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AKUAMMA-ALKALOIDS—IX[1]

THE ZINC-HYDROCHLORIC ACID REDUCTION OF PICRALINE

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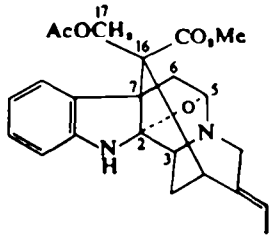
Abstract—Picraline (I) is reduced by zinc and conc. hydrochloric acid to an indolic ester, $C_{21}H_{26}N_2O_2$, for which the structure IV is proposed. A probable rationalization of this extraordinary reaction is discussed.

IN THE course of experiments designed to effect a partial reduction of picraline[1,2] (I) at C-2, it was found that zinc dust and conc. hydrochloric acid, at or below room temperature, led to the formation of a compound, $C_{21}H_{26}N_2O_2$, in up to 50% yield. It was very soon apparent that, in spite of the mild reaction conditions, this product was the result of a deep seated skeletal change.



I

The UV and IR spectra of the product indicated the presence of an indole chromophore, an ester grouping, and an indolic N-hydrogen. The NMR spectrum confirmed these features, showing an N-hydrogen signal (8·35 ppm) removed on addition of deuterium oxide, signals due to four aromatic hydrogen atoms (6·8–7·5 ppm), and a methoxyl singlet (3·6 ppm). The presence of an ethylidene function in the molecule was shown by the usual resonances, a methyl doublet (1·6 ppm) and a complementary vinyl hydrogen quartet (5·43 ppm). In addition, the spectrum showed a three hydrogen triplet (1·04 ppm) which indicated the unanticipated presence of an ethyl group. Finally, the NMR spectrum showed the heterocyclic ring to be only monosubstituted, a finely split one hydrogen signal (6·08 ppm) being assigned to a pyrrole ring C-hydrogen. The fine splitting, caused by coupling with the indolic N-hydrogen,[3] was eliminated after exchange with deuterium oxide. That the side chain is affixed at the indole 2-position and thus that the signal at 6·08 ppm is due to

[1] Part VIII. A. Z. Britten, G. F. Smith and G. Spiteller, *Chem. & Ind.* 1492 (1963).
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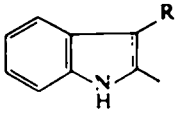
[3] J. A. Elvidge and R. G. Foster, *J. Chem. Soc.* 981 (1964).

an indole C-3 hydrogen was proved both spectroscopically and chemically. It has been shown[4] that the resonance position of a hydrogen situated at the indole 3-position is, in contrast to one at a 2-position, largely concentration independent. The signal due to the indole proton of the indolic ester appeared at 6·20 ppm in 25% deuterochloroform solution and at 6·18 ppm in 12% deuterochloroform solution.

A second spectroscopic observation on the resonance position of indole C-hydrogen signals demonstrated that a C-3 hydrogen shows only a small (ca. 0·2 ppm) variation with different solvents, whereas a C-2 hydrogen is characterized by a much greater (ca. 0·7 ppm) shift.[5] The resonance position of the pyrrole ring C-hydrogen of the indolic ester appeared at 6·08 ppm in 15% carbon tetrachloride solution and at 6·18 ppm in 15% acetone solution.

Treatment of the indolic ester with dimethyl formamide–phosphorus oxychloride, a reagent known to introduce a formyl grouping into the 3-position of indole,[6] gave a crystalline compound, $C_{22}H_{28}N_2O_3$, the UV spectra of which, in both neutral and alkaline solution, overlaid those of 3-formyl indole[6] and were entirely different from those of 2-acyl indoles.[7] The IR spectrum of the formyl indole, in addition to the ester absorption, showed a new carbonyl band at 1650 cm^{-1} consistent with a 3-acyl indole but not a 2-acyl indole.[7] The NMR spectrum no longer showed a resonance in the region of 6·0 ppm but did possess a new signal at 10·1 ppm caused by the aldehydic C-hydrogen. Other features of the NMR spectrum were analogous to those of the original indole. The data adduced thus far can be summarized by the partial formula (II) for the indolic ester and III for its formyl derivative.

