SYNTHESIS AND ANTIARRHYTHMIC ACTIVITY OF EPIMERIC 17-AMINO-5α-ANDROSTAN-3-OLS AND THEIR DERIVATIVES

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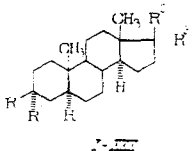
Some steroidal amines which do not possess hormonal properties display antiarrhythmic, hypotensive, or cardiotonic activity [3, 6, 9]. Campbell and Williams [5] recommend the use of 3α-amino-5α-androstan-2β-ol-17-one for the medical treatment of cardiac arrhythmias. We have now synthesized from home-produced plant material some readily accessible, simpler 5α-steroids, namely the 17-amino-5-α-androstan-3-ols (I-IV) which are epimeric at C(3) and C(7), and examined their antiarrhythmic activity. The greatest activity was shown by the 3β, 17β-epimer (I), which was used to obtain a series of N-alkyl and N-aminoacyl derivatives.

The aminoalcohols (I) and (II) were obtained as described in [2]. Aminosteroids (III) and (IV) were synthesized from the formamido-derivatives of the aminoalcohols (I) or (II) by epimerization at C(3) by the Mitsunob method, by treatment with diethyl azidodicarboxylate, triphenylphosphine, and formic acid in THF.

Acylation of the aminoalcohol (I) with chloroacetyl chloride gave the NO-diacetyl derivative (V). The O-chloroacetyl group in (V) was removed by boiling with KOH in aqueous methanol. Nucleophilic replacement of the Cl in the N-chloroacetyl residue of the 3β-hydroxy-17β-aminosteroid (VI) by an aminoalkyl radical or the residue of a nitrogeneous heterocycle gave the N-aminoacetylated aminoalcohols (VII-X). Treatment of the NO-bischloroacetyl derivative (V) with morpholine or sodium thiosulfate gave the NO-di-(4-morpholinoacetyl) compound (XI) or the Bunte salt (XII), and reduction of the N-acyl derivatives (XIII,XV, XVII, XIX, XXI, XXIII) gave (XIV, XVI, XVIII, XX, XXII, and XXIV). The ketone (XXV) was converted by the method given in [4] into the dimethylamino-compound (XXVI). Alkylation of (XXVI) with methyl iodide or ethyl bromide afforded the quaternary ammonium compounds (XXVII) and (XXVIII). Alkylation of the aminosteroid (I) with chloroacetamide gave (XXIX). For biological testing, all the amines were converted into their hydrochlorides (Ia-IVa, VIIa-IXa, XIa, XIVa, XVIa, XVIIIa, XXa, XXIIa, XXIVa, XXVIa, and XXIXa-XXXa)* by solution in anhydrous ethanol and treatment with a solution of hydrogen chloride in anhydrous ethanol to pH 2.0-3.0.



R = H (III—IV, XXI—XXIV); OH (I—II, VI—X, XIV, XVI, XVIII, XX, XXV—XXX); $OCOCH_2Cl$ (V); $OCOCH_2$morpholyl (XI); $OCOCH_2SSO_3Na$ (XII); OCHO (XIII, XIX); $OCOCH_3$ (XV); $OCOCH_2OCOCH_3$ (XVII).
R^1 = H (I—II, V—XX, XXV—XXX); OH (III—IV, XXII, XXIV); OCHO (XXI, XXII).
R^2 = H (II, IV, XIX, XX, XXIII—XXIV); NH_2 (I, III); $NHCOCH_2Cl$ (V, VI);

$NHCOCH_2N(C_2H_5)_2$ (VII); $NHCOCH_2\overline{NCH_2CH_2NHCH_2}CH_2$ (VIII);

$NHCOCH_2\overline{NCH_2CH_2N(CH_3)CH_2}CH_2$ (IX); $NHCOCH_2SSO_3Na$ (X, XII); $NHCOCH_2$morpholyl (XI); NHCHO (XIII, XXI); $NHCH_3$ (XIV, XXII); $NHCOCH_3$ (XV); $NHCH_2CH_3$ (XVI); $NHCOCH_2OCOCH_3$ (XVII); $NHCH_2CH_2OH$ (XVIII); $N(CH_3)_2$ (XXVI); $N^+(CH_3)_2I^-$ (XXVII); $N^+(CH_3)_2C_2H_5Br^-$ (XXVIII); $NHCH_2CONH_2$ (XXIX);

*The hydrochlorides are designated by the same numbers as their free bases, with the suffix *a*.

