The Senecio *Alkaloids. Part X.* The Structure of Rosmarinecine and its Synthesis from Retronecine.*

By L. J. Dry, M. J. Koekemoer, and F. L. Warren.

[Reprint Order No. 5702.]

Rosmarinecine (I), proved to be a trihydroxy-compound by the formation of a tri-*O*-acetate (II) and trichloride (III), is dehydrated to anhydrorosmarinecine (VI). The hydroxyl group of anhydrorosmarinecine has been replaced by chlorine to give anhydrochloroplatynecine which is reduced to anhydroplatynecine (IX), which in turn is readily formed from platynecine and one mol. of toluene-*p*-sulphonyl chloride.

Retronecine (X) is oxidised by perbenzoic acid to epoxyretronecine *N*-oxide (XI) which is reduced catalytically with Raney nickel to rosmarinecine (I), and with platinum oxide to epoxyretronecine (XII) which in turn, with Raney nickel, gives rosmarinecine (I).

The reactions confirm the general structure previously advanced and permit a complete definition of the spatial configuration of the molecule.

Rosmarinecine is a saturated tertiary amine for which structure (I) was proposed by Richardson and Warren (*J.*, 1943, 452). In advancing this structure the existence of a methylpyrrolizidine skeleton, characteristic of other *Senecio* alkaloids, was assumed. Furthermore, whereas experimental evidence did not exclude one alternative formula, structure (I) was preferred as it represented rosmarinecine as the hydroxyl derivative of platynecine (V), the dehydration of which would give retronecine.

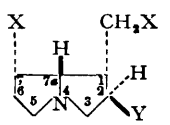
* Part IX, *J.*, 1952, 3445.

To test the validity of these assumptions additional experiments have been carried out. The existence of three hydroxyl groups was established by the acetylation of rosmarinecine to give tri-*O*-acetylrosmarinecine (II), characterised as its picrate, m. p. 138—139°, whilst the action of thionyl chloride gave a trichloro-compound (III). Benzoylation, however, gave only a dibenzoate (IV), the formulation of which follows from the work of Orechov and Konovalova (*Ber.*, 1936, **69**, 1908) who benzoylated the two hydroxyl groups of platynecine (V).

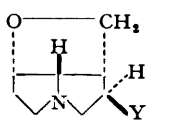
Orechov, Konovalova, and Tiedebel (*Ber.*, 1935, **68**, 1886) found that platynecine (V) and thionyl chloride gave anhydroplatynecine (IX) in high yield and only small quantities of the dichloro-derivative. Accordingly it appeared attractive to treat rosmarinecine (I) with this reagent to form the furan ring and replace the 2-hydroxyl group with chlorine to form anhydrochloroplatynecine (VIII). The reaction of rosmarinecine and thionyl chloride, however, resulted in the formation in good yield of a 2 : 7-dichloro-1-chloromethylpyrrolizidine, characterised as its picrate. This observation is more in accordance with the finding by Adams *et al.* (*loc. cit.*) that thionyl chloride and platynecine gave dichloromethylpyrrolizidine (I; but X = Cl, Y = H).

To establish that two of the hydroxyl groups were in an $\alpha\delta$-position to one another rosmarinecine was dehydrated with sulphuric acid to give anhydrorosmarinecine (VI), characterised as its picrate and containing one hydroxyl group since it yielded a monoacetyl derivative (VII), isolated as picrate, m. p. 190—192°. In the initial experiments the anhydro-compound was extracted from inorganic salt with chloroform in a Soxhlet apparatus; then in place of the base there slowly separated anhydrorosmarinecine dichloromethochloride, m. p. 198—200°. The anhydrorosmarinecine (VI) with thionyl chloride gave anhydrochloroplatynecine (VIII) which was reduced catalytically to anhydroplatynecine (IX), characterised as its picrate, m. p. 265—268° (decomp.) (cf. Orechov and Konovalova, *loc. cit.*).

