stirrer. The exhaust gases from the reaction mixture were passed through a series of three 250 ml gas washing bottles which contained a sat. $Ba(OH)_2$ aq.

Materials and reagents. Commercial "Clorox" bleach was used without purification as the source of the 5·25% NaOCl aq. For TLC, silica gel G and aluminum oxide G were obtained from Brinkman Instruments, Inc.

Oxidative decarboxylation of N-*methyl-2-pipecolic acid hydrochloride by hypochlorite*

A soln of 8·19 g (45·6 mmoles) N-methyl-2-pipecolic acid hydrochloride in 25 ml water was placed in the 3-necked flask of the decarboxylation apparatus. To this soln was added dropwise 60 ml (one equiv) of a 5·25% NaOCl aq. $BaCO_3$ formation in the gas washing bottles was observed after a few min, and the reaction temp increased to about 50°. After 3 hr, the N_2 flow was stopped, and the $BaCO_3$ in the gas washing bottles was collected and dried, 5·084 g (56·5% of theoretical CO_2).

The reaction mixture was saturated with K_2CO_3, exhaustively extracted with ether and the ethereal extract dried over Na_2SO_4. Evaporation of the solvent gave an orange residual oil which was distilled under reduced press. The fraction, b.p. 65–68° at 0·25 mm, n_D^{27} 1·5068, yielded X (lit.[15, 16] 130–132° at 18 mm. and 143–144° at 22 mm) 2·38 g (53·6%). The IR spectrum (liquid film): 3·38, 3·48, 3·58, 5·99 and 6·89 μ; and the UV absorption (EtOH): λ_{max} 220 mμ (ε 4860), were identical with that of an authentically prepared specimen.[13] A picrate prepared by the method of Schopf,[14] m.p. 130·8–131·6°, m.p. 130·8–131·4° as a mixture with authentic picrate.

Oxidative decarboxylation of N,N-*dimethylglycine*

A mixture of 0·494 g (3·93 mmoles) N,N-dimethylglycine hydrochloride[15] in 19·60 ml 0·1 M citric acid and 0·4 ml 0·2M disodium phosphate was placed in the reaction apparatus. Between the reaction apparatus gas outlet tube and the $Ba(OH)_2$ gas washing bottles was placed a "cold finger" trap cooled by a mixture of 5·25% dry ice and acetone. To the stirred soln in the reaction flask was then added dropwise 10·90 ml of 5·2% NaOCl aq (2 equivts). After 1 hr of stirring under N_2, the reaction was stopped and the $BaCO_3$ was collected, dried and weighed (0·747 g, 96% of the theoretical CO_2).

An estimation of the soln formaldehyde content was obtained by the method of Battersby.[6] A one-quarter portion of the reaction soln was added to a mixture of 0·3 g 5,5-dimethyl-1,3-cyclohexanedione in 8 ml EtOH and 20 ml water. After standing overnight at room temp, the yield of white needles was 0·22 g (78%), m.p. 190·5–191° (lit.[8] m.p. 198–191°). Mixture with an authentic specimen melted at 190·5–191·8°.

To a second portion of the reaction soln was added a dil NaOH aq to lower the pH to 6. After the soln was evaporated to dryness, the residue was dissolved in a little water and transferred to a 3-necked flask fitted with N_2 inlet bubbler, dropping funnel, stirrer and gas outlet tube. An excess of conc NaOH aq was added, and the exhaust gases from the soln were passed through a gas washing bottle which contained an EtOH soln of picric acid. After 8 hr, tests with pH paper indicated the absence of volatile amine in the exhaust gas. The crystalline dimethylamine picrate which had formed in the washing bottle was collected

and dried, (38 mg 0·7%) m.p. 155·5–157·5°. Mixture of authentic and isolated samples melted at 156·5–158°. The liquid in the "cold finger" trap was transferred to an Erlenmeyer flask with the aid of 10 ml $CHCl_3$, and sufficient Na_2SO_4 was added to remove the traces of moisture. After 30 min of drying, the presence of XXII in the $CHCl_3$ soln was indicated by the IR spectrum, (Chf) 3·37, 3·50, 6·85, 7·00, 8·49, 8·73, 10·01 and 11·01 μ, which was identical in all respects with that of an authentic specimen. The Chf. soln was dissolved in 1 l. water. The aqueous soln had an UV absorption at 263 mμ [lit.[16] 263 mμ (300)]. An estimation of the chlorodimethylamine yield was obtained by measurement of the soln optical density (1·46) and was found to be 388 mg (25%).

