Antibiotics from Higher Plants. *Thalictrum rugosum*. New Bisbenzylisoquinoline Alkaloids Active *vs Mycobacterium smegmatis*

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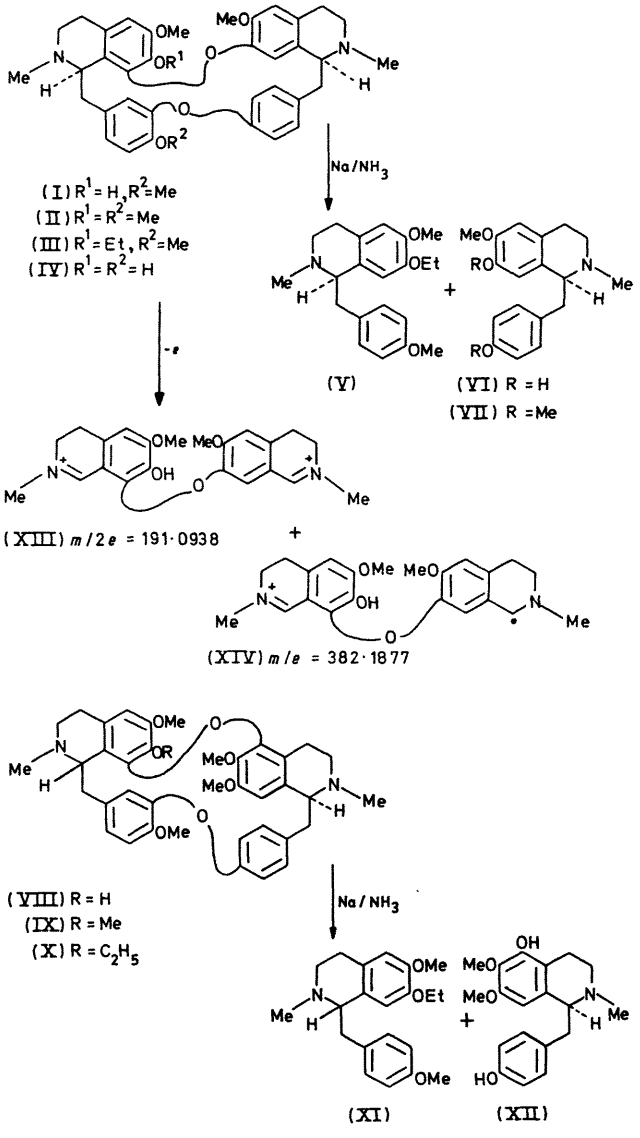
Summary Extracts of *Thalictrum rugosum* were found to be reproducibly active against mycobacteria, the active agents were isolated, and four were identified to be bisbenzylisoquinoline alkaloids of known and unknown structure.

EXTRACTS of *Thalictrum rugosum* Ait. (*T. glaucum* Desf.)[1-3] were found to be active *in vitro* against *Mycobacterium smegmatis* ATCC 607. The plant was fractionated systematically and the bioactive fractions were all found to be alkaloids, separable by silica gel chromatography and solvent extractions. Berberine (active), magnoflorine (inactive), thalidasine (IX) (active), and obamegine (IV) (active) were previously known, although their potential antitubercular activity had not previously been reported. Two new bases, named thalrugosine (I) and thalrugosidine (VIII), are very weakly active and their structures were proven by conventional reactions.

Thalrugosine (I), m.p. 212—214° (decomp.) $C_{37}H_{40}N_2O_6$ (M^+ 608·2848), analyses correctly as the hemihydrate (C,H,N), $[\alpha]_D^{30}$ +128 (MeOH), λ_{max} (MeOH) 283 nm (log ϵ 3·78), n.m.r. δ ($CDCl_3$) 2·31 and 2·50 (s, 2 × NMe), 3·77, 3·90, and 3·91 (s, 3 × OMe), 6·10—7·43 (m, 10 × ArH) p.p.m. Treatment of thalrugosine with excess of diazomethane at room temperature for eight days gave isotetandrine (II), confirmed by direct comparison with an authentic specimen.[4] The comparison included exact correspondence of c.d. curves and specific rotations leading to the absolute configuration depicted in the formulae.[5] Placement of the phenolic hydroxy-group in the isoquinoline portions was apparent from the mass spectrum[6,†] [formulae of most significant peaks, (XIII) and (XIV)]. Location at C(7) was strongly suggested by the appearance of a new OMe peak at δ 3·15 in the n.m.r. spectrum of (II). This characteristic resonance frequency (as well as the separation of the NMe bands) is a consequence of the geometry of the rings when coupled by two ether bridges in this specific pattern.[7] Chemical confirmation of the structure and absolute configuration was obtained by cleavage of the *O*-ethyl ether [(III), prepared with ethereal diazoethane]. Cleavage fragment (V) was characterized by n.m.r. spectra, the m.p. of its crystalline methiodide[8] (101—104°C), and its c.d. spectrum ($[\theta]_{288}$ −7640, $[\theta]_{272}$ +1600, $[\theta]_{230}$ −37,300, $[\theta]_{206}$ −53,280). The other fragment (VI) was characterized, after methylation, by direct comparison with an authentic specimen of *O*-methylarmepavine[9] and by c.d. spectrum ($[\theta]_{288}$ +7360, $[\theta]_{272}$ −1230, $[\theta]_{230}$ +36,790 and $[\theta]_{216}$ +26,160).

The other cryptophenolic base, thalrugosidine (VIII), m.p. 172—174°, $C_{38}H_{42}N_2O_7$ (M^+ 638), analyses correctly (C,H,N), $[\alpha]_D^{30}$ −185 (MeOH), λ_{max} (MeOH) 275 (log ϵ 3·99) and 282 nm (log ϵ 3·99), n.m.r. δ ($CDCl_3$) 2·25 and 2·60 (s, 2 × NMe), 3·51, 3·75, 3·85, and 3·87 (s, 4 × OMe) and 6·3—7·7 (m, 9 × ArH) p.p.m., c.d. (MeOH) $[\theta]_{286}$ −20,335, $[\theta]_{267}$ +5880, $[\theta]_{248}$ +17,150, $[\theta]_{241}$ +9800, and $[\theta]_{226}$ −3430. Methylation with ethereal diazomethane produced thalidasine (IX) identical (i.r., n.m.r., c.d. and t.l.c.) with



an authentic sample. The position of the phenolic hydroxy-group was proven as before. Cleavage with liquid ammonia provided the antipode (XI) of the thalrugosine cleavage product (V), as shown by its c.d. spectrum, and a phenolic product (XII) which was identical in every respect (including c.d. spectrum) with the corresponding cleavage product of thalidasine (IX).

† Complete high resolution mass spectra were obtained from R. Foltz of The Battelle Memorial Institute, Columbus, Ohio.

The details of these experiments and our biological results will be reported after completion of our work with some of the minor constituents. This communication indicates the novel biological activity of this well known class of alkaloids.

We thank the Warren–Teed Division of Roehm and Haas and the NIH, USPHS for financial support and Rodger White (Warren–Teed) and F. W. Denison (Abbott Laboratories) for helping provide the biological data.

(*Received, March 22nd,* 1971; *Com.* 336.)

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