Leonard and Felley (*J. Amer. Chem. Soc.*, 1950, **72**, 2537) placed the hydroxymethyl group of platynecine *trans* to the 7*a*-hydrogen atom in view of the ready dehydration to a furan ring. There was no evidence of the orientation of the 7-hydroxyl group because inversion during ring closure could not be excluded. We attempted to obtain information on the orientation of this hydroxyl group by the preparation of the toluene-*p*-sulphonyl ester of the primary hydroxyl group and the fission of this ester to form anhydroplatynecine; however, either there was no reaction or the product was anhydroplatynecine. The ready removal of toluene-*p*-sulphonic acid was indicative of the close proximity of the secondary hydroxyl group. This reaction occurs by the elimination of the sulphonate anion with the hydrogen ion from the 7-hydroxyl group and no inversion can occur. Thus the 7-hydroxyl group is *cis* to the 1-hydroxymethyl group and both are *trans* to the 7*a*-hydrogen atom.



(I): X = Y = OH
(II): X = Y = OAc
(III): X = Y = Cl
(IV): X = OBz, Y = OH
(V): X = OH, Y = H



(VI): Y = OH
(VII): Y = OAc
(VIII): Y = Cl
(IX): Y = H

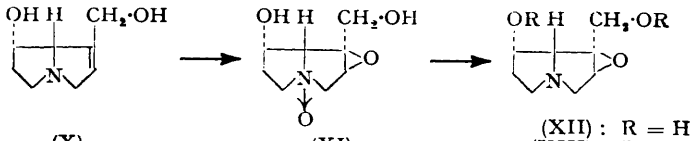
The N–$C_{(7a)}$ bond being assumed to be in the plane of the paper, the two rings are inclined towards each other behind the plane of the paper, thus:

An attempt was made to synthesise rosmarinecine (I) from retronecine (X) by way of the epoxide. Catalytic reduction of retronecine gave platynecine (V) (cf. Adams and Hamlin, *J. Amer. Chem. Soc.*, 1942, **64**, 2597) in which the hydrogen added to the outer fold of the pyrrolizidine nucleus, as was to be expected as the side above the plane of the paper is less structurally hindered. For the same reason it was expected that epoxyretronecine would have the β-configuration * (XII) and when opened by catalytic

* β refers to a bond projecting above the plane of the paper when the formula is oriented as shown in (I)—(IX).

reduction could give two products, one of which would be rosmarinecine (I). Since it was found here that rosmarinecine could not readily be directly dehydrated to senecionine (see following paper), it seemed likely that the 1-hydrogen atom, known to be β, and the hydroxyl group at $C_{(4)}$ were *cis* to each other, and that rosmarinecine therefore had a β-hydroxyl group at the latter position.

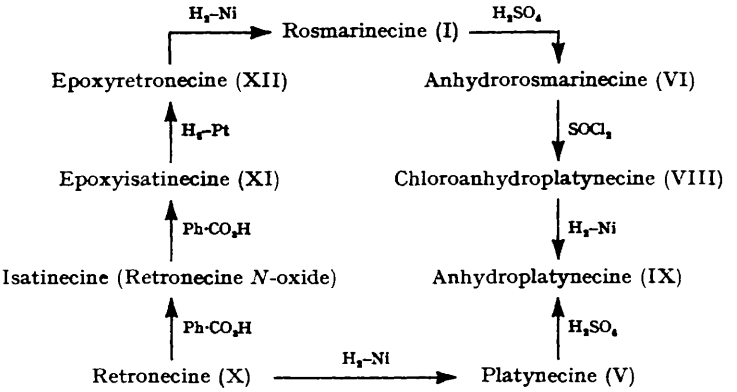
Retronecine readily reacted with perbenzoic acid to give isatinecine (retronecine *N*-oxide), which then slowly took up another atom of oxygen to give epoxyisatinecine. Isatinecine, however, could be epoxidised satisfactorily only in the presence of an initial excess of benzoic acid, a precaution unnecessary in the case of retronecine since the rapid formation of the *N*-oxide was accompanied by the generation of the required benzoic acid. The epoxyisatinecine was readily reduced with zinc dust (cf. Koekemoer and Warren, *J.*, 1951, 66), and catalytically in the presence of Adams platinic oxide, to give epoxyretronecine (XII) in quantitative yield. The epoxide was extremely stable to both