N-*Methyl*-DL-*tryptophan*. This compound, prepared by the method of Miller and Robson[19] and also by Eschenmoser's procedure,[18] had m.p. 288–289° (dec after preliminary softening) (lit.[18] 279–290°).

3-*Methyl*-2,3,4,5-*tetrahydro*-β-*carboline*-4-*carboxylic acid* (XXIII). This compound was prepared according to the method of Robson[19] by incubation of N-methyl-DL-tryptophan with formaldehyde. The carboline-carboxylic acid melted with dec at 195–196° (lit.[19] 208° after softening at 194°).

Oxidative decarboxylation of 3-*methyl*-2,3,4,5-*tetrahydro*-β-*carboline*-4-*carboxylic acid*.

1. *By ten equivalents of hypochlorite*. To an aqueous soln of 1·00 g (4·35 mmoles) 3-methyl-2,3,4,5-tetrahydro-β-carboline-4-carboxylic acid in the decarboxylation apparatus was added 40·9 ml of a 5·25% NaOCl aq (10 equivs). Sufficient dil HCl was then added to make an initial soln of pH 1·8 (predetermined by an aliquot). After 45 min stirring under N_2 flow, the reaction was stopped and the reaction mixture was filtered to remove 177 mg of a yellow ppt. The $BaCO_3$ in the gas washing bottles was collected and weighed (0·620 g, 72·5% theoretical CO_2). The reaction mixture was extracted with two 50 ml portions of ether to remove any non-basic components. The reaction mixture was then saturated with K_2CO_3 and exhaustively extracted with ether. After the fluorescent yellow ether extract was dried over Na_2SO_4 and the solvent evaporated at reduced press, 340 mg of a crude yellow residue remained.

This residue was dissolved in 5 ml MeOH and applied to preparative thin-layer plates (aluminum oxide G, 20 × 20 cm plates, double thickness, $CHCl_3$–MeOH 85:15 v/v). After development and drying of the plates, (solvent front 17 cm) two main yellow bands had separated in addition to a third colorless area (observed by exposure to iodine vapors).

Exhaustive MeOH extraction of the alumina from the slowest moving fraction (2·5–5·5 cm) and evaporation of the solvent at reduced press gave 60 mg (6·4%) of XXVI, m.p. 220–225° dec. The UV absorption, λ_{max} (EtOH) 211 mμ (ε 13,600), 238 mμ (ε 13,000), 254 mμ (ε 15,000), 287 mμ (ε 10,300), 308 mμ (ε 7800), 332 mμ (ε 2000) and 389 mμ (ε 1550), was very similar to the absorption of 3-methylnorharman.

The IR (Chf) had bands at 3·40, 6·15, 6·80, 7·38, 7·62 and 7·81 μ. In $CDCl_3$, the NMR of the mono-chloro compound had a peak at 5·87 τ and a multiplet centered at 2·44 τ of approximate relative intensities of 3 to 6.

A picrate was prepared by the addition of an ethanolic picric acid soln to an ethanolic soln of the mono-chloro-3-methylnorharman. After recrystallization from EtOH, the picrate melted with dec at 287–291° with preliminary softening. (Found: C, 48·59; H, 2·81; N, 15·55; Cl, 8·02. Calc. for $C_{18}H_{12}N_5ClO_7$: C, 48·85; H, 2·72; N, 15·74; Cl, 7·96%.)

The next fastest flowing fraction (9·5–12·5 cm) yielded 50 mg (4·6%) of XXVIII by the exhaustive MeOH extraction procedure. The UV had absorption at λ_{max} (EtOH) 214 mμ (ε 10,500), 255 mμ (ε 13,300), 287 mμ (ε 18,450), 306 mμ (ε 5380), 319 mμ (ε 3800) and 329 mμ (ε 3270). The IR (Chf) had bands at 3·40, 6·15, 6·29, 6·63, 6·80, 7·63 and 7·82 μ.

In $CDCl_3$, the dichloro product NMR had a peak at 5·80 τ and a multiplet in the region 2·1 to 2·3 τ of approximate relative intensities of 3 to 5.