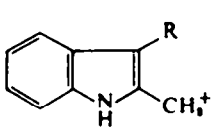


—CO_2Me
—Et
=CH·Me
$C_7H_{10}N$

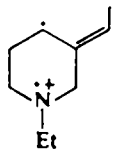
II, R = H
III, R = CHO

Structural information on the aliphatic portion of the indolic ester was obtained by a comparison of the mass spectrometric fragmentations of the ester, its formyl derivative, and the alcohol, $C_{20}H_{28}N_2O$, and deuteroalcohol, $C_{20}D_2H_{26}N_2O$, obtained from the indolic ester by LAH and LAD reductions respectively. Each compound displayed a characteristic[8] ion, corresponding to an indole moiety carrying one extra carbon atom, at *m/e* 130 (the formyl derivative also showed an ion at *m/e* 158). Since the position of substitution of the indole ring is established, structures *a* and *b* can be assigned to the ions at *m/e* 130 and 158 respectively. Two further ions common to the spectra of all four compounds occur at *m/e* 138 and 136 resulting from fission at a position allylic to the ethylidene double bond. These ions are characteristic[8] of piperidine moieties, in this case carrying an N-ethyl substituent, and can be represented, on the reasonable assumption that the ethylidene group is oriented on the piperidine ring in the same sense as in the starting material, by *c* and *d*.

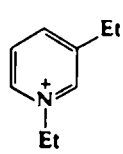
[4] M. G. Reinecke, H. W. Johnson Jr., and J. F. Sebastian, *Chem. & Ind.* 151 (1964).
[5] R. V. Jardine and R. K. Brown, *Canad. J. Chem.* **41**, 2067 (1963).
[6] G. F. Smith, *J.*, 1954, 3842.
[7] J. A. Ballantine, C. B. Barrett, R. J. S. Beer, B. G. Boggiano, S. Eardsley, B. E. Jennings and A. Robertson, *J. Chem. Soc.* 1957, 2227.
[8] H. Budzikiewicz, C. Djerassi and D. H. Williams, *Structure Elucidation of Natural Products by Mass Spectrometry* Vol. 1. *Alkaloids*, Holden-Day, San Francisco (1964).



a, R = H
b, R = CHO

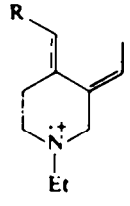


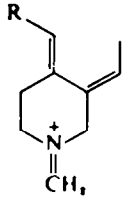
c

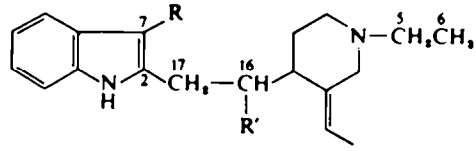


d

The base peaks in the spectra of the indolic ester and its formyl derivative occur at *m/e* 209, $C_{12}H_{16}NO_2$, an ion corresponding to an aliphatic portion of the molecule formed by benzylic fission with transference of one hydrogen atom to the aromatic half. In each case the ion at *m/e* 209 loses a methyl radical giving rise to an ion at *m/e* 194, a strong indication of the presence of an N-ethyl grouping which loses the methyl radical by α-fission. Similarly the alcohol shows a base peak at *m/e* 181 $C_{11}H_{19}NO$ (183) which subsequently loses a methyl radical giving rise to an ion at *m/e* 166 (168). These fragments demonstrate that the piperidine moiety *c* is joined to the indole portion *a* by a —CH(CO$_2$Me)— grouping in the indolic ester and a —CH(CH$_2$OH)— grouping in the derived alcohol. On the basis that the ester-bearing carbon is attached to the piperidine nucleus in the same relationship to ethylidene and nitrogen as in picraline, the ions at *m/e* 209 and 194 can be represented by *e* and *f* respectively, while the corresponding ions from the two alcohols, at *m/e* 181, 166 and 183, 168 can be formulated as *g*, *h* and *i*, *j* respectively.







e, R = CO$_2$Me f, R = CO$_2$Me
g, R = CH$_2$OH h, R = CH$_2$OH
i, R = CD$_2$OH j, R = CD$_2$OH

IV, R = H R′ = CO$_2$Me
V, R = CHO, R′ = CO$_2$Me
VI, R = H, R′ = CH$_2$OH

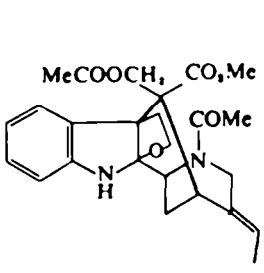
Thus, with the very reasonable assumptions of the relative orientations of carbomethoxyl bearing carbon and ethylidene group on the piperidine ring, the part structure (II) for the indolic ester can be extended to the representation IV, the formyl derivative being given structure V and the alcohol formula VI.

