[Chem. Pharm. Bull. 14(2) 174~186 (1966)] UDC 547.92.07

27. Wataru Nagata, Tsutomu Sugasawa, Masayuki Narisada, Toshihiko Okada, Kazuyuki Sasakura, Masayuki Murakami, and Yoshio Hayase : Synthesis of 17-Hydroxyimino Steroids and their O-Alkyl Derivatives.

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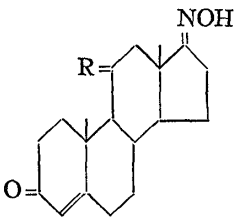
The central nervous system depressing activity of steroid compounds, especially the derivatives of pregnane, have been well recognized.[1] For example, sodium 21-hydroxypregnane-3,20-dione hemisuccinate[2] had been provided for clinical use as a commercial name "Viadril." Several years ago some 17-hydroxyimino steroids, *e.g.* androst-4-ene-3,17-dione 17-oxime (I) or adrenosterone 17-oxime (II), were found to show a marked anesthetic activity in rats in these laboratories.[3] Since the activity of steroids possessing the 17-hydroxyimino functional group had not been known at that time,[4] our interest was drawn to examine an activity-structure relation on a series of 17-hydroxyimino steroids.



I : R=H_2
II : R=O

Recently, much efforts have been focussed on obtaining a potential hypocholesterolemic agent. Thus, in 1959 1-[*p*-(2-diethylaminoethoxy)phenyl]-1-(*p*-tolyl)-2-(*p*-chlorophenyl)ethanol (MER-29) was reported to be a hypocholesterolemic compound by Blohm, *et al.*[5,6] and then 3β-(2-dialkylaminoethoxy)steroids were shown by Cantrall, *et al.*[7] to reduce markedly the concentration of serum cholesterol in rats.[8] These compounds are known to inhibit the reduction of the double bond in position 24, after cyclization of the squalene chain and consequently to induce an accumulation of desmoterol *in vivo*.[*2,9~11]

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[*2] According to Goodman, *et al.* (J. Biol. Chem., **238**, 1287 (1963)) Δ^7-cholestenol seems to be in the major pathway of cholesterol biosynthesis. Furthermore, Niemiro and Fumagalli (Biochem. Biophys. Acta, **98**, 624 (1965)) have recently shown that the reduction step of Δ^7-cholesterol derived from Δ^7-cholestenol biosynthetically, is blocked by *trans*-1,4-bis(2-chlorobenzylaminomethyl)cyclohexane dihydrochloride (AY-9944), 20,25-diazacholesterol and MER-29.

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3) The work will be published Ann. Rept. Shionogi Res. Lab., **15**, 29(1965) by T. Miyake, T. Hori, S. Sekihara, K. Horibe.
4) During progress of our work, Upjohn group made patent claims for some A-ring non-substituted androstan-17-one oximes having a similar activity. J.C. Babcock : C.A., **54**, 2440f (1960); U.S. Pat., 2,863,889, Dec. 9, 1958.
5) T.R. Blohm, R.D. Mackenzie : Arch. Biochem. Biophys., **85**, 245 (1959).
6) T.R. Blohm, T. Kariya, M.W. Langhlin : *Ibid.*, **85**, 250 (1959).
7) E.W. Cantrall, R. Littell, S.M. Stelar, W.P. Cekleniak, H.J. Albers, S. Gordon, S. Bernstein : Steroids, **1**, 173 (1963).
8) A similar effect of 3-(2-dialkylaminoethoxy)androstan-17-one oximes has appeared in the patent. R.D. Birkenmeyer, D. Lednicer, F. Kagan : U.S. Pat., 3,000,910, Sept. 19, 1961.
9) J. Avigan, D. Steinberg, M.J. Thompson, E. Mosettig : Prog. in Cardiovascular Disease, **2**, 525 (1960).
10) W.L. Holmes : 1st International Pharmacological Meeting, **2**, 77 (1963). Pergamon Press, Ed. by E.C. Horning.
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A structural inspection of both series of the compounds suggests that a common substituent, the dialkylaminoethoxy group may play an important role. On the other hand, steroids having a 20,25- or 22,25-diaza and 25-monoaza cholesterol side chain have also been reported to be potent inhibitors of cholesterol biosynthesis and the site of action is considered to be between mevalonate and 3-hydroxy-3-methylglutarate, Δ^{24}-stenols and corresponding reduced-stenols, and/or Δ^{7}-cholesterol and cholesterol.*[2, 12~21]

These findings in other laboratories led us to convert the 17-oximes into the corresponding dialkylamino ethyl ethers, which may exhibit a high hypocholesterolemic activity, since they contain a side chain of almost the same length as that of cholesterol and involving the necessary 2-dialkylaminoethoxy grouping in the molecules.[22] As shown in the later part of the present paper, many of these compounds are shown to actually have a marked hypocholesterolemic activity.

General Synthetic Processes

A number of 17-oximes and their O-alkyl derivatives in both androstane and estrane series were synthesized by applying the following processes A~E to the corresponding starting materials. The choice was made upon consideration mainly of other functional groups present in starting or intermediate steroid molecules. The physical properties, the synthetic processes and the yields of both products and main intermediates are summarized in Table I. Of two possible geometrical isomers for 17-oximes and their O-alkyl derivatives only one isomer could be isolated, except for when process E (*vide infra*) was applied and was assumed to have *anti*-form, because it is believed that this form of oximes[23] is more stable than the *syn*-form and that the transition state leading to the *anti*-oxime ether may have an energy lower than that in the case of the *syn*-isomer.

Process A——The 17-oximes in every series were prepared from the corresponding 17-ketones in a usual manner.

Process B——Some hemisuccinates of hydroxy-17-hydroxyimino steroids were prepared by applying the process A to 17-oxohemisuccinates derived from the corresponding hydroxy steroids with succinic anhydride and pyridine.