A picrate was prepared using the same procedure employed in the preparation of the mono-chloro-3-methylnorharman picrate. After recrystallization from EtOH, the picrate melted with dec at 266–267·5° (Found: C, 45·11; H, 2·38; N, 14·68; Cl, 14·90. Calc. for $C_{18}H_{11}N_5Cl_2O_7$: C, 45·03; H, 2·31; N, 14·60; Cl, 14·77%.)

The fastest moving fraction of the thin-layer chromatogram (12·5–15·5 cm) after the exhaustive MeOH extraction procedure yielded 216 mg of a mixture of components. Recrystallization from ether gave 74 mg of XXVIII, m.p. 218–219°. IR, (Chf) had bands at 3·32, 5·77, 5·90, 6·16, 6·86, 7·62 and 7·82 μ. The UV had absorption at 257 mμ (ε 10,180) (EtOH).

In $CDCl_3$, the lactam-oxindole NMR had an AB quartet (2 protons) at 7·61 τ and 7·11 τ (J_{AB} 17 c/s), a singlet (3 protons) 7·16 τ, an AB quartet (2 protons) at 6·72 τ and 6·34 τ (J_{AB} 10 c/s) and a multiplet at about 3·1 τ (approximately 3 protons). (Found: C, 50·76; H, 3·58; N, 9·75; Cl, 24·90. Calc. for $C_{12}H_{10}N_2Cl_2O_2$: C, 50·53; H, 3·57; N, 9·84; Cl, 24·3%.)

Hydrogenolysis of the monochloro-3-methylnorharman

A soln of 32 mg of the monochloro-3-methylnorharman (0·15 mmoles) in 50 ml EtOH was subjected to low press hydrogenation for 30 min with 26 mg 30% Pd–C. After filtration to remove the catalyst, the colorless soln was evaporated to dryness under reduced press to yield 32 mg of 3-methylnorharman hydrochloride. The UV absorption, λ_{max} (EtOH) 219 mμ (ε 14,140), 255 mμ (ε 27,700), 309 mμ (ε 14,000), and 377 mμ (ε 3260) was identical within experimental error to an authentic sample.

The hydrochloride was dissolved in water, saturated with K_2CO_3 and extracted with ether. The ethereal extract was dried over Na_2SO_4 and then evaporated at reduced press to yield 20 mg of 3-methylnorharman. The IR, (Chf) 3·42, 6·16, 6·79, 7·52 and 8·03 μ, was identical with that of an authentic sample.[2c] A picrate was prepared using the procedure employed in the preparation of the 3-methylnorharman picrate. m.p 263–264° (dec), mixture 264–265° (dec). (Found: C, 52·68; H, 2·94; N, 17·11. Calc. for $C_{18}H_{13}N_5O_7$: C, 52·55; H, 3·19; N, 17·02%.)

Hydrogenolysis of the dichloro-3-methylnorharman

To 30 mg of the dichloro-3-methylnorharman (0·12 mmoles) in 80 ml EtOH was added 37 mg 30% Pd–C powder and subjected to low press hydrogenation for 30 min. After filtration of the catalyst and evaporation of the solvent at reduced press, 28 mg of a mixture of products was isolated. The reaction products were dissolved in water, saturated with K_2CO_3 and the aqueous soln was extracted with ether. The ethereal extract was dried over Na_2SO_4 and evaporated. The residue was separated and purified by preparative TLC (aluminum oxide G, double thickness 20 × 20 cm plates, $CHCl_3$–MeOH 85:15, v/v) Exhaustive extraction of the slowest moving yellow fraction with MeOH and evaporation of the solvent at reduced press yielded a product identified as XXV, by a comparison of the IR spectrum, (Chf) 3·41, 6·15, 6·78 and 7·50 μ, with an authentic specimen.[22] The picrate melted at 268–270° (mixture 267–269·5°).