The conversion of picraline into the indole (IV) under such mild conditions (optimum yields at −30°) is quite extraordinary. Such a conversion must necessarily involve a fairly long sequence of reactions, it is therefore almost impossible to write down a complete speculative reaction scheme and feel confident of the details. An examination of the formulae of starting material and product reveals that the overall reaction involves three carbon–carbon bond cleavages and the formation of one new carbon–carbon link. Thus the C7–C16, the C2–C3 and C7–C6 bonds are no longer present in the indolic ester, whereas a new bond, C2–C17 has been formed.

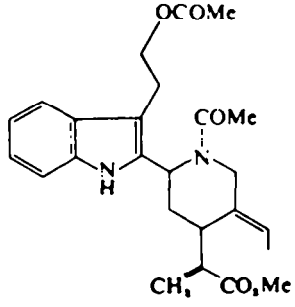
Only one of these changes, C7–C16 fission, has any clear precedent in the literature, viz. the zinc–hydrochloric acid transformation of aspidodasycarpine diacetate (VII)

to the indole (VIII).[9] This change is envisaged as involving an intermediate (IX) formed by complexing of zinc with the C2 carbon atom of an equilibrium concentration of ring opened indoleninium species[10] (N_a—C—O— → N_a^+=C + HO—) in a manner analogous to that postulated for the Clemmensen reduction of ketones.[11] Fragmentation[12] (arrows in IX) of the intermediate would then lead directly to the observed product (VIII).

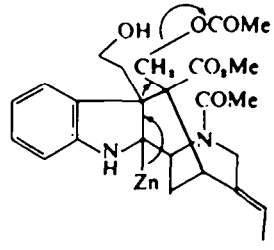
The C2–C3 bond fission in the reduction of picraline (XIV → XVII) may have an analogue in a reverse Mannich type reaction as postulated[13] for the hydrochloric acid catalysed conversion of the indole (X) into the indoline (XI), and presumably also occurring in the conversion of the indole (XII) into the 3H-indole (XIII).[14]



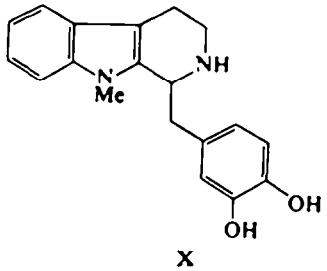
VII



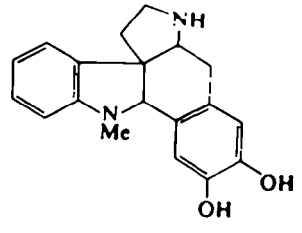
VIII



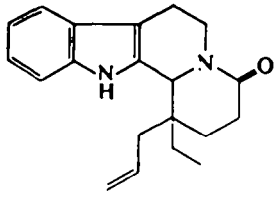
IX



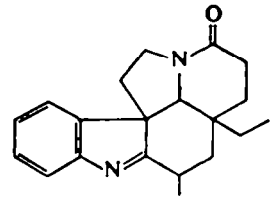
X



XI



XII



XIII

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[13] J. Harley-Mason and W. R. Waterfield, *Tetrahedron* **19**, 65 (1963).

[14] J. E. D. Barton and J. Harley-Mason, *Chem. Comms.* 197 (1965).

There would seem to be no clear analogies in indole alkaloid chemistry for the fission of the C6–C7 bond or the formation of the C2–C17 linkage. In principle, the first of these is likely to involve heterolysis leading in the first instance to a vinylamine group. E.g.

