HETEROCYCLIC STEROIDS

II. PREPARATION AND N.M.R. SPECTRA OF 17,17-DIALKYL-13(14)-UNSATURATED STEROIDS[1]

E. CASPI[2] AND D. M. PIATAK

Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts, U.S.A.

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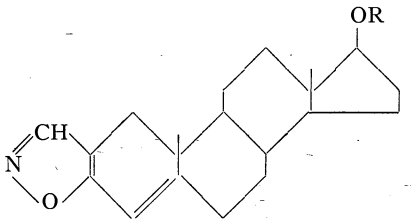
ABSTRACT

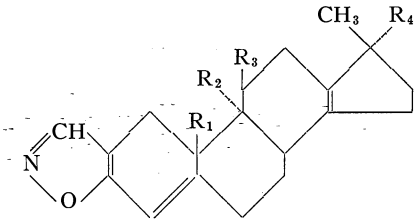
A series of 17,17-dialkyl-13(14)-unsaturated steroids was prepared via the Wagner–Meerwein rearrangement. Some of the steroids were synthesized with an isoxazole ring or a pyrazole ring attached to ring A. The n.m.r. spectra of the compounds prepared are discussed.

During investigations on steroidal isoxazoles (1) 17β-acetoxyandrost-4-eno[2,3*d*]isoxazole (I) and 17,17-dimethyl-18-norandrosta-4,13(14)-dieno[2,3*d*]isoxazole (III) were found to have tumor-inhibiting properties when assayed by the method of Abe *et al.* (2). Further biological data disclosed that the 17β-acetoxyisoxazole I had 1/5 of the androgenic activity of testosterone, while the 17,17-dimethylisoxazole III was devoid of accompanying activity. In order to explore these observations, several steroidal analogues were prepared. In addition, the n.m.r. spectra of the compounds are discussed.

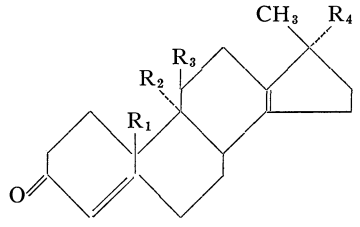
Preparation of 17,17-dimethyl-18-norandrosta-4,13(14)-dien-3-one (VI), 2α,17,17-trimethyl-18-nor-5α-androst-13(14)-en-3-one (IX), 17β-methyl-17α-ethyl-18-norestra-4,13-(14)-dien-3-one (VII), and 17,17-dimethyl-9α-fluoro-11β-hydroxy-18-norandrosta-4,13-(14)-dien-3-one (VIII) involved simple Wagner–Meerwein rearrangement of the



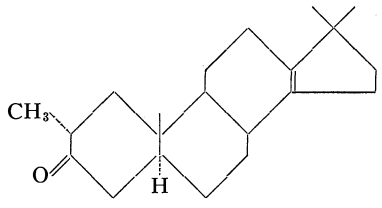
I: R = Ac
II: R = CH_3



III: R_1 = CH_3; R_2 = H; R_3 = H; R_4 = CH_3
IV: R_1 = H; R_2 = H; R_3 = H; R_4 = CH_2CH_3
V: R_1 = CH_3; R_2 = F; R_3 = OH; R_4 = CH_3



VI: R_1 = CH_3; R_2 = H; R_3 = H; R_4 = CH_3
VII: R_1 = H; R_2 = H; R_3 = H; R_4 = CH_2CH_3
VIII: R_1 = CH_3; R_2 = F; R_3 = OH; R_4 = CH_3



