= $(CH_2)_2N(C_2H_5)_2$.—Compound **3** (70 g, 0.30 mol) was dissolved in 850 ml of xylene and added over 15 min to a cool mixture of $Et_2N(CH_2)_2OH$ (0.60 mol and 2 g (0.10 g-atom) of Na. After refluxing for 5 hr, the condenser was disconnected and 100 ml of distillate collected. Fresh xylene (100 ml) was added and the reaction proceeded overnight. The solvents were removed until about 50 ml remained. After cooling, the residue was triturated with concentrated HCl (200 ml) until a solid residue formed. This solid was dissolved in EtOAc–Et_2O (5:1) and treated with 20% NaOH until basic. The aqueous extracts were reextracted with EtOAc–Et_2O (2:1), and the organic layers were combined, washed with saturated NaCl, and dried ($CaCl_2$). Evaporation of the solvents and treatment of the residue with alcoholic HCl, and Et_2O and refrigeration, yielded crude **38**·HCl, which on treatment with C and recrystallization from absolute EtOH gave 17.4 g, 16.5%, of **38**, mp 190–191°. *Anal.* ($C_{13}H_{27}ClN_2O_2$) C, H, Cl, N.

Method B. 3-(3-Dimethylaminopropyl)-9-methyl-1,2,3,4-tetrahydrocarbazole-3-carboxylate (42) [V, R′ = CH_3; R = $(CH_2)_3N(CH_3)_2$].—Compound **12**, 48 g (0.20 mol), was dissolved in 150 ml of absolute EtOH and added to a solution of KOH (11.2 g, 0.20 mol) in 250 ml of absolute EtOH. After refluxing for 1.5 hr, the solvent removed *in vacuo*, the K salt (III, R′ = CH_3; R = K, 16 g, 0.07 mol) was suspended in 300 ml of dry toluene, stirred, and heated to reflux, and 10 g (0.07 mol) of $(Me)_2N(CH_2)_3Cl$ in 50 ml of dry toluene added over 1 hr. After 8 hr an additional 5 g of chloride was added and the mixture refluxed for a total of 72 hr. The mixture was cooled and worked up in the usual manner. Distillation produced an oil, 13.4 g, 60.9% [bp 180–187° (0.07 mm)]. *Anal.* ($C_{19}H_{26}N_2O_2$) C, H, N. The **hydrochloride** of **42** had mp 188–190° (EtOH). *Anal.* ($C_{19}H_{27}ClN_2O_2$) C, H, Cl, N. Compounds **40–45** in Table III were synthesized by this method.

3-Diethylcarboxamido-1,2,3,4-tetrahydrocarbazole (45).—To a 500-ml aliquot of the acid chloride of III (R = R′ = H, *ca.* 30.6 g, 0.14 mol) in a 1-l. flask was added a 3 *M* excess (30.7 g) of Et_2NH and the solution refluxed for 1 hr. After cooling, the solution was washed (10% HCl, H_2O, 10% NaOH, and saturated NaCl). The organic layer was dried (Na_2SO_4) and evaporated to an oil which, after distillation [bp 215–220° (0.2 mm)], solidified into a glass; yield, 22 g, 69.9%. Recrystallization produced crystals, mp 130–131° (Et_2O). *Anal.* ($C_{17}H_{22}N_2O$) C, H, N.

3-Diethylaminomethyl-1,2,3,4-tetrahydrocarbazole (46) (VII).—The amide **45** (6 g, 0.02 mol), dissolved in a mixture of dry C_6H_6 (100 ml) and anhyd Et_2O (100 ml), was added to a solution containing 3.5 g of LAH in anhyd Et_2O. After refluxing overnight, the mixture was decomposed with H_2O and worked up in the usual manner. The residue was distilled [bp 150–155° (0.5 mm)] to produce a yellow oil, 4.5 g (87.9%). *Anal.* ($C_{17}H_{24}N_2$) C, H, N. **46**·HCl had mp 221–224° (EtOH). *Anal.* ($C_{17}H_{25}ClN_2$) Cl.

