The Site of the Hydroxyl Groups in Lycorine.

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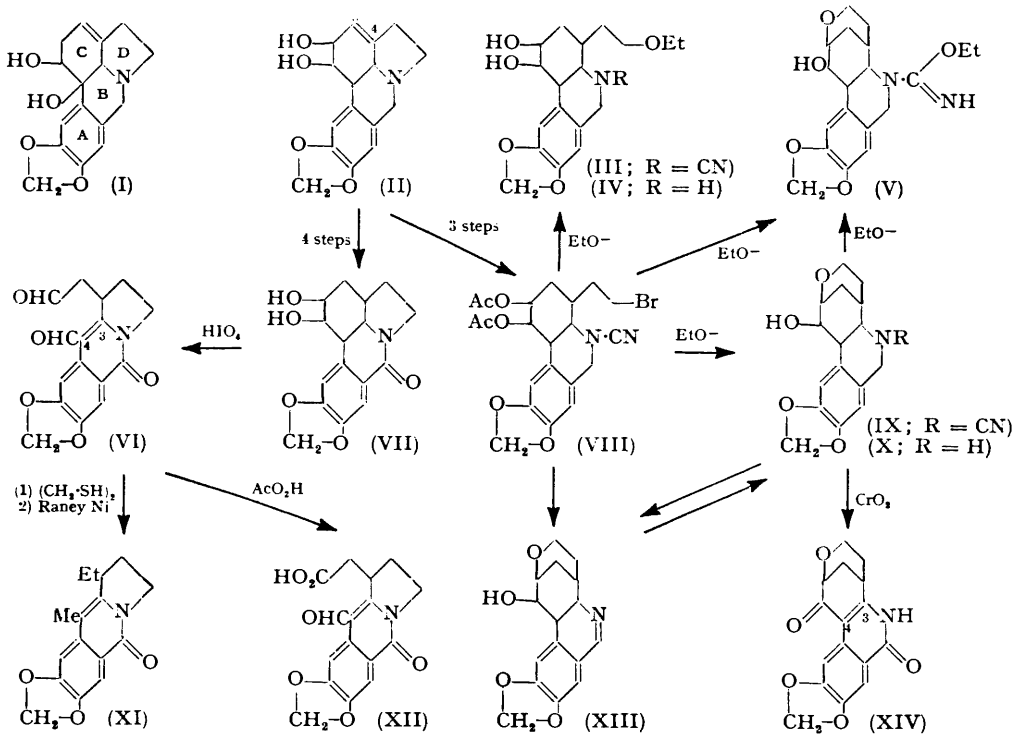
The glycol cleavage product of dihydrolycorinone is now shown to be a 4-acyl*iso*carbostyril derivative, as is also one of the degradation products of diacetyl-ω-bromo-*N*-cyanodihydro*seco*lycorine. These results receive a satisfactory interpretation on the basis of formula (II) for lycorine, which has a disecondary glycol grouping.

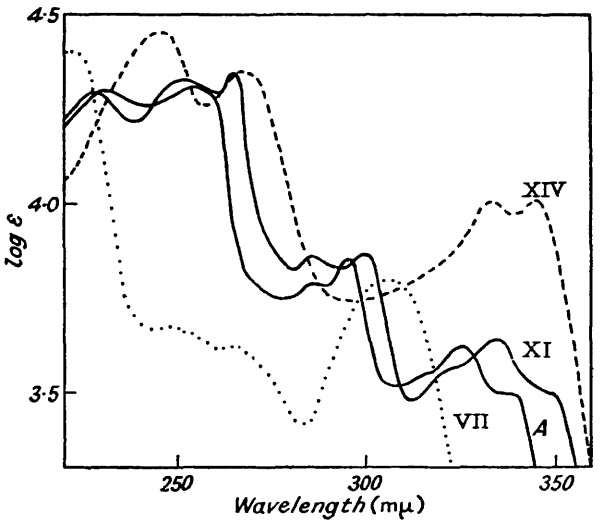
WENKERT (*Chem. and Ind.*, 1954, 1175), in the light of his reinterpretation of some of Kondo's work (Kondo and Katsura, *Ber.*, 1939, **72**, 2083; 1940, **73**, 112), suggested that lycorine must contain the secondary-tertiary glycol grouping shown in (I). There is however an alternative explanation of these experimental results in agreement with the structure (II) for which considerable support already exists (Humber, Kondo, Kotera, Takagi, Takeda, Taylor, Thomas, Tsuda, Tsukamoto, Uyeo, Yajima, and Yanaihara, *J.*, 1954, 4622). In 1939, Kondo and Katsura investigated the action of cyanogen bromide on diacetyldihydrolycorine and obtained the derivative (VIII) which they called diacetyldihydrolycorinebromocyanide but the revised name, diacetyl-ω-bromo-*N*-cyanodihydro*seco*lycorine seems more appropriate (*seco* is here used, as in steroid chemistry, to denote ring fission with addition of two hydrogen atoms at the point of fission); Kondo's terminology has been rationalised below when necessary. Alkaline hydrolysis of the *seco*-compound afforded two bromine-free products, one of which was the *N*-cyano-derivative of the other. The formulæ (IX) and (X) were advanced for these anhydro-