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$NHCH_2CH_2NH_2$ (XXX).
R^3 = H (I, III, V—XVIII, XXI—XXII, XXVI—XXX); NH_2 (II, IV); NHCHO (XIX, XXIII); $NHCH_3$ (XX, XXIV). $R^2 + R^3 = O$ (XXV).

The structures of the isomeric 17-amino-5α-androstan-3-ols (I-IV), and those of their derivatives (V-XII, XIV, XVI, XVIII, XX, XXII, XXIV, and XXVII-XXX) were in good agreement with their elemental analyses, IR and mass spectra (Table 1). The elemental analyses, yields, and melting points of the hydrochlorides (Ia-IVa, VIIa-IXa, XIa, XIVa, XVIa, XVIIIa, XXa, XXIIa, XXIVa, XXVIa, and XXIXa-XXXa) are given in Table 2. The ^1H NMR spectra enabled the epimeric alcohols (I-IV) to be distinguished: in the spectra of the 17β-epimers (I and (III), triplets were present for the 17α-protons with δ 2.6 ppm and $^2J_{H,H}$ 8.8-8.9 Hz, whereas in those of the 17α-epimers (II) and (IV) doublets for the 17β protons were present with chemical shift 2.90 ppm and $^2J_{H,H}$ 7.3 and 6.8 Hz. The 3β-hydroxy compounds (I) and (II) showed broad multiplet signals for the 3α protons with δ 3.59 ppm, while in the spectra of the 3α-epimers (III) and (IV) the 3β-protons were seen as narrow signals with δ 4.04. The 17α protons in the spectra of (V-XII) and (XVII) were present as a quartet with a chemical shift in the range 3.92-3.62 ppm, and in those of (XIV, XVI, XVIII, XXVII, and XXIX-XXX) as triplets with δ 3.46-2.40 ppm.

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IR spectra were obtained on a UR-20 instrument (East Germany) in vaseline oil, PMR spectra on a Bruker WP-200 SY (200 MHz), and mass spectra on an MAT-112 GC-MS.

3β-Chloroacetoxy-17β-chloroacetylamino-5α-androstane (V) and 3β-Hydroxy-17β-chloroacetylamino-5α-androstane (VI). To a mixture of 9 g (30.87 mmole) of (I) and 9 g (107.13 mmole) of sodium bicarbonate in 580 ml of DMF was added at 20°C over 30 min 18 ml (238.3 mmole) of chloroacetyl chloride. After 24 h, the mixture was poured into 2 liters of ice water, washed with water, and the product (11 g) separated by column chromatography on silica gel, eluting sucesssively with benzene—acetone 20:1, 10:1, and 4:1. From the appropriate fractions of the eluate there were obtained after evaporation 9.6 g of (V) and 0.5 g of (VI).

3β-Hydroxy-17β-chloroacetylamino-5α-androstane (VI). To a solution of 4 g (8.99 mmole) of (V) in 250 ml of methanol was added 10 ml of 1 N aqueous KOH, the mixture boiled for 10 min, the solvent removed under reduced pressure until the volume had been reduced by half, poured into 400 ml of water, and the solid (3.05 g) filtered off and purified on a column of silica gel (40/100) using the solvent systems benzene and benzene—acetone (15:1). The solvent was removed from the appropriate fractions to give, after removal of the solvent under reduced pressure, 2.8 g of (VI).