3-Hydroxymethyl-1,2,3,4-tetrahydrocarbazole (47).—Reduction of 12.5 g (0.05 mol) of **3** with 7 g of LAH occurred on refluxing overnight. The carbinol, **47**, mp 95.5–98.° (Et_2O–ligroin), 9.7 g, 92.4%, was obtained on distillation of the residue [bp 167–177° (0.1 mm)]. *Anal.* ($C_{13}H_{15}NO$) C, H, N.

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16-Oxygenated 17α-Methyl-5β-androstanes

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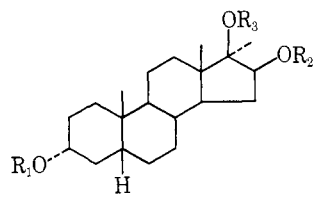
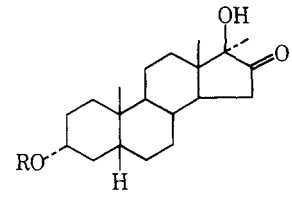
Very recently, we have demonstrated that in rabbits 17α-methyltestosterone, a more potent androgen than testosterone in oral therapy, is converted into 16-oxygenated 17α-methyl-5β-androstanes, **1** and **4**, in high yields, and **6** in very minor yield.[1] The preferential formation of the 16β-hydroxy-5β-steroid to its 16α-hydroxy isomer was the first instance with respect to the metabolism of C_{19} and other steroids in the animal body and seemed to be attributable to a steric effect of the 17α-Me since 16-hydroxylation of C_{19} steroids is known to occur at α *in vivo*[2,3] and *in vitro*.[4–6] Our attention, therefore, has been focused on the role of the 17α-Me in the conversion of 17α-methyltestosterone into **1** and interconversion of **1** into **6** through **4**. Further systematic investigations on this problem were required on these 16-oxygenated steroids, of which **1** has already been synthesized in good yield from 3α,17-dihydroxy-5β-androst-16-ene diacetate.[1] We now wish to report the synthesis of **4**, **6**, and their derivatives.



1, $R_1 = R_2 = R_3 = H$

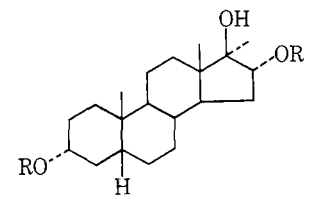
2, R_1 = COPh; R_2, R_3 = $=C(CH_3)_2$

3, R_1 = COPh; $R_2 = R_3 = H$



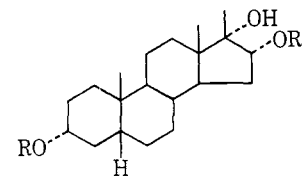
4, R = H

5, R = COPh



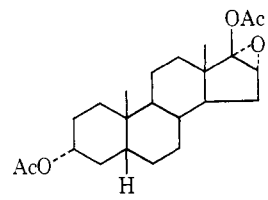
6, R = H

7, R = Ac



8, R = H

9, R = Ac



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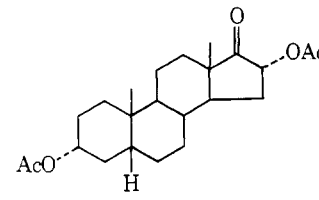

11

The 16α-hydroxy steroid **6** was synthesized by the acid treatment of **10**,[1] followed by the Grignard reaction of the resulting 16α-acetoxy-17-ketosteroid **11**. The reaction of **11** with MeMgI did not proceed stereoselectively and gave a mixture of two triols, **6** and **8**, in a ratio of 3:1, while the same Grignard reaction of 16-epimer of **11** resulted in specific production of **1**. This indicates an interfering effect of the 16α-OH on the α-side attack of the reagent at the 17-C=O. Assignment of the structures of both triols was carried out by the acetonide formation test and comparison of chemical shift value of 18-Me protons of their diacetates, **7**

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and **9**; only **8** gave the corresponding acetonide which showed characteristically increased R_f values on tlc, and the chemical shift value of the 18-CH_3 of **9** was smaller than that of **7**.

