Structure of Nic-2, A Major Steroidal Constituent of the Insect Repellent Plant *Nicandra physaloides*

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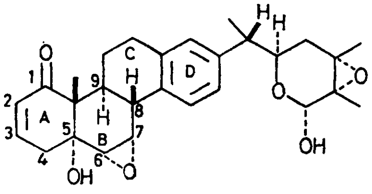
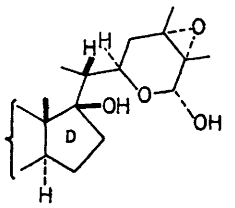
Summary The second most abundant substance in extracts of *Nicandra physaloides* (Solanaceae) is shown by spectral methods to be the first natural 17β-hydroxysteroid with more than two carbons in the side chain.

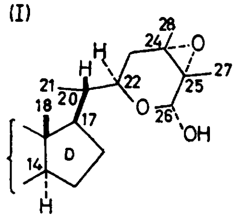
Nicandrenone ('Nic-1'), an insect repellent from the Peruvian weed *Nicandra physaloides*, has recently been shown to possess structure (I)[1,2] and the suggestion has been made[2] that it is biosynthesized from Nic-3 (III), which accompanies it in the plant.[3] We present information leading to the conclusion that Nic-2, second in abundance only to Nic-1 among the constituents of the mixture of steriodal derivatives obtained from *N. physaloides* by the procedure of Nalbandov, *et al.*[4] has structure (II), and is thus a possible biosynthetic intermediate between Nic-3 (III) and Nic-1 (I).



(I)

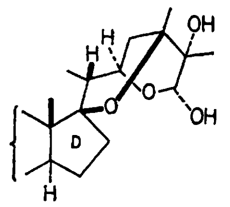


(II)



(III)

Nic-2, m.p. 224—225°, was purified by chromatography on silica gel[4] and recrystallization from benzene. The molecular formula $C_{28}H_{40}O_7$ was indicated by a combination of elemental analysis (after drying for 20 h at 130° *in vacuo*), mass spectrometry (M^+ absent, but large peak at $M^+ - 18$ for loss of water), and ^{13}C n.m.r. spectroscopy (C and H count). ^1H and ^{13}C n.m.r. spectral comparison with Nic-1 and Nic-3 showed the A ring, lower B ring, and side chain to be the same in Nic-2 as in the other compounds (Table), and further strongly suggested that Nic-2 is like Nic-3 (III) except that a tertiary hydrogen at C-8, -9, -14, or -17 has been replaced by a hydroxy-group (singlet in off-resonance ^{13}C n.m.r. spectrum at δ 79 in pyridine solution). The location of this OH group was narrowed to 14β or 17β by noting the downfield location (δ 1·10) of the absorption due to the 18-methyl group (^1H n.m.r., pyridine) as compared to Nic-3 (III, δ 0·60).[3,5] The latter was favoured when the C-20 hydrogen, normally buried at δ 1·8 ($CHCl_3$; 75°), was shifted to an open region (δ 4·7) by the addition of [$^2H_{30}$]Eu(fod)$_3$ and appeared as a 1:4:6:4:1 quintet (*J* 7 Hz). That this quintet was due to C-20-H was verified by spin decoupling on the shifted spectrum. Irradiation of the C-21 methyl protons at δ 2·1 collapsed this quintet to a doublet, irradiation of the C-22 proton at δ 8·7 reduced it to a quartet, and simultaneous irradiation at both these positions gave a singlet. Since it



(IV)

TABLE. N.m.r. parameters for Nic-1 and Nic-2 in $DCCl_3$

^{13}C shifts, δ p.p.m.			^{1}H shifts, δ p.p.m.			$J_{H,H}$/Hz		
	Nic-1	Nic-2		Nic-1	Nic-2		Nic-1	Nic-2
C-1	203 (s)	203 (s)	H-2	5·9	5·8	$J_{2,3}$	10	10
C-2	129 (d)	129 (d)	H-3	6·6	6·6	$J_{2,4}$	3 & 4	3 & 4
C-3	140 (d)	139 (d)	H-4	*ca.* 2·7	*ca.* 2·6	$J_{6,7}$	4	4
C-5	73 (s)	73 (s)	H-6	3·2	3·3			
C-6,7	56 (d)	57 (d)	H-7	4·0	3·0			
	57 (d)	58 (d)						
			H-20	2·8	1·9			
C-22	68 (d)	68 (d)	H-21	1·3	1·0	$J_{20,21}$	7	7
C-24,25	64 (s)	63 (s)	H-22	3·9	*ca.* 3·8	$J_{20,22}$	6	8
	65 (s)	64 (s)	H-26	5·0	5·0			
C-26	92 (d)	92 (d)	H-27	1·4	1·4			
			H-28	1·4	1·4			

is very unlikely that the coupling constant between methinyl protons on C-17 and C-20 would be zero, there can be no C-17 proton, and the hydroxy-group must be there as shown in (II). Nic-2 thus joins the small group of naturally-occurring 17β-hydroxy-17α-alkyl steroids; the others are pregnane derivatives.[6]

After this work was submitted for publication, Professor Crombie kindly informed us[7] that an *X*-ray study has revealed one of the other *N. physaloides* constituents to be (IV), which probably arises from (II) in the plant.

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[7] Personal communication from L. Crombie.