Tetrahedron, 1965, Vol. 21, pp. 1761 to 1766. Pergamon Press Ltd. Printed in Northern Ireland

MODIFIED STEROID HORMONES—XL

SOME HETEROCYCLIC TYPES

M. G. LESTER, V. PETROW and O. STEPHENSON
Chemical Research Department, The British Drug Houses Ltd.,
Graham Street, London N. 1

(*Received* 15 *February* 1965)

Abstract—The preparation of 17β-hydroxy-17α-methylandrostano [2,3-b]-(5′-hydroxyindole) along with other novel indolosteroids is described.

THE importance of the cyclopentenophenanthrene ring system in hormonally-active compounds requires no comment. But this unique tetracyclic skeleton is also, *par excellence*, a nucleus with inherent CNS/behavioural activity. Thus the gonadal hormones play a role in the establishment of the male and female psyche and as is becoming increasingly clear, they may also play a role in the causative mechanisms of psychiatric disorder. Thus, the ovarian hormones are paramount in bringing on the premenstrual syndrome with its attendant psychiatric symptoms, which on occasion can be tragic in their outcome.

In seeking to potentiate the CNS/behavioural activities of this group of compounds, we turned to the combination of CNS-effective moieties with steroidal types, hoping thereby to increase pharmacodynamic activity at the expense of hormonal potency.[1] To this end we have studied the preparation of 5′-hydroxyindolosteroids (cf. I; R = OH) in the expectation that the structural resemblance to 5-hydroxytryptamine may be a factor in the appearance of significant CNS-activity.

The general method of preparation of indolosteroids, involving interaction of a 3-ketosteroid with a phenylhydrazine as described by Dorée,[2] has been well documented, but, as far as we know, no compounds containing a 5′-hydroxyl group (cf. I; R = OH), have been reported.

In preliminary attempts to prepare the required compounds, androstan-17β-ol-3-one was converted into 17β-acetoxyandrostano-(2,3-b)-(5′-methoxyindole) (Ia) by reaction with *p*-methoxyphenylhydrazine in boiling acetic acid. However, attempted demethylation of this compound (Ia) by heating with aluminium chloride in benzene or 45% hydrogen bromide in glacial acetic acid for several hours failed to yield crystalline products and indeed, no phenolic material could be detected in the reaction mixtures in either case.

The 5′-nitro compound (Ib) was next prepared as above, using *p*-nitrophenylhydrazine in place of the somewhat unstable *p*-methoxyphenylhydrazine. Catalytic reduction of the product with hydrogen and palladized charcoal in ethanol gave the required amine (Ic) but attempts to convert this into the corresponding 5′-hydroxy compound, failed.

[1] G. Cavallini, *Farmaco* **10**, 644 (1955); G. Cavallini and E. Massarani. *J. Med. Pharm. Chem.* **1**, 365 (1959).

[2] C. Dorée, *J. Chem. Soc.* **95**, 638 (1909).

Subsequent experiments were carried out using 17α-methylandrostan-17β-ol-3-one as the steroidal starting material. This was converted into the 5'-benzyloxyindolo compound (Id) by reaction with *p*-benzyloxyphenylhydrazine,[3] but attempts to remove the benzyl group by catalytic hydrogenation under a variety of conditions were abortive.

Success was finally achieved *via* the 5'-benzoyloxyindole (Ie). *p*-Benzoyloxyaniline was prepared by an improved method whereby *p*-benzoyloxynitrobenzene was reduced catalytically with hydrogen and palladized charcoal instead of with zinc in ethanolic acetic acid as described.[4] The amine was converted into *p*-benzoyloxyphenylhydrazine which reacted smoothly with 17α-methylandrostan-17β-ol-3-one in acetic acid to yield the 5-benzoyloxy derivative (Ie). The latter compound was hydrolysed smoothly in aqueous ethanolic sodium hydroxide solution to yield 17β-hydroxy-17α-methylandrostano [2,3-b]-(5'-hydroxyindole). (If).