The 16-ketosteroid **4** was synthesized from **2** which has been previously described, through a three-step sequence involving mild hydrolysis of the isopropylidenedioxy group, followed by oxidation of the resulting 16β,17β-glycol **3** with cold dilute Jones reagent. The 16-ketosteroid **4** obtained was a glassy solid as observed with the urinary metabolite, their ir spectra being superimposable.

Experimental Section

All melting points were taken with a micro melting point apparatus and are uncorrected. The ir data were obtained on a Hitachi spectrophotometer. Nmr spectra were determined on a Varian HA 100 spectrometer in $CDCl_3$ using TMS as an internal standard. Elemental analyses are indicated only by symbols of the elements, and analytical results obtained were within $\pm 0.4\%$ of the theoretical values.

3α,16α-Diacetoxy-5β-androstan-17-one (11).—To a cold solution of **10** (5 g) in AcOH (30 ml) was added dropwise a cold mixture of AcOH and 60% $HClO_4$ (5:1 ml). After 5 hr, the reaction mixture was diluted with Et_2O, washed (5% $NaHCO_3$), and dried (Na_2SO_4). Evaporation of the solvent gave a solid which was recrystallized from *i*-Pr_2O to yield 3.8 g (76%) of **11**: mp 193–194°; λ_{max}^{KBr} 1747, 1244 cm^{-1}; nmr 0.96 (6 H, s), 2.05 (3 H, s), 2.14 (3 H, s), 4.74 (1 H, septet), 5.39 ppm (1 H, d, J = 7.5). *Anal.* ($C_{28}H_{34}O_5$) C, H.

17α-Methyl-5β-androstane-3α,16α,17β-triol (6).—Compound **11** (3.5 g) was treated with 3.6 equiv of MeMgI in abs Et_2O in the usual manner. The crude product obtained showed two spots at R_f values of 0.55 and 0.31 on silica gel tlc obtained in C_6H_6–EtOAc (1:2). The mixture was then resolved on a silica gel column using C_6H_6–MeAc (4:1) as an eluent; compound **6**, the lower R_f material, was obtained as the second eluate in 2.1 g (73%) yield after elution of the higher R_f material and recrystallized from MeOH: mp 220–221°; λ_{max}^{KBr} 3416, 1058, 1039 cm^{-1}; *Anal.* ($C_{20}H_{34}O_3$) C, H; nmr of diacetate **7**: singlets (3 H) at 0.94 (13-CH_3), 0.97, 1.09, 2.04, 2.12, septet (1 H) at 4.74, doublet (1 H, J = 9) at 5.02 ppm.

17β-Methyl-5β-androstane-3α,16α,17α-triol (8).—Compound **8** was obtained in 0.6 g (21%) yield as the first eluate from the column mentioned above and recrystallized from MeAc–MeOH: mp 241–242°; *Anal.* ($C_{20}H_{34}O_3$) C, H; nmr of diacetate **9**: singlets (3 H) at 0.72 (13-CH_3), 0.95, 1.16, 2.03, 2.13, multiplet (2 H) at 4.99 ppm. Treatment of **8** with acetone containing a catalytic amount of $HClO_4$ (1 drop of the 60% acid to 10 ml of MeAc) increased its R_f value from 0.31 to 0.72 on tlc obtained as mentioned above, while **6** showed the unchanged R_f before and after the same treatment.