alkaline and acid hydrolysis. The compound (XII) was readily acetylated to a liquid diacetyl compound (XIII), isolated as picrate, m. p. 151—152°. Reduction of (XI) or (XII) with Raney nickel gave a semi-solid gum. The bulk of the product, which contained no glycol grouping (Criegee test, *Ber.*, 1931, **64**, 260), was rosmarinecine since it readily gave rosmarinecine picrate, m. p. 170°, triacetyl rosmarinecine picrate, m. p. 139°, and dibenzoyl rosmarinecine picrate, m. p. 179—180°.

The configuration of the hydroxyl groups assigned from the synthetic experiments is in agreement with our inability to obtain an *iso*propylidene ether with acetone.

Since the structures of retronecine (X), platynecine (V), and anhydroplatynecine (IX) are established (cf. Adams and Hamlin, *J. Amer. Chem. Soc.*, 1942, **64**, 2597; Adams and Leonard, *ibid.*, 1944, **66**, 257), that of rosmarinecine (I) previously advanced by Richardson and Warren (*loc. cit.*) is confirmed. Further these experiments indicate the similarity in the stereoconfiguration of the hydroxyl groups in platynecine and rosmarinecine as well as in retronecine.



Experimental

Some analyses are by Mrs. Y. Merchant of these laboratories.

Tri-O-*acetylrosmarinecine* (II).—Rosmarinecine (500 mg.) was refluxed with acetic anhydride (10 ml.), and the product poured into water and basified with sodium carbonate. The chloroform extract gave an oil which yielded with picric acid *tri*-O-*acetylrosmarinecine picrate*, monoclinic needles (from ethanol), m. p. 138—139·5° (Found: C, 45·6; H, 4·4; N, 10·7. $C_{20}H_{24}O_{13}N_4$ requires C, 45·5; H, 4·6; N, 10·6%).

Di-O-benzoylrosmarinecine (IV).—Rosmarinecine (3·1 g., 1 mol.) in pyridine (20 ml.) was treated at 0° with redistilled benzoyl chloride (5 ml., 2·4 mols.) dropwise. After 5 min. at 20° and 5 min. at 40° the dark red solution was poured on ice-water, treated with ammonia, and extracted with ether. The resulting solid from the ether extract, freed from pyridine in a vacuum and crystallised several times from 80% ethanol, gave the *dibenzoate*, m. p. 179—180° (Found : C, 69·1, 69·5; H, 6·1, 6·2. $C_{22}H_{23}O_5N$ requires C, 69·3; H, 6·1%), in quantitative yield.

Anhydrorosmarinecine (VI).—Rosmarinecine (2 g.) was added in portions to 70% sulphuric acid (15 ml.) at 0° and then heated at 100° for 2 hr. The cooled solution was poured into water, decolorised with charcoal, made alkaline with solid potassium hydroxide (30 g.), reacidified with dilute sulphuric acid, and evaporated under reduced pressure. The solid was ground with sodium carbonate and extracted (Soxhlet) with ethanol. The extract gave an oil which easily sublimed at 37°/6 μ to give anhydrorosmarinecine as colourless, very deliquescent prisms, m. p. 63—66° (Found : C, 59·4; H, 7·7; N, 8·9. Calc. for $C_8H_{13}O_2N$: C, 61·9; H, 8·4; N, 9·0%). This gave a *picrate*, which crystallised from ethanol in needles, m. p. 183—185° (Found : C, 43·7; H, 4·3; N, 14·4. $C_{14}H_{16}O_9N_4$ requires C, 43·75; H, 4·2; N, 14·6%). The *picrolonate* crystallised from ethanol in yellow laminæ, m. p. 232—234° (Found : C, 51·8; H, 5·2; N, 16·1. $C_{18}H_{21}O_7N_5$ requires C, 51·55; H, 5·05; N, 16·7%). The distilled anhydrorosmarinecine gave acetylanhydrorosmarinecine picrate, m. p. 190—192°, identical with that described below.

