(32) in 500 ml of Et_2O added rapidly. The reaction mixture was allowed to stand for 15 hr at 25°. It was cooled in ice and slowly 600 ml of ice–H_2O added. The organic layer was washed with H_2O, evaporated iv, and recrystallized from *i*-PrOH to give a yield of 87% of pure **4a**. Nmr indicated an enamine structure rather than an imine by showing a singlet at 5.1 representing the H on the olefinic α-C. This singlet ranging from 4.8 to 5.8 was typical for all enamines **a**, except enamine **27a** (which carries an alkyl substituent on the α-C); ir (KBr) 3420 (sharp singlet), 1630, 1600 cm^{-1}.

1-(Benzyl-*tert*-butylamino)-3-(2-quinolyl)-2-propanone (Amino Ketone 4b). A mixture of 0.2 mol of **4a** and 250 ml of 3 *N* HCl was heated at 80° for 0.5 hr. It was treated in the cold with an excess of K_2CO_3. The product was taken up in PhH–Et_2O, washed with H_2O, and recrystallized from *i*-PrOH. The yield was 82%; ir (KBr) 3470 (broad), 1635 cm^{-1}; nmr ($CDCl_3$) 6.6 and 6.8 (d, 1 H), 5.9 ppm (s, 1 vinylic H); uv max (MeOH) 408 nm.

1-(Benzyl-*tert*-butylamino)-3-(2-quinolyl)-2-propanol (Amino Alcohol 4c). To a stirred solution of 0.2 mol of **4b** in 1.5 l. of EtOH was added gradually at 25° 0.5 mol of $NaBH_4$. After 4 hr it was heated to 60° for 0.5 hr, 200 ml of H_2O added, and EtOH evaporated iv. The product was taken up in Et_2O, washed with H_2O, and recrystallized from *i*-Pr_2O: yield 83%.

1-(*tert*-Butylamino)-3-(2-quinolyl)-2-propanol (4). A solution of 0.2 mol of **4c** in 650 ml of MeOH was treated with 2 g of 20% Pd/C[19] and hydrogenated at 40–50 psi until the calculated amount of H_2 was taken up (2–4 hr). The product was isolated as a dihydrochloride which crystallized from *i*-PrOH: mp 180–182°. *Anal.* ($C_{16}H_{22}N_2O \cdot 2HCl$) C, H, N. It was converted to **4** by addition of excess aqueous K_2CO_3. Product was taken up in Et_2O, washed with H_2O, and crystallized from *n*-hexane: yield 28%.

Preparation of 4 by Procedure B. To a solution of 0.25 mol of quinaldine in 500 ml of Et_2O was added at 15° 0.5 mol of BuLi. After 1 hr it was cooled with ice and 0.25 mol of (*tert*-butylamino)acetonitrile was added and allowed to stand for 20 hr. The resulting brown solution was diluted with Et_2O to 2 l. and cooled. Introduction of excess HCl gave a yellow hygroscopic amorphous powder. Solution in 2 l. of 85% EtOH was allowed to stand for 5 hr at 25°. $NaBH_4$ reduction as described in the preparation of **4c** and recrystallization from *n*-hexane gave 29 g (45%) of **4**: ir (KBr) sharp absorption peak at 3272 cm^{-1} superimposed on broad absorption; ir (CCl_4) 3400 cm^{-1} (broad).

1-(*tert*-Butylamino)-3-(6-phenanthridinyl)-2-propanone Oxalate (17). A mixture of 0.1 mol of **16b**, 0.2 mol of concentrated HCl, and 1 g of 20% Pd/C in 350 ml of MeOH was hydrogenated at 50 psi. The product was converted to the oxalate: uv max (MeOH) 415, 395, 252, 242 nm. This amino ketone and others in Table II are characterized by a strong uv absorption between 390 and 450 nm [the uv max (MeOH) for **19b** is at 345 nm], typical of similar β-keto heterocycles[20] stabilized by intramolecular H bonding.

Acknowledgment. The authors wish to express their appreciation to Mr. W. M. Pearlman for the performance of many catalytic debenzylations, to Mr. C. E. Childs and associates for the microanalyses, and to Dr. J. M. Vandenbelt and his staff for many spectral data.

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Pancuronium Bromide and Other Steroidal Neuromuscular Blocking Agents Containing Acetylcholine Fragments

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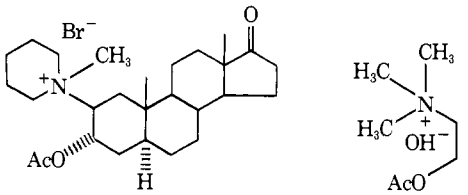
Incorporation of acetylcholine-like fragments into rings A and D of 5α-androstane yielded series of bisquaternary ammonio steroids, some of which proved to be potent neuromuscular blocking agents. One of the series, pancuronium bromide (3α,17β-diacetoxy-2β,16β-dipiperidino-5α-androstane dimethobromide, Pavulon), has proved a clinically useful agent of medium duration of action. It is proposed that its potency and lack of side effects are associated with the individual geometries and electronic structures of its two acetylcholine-like fragments and that the ring D fragment in particular contributes to the high potency and medium duration of action of this agent. The preparation of these amino steroids and structure–activity relationships within the series are also described.

In the course of investigating the synthesis and pharmacology of 2β-amino-3α-hydroxy-5α-androstanes and derivatives[1] and the corresponding 3α-amino-2β-hydroxy isomers, Lewis, *et al.*,[2] observed that the corresponding monoquaternary salts possessed neuromuscular blocking activity, the most potent of these compounds being 3α-acetoxy-2β-piperidino-5α-androstan-17-one methobromide (1) which has $\frac{1}{16}$th the potency of *d*-tubocurarine. In this compound, 1, the 2β-piperidinio and 3α-acetoxy groups are almost certainly both pseudo-equatorial due to the twisted boat conformation of ring A.[1] We assume that in this preferred conformation, which may be rigid due to steric compression[3] of ring-A substituents, the acetylcholine-like fragment of 1 resembles a specific molecular con-

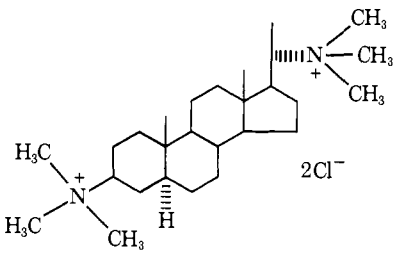
formation of the neurohumoral transmitter, acetylcholine (2). This molecule, 2, is known to be released at nerve endings and to be highly specific in inducing muscle contractions. Therefore, it is reasonable to expect that a rigid acetylcholine-like substance such as 1 would occupy the transmitter's site of action and block neuromuscular transmission.

Comparison of the monoquaternary ammonioandrostane 1 with the semirigid structures, *d*-tubocurarine and the steroidal neuromuscular blocking agent malouétine [3β,20α-bis(trimethylammonio)-5α-pregnane dichloride], both of which have two nitrogen atoms in the range 10–14 Å apart, suggested that addition of a second acetylcholine-like fragment to ring D of the androstane nucleus might improve activity. In order to have the interonium distance greater than 10 Å, the second nitrogen atom must be attached to carbon atom C_{16}; 2β,16β-dipiperidino-3α,17β-diacetoxy-5α-androstane dimethobromide (31) fulfills this requirement and, in addition, the 16 and 17 substituents like those at 2 and 3 in 1 are pseudo-equatorial.

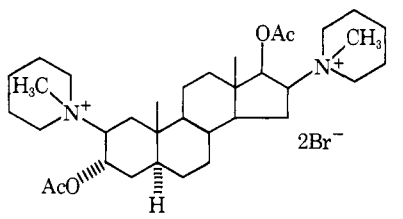


1

2



malouétine



31

Chemistry. The most convenient route[1,4] to a 2β,16β-dipiperidino-3,17-dioxy-5α-androstane is the condensation of 2α,3α:16α,17α-diepoxy-17β-acetoxy-5α-androstane (3) with aqueous[5] piperidine to give 2β,16β-dipiperidino-3α-hydroxy-5α-androstan-17-one (**4a**) contaminated with some of the 16α epimer **5a**; crystallization of the crude condensation product gave the 16β epimer **4a** in 50% yield. The structure of **4a** is proven by the X-ray crystallographic study[3] on its derivative **31**. Treatment of 2α,3α-epoxy-17β-hydroxy-5α-androstan-16-one with aqueous piperidine also gave the 16β epimer **4a** but in poor yield.