IX

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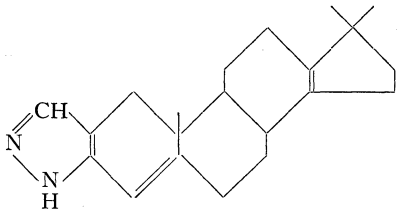
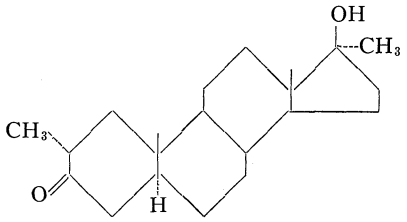
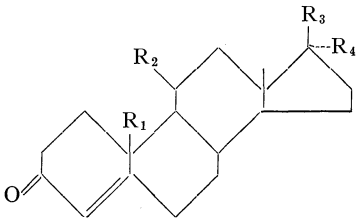


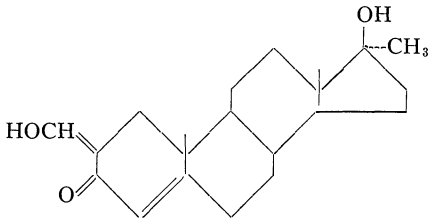
X



XI



XII: $R_1 = CH_3$; $R_2 = H$; $R_3 = OH$; $R_4 = CH_3$
XIII: $R_1 = CH_3$; $R_2 = H$; $R_3 = OAc$; $R_4 = H$
XIV: $R_1 = CH_3$; $R_2 = OH$; $R_3 = OH$; $R_4 = CH_3$
XV: $R_1 = H$; $R_2 = H$; $R_3 = OH$; $R_4 = CH_2CH_3$



XVI

corresponding 17β-hydroxy-17α-alkylandrostanes. Structural assignments were based primarily on elemental analysis and n.m.r. spectroscopy.

Confirmation of the α orientation of the 2-methyl group of IX was established by its optical rotary dispersion curve, which was identical in shape with that of 17β-hydroxy-2α-methyl-5α-androstan-3-one; their magnitudes of molar rotation were also the same. Stereochemistry of the migrating methyls was rationalized on mechanistic grounds as being β, since Wagner–Meerwein rearrangements are known to proceed with "retention" of configuration (3).

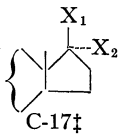
The steroidal pyrazole 17,17-dimethyl-18-norandrosta-4,13(14)-dieno[3,2*c*]pyrazole (X) was conveniently prepared by refluxing hydrazine hydrate with 2-hydroxymethylene-17,17-dimethyl-18-norandrosta-4,13(14)-dien-3-one in ethanol according to the procedure of Clinton *et al.* (4). The compound gave the correct analysis, a λ_{max}^{MeOH} 260 mμ, and characteristic infrared bands at 1675, 1630, and 1560 cm^{-1} (4).

The isoxazoles were obtained as described previously (1) by refluxing the corresponding 2-hydroxymethylene steroids in glacial acetic acid with hydroxylamine hydrochloride. The 17β-methyl-17α-ethyl-18-norestra-4,13(14)-dieno[2,3*d*]isoxazole (IV) was prepared from 17β-methyl-17α-ethyl-18-norestra-4,13(14)-dien-3-one (VII); the fluoroisoxazole V, from 11β,17β-dihydroxy-9α-fluoro-17α-methylandrost-4-en-3-one (4); and the 17β-methoxy isoxazole II, from 17β-methoxyandrost-4-en-3-one (5). Concomitant Wagner–Meerwein rearrangement occurred with isoxazole formation in the preparation of V. Identification of the isoxazoles was made by elemental analyses and ultraviolet, infrared, and n.m.r. spectroscopy.

Certain pertinent n.m.r. bands are listed in Table I. In compounds with a 17,17-dialkyl group, i.e. III to X, the methyl at 17 (or 17-*gem*-dimethyl) is observed at τ = 9.00–9.05, quite significantly shifted upfield from the tertiary 17α-methyl in 17β-hydroxy-17α-alkyl compounds, XI, XII, and XVI. This shift (+0.3 p.p.m.) is consistent with the expected downfield shift (7) of tertiary alkyl moieties when an oxygen function is added to the

