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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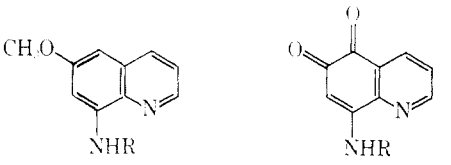
The therapeutic activity of the important 6-methoxy-8-alkylaminoquinoline antimalarial agents (I) has been attributed to their *in vivo* conversion into 5,6-quinolinequinones (II).[2,3] This information in combination with the fact that certain imidazole and benzimidazole derivatives have shown slight 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.

(2) (a) F. Schönhöfer, *Z. Physiol. Chem.*, **274**, 1 (1942). (b) N. L. Drake and Y. T. Pratt, *J. Amer. Chem. Soc.*, **73**, 544 (1951). (c) E. S. Josephson, J. Greenberg, D. J. Taylor, and H. L. Bami, *J. Pharmacol. Exp. Ther.*, **103**, 7 (1951). (d) E. S. Josephson, D. J. Taylor, J. Greenberg, and A. P. Ray, *Proc. Soc. Exp. Biol. N. Y.*, **76**, 700 (1951).

(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).

(4) F. Y. Wiselogle, "A Survey of Antimalarial Drugs: 1941–1945," Vol. II, J. W. Edwards, Ann Arbor, Mich., 1946.

(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).

(6) F. I. Carroll and J. T. Blackwell, to be published in *J. Heterocycl. Chem.*

(7) Testing was carried out by Dr. L. Rane of the University of Miami, Miami, Fla.

(8) T. S. Osdene, P. B. Russell, and Leo Rane, *J. Med. Chem.*, **10**, 431 (1967).

TABLE I
4-(3′-*N*,*N*-DIETHYLAMINOPROPYLAMINO)-3-ACYLAMINO-1,2-NAPHTHOQUINONES (III)

Compound[a] III	R	Recrystn solvent	Mp °C	% yield[b]	Molecular formula[c]
a	CH_3	CH_2Cl_2–EtOAc	144–148	47	$C_{19}H_{25}N_3O_3 \cdot 0.5H_2O$
b	$CH_3(CH_2)_4$	CH_2Cl_2–EtOAc	149–151	46	$C_{23}H_{33}N_3O_3 \cdot 0.5H_2O$
c	$C_6H_5CH_2$		*d*		
d	3,4,5-$(CH_3O)_3$-$C_6H_2CH_2$		*d*		
e	$C_6H_5CH{=}CH$	CH_2Cl_2–EtOAc	148–150	70	$C_{26}H_{29}N_3O_3 \cdot 0.25H_2O$
f	$C_6H_{11}(CH_2)_3$	C_6H_6	127–128	40	$C_{27}H_{39}N_3O_3 \cdot 0.25H_2O$
g	C_6H_{11}	CH_2Cl_2–EtOAc	156–158	59	$C_{24}H_{33}N_3O_3 \cdot 0.25H_2O$

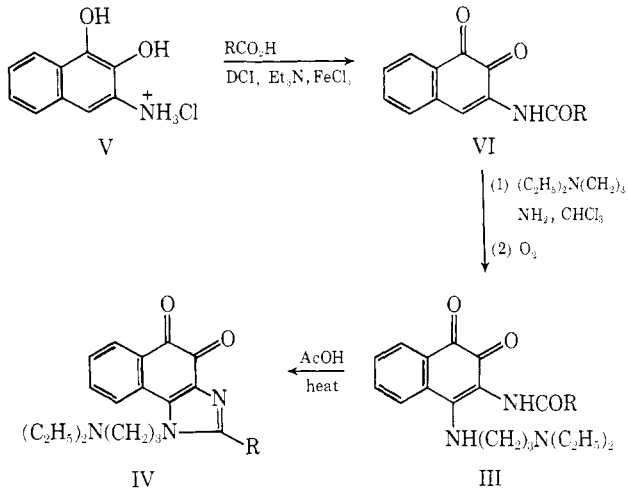
[a] A typical procedure is given in the Experimental Section. [b] Based on pure compound isolated. [c] Analyzed for C, H, N (see ref 11). [d] These compounds were not obtained analytically pure.

TABLE II
1-(3′-*N*,*N*-DIETHYLAMINOPROPYL)