Reduction of **4a** with $NaBH_4$ in MeOH–CH_2Cl_2 solution gave the 3α,17β-diol **6a** in 96% yield from which the diacetate, dipropionate, dipivalate, and dibenzoate were prepared easily; the diformate, however, was difficult to isolate since this ester is readily hydrolyzed. The 17β-alcohol was also the major product in the reduction of the 3α-acetoxy 17-ketone **4b** with $NaBH_4$ in *t*-BuOH. Under the weakly alkaline conditions the 16β-dipiperidino 17-ketone **4b** exists in equilibrium with the 16α-piperidino epimer **5b** in which approach to the 17-ketone is sterically hindered by the C_{13}-angular methyl group on the β face and by the large C_{16}-piperidino substituent on the α face. The 16β isomer, however, is relatively unhindered on the α face of the molecule and, hence, is reduced more quickly than the 16α epimer which epimerizes to restore equilibrium. This explains formation of the 16β-piperidino-17β-ol as the major product. Only small amounts of the cis-epimeric 16α-dipiperidino-17α-ol were isolated after subsequent hydrolysis to the 3α,17α-diol **7a**. Esterification of the 3α,17β-diol 3-monoesters gives access to mixed 3α,17β-diesters, *e.g.*, **6f**.

In order to prepare the 17-monoacetate **6e** the dihydrochloride of the ketol **4a** was converted with ethyl vinyl ether and *p*-toluenesulfonic acid as catalyst to a mixture of 3-ethylethoxy ethers **4c**. Then the 17-keto function was reduced to the 17β-alcohol **6d**; acetylation of the latter followed by removal of the ether-protecting group gave the 17β-acetoxy-3α-ol **6e**.

An attempt to remove the 17-oxygen function of **4a** by Wolff–Kishner reduction yielded only the monoamino steroid **8a**, which was acetylated and converted to the methobromide **66**. The reductive removal of the 17-ketone and neighboring 16β-piperidino group parallels the Wolff–Kishner reduction[6] of 2β-acetoxycholestan-3-one and the isomeric 3β-acetoxy-2-one to cholestane.

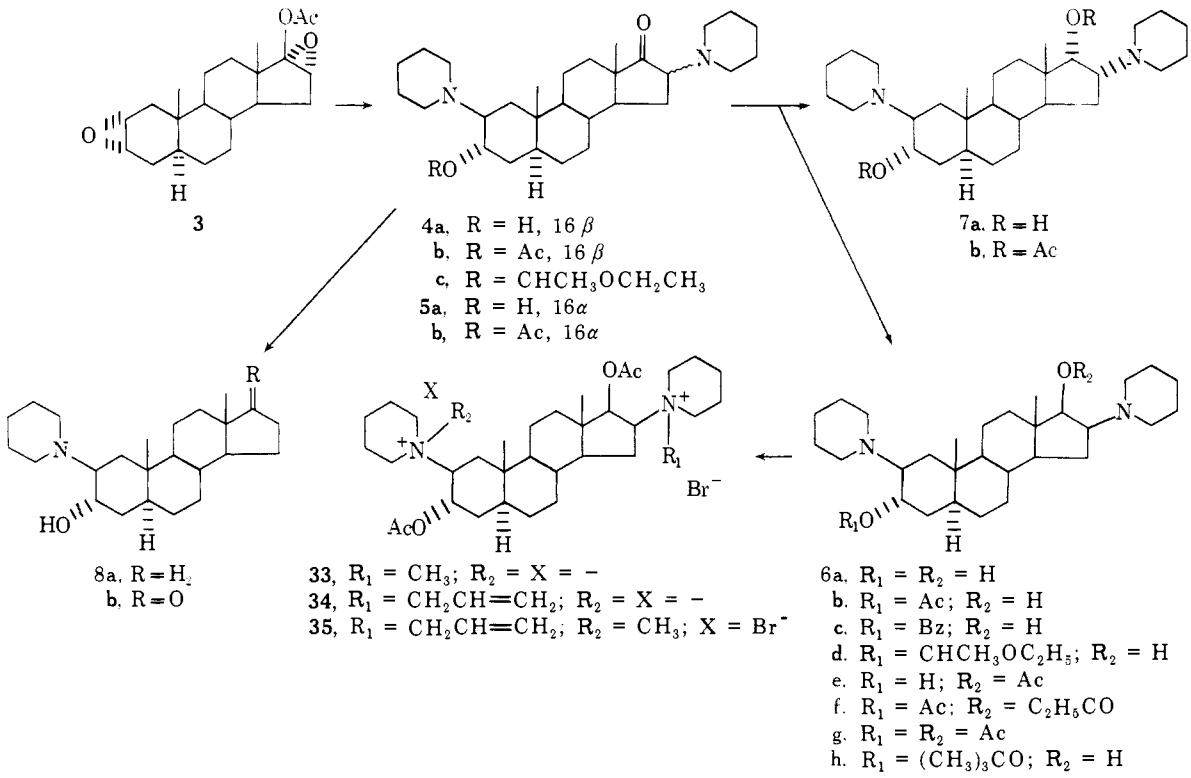
In a manner similar to the routes described above, 2β,16β-dipyrrolidino-5α-androstane-3α,17α-diol, 2β,16β-dimorpholino-5α-androstan-3α-ol-17-one, and 2β,16β-dimorpholino-5α-androstane-3α,17β-diol and its diacetate have also been prepared.

Treatment of these 2β,16β-diamino-5α-androstanes with an alkyl halide gives mixtures of mono- and bisquaternary ammonium salts from which the latter are usually isolated by crystallization. The rate of alkylation of the 16-nitrogen atom is greater than that of the 2-nitrogen atom. This is shown by the monomethylation of the dipiperidino diacetate **6g** with methyl bromide in ether solution when the monomethobromide **33** precipitates out of the reaction solution in 74% yield. Treatment of this salt with sodium methoxide in boiling DMF gives 2β-piperidinoandrosterone **8b** in quantitative yield; such an elimination of a quaternary ammonio substituent has been described by Kerwin, *et al.*,[7] and since there is only elimination of the 16β-piperidino substituent there can be no quaternary nitrogen atom at carbon C_2 in the monomethobromide which must have exclusively structure **33**.

The presence of the monomethobromide **33** presents a problem in obtaining ^{14}C-labeled **31** (required for metabolic studies), since a product with the high level of radioactivity required cannot be crystallized as this would induce autoradiolysis in the solid state. Hence, an efficient chromatographic method separating pure **31** from the monomethobromide **33** has been developed.

The monoallobromide **34** is easily prepared also and this like other 16-monoquaternaries can be further alkylated, *e.g.*, the mixture bisquaternary **35**.

Since the monoquaternary **33** is almost as potent as the bisquaternary **31**, it was of interest to prepare 17β-acetoxy-16β-piperidino-5α-androstane methobromide **65**, lacking both the 3α-acetoxy group and the 2β-tertiary nitrogen atom in order to determine the contribution of these ring A substituents. Its lack of neuromuscular blocking activity suggests that a second amino group in ring A is necessary for activity. Presumably, as in the case of tubocurarine, the tertiary amino group is converted into an ammonio group by salt formation at physiological pH.



Since pancuronium bromide (**31**) is an ideal neuromuscular blocking agent with medium duration of action,[8,9] some minor changes in the substituents at positions 2, 3, 16, and 17 were made in an attempt to retain potency but shorten the duration of neuromuscular blockade. For instance, the 16β and 17β substituents were interposed to give **56** and the 17α epimer **50** of **31** was prepared; the chemistry involved is described below.