Treatment of *p*-benzyloxyphenylhydrazine with *p*-chlorobenzyl chloride in the presence of sodamide in liquid ammonia and tetrahydrofuran gave 1-(*p*-benzyloxyphenyl)-1-(*p*-chlorobenzyl)-hydrazine which was condensed with 17α-methylandrostan-17β-ol-3-one to give a small yield of the 5'-benzyloxy-1'-(*p*-chlorobenzyl)-indolo steroid (Ig). On the other hand, reaction of *p*-benzoyloxyphenylhydrazine with *p*-chlorobenzyl chloride in the presence of sodamide in liquid ammonia did not give the expected 1-(*p*-benzoyloxyphenyl)-1-(*p*-chlorobenzyl)-hydrazine, but, due to migration of the benzoyl group yielded 1-benzoyl-1-(*p*-hydroxyphenyl)-hydrazine. The latter compound was most readily obtained by the action of sodamide on *p*-benzoylphenylhydrazine in a mixture of liquid ammonia and tetrahydrofuran. It was reacted with 17α-methylandrostan-17β-ol-3-one to give a small yield of the 1'-benzoyl-5'-hydroxyindolo steroid (Ih). 2α,17α-Dimethylandrostan-17β-ol-3-one was condensed with phenylhydrazine in acetic acid at reflux temperature to give a 30% yield of the crystalline indolenine (II) after purification by chromatography. When this was heated with acetic anhydride O,N-diacetylation occurred with migration of the 1',2'-double bond to yield the product (III). This reaction at the N-atom of the indole ring led us to attempt alkylation of the compound (II) but no reaction occurred with *p*-chlorobenzyl chloride using sodamide in liquid ammonia as condensing agent. When the reaction was carried out with sodium hydride in a mixture of dimethylformamide and toluene, products of indeterminate structure were obtained.

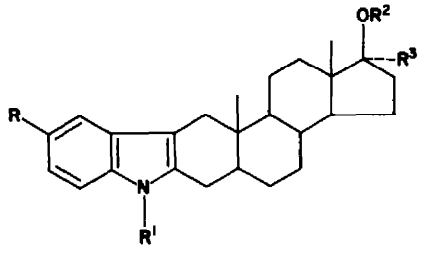
Finally, whilst this work was in progress, the preparation of long-acting hypotensive agents such as the N-[2-(2-methylpyridyl-5)-ethyl]-2,3-dialkyl indoles (IV) was described[5] by Russian chemists. We therefore carried out exploratory reactions and attempted to react 2-vinylpyridine with 17β-hydroxy-17α-methylandrostano (2,3-b) indole using sodium as condensing agent according to the method of Magnus and Levine.[6] This method failed but success was ultimately obtained by carrying out the reaction in dimethylformamide using sodium hydride at 60°. The product (Ii) formed

[3] G. Bernini, *Ann. Chim. Rome* **43**, 559 (1953).

[4] M. O. Forster and H. E. Fierz, *J. Chem. Soc.* **91**, 855 (1907).

[5] E. V. Vinogradova, A. N. Grinev, I. K. Danusevich, M. F. Dzik, B. V. Dubovik, A. S. Zakharevskii, T. Yu. Il'yuchenok, A. N. Kost, G. I. Martinovich, A. V. Miklevich, L. F. Pil'tienko, I. V. Rachkovskaya, N. A. Reut, V. I. Talapin, N. Z. Tamarina, A. P. Terent'ev and K. S. Shadurskii, *Fed. Proc.* **22**, No. 6, Part II.

[6] G. Magnus and R. Levine, *J. Amer. Chem. Soc.* **78**, 4127 (1956).



I

(a) R = OMe, $R^1 = R^3 = H$, R^2 = CO·Me
(b) R = NO_2, $R^1 = R^3 = H$, R^2 = CO·Me
(c) R = NH_2, $R^1 = R^3 = H$, R^2 = CO·Me
(d) R = Ph·CH_2·O, $R^1 = H$, R^2 = CO·Me, R^3 = Me
(e) R = Ph·CO·O, $R^1 = R^3 = H$, R^2 = Me
(f) R = OH, $R^1 = R^3 = H$, R^2 = Me