3β-Hydroxy-17β-diethylaminoacetylamino-5α-androstane (VII), 3β-Hydroxy-17β-piperazinoacetylamino-5α-piperazinoacetylamino-5α-androstane (VIII), 3β-Hydroxy-17β-[(N-methylpiperazino)acetylamino]-5α-androstane (IX) and 3β-Morpholino-acetoxy-17β-morpholinoacetylamino-5α-androstane (XI). Obtained by boiling (V) or (VI) for 4-6 h with an 8—80 fold excess of the appropriate amine in 2-propanol.

Sodium N-(3β-Hydroxy-5α-androstanyl)-17β-amino(α-oxoethyl)thiosulfate (X) and Disodium N,O-(5α-androstanyl)-17β-amino(α-oxoethyl)hydroxy(α-oxoethyl)bisthiosulfate (XII). Obtained from (V) or (VI) by boiling for 8 h with a sixfold excess of sodium thiosulfate in aqueous ethanol.

3β-Acetoxy-17β-acetylamino-5α-androstane (XV). A mixture of 0.2 g (0.69 mmole) of (I), 5 ml of pyridine (redistilled over KOH), and 5 ml of acetic anhydride was kept for 20 h at 20°C, 100 ml of water added, the solid filtered off, washed with water to pH 7.0, and crystallized from methanol to give 0.21 g (81%) of (XV), mp 196-198°C. IR spectrum, ν_{max}, cm^{-1}: 1570 s, 1660 s, 1740 s, 3290 br. According to [10], mp 195-196°C.

3β-Acetoxyacetoxy-17β-acetoxyacetylamino-5α-androstane (XVII). A mixture of 2.2 g (4.95 mmole) of (V), 2.2 g (22.42 mmole) of anhydrous potassium acetate, and 200 ml of DMF was stirred for 3 h at 100°C, then 400 ml of water added at 20°C, the solid filtered off, washed with water, and the product (2.4 g) chromatographed on a column of silica gel, eluents benzene and benzene—acetone 20:1 and 10:1. Evaporation of the appropriate fractions gave 2 g (82%) of (XVII), mp 68-70°C. IR spectrum, ν_{max}, cm^{-1}: 1590 s, 1670 s, 1765 s, 3250 br. Found: M^+ 491. $C_{27}H_{41}NO_7$. Calculated: M 491.69.

3β-Hydroxy-17β-(N-methylamino)-5α-androstane (XIV), 3β-Hydroxy-17β-ethylamino-5α-androstane (XVI), 3β-Hydroxy-17β-(2-ethanolamino)-5α-androstane (XVIII), 3β-Hydroxy-17α-(N-androstane (XX), 3α-Hydroxy-17β-(N-methylamino)-5α-androstane (XXII), and 3α-Hydroxy-17α-(N-methylamino)-5α-androstane (XXIV). The amides (XIII, XV, XVII, XIX, XXI, and XXIII) were reduced to

TABLE 1. Physicochemical Properties of 17-Amino-5α-androstan-3-ols V-XII, XIV, XVI, XVIII, XX, XXII, XXIV, XXVII-XXX