The diepoxide **3** on condensation with anhydrous piperidine, morpholine, pyrrolidine, or dimethylamine gives mixtures of two isomers. A consideration of the molecular rotational difference of the morpholino isomers **9b** and **10b** indicates[5] that the isomer (MD −500) is 17β-morpholino-16-oxo-2α,3α-epoxyandrostane (**10b**) and the isomer (MD +466) is the 16β-morpholino-17-oxo isomer **9b**. Fractional crystallization yields the 16β-amino-17-ones **9a,b** and the 17β-amino-16-ones **10a-d**; reduction of these 17- and 16-ketones with sodium borohydride yields the corresponding 17β- and 16β-alcohols **11a** and **12a,b,d**. The mixture of the pyrrolidino isomers **9c** and **10c** is not resolved easily but $NaBH_4$ reduction yields a mixture from which the 17β-pyrrolidino-16β-ol **12c** can be isolated by fractional crystallization; the 16β-dimethylamino-17β-ol **11b** can be isolated in a similar way. Condensations of these 2α,3α-epoxy-16β- and -17β-amines with the appropriate aqueous amines give the corresponding 2β-amino-3α-hydroxy derivatives, 16β-dimethylamino-2β-piperidino-5α-androstane-3α,17β-diol and **13a-f**, from which the diacetoxy dimethohalides have been prepared.

Epoxidation of 5α-androsta-2,16-diene yielded the 2α,3α,16α,17α-diepoxide **14a** which condensed with aqueous piperidine, morpholine, and pyrrolidine to give the 2β,16β-diamino-3α,17α-diols **15a-c**, respectively. Of the corresponding diacetates only the pyrrolidino and piperidino analogs yielded a dimethiodide **50** and dimethobromide **43**, respectively.

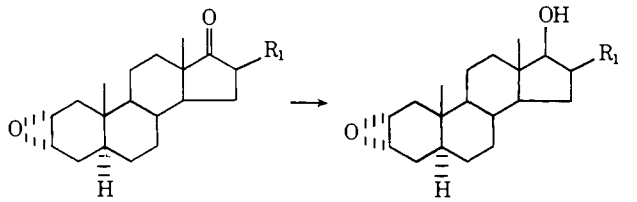
Epoxidation of 3,17-diacetoxy-5α-androsta-2,16-diene gave the diepoxide **14b** which condensed with aqueous piperidine and aqueous morpholine to give the 2α,16β-diamino-3,17-diones **16a,b** in low yield. The structures were assumed by analogy with the work of Hassner and Catsoulacos who reported[4] that condensation of a 3β-acetoxy-2α,3α-epoxy-5α-androstane with a secondary amine gives a 2α-amino 3-ketone. Reduction of the dimorpholinodione **16b** with $NaBH_4$ gave the 2α,16β-dimorpholino-3β,17β-diol **17a**; this showed only bonded hydroxyl groups in its infrared spectrum (3380–3420 cm^{-1}) in contrast to the epimeric 2β,16β-dimorpholino-3α,17β-diol which showed free hydroxyl at 3600 cm^{-1} (3α-OH) in addition to bonded hydroxyl at 3260–3420 cm^{-1}; the dimorpholino diacetate **17b** readily gives a dimethiodide.

Leuckart condensations of 2β-piperidino- and 2β-morpholino-5α-androstan-3α-ol-17-one with piperidine and pyrrolidine in the presence of formic acid gave the corresponding 3α-hydroxy-2β,17β-diamino steroids **18a-d**. The acetates of these compounds were converted to bisquaternary ammonium salts. Leuckart condensations of 3α-piperidino-5α-androstan-2β-ol-17-one with piperidine and pyrrolidine in the presence of formic acid yielded the 2β-hydroxy-3α,17β-diamino steroids **19a,b** which were acetylated and converted to dimethobromides.

Finally, in contrast to the incorporation of two acetylcholine-like fragments into the steroid nucleus the dimethobromide **64**, which has two such fragments extra to the steroid nucleus, was prepared from 5α-androstane-3,17-dione *via* 3β,17β-bis(*N*-methyl-*N*-2′-hydroxyethylamino)-5α-androstane diacetate.

Structure-Activity Relationships. Consideration of the structure of the compounds and their potency and duration of neuromuscular blocking action listed in Tables III–VII revealed several governing factors which are outlined in this discussion.

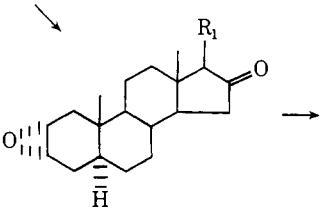
For high potency it is probably essential to have two nitrogen atoms in the molecule, since the monoquaternary salts **65** and **66** which lack a secondary nitrogen atom are almost inactive. At least one of these nitrogen atoms should be quaternized; for example, both the dimethobromide **31** and monomethobromide **33** are very potent in



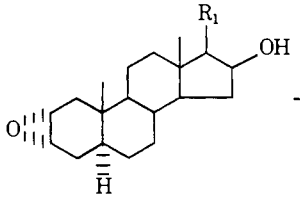
9a, R_1 = piperidino
b, R_1 = morpholino
c, R_1 = pyrrolidino

11a, R_1 = piperidino
b, R_1 = dimethylamino

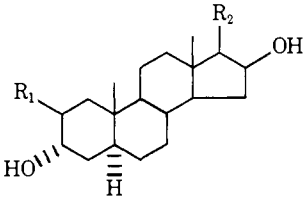
3



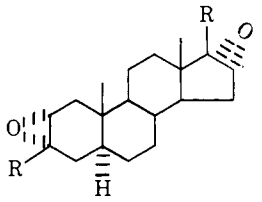
10a, R_1 = piperidino
b, R_1 = morpholino
c, R_1 = pyrrolidino
d, R_1 = dimethylamino



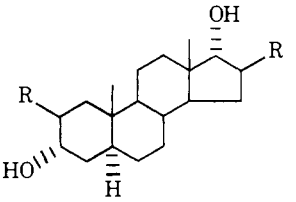
12a, R_1 = piperidino
b, R_1 = morpholino
c, R_1 = pyrrolidino
d, R_1 = dimethylamino



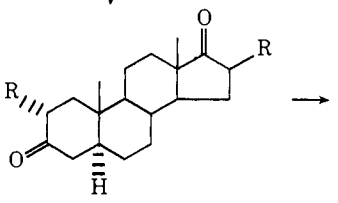
13a, R_1 = piperidino; R_2 = dimethylamino
b, R_1 = piperidino; R_2 = pyrrolidino
c, R_1 = morpholino; R_2 = pyrrolidino
d, R_1 = R_2 = piperidino
e, R_1 = R_2 = morpholino
f, R_1 = R_2 = pyrrolidino



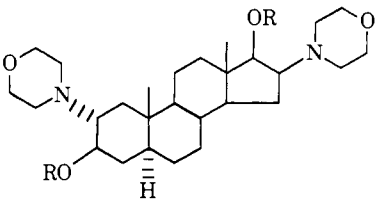
14a, R = H
b, R = OAc



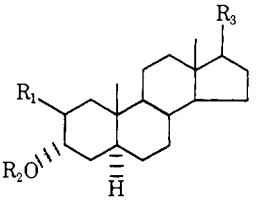
15a, R = piperidino
b, R = morpholino
c, R = pyrrolidino



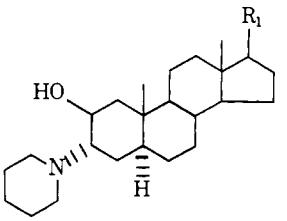
16a, R = piperidino
b, R = morpholino



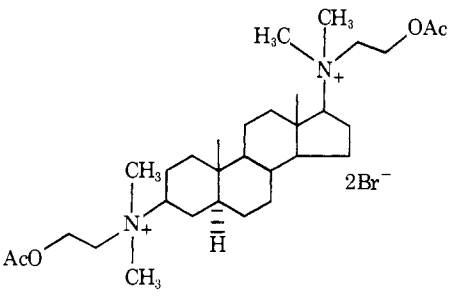
17a, R = H
b, R = Ac



18a, R_1 = R_3 = piperidino; R_2 = H
b, R_1 = piperidino; R_2 = H; R_3 = pyrrolidino
c, R_1 = morpholino; R_2 = H; R_3 = piperidino
d, R_1 = morpholino; R_2 = H; R_3 = pyrrolidino



19a, R_1 = piperidino
b, R_1 = pyrrolidino



64

contrast to the total inactivity of the dihydrochloride of **6g**.