products based on ultimate analyses, formation of a monoacetate, and the fact that the keto-lactam obtained on oxidation was shown not to have a methylene group adjacent to the carbonyl moiety. The keto-lactam was soluble in alkali and reprecipitated unaltered

after acidification and could be *N*-methylated by base and methyl sulphate, then becoming insoluble in alkali. This behaviour was clearly that of an *iso*carbostyril, as was partially recognised by these authors (Kondo and Katsura, *Ber.*, 1939, **72**, 2084, footnote 7), but they put forward the unacceptable structure (XIV; 3 : 4-double bond saturated) for the keto-lactam. Their analytical results as well as ours were in agreement with the *iso*carbostyril formulation (XIV) with which the infrared absorption was consistent, *i.e.*, absence of isolated carbonyl or hydroxyl bands, and presence of a broad band at 1660 cm.$^{-1}$ (overlapping conjugated keto- and lactam groupings). The ultraviolet absorption spectrum (curve XIV) was similar to that of 5 : 6-methylenedioxy*iso*carbostyril (curve *A*) in the long wavelength region, as expected, but quite different from that of corresponding dihydro*iso*-carbostyril, dihydrolycorinone (curve VII).

By treating the *seco*-compound (VIII) with potassium hydroxide in dry ethanol, we have isolated four other compounds besides the expected anhydro-*N*-cyanodihydro*seco*-



(*A*) 6 : 7-*Methylenedioxy*iso*carbostyril.*
(VII) *Dihydrolycorinone.*
(XI) *Ethyl compound from the dialdehyde.*
(XIV) *Keto-lactam.*

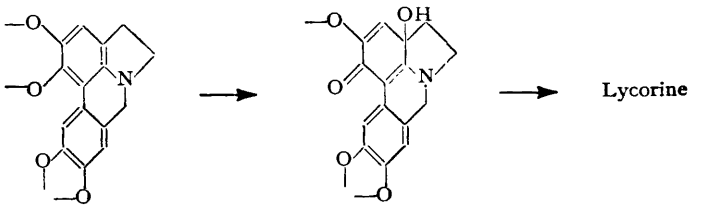
lycorine (IX). One of these, the imidate (V), was present in considerable quantity and was also prepared from the above anhydro-*N*-cyano-compound by the action of hot ethanolic potassium hydroxide. Small amounts of anhydrodihydro*seco*lycorine (X), previously isolated by Kondo and Katsura, along with its dehydro-compound (XIII) were present, and, lastly, since ethoxide ion was present in the reaction medium it was not surprising that the ethoxy-derivative (III) should have been formed. Since the ethoxy-derivative did not lose weight on drying and its further hydrolysis product (IV) still contained the ethoxy-group this assignment must be correct.

From the oxidative study described above it would appear that the oxo*iso*carbostyril residue present in (XIV) is very readily formed and this enabled us to interpret correctly the lead tetra-acetate oxidation of dihydrolycorinone (VII). Although Kondo and Katsura (1940) showed that two mols. of lead tetra-acetate were consumed they suggested formula (VI; 3 : 4-double bond saturated) for the dialdehyde (isolated as its oxime) for which only one mol. of oxidant was required; (VI) would be the predicted formula. Repetition of this work, but with periodic acid as oxidant, gave a dialdehyde, characterised as its oxime, whose properties were in agreement with those given in the earlier work except for the revision of the formula which had two hydrogen atoms less. Also, as predicted, it was insoluble in alkali and its ultraviolet absorption spectrum was almost superimposable upon that of the keto-lactam (XIV). The dialdehyde was converted *via* its bis(ethylene dithio-ketal), followed by desulphurisation with Raney nickel, into the ethyl derivative (XI) whose ultraviolet absorption spectrum (curve XI) exhibited the expected bathochromic shift in the 350-mμ region relative to that of 6 : 7-methylenedioxy*iso*carbostyril (curve *A*). Owing to the paucity of material we were unable to reinvestigate the oxidation of the dialdehyde

(VI) with peracetic acid but the recorded analytical data are in agreement with those for the aldehydo-acid (XII). No skeletal changes have occurred in the formation of dihydrolycorinone since lithium aluminium hydride reduction gave back the starting material, dihydrolycorine.