Compound	Yield, %	mp, °C (solvent for crystallization)	Found, %			Empirical formula	Calculated, %			M		IR spectrum, cm^{-1}
			C	H	N		C	H	N	found by mass spectrometry	calculated	
V	70	203—5	62,47	8,14	3,48 (Cl 15,97)	$C_{23}H_{36}Cl_2NO_3$	62,15	7,95	3,15 (Cl 15,95)	443/445 ($^{35}Cl/^{37}Cl$)	444,49	1545 m, 1665 s, 1760 s, 3410 m, 3420 m,
VI	85	213—4	68,27	9,45	4,12 (Cl 9,42)	$C_{21}H_{34}ClNO_2$	68,53	9,33	3,81 (Cl 9,63)	367/369 ($^{35}Cl/^{37}Cl$)	368,01	1575 m 1670 s, 3230 br, 3300 br
VII	74	215—7 (benzene)	74,61	10,73	6,56	$C_{25}H_{44}N_2O_2$	74,19	10,98	6,92	404	404,71	1530 m, 1670 s, 3320 m, 3450 br,
VIII	66	238—40 (ethanol)	71,73	10,52	9,72	$C_{25}H_{43}N_3O_2$	71,88	10,4	10,06	417	417,71	1550 s, 1660 s, 3260 m, 3350m, 3480 br
IX	72	237—9 (ethanol)	71,96	10,75	9,43	$C_{26}H_{45}N_3O_2$	72,33	10,53	9,74	431	431,74	1520 s, 1690 s, 3190 br, 3340 m
X	68	256—60 decomp. (abs. ethanol	53,56	7,38	2,74 (S 13,91)	$C_{21}H_{34}NNaO_5S_2$	53,93	7,34	3,0 (S 13,71)	...	...	1580 s, 1670 s, 3120 br, 3330 br
XI	69	164—6 (ethanol)	67,92	9,51	7,39	$C_{31}H_{51}N_3O_5$	68,21	9,44	7,7	545	545,85	1520 s, 1690 s, 1740 s, 3390 m
XII	76	275—80	42,53	5,62	2,45 (S 19,67)	$C_{23}H_{35}NNa_2O_9S_4$	42,91	5,49	2,18 (S 19,92)	...	...	1560 m, 1660 m, 1740 m 3400 br,
XIV	81	209—10 (ethanol)	78,28	11,34	4,32	$C_{20}H_{35}NO$	78,61	11,57	4,59	305	305,56	3285 m, 3390 br,
XVI	71	173—5 (chloroform)	78,59	11,83	4,17	$C_{21}H_{37}NO$	78,92	11,69	4,38	319	319,59	3290 w, 3340 br,
XVIII	49	188—90 (ethanol)	75,25	11,01	4,14	$C_{21}H_{37}NO_2$	75,15	11,14	4,18	335	335,59	3300 br
XX	91	157—9	78,74	11,26	4,48	$C_{20}H_{35}NO$	78,61	11,57	4,59	305	305,56	3295 m, 3370 br
XXII	85	195—7	78,23	11,31	4,19	$C_{20}H_{35}NO$	78,61	11,57	4,59	305	305,56	2500—3290 (max. 3140) 3310 m.
XXIV	76	142—4 (ethanol)	78,26	11,70	4,71	$C_{20}H_{35}NO$	78,61	11,57	4,59	305	305,56	3280 br
XXVII	57	293—7 (diethyl ether)	57,47	8,59	3,28 (I 27,16)	$C_{22}H_{40}INO$	57,25	8,75	3,04 (I 27,5)	...	...	3400 br
XXVIII	56	306—9 (acetone)	64,83	10,05	3,56 (Br 18,19)	$C_{23}H_{42}BrNO$	64,45	9,9	3,27 (Br 18,65)	...	...	3350 br
XXIX	79	206—8	72,17	10,38	8,25	$C_{21}H_{36}N_2O_3$	72,35	10,43	8,04	348	348,59	1620 pl, 1680 s, 3200 br, 3360 br
XXX	74	121—3 (ethanol—hexane)	75,12	11,68	8,14	$C_{21}H_{38}N_2O$	75,37	11,47	8,37	334	334,61	1610 w, 3200 br, 3350 br

