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17α-Methyl-17β-hydroxy-5α-androstano[2,3-*c*]furazan (Androfurazanol),*1 A New Active Anabolic Steroid

In recent years a number of androstane derivatives possessing heterocycles fused at 2,3-positions have been synthesized. Among them steroidal pyrazoles,[1] isoxazoles[2] and thiazoles[3] were reported to have favorable anabolic activities, all of which have five-membered heterocyclic rings containing two hetero atoms. Androstano[2,3-*d*]-triazoles[4] are an another group of compounds synthesized so far which have three hetero atoms in their heterocyclic moiety, although their biological activities have not yet been published in detail. Interest in the concept of isosterism[5] prompted us to synthesize steroidal[2,3-*c*]furazans and to examine their biological effects. This communication deals with the synthesis and the results of biological assays of 17α-methyl-17β-hydroxy-5α-androstano[2,3-*c*]furazan (V) (hereafter referred to as androfurazanol), a new active anabolic steroid.

Reaction of 17α-methyl-17β-hydroxy-5α-androstan-3-one (I) with *t*-butyl nitrite in presence of potassium *t*-butoxide or hydrochloric acid gave in good yield 2-hydroxyimino-17α-methyl-17β-hydroxy-androstan-3-one (II) [m.p. 249~251°(decomp.). $[\alpha]_D$ +39°(pyridine). UV λ_{max}^{EtOH} mμ : 243 (ε 7,000). IR ν_{max}^{KBr} cm^{-1} : 3445, 3210, 1717, 1615, 978. *Anal.* Calcd. for $C_{20}H_{31}O_3N$: C, 72.03; H, 9.37; N, 4.20. Found: C, 71.77; H, 9.20; N, 3.99.]. Treatment of II with hydroxylamine hydrochloride and pyridine afforded quantitatively 2,3-bis(hydroxyimino)-17α-methyl-androstan-17β-ol (IV) [m.p. 234~235°(decomp.). $[\alpha]_D$ +63.6°(pyridine). UV λ_{max}^{EtOH} mμ : 238~241 (ε 6,600). IR ν_{max}^{KBr} cm^{-1} : 3370, 1640~1630, 970, 942, 932, 921. *Anal.* Calcd. for $C_{20}H_{32}O_3N_2$: C, 68.93; H, 9.26; N, 8.04. Found : C, 68.93; H, 9.42; N, 7.98.]. Alternatively, oximation of 17α-methyl-17β-hydroxy-androstane-2,3-dione (III), obtained by base-catalysed air oxidation of I according to the method of Camerino, *et al.*,[6] furnished the same dihydroxyimino compound (IV) as above. Cyclization of the dioxime (IV) was effected by treatment with potassium hydroxide in ethylene glycol at 160~200°, thus affording in satisfactory yield the desired compound, 17α-methyl-17β-hydroxy-5α-androstano [2,3-*c*] furazan (V) [m.p. 152~153°. $[\alpha]_D$ +39.4°($CHCl_3$). UV λ_{max}^{EtOH} mμ : 217 (ε 4,300). IR ν_{max}^{KBr} cm^{-1} : 3430, 1623, 1590, 1500, 1470, 1450, 1430, 1402, 1390, 1224, 1002, 958, 885, 876, 760, 740. *Anal.* Calcd. for $C_{20}H_{30}O_2N_2$: C, 72.69; H, 9.15; N, 8.48. Found : C, 72.76; H, 9.06; N, 8.45.]. The structure of V follows from its elemental analysis and spectral properties.

*1 A part of this communication was read at the Kanto Branch Meeting of Pharmaceutical Society of Japan, Tokyo, July 18, 1964.

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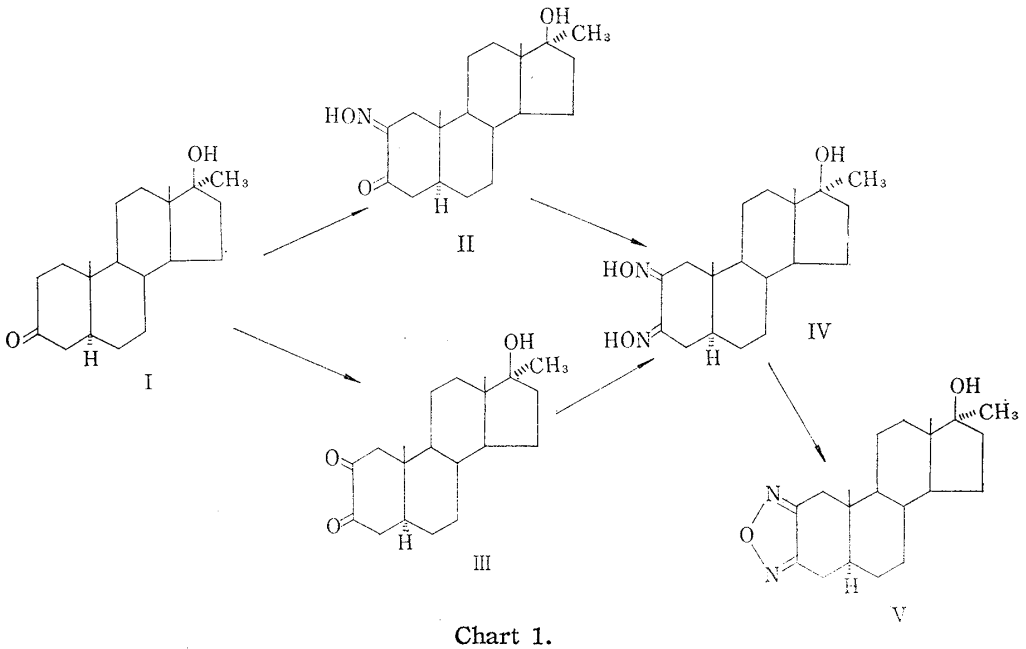