Process C——For the synthesis of the 17-oximes carrying Δ^{4}-3-ketone group, protection of the latter group necessary before oximination was carried out successfully by the method of Djerassi.[24] Namely the corresponding starting materials were transformed with ethyl orthoformate in the presence of pyridine hydrochloride to 3-ethoxy-3,5-dien-17-ones, which was then converted into the corresponding 17-oximes according to the process A. Successive hydrolysis with 70% acetic acid gave the desired products.

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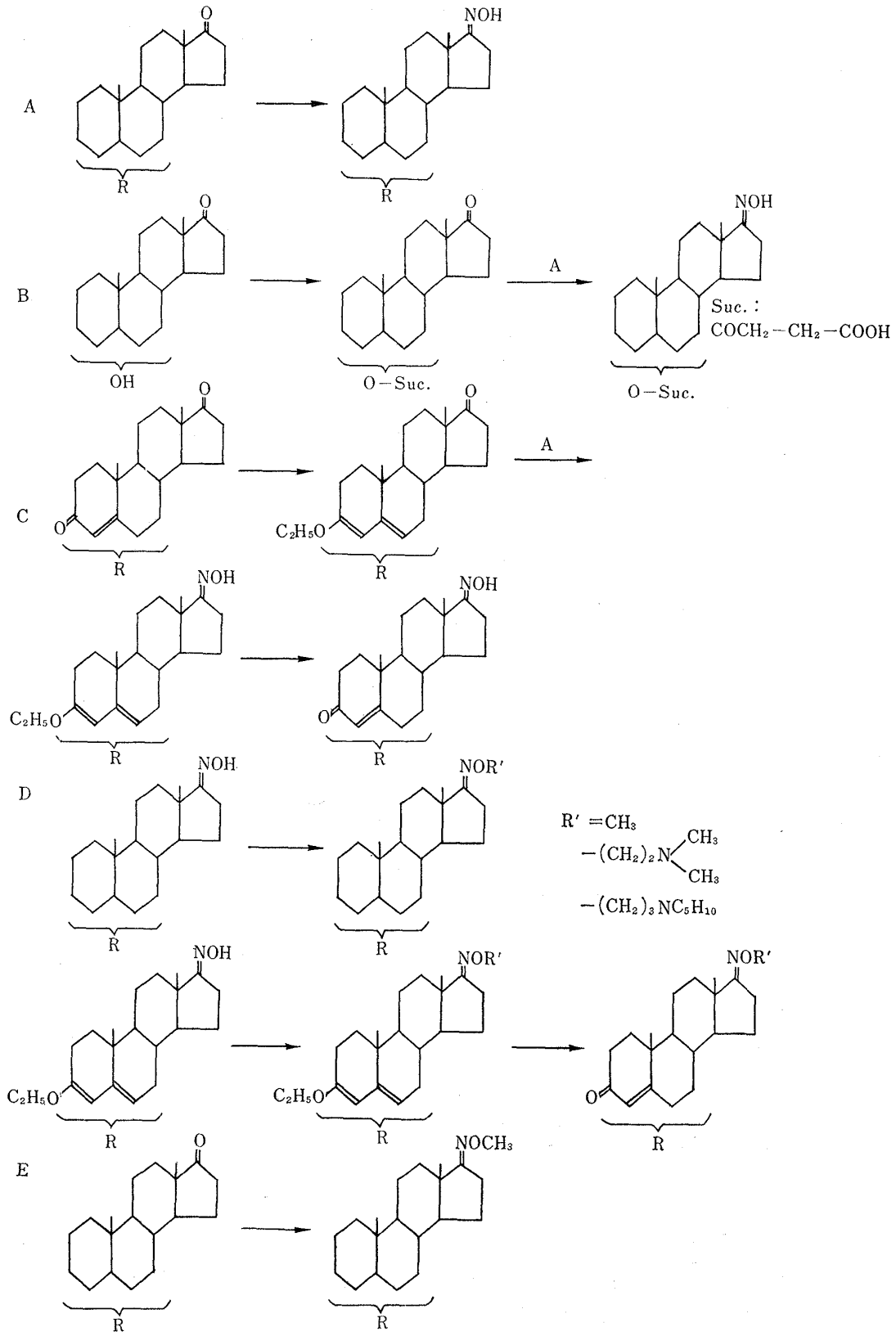

Chart 1.

Process D——The 17-oxime O-alkyl derivatives were prepared by treatment of the 17-oximes with the corresponding methyl or dialkylaminoethyl halogenide in appropriate solvent in the presence of sodium methoxide or ethoxide. That the products possess correctly the structure of an O-alkyl derivative (ether) and not of an alternative N-alkyl derivative was shown by the lack of strong absorption bands at about 240 mμ in ultraviolet- and around 1600 and 1170 cm^{-1} in infrared-spectra, which are ascribable to a nitrone group.[25] Further confirmation was performed in the case of 3β-hydroxy-17-methoxyimino-5α-androstane (X) by direct comparison with a sample prepared from 3β-hydroxy-5α-androstan-17-one (Ⅲ) according to the process E (*vide infra*). It is noteworthy that in the methylation of 5α- and 5β-androstan-17-one oximes (Ⅷ) and (Ⅷa) we observed, besides the desired ethers (O-methyl derivatives), formation of N-methyl derivatives (Ⅺ) and (Ⅺa) as by-products, whose structures were confirmed by elemental analyses and optical data (see Table I).

The preparation of the 17-oxime O-alkyl derivatives carrying the Δ^4-3-keto group was performed advantageously *via* the above mentioned 3-ethoxy-3,5-dien-17-oximes, which were subjected to the process D and then hydrolyzed by acid.

Process E——Some 17-oxime O-methyl derivatives were prepared directly from the corresponding 17-ketones and hydroxylamine methyl ether. In contrast to the process D, this procedure gave a mixture probably composed of *syn*- and *anti*-isomers, as judged by the broad melting point of the crude product.