Oxidative decarboxylation of 3-methyl-2,3,4,5-tetrahydro-β-carboline-4-carboxylic acid

2. *By one equivalent of hypochlorite.* To an aqueous soln of 200 mg (0·868 mmoles) 3-methyl-2,3,4,5-tetrahydro-β-carboline-4-carboxylic acid in the reaction apparatus was added 1·32 ml of a 5·25% NaOCl aq. Sufficient dil HCl was then added in order to adjust the initial solution pH to 2. After 45 min of stirring under N_2, the reaction was stopped. The reaction mixture was immediately saturated with K_2CO_3 and exhaustively extracted with ether. After drying the ethereal extract over Na_2SO_4 and evaporation of the solvent at reduced press, there remained 12 mg of a crude yellow residue. The $BaCO_3$ in the gas washing bottles was collected and weighed (11 mg, 6·4%). The residue from the ether extraction was dissolved in 1 ml MeOH and applied to preparative thin layer plates (aluminum oxide G, double thickness, 20 × 20 cm plates, $CHCl_3$–MeOH 85:15 v/v). After development and drying of the plates at room temp, 4 yellow bands had separated (solvent front 17·0 cm). Exhaustive MeOH extraction of the alumina from slowest flowing fraction (0–3·5 cm) and evaporation of the solvent at reduced press gave 4 mg (5%) of 3-methylnorharman. The UV absorption λ_{max} 218 mμ (ε 1,450), 233 mμ (ε 10,600), 254 mμ (ε 18,100), 283 mμ (ε 10.500), 309 mμ (ε 10·950), 332 mμ (ε 2000), 376 mμ (ε2420), (EtOH); and IR spectrum, (Chf) 3·40, 6·15, 6·76, 7·51 and 8·02 μ, were identical to the spectra of an authentically prepared sample of XXV.[22] A picrate was prepared by the addition of an ethanolic soln of the 3-methylnorharman to a conc soln of picric acid in EtOH, m.p. 265–269°. A mixture m.p. with an authentic picrate melted at 263–266°.

The second band (3·5–6·5 cm) yielded a yellow residue (1 mg, 1%) by the MeOH extraction procedure The UV had absorption at λ_{max} (EtOH) 254, 262, 286, 309, 332 and 380 mμ. A comparison of the R_f value (0·29) and the IR spectrum, (Chf) 3·40, 6·13 and 6·83 μ, indicated that the residue was XXVI (same product as obtained from the 10 equiv reaction).

The third band (6·5–9·0 cm) yielded an additional 1 mg of yellow compound by the MeOH extraction procedure. This material was probably a chlorinated 3-methylnorharman deriv but was not comparable to any of the previously characterized compounds.

The fourth yellow band (12·5–14 cm) yielded 1 mg of compound by the previously described MeOH extraction procedure. A comparison of the UV spectrum λ_{max} (EtOH) 255 mμ, 286 mμ, the IR spectrum (Chf) 3·40, 61·5, 6·29, 6·63, 7·63 and 7·82 μ, and the R_f value (0·79) with an authentic sample of XXVIII indicated that the compounds were identical.

A picrate was prepared by the addition of an ethanolic soln of the fourth fraction to a conc ethanolic soln of picric acid, crude m.p. 255–260° dec. A mixture m.p. with an authentic picrate melted at 260–266° dec.

Quinolizidine-4-carboxylic acid hydrobromide. This compound was synthesized by the 6-step method of

Maris and Hudlicky,[9] m.p. 291–293° dec (lit.[9] m.p. 282–283°). The IR (Nujol) had bands at 3·40, 3·49, 5·75 and 6·88 μ.

Quinolizidine-4-carboxylic acid. To 1·0 g (3·8 mmoles) quinolizidine-4-carboxylic acid hydrobromide in 25 ml water was added sufficient dil NaOH aq to adjust the solution pH to 7·0. After evaporation to dryness, the residue was extracted with hot MeOH (1 l.). Evaporation of the solvent at reduced press and recrystallization of the residue from MeOH yielded white crystals, m.p. 266·5–267° dec. The IR (Nujol) had bands at 3·3–3·42, 3·61, 3·32, 6·1–6·2, 6·9 and 7·3–7·4 μ.

In D_2O, the NMR of the hydrobromide salt had multiplets centered at 6·21, 6·88 and 8·15 τ of approximate integrated intensities of 2:2:12. A proton signal for water was visible at 5·25 τ. (Found: C, 66·11; H, 9·42; N, 7·50. Calc. for $C_{10}H_{17}NO_2$: C, 66·01; H, 9·35; N, 7·64%.)

Attempted oxidative decarboxylation of quinolizidine-4-carboxylic acid.