Chart 1.

The biological activities of androfurazanol are shown in Table I. From the experiments on myotrophic, nitrogen-retaining and androgenic activities androfurazanol proved to be relatively more anabolic than androgenic. Androfurazanol was practically devoid of estrogenic activity. This steroid had a little estrus inhibiting effect and its progestational activity was considerably weak. No change was found in either Na or K excretion even at high dose levels of androfurazanol. It should be noted that andofurazanol prevented the growth inhibition and adrenal atrophy produced by cortisone acetate.

Detailed reports will be published in the near future.

Table I. Biological Activities of Androfurazanol

Activity	Animal	Route of administration	Relative potency
Myotrophic (Growth of the levator ani muscle)	rat	s. c.	1.0~1.5 (TP=1.0)
		p. o.	2.7~3.3 (MT=1.0)
Androgenic (Growth of the ventral prostate and seminal vesicles)	〃	s. c.	0.19~0.26 (TP=1.0)
		p. o.	0.73~0.94 (MT=1.0)
Androgenic (Chick's comb assay)	chick	inunction	0.28 } (TP=1.0)
		s. c.	0.51 }
Nitrogen-retaining	rat	p. o.	29 (MT=1.0)
Estrogenic (Vaginal cornification)	〃	s. c.	inactive at dose levels of 0.1 to 10 mg./kg.
Estrus-inhibiting (Disappearance of estrous stage)	〃	〃	0.1 (TP=1.0)
Progestational (Clauberg test)	rabbit	〃	0.036 (progesterone=1.0)
Anticatabolic (Anticortisone)	rat	〃	active at dose levels of 1 to 4 mg./rat/day
Electrolyte-excreting	〃	〃	no change in either Na or K excretion at dose levels of 0.1 to 2 mg./rat

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Central Research Laboratory,
Daiichi Seiyaku Co., Ltd.,
Minamifunabori-cho, Edogawa-ku, Tokyo

Masao Shimizu (清水正夫)
Genkichi Ohta (太田元吉)
Katsujiro Ueno (上野勝次郎)
Toshio Takegoshi (竹越敏夫)
Yasuo Oshima (大島康夫)
Akira Kasahara (笠原 明)
Takeshi Onodera (小野寺 威)
Michiko Mogi (舞木紀子)
Haruo Tachizawa (立沢晴男)

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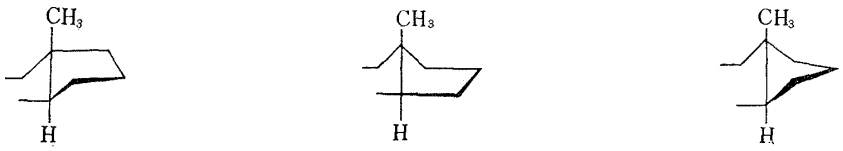
Proton Magnetic Resonance Study of Some 17-Substituted Steroids

Both 17α- and 17β-chlorosteroids have been already prepared and the configuration of the chlorine atom has also been established.[1~3] It may be expected that 17-proton of the steroid, in which halogen, hydroxy group or other substituent is combined at C-17, is analysed as ABX type pattern in proton magnetic resonance, and application of the Karplus equation to the coupling constant is used as an effective mean not only for the elucidation of the configuration at C-17 but also for some informations on the conformation of ring D of the steroid. The consideration concerning the conformation of ring D from the coupling constant of 17-proton in 17-chloro- and 17-hydroxysteroips will be described in this communication.

Recently, Brutcher and Bauer[4] have described that three possible conformations, *aiz.* envelope conformations (I) and (II), and half-chair conformation (III) (Chart 1) can be



I II III

Chart 1.

considered to ring D of a steroid, and some discussions have been made from the calculation of bond-bending and torsional energies as well as interaction energies for 1,3-substituents. When the above-mentioned problem is studied by the simple application of the Karplus equation to the coupling constant of a proton at C-17 of 17-substituted steroids, the following two facts must be considered beforehand. 1) It is well-known that the vicinal coupling constant becomes smaller in proportion to the increase of electronegativity of a substituent.[5~8] Even when an electronegative group such as

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