1056. *The* Senecio *Alkaloids. Part XVIII.*[1] *The Structure of Hygrophylline, the Alkaloid from* Senecio hygrophylus *Dyer and Sm.*

By F. D. SCHLOSSER and F. L. WARREN

The alkaloid, $C_{18}H_{27}NO_6$, now named hygrophylline, from *Senecio hygrophylus* Dyer and Sm., is hydrolysed to platynecine and a new acid, hygrophyllinecic acid, isolated as its monolactone (II), $C_{10}H_{14}O_5$, which gives a dilactone (III) and is reduced to dihydrosenecic acid lactone (IV). From n.m.r. and u.v. spectra, and oxidation studies, the structure of hygrophyllinecic acid is given as 2*L*,3*R*,4*R*-2,4-dihydroxy-3-methylhept-*trans*-5-ene-2,5-dicarboxylic acid.

RICHARDSON and WARREN[2] isolated, from *Senecio hygrophylus* Dyer and Sm., two alkaloids, platyphylline (I; X = Y = H) and rosmarinine (I; X = H, Y = OH), and reported after flowering the plant yielded an alkaloid, $C_{18}H_{27}NO_6$, m. p. 174°. We have found this alkaloid in good yield in pre-flowering material. This alkaloid gave, on hydrolysis with acid, platynecine and a new acid, hygrophyllinecic acid, isolated as its monolactone $C_{10}H_{14}O_5$, m. p. 180—181°, which was converted by distillation into its dilactone, $C_{10}H_{12}O_4$, m. p. 103—105°. Alkaline hydrolysis gave platynecine and intractable acid products.

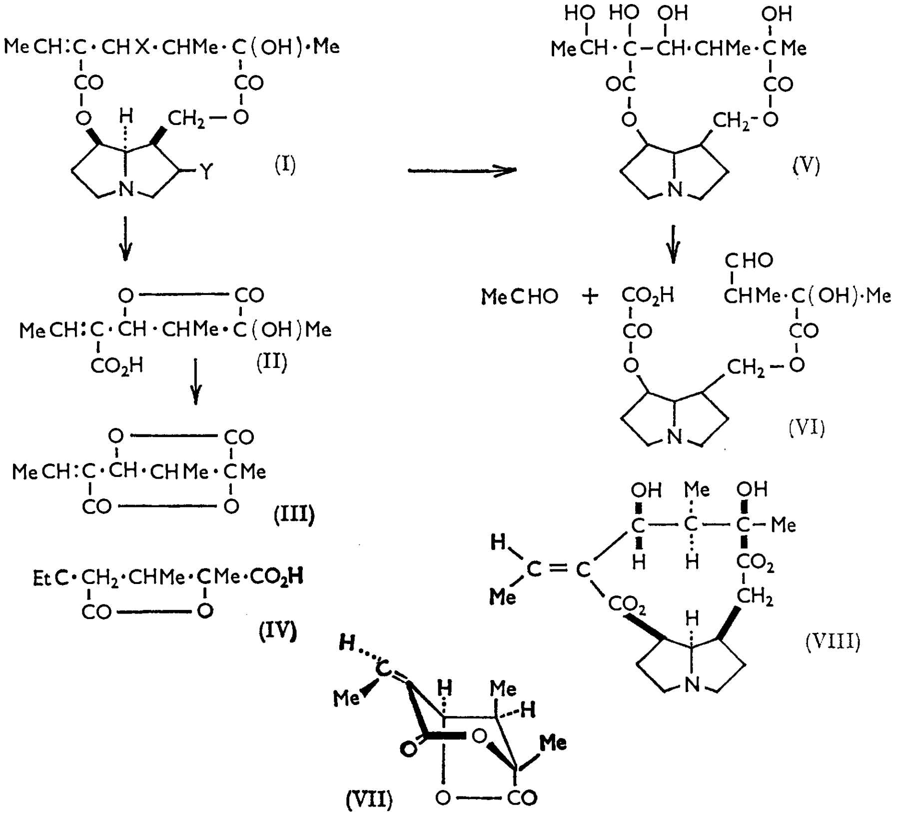
Kuhn–Roth determination on the alkaloid itself showed three *C*-methyl groups. The n.m.r. spectrum of the alkaloid [τ 9·1 (doublet), 8·7 (singlet), and 8·0 (doublet)] and of hygrophyllinecic acid dilactone [τ 9·0 (doublet), 8·5 (singlet), and 7·7 (doublet)] can be accommodated in groupings $\mathrm{MeCH}{<}$, $\mathrm{MeC}{\leqslant}$, and $\mathrm{MeCH}{=}$, respectively. Additional peaks for the dilactone were indicative of the groupings $\mathrm{MeCH{:}C}{\leqslant}$ (τ 3·3, single proton showing 1 : 3 : 3 : 1 splitting) and $-\overset{|}{\underset{|}{\mathrm{C}}}-\mathrm{CH(O-)\cdot CHMe-}$ (τ 5·05, doublet with each peak showing fine splitting, and τ 7·2—7·8 complex splitting).