TABLE 2. Properties of 17-Amino-5α-androstan-3-ol Hydrochlorides

Compound	Yield, %	mp, °C	Found, Cl, %	Empirical formula	Calculated, Cl, %
I a	82	317—320	11,15	$C_{19}H_{33}NO \cdot HCl$	10,81
II a	75	291—295	10,37	$C_{19}H_{33}NO \cdot HCl$	10,81
III a	80	296—300	10,66	$C_{19}H_{33}NO \cdot HCl$	10,81
IV a	82	282—286	11,29	$C_{19}H_{33}NO \cdot HCl$	10,81
VII a	79	254—256	7,74	$C_{25}H_{44}N_2O_2 \cdot HCl$	8,04
VIII a	91	303—307	14,51	$C_{25}H_{43}N_3O_2 \cdot 2HCl$	14,45
IX a	69	263—266	13,64	$C_{28}H_{45}N_3O_2 \cdot 2HCl$	14,05
XI a	71	210—215	11,89	$C_{31}H_{51}N_3O_5 \cdot 2HCl$	11,46
XIV a	71	295—299	9,85	$C_{20}H_{35}NO \cdot HCl$	10,37
XVI a	87	249—253	10,36	$C_{21}H_{37}NO \cdot HCl$	9,96
XVIII a	67	280—285	9,71	$C_{21}H_{37}NO_2 \cdot HCl$	9,53
XX a	80	273—276	9,68	$C_{20}H_{35}NO \cdot HCl$	10,37
XXII a	69	272—286	10,30	$C_{20}H_{35}NO \cdot HCl$	10,37
XXIV a	60	272—276	10,72	$C_{20}H_{35}NO \cdot HCl$	10,37
XXVI a	72	281—285	10,28	$C_{21}H_{37}NO \cdot HCl$	9,96
XXIX a	83	232—236	9,20	$C_{21}H_{36}N_2O_2 \cdot HCl$	9,21
XXX a	79	228—232	16,92	$C_{21}H_{38}N_2O \cdot 2HCl$	17,4

Note. All the hydrochlorides were isolated by reprecipitation from anhydrous ethanol with dry diethyl ether.

TABLE 3. Antiarrhythmic Activity of Salts of 17-Amino-5α-androstan-3-ols in Aconitine Arrhythmia in Rats (intravenous or intraperitoneal administration)

Compound	ED_{50}, mg/kg	LD_{50}, mg/kg	Therapeutic ratio
I a*	2,4 (1,03—3,37)	40 (31,64—65,21)	16,6
II a*	7,4 (4,9—9,9)	56 (46,79—65,21)	7,6
III a	27,5 (24,85—30,15)	185 (145,95—224,05)	6,73
IV a	Inactive	98 (79,65—116,35)	—
VII a	»	270 (191,9—348,1)	—
VIII a	»	270 (191,9—348,1)	—
IX	»	1000	—
X	»	650 (602,88—697,12)	—
XI a	»	410 (314,32—505,68)	—
XIIa	»	290 (253,4—326,36)	—
XIV a*	2 (1,38—2,62)	42,5 (37,8—47,25)	21,3
XVI a	Inactive	370 (277,41—462,7)	—
XVIII a*	3,5 (2,3—4,7)	37,0 (28,4—45,6)	10,6
XX a	42,0 (20,13—68,87)	355,0 (321,81—388,19)	8,45
XXII a	26,0 (14,29—37,71)	115 (106,8—123,2)	4,42
XXIV a	Inactive	100 (49,62—150,38)	—
XXVI a*	2,8 (1,92—3,68)	36,0 (31,08—40,92)	12,9
XXVII	3,4 (0,69—6,11)	17,5 (10,82—24,18)	5,15
XXVIII	Inactive	88 (79,42—96,58)	—
XXIX a	»	625 (512,6—737,4)	—
XXX a	»	570 (495,41—644,59)	—
Quinidine*	3,3 (1,74—4,86)	78 (67,5—88,5)	23,6
Quinidine	14 (9,2—18,5)	195 (165,11—224,89)	13,9

Note. Range of variation shown in brackets. An asterisk indicates that the compound was given intravenously.

to the aminoalkyl compounds (XIV, XVI, XVIII, XX, XXII, and XXIV) by boiling for 7-18 h with an excess of lithium aluminohydride in THF.

3β-Hydroxy-17β-(NN-dimethylamino)-5α-androstane (XXVI). Obtained as described in [4], mp 210-212°C (from ethyl acetate). According to [4], mp 209-210°C (from ethyl acetate).