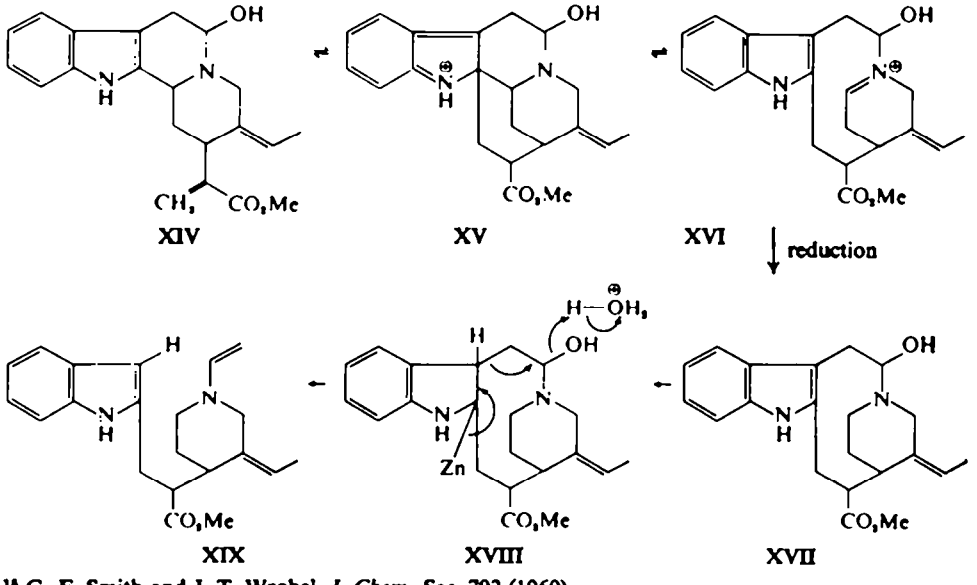
$$C7\text{–}C6\text{–}C5{=}N_b^+ \rightarrow C^+7 + C6{=}C5\text{–}N_b$$

or

$$C7\text{–}C6\text{–}C5N_b\text{–}O + H^+ \rightarrow C^+7 + C6{=}C5\text{–}N_b + HO$$

More difficult to rationalize is the production of a C2–C17 bond. Although the authors do not propose a reaction sequence for the Lewis acid-catalysed conversion of the synthetic indole (XII) into the indolenine (XIII),[14] this transformation may involve the type of reaction suggested for the formation of the C2–C17 bond in the following reaction scheme. The following sequence of reactions is not intended to be definitive, but rather to indicate the types of reactions which are likely to be involved in the formation of the indolic ester (IV).

Proton induced opening of the N_a—C—O system of picraline followed by complexing with zinc and fragmentation in a manner exactly analogous to that postulated[9] for the formation of the indole (VIII) would lead to the intermediate (XIV). A series of equilibria are now open to XIV, involving initial Michael addition of the indole 2-position to the α,β-unsaturated ester moiety to give XV and subsequent participation of the N_b p-electrons, in a reverse Mannich sense, to give the immonium species (XVI).[13] This last alternative is not available to the aspidodasycarpine indole (XIII), since the aliphatic nitrogen is nonbasic, which may explain why VIII undergoes no further transformation. Reduction of the immonium form[15] (XVI) would give XVII. Protonation of the indole ring at the 3-position[16] and complexing of zinc at C2 as before, would give rise to XVIII, fragmentation of which (arrows) would then lead to XIX in which it is only necessary to effect the reduction of the vinylamine group to arrive at the structure (IV) demonstrated for the indolic ester.



[14] G. F. Smith and J. T. Wrobel, *J. Chem. Soc.* 792 (1960).
[15] R. L. Hinman and J. Land, *Tetrahedron Letters* No 21, 12 (1960).

EXPERIMENTAL

Action of zinc–hydrochloric acid on picraline (I). Picraline (370 mg) in conc HCl (15 ml) was maintained between −20° and −30° while Zn power (5 g) was added in portions during 20 min. The reaction mixture was poured into ice water (150 ml) and the excess Zn filtered off. The filtrate was made alkaline with ice cold NH_4OH and extracted with ether. The dried ethereal solution, on evaporation, gave a gum (217 mg) which was purified by TLC (silica gel G, AcOEt–C_6H_6–MeOH, 2:2:1), the band at R_f 0·6 was eluted to give the *indole* II (157 mg), homogeneous by TLC, ν_{max} (CCl_4) 3410 m, 3350 w, 1735 vs cm^{-1}, λ_{max} (EtOH) 223, 272, 288 mμ (ε 33,000, 10,500, 9,300), λ_{min} 238, 286 mμ (ε 4,100, 8,900), λ_{max} (conc. H_2SO_4) 233,240, 294 mμ (ε 12,100, 11,800, 12,500), λ_{min} 238, 248 mμ (ε 11,600, 9,300), 1·04 (3H triplet J = 7 c/s, $C\underline{H}_3CH_2$), 1·60 (3H doublet J = 6 c/s, $C\underline{H}_3CH$=), 3·60 (3H singlet, $C\underline{H}_3O_2C$), 5·43 (1H quartet J = 6 c/s, =$C\underline{H}CH_3$), 6·08 (1H doublet J = 1c/s, N_2C=C$\underline{H}$), 6·80–7·50 (4H, $\underline{H}$Ar), 8·35 ppm (1H broad, $\underline{H}N_a$) *m/e* 340 (M^+, 4%), 209(100), 196(11), 194(7), 138(10), 136(4), 130(5), metastable ion at *m/e* 180·1 for 209 → 194, (Found: 340·2147; C, 73·0; H, 8·05 mol. wt. 209·1411; $C_{21}H_{20}N_2O_2$ requires: mol wt. 340·2151; C, 74·08; H, 8·29%: $C_{13}H_{13}NO_2$ requires: 209·1416.)