Ozonisation of hygrophyllinecic acid monolactone gave acetaldehyde and carbon dioxide, which indicated that the ethylidene group was part of the system $-\mathrm{MeCH{:}C(CO_2H)}-$.

---

[1] Part XVII, C. A. Hughes, C. G. Gordon-Gray, F. D. Schlosser, and F. L. Warren, *J.*, 1965, 2370.
[2] M. F. Richardson and F. L. Warren, *J.*, 1943, 452.

Lithium aluminium hydride reduction of hygrophylline, and periodate oxidation of the neutral product, showed one glycol grouping and gave formaldehyde, indicative of the group $>$C(OH)$\cdot$CH$_2\cdot$OH from an α-hydroxy-acid. Attempts to prepare the 2,4-dinitrophenylhydrazone of the residual ketone gave only the 2,4-dinitrophenylhydrazone of acetaldehyde, probably due to a retroaldol degradation. The groupings indicated could well be accommodated in the general carbon skeleton for the necic acids,[3] and lead to the structure for hygrophyllinecic acid monolactone (II) and dilactone (III).



Proof for these structures was forthcoming by the hydrogenolysis of hygrophyllinecic acid monolactone with Adams catalyst activated with perchloric acid, to give dihydrosenecic acid identified as its lactone (IV), m. p. 122—124°,[4] so that hygrophyllinecic acid is hydroxysenecic acid. This catalyst, reported as reducing esters [5] and δ-lactones [6] to ethers, in our case effected hydrogenolysis of the γ-lactone, indicative that the hydroxyl group was in the allylic position. This was confirmed as follows. Hygrophylline (I; X = OH, Y = H) was oxidised with performic acid to dihydroxydihydrohygrophylline (V), which on oxidation with sodium periodate gave actaldehyde and a product formulated as (VI), which on hydrolysis gave oxalic acid.

Since the absolute configuration of senecic acid is known,[7] the structure of hygrophyllinecic acid can be represented as in (VII), *i.e.*, 2*L*,3*R*,4*R*-2,4-dihydroxy-3-methylhept-*trans*-5-ene-2,5-dicarboxylic acid. It is impossible to form the dilactone if the 4-hydroxyl

---

[3] M. Kropman and F. L. Warren, *J.*, 1950, 700.
[4] R. Adams and T. R. Govindachari, *J. Amer. Chem. Soc.*, 1949, **71**, 1953.
[5] J. D. Chanley and T. Mezzetti, *J. Org. Chem.*, 1964, **29**, 228.
[6] J. T. Edward and J. M. Ferland, *Chem. and Ind.*, 1964, 975.
[7] J. Fridrichsons, A. McL. Mathieson, and J. D. Sutor, *Tetrahedron Letters*, 1960, No. 23, 35.

group has the opposite configuration, and the *trans*-geometry is assigned since the absorption peak 220 mμ has ε 4800.[3] Since the absolute configuration of platynecine [8] is known, the structure of the alkaloid may be given as (VIII).

EXPERIMENTAL

Extraction.—Dried and ground material (1 kg.) from *Senecio hygrophylus* C.A. Sm. was extracted as previously described,[9] to give hygrophylline which crystallised from acetone in prisms (23 g.), m. p. 173—174°, $[\alpha]_D^{20}$ $-67{\cdot}3°$ (*c* 2·9 in ethanol) (Found: C, 61·4; H, 8·1%; *C*–Me, 2·6. Calc. for $C_{18}H_{27}NO_6$: C, 61·2; H, 7·2%; *C*–Me, 3·0). Richardson and Warren [2] gave un-named alkaloid, m. p. 174°.

Hydrolysis of Hygrophylline.—Hygrophylline (1 g.) and 2N-sulphuric acid (25 ml.) were heated under reflux for 3 hr. The cooled solution, extracted continuously with ether, gave a solid (550 mg.) which, crystallised from benzene, gave *hygrophyllinecic acid monolactone* (250 mg.), m. p. 181°, $[\alpha]_D^{20}$ $-187{\cdot}9°$ (*c* 3·3 in ethanol), $\lambda_{max.}$ 220 (ε 4830) [Found: C, 56·4; H, 6·5%; Equiv. 220 and 113 (back titration). $C_{10}H_{14}O_5$ requires C, 56·1; H, 6·6%; Equiv. 214 and 107]. The original hydrolysis solution was made alkaline, and continuously extracted with chloroform, to give an oil which formed a picrate (Found: C, 45·4; H, 4·35. Calc. for $C_{14}H_{16}N_4O_8$: C, 45·65; H, 4·4%), m. p. 278° undepressed by admixture with anhydroplatynecine picrate. Hydrolysis of hygrophylline in alkaline solution gave platynecine.

