The Synthesis of 1-(4-Hydroxy-3-methyl-*cis*-but-2-enyl)guanidine, the naturally occurring Hydroxygalegine

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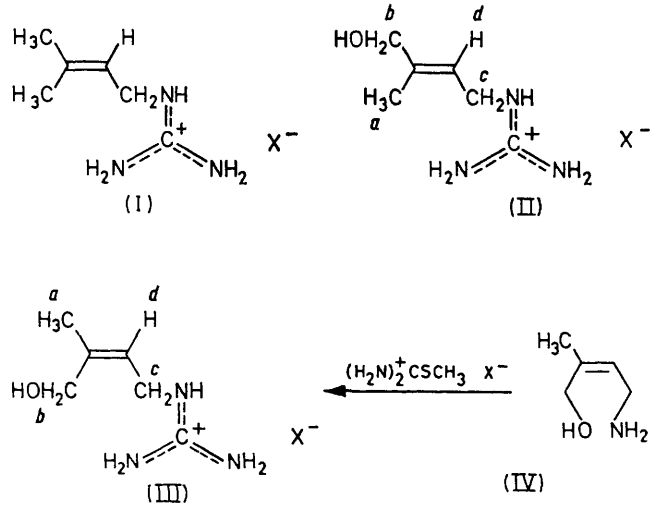
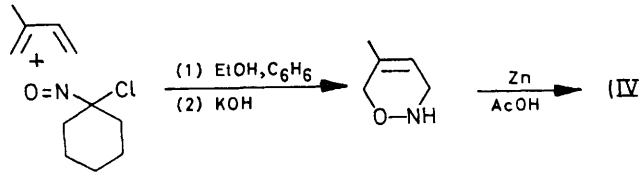
Summary The synthesis of 1-(4-hydroxy-3-methyl-*cis*-but-2-enyl)guanidine in a stereoselective manner has confirmed the structure previously assigned to the hydroxygalegine found in *Galega officinalis*.

HYDROXYGALEGINE has been isolated, along with galegine (I, base), from the seeds of *Galega officinalis* or common goatsrue,[1-3] and the structure has been assigned as 1-(4-hydroxy-3-methyl-*cis*-but-2-enyl)guanidine (III, base).[1-5] The gross structure was confirmed by the synthesis of the



dihydro-derivative,[4] and *cis*-stereochemistry was inferred by non-identity with synthetic 1-(4-hydroxy-3-methyl-*trans*-but-2-enyl)guanidine (II, base).[5] With the development of a stereoselective synthesis of 4-hydroxy-3-methyl-*cis*-but-2-enylamine (IV),[6] the desired precursor for 1-(4-hydroxy-3-methyl-*cis*-but-2-enyl)guanidine has become available, and, accordingly, structural confirmation by synthesis of the natural hydroxygalegine could be realized.



The key to ensuring the stereochemistry of the precursor (IV) was in the utilization of cyclic intermediates, starting with a Diels–Alder reaction between isoprene and 1-chloro-1-nitrosocyclohexane,[7] followed by basification and reduction of the 5-methyl-3,6-dihydro-1,2-oxazine formed with zinc and acetic acid. The crude 4-hydroxy-3-methyl-*cis*-but-2-enylamine (IV) was used directly in the reaction with *S*-methylisothiourea sulphate,[8] and the product was converted into derivatives (III)† of 1-(4-hydroxy-3-methyl-*cis*-but-2-enyl)guanidine which could be compared with those described for the naturally occurring hydroxygalegine: picrate, $C_{12}H_{16}N_6O_8$, m.p. 149–151° (reported,[3] 152°); flavianate, $C_{16}H_{19}N_5O_9S$, m.p. 166–167° (reported, 173–174°,[2] 173—176° after softening at 166°[3]); picrolonate, $C_{16}H_{21}N_7O_6$, m.p. 261–263° (dec.) [reported,[3] 260—262° (dec.)].

Further identification of the synthetic product was achieved by comparison of the ^{1}H n.m.r. spectra (Table) of (III) picrate with synthetic (II) picrate, *i.e.*, relative

† Satisfactory elemental analyses were obtained for all derivatives.

Comparative ^{1}H *n.m.r.*[a]

Synthetic (III) picrate		Proton	Synthetic (II) picrate		
1·78	s[b]	a	1·63	s	
4·05	d *J* 5—6	b	3·95—	m	
3·88	d of d	c	3·75		
5·30	t *J* 7	d	5·50	t	*J* 6—7
4·98	t *J* 5—6	OH	4·92	m	
7·46	m	NH	7·50	m	
7·07	m	$(NH_2)_2$	7·05	m	

[a] Chemical shifts, δ, from $(CH_3)_4Si$ in $(CD_3)_2SO$. [b] Multiplicity.

chemical shifts and couplings of the a, b, c, d protons, which established the *cis–trans*-relation between these two isomers.[6,9] Moreover, the ^{1}H n.m.r. spectra of the picrates were in close correspondence with the spectra previously reported[5] for natural (III) chloride as compared with synthetic (II) chloride.

We thank Eli Lilly and Company for a fellowship held by one of us (A.J.P.).

(*Received, November* 11*th*, 1971; *Com.* 1952.)

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