Replacing the 16β-piperidino substituent of **31** with dimethylamino **48** leads to a decrease in potency from 9.41 to 0.40 without much change in duration of action. The other trimethylammonio compound **64** has two acetylcholine-like fragments completely extra to the steroid nucleus and also has a low potency of 0.37. Comparing the morpholino derivatives **44**, **45**, and **47** with the corresponding piperidino derivatives **20**, **21**, and **31**, it is evident that the latter are significantly more potent in all instances. Also, a 2β-ammonio substituent may confer greater potency than one of a 2α configuration as **51** is less active than its 2β epimer **47**.

The high potency of the dipyrrolidino derivative **50** which has a 17α-acetoxy group suggests that the 17α epimer of **31** would be highly potent but we were unable to prepare it in pure form.

Interposing the 16,17 substituents of compounds **21** and **31** gives the isomers **55** and **56**, respectively, which are markedly less potent without largely differing in duration of action; indeed this series (Table V) is relatively uninteresting except to indicate that there is an optimal interonium distance for potency in these diammonio steroids.

A further illustration of this is provided by the greater potency of the 3α,17β-diammonio compound **63** over the 2β,17β-diammonio isomer **58** in which the 2,3-pseudoequatorial substituents have been interposed. A study of the Dreiding models of these compounds indicates that an interonium distance of about 11 Å is superior to one of 10 Å. The interonium distance in a crystal structure[3] of the potent compound **31** is 11.08 Å.

On the basis of these observations more effort was applied to study derivatives in the most interesting series (Table III). The diesters yielded the most potent com-

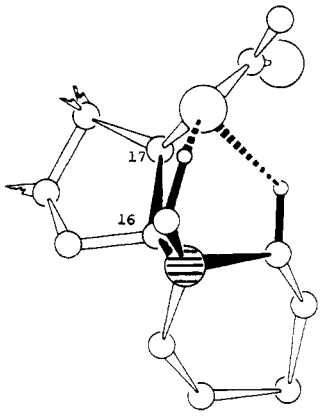


Figure 1.

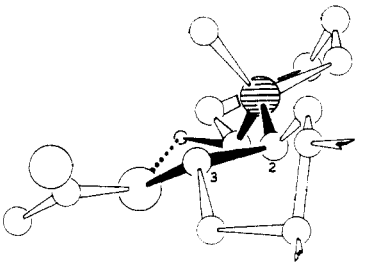


Figure 2.

pounds with the diacetate **31** > dipropionate **38** > dipivalate **39** > diformate **25** > dibenzoate **42**. Potency appears to decrease with increasing lipophilicity, the exception to this being the diformate **25** which, however, is probably hydrolyzed very quickly *in vivo* to the poorly active diol **21**. In the less potent alcohol series the 17-monoacetate **24** which has half the potency of **31** is > 3-monoacetate **28** > 3,17-diol **21** = the 3-ol-17-one **20** which has less than 10% the potency of **31** and the 3-monopivalate **40** = 3-monoacetate **28** which is > 3-monobenzoate **41**. With respect to duration of action the long-acting dibenzoate **42** ≫ diacetate **31** > 17-monoacetate **24** > 3-monobenzoate **41** > 3-monoacetate **28** = 3,17-diol **21**. Hence, potency and prolonged action are associated with the presence of a 17-ester.

In view of the fact that the free diol **21** has a very low potency and short duration of action compared to the 3,17-diesters **31**–**39** and **42**, it is probable that duration of activity of the diesters is dependent on rates of hydrolysis of the 3- and 17-ester groups; for example, the dibenzoate **42** is still active after 3 hr.

Since the 3-monoesters are shorter acting than the 17-monoesters, it seems probable that the 3-esters hydrolyze more readily than the 17-esters. In the case of the diacetate **31**, this is in agreement with the observation that the main metabolite in the dog is the 17-monoacetate† **24**.

The remaining variations in the dipiperidino series (Table III) are the quaternizing groups R_3 and R_4 which become more difficult to introduce with increasing bulk, *e.g.*, ethyl and benzyl are more difficult to introduce than methyl and allyl.

In the 3,17-diacetates of this series the most potent, diMe, **31** > Me, allyl **35** > dipropargyl **36** = monomethyl **33** > monoallyl **34**. In the corresponding diols of this series the diallyl **22** > dipropargyl **23** = diMe **21**. This shows that the optimal *N*-alkyl group in the 17-ester series is Me whereas in the 17-alcohol series the allyl group gives the most potent compound **22**.

Finally, it is remarked that although the dimethiodides **29** and **32** are of the same order in potency and duration of action as their corresponding dimethobromides **28** and **31**, respectively, and are more readily prepared, they tend to be less stable on storage.

Pancuronium Bromide‡ (**31**). This compound (2β,16β-dipiperidino-5α-androstane-3α,17β-diol diacetate dimethobromide) is advocated for use in clinical situations where a nondepolarizing (competitive) muscle relaxant of medium duration of action is required due to its high potency with minimal side effects.[10] This specific pharmacological profile[10-13] prompted studies[3] of its molecular structure which revealed a certain rigidity and suggested unique hydrogen bonding systems, involving quasi-six-ring formation (C–C–N$^+$–C–H---O–COCH$_3$), within each of the molecule's acetylcholine-like fragments. Such hydrogen bonding in acetylcholine itself was first suggested by Sutor[14] but the only publication to indicate that it does exist is the quantum theoretical study of the molecular electronic structure of acetylcholine by Beveridge and Radna[15] who are the latest workers to associate particular preferred conformations of acetylcholine with individual physiological roles. With reference to pancuronium bromide (**31**) it is interesting to note that the hydrogen bonding system in the ring D acetylcholine fragment (Figure 1) involving two quasi-six rings is more complex than that system in the ring A acetylcholine fragment (Figure 2). The probability that ring D substituents contribute more to the potency and medium duration of action in this series (Table III) rather than those attached to ring A is in agreement with the 17-monoacetate **24** being markedly more potent than the isomeric 3-acetate **28** and the 16-monoquaternary **33** being almost equipotent with the bisquaternary **31**. Hence, the high potency and specificity of action of this agent at a neuromuscular receptor site may be associated with the particular molecular geometries and electronic structures of the acetylcholine-like fragments in the molecule.

Dacuronium Bromide (**28**). Clinical studies[16,17] with this compound (2β,16β-dipiperidino-5α-androstane-3α,17β-diol 3α-acetate dimethobromide) showed that it possesses a rapid onset of action, which is of shorter duration than that of pancuronium bromide but lacks sufficient potency to be a clinically useful drug. However, this disappointing result prompted further studies which will be the subject of a further communication.

Experimental Section§

2α,3α:16α,17α-Diepoxy-17β-acetoxy-5α-androstane (**3**). Enol acetylation of 5α-androst-2-en-17-one with isopropenyl acetate using H_2SO_4 catalyst yielded 17-acetoxy-5α-androsta-2,16-diene. A solution of *m*-chloroperbenzoic acid (615 g, 85% pure, 2.4 mol) in Et_2O (1.3 l.) was added over 3 hr to a cooled, stirred solution of this diene (394 g) in Et_2O (3.5 l.). After standing at 20° for 18 hr, the deposited crystalline solid (240 g, 55%) was filtered off and a sample crystallized from Et_2O to give the pure 2α,3α:16α,17α-diepoxide: mp 164–167°; $[\alpha]^{20}D$ +25°. *Anal.* ($C_{21}H_{30}O_4$) C, H.