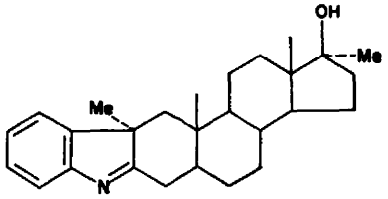
(g) R = Ph·CH_2·O, R^1 = Cl–  –CH_2–, $R^2 = H$, R^3 = Me

(h) R = OH, R^1 = Ph·CO, $R^2 = H$, R^3 = Me

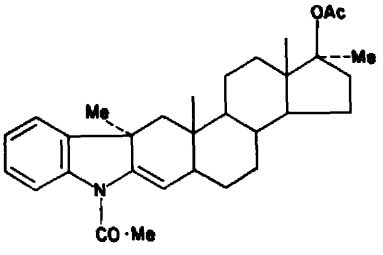
(i) $R = R^2 = H$, R^1 =  –CH_2·CH_2, R^3 = Me

(j) $R = H$, R^1 =  –CH_2·CH_2, R^2 = CO·Me, R^3 = Me

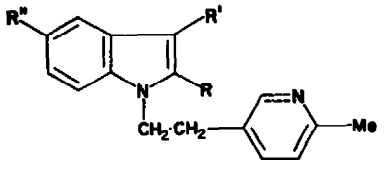
(k) $R = R^3$ = Me, R^1 =  –CH_2·CH_2, R^2 = H.



II



III



IV

a hydrochloride salt, showed single OH absorption in the 3500–3000 cm^{-1} region and yielded an acetate ester (Ij) on heating with acetic anhydride for 1 hour. The IR spectrum of the latter compound had no band present between 3500 and 3000 cm^{-1} showing that the indole nitrogen was tertiary, whilst bands at 1750 and 1280 cm^{-1} confirmed the presence of an acetoxy group.

The analogous 5′-methyl compound (Ik) was similarly prepared by reaction of 17β-hydroxy-17α-methylandrostano (2,3-b)-(5′-methyl indole) with 2-vinylpyridine using the above method with somewhat longer heating.

All attempts to replace 2-vinylpyridine in the above reactions by 2-methyl-5-vinylpyridine to yield compounds more closely related to those (cf. IV) prepared by Vinogradova *et al.*,[5] were unsuccessful.

EXPERIMENTAL

IR measurements were made for Nujol mulls with a Perkin–Elmer Infracord Spectrophotometer; no calibration corrections were applied.

17β-Acetoxyandrostano-[2,3-b]-(5′-methoxyindole). A solution of androstan-17β-ol-3-one (2 g) in acetic acid (25 ml) was treated with *p*-methoxyphenylhydrazine and the mixture heated under reflux for 3 hr. Dilution with water furnished the *product* (0·75 g) m.p. 248–252° from aqueous EtOH, ν_{max} 3400(NH), 1735(C=O), 1630, 1600, 1575 (aromatic C=C), 832, 800 cm^{-1} (indole ring). (Found: C, 76·7; H, 8·7; N, 3·4. $C_{36}H_{47}NO_3$ requires: C, 77·2, H, 8·6; N, 3·2%.)

17β-Acetoxyandrostano-[2,3-b]-(5-nitroindole). A solution of androstan-17β-ol-3-one (5 g) and *p*-nitrophenylhydrazine (3 g) in acetic acid (50 ml) and conc. HCl (20 ml) was heated on the steam-bath for 4 hr. The yellow crystals were collected and washed with water then ether. The *product* (3 g) had m.p. >310° (from $CHCl_3$–EtOH), ν_{max} 3360(NH), 1730(C=O), 1625, 1575 (aromatic C=C), 1510 (NO_2), 890, 830 (indole ring), 758, 745 cm^{-1} (NO_2?). (Found: C, 71·6; H, 7·7; N, 6·1. $C_{27}H_{34}N_2O_4$ requires: C, 72·0; H, 7·6; N, 6·2%.)

