Hypocholesterolemic Agents. 7.[1a] The C-17 Epimer of 20,25-Diazacholesterol[1b]

V. V. RANADE, F. KOHEN, AND R. E. COUNSELL*

Laboratory of Medicinal Chemistry, College of Pharmacy, University of Michigan, Ann Arbor, Michigan 48104

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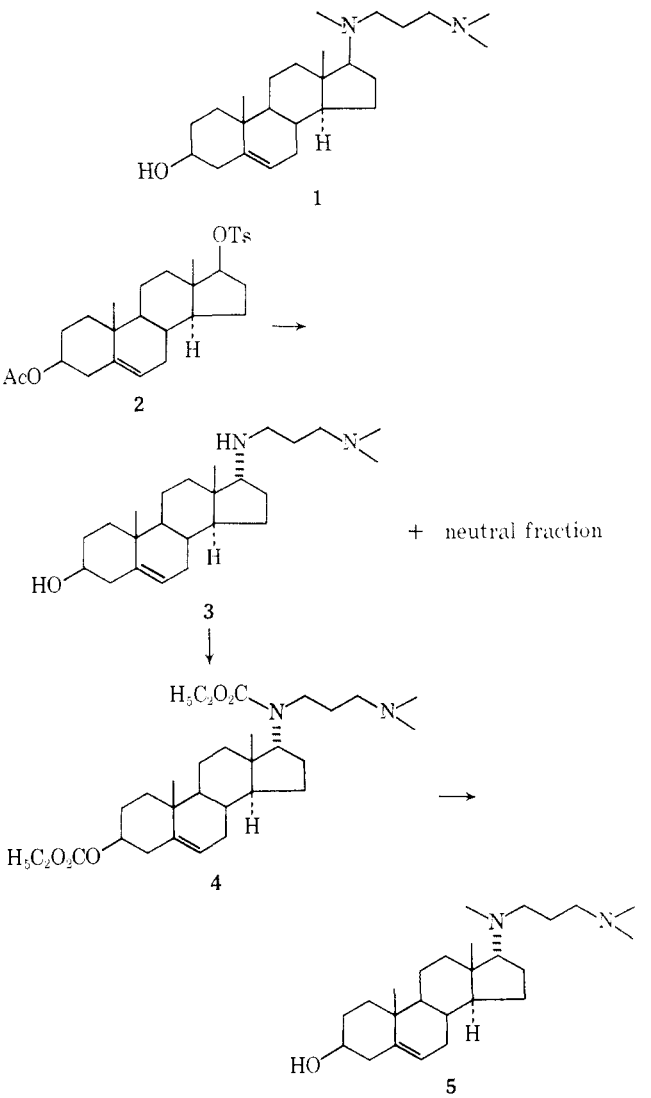
The potent hypocholesterolemic properties of 20,25-diazacholesterol (1) prompted the synthesis of the 17α-epimer (**5**) in order to determine the effect of altering the stereochemistry of the side chain on biological activity.

One approach to the development of hypocholesterolemic agents has been the synthesis of compounds which will inhibit the endogenous synthesis of cholesterol. Previous papers in the series described the synthesis and potent hypocholesterolemic properties of certain aza-and diazacholesterols.[2] Not only have these compounds been shown to inhibit cholesterol synthesis in laboratory animals[3] and man,[4] but their ability to interfere with cholesterolgenesis in insects has also been observed.[5]

Studies with azacholesterols having the heteroatom at different positions of the cholesterol side chain showed that whereas 23-, 24-, and 25-azacholesterol had considerable hypocholesterolemic activity in rats, the 20- and 22-azacholesterols were essentially inactive in this regard. An examination of molecular models revealed that the β orientation of the C-17,20 bond would decrease the ability of atoms at the 20 and 22 positions to interact with a receptor surface should adsorption occur by the sterically less hindered α-face of the steroid molecule.[2a] While many other explanations may account for the observed activities of the isomeric azacholesterols, it was of interest to examine what effect altering the stereochemistry of the side chain would have on the biological activity of these compounds.