1. *By one equivalent of hypochlorite.* To a soln of 0·690 g (3·76 mmoles) quinolizidine-4-carboxylic acid dissolved in 25 ml water and placed in the decarboxylation apparatus was added 5·03 ml of a 5·25% NaOCl aq (one equiv). Sufficient dil HCl (predetermined by an aliquot) was added to secure an initial reaction soln with pH 2·5. After 3·5 hr of stirring under a N_2 flow the reaction mixture was neutralized with dil NaOH aq and evaporated to dryness under reduced press at 50°. The $BaCO_3$ in the gas washing bottles amounted to only 23 mg (3·2%). The reaction residue was extracted with five 50 ml portions of abs EtOH. The ethanolic soln was then evaporated to dryness under reduced press to yield a heavy oil.

This residue was dissolved in MeOH and applied to preparative thin-layer plates (silica gel G, double thickness, 20 × 20 cm plates, 96% EtOH–water 63:37 v/v). After development of the plates (solvent front 17 cm) two main bands had separated and were detected by exposure to I_2 vapors.

By warm EtOH extraction (2 l.) and evaporation of the solvent at reduced press, 311 mg of $\Delta^{5,10}$-dehydroquinolizidine-4-carboxylic acid was isolated from the slowest moving fraction (5·0–7·0 cm). The IR (liquid film) had bands at 2·9–3·0, 3·4–3·5, 5·99, 6·18 and 6·95 μ; the UV (EtOH) had absorption at 220 mμ (ε 2345).

In D_2O, the NMR had peaks at 5·65, 6·3, 7·85 and 8·2 τ of approximate integrated intensities of 1:2:4:8. A proton signal for water was visible at 5·28 τ.

A picrate, prepared by the addition of an ethanolic soln of picric acid (saturated) to an ether–EtOH soln of the amino acid, crystallized only after standing in the refrigerator for 2 weeks. The picrate, after recrystallization from EtOH, melted with dec at 158·5–159·5°. (Found: C, 47·19; H, 4·48; N, 13·82. Calc. for $C_{16}H_{18}N_4O_9$: C, 46·84; H, 4·42; N, 13·67%.)

The other main fraction of the thin-layer chromatogram (7·0–9·5 cm) was isolated by an extraction with 2 l. EtOH. Evaporation of the solvent at reduced press yielded 311 mg of the starting amino acid.

After accounting for the unreacted starting material, the yield of $\Delta^{5,10}$-dehydroquinolizidine-4-carboxylic acid was 84%.

Reduction of $\Delta^{5,10}$-dehydroquinolizidine-4-carboxylic acid

1. *By platinum oxide.* To a soln of 64 mg (0·36 mmoles) $\Delta^{5,10}$-dehydroquinolizidine-4-carboxylic acid in 20 ml EtOH was added 50 mg of PtO_2. After hydrogenation for 2 hr, the soln was filtered and the solvent evaporated to yield 52 mg (77%) quinolizidine-4-carboxylic acid, m.p. 266–267° dec (mixture m.p. 266·5–267° dec). The IR, (Nujol): 3·3–3·42, 3·61, 3·92, 6·1–6·2, 6·9 and 7·3–7·4 μ, was identical with that of authentic quinolizidine-4-carboxylic acid.

2. *By sodium borohydride.* To a soln of 46 mg (0·26 mmoles) $\Delta^{5,10}$-dehydroquinolizidine-4-carboxylic acid in 5 ml MeOH was added with stirring a soln of 37 mg $NaBH_4$ in 5 ml MeOH (4 equivs). After 2 hr of stirring at room temp, the reaction mixture was treated with 2 ml conc HCl and evaporated to dryness under reduced press at 50°. After purification by TLC (silica gel G, double thickness, 20 cm × 20 cm plates. 96% EtOH–water 63:37 v/v) 30 mg (65%) of quinolizidine-4-carboxylic acid was isolated. A hydrochloride salt was prepared by passing dry HCl gas into an ethanolic soln of the amino acid, m.p. 277–278° dec. Mixture with an authentic hydrochloride melted at 277–278°. The IR (Nujol): 3·3–3·4, 3·70, 3·94, 5·80, 6·90 and 8·3 μ, was identical in every detail to that of authentic quinolizidine-4-carboxylic acid hydrochloride.