1) Preparation of the 17-Oximes and their O-Alkyl Derivatives in Androstane Series

All titled compounds were prepared from the known 3β-hydroxy-5α- and 5β-androstan-17-ones (Ⅲ) and (Ⅲa), which are derived from dehydroepiandrosterone by the known method.[26] For the synthesis of 5α-androstane-3,17-dione 17-oxime (Ⅴ), the 3-keto group was selectively protected by treatment with *p*-toluenesulfonic acid in methanol to give the 3-dimethyl ketal (Ⅳ),[27] which was then converted into the disired Ⅴ[28] by oximination followed by hydrolysis with 70% perchloric acid at room temperature. The 5β-epimer (Va) was analogously obtained from Ⅲa. Application of the process D to 3β-hydroxy-5α- and 5β-androstan-17-one 17-oxime (Ⅷ) and (Ⅷa) led to the corresponding O-methyl derivatives (X) and (Xa).

The process D instead of E for the preparation of 17-oxime O-dimethylaminoethyl derivatives was selected, not only because of a predicted disadvantage in a preparation of hydroxylamine dimethylaminoethyl ether but also because of possible contamination of an undesired *syn*-isomer (*vide supra*). From 3β-hydroxy-17-(2-dimethylaminoethoxyimino)-5α-androstane (Ⅸ), the 3-keto and 3α-chloro*3 derivatives, (XIII) and (XIV), were prepared by oxidation with chromium trioxide and by treatment of the crude tosylate of Ⅸ with lithium chloride in dioxane, respectively.

Treatment of the 3β-tolylate of Ⅲ with collidine[30] led to androst-2-en-17-one (XV) ($[\alpha]_D^{21.5}$ 148.6±2 $CHCl_3$ m.p. 107~109°), probably contaminatied with 20~30% of the Δ^3-isomer as judged by comparison of the optical rotation with those of the pure

*3 The assignment of 3α-configuration was based upon the analogy with the corresponding bromination[29] and upon the NMR data (see Table I).

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Δ^2-($[\alpha]_D^{26}$ +153.2 (±2°) in $CHCl_3$)*4, [31] and Δ^3-($[\alpha]_D^{22}$ +136° in $CHCl_3$) isomers.[33] The 17-oxime (XVI)[34] and its O-(2-dimethylaminoethyl) derivative (XVII) from XV may therefore be contaminated with a small amount of their Δ^3-isomers. The A-ring non-substituted derivatives (XIX) and (XX) were prepared from the corresponding A-ring saturated 17-ketone (XVIII),[35] which was obtained from XV by catalystic reduction on palladium charcoal.

For the synthesis of 3α-hydroxy-5β-androstan-17-one oxime (XXVII), and its derivatives (XXV) and (XXVI), dehydroepiandrosterone was ketalized and then oxidized by the Oppenauer method to give androst-4-ene-3,17-dione 17-ethyleneketal (XXII),[36] which was further hydrogenated to 5β-androstanedione ketal (XXIII) by applying the Suvorov method,[37] suited for giving a 5β-epimer predominantly. Reduction with lithium aluminum tri-*tert*-buthoxy hydride, followed by deketalization gave the 3α-hydroxy-17-ketone (XXIV),[38] from which the desired XXVII, XXV, and XXVI were obtained in the usual way. The 3,5-dien-17-one oxime[39] (XXIX) was also obtained from XXII by treatment with lithium aluminum tri-*tert*-butoxy hydride followed by dehydration with acetic acid and subsequent oximation.

In turn, the 17-oximes and their O-(2-dimethylaminoethyl) derivatives having a Δ^4-3-keto functional group in the A-ring such as the compounds (I) and (XXXVI), the corresponding 19-nor derivatives (XXXI) and (XXXIII), and the 11-oxo derivatives (II) and (XL) were synthesized from androst-4-ene-3,17-dione, 19-nor-androst-4-ene-3,17-dione, and adrenosterone, respectively, by applying the process C and D. The 3,17-dioxime (XLI) was also prepared from adrenosterone in a usual way.

The hemisuccinate (XLVI) was prepared from 11α-hydroxyandrost-4-ene-3,17-dione (XLII).[40] Treatment of XLII with succinic anhydride in pyridine to give XLIII, was followed by the process C.

2) Preparation of the 17-Oxime Ether Derivatives in Estrone Series

17-(2-Dimethylaminoethoxyimino) derivative (XLVII) was prepared from estrone methyl ether 17-oxime by the process D. Application of the process D to estrone 17-oxime gave the bis ether (XLVIII) and the mono ether (XLIX) in a ratio of 1:5 after separation by chromatography. The structure of the latter was established by the fact that the ultraviolet absorption maximum at 275 (2330) and 285 mμ (2077) in ethanol showed no red shift in an alkaline medium, which should be expected for the 17-O-alkylated monooxime carrying a free phenol group.

*4 A pure sample of androst-2-en-17-one was prepared according to the method of Bowers, *et al.*,[31] except for using $LiAl(OC_4H_9)_3H$ instead of $NaBH_4$. The physical properties m.p. 102~104° and $[\alpha]_D$ 150° ($CHCl_3$) were obtained for this sample. It is well known that solvolytic treatment of 3β-tosyloxy-5α-cholestane and 3β-tosyloxy-5α-androstan-17-one does not afford a uniform elimination product, but only a sharply melting crystal mixture enriched with the Δ^2-isomer.[32]

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38) *a*) L. Ruzicka, M. W. Goldberg, J. Meyer, H. Brüngger, E. Eichenberger: Helv. Chim. Acta, **17**, 1395 (1934). *b*) Gildden Co.: C. A., **50**, 7887a (1956); Brit. Pat. 736,817, Sept. 14, 1955.
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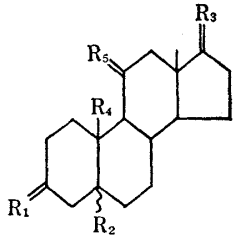
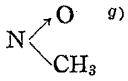
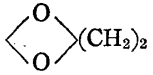
43) W. Nagata, M. Narisada, T. Sugasawa: Tetrahedron Letters, **1962**, 1041.