Our first approach to this problem was to determine the effect of epimerization at C-17 on the biological properties of 20,25-diazacholesterol (**1**). The most direct route to the 17α epimer (**5**) appeared to be aminolysis of the 17β-tosyloxy derivative with the appropriate secondary amine. Several laboratories[6] have displaced the 17β-tosylate group with N_3^- and subsequently reduced the resulting 17α-azido androstane derivatives to 17α-amino steroids. Moreover, Davis and coworkers[7] found that 17α-pyrrolidin-1′-yl-5α-androstan-3β-ol could be obtained in 42% yield by treating 5α-androstane-3β,17-diol 3-acetate 17-tosylate with pyrrolidine in a sealed tube at 170–180° in the absence of solvent.



Attempts to prepare **5** directly by heating androst-5-ene-3β,17-diol 3-acetate 17-tosylate (**2**) with 1-(*N*-methyl)-(3-dimethylamino)propylamine proved unsuccessful. Only traces of aminosteroids could be detected. On the other hand, similar treatment of **2** with the primary amine, 3-dimethylaminopropylamine, afforded 17α-(3-dimethylaminopropyl)aminoandrost-5-en-3β-ol (**3**) in 23% yield.

Acetylation of the neutral fraction followed by chromatography on silicic acid treated with $AgNO_3$ yielded three isomeric 3β-acetoxyandrostadienes (**6**, **7**, **9**) (18%),

* To whom correspondence should be addressed.

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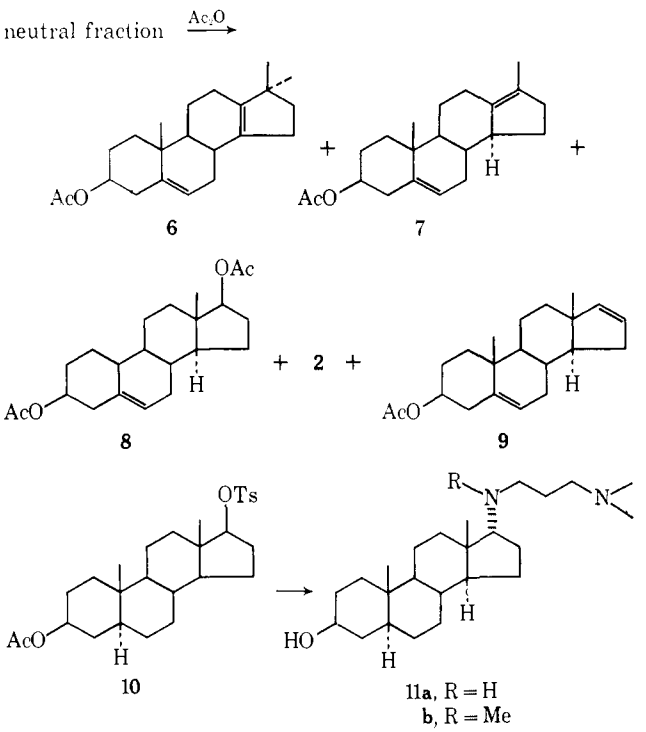

androst-5-ene-3β,17β-diol diacetate (**8**) (5%), and recovered starting material (**2**) (14%). The olefinic byproducts (**6**, **7**, and **9**) were identified readily by nmr. The more mobile 3β-acetoxyandrostadiene (**6**) analyzed for $C_{21}H_{30}O_2$. The nmr spectrum showed only one tertiary Me corresponding to the C-19 at δ 1.03, and one secondary Me at δ 1.00 (d, J = 6.5 cps). The presence of one vinyl proton at δ 5.58 corresponding to C-6 H, and the absence of cyclopropyl protons indicated that the additional double bond was tetrasubstituted. These results are in agreement with structure **6**, an 18-nor-17β-methyl-13(14)-androstene system, which may be envisaged as formed by a 1,2 shift of the C-18 CH_3 to the initially formed C-17 carbonium ion and subsequent loss of a proton at C-14.