3. *By sodium borodeuteride.* To a soln of 206 mg (1·15 mmoles) $\Delta^{5,10}$-dehydroquinolizidine-4-carboxylic acid in 10 ml abs MeOH was added with stirring a soln of 200 mg $NaBD_4$ in 5 ml abs MeOH. The addition produced an immediate evolution of gas. After 3 hr of stirring at room temp, the reaction mixture was treated with 2 ml conc HCl and evaporated to dryness under reduced press at 50°. The residue was purified by preparative TLC (silica gel G, double thickness, 20 × 20 cm plates, 96% EtOH–water 63:37 v/v)

The position of the product on the thin-layer plate was determined by exposure of a small portion of the plate to I_2 vapors (7–10·5 cm) (solvent front 17 cm). Extraction of the silica gel with warm 95% EtOH yielded 10-deuterioquinolizidine-4-carboxylic acid, which after recrystallization from an ether–MeOH mixture melted at 265·8–266·6°dec. The IR (Nujol): peaks at 3·3–3·4, 3·72, 3·90, 6·16, 6·78, 6·89 and 8·14 μ. In D_2O, the NMR had multiplets centered at 6·36, 7·0 and 8·16 τ of approximate integrated intensities of 2:1:12. A proton signal for water was visible at 5·30 τ.

4-Carbomethoxyquinolizidine. To a rapidly stirred soln of 1·0 g (3·8 mmoles) quinolizidine-4-carboxylic acid hydrobromide in 25 ml abs MeOH at −20° was added dropwise 1 ml of freshly distilled $SOCl_2$. After 1 hr of stirring at −20°, the reaction mixture was stirred for an additional 1·5 hr at room temp. The reaction mixture was evaporated to dryness at reduced press and dissolved in 5 ml MeOH. Upon the addition of ether a solid was obtained which was considered, on the basis of an examination of its IR spectrum, to be a mixture of starting material and the ester product.

This solid was dissolved in MeOH and applied to preparative thin-layer plates (silica gel G, double thickness 20 × 20 cm plates, 96% EtOH–water 63:37 v/v). After development of the plates (solvent front 17 cm), two bands could be observed by exposure of a small portion of the plate to I_2 vapors (7–9·5 cm starting amino acid) (9·5–11 cm amino acid ester). By warm EtOH extraction and evaporation of the solvent at reduced press, the amino acid ester was isolated. After recrystallization from a mixture of MeOH–ether, the ester melted with dec at 194–195°. The IR (Nujol): bands at 3·40, 3·50, 5·71, 6·83, 7·50, 7·55, 7·63 and 7·71 mμ.

In D_2O, the NMR had a singlet at 5·80 τ, a broad multiplet at 5·5 to 7·0 τ and a multiplet centered at 7·86 τ of approximate integrated intensities of 3:4:12. A proton signal for water was visible at 5·03 τ.

Equilibration and hydrolysis of 4-carbomethoxyquinolizidine

A soln of 6 mg (0·25 mmoles) Na dissolved in anhyd MeOH was added in a N_2 atm to a soln of 50 mg (0·253 mmoles) 4-carbomethoxyquinolizidine in 5 ml anhyd MeOH. The reaction mixture was refluxed under N_2 for 4 hr. After cooling to room temp, 5 ml of a 10% NaOH aq was added and the mixture was refluxed for an additional hr. Addition of dil HCl adjusted the soln pH to 7 and the mixture was evaporated to dryness under reduced press at 40°. The residue was triturated with 5 ml anhyd MeOH and filtered. To the MeOH filtrate was added a few drops of dil HCl and the soln was evaporated to dryness. The hydrochloride salt was recrystallized from a MeOH–ether mixture to yield 40 mg (73%) quinolizidine-4-carboxylic acid hydrochloride, m.p. 273–274° dec (mixture m.p. 271·5–272° dec). The IR (Nujol): 3·3–3·4, 3·70, 3·94, 5·79, 6·88 and 8·3 μ, was identical in every detail with that of authentic quinolizidine-4-carboxylic acid hydrochloride.