TABLE I.



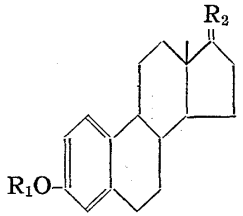
Compound number	R_1	R_2	R_3	R_4[a]	R_5[b]	Preparation process and reference	Yield (% of recovered starting material)	m.p. (°C) (crystallization solvent)	$[\alpha]_D$ (temp. solvent)	Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Obs. C	Obs. H	Obs. N
Ⅲ	OH / H	—H	O			26										
Ⅲa	〃	—H	〃			26										
Ⅳ	$(CH_3O)_2$	—H	〃			27	84	125～126 (CH_2Cl_2/MeOH)	+82.3 (26°) ($CHCl_3$)	$C_{21}H_{36}O_3$	74.95	10.78		75.48	10.59	
Ⅳa	〃	—H	〃			27	78	104～106 (MeOH)	+91.9 (25.5°) 〃	〃	74.95	10.78		74.94	10.30	
Ⅴ	O	—H	NOH			28	84	248～251 (CH_2Cl_2/ether)	+40.1 (25.5°) 〃	$C_{19}H_{29}O_2N$	75.20	9.63	4.62	74.60	9.81	5.06
Ⅴa	〃	—H	〃				68	243～245 〃	+40.4 (25.5°) 〃	〃	75.20	9.63	4.62	74.92	9.79	4.58
Ⅵ	OSuc / H	—H	O			B	87	255～257 ($CHCl_3$/ether)	+59.9 (24°) 〃	$C_{23}H_{34}O_5$	70.74	8.78		70.64	8.86	
Ⅵa	〃	—H	〃			〃	74	224.5～228 (ether)	+69.9 (25.5°) 〃	〃	70.74	8.78		70.69	8.85	
Ⅶ	〃	—H	NOH			B, A	98	243～245 ($CHCl_3$/MeOH)	+16.3 (24.5°) ($CHCl_3$:MeOH =3:1)	$C_{23}H_{35}O_5N$	68.12	8.70	3.45	67.85	8.65	3.50
Ⅶa	〃	—H	〃			〃	90	212～214 (ether/petr. ether)	+31.5 (25°) (EtOH)	〃	68.12	8.70	3.45	67.97	8.56	3.37

Ⅷ		—H	NOH	41										
Ⅷa	〃	—H	〃	A	90	214～216 (CHCl$_3$/ether)	+38.0 (25°) (EtOH)	$C_{20}H_{32}O_2N$	74.71	10.23	4.59	74.31	10.21	4.30
Ⅸ	〃	—H	DAEI[c]	D	59 (24)	137.5～9.5 (CH$_2$Cl$_2$/acetone)	+33.1 (24.5°) ($CHCl_3$)	$C_{23}H_{40}O_2N_2$	73.35	10.71	7.44	73.47	10.81	7.61
Ⅸ HCl						238～246 (d.p.)	+27.8 (23.5°) (EtOH)	$C_{23}H_{41}O_2N_2$-Cl·H$_2$O	64.08 Cl; 8.23	10.05	6.50	63.90 Cl; 8.56	9.81	6.29
Ⅸ CH_3I						265～270 (d.p.) (MeOH)	+23.8 (23.5°) ($CHCl_3$:MeOH =1:1)	$C_{23}H_{40}O_2N_2$·CH_3I	55.59 I; 24.48	8.36	5.40	55.95 I; 23.74	8.47	5.30
Ⅸa		—H	DAEI	D	30 (47)	100～103 (acetone)	+34.4 (23.5°) ($CHCl_3$)	$C_{23}H_{40}O_2N_2$·½H$_2$O	71.64	10.72	7.27	71.41	10.81	7.21
Ⅹ	〃	—H	$NOCH_3$	〃	37, 13[e] (14) (25)	216～217 (CH$_2$Cl$_2$/acetone)	+37.8 (23.5°) 〃	$C_{20}H_{33}O_2N$	75.19	10.41	4.38	75.18	10.45	4.62
				E	64									
Ⅹa	〃	—H	〃	D	30, 46[e] (15)	169～171 (CH$_2$Cl$_2$/ether)	+46.6 (23.5°) (MeOH/ether)	〃	75.19	10.41	4.38	75.35	10.40	4.42
				E	16	153～178[f] (CH$_2$Cl$_2$/ether)								
Ⅺ	〃	—H	 [g]	D	9	204～209 (MeOH/ether)	+25.0 (24.0°) ($CHCl_3$:MeOH =3:1)	$C_{20}H_{33}O_2N$	75.19	10.41	4.38	75.62	9.93	4.22
Ⅺa	〃	—H	〃 [h]	〃	20	173～178 〃	+29.6 (24.5°) ($CHCl_3$)	〃	75.19	10.41	4.38			4.18
Ⅻ	〃	—H	PPI[d]	〃	34 (46)	124～126 〃		$C_{27}H_{46}O_2N_2$	75.30	10.77	6.51	75.49	10.87	6.43
Ⅻ HCl						239～248 〃	+23.1 (23°) ($CHCl_3$)	$C_{27}H_{46}O_2N_2$·HCl·½H$_2$O	68.11	10.16	5.88	68.37	10.28	5.99
ⅩⅢ HCl	O	—H	DAEI		72	217～222 (CHCl$_3$/ether)	+46.1 (24°) 〃	$C_{23}H_{38}O_2N_2$·HCl·H$_2$O	67.21	9.59	6.53	67.28	9.43	6.24