Hygrophyllinecic Acid Dilactone.—The monolactone (50 mg.), sublimed three times at 120°/0·5 mm., gave a semicrystalline gum which was treated with cold sodium hydrogen carbonate solution and extracted with ether. The ether solution gave a solid which resublimed to give *hygrophyllinecic acid dilactone* (20 mg.), m. p. 103—105°, $[\alpha]_D^{20}$ $-97{\cdot}6°$ (*c* 3·3 in ethanol). $\lambda_{max.}$ 220 mμ (Found: C, 61·1; H, 6·3. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·2%).

Ozonolysis of Hygrophyllinecic Acid Monolactone.—The monolactone (100 mg., 1 mol.) in ethyl acetate was ozonised at −10°. The water-decomposed ozonide gave acetaldehyde, precipitated as acetaldehyde dimedone (80 mg., 0·56 mol.), m. p. 140°, and carbon dioxide, precipitated as barium carbonate (85 mg., 0·91 mol.).

Hydrogenolysis of Hygrophyllinecic Acid Monolactone.—Hygrophyllinecic acid monolactone (100 mg.), acetic acid (40 ml.), 70% perchloric acid (0·1 mol.), and Adams catalyst were shaken with hydrogen at 700 lb./in.^{2} for 6 hr. The oily product was distilled at 140°/0·5 mm. to an oil which slowly solidified, and which, recrystallised from ether–light petroleum, gave dihydrosenecic acid lactone (Found: C, 59·5; H, 8·1. Calc. for $C_{10}H_{16}O_4$: C, 60·0; H, 8·05%), m. p. 122—124° undepressed with authentic specimens.

Lithium Aluminium Hydride Reduction of Hygrophylline.—Hygrophylline (500 mg., 1 mol.) was extracted with ether into lithium aluminium hydride (350 mg.), and worked up to give a neutral product (200 mg.). The neutral product (100 mg.) was oxidised with 0·2N-sodium metaperiodate (25 ml.; 5mM) for 2 days, and the excess determined with 0·1N-sodium thiosulphate (61·3 ml.; 3·7mM). The solution was distilled under reduced pressure into dimedone, to give formaldehyde dimedone (80 mg., 0·2 mol.), m. p. 190—191°. The residue, in water, was extracted with ether to give an oil (30 mg.), which gave a 2,4-dinitrophenylhydrazone purified by chromatography on alumina using benzene as solvent, to yield needles of acetaldehyde 2,4-dinitrophenylhydrazone.

Performic Oxidation of Hygrophylline.—Hygrophylline (500 mg.), 30% hydrogen peroxide (1·5 ml.), and formic acid (4 ml.) were set aside for 2 days. The formic acid was removed under reduced pressure, 0·5N-hydrochloric acid (100 ml.) and zinc dust (3 g.) were added, and the mixture was stirred for 4 hr. The solution was basified with ammonia and extracted with chloroform. The extract gave a gum which crystallised from ether to yield *dihydroxydihydrohygrophylline* (350 mg.), m. p. 85—87° (Found: C, 55·6; H, 7·9. $C_{18}H_{29}NO_8$ requires C, 55·8; H, 7·5%).

Periodate Oxidation of Dihydroxydihydrohygrophylline.—The dihydroxy-compound (100 mg., 1 mol.) and 0·2M-sodium metaperiodate (25 ml.) were set aside for 2 days. Nitrogen was passed through the solution at 90°, and into dimedone, to yield acetaldehyde dimedone, m. p. 140°. The residual solution was boiled, cooled, neutralised, barium chloride solution added, and the

---

[8] M. E. von Klemperer and F. L. Warren, *J.*, 1958, 4574.
[9] M. J. Koekemoer and F. L. Warren, *J.*, 1951, 66.

barium oxalate (22·2 mg., 0·35 mol.) filtered off, identified by infrared spectrum, and estimated by titration with 0·0081N-permanganate (Found: 20·0 ml. $BaC_2O_4H_2O$ requires 21·6 ml.).

The authors thank Dr. K. Pachler for n.m.r. spectra, and acknowledge grants from African Explosives and Chemical Industries.

C.S.I.R. NATURAL PRODUCTS RESEARCH UNIT,
DEPARTMENT OF CHEMISTRY AND CHEMICAL TECHNOLOGY, UNIVERSITY OF NATAL,
PIETERMARITZBURG, SOUTH AFRICA.

[*Received, May* 14*th*, 1965.]