LAH *reduction of the indole* II. The indole, II (133 mg) in ether (30 ml) was reduced with LAH (200 mg) at room temp for 12 hr. Decomposition of the reaction mixture with water and evaporation of the dried ether solution led to a semicrystalline mass (109 mg) which was crystallized from ether–acetone to give the *indole alcohol* III, m.p. 161–163°, ν_{max} (nujol) 3,400 m cm^{-1}, λ_{max} (EtOH) 222, 277, 289 mμ (ε 34,300, 8,700, 8,300), λ_{min} 242, 288 mμ (ε 4,300, 8,150), λ_{max} (conc. HCl) 235, 239, 279 mμ (ε 8,200, 8,150, 8,200), λ_{min} 237, 248 mμ (ε 8,100, 7,700), *m/e* 312(M^+, 3%), 181(100), 168(29), 166(13), 138(62), 136(30), 130(51), metastable ion at *m/e* 152·3 for 181 → 166. (Found: C, 75·25; H, 8·73; N, 10·38. $C_{20}H_{20}N_2O$ requires: C, 76·88; H, 9·03; N, 8·97%.)

LAD *reduction of the indole* II. The reduction was carried out exactly as for LAH and the product crystallized from ether–acetone, *m/e* 314(M^+, 3%), 183(100), 170(29), 168(19), 138(53), 136(30), 130(51).

Action of dimethylformamide–phosphorus oxychloride on the indole II. The indole (93 mg) in dimethyl formamide (1 ml) was added to 1 ml of a solution of $POCl_3$ in dimethyl formamide (0·5 ml in 20 ml) at 10°. The reaction mixture was heated at 45° for 1 hr, cooled and poured onto ice. 5% NaOHaq (5 ml) was added and, after 10 min at room temp, the solution was extracted with ether. The dried, evaporated ethereal solution yielded a gum (75 mg) which was purified by TLC (elute band at R_f 0·2) and crystallized from ether to give the *formyl indole*, V, m.p. 137–141°, ν_{max} ($CHCl_3$) 3,200 s, 1,720 vs, 1,650 vs, λ_{max} (EtOH) 215, 246, 264, 302 mμ (ε 43,200, 25,000, 18 400, 14,700), λ_{min} 230, 255, 283 mμ (ε 19,500, 17,300, 12,500), λ_{max} (EtOH–1% NaOH) 247, 268, 329 mμ (ε 17,200 23,000, 14,800), λ_{min} 241, 251, 295 mμ (ε 17,150 17,100, 12,300), 1·00 (3H triplet J = 7 c/s, $C\underline{H}_3CH_2$), 1·67 (3H doublet J = 6 c/s, $C\underline{H}_3CH$=), 3·65 (3H singlet, $C\underline{H}_3O_2C$), 5·50 (1H quartet J = 6 c/s), 7·10–7·50 (4H,$\underline{H}$Ar), 8·20(1H broad, $\underline{H}N_a$), 10·10 ppm (1H singlet, C$\underline{H}$O), *m/e* 368(22%), 209(100), 196(63), 194(36), 158(22), 138(31), 136(32), 130(15), metastable ions at *m/e* 180·1 for 209 → 194, 118·7 for 368 → 209. (Found: mol. wt. 368·2103; $C_{23}H_{28}N_2O_3$ requires: mol. wt. 368·2100.)

We thank Dr. J. M. Wilson and Professor A. R. Battersby for the mass spectral measurements.