Extraction of the solid ground with sodium carbonate (see above) with chloroform resulted in the gradual separation of a solid from the chloroform extract. Recrystallisation of this product several times from methanol–acetone gave *anhydrorosmarinecine dichloromethochloride* as monoclinic prisms, m. p. 198—200° (decomp.) [Found : C, 39·2, 39·2; H, 5·7, 5·3; N, 4·9; Cl, 38·4; Cl (ionic) 16·4. $C_9H_{14}O_2NCl_3$ requires C, 39·4; H, 5·1; N, 5·1; Cl, 38·7; Cl (ionic) 12·9%].

The crude product (150 mg.) was acetylated as described for rosmarinecine. The oily product with picric acid gave *O-acetylanhydrorosmarinecine picrate* which crystallised from ethanol in birefringent needles, m. p. 190—192° (Found : C, 45·1; H, 4·1; N, 13·2. $C_{16}H_{18}O_{10}N_4$ requires C, 45·1; H, 4·3; N, 13·1%). *Anhydrorosmarinecine hydrochloride* crystallised from ethanol–acetone as prismatic needles, m. p. 173—176° [Found : C, 50·3; H, 7·5; N, 7·2; Cl (ionic), 17·6. $C_8H_{14}O_2NCl$ requires C, 50·1; H, 7·4; N, 7·3; Cl, 18·5%].

Anhydrochloroplatynecine (VIII).—Anhydrorosmarinecine (400 mg.) was treated at 0° with redistilled thionyl chloride, a copious evolution of hydrogen chloride occurring. After 6 hours' heating under reflux the excess of reagent was removed under reduced pressure. The sticky residue was treated with cold water. The solution, extracted with chloroform to remove resins, was made alkaline with sodium carbonate and re-extracted with chloroform. An oily product from the chloroform gave with picric acid *anhydrochloroplatynecine picrate* which crystallised from ethanol in prismatic needles, m. p. 204—208° (Found : C, 42·0; H, 3·5; N, 14·4; Cl, 8·9. $C_{14}H_{15}O_8N_4Cl$ requires C, 41·75; H, 3·75; N, 13·9; Cl, 8·8%).

Anhydroplatynecine (IX).—Anhydrochloroplatynecine (130 mg.), recovered from the picrate, in ethanol (5 ml.) was added to Raney nickel (500 mg.; Covert and Adkins, *J. Amer. Chem. Soc.*, 1 32, **54**, 4117) in ethanol (25 ml.) in an atmosphere of hydrogen. Absorption of hydrogen was complete in 3 hr. (19·8 ml. Calc. for $C_8H_{12}ONCl$: 18·3 ml.). The product was an oil, the picrate of which crystallised from ethanol to give anhydroplatynecine picrate, m. p. and mixed m. p. 264—268° (Found : C, 46·0; H, 4·4; N, 15·2. Calc. for $C_{14}H_{16}O_8N_4$: C, 45·6; H, 4·4; N, 15·2%).

Trichloride (III) *from Rosmarinecine*.—Rosmarinecine (750 mg.) was treated with freshly distilled thionyl chloride (5 ml.) at 0° and then heated for 3 hr. on a water-bath. The product, worked up as described above, gave an oil which gave a *picrate*, m. p. 194—196° (Found : C, 36·7; H, 3·2; N, 13·7; Cl, 22·65. $C_{14}H_{15}O_7N_4Cl_3$ requires C, 36·7; H, 3·3; N, 12·2; Cl, 23·0%).