It should be noted that for ether formation in (IX) and (X) the hydroxyl group and the ethylene residue in (VIII) must lie on the same side of ring C, and if the B/C ring junction is *trans* and the hydroxyl group equatorial (Humber *et al.*, *loc. cit.*) this would mean that in dihydrolycorine ring D is *trans* fused to ring C, which would be unusual for an octahydroindole. For this reason lycorine is now regarded as having a *cis*-fused B/C ring junction, but the unequivocal solution of this stereochemical problem must await further work.

The structure of lycorine as well as that of lycorenine (Kitagawa, Taylor, Uyeo, and Yajima, *J.*, 1955, 1066) fit well into Wenkert's scheme for the biogenesis of the pyrrocoline alkaloids (*Chem. and Ind.*, 1953, 1088) but not with his revision (Wenkert and Hansen, *ibid.*, 1954, 1262). The latter scheme was put forward to conform with his ideas as to the structures of these alkaloids and to accommodate Robinson's objection (*ibid.*, 1953, 1317) in the former to the final step, reduction of the aromatic nucleus. However the formation of ring C in lycorine from an aromatic ring may simply be that as a consequence of further oxidation the ring becomes readily reducible, as in the example shown below.



Experimental

Absorption spectra were taken in 95% ethanol unless otherwise stated.

Dihydrolycorine.—Dihydrolycorinone (0·1 g.) and lithium aluminium hydride (0·2 g.) in tetrahydrofuran (30 ml.) were heated under reflux with stirring for 5 hr. Water was added and the reaction mixture was extracted several times with chloroform, dried (K_2CO_3), and evaporated to dryness. The basic portion of the residue crystallised from ethanol to give colourless needles (25 mg.), m. p. 248° (decomp.), undepressed by dihydrolycorine.

Dialdehyde (VI).—Aqueous periodic acid (0·1M; 60 ml.) was added to dihydrolycorinone (0·3 g.) in 20% acetic acid (60 ml.) and kept at 40—50° for 5 hr. The mixture was extracted with ethyl acetate (5 × 60 ml.), and the combined extracts were dried (K_2CO_3) and evaporated to dryness in an atmosphere of carbon dioxide. Trituration of the residue with methanol gave crystals which were recrystallised from the same solvent, affording the *dialdehyde* (32 mg.) which after drying had m. p. 212° (decomp.), $[\alpha]_D$ +101° (*c* 0·4 in EtOH) (Found, on a sample dried *in vacuo* over P_2O_5 at 110° for 8 hr.: C, 64·5; H, 4·6. $C_{16}H_{13}O_5N$ requires C, 64·2; H, 4·4%). The infrared absorption spectrum showed bands in the carbonyl region at 1730, 1661 (shoulder), 1639, and 1613 cm.$^{-1}$ (shoulder), and the ultraviolet absorption spectrum had $\lambda_{max.}$ in 95% EtOH 249, 266, 309, 332, and 346 mμ (log ε 4·40, 4·36, 3·86, 3·96, and 3·97), and in 0·001N-ethanolic potassium hydroxide $\lambda_{max.}$ 250, 264 (inflexion), 300, 330, and 344 mμ (log ε 4·32, 4·21, 3·79, 3·72, and 3·67). The dioxime after four crystallisations from ethanol had m. p. 252—253° (decomp.) (Found: C, 58·1, 57·6; H, 4·8, 4·7; N, 12·5. Calc. for $C_{16}H_{15}O_5N_3$: C, 58·4; H, 4·6; N, 12·8%). Kondo and Katsura (1940) recorded m. p. 233° for the dioxime.