XIV[6] HCl		--H	DAEI		50	210~216 (CH_2Cl_2/ether)	+39.8 (26°) ($CHCl_3$)	$C_{23}H_{39}ON_2Cl \cdot HCl \cdot \frac{1}{2}H_2O$	62.71	9.38	6.36	62.42	9.36	6.28
									Cl; 16.10			Cl; 16.02		
XIV $HClO_4$						216~220 (MeOH)	+34.6 (26°) 〃	$C_{23}H_{39}ON_2Cl \cdot HClO_4$	55.75	8.14	5.65	55.71	8.19	5.65
									Cl; 14.31			Cl; 14.14		
XV	H Δ^2	--H	O	30, 32, 42	90	107~109 〃	+148.6 (23.5°) 〃							
XVI	〃	〃	NOH	A, 34	91	156~160 〃	+67.1 (23.5°) 〃	$C_{19}H_{29}ON$	79.39	10.17	4.87	79.31	10.25	5.03
XVII HCl	〃	〃	DAEI	D	55 (28)	206~212 (CH_2Cl_2/ether)	+61.1 (24.5°) 〃	$C_{23}H_{38}ON_2 \cdot HCl \cdot \frac{1}{2}H_2O$	68.37	9.98	6.93	68.48	9.88	7.21
									Cl; 8.78			Cl; 9.05		
XVIII	2H	〃	O	35		124~125 (MeOH)								
XIX	〃	〃	NOH	A	96	179~180 (CH_2Cl_2/MeOH)	+18.5 (24.5°) ($CHCl_3$)	$C_{19}H_{31}ON$	78.58	10.63	4.99	78.84	10.83	4.84
XX HCl	〃	〃	DAEI	D	59 (19)	225~228 (MeOH/acetone)	+26.7 (23.5°) 〃	$C_{23}H_{41}ON_2Cl$	69.57	10.41	7.06	69.39	10.25	7.07
									Cl; 8.93			Cl; 9.00		
XXI		Δ^5	NOH	42		201~203 (CH_2Cl_2/MeOH)								
XXII	O	Δ^4		36		149~150 (acetone)								
XXIII	〃	—H	〃		82	103~105 (MeOH/acetone)								
XXIV		〃	O	38	71	142~145[7] 153~155 (MeOH/ether)	+100.2 (22.0°) ($CHCl_3$)	$C_{19}H_{30}O_2$	78.57	10.41		78.86	10.49	
XXV		〃	〃	B	94	169~170 (ether)	98.8 (24.0°) 〃	$C_{23}H_{34}O_5$	70.74	8.78		70.99	8.70	
XXVI	〃	〃	NOH	B, A	97	123~126 (ether/MeOH)	+25.4 (23.0°) 〃	$C_{23}H_{35}ON \cdot \frac{1}{2}H_2O$	66.63	8.75	3.38	66.17	8.93	3.41
XXVII		〃	〃	A	64	229~230 〃	+53.4 (23.0°) (EtOH)	$C_{19}H_{31}O_2N$	74.71	10.23	4.59	74.80	10.24	4.58

XXVIII	H Δ^3	Δ^5	O		39	63[k]	94～95 (MeOH ether)	−102.5 (24.5°) ($CHCl_3$)								
XXIX	〃	〃	NOH		A, 39	96	158～164[j] 166～171 (CH_2Cl_2 MeOH)	−204.6 (25.0°) 〃	$C_{19}H_{27}O_2N$	79.95	9.54	4.91	78.16	9.39	4.76
XXX	OEt Δ^3	〃	〃	H	C		not purely isolated									
XXXI	O	Δ^4	〃	〃	〃	29[l]	208～213 (CH_2Cl_2 MeOH)	+56.8 (27.0°) ($CHCl_3$)	$C_{18}H_{25}O_2N$	75.22	8.77	4.87	74.95	8.87	4.96
XXXII	OEt Δ^3	Δ^5	DAEI	〃	D		not isolated									
XXXIII	O	Δ^4	〃	〃	〃	48[m]	193～201 (MeOH acetone ether)	+52.1 (25.0°) (AcOEt)	$C_{22}H_{35}O_2N_2Cl$	66.90 Cl; 8.98	8.93	7.09	66.21 Cl; 9.81	9.06	6.90
XXXIV	OEt Δ^3	Δ^5	NOH		C, 23		not isolated									
I	O	Δ^4	〃		〃	43[n]	202～204 (AcOEt)									
XXXV	OEt Δ^3	Δ^5	DAEI		D		not isolated									
XXXVI HCl	O	Δ^4	〃		〃	5[o] (35)	192～194 (AcOEt)		$C_{23}H_{37}O_2N_2Cl\cdot H_2O$	64.84	9.22	6.58	65.03	9.18	6.85
XXXVII[p]	〃	〃	$NOCH_3$		〃	22 (15)	169～170 (MeOH ether)	+136.3 (27°) ($CHCl_3$)	$C_{20}H_{29}O_2N$	76.15	9.27	4.44	76.26	9.26	4.48
XXXVIII	OEt Δ^3	Δ^5	NOH	O	C, 43	79	187～190 (d.p.) (CH_2Cl_2 EtOH)	−116.5 (33.0°) 〃	$C_{21}H_{29}O_3N$	73.43	8.51	4.08	73.64	8.64	3.93
II	O	Δ^4	〃	〃	〃, 43	93	250～252 (d.p.) (acetone)	+158.7 (33.0°) 〃	$C_{19}H_{25}O_3N$	72.35	7.99	4.44	72.69	8.15	4.54
XXXIX	OEt Δ^3	Δ^5	DAEI	〃	D		not isolated									
XL	O	Δ^4	〃	〃	〃	4[q] (6)	98～100 (MeOH acetone)	+147.1 (23.0°) (MeOH)	$C_{23}H_{34}O_3N_2\cdot \frac{1}{2}H_2O$	69.84	8.92	7.08	69.97	8.76	7.10
XLI	NOH	〃	NOH	〃	A	67	156～167[r] (acetone ether)	+207 (24.5°) ($CHCl_3$)	$C_{19}H_{26}O_3N_2$	69.06	7.93	8.48	68.54	8.03	8.29
XLII	O	〃	O	H OH	40		not isolated									