TABLE I

Summary of n.m.r. bands*

Compound	Methyls C-19	Methyls C-18†	 C-17‡	C-4 proton	C-2 group
I	8.97	9.15	—	3.81	1.99§
II	8.98	9.19	$X_1 = OCH_3 = 6.53$	3.84	1.97§
III	9.03	—	$X_1 = X_2 = CH_3 = 9.03$	3.80	1.98§
IV	—	—	$X_1 = CH_3 = 9.03$		
			$X_2 = Et = 9.25$ ($J = 6.7$ c.p.s.)	3.78	2.04§
V	8.68	—	$X_1 = X_2 = CH_3 = 9.00$	3.72	1.93§
VI	8.83	—	$X_1 = X_2 = 9.05$	4.25	—
VII	—	—	$X_1 = CH_3 = 9.04$		
			$X_2 = Et = 9.27$ ($J = 6.7$ c.p.s.)	4.14	—
VIII	8.48	—	$X_1 = X_2 = CH_3 = 9.02$	4.18	—
IX	8.95	—	$X_1 = X_2 = CH_3 = 9.04$	—	8.98‖ ($J = 8.5$ c.p.s.)
X	9.08	—	$X_1 = X_2 = 9.04$	3.79	
X¶	9.05	—	$X_1 = X_2 = 9.00$	3.72	1.93,** 2.54††
XI	8.92	9.13	$X_1 = OH$		
			$X_2 = CH_3 = 8.79$	—	9.01‖ ($J = 5.5$ c.p.s.)
XII	8.82	9.10	$X_1 = OH$		
			$X_2 = CH_3 = 8.82$	4.29	—
XIII	8.81	9.17	—	4.28	—
XIV	8.53	8.84	$X_1 = OH$		
			$X_2 = CH_3 = 8.84$	4.32	—
XV	—	9.08	$X_2 = CH_2CH_3 = 9.02$ ($J = 7$ c.p.s.)	4.18	—
XVI	8.96	9.09	$X_1 = OH$		
			$X_2 = CH_3 = 8.78$	4.21	2.64‡‡

*Spectra taken on $CDCl_3$ solutions unless otherwise noted. Results expressed in τ units as described previously (1).
†If no C-18 value is given, the compound has a 13(14)-double bond.
‡Values are given only for methyl groups.
§Proton on 3′-carbon of isoxazole ring.
‖Protons on C-2α-methyl.
¶CD_3OD solution.
**Proton on 5′-carbon of pyrazole ring.
††Proton on 2′-nitrogen of pyrazole ring.
‡‡Proton on carbon of hydroxymethylene at C-2.

carbon bearing the alkyl moiety. The *secondary methyl* of the ethyl moiety in the *gem*-dialkyl compounds IV and VII shows an analogous upfield shift. The structure of compounds containing the 17,17-dialkyl-13(14)-ene moiety was deduced from this upfield shift, the disappearance of an 18-methyl band, and the absence of a band ($\tau \approx 4$) attributable to a vinyl proton at other than C-4.

Of interest is the variation in chemical shift for the C-19 methyl group brought about by substitution of a hydroxymethylene at C-2 or a hydroxy function at C-11. An upfield shift of ca. +0.2 p.p.m. is seen in the instance where the C-2 position is substituted by hydroxymethylene, e.g. XII to XVI. This upfield shift of +0.2 p.p.m. is also evident when an isoxazole or pyrazole ring is formed at the C-2, C-3 positions, e.g. XIII to I, VI to III, VIII to V, and VI to X. The 11β-hydroxyl causes the known downfield shift (8) of the 19-methyl (−0.3 p.p.m.) as evidenced in the shift from $\tau = 8.8$ to $\tau = 8.5$ for XIV to XII and for VI to VIII and in the shift from $\tau = 9.0$ to $\tau = 8.7$ for III to V. The 9α-fluorine does not appear to have a pronounced influence on the 19-methyl. These chemical shifts are additive as illustrated with the value for the 19-methyl of VI ($\tau = 8.83$). By adding the upfield shift of +0.2 p.p.m. for substitution at C-2 and the downfield shift of −0.3 p.p.m. for substitution at C-11, the figure arrived at ($\tau = 8.73$) is in fair agreement with the value for V ($\tau = 8.68$).