Dialdehyde Bis(ethylene Dithioketal).—The aldehyde (32 mg.), ethanedithiol (0·3 ml.), and boron trifluoride–ether complex (0·2 ml.) were gently warmed with stirring and after 10 min. methanol was added. The precipitate (35 mg.), m. p. 247—249° after crystallisation from ethanol, gave the pure *derivative*, m. p. 255° (Found: C, 53·4, 53·1; H, 4·6, 4·6; S, 28·1. $C_{20}H_{21}O_3NS_4$ requires C, 53·2; H, 4·7; S, 28·4%).

Desulphurisation. The bisdithioketal (50 mg.), Raney nickel (7 g.), and dry methanol (100 ml.) were refluxed for 8 hr. After filtration from the catalyst and evaporation under reduced pressure the resulting oil was chromatographed over activated alumina in benzene.

After initial elution of a small amount of oil the pure *compound* (XI) was obtained from the succeeding fractions which on crystallisation from acetone gave colourless needles (29 mg.), m. p. 153—154°, $[\alpha]_D$ +11·1° (*c*, 2·0 in EtOH) (Found: C, 70·9; H, 6·2; N, 5·1; *C*-Me, 10·4, 7·8. $C_{16}H_{17}O_3N$ requires C, 70·8; H, 6·3; N, 5·2; 2*C*-Me, 11·1%). The ultraviolet absorption spectrum had $\lambda_{max.}$ 229, 250, 265, 286, 300, 322 (inflexion), 335, and 350 mμ (inflexion) (log ε 4·30, 4·34, 4·35, 3·86, 3·87, 3·56, 3·64, and 3·51).

*Diacetyl-ω-bromo-*N-*cyanodihydro*seco*lycorine* (VIII).—Equal quantities of diacetyl-lycorine and cyanogen bromide were heated under reflux in dry benzene to yield the *seco*-compound, m. p. 177—178°, $[\alpha]_D$ −71·6° (*c* 0·6 in $CHCl_3$) (Found: C, 52·7; H, 4·9. Calc. for $C_{21}H_{23}O_6N_2Br$: C, 56·2; H, 4·8%). It reacted only slowly with silver nitrate solution.

Action of Base on the seco-*Compound* (VIII).—A solution of the *seco*-compound (0·5 g.) and potassium hydroxide (1·3 g.) in dry ethanol (25 ml.) was kept at room temperature for 4 hr. after which carbon dioxide was introduced, the precipitated potassium carbonate filtered off, and the resulting solution taken to dryness. The residue in chloroform was shaken with dilute hydrochloric acid to remove the basic portion, and the neutral material gave after crystallisation from ethanol anhydro-*N*-cyanodihydro*seco*lycorine (IX) (180 mg.), m. p. 215—217°, $[\alpha]_D$ −197° (*c* 0·5 in $CHCl_3$) (Found: C, 64·9; H, 5·8. Calc. for $C_{17}H_{18}O_4N_2$: C, 65·0; H, 5·8%). The mother-liquors from the crystallisation were chromatographed over activated alumina, and the first fraction eluted with benzene–chloroform (1 : 16) gave a further quantity of the anhydro-cyano-compound (20 mg.) but the succeeding eluates furnished a solid (25 mg.) which after crystallisation from ethanol yielded *anhydro-*N-*cyano-ω-ethoxydihydro*seco*lycorine* (III), m. p. 187—188°, $[\alpha]_D$ −174° (*c* 0·7 in $CHCl_3$) (Found: C, 63·2; H, 6·7; OEt, 13·0. $C_{19}H_{24}O_5N_2$ requires C, 63·3; H, 6·7; OEt, 12·5%). This compound did not lose weight on drying *in vacuo* and is probably identical with the " alcoholate of dihydrocyanolycorine anhydride, m. p. 182° " of Kondo and Katsura (1939).

The aqueous acidic solution obtained as above was basified and extracted with chloroform to afford an oil (40 mg.). The combined oily fractions (0·5 g.) from a series of runs were chromatographed over activated alumina and eluted with benzene–chloroform (1 : 16). The first elutate furnished *anhydrodehydrodihydro*seco*lycorine* (XIII) (15 mg.), m. p. 226° identical with that of a sample prepared from anhydrodihydro*seco*lycorine (see below). Further elution with the same solvent mixture gave a semicrystalline product (150 mg.) which after drainage on a porous plate was crystallised from ethyl methyl ketone, to give the *imidate* (V), m. p. 110°, which after drying at 105° *in vacuo* rose to 156—158°, $[\alpha]_D$ −89·8° (*c* 0·6 in $CHCl_3$) (Found: C, 63·2; H, 6·6; N, 7·4; OEt, 12·5. $C_{19}H_{24}O_5N_2$ requires C, 63·3; H, 6·7; N, 7·8; OEt, 12·5%). The infrared spectrum showed a strong band at 1608 cm.$^{-1}$ (CN) which should be compared with the band at 1600 cm.$^{-1}$ for *O*-ethyl-*N*-methyl-*N*-phenyl*iso*urea. The imidate (140 mg.) was also obtained as the major product of the action of hot ethanolic potassium hydroxide on anhydro-*N*-cyanodihydro*seco*lycorine (200 mg.) for 2 hr. Further elution of the above column with acetone gave an oil from which anhydrodihydro*seco*lycorine (16 mg.) was isolated after crystallisation from ethyl methyl ketone.