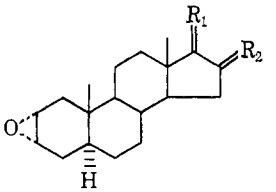
Condensation of 2α,3α:16α,17α-Diepoxy-17β-acetoxy-5α-androstane (**3**) **with Secondary Amines. Method A (Aqueous).** A solution of the diepoxide (84 g) in a secondary amine (750 ml) and H_2O (84 ml) was boiled under reflux for 3–5 days, the solution cooled, and H_2O added to precipitate the solid product which was filtered off, washed neutral with H_2O, and extracted with 2 *N* HCl. The solution was filtered free of nonbasic material

†Personal communication from F. van der Veen, N.V. Organon, OSS, Holland.

‡Pavulon, N.V. Organon.

§Melting points were taken on a Kofler block under microscopic magnification and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements are within 0.4% of the theoretical values.

Table I



No.	R_1[a]	R_2	Mp, °C	$[\alpha]_D$, deg[b]	Formula	Analyses
10a	P, H	O	182–190	−160	$C_{24}H_{37}NO_2$	C, H, N
10b	M, H	O	169–173	−134	$C_{23}H_{35}NO_3$	C, H, N
9b	O	M, H	168–173	+125	$C_{23}H_{35}NO_3$	C, H, N
10d	D, H	O	156–161	−166	$C_{21}H_{33}NO_2$	C, H, N
12c	Py, H	OH, H	169–171	−3	$C_{23}H_{37}NO_2$	C, H, N
12a	P, H	OH, H	182–190	−6.5	$C_{24}H_{39}NO_2$	C, H, N
12b	M, H	OH, H	234–239	−5	$C_{23}H_{37}NO_3$	C, H, N
12d	D, H	OH, H	162–164	−2	$C_{21}H_{35}NO_2$	C, H, N
11a	OH, H	P, H				
11b	OH, H	D, H	113–116	+17	$C_{21}H_{35}NO_2$	C, H, N

[a] P = piperidino, Py = pyrrolidino, M = morpholino, and D = dimethylamino, all amino and OH groups having the β configuration. [b] All rotations are in chloroform.

and alkali added to the cooled filtrate to precipitate a solid which was filtered off and dissolved in CH_2Cl_2 and the dried (Na_2SO_4) solution was concentrated before adding Me_2CO. Crystallization from Me_2CO gave (a) 2β,16β-dipiperidino-5α-androstan-3α-ol-17-one [**4a**, 71 g (66%); mp 179–185°; $[\alpha]^{20}D$ +110°. *Anal.* ($C_{29}H_{49}N_2O_2$) C, H, N] and (b) 2β,16β-dimorpholino-5α-androstan-3α-ol-17-one [62 g (56%); mp 207–228°; $[\alpha]^{20}D$ +149°. *Anal.* ($C_{27}H_{44}N_2O_4$) C, H, N]. The 2β,16β-dipyrrolidino analog was not isolated.

Method B (Anhydrous). The diepoxide 3 was added to the boiling secondary amine, the solution boiled under reflux for several hours, and the product isolated in the usual manner. In most cases fractional crystallization yielded the 17β-amino-2α,3α-epoxy-5α-androstan-16-one (**10a,b,d**, 10–20%) and, in the case with morpholine, also 16β-morpholino-2α,3α-epoxy-5α-androstan-17-one (**9b**, 70%). The pyrrolidine condensation did not yield a pure product so easily and subsequent reduction of the product with $NaBH_4$ in MeOH solution was necessary before isolating the 17β-pyrrolidino-16β-ol (**12c**, 58%). The amino ketones and their reduction products obtained thus are described in Table I.

Condensation of 2α,3α-Epoxy-5α-androstan-17β-ol-16-one with Aqueous Piperidine. Rearrangement of the diepoxide 3 with alkali gave 2α,3α-epoxy-5α-androstan-17β-ol-16-one which was condensed with boiling aqueous piperidine to yield 2β,16β-dipiperidino-5α-androstan-3α-ol-17-one (**4a**, 10%) identical (melting point and ir) with the product described above.

The 3α-acetate **4b** had mp 152–156°, $[\alpha]^{20}D$ +98°. An unusual and optimal method of preparing this 3α-acetate was to use AcCl in CH_2Cl_2 solution without pyridine since the hydrogen-bonded amino alcohol catalyses the acetylation. The 3α-benzoate was prepared in a similar manner. *Anal.* ($C_{36}H_{57}N_2O_3$) C, H, N.

3β-Acetoxy-2β,16β-dipiperidino-5α-androstan-17β-ol (6b). $NaBH_4$ (16 g) was added to a stirred solution of 3α-acetoxy-2β,16β-dipiperidino-5α-androstan-17-one (51 g) in methylene dichloride (150 ml) and methanol (150 ml) and the reaction was stirred for a further 1 hr. Water was added, the product extracted with ether, and the extract washed well with water and dried (Na_2SO_4). Concentration of the ether solution yielded the 17β-alcohol (20 g, 40%). Recrystallization from ether gave needles: mp 177–179°; $[\alpha]^{20}D$ +30°. *Anal.* ($C_{31}H_{52}N_2O_3$) C, H, N. The 17β-propionate **6f** had mp 105–110°.

The material in the mother liquors was hydrolyzed in aqueous methanolic alkaline solution and the product fractionally crystallized from Et_2O to give 2β,16α-dipiperidino-5α-androstane-3β,17β-diol (**7a**, 1 g, 6%): mp 245–249°; $[\alpha]^{20}D$ +32°. *Anal.* ($C_{29}H_{50}N_2O_2$) C, H, N. The 3α,17α-diacetate **7b** had mp 199–203°.

2β,16β-Dipiperidino-5α-androstane-3α,17β-diol (6a). $NaBH_4$ (30 g, 4.7 mol) was added over 15 min to a cooled stirred solution of the 2β,16β-dipiperidino 17-ketone **4a** (77 g) in CH_2Cl_2 (100 ml) and MeOH (300 ml) at 18°; crystallization started shortly after the addition. After stirring for 18 hr and cooling to 5°, prisms (74 g, 96%), mp 152–158°, were filtered off. An analytical sample had mp 155–158°, $[\alpha]^{20}D$ +48°. *Anal.* ($C_{29}H_{50}N_2O_2$) C, H, N. The dimorpholino- and dipyrrolidinodiols were prepared in a similar manner. *Anal.* ($C_{27}H_{46}N_2O_4$) C, H, N and ($C_{27}H_{46}N_2O_2$), respectively. Diester derivatives are described in Table II.

Table II. 3,17 Diesters[a] of 2β,16β-Dipiperidino-5α-androstane-3α,17β-diol

Ester	Mp, °C	$[\alpha]_D$[b]	Formula	Analyses
Diformate	164.5–167		$C_{31}H_{50}N_2O_4$	C, H, N
Diacetate	136–139	23	$C_{33}H_{54}N_2O_4$	C, H, N
Dipropionate	104–109	31	$C_{35}H_{58}N_2O_4$	C, H, N
Dipivalate[c]	218–235	23	$C_{39}H_{68}Cl_2N_2O_4$	C, H, Cl, N
Dibenzoate[c]	209–211	51	$C_{43}H_{60}Cl_2N_2O_4$	C, H, Cl, N
Diacetate[d]	131–140	55	$C_{31}H_{50}N_2O_6$	C, H, N

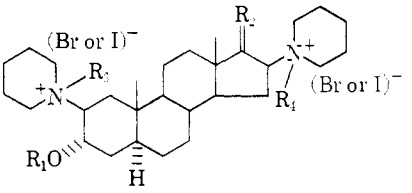
[a] The ir spectra of these compounds showed no absorption in the hydroxyl region. [b] Chloroform. [c] Purified as dihydrochloride. [d] Of 2β,16β-dimorpholino analog.