17β-Acetoxyandrostano-[2,3-b]-(5′-aminoindole). A suspension of the foregoing nitro compound (3 g) in EtOH (300 ml) was hydrogenated at 60° using a 10% Pd—C catalyst, (0·6 g). The *product* (1·8 g) had m.p. 295–300° from $CHCl_3$–EtOH, ν_{max} 3420, 3320 (shoulder) (NH); 1725 (C=O); 1645, 1605, 1470 (aromatic C=C), 850, 840, 800 cm^{-1} (indole ring). (Found: C, 77·4; H, 8·4; N, 6·8; $C_{27}H_{36}N_2O_2$ requires: C, 77·1; H, 8·6; N, 6·7%.)

17β-Acetoxy-17α-methylandrostano [2,3-b]-*(5′-benzyloxyindole).* This was prepared in 63% yield by reaction of 17α-methylandrostan-17β-ol-3-one with *p*-benzyloxyphenylhydrazine in acetic acid. It had m.p. 122–125° from acetic acid, ν_{max} 3300(NH), 1720(C=O), 1635, 1600, 1575 (aromatic C=C), 855, 803 (indole ring), 740, 700 cm^{-1} (mono-substitution). (Found: C, 79·6;, H, 8·4; N, 3·0. $C_{35}H_{43}NO_3$ requires: C, 79·95; H, 8·2; N, 2·7%.)

p-Benzoyloxyphenylhydrazine. A solution of *p*-benzoyloxyaniline (10 g) in acetic acid (50 ml) was treated with 7·5 N HCl (10 ml), cooled to 0° with stirring and the pasty mixture diazotized by the dropwise addition of a solution of $NaNO_2$ (3·3 g) in water (6·7 ml). The solution was then added with stirring to a solution of $SnCl_2 \cdot 2H_2O$ (4·5 g) in 10 N HCl (50 ml) and allowed to stand at 0° for 2 hr. The solid was collected, washed with ether, transferred to a separating funnel containing $CHCl_3$ and water and made strongly alkaline with NaOH aq. The $CHCl_3$ extracts were washed, dried and evaporated to yield the *product* (5·7 g), m.p. 99–100° from benzene–light petroleum (b.p. 60–80°), ν_{max} 3200(NH), 1720(C=O) 1625, 1600, 1575, 1500 (aromatic C=C), 871, 816 (disubstitution), 705, 687 cm^{-1} (mono-substitution). (Found: C, 68·7; H, 5·2; N, 11·9. $C_{13}H_{12}N_2O_2$ requires: C, 68·4; H, 5·3; N, 12·3%.)

17β-Hydroxy-17α-methylandrostano[2,3-b]-*(5′-benzoyloxyindole).* This compound was obtained in 74% yield by reaction of 17α-methylandrostan-17β-ol-3-one with *p*-benzoyloxyphenylhydrazine in acetic acid. It had m.p. 230–232° from aqueous EtOH, ν_{max} 3500(NH), 3300(OH), 1710 (C=O), 1625, 1580 (aromatic C=C) 890, 798 (indole ring), 718, 712 cm^{-1} (monosubstitution).

17β-Hydroxy-17α-methylandrostano-[2,3-b]-(5′-hydroxyindole). A solution of the foregoing 5-benzoyloxyindole (3·4 g) in EtOH (20 ml) was treated with 2 N NaOH (50 ml) and the mixture heated on the steam-bath for 2 hr. It was cooled and poured with stirring into water. The *product* (0·9 g)

had m.p. 266° (dec) from aqueous EtOH, ν_{max} 3490(NH), 3300, 3200(OH), 1625, 1590 (aromatic C=C), 858, 840, 810, 800 cm^{-1} (indole ring).

1-(p-*Benzyloxyphenyl*)-1-(p-*chlorobenzyl*)-*hydrazine*. A solution of *p*-benzyloxyphenylhydrazine (5 g) in tetrahydrofuran (25 ml) was added to a solution of $NaNH_2$ [prepared from Na (0·5 g)] in liquid NH_3 (200 ml). The mixture was stirred for 3 hr when *p*-chlorobenzyl chloride (3 ml) was added and stirring was continued for 1 hr further. The ammonia was allowed to evaporate when the residual solution was poured into excess of water and extracted with $CHCl_3$. The $CHCl_3$-extracts were dried and the $CHCl_3$ evaporated at 0·5 mm press. leaving a gum which was chromatographed on alumina. Elution with benzene–$CHCl_3$ yielded the *product* (3·7 g), m.p. 122–124° from ether-light petroleum (b.p. 40–60°), ν_{max} 3350(NH), 1620, 1600, 1580, 1510, 1490 (aromatic C=C), 860–800 complex series of bands (disubstitution), 748, 702 cm^{-1} (monosubstitution). (Found: C, 71·3; H, 5·5; N, 8·2; Cl, 10·9. $C_{30}H_{19}ClN_2O$ requires: C, 70·9; H, 5·65; N, 8·3; Cl, 10·5%.)