*Anhydrodihydro*seco*lycorine* (X).—Anhydro-*N*-cyanodihydro*seco*lycorine (100 mg.) and 30% sulphuric acid (5 ml.) were heated under reflux for 1·5 hr. then diluted with water and extracted with chloroform. The aqueous solution was basified and extracted with chloroform, to yield the anhydro-*seco*-compound, m. p. 198°, $[\alpha]_D$ −181° (*c* 0·5 in $CHCl_3$) (Found: C, 66·5; H, 6·6. Calc. for $C_{16}H_{19}O_4N$: C, 66·4; H, 6·6%). The action of acid on the imidate (V) gave the same product in 60% yield.

*Dehydrodihydro*seco*lycorine* (XIII).—Repeated evaporation of a chloroform solution of the above anhydro-*seco*-compound to dryness on a water-bath gave the *dehydro-compound* readily separable from the starting material because of its low solubility in ethyl methyl ketone from which it crystallised with m. p. 226°, $[\alpha]_D$ −81° (*c* 0·3 in $CHCl_3$) (Found: C, 67·1; H, 5·9. $C_{16}H_{17}O_4N$ requires C, 66·9; H, 6·0%). The ultraviolet absorption spectrum showed $\lambda_{max.}$ 320, 290, and 230 mμ (log ε 4·24, 3·62, and 3·62) similar to those of 3 : 4-dihydro*iso*quinolines (Tomita, Uyeo, Sawa, Doi, and Miwa, *J. Pharm. Soc. Japan*, 1949, **69**, 22). Hydrogenation in acetic acid with platinum oxide catalyst regenerated the original anhydro-compound (X).

*ω-Ethoxydihydro*seco*lycorine* (IV).—*N*-Cyano-ω-ethoxydihydro*seco*lycorine (100 mg.) and 30% sulphuric acid (5 ml.) were heated under reflux for 1 hr. The cooled solution was diluted with water and extracted with chloroform to recover unchanged starting material (10m g.), then made alkaline, and the chloroform extract was chromatographed over activated alumina. The first and third eluates were oily and yielded no crystalline material; however the second eluate gave a solid (49 mg.) which furnished pure *ω-ethoxydihydro*seco*lycorine* (30 mg.),

m. p. 167—168°, $[\alpha]_D$ −168° (*c* 0·5 in $CHCl_3$), after one crystallisation from ethyl methyl ketone (Found : C, 64·1; H, 7·4; N, 4·1; OEt, 13·6. $C_{18}H_{25}O_5N$ requires C, 64·5; H, 7·5; N, 4·2; OEt, 13·4%).

Keto-lactam (XIV).—This was prepared by chromic acid oxidation of anhydro-*N*-cyanodihydro*seco*lycorine (IX) (280 mg.) by Kondo and Katsura's procedure (1939). The crude compound, after three crystallisations from ethanol, furnished the pure *keto-lactam* (28 mg.), m. p. 337° (lit., 341°) (Found : C, 64·2, 63·9; H, 4·6, 4·5. $C_{16}H_{13}O_5N$ requires C, 64·2; H, 4·4%). The ultraviolet absorption spectrum showed $\lambda_{max.}$ in 95% EtOH 246, 266, 332, and 345 mμ (log ε 4·46, 4·35, 4·0, and 4·01) and in 0·001N-ethanolic potassium hydroxide 232, 271, 304, 316, 355, and 370 mμ (log ε 4·10, 4·32, 3·78, 3·79, 4·07, and 4·13). In the infrared there was a strong band with a broad peak at 1667—1650 cm.$^{-1}$ with a medium strength shoulder at 1642 cm.$^{-1}$.

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