The chemical shift of the vinylic proton at C-4 varies significantly with substitution

TABLE II

Summary of physical data of compounds prepared

Compound	M.p. (°C)	Yield (%)	λ_{max}	ϵ	Infrared (cm^{-1})			Calc. (%)			Found (%)		
								C	H	N	C	H	N
II	102–105	59.1	285	10,500	1,625	1,590	1,100	77.02	8.93	4.28	77.21	8.85	4.35
IV	94–98	14.8	286	11,000	1,635	1,615		81.51	8.80	4.53	81.53	8.83	4.92
V	206–211	53.3	283	11,000	3,390	1,635	1,610	73.44	7.63		73.68	7.91	
VI	66–70	100	240	16,500	1,670	1,610		84.45	9.92		84.26	9.97	
VII	83–85	100	250	16,800	1,665	1,615		84.45	9.92		84.60	9.79	
VIII	205–207	72.4	238	17,500	3,360	1,660	1,615	75.43	8.55		75.55	8.60	
IX	118–121	64.7	—	—	1,710			83.94	10.73		83.68	10.86	
X	191–195	23.4	260	10,500	3,270	1,675	1,630	81.77	9.15	9.08	81.74	9.03	9.13
					1,560								

at C-2 and C-3, while little effect is observed by substitution at C-9 and C-11. A pronounced downfield shift of −0.4 p.p.m. is brought about by the formation of an isoxazole or pyrazole ring at the C-2, C-3 positions, as seen by comparing VI to VIII and XVI with I to II and III to V.

In the case of the attached heterocyclic rings the proton on the carbon at the 3′-position of the isoxazole ring or at the 5′-position of the pyrazole ring exhibits a value of τ = 1.9–2.0. These chemical shifts seem to be characteristic for the —N=CH—C= grouping.

Preliminary biological evaluation indicated that there was no consistent enhancement of antitumor activity for the compounds prepared. A full report will be published in a later communication.

EXPERIMENTAL*

Preparation of 17,17-Dialkyl-3-ketones VI, VII, VIII, and IX

To a solution of the 17β-hydroxy-17α-alkylsteroid (1.00 g) in glacial acetic acid (15 ml) was added glacial acetic acid saturated with hydrogen chloride (1.0 ml). The solution was then heated at reflux for 10 minutes. The solution was cooled, water added, and most of the acetic acid removed *in vacuo*. The steroids were recovered with ether, washed with saturated sodium bicarbonate solution, then water, dried, and concentrated *in vacuo*. The compounds crystallized readily upon trituration with methanol. (See Table II for analytical results.)

17,17-Dimethyl-18-norandrosta-4,13(14)-dieno[3,2c]pyrazole (X)

The 2-hydroxymethylene derivative of I was prepared via the sodium hydride procedure of Weisenborn *et al.* (6).

A solution of the obtained 2-hydroxymethylene compound (4.42 g) and hydrazine hydrate (85%; 1.7 g) in 100 ml ethanol was heated at reflux for 4 hours. The solvent was removed *in vacuo*. Chromatography of the reaction mixture on silica followed by recrystallization from acetone gave pure 17,17-dimethyl-18-norandrosta-4,13(14)-dieno[3,2*c*]pyrazole. (See Table II for analytical results.)

Preparation of Isoxazoles

The isoxazole steroids were prepared from 2-hydroxymethylene derivatives and hydroxylamine hydrochloride in glacial acetic acid, exactly as described in our previous communication (1).

ACKNOWLEDGMENT

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**Melting points were taken on a micro hot stage and are corrected. Elemental analyses were provided by Dr. A. Schöeller, Kronach, Germany. Ultraviolet spectra were recorded with a Cary Model 14 spectrometer. Infrared spectra were taken on KBr blotters with a Perkin–Elmer Model 237 spectrometer.*