XLIII	O	Δ^4	O		B	67	194～195 (acetone/ether)	+125.6 (27.0°) ($CHCl_3$)	$C_{23}H_{30}O_6$	68.63	7.51		68.92	7.59	
XLIV	OEt Δ^3	Δ^5	〃	〃	C		not isolated								
XLV	〃	〃	NOH	〃	C, A		〃								
XLVI	O	Δ^4	〃	〃	C	38[s])	136～139 (MeOH)	+63.6 (25.5°) (EtOH)	$C_{23}H_{31}O_6N \cdot H_2O$	63.43	7.64	3.22	63.27	7.82	3.33



XLVII	CH_3	DAEI		D	50 (24)	193～199 (MeOH/ether)	+36.4 (24.0°) (EtOH)	$C_{23}H_{34}O_2N_2 \cdot HCl$	67.81 Cl; 8.71	8.67	6.88	68.41 Cl; 8.13	8.93	6.16
XLVIII	DAE[t])	〃		〃	24	44～49 (AcOEt/pentane)	+53.4 (26.0°) ($CHCl_3$)	$C_{26}H_{41}O_2N_2 \cdot \frac{1}{2}H_2O$	71.52	9.70	9.62	71.69	9.78	9.51
XLVIII $2(COOH)_2$						186～192 (MeOH/ether)	+37.4 (25.0°) (H_2O)	$C_{30}H_{45}O_{10}N_3$	59.29	7.46	6.92	59.28	7.46	6.60
XLIX	DAE	NOH		D	10	167～173 (MeOH)	+55.3 (26.0°) ($CHCl_3$)	$C_{22}H_{32}O_2N_2$	74.12	9.05	7.86	73.87	9.06	7.85

a) $R_4=CH_3$. Unless otherwise stated.
b) $R=H_2$. Unless otherwise stated.
c) DAEI=$NO(CH_2)_2N<^{CH_3}_{CH_3}$
d) PPI=$NO(CH_2)_3C_5H_{10}N$
e) The preparation was made in dioxane-benzene at room temperature instead of dioxane-CH_3OH
f) The melting point was not raised by further recrystallization.
g) Hygroscopic. UV λ_{max}^{EtOH} 242 mμ(ε 9,900), IR $\lambda_{max}^{CHCl_3}$ cm^{-1}: 1605, 1168.
h) Hygroscopic. UV λ_{max}^{EtOH} 242 mμ(ε 10,326), IR $\lambda_{max}^{CHCl_3}$ cm^{-1}: 1626, 1162.
i) The signals of the C-3 proton on chlorine-bearing carbon and the C-22 methylene protons appear as a coalescing multiplet (half height band width=11 c.p.s.) at about 5.5 τ.
j) Double melting point.
k) Calculated from XXII.
l) Calculated from 19-nor-androst-4-ene-3,17-dione.
m) Calculated from XXX.
n) Calculated from androst-4-ene-3,17-dione.
o) Calculated from XXXIV.
p) This compound was prepared by direct etherification of I.
q) Calculated from XXXIX.
r) M.p. was not clear.
s) Calculated from XLIII.
t) DAE=$(CH_2)_2N<^{CH_3}_{CH_3}$

Biological Activities

Anesthetic Activity[3,44]——The compounds (I) and (II) produce a long-acting anesthetic action in mice, when administered intraperitoneally at a dosage of 3 mg. per mouse. Deep anesthesia is induced within 5 minutes after the injection and the righting reflux is lost thereafter for 6 to 7 hours. No manifestation of pre- and post-anesthetic excitation is characteristic. Reduction of Δ^4-3-keto grouping or another modification on A ring decrease the activity, suggesting that the coexistence of this and the free-17-oximino group is needed for the manifestation of a potent anesthetic activity.

Hypocholesterolemic Effect[45]——Most of the steroids carrying a dimethylaminoethoxyimino side chain at C-17 show a potent hypocholesterolemic activity in rats, when administerated by subcutaneous injection (at a daily dose of 1 mg. per rat for 10 days). The results are listed in Table II. Among the compounds tested, 3α-chloro-5α-androstane derivative (XIV) exhibits a highest potency, exceeding that of 1-[(*p*-2-diethylaminoethoxy) phenyl]-1-(*p*-tolyl)-2-(*p*-chlorophenyl)ethanol (MER-29). Mode of action of these steroids is proved to be inhibition of cholesterol biosynthesis as in the case of MER-29. Whereas the compound (IX) could not decrease plasma cholesterol by oral administration, the compound (XLVIII) showed a marked activity even on this treatment.

Table II. Hypocholesterolemic Activities of the 17-(2-Dimethylaminoethoxyimino Steroids in the Castrated Male Rats, expressed as %-Decrease against the Control Level

Compound	Hypocholesterolemic activity (%)	Compound	Hypocholesterolemic activity (%)
Androstane series		Oestrane series	
IXa	14	XLVIII-2(COOH)$_2$	29
IX	23	XLVIII-HCl	22
XIII	7	XLVII-HCl	26
IX-CH_3I	4	XXXIII-HCl	−5
XL	13		
XX	25		
XVII	27		
XIV-$HClO_4$	33		
XIV-HCl	39		

Anti Fungal and Anti Bacterial Activity[46]——Among the 17-dimethylaminoethoxyimino steroids tested, the compounds belonging to 5α-androstane and $\Delta^{1,3,5(10)}$-estrane series were shown to be active against gram-positive bacteria, *Mycobacterium tuberculosis*, or fungi. While the compounds (XX), (XVII), and (XIV) (as hydrochloric acid and/or perchloric acid salts) are active against gram-positive bacteria, *Mycobacterium tuberculosis* and fungi, XLVIII (as oxalic acid salt) is active only against the mycobacteria, IX (as free base or methiodide) and XIII only against fungi, and XVLII-hydrochloride only against gram-positive bacteria. Further XLIX was shown to be active against both gram-positive bacteria and fungi. A high antidermatophytes activity of the compound (X) is noteworthy. The compound was shown to be almost as potent as griseofulvin[47] and its antifungal spectrum was noted to be more broad than that of the latter.