3α,17β-Dihydroxy-17α-methyl-5β-androstan-16-one (4).—A suspension of finely pulverized **2**[1] (2 g) in a mixture of 5 *N* HCl (5 ml), MeOH (50 ml), and acetone (100 ml) was refluxed for 2 hr. The reaction mixture, which turned into a homogenous solution, was neutralized ($NaHCO_3$) and filtered. The crude product obtained on evaporation of the solvent from the filtrate was recrystallized from MeOH–AcMe to give **3** in 1.2 g (66%) yield: mp 245–247°; λ_{max}^{KBr} 3521, 1698, 1284, 1073, 1056, 724, 719 cm^{-1}. *Anal.* ($C_{27}H_{38}O_4$) C, H. Compound **3** (1.2 g) was dissolved in a mixture C_6H_6–AcMe (1:2; 50 ml), cooled at −3°, and treated dropwise under stirring with a cooled and diluted Jones reagent, consisting of 160 mg of CrO_3, 1 ml of H_2O, 0.1 ml of H_2SO_4, and AcMe to make a final volume of 10 ml. After 10 min, the reaction was stopped by addition of *i*-PrOH. Usual work-up followed by silica gel column chromatography of the crude product obtained gave **5** and **2** in 0.2 g and 0.6 g yields, respectively. Compound **5**, recrystallized from acetone, melted at 182–183°: λ_{max}^{KBr} 3488, 1754, 1706, 1074, 1023 cm^{-1}; nmr singlets (3 H) at 0.80, 1.11, 1.20, septet (1 H) at 4.82, singlet at 7.75 ppm. *Anal.* ($C_{27}H_{36}O_4$) C, H. Hydrolysis of **5** in a refluxing mixture of acetone and methanolic KOH gave a glassy solid **4** in 60 mg yield. The ir spectrum of **4** was superimposable with the previously reported urinary metabolite.[1]

Synthesis of 1-(3′-*N*,*N*-Diethylaminopropyl)-2-alkylnaphth[1,2-*d*]imidazole-4,5-diones[1]

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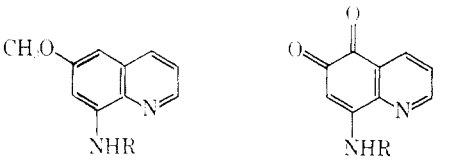
The therapeutic activity of the important 6-methoxy-8-alkylaminoquinoline antimalarial agents (I) has been attributed to their *in vivo* conversion into 5,6-quinolinequinones (II).[2,3] This information in combination with the fact that certain imidazole and benzimidazole derivatives have shown slight antimalarial activity[4,5] led us to prepare some 4-(3′-*N*,*N*-diethylaminopropylamino)-3-acylamino-1,2-naphthoquinones (III) and 1-(3′-*N*,*N*-diethylaminopropyl)-2-alkylnaphth[1,2-*d*]-



I II

imidazole-4,5-diones (IV) for evaluation as potential antimalarial agents.

The synthetic procedure reported earlier[6] for the preparation of disubstituted naphth[1,2-*d*]imidazole-4,5-diones and outlined in Scheme I was used to synthesize the compounds III and IV listed in Tables I and II, respectively. Specific N-monoacylation of 3-amino-1,2-naphthalenediol hydrochloride (V) followed by oxidation gave the 3-acylamino-1,2-naphthonaphthoquinones (VI). The addition of 3-diethylaminopropylamine to VI in $CHCl_3$ followed by exposure of the reaction mixture to O_2 gave the addition products III. Treatment of III with refluxing AcOH followed by chromatography on Al_2O_3 afforded the imidazole derivatives IV.

Compounds IIIb and e and IVa, b, d, e, and f were screened for potential antimalarial activity against *Plasmodium berghei* in mice.[7,8] Compounds IIIb and

(1) This investigation was carried out under Contract No. DADA-17-68-C-8055 with the Department of the Army and the U. S. Army Research and Development Command. This paper is Contribution No. 708 from the Army Research Program on Malaria.

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(3) Schönhöfer postulated that the action of 6-methoxy-8-aminoquinolines was related to the formation of quinonoid products in the host (ref 2a). *In vitro* studies reported by Drake and Pratt supported Schönhöfer's hypothesis (ref 2b). Additional supporting evidence was brought forth by Josephson *et al.* (ref 2c), when they identified a highly active pamaquine metabolite as the 5,6-quinolinequinone derivative. *In vitro* tests showed that its antimalarial activity against *P. gallinaceum* was about 16 times that of pamaquine (ref 2d).

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(5) 2,2′-(Vinylenedi-*p*-phenylene)bis(4-methylimidazole) showed a quinine equivalent of 10Q and 5-chloro-1-(4-diethylamino-1-methylbutyl)-benzimidazole showed an activity of 0.4Q against *P. lophurae* in ducks (ref 4).

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