17β-*Hydroxy*-17α-*methylandrostano* [2,3-b]-(5′-*benzyloxy*-1′-p-*chlorobenzyl*)*indole*. This compound was obtained in 12% yield by reaction of 17α-methylandrostan-17β-ol-3-one with 1-(*p*-chlorobenzyl)-1-(*p*-benzyloxy)phenylhydrazine in acetic acid at reflux temp. The product was purified by chromatography on alumina followed by elution with a 50% benzene–$CHCl_3$ mixture and had m.p. 120–125° from ether–light petroleum (b.p. 40–60°), ν_{max} 3460(OH), 1620, 1580 1510 (aromatic C=C), 835,800 (indole and *p*-disubstitution), 754, 695 cm^{-1} (monosubstitution). (Found: C, 78·6; H, 7·8; Cl, 6·1; N, 2·3. $C_{40}H_{46}ClNO_2$ requires: C, 79·0; H, 7·6; Cl, 5·8; N, 2·3%.)

1-*Benzoyl*-1-(p-*hydroxyphenyl*)*hydrazine*. A solution of *p*-benzoyloxyphenylhydrazine (2·3 g) in tetrahydrofuran (20 ml) was added with stirring to a solution of $NaNH_2$ [prepared from Na (0·25 g)] in liquid NH_3 (50 ml) and stirring was continued for 2 hr. The ammonia was then allowed to evaporate and the residue was partitioned between water and $CHCl_3$. The aqueous fraction was acidified to pH 4 by addition of dil. HCl aq, and re-extracted with $CHCl_3$. The $CHCl_3$-extracts were washed, dried and evaporated to yield the *product* (0·75 g) m.p. 165° (dec) from water, ν_{max} 3300(shoulder), 3140(NH and OH), 1650, 1600, 1570, 1510 (C=O and aromatic C=C), 845 (*p*-disubstituted ring), 720, 695 (monosubstituted ring). (Found: C, 68·6; H, 5·2; N, 12·2. $C_{13}H_{12}N_2O_2$ requires: C, 68·4; H, 5·3; N, 12·3%.)

17β-*Hydroxy*-17α-*methylandrostano* [2,3-b]-(1′-*benzoyl*-5′-*hydroxyindole*). This compound was prepared in 16% yield by reaction of 17α-methylandrostan-17β-ol-3-one with the foregoing phenylhydrazine in acetic acid at reflux temp. A $CHCl_3$-solution of the crude reaction product was chromatographed on alumina. Elution with $CHCl_3$ yielded unchanged ketone (1·0 g) and elution with 10% MeOH in $CHCl_3$ furnished a crude product (2·8 g) followed by unchanged phenylhydrazine. The pure *product* had m.p. 170° (dec) after crystallization from MeOH then acetone, ν_{max} 3350, 3250(OH), 1690(C=O), 1650, 1610, 1580 (aromatic C=C) 854, 810, 773, 734, 716, 700 (indole and benzene rings). (Found: C, 79·3; H, 7·8; N, 3·3. $C_{28}H_{29}NO_2$ requires: C, 79·6; H, 7·9; N, 2·8%.)

17β-*Hydroxy*-17α-*methylandrostano* [2,3-b]-(5′-*methylindole*). This compound was obtained in 85% yield. It had m.p. 269–274° from $CHCl_3$–EtOH, ν_{max} 3520(NH), 3230(OH), 1600 (aromatic C=C), 810 cm^{-1} (indole ring). (Found: C, 82·6; H, 9·7; N, 3·7. $C_{27}H_{37}NO$ requires: C, 82·8; H, 9·5; N, 3·6%.)