17β-Acetoxy-2β,16β-dipiperidino-5α-androstan-3α-ol (6e). A solution of 2β,16β-dipiperidino-5α-androstan-3α-ol-17-one (**4a**, 25 g) in CH_2Cl_2 (100 ml) was saturated with HCl gas, evaporated to dryness, and slaked with Et_2O. The solid dihydrochloride was filtered, washed quickly with Et_2O, and suspended in ethyl vinyl ether (250 ml). *p*-Toluenesulfonic acid (75 mg) was added over 15 min and the solution stirred at 20° for 4 days. Solid K_2CO_3 was added and after 10 min aqueous 10% K_2CO_3 solution. The product was extracted with benzene; the extract was washed neutral with water, dried (Na_2SO_4), and evaporated to dryness to give an orange oil which was dissolved in petroleum ether and percolated down a column (12 × 2.5 cm diameter) of alumina. Elution with petroleum ether yielded a fraction as a yellow oil (31.4 g), the racemic mixture of 3α-ethoxy ethyl ethers **4c** containing no free 3α-OH. This oil was dissolved in MeOH (250 ml) and reduced with $NaBH_4$ (7 g, 3.1 mol) to precipitate a gummy product which was worked up through CH_2Cl_2 and crystallized from aqueous $(CH_3)_2CO$ to give a crop of 17β-alcohol (11.5 g). Further material (3.1 g) of the same quality was obtained by chromatography on alumina. Crystallization from acetone gave a sample of a 2β,16β-dipiperidino-3α-(1′-ethylethoxy)-5α-androstan-17β-ol (**6d**): mp 126–129°; $[\alpha]^{20}D$ +14°. *Anal.* ($C_{33}H_{58}N_2O_3$) C, H, N.

The crude racemate of 17β-hydroxy 3-ethers (14 g) was acetylated in Ac_2O–pyridine at room temperature overnight, the reaction poured into cold aqueous $KHCO_3$ solution, and the product worked up through Et_2O to give a gum (*ca.* 14 g) which was dissolved in MeOH (75 ml). Concentrated HCl (14 ml) was added carefully, keeping the temperature below 5° over 25 min, and then the reaction was poured into cold aqueous $KHCO_3$ solution and the product isolated in Et_2O solution which was concentrated to give the 17β-acetoxy-3α-ol (**6e**, 9.38 g, 36%): mp 192–195°; $[\alpha]^{20}D$ +41°. *Anal.* ($C_{31}H_{52}N_2O_3$) C, H, N.

2β,16β-Diamino-5α-androstane-3α,17α-diols and Diacetates. Epoxidation of 5α-androsta-2,16-diene (15.4 g) gave

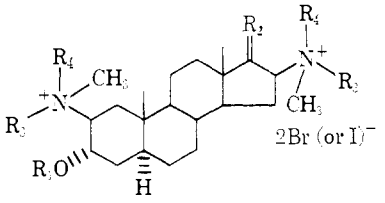
Table III. Di- and Monomethohalides of 2β,16β-Dipiperidino-3,17-dioxyandrostanes



No.	R_1	R_2	R_3	R_4	Mp, °C	Formula	Neuromuscular blocking[a] Potency	Neuromuscular blocking[a] Duration (TC = 1.0)	Acute toxicity,[b] LD_{50}, mg/kg (95% limits)
20	H	O	CH_3	CH_3	215–221	$C_{31}H_{54}Br_2N_2O_2$	0.67	0.47	4.25 (4.05–4.46)
21	H	β-OH, H	CH_3	CH_3	220–224	$C_{31}H_{56}Br_2N_2O_2$	0.55	0.53	3–10
22	H	β-OH, H	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	183–190	$C_{35}H_{60}Br_2N_2O_2$	2.50	1.00	
23	H	β-OH, H	$CH_2C{\equiv}CH$	$CH_2C{\equiv}CH$	208–211	$C_{35}H_{56}Br_2N_2O_2$	0.77	0.44	1–3
24	H	β-AcO, H	CH_3	CH_3	215–225	$C_{33}H_{57}Br_2N_2O_3$	5.15	1.00	0.053 (0.050–0.055)
25	HCO	β-HCO, H	CH_3	CH_3		$C_{33}H_{56}Br_2N_2O_4$	1.30	0.46	
26	Ac	O	*c*	CH_3	288–291	$C_{32}H_{53}BrN_2O_3$	0.39	0.44	1.73 (1.57–1.90)
27	Ac	O	CH_3	CH_3	250–257	$C_{33}H_{56}Br_2N_2O_3$	1.53	0.37	
28	Ac	β-OH, H	CH_3	CH_3	210–213	$C_{33}H_{57}Br_2N_2O_3$	1.72	0.49	2.91 (2.67–3.17)
29	Ac	β-OH, H	CH_3	CH_3	240–249	$C_{33}H_{58}I_2N_2O_3$	1.29	0.32	3.70 (3.49–3.90)
30	Ac	β-OH, H	*c*	CH_3	246–252	$C_{32}H_{55}BrN_2O_3$	0.40	0.45	0.3–1
31	Ac	β-AcO, H	CH_3	CH_3	212–215	$C_{35}H_{60}Br_2N_2O_4$	9.41	1.15	0.047 (0.045–0.050)
32	Ac	β-AcO, H	CH_3	CH_3	213–217	$C_{35}H_{60}I_2N_2O_4$	15.0	1.1	0.049 (0.045–0.054)
33	Ac	β-AcO, H	*c*	CH_3	227–229	$C_{34}H_{57}BrN_2O_4$	6.0	0.77	0.061 (0.035–0.067)
34	Ac	β-AcO, H	*c*	$CH_2CH{=}CH_2$	185–190	$C_{36}H_{59}BrN_2O_4$	3.44	0.89	0.071 (0.065–0.077)
35	Ac	β-AcO, H	CH_3	$CH_2CH{=}CH_2$	177–182	$C_{37}H_{62}Br_2N_2O_4$	7.23	1.16	0.045 (0.040–0.050)
36	Ac	β-AcO, H	$CH_2C{\equiv}CH$	$CH_2C{\equiv}CH$	188–190	$C_{39}H_{60}Br_2N_2O_4$	6.31	0.81	0.096 (0.094–0.097)
37	Ac	β-EtCOO, H	CH_3	CH_3	208–211	$C_{36}H_{62}Br_2N_2O_4$	5.60	0.85	
38	EtCO	β-EtCOO, H	CH_3	CH_3	195–200	$C_{37}H_{64}Br_2N_2O_4$	7.10	0.95	0.28 (0.23–0.37)
39	$(CH_3)_3CCO$	β-$(CH_3)_3CCOO$, H	CH_3	CH_3	230–242	$C_{41}H_{72}I_2N_2O_4$	3.80	1.47	
40	$(CH_3)_3CCO$	β-OH, H	CH_3	CH_3	226–236	$C_{36}H_{64}I_2N_2O_3$	1.70	0.50	2.35 (1.70–3.0)
41	PhCO	β-OH, H	CH_3	CH_3	203–209	$C_{38}H_{60}I_2N_2O_3$	0.84	0.72	0.3–1
42	PhCO	β-PhCOO, H	CH_3	CH_3	204–215	$C_{45}H_{64}Br_2N_2O_4$	1.00	>3.0	
43	Ac	H, α-AcO	CH_3	CH_3	207–213	$C_{35}H_{60}Br_2N_2O_4$	6.15	0.75	1.61 (1.52–1.70)

[a] Intravenously in anaesthetized cat sciatic–gastrocnemius preparation.[8] [b] Intravenously in conscious mice.[8] [c] Not quaternized.