Epoxyisatinecine (XI).—(*a*) Isatinecine (4·5 g., 1 mol.) in chloroform (135 ml.) containing benzoic acid (6 g.) was added dropwise at −10° to a stirred solution of perbenzoic acid (7 g., 1·9 mols.) in chloroform (110 ml.) and kept at −6° for 8 days; oxidation was then complete. The solution was extracted with 2N-hydrochloric acid (100 ml.); the aqueous extract was washed with chloroform, made alkaline with sodium carbonate, and evaporated to dryness under reduced pressure. Extraction of the powdered residue with boiling ethanol (150 ml.) gave the *epoxide* as a white solid (4·3 g.) which crystallised from methanol as monoclinic prisms, decomp. 200°, $[\alpha]_D^{21}$ −40·5° (*c*, 1·2 in H_2O) (Found : C, 51·5; H, 7·2; N, 7·65. $C_8H_{13}O_4N$ requires C, 51·3; H, 7·0; N, 7·6%).

(*b*) Retronecine, treated similarly with perbenzoic acid, absorbed 1 atom of oxygen in

30 min. to give isatinecine, and 2 atoms after 140 hr. to give epoxyisatinecine identical with the above.

Epoxyretronecine (XII).—(*a*) Epoxyisatinecine was reduced with zinc dust and hydrochloric acid, and the product worked up as described for the reduction of platynecine *N*-oxide (Koekemoer and Warren, *loc. cit.*). The product crystallised from ethanol–acetone, to give *epoxyretronecine* as prismatic needles, m. p. 172—173°, $[\alpha]_D^{22}$ −40·9° (*c*, 0·95 in H_2O) (Found : C, 55·9; H, 7·7; N, 8·0. $C_8H_{13}O_3N$ requires C, 56·2; H, 7·7; N, 8·2%). (*b*) Epoxyisatinecine, reduced with hydrogen in the presence of Adams catalyst, gave epoxyretronecine (Found : C, 56·1; H, 7·5; N, 7·9%).

Di-O-*acetylepoxyretronecine* (XIII).—Epoxyretronecine was refluxed with acetic anhydride and the oily product, treated with picric acid, gave *di*-O-*acetylepoxyretronecine picrate* which crystallised from ethanol in yellow needles, m. p. 151—152° (Found : C, 44·8; H, 4·2; N, 11·3. $C_{18}H_{20}O_{12}N_4$ requires C, 44·6; H, 4·2; N, 11·6%).

Reduction of Epoxyisatinecine.—Epoxyisatinecine (1·25 g.) in absolute ethanol (100 ml.) with Raney nickel (2 g.) absorbed hydrogen (301 ml. at N.T.P., *i.e.*, 1·7 mols.) in 2 hr. The product was partly solid and gave a crystalline *picrate*, m. p. 169—170° after recrystallisation from ethanol, undepressed by rosmarinecine picrate, m. p. 170° (Found : C, 42·1; H, 4·7; N, 14·3. $C_{14}H_{18}O_{10}N_4$ requires C, 41·8; H, 4·5; N, 13·9%). The *metho-Reineckate* was readily purified from aqueous acetone (Found : C, 31·1; H, 4·8; N, 19·2; S, 25·4. $C_{13}H_{24}O_3N_7S_4Cr$ requires C, 30·8; H, 4·8; N, 19·4; S, 25·3%). The picrate of the acetylated product, m. p. 139°, and the benzoyl derivative, m. p. 179—180°, likewise showed no m. p. depression when mixed with triacetylrosmarinecine picrate and dibenzoylrosmarinecine respectively.

Reduction of epoxyretronecine by this method gave a gum which yielded derivatives identical with those above.

The authors acknowledge a bursary (to M. J. K.) and grants from the South African Council for Scientific and Industrial Research, with respect to this and the following paper.

Department of Chemistry and Chemical Technology,
University of Natal, Pietermaritzburg, S. Africa. [*Received, September 6th*, 1954.]