44) R. Kido, K. Hirose, M. Eigyo, H. Jyoyama, H. Satoh: Ann. Repts. Shionogi Research Lab., **15**, 35 (1965).
45) T. Miyake, K. Uchida, M. Kadowaki: *Ibid.*, **15**, 39 (1965).
46) H. Nishimura, K. Tawara, Y. Tanaka: *Ibid.*, **15**, 46 (1965).
47) L. Goldman, J. Schwarz, R. H. Preston, A. Beyer, J. Loutzenhiser: J. Am. Med. Assoc., **172**, 532 (1960).

Experimental

1) **Process A**——A mixture of 17-keto steroids, $NH_2OH \cdot HCl$ and AcONa (weight ratio 1:1:2) in EtOH and H_2O (volume ratio 10:1) was heated under reflux for 15~30 min. It was evaporated at reduced pressure and the residue extracted with $CHCl_3$. The $CHCl_3$-solution was washed, dried and evaporated, and the resulting residue was recrystallized from the suitable solvent (Table I) or submitted directly to the next reaction.

2) **Process B**——Hydroxy-17-keto steroids (1 part) dissolved in pyridine (6~7 parts in volume) and succinic anhydride (3 mol. equ.) were warmed at 70~80° for 8 hr. (in the case of XLIII, 48 hr.). To decompose the excess of succinic anhydride a cooled reaction mixture was diluted with water and allowed to stand for 1 hr. at room temperature. It was then poured on a 2*N* HCl-ice mixture and extracted with ether. The ether solution was washed with H_2O, dried, and evaporated to give the corresponding products, which were recrystallized from ether. In the case of XLIII, the ether extracts were dissolved in acetone and decolorized with active charcoal before the recrystallization from ether.

3) **Process C**——Δ^4-3,17-Diketo steroids (1 part) dissolved in a solution of abs. benzene (25 parts in volume), abs. EtOH (2.5 parts in volume) and ethyl-orthoformate (3 parts in volume) were refluxed with pyridine hydrochloride (1/20 parts) for 15 min. The cooled solution was poured into 2*N* Na_2CO_3 and extracted with benzene, washed with H_2O, dried, and evaporated to furnish the corresponding 3-ethoxy-3,5-dien-17-ones. The crude 3-ethoxy-3,5-dien derivatives was treated according to process A. The resulting 3-ethoxy-3,5-dien-17-one oximes were dissolved in 70% AcOH (20 times volume) and heated on a steam-bath for 10 min. The solvent was removed *in vacuo* and the residue was extracted with $CHCl_3$, washed with 2*N* Na_2CO_3 followed with H_2O, dried, evaporated and crystallized from suitable solvents. In the case of I, crude XXXIV (1 part) was dissolved in EtOH (30 parts in volume) and 60% $HClO_4$ (1 part) and allowed to stand at 0° for 15 hr. To this solution pyridine (15 times volume) was added and the volatile component was removed *in vacuo*. The residue was diluted with 2*N* Na_2CO_3 and extracted with $CHCl_3$, washed with H_2O, dried and evaporated to give crude I.

4) **Process D**——i) Preparation of 17-oxime O-methyl derivatives. To a stirred CH_3OH and dioxane (1:2) solution (55 parts in volume) of 17-hydroxyimino steroids (1 part), CH_3I (5 mol. equ.) and powdered $NaOCH_3$ (10 mol. equ.) were added simultaneously in 6 portions in each over 5 hr. at room temperature and the mixture was warmed at 40~50° for further 3 hr. The reaction mixture was poured into 2*N* HCl-ice mixture, extracted with $CHCl_3$, washed with H_2O, dried and evaporated. The residue obtained was chromatographed by thin-layer plates (silica gel G. F. thickness 500 mμ 20×20 cm. benzene-AcOEt =2:1 coloration with I_2) and the corresponding layers were cut off, extracted with a mixed solvent of CH_2Cl_2 and CH_3OH (3:1~2:1), filtered evaporated and recrystallized.

ii) Preparation of 17-oxime O-dimethylaminoethyl derivatives. To a stirred C_2H_5OH solution (60 parts in volume) of 17-hydroxyimino steroids (1 part), N-(2-chloroethyl)dimethylaminohydrochloride (2 mol. equ.) and 1*N* C_2H_5ONa solution (5 mol. equ.) were added simultaneously in 6 portions over 3 hr. under refluxing. After the completion of addition it was refluxed for further 2 hr. After dilution with ice-water it was extracted with $CHCl_3$, washed with saturated salt water, dried and evaporated. The residue obtained was purified through chromatography (30 parts Al_2O_3) and/or its salt formation. In many cases a considerable amount of the starting materials were recovered as indicated in Table I.

iii) Preparation of 3β-hydroxyl-17-(3-piperidinopropyloxyimino)-5α-androstane (XI). XI was obtained in an analogous manner to ii) from VIII and 1-(3-bromopropyl)piperidine hydrobromide.

5) **Process E**——17-Keto steroids (1 part) dissolved in C_2H_5OH (ca. 20 parts in volume) were refluxed with a suspension of O-methyl hydroxylamine-HCl (1.5 mol. equ.), NaOAc (3 mol. equ.) in H_2O for 2 hr. and it was allowed to stand overnight at room temperature. The volatile component was removed *in vacuo* and the residue was diluted with H_2O, extracted with $CHCl_3$, washed with H_2O, dried and evaporated to furnish the corresponding products, which were recrystallized from the suitable solvent.

6) **Oxidation of IX to XIII**——To IX (1.785 g.) dissolved in AcOH (17.8 ml.) a solution of CrO_3 (1.42 g.) in AcOH (14.2 ml.) and H_2O (1.42 ml.) was added in portion under ice-cooling and the mixture was kept for 3.5 hr. at room temperature. It was alkalified with K_2CO_3, poured into ice-water, extracted with $CHCl_3$, washed with H_2O, dried and evaporated to afford an amorphous residue (1.44 g.). It was dissolved in $CHCl_3$ (10 ml.) and abs. ether (20 ml.) and bubbled with dry HCl-gas under ice-cooling. The precipitate was filtered and washed with abs. ether, dried and recrystallized.