Table IV. Dimethohalides of Other 2ξ,16ξ-Diamino-3,17-dioxy-5α-androstane Derivatives



No.	R_1	R_2	NR_3R_4	Mp, °C	Formula	Potency	Duration	Toxicity
44	H	O	Morpholino	246–250	$C_{29}H_{50}I_2N_2O_4$	0.06	0.80	15.4 (14.8–16.0)
45	H	β-OH, H	Morpholino	241–245	$C_{29}H_{52}I_2N_2O_4$	0.01		
46	H	β-OH, H	Pyrrolidino	290	$C_{29}H_{52}Br_2N_2O_2$	0.17	0.32	1–3
47	Ac	β-OAc, H	Morpholino	210–215	$C_{33}H_{56}I_2N_2O_6$	3.44	0.96	0.16 (0.145–0.176)
48	Ac	β-OAc, H	*a*	254–257	$C_{32}H_{56}Br_2N_2O_4$	0.40	1.05	0.33 (0.30–0.35)
49	H	H, α-OH	Morpholino	221–225	$C_{29}H_{52}I_2N_2O_4$	<0.10		3–10
50	Ac	H, α-OAc	Pyrrolidino	222–226	$C_{33}H_{56}I_2N_2O_4$	5.9	1.0	0.38 (0.33–0.44)
51	Ac	β-OAc, H	Morpholino[b]	214–220	$C_{33}H_{56}I_2N_2O_4$	0.95	0.95	3.25 (2.99–3.53)

[a] 2β-Piperidino-16β-dimethylamino. [b] 2α instead of 2β.

2α,3α:16α,17α-epoxy-5α-androstane (**14a**, 10.1 g, 58%) which was condensed with the secondary amines morpholine, piperidine, and pyrrolidine to give the diamino diols **15a–c**. Acetylation yielded 2β,16β-dimorpholino-3α,17α-diacetoxy-5α-androstane [mp 116–120° (34%). *Anal.* ($C_{31}H_{50}N_2O_6$) C, H, N], 2β,16β-dipiperidino-3α,17α-diacetoxy-5α-androstane [mp 98–102° (17%). *Anal.* ($C_{33}H_{54}N_2O_4$) C, H, N], and 2β,16β-dipyrrolidino-3α,17α-diacetoxy-5α-androstane (29%) as a clear gum showing no absorption at 3300–3600 cm^{-1}.

2α,16β-Diamino-5α-androstane-3β,17β-diols and Diacetates. Epoxidation of 3,17-diacetoxy-5α-androsta-2,16-diene (106 g) gave the 2α,3α:16α,17α-diepoxide **14b** (49.5 g, 43%) which was condensed with aqueous piperidine and morpholine to give 2α,16β-dipiperidino-5α-androstane-3,17-dione [**16a** (21%), mp 180–184°] and 2α,16β-dimorpholino-5α-androstane-3,17-dione (**16b**, 34%), respectively.

Reduction of the dimorpholinodione with $NaBH_4$ gave 2α,16β-dimorpholino-5α-androstane-3β,17β-diol (**17a**, 80%): mp 223–229°; $[\alpha]^{20}D$ ($CHCl_3$) +9°. *Anal.* ($C_{27}H_{46}N_2O_4$) C, H, N. Acetylation gave the diacetate **17b**: mp 159–164°; $[\alpha]D$ +37°. *Anal.* ($C_{31}H_{50}N_2O_6$) C, H, N.

3α,17β-Diacetoxy-16β-dimethylamino-2β-piperidino-5α-androstane. 16β-Dimethylamino-2α,3α-epoxy-5α-androstan-17β-ol (2.3 g) was condensed with aqueous piperidine and crystallized

Table V. Dimethohalides of 2β,17β-Diamino-5α-androstane-3α,16β-diols and Diacetates

No.	Substituents 2β	17β	3α,16β	Mp, °C	Formula	Potency	Duration	Toxicity
52	Py	Py	OAc	220–231	$C_{33}H_{56}I_2N_2O_4$	0.13	1.5	1.73 (1.53–1.95)
53	P	Py	OAc	241–244	$C_{34}H_{58}I_2N_2O_4$	0.70	1.1	0.45 (0.39–0.51)
54	M	Py	OAc	203–204	$C_{33}H_{56}I_2N_2O_3$			
55	P	P	OH	203–208	$C_{31}H_{56}I_2N_2O_2$	0.15	0.62	3–10
56	P	P	OAc	224 dec	$C_{35}H_{60}Br_2N_2O_4$	0.59	0.73	0.3–1
57	P	D	OAc	255–258	$C_{32}H_{56}I_2N_2O_4$	0.57	1.0	0.37 (0.35–0.39)

Table VI. Dimethohalides of 2β,17β-Diamino-5α-androstan-3α-ol Acetates and 3α,17β-Diamino-5α-androstan-2β-ol Acetates

No.	Substituents 2β	3α	17β	Mp, °C	Formula	Potency	Duration	Toxicity
58	P	OAc	Py	205–209	$C_{35}H_{56}Br_2N_2O_2$	0.20	0.70	1.84 (1.7–2.0)
59	P	OAc	P	208–213	$C_{33}H_{58}Br_2N_2O_2$	<0.10		2.85 (2.81–2.89)
60	M	OAc	Py	211–216	$C_{32}H_{56}I_2N_2O_3$			
61	M	OAc	P	205–211	$C_{31}H_{54}I_2N_2O_3$			
62	OAc	Py	Py	207–209	$C_{31}H_{54}Br_2N_2O_2$	0.48	0.65	2.53 (1.93–3.3)
63	OAc	P	Py	200–202	$C_{32}H_{56}Br_2N_2O_2$	1.15	0.75	2.02 (1.87–2.18)

Table VII. Miscellaneous

No.	Compound Name	Mp, °C	Formula	Potency	Duration	Toxicity
64	3β,17β-Di(methyl-2′-acetoxyethylamino)-5α-androstane dimethobromide	219–229	$C_{31}H_{64}Br_2N_2O_4$	0.37	0.44	3.6 (3.35–3.87)
65	17β-Acetoxy-16β-piperidino-5α-androstane methobromide	240–241	$C_{27}H_{46}BrNO_2$	<0.10		
66	3α-Acetoxy-2β-piperidino-5α-androstane methobromide	229–232	$C_{27}H_{46}BrNO_2$	<0.10		

from $(CH_3)_2CO$–Et_2O to give 16β-dimethylamino-2β-piperidino-5α-androstane-3α,17β-diol (600 mg, 21%), mp 197–205°. *Anal.* ($C_{26}H_{46}N_2O_2$) C, H, N. The diacetate was noncrystalline and showed no hydroxyl peak in its ir spectrum.

2β,17β-Diamino-5α-androstane-3α,16β-diols and Diacetates. Condensation of the 17β-amino-2α,3α-epoxy-5α-androstan-16β-ols (**12a–d**) with the appropriate aqueous secondary amines yielded the corresponding 2β,17β-diamino-3α,16β-diols (60–90%) and corresponding diacetates; their dimethohalo derivatives are described in Table V.

2β,17β-Diamino-5α-androstan-3α-ols and Acetates. General Procedure. A solution of a 2β-amino-5α-androstan-3α-ol-17-one (5 g) in a secondary amine (6 ml) and formic acid (1 ml) was boiled under reflux for 18 hr. The products were crystallized from Et_2O to give the title compounds **18a–d** (60–90%) which were acetylated to the following 3α-acetates. 3α-Acetoxy-2β-piperidino-17β-pyrrolidino-5α-androstane, mp 173–179°. *Anal.* ($C_{30}H_{50}N_2O_2$) C, H, N. 3α-Acetoxy-2β,16β-dipiperidino-5α-androstane, mp 141–146°. *Anal.* ($C_{31}H_{52}N_2O_2$) C, H, N. 3α-Acetoxy-2β-morpholino-17β-pyrrolidino-5α-androstane, mp 243–249°. *Anal.* ($C_{29}H_{48}N_2O_3$) C, H, N. 3α-Acetoxy-2β-morpholino-17β-piperidino-5α-androstane, mp 223–227°. *Anal.* ($C_{30}H_{50}N_2O_3$) C, N, N.