N-(3β-Hydroxy-5α-androstan-17β-yl)-NNN-trimethylammonium Iodide (XXVIII). From 0.18 g (0.51 mmole) of (XXVIa) and 2.5 ml (4.02 mmole) of freshly distilled methyl iodide in 35 ml of diethyl ethyl at 20°C for 12 h, there was obtained 0.13 g of (XXVII).

N-(3β-Hydroxy-5α-androstan-17β-yl)-NN-dimethyl-N-ethylammonium Bromide (XXVIII). A suspension of 1.2 g (3.76 mmole) of (XXVI) in 100 ml of ethyl bromide, redistilled over calcium chloride, was boiled for 20 h, the solid filtered off at 20°C, and crystallized from acetone to give 0.9 g of (XXVIII). On standing, 0.4 g of the starting material (XXVI) separated from the filtrate.

3β-Hydroxy-17β- aminoacetamido-5α-androstane (XXIX). To a mixture of 1 g (3.43 mmole) of (I), 1 g of sodium bicarbonate, and 55 ml of DMF was added at 40°C over 20 min a solution of

0.65 g (6.95 mmole) of chloroacetamide in 10 ml of DMF, and the mixture stirred for 7 h at 80-90°C. It was then poured at 20°C into 100 ml of water, and after 12 h the solid was filtered off, washed with water, and recrystallized from ethanol to give 0.95 g of (XXIX).

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Antiarrhythmic activity was examined in male non-narcotized rats weighing 160-200 g.

Aconitine arrhythmia was induced by the intravenous administration of aconitine hydrobromide in a dose of 50 μg/kg [1]. The compounds were given intravenously or intraperitoneally (if insoluble) in isotonic 0.9% sodium chloride solution as a suspension with Tween-80. The ability of the compounds to retard the appearance of arrhythmia in comparison with the controls was assessed. As a measure of activity, the ED_{50} values were calculated (mg/kg) [8]. The results are given in Table 3.

Calcium chloride arrhythmia was induced by intravenous administration of calcium chloride solution in a dose of 250-300 mg/kg [7]. In the experimental groups, the compounds were administered in a dose of 50 mg/kg intraperitoneally as a suspension with Tween-80, 15 min before administration of calcium chloride. The numbers of deaths of the animals from cardiac fibrillation following administration of the compounds were recorded in comparison with the controls. None of the test compounds showed any antiarrhythmic activity in these tests.

Acute toxicities were determined in intact white mice of both sexes, weighing 16-18 g. The test compounds were administered intravensouly or intraperitoneally (if soluble) in isotonic 0.9% sodium chloride solution, or as suspensions with Tween-80. Each dose was tested in 5-6 animals. Observations of the condition of the animals were made over a period of three days. The LD_{50} values were calculated by the method of Miller and Teinter [8]. The results are given in Table 3.

The therapeutic index of the test compounds in aconitine arrhythmia was calculated as the ratio LD_{50}/ED_{50}.

The results of the tests are shown in Table 3, from which it will be seen that some of the compounds show high activity in aconitine arrhythmia. Compounds (XVIIIa) and (XXVII) were close to quinidine in activity by the intravenous route, and (Ia), (XIVa), and (XXVIa) were even more active than the latter. These compounds were however more toxic than quinidine, and had a lower therapeutic ratio.

In calcium chloride arrhythmia, administration of the test compounds to rats in the abdominal cavity in this dose (50 mg/kg) had no antiarrhythmic effect.

These studies have shown that in aconitine arrhythmia, of the four theoretically possible isomers of 17-amino-5α-androstan-3-ol (I-IV), when administered to rats as the hydrochlorides, the greatest activity in preventing the development of disturbances of cardiac rhythm is shown by the 3β-, 17β- and 3β, 17β-epimers [sic] (I) and (II), the ED_{50} values being 2.4 and 7.4 mg/kg (Table 3). Changing the configuration at C(3) results in a decrease in antiarrhythmic activity by a factor of ten, the ED_{50} of (III) being 27.5 mg/kg. The 17β-epimer (IV) is inactive. Hence, for the expression of antiarrhymic activity in unsubstituted 17-amino-5α-androstan-3-ols, the most favorable orientation of the hydroxyl and amino groups in the 3 and 17-positions is diequatorial.