7) **Preparation of XIV from IX *via* the Latter Tosylate**——To an ice cooled solution of IX (2.09 g.) in pyridine (21 ml.) 3.17 g. of tosyl chloride were added in portion and kept overnight at room temperature. To decompose the excess tosyl chloride the mixture was diluted with ice-water and stirred for 2 hr. It was extracted with $CHCl_3$, washed with 2*N* Na_2CO_3 and H_2O dried and evaporated to give crude IX-tosylate (2.99 g.). The crude IX-tosylate (1.34 g.) and LiCl (1.12 g.) were refluxed in abs. dioxane (84 ml.) for 15 hr. The mixture was poured into ice-water and extracted with CH_2Cl_2, washed with H_2O, dried and evaporated. The residue obtained (1.042 g.) was chromatographed with Al_2O_3 (30 g.) and the eluates

from a mixed solvent of petrol ether and benzene (7:3) to benzene were collected and evaporated to give an amorphous residue (625 mg.), which was converted into Ⅳ-HCl analogously to XIII-HCl.

8) **Preparation of XIV from III *via* III-Tosylate**——Crude Ⅲ-tosylate (500 mg.) prepared analogously to the crude Ⅸ-tosylate was heated under reflux in collidine (15 ml.) for 4 hr. The cooled solution was diluted with ice-water and 2*N* H_2SO_4. It was extracted with ether, washed with 2*N* H_2SO_4, and H_2O, dried and evaporated to afford a residue (310 mg.), which was recrystallized from CH_3OH. The first crop 168 mg. of m.p. 107~109°, the second crop 109 mg. of m.p. 106~108°.

9) **Selective Dimethyl Ketalization of 5α-Androstane-3,17-dione to IV**——5α-Androstane-3,17-dione (300 mg.) was refluxed with *p*-toluenesulfonic acid (15 mg.) in abs. CH_3OH (4 ml.) for 20 min. The cooled solution was poured into 2*N* Na_2CO_3, extracted with CH_2Cl_2, washed with H_2O, dried evaporated and recrystallized.

10) **Hydrolysis of 17-Hydroxyimino-3,3-dimethoxy-5α-androstane to V**——Crude 17-hydroxyimino-3,3-dimethoxy-5α-androstane (207 mg.) was kept with 30% $HClO_4$ (0.5 ml.) in dioxane (2 ml.) at room temperature for 30 min. The mixture was poured into H_2O, extracted with CH_2Cl_2, washed with H_2O, dried, evaporated and recrystallized.

11) **Selective Dimethyl Ketalization of 5β-Androstane-3,17-dione to IVa**——5β-Androstane-3,17-dione (3 g.) was refluxed with *p*-toluenesulfonic acid (150 mg.) in abs. CH_3OH (40 ml.) for 2.5 hr. and kept further 40 hr. at room temperature. It was worked up analogously to 9).

12) **Hydrolysis of 17-Hydroxyimino-3,3-dimethoxy-5β-androstane to Va**——Va was obtained analogously to 10).

13) **Hydrogenation of XXII to XXIII**——XXII (7.0 g.) dissolved in abs. pyridine (105 ml.) was shaken with 5% Pd-$CaCO_3$ (1.4 g.) in H_2-atmosphere. After absorption of 1.1 mol. equivalent of H_2 the catalyst was removed by filtration and the solvent was evaporated *in vacuo*. The residue obtained was extracted with CH_2Cl_2-ether mixture, washed with 2*N* HCl, H_2O, dried, evaporated and recrystallized.

14) **Reduction and Deketalization of XXIII to XXIV**——To a suspension of $LiAl(OC_4H_9)_3H$ (8.7 g.) in abs. tetrahydrofuran (43 ml.) a solution of XXII (5.72 g.) in abs. tetrahydrofuran (57 ml.) was added in portion under ice-cooling and stirring over 20 min. It was stirred at room temperature for further 3 hr. The reaction mixture was decomposed with H_2O-tetrahydrofuran mixture (2 ml. and 8 ml.) under ice-cooling. The precipitate was filtrated by suction and washed 3 times with a mixture of ether and $CHCl_3$ (3:1). The combined organic solvent was washed with 2*N* NaOH, H_2O, dried and evaporated. The residue was crystallized from MeOH to give 5.34 g. of 3β-hydroxy-5β-androstan-17-one cyclic ethylene ketal (94%), m.p. 130~132°. 3β-Hydroxy-5β-androstan-17-one cyclic ethylene ketal (4.89 g.) was warmed with 70% AcOH on the boiling water-bath for 30 min. After evaporation of a volatile component *in vacuo*, the residue was extracted with a mixture of ether and $CHCl_3$ (3:1), washed with 2*N* Na_2CO_3, H_2O, dried, evaporated.

15) **Reduction and Deketalization accompanied with Dehydration of XXII to XXVIII**——XXII (4.28 g.) was treated analogously to 14) with $LiAl(OC_4H_9)_3H$ in tetrahydrofuran to afford 3.6 g. of 3β-hydroxyandrost-4-en-17-one cyclic ethylene ketal (84%) on recrystallization from $CHCl_3$-ether, m.p. 209~214°. 3β-Hydroxyandrost-4-en-17-one cyclic ethylene ketal (4.70 g.) was treated analogously to 14) with 70% AcOH and the extract was concentrated *in vacuo* and then chromatographed on Al_2O_3 (100 g.). Elution with petrol ether-benzene 9:1 to 4:1 gave XXVIII.

Summary

A variety of the steroidal 17-oximes and their O-alkyl, especially O-(2-dimethylaminoethyl) derivatives are prepared from the corresponding 17-ketones. A marked anesthetic, hypocholesterolemic and/or antifungal activities of some of these compounds are described.

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