The rearrangement of 2-methyltryptophan to 4-acetylquinoline

To a soln of 1·5 ml 10% NaOH aq and 321 mg (1·48 mmoles) DL-2-methyltryptophan[21,22] in 10 ml distilled water was added 4N HCl dropwise to pH 8. The soln was diluted immediately with 120 ml distilled water followed by addition of 43 ml, 3·0 mmoles (0·52%) NaOCl aq (prepared by dilution of 1 part Clorox bleach with 9 parts distilled water). The mixture was heated to 50° over a period of 20 min in a water bath, then held at this temp for 20 min longer. The warm soln was extracted several times with benzene. The combined benzene extracts were treated with 100 ml 2N HCl for ½ hr at room temp. then extracted 4 times with 25 ml portions of 2N HCl. The acid layers were combined, basified carefully with NaOH pellets while being cooled in ice and extracted thoroughly with $CHCl_3$. The combined extracts were washed with water, saturated brine and dried over Na_2SO_4. The filtered soln, upon removal of the $CHCl_3$, yielded 57 mg (22·4%) of a brown oil. The IR spectrum of this oil was very similar to that of crude authentic 4-acetylquinoline. The picrate, m.p. 165–169° (reported m.p. 165–170°)[23] and 2,4-dinitrophenylhydrazone, m.p. 264–265°, showed no depression of m.p. when mixed with the corresponding derivatives of authentic 4-acetylquinoline. The pure picrates of the 2-methyltryptophan product and authentic 4-acetylquinoline were decomposed with Na_2CO_3 aq. The resulting oils showed essentially identical UV spectra: λ_{max} 316 mμ (ε 4900).

Kynurine from kynuronine

DL-Kynurenine sulfate, 91·8 mg, 0·3 mmole, was dissolved in 3 ml water and adjusted to pH 8 with 10% NaOH aq. The resulting soln was treated with 4·30 ml (0·3 mmole) 0·52% NaOCl aq. The mixture was heated at 50° for 2 hr. The solvent was removed under vacuum and the residue was extracted repeatedly with acetone. The acetone extracts were combined, filtered and distilled under vacuum to yield 44 mg

(theory, 43·5 mg) of a partially crystalline, tan solid. A soln of the solid in dil HCl, on treatment with 2 drops of chloroplatinic acid, precipitated a light orange, micro-crystalline double salt, decomposition point 224° (reported 217°). The double salt was suspended in 0·5 ml water and 0·5 ml dil NH_4OH was added. A yellow ppt was formed which was filtered and the filtrate was taken to dryness under vacuum The residue was extracted with acetone several times. The acetone extracts were combined, filtered and distilled under vacuum to yield an amber residue. UV spectrum, λ_{max} 318 mμ, log ε_{max} 3·94, λ_{max} 331 mμ, log ε_{max} 4·00, λ_{min} 260 mμ, log ε_{min} 3·18 in 95% EtOH. An authentic sample of kynurine showed an identical UV spectrum in all respects except that the log ε values are uniformly slightly higher.

Norharman from 3-carboxy-1,2,3,4-tetrahydro[-9H-]pyrido-[3.4-b] indole

To a soln of 150 mg (0·695 mmole) 3-carboxy-1,2,3,4-tetrahydro-9H-pyrido[3.4-b]indole[24] and 0·75 ml 10% NaOH aq in 2 ml distilled water was added 4N HCl dropwise to pH 8. The soln was diluted immediately with 60 ml distilled water followed by 20 ml (1·4 mmoles) 0·52% NaOCl aq. The soln was heated to 40° and held at 40–50° for 20 min in a water bath. The soln was extracted several times with AcOEt The combined extracts were extracted repeatedly with 2N HCl. The soln had a characteristic brilliant blue fluorescence in UV light. The combined acid extracts were cooled in an ice bath and basified (litmus) carefully with KOH pellets. The soln was extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed with water, and brine, and then dried over Na_2SO_4. The soln was filtered and the solvent was evaporated under N_2 to yield 16 mg (14%) crude material. Recrystallized from EtOH–water. m.p 200–200·8°, uncorr (reported m.p. 198·5°);[25] picrate m.p. 263–264° dec, uncorr (reported m.p. 262° dec).[27] UV spectrum in 95% EtOH was sharper and clearer than the published spectrum but shows the same general characteristics, λ_{max} 350 mμ, log ε_{max} 3·64, λ_{min} 344 mμ, log ε_{min} 3·57, λ_{max} 337 mμ, log ε_{max} 3·62, λ_{min} 301 mμ, log ε_{min} 2·91, λ_{max} 278 mμ, log ε_{max} 4·24, λ_{min} 265 mμ, log ε_{min} 3·64. Published spectrum. λ_{max} 337 mμ (broad absorption) log ε_{max} 3·8, λ_{min} 300 mμ, log ε_{min} 3·1, λ_{max} 275 mμ, log ε_{max} 4·4, λ_{min} (*ca.*) 260 mμ, log ε_{min} 3·85.

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