Monomethylation of the 17β-amino group has no marked effect on activity (cf. the activities of (Ia) and (XIVa), (IIIa) and (XXIIa)). Conversion of the primary 17β-amino group into a tertiary or quaternary group results in a slight reduction in antiarrhythmic activity (XXVIa, XXVII). Introduction of a β-hydroxyethyl grouping (XVIIIa) results in maintenance of activity, while introduction of the β-aminoethylamino group (XXXa) destroys the activity. Aminoacetyl derivatives of the 17β-aminosteroid (VIIa-XIa, X, XIa, and XII) no longer possess the ability to prevent the development of cardiac arrhythmias in rats.

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SYNTHESIS AND ANTIHYPERTENSIVE ACTIVITY OF N-ACETYLMERCAPTOPROPIONYL-6-(2'-PHENYLETHYL)PIPECOLINIC ACIDS

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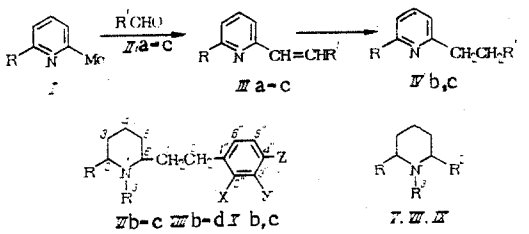
The search for drugs with antihypertensive activity has in recent years been closely associated with the control of the renin-angiotensin and kallikrein-kinin systems, which operate on the vascular tonus, and with the normalizing balances of water and electrolytes in the body [8, 11].

These systems carry out their functions by generating the powerful pressor octapeptide angiotensin II, and the straight-chain peptides possessing higher depressor activity, subsumed under the general title of kinins. The formation of the pressor angiotensin II from angiotensin I, which has little biolical activity, and deactivation of the depressor kinins is effected in the body by the catalytic action of the same enzyme, dipeptidylcarboxypeptidase (DCP). Inhibition of this enzyme prevents the formation of angiotensin II, simultaneously inhibiting the breakdown of kinins, with the overall result of a decrease in arterial pressure (AP).

One of the most effective inhibitors of DCP, which has found practical application in the treatment of malignant and renovascular hypertonia and of hypertonic disease with high AP levels, is N-[(2S)-3-mercapto-2-methylpropionyl]-L-proline, which has received the commercial designation Captopryl.

Our studies with piperidine analogs of Captopryl [5] have shown the desirability of examining N-acetylmercaptopropionyl derivatives of pipecolinic acids as novel antihypertensive drugs. In the course of these studies, it was found that those compounds of this type with a sterically hindered amide function showed the greatest antihypertensive and DCP inhibitory effect. Such steric hindrance is usually achieved in Captopryl type compounds by branching of the side chain of the acylating group. We have shown that it is possible to attain the same effect by introducing screening groups into the heterocyclic framework, rather than into the side chain.

Continuing these studies, we have now synthesized and examined the antihypertensive activity of the hitherto unknown N-acetylmercaptopropionylpipecolinic acids, bearing in the 6-position of the piperidine ring a variety of substituted phenyl and cyclohexylethyl residues.



I, IIIa-c IVb, c, V, VIb, c: R = COOEt; VII, VIIIb-d IX, Xb, c, R = COOH; IIa-c IIIa-c IVb, c: $R^1 = C_6H_2X$-2-Y-3-Z-4; V, VIb, c., VII, VIIIb-d $R^3 = H$; IX, Xb, c: $R^3 = COCH_2CH_2SAc$; V, VII, IX: $R^2 = CH_2CH_2C_6H_{11}$ cyclo, II, III: X = Y = = Z = H (a); II, III, IV, VI, VIII, X: X = Z = Cl, Y = H (b), X = H, Y = Z = = OMe (c); VIIId: X = H, Y = Z = OH.

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