The second isomeric androstadiene eluted from the column also analyzed for $C_{21}H_{30}O_2$. The nmr spectrum showed the C-19 Me at δ 1.13, a vinyl Me peak at 1.65, and the C-6 vinyl hydrogen at 5.54. Structure **7** is readily assigned to this product. Its formation can be viewed as a 1,2 shift of the C-18 Me to the C-17 carbonium ion, followed by a loss of a proton at C-17.

The more polar 3β-acetoxyandrostadiene **9** also analyzed for $C_{21}H_{30}O_2$. The nmr spectrum showed 3 vinyl protons at δ 5.58 (C-6 H) and 5.81 (m, 2 H). The C-19 Me appeared at δ 1.16 and the C-18 Me at 0.80. Since both angular Me groups were present, it was apparent that no rearrangement of the C-18 Me had occurred. Structure **9** was thus assigned and can be viewed as arising by a simple bimolecular elimination of the tosylate group.

The secondary amine **3** was converted into the desired diazacholesterol analog **5** by LAH reduction of the urethane derivative **4**. The corresponding 5,6-dihydro analog of **11b** was prepared from 5α-androstane-3β,17β-diol 3-acetate 17-tosylate (**10**) by a similar sequence of reactions.

The configuration of the 17α-aminated products was confirmed by nmr spectroscopy. A series of 17α-amino androstane derivatives was synthesized by standard methods and the nmr spectra in $CDCl_3$ and pyridine compared with the spectra obtained with the corresponding 17β epimer. A downfield shift of 2.5–5.5 cps was observed for the C-18 Me resonances in the 17β-amino series when the spectra were taken in pyridine. This effect was not displayed by the 17α-amino compounds. In this way a pair of epimeric C-17 aminosteroids can be easily distinguished.

Preliminary Biological Results.—20,25-Diazacholesterol (**1**) and the 17α epimer **5** were found to be about equal in their capacity to inhibit the development of tobacco hornworms.[8] On the other hand, **5** was much less effective in blocking the dealkylation of sitosterol by these insects.[8]

The hypocholesterolemic activity of **5** was evaluated in male rats made hypercholesterolemic with propylthiouracil by the method of Ranney and Cook.[9] Whereas 20,25-diazacholesterol was found to produce a demonstrable reduction in serum cholesterol at an oral dose of 0.3 mg/kg, the epimer **5** showed no effect at 5.0 mg/kg.[10] These results are consistent with previous studies which have indicated that any structural departure from the cholesterol molecule usually leads to a marked reduction of hypocholesterolemic activity.

Experimental Section[11]

17α-(3-Dimethylaminopropyl)aminoandrost-5-en-3β-ol (3).—A soln of androst-5-ene-3β,17β-diol 3-acetate 17-tosylate[12] (4.0 g) in freshly distd 3-dimethylaminopropylamine (6 ml) was heated to gentle reflux with stirring under N_2 for 48 hr. The solvent was removed completely *in vacuo*, and the residue was extd with 10% HCl and Et_2O. The organic and the aq phases were sepd and the latter made alkaline with 10% NaOH soln. The ppt was filtered, washed well with H_2O, and recrystd from dil Me_2CO to give **3** (0.7 g, 23.3%) as colorless needles: mp 141–143°; $[\alpha]D$ −91.2°; nmr ($CDCl_3$) δ 0.72 (C-18 CH_3); nmr (pyridine) δ 0.73 (C-18 CH_3). *Anal.* ($C_{24}H_{42}N_2O$) C, H.

The Et_2O layer from the original extn was washed with dil $NaHCO_3$ soln and H_2O and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue acetylated with Ac_2O and pyridine. The usual work-up afforded a mixture of products (1.6 g) which was chromatographed on silicic acid (Mallinckrodt) impregnated with 5% $AgNO_3$. Elution with hexane–C_6H_6 (8:2, 200 ml) gave **17β-methyl-18-norandrosta-5,13(14)-dien-3β-ol 3-acetate (6)** (200 mg, 8%): mp 84–85°; $[\alpha]D$ −173°; nmr ($CDCl_3$) δ 1.00 (d, 3 H, J = 6.5 cps, C-17 CH_3). *Anal.* ($C_{21}H_{30}O_2$) C, H.

Further elution with the same solvent system (500 ml) gave a mixture of **6** and **7** (250 mg). This was followed by a fraction (200 ml) contg only **17-methyl-18-norandrosta-5,13(17)-dien-3β-ol 3-acetate (7)** (110 mg, 4.4%): mp 98–99° (from MeOH); $[\alpha]D$ −132°; nmr ($CDCl_3$) δ 1.65 (s, 3 H, C-17 CH_3). *Anal.* ($C_{21}H_{30}O_2$) C, H.

Elution with hexane–C_6H_6 (7:3) (400 ml) gave **androst-5-ene-3β,17β-diol diacetate** (8) (150 mg, 5%): mp 162–163° (lit.[13] mp 157–157.5°).

Elution with hexane–C_6H_6 (1:1) afforded the starting material **2** (550 mg, 13.75%). Elution with C_6H_6 gave **androsta-5,16-**

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(11) The nmr spectra were obtd with a Varian A-60A spectrometer, optical rotations in $CHCl_3$. The melting points were measured on a Fisher-Johns apparatus and are not corrected. Where analyses are indicated by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

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dien-3β-ol acetate (**9**) (200 mg) (6%): mp 89–90° (from MeOH); $[\alpha]D$ −122°; nmr ($CDCl_3$) δ 0.80 (C-18 CH_3), 1.16 (C-19 CH_3), 5.58 (C-6 H), and 5.81 (m, C-17 and C-16 vinyl protons). *Anal.* ($C_{21}H_{30}O_2$) C, H.

***N*-Methyl-*N*-(3-dimethylamino)propyl-17α-aminoandrost-5-en-3β-ol (5).**—To a soln of **3** (0.3 g) in dry C_6H_6 (7 ml) and $N(Et)_3$ (1.5 ml) a soln of EtOCOCl (0.5 ml) in dry C_6H_6 (2 ml) was added dropwise and the mixture was refluxed for 4 hr. The reaction mixture was then allowed to cool and washed with H_2O. The organic phase was sepd, dried (Na_2SO_4), and evapd. The residue was characterized as **4**, and was used without further purification. To a slurry of LAH (0.3 g) in dioxane a soln of **4** (0.2 g) in dry dioxane (10 ml) was added, and the mixture was refluxed under N_2 for 24 hr. The excess hydride was decompd by successive dropwise addn of aq dioxane (1:3, 4 ml), 20% NaOH soln, and H_2O. The insol salts were removed by filtration and washed with hot dioxane. The filtrate was then evapd and the oily residue was extd with Et_2O. The Et_2O ext was washed with H_2O, dried (Na_2SO_4), and evapd. The oily residue solidified upon addn of H_2O. Recrystn from Me_2CO gave **5** (0.1 g, 33.3%): mp 85–87°; $[\alpha]D$ −93.3°; nmr ($CDCl_3$) δ 0.71, nmr (pyridine) δ 0.72 (C-18 CH_3). *Anal.* ($C_{25}H_{44}N_2O$) C, H.

17α-(3-Dimethylaminopropyl)amino-5α-androstan-3β-ol (11a).—A soln of 5α-androstan-3β,17β-diol 3-acetate 17-tosylate[14] (2.0 g) in freshly distd 3-dimethylaminopropylamine (30 ml) was refluxed for 48 hr and worked up as described above. The basic fraction afforded (250 mg, 16.6%): mp 147–149°; nmr ($CDCl_3$) δ 0.73 (C-18 CH_3); nmr (pyridine) δ 0.74 (C-18 CH_3). *Anal.* ($C_{24}H_{44}N_2O$) C, H. The neutral fraction was not examined in this case.

***N*-Methyl-*N*-(3-dimethylamino)propyl-17α-amino-5α-androstan-3β-ol (11b).**—Methylation of **11a** as described above afforded **11b** (34%) which was isolated as the dihydrochloride salt. Recrystn from *i*-PrOH gave a white solid; mp 278–280° dec; nmr (of free base) ($CDCl_3$) δ 0.72 (C-18 CH_3); nmr (pyridine) δ 0.72 (C-18 CH_3). *Anal.* ($C_{25}H_{48}Cl_2N_2O \cdot H_2O$) C, H.

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Hypoglycemic Cyclic Amidines

L. I. BARSKY AND W. L. BENCZE*

Research Division, CIBA Pharmaceutical Company, Division of CIBA Corporation, Summit, New Jersey 07901

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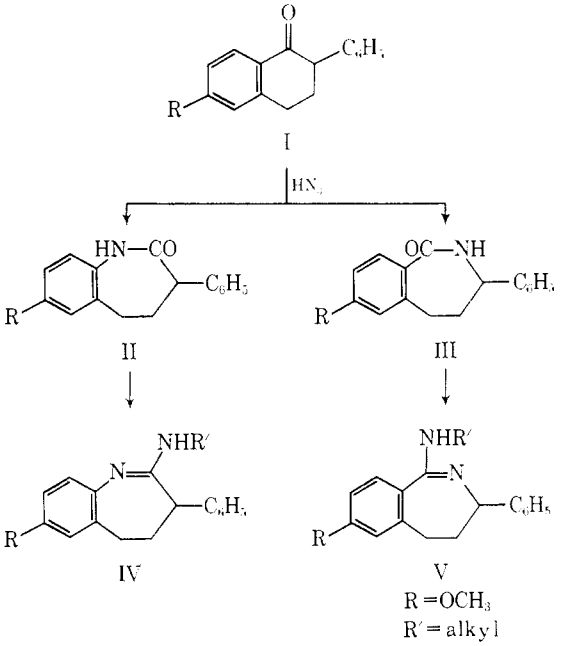
Substituted tetralones were converted into cyclic lactams and amidines. Nine out of sixteen cyclic amidines exhibited weak to moderate hypoglycemic activity in the rat.

Substituted tetralones[1] and dihydro- or tetrahydronaphthalenes derived from them[2,3] have been studied repeatedly in our laboratories in the past 10 years. The present report describes the preparation of a number of cyclic amidines derived from a variety of substituted tetralones and the hypoglycemic activity exhibited by some of them.

Scheme I illustrates the types of compounds which have been prepared. In general, tetralone[4] and a few 2-aryl substituted tetralones (I) yield only one of the two possible lactams when subjected to the Schmidt reaction. These lactams are 1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-ones (II). However, 6-methoxy-2-phenyltetralone (I, R = OCH_3) gave both the acylanilide (II) and the benzamide (III) type lactams. Werner and coworkers found that both lactams were produced when 3- or 4-phenyltetralones were subjected to the Schmidt reaction.[5] Evans and Lockhart studied the effects of various substituents of tetralones which guided the course of the Schmidt reaction either to afford the acylanilide or the benzamide type lactams.[6] Identification of the isomeric benzazepinones II and III was facilitated by the ease of hydrolytic fission of the acylanilide type lactams (II) by hydrochloric acid, in contrast to the stability of the benzamide type lactams (III), which under the same conditions were unaffected by acid treatment.[6]

SCHEME I



In addition, the uv, ir, and nmr spectra were found to be useful tools in the assignment of the correct structure to the isomeric benzazepinones.[6,7] We have made use of both the spectral and chemical tools in the identification of the lactams obtained from the tetralones by the Schmidt reaction. Table I shows the acylanilide type lactums, while Table II depicts the benzamide type lactums. The amidines derived from these lactums are compiled in Tables III and IV, re-

* To whom correspondence should be addressed.

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