2α,17α-*Dimethyl*-17-*hydroxyandrostano*-[2,3-b]*indolenine*. A mixture of 2α,17α-dimethyl-17β-hydroxyandrostan-3-one (1 g) and phenylhydrazine (0·3 ml) in acetic acid (30 ml) was heated under reflux for 3 hr. The acetic acid was distilled off at red. press. and the residue was dissolved in MeOH (5 ml) and poured into water. The solid was extracted with benzene, the benzene was washed with water, dried and chromatographed on alumina. Elution with benzene containing increasing amounts of $CHCl_3$ (up to 50%) gave the product (0·4 g) m.p. 237–245° from MeOH. ν_{max} 3250(OH), 1605, 1575 (aromatic C=C and C=N), 775, 750 cm^{-1} (indolenine ring). (Found: C, 82·5; H, 9·3; N, 3·5. $C_{27}H_{37}NO$ requires: C, 82·8; H, 9·5; N, 3·6%.)

17β-*Acetoxy*-2α,17α-*dimethylandrost*-3-eno[2,3-b]-(1′-*acetyl*-2′,3′-*dihydroindole*). This compound was obtained when the foregoing indolenine was heated with acetic anhydride at reflux temp for 30 min. It had m.p. 215–218° from EtOH ν_{max} 1720 (acetate CO), 1660 (amide CO), 1635, 1595 (aromatic C=C), 762 cm^{-1} (dihydroindole ring). (Found: C, 78·6; H, 9·2; N, 3·5. $C_{31}H_{41}NO_3$ requires C, 78·25; H, 8·7; N, 2·9%.)

17β-*Hydroxy*-17α-*methylandrostano*[2,3-b]-{1′-β-(2-*pyridyl*)*ethyl*]-*indole*}. A mixture of 17β-hydroxy-17α-methylandrostano [2,3-b]-indole (3·8 g), 2-vinylpyridine (1·1 g) and 50% NaH dispersion-in oil (0·48 g) in dimethylformamide (50 ml) was heated at 60° with stirring under N_2. The cooled

mixture was diluted with water and extracted with $CHCl_3$ and the extracts were washed with water and dried. The $CHCl_3$ was evaporated at red. press. to yield the *product* (2·1 g), m.p. 184–186° (from EtOH), ν_{max} 3250(OH), 1615, 1600, 1580 (aromatic C=C), 774, 758(shoulder)(pyridine ring), 750 cm^{-1} (indole ring). (Found: C, 82·5; H, 8·8; N, 5·4. $C_{33}H_{42}N_2O$ requires: C, 82·1; H, 8·8; N, 5·8%.)

17β-Acetoxy-17α-methylandrostano [2,3-b]-{*1′-[β-(2-pyridyl)ethyl]indole*}. This was obtained by acetylation of the foregoing compound with acetic anhydride at reflux temp for 1 hr, ν_{max} 1750 (acetoxy), 1625, 1600, 1580 (aromatic C=C), 783 (pyridine ring?), 765 (pyridine ring), 740 cm^{-1} (indole ring). (Found; C, 80·1; H, 8·4; N, 5·5. $C_{35}H_{44}N_2O_2$ requires: C, 80·1; H, 8·45; N, 5·3%.)

17β-Hydroxy-17α-methylandrostano [2,3-b]-{*5′-methyl-1′-[β-(2-pyridyl)ethyl]indole*}. A mixture of 17β-hydroxy-17α-methylandrostano [2,3-b]-(5′-methylindole), (3·9 g), 2-vinylpyridine (2·2 g) and a 50% dispersion of NaH in oil (0·96 g) in dimethylformamide (50 ml) was heated at 60° under N_2 for 5 hr. The *product*, isolated by dilution with water and extraction with $CHCl_3$ had m.p. 229–232° from $CHCl_3$–EtOH, ν_{max} 3250(OH), 1600, 1570 (aromatic C=C), 808 (indole ring), 752 cm^{-1} (pyridine ring) (Found: C, 82·2; H, 8·9; N, 5·6. $C_{34}H_{44}N_2O$ requires; C, 82·2; N, 8·9; N, 5·6%.)