3α,17β-Diamino-5α-androstan-2β-ols (19a,b) and Acetates. Similarly, a Leuckart condensation with pyrrolidine and 2β-hydroxy-3α-amino-5α-androstan-17-one yielded the 17β-pyrrolidino compounds **19a,b** (75%) which were acetylated to give 2β-acetoxy-3α-piperidino-17β-pyrrolidino-5α-androstane [mp 207–212°. *Anal.* ($C_{30}H_{50}N_2O_2$) C, H, N] and 2β-acetoxy-3α,17β-dipyrrolidino-5α-androstane [mp 192–196°. *Anal.* ($C_{29}H_{48}N_2O_2$) C, H, N]

3β,17β-Bis(*N*-methyl-*N*-2′-hydroxyethylamino)-5α-androstane Diacetate. A Leuckart condensation of 5α-androstane-3,17-dione with methyl-2-hydroxyethylamine gave the diaminodiol (39%), mp 168–173°. *Anal.* ($C_{25}H_{46}N_2O_2$) C, H, N. Acetylation gave the diacetate as a clear gum showing no absorption in the 3300–3600-cm^{-1} region.

Wolff–Kishner Reduction of 2β,16β-Dipiperidino-5α-androstan-3α-ol-17-one (4a). A solution of the 17-ketone (5 g) in hydrazine hydrate (64%, 7 ml) was boiled under reflux for 1.5 hr and cooled, and KOH pellets (7 g) were added carefully. The solution was boiled under reflux for a further 3 hr, and the product was worked up through Et_2O, dissolved in petroleum ether, and percolated down a column (15 × 2.5 cm) of alumina. Elution with petroleum ether (2 l.) and C_6H_6 (200 ml) gave a fraction which crystallized from $(CH_3)_2CO$ to give 2β-piperidino-5α-androstan-3α-ol (**8a**) in plates (1.5 g, 38%): mp 154–156°; $[\alpha]^{20}D$ ($CHCl_3$) +80°; ν_{max} 3360–3410 cm^{-1} (N-bonded OH). *Anal.* ($C_{24}H_{41}NO$) C, H, N. The acetate had mp 99.5–102°. *Anal.* ($C_{26}H_{43}NO_2$) C, H, N.

17β-Acetoxy-16β-piperidino-5α-androstane. Condensation of 16α,17α-epoxy-17β-acetoxy-5α-androstane (4 g) with aqueous piperidine gave 16β-piperidino-5α-androstan-17-one (1.65 g, 38%) which was reduced with $NaBH_4$ and the 17β-alcohol acetylated to give the title compound (1.5 g, 31%): mp 145–147°; $[\alpha]^{20}D$ +7°. *Anal.* ($C_{26}H_{43}NO_2$) C, H, N.

Mono- and Bisquaternary Ammonium Steroids. In general, the bisamino-5α-androstanes were treated with an alkyl halide in CH_2Cl_2 or CH_3CN solution in the dark at 20° for 7–14 days. If precipitation occurred before the bisalkylation was largely complete, addition of MeOH effected solution although this caused partial hydrolysis of acetate groups if present. Products were crystallized from CH_2Cl_2–$(CH_3)_2CO$ or *i*-PrOH–$(CH_3)_2CO$ in 60–70% yield.

In order to isolate monoquaternary ammonium derivatives the reactions were carried out in Et_2O solution which precipitated the sparingly soluble 16β-ammonio-2β-amino-5α-androstanes (**26**, **30**, **33**, and **34**) on their formation. These could be converted to 2β,16β-bisammonio derivatives on treatment with the same or another alkyl halide in solution. The mono- and diammonio compounds are described in Tables III–VII.

Preparation of Pure Pancuronium Bromide (31) without Crystallization. A solution of 3α,17β-diacetoxy-2β,16β-dipiperidino-5α-androstane (**6g**, 1 g) and CH_3Br (3.5 g) in CH_3CN (2.5 ml) was maintained at 40° for 30 hr and evaporated to dryness to give a residue (1.54 g). Previous similar experiments had indicated that this product was a mixture of the methobromide **33** (*ca.* 10% by quantitative tlc) ‡ and the dimethobromide **31** and that

‡ Two tlc systems are used to identify likely impurities: (a) system, BuOH–H_2O (85:15) on Al_2O_3–G (Merck) developer I_2, separates mono- and dimethobromide; (b) system, pyridine-AcOH-BuOH-H_2O (10:3:15:12) on Kieselgel G (Woelm) developer H_2SO_4; MeOH, separates 3- and/or 17-hydroxy derivatives.

the reaction had reached equilibrium; higher temperatures either did not drive the reaction to completion or caused decomposition. This product was easily purified by crystallization. However, in order to identify positively the impurity and to achieve a synthesis for ^{14}C dimethobromide **31**, which precludes crystallization, this product was chromatographed on acid-washed alumina (70 wt) and eluted with *i*-PrOH–EtOAc (3:1) to yield the monomethobromide** **33** (60 mg); further elution with *i*-PrOH–EtOAc (3:1) and *i*-PrOH yielded pure dimethobromide **31** (1.04 g, 77%).

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That this methobromide has a 16-ammonio substituent was proved by its loss during the modified Hoffman degradation achieved by boiling a solution of the methobromide (100 mg) and NaOMe (300 mg) in DMF under reflux for 30 min. The sole product was crystallized from acetone to yield 2β-piperidino-5α-androstan-3α-ol-17-one (8b**, 60 mg).

Synthesis and Central Nervous System Depressant Activity of Some 5-(2-Substituted alkyl)-2-oxazolidinones[1]

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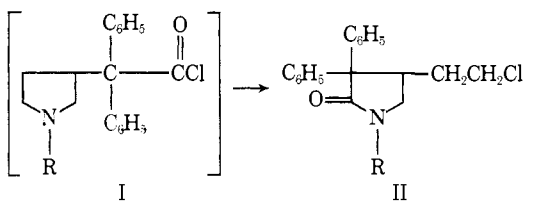
Received March 22, 1973

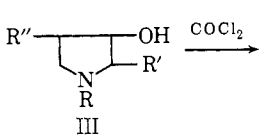
A novel method for preparing 5-(2-chloroalkyl)-2-oxazolidinones from 1-substituted 3-pyrrolidinols and phosgene is described. These compounds are intermediates for a series of 5-[2-(4-phenylpiperazino)alkyl]-2-oxazolidinones which are active CNS depressants.

A previous report from this laboratory described the conversion of α-(1-substituted 3-pyrrolidinyl)-1,1-diphenylacetic acids to the corresponding acid chlorides and their facile rearrangement to 1-substituted 4-(2-chloroethyl)-3,3-diphenyl-2-pyrrolidinones[2] (I → II).

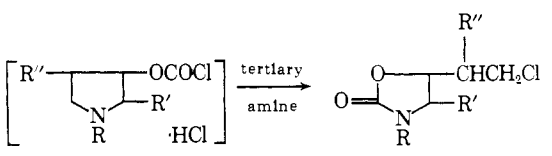


I II

By an analogous reaction a series of 3-substituted 2-oxazolidinones having a 2-substituted alkyl group in the 5 position has been prepared from 1-substituted 3-pyrrolidinols and phosgene.



III



IV V

Compound V has been proven to be a useful intermediate to pharmacologically active compounds since the halogen of this molecule is easily replaced by various basic moieties. When the halogen of V is substituted by 4-phenylpiperazines, the resulting compounds (R equal to hydrogen or lower alkyl) exhibit major tranquilizing properties in animals. This has led to the preparation of a number of substituted 4-phenylpiperazine derivatives.

Chemistry. The 5-(2-chloroalkyl)-3-substituted 2-oxazolidinones were prepared by adding the properly substituted pyrrolidinol to a solution of phosgene in chloroform. The resulting carbonyl chloride hydrochloride (IV) was not isolated but its presence in solution was suggested by characteristic infrared absorption bands. When a solution containing IV was neutralized with triethylamine, the neutral oxazolidinone V was obtained. These 5-(2-chloroethyl)-2-oxazolidinones were stable in the presence of dilute acids or dilute alkali (when kept cold) and could be distilled with a minimum of decomposition at temperatures below 150°. The yield of purified products by this method ranged from approximately 35 to 70% of theoretical. The compounds of this type which have been prepared and identified are shown in Table I (compounds **1–7**).

An intermediate of type V where R, R′, and R″ are hydrogen (compound **8**) was prepared by the stepwise degradation of compound **10**.

Compound **8** was also prepared by reacting 1-chloro-3,4-epoxybutane with urethane and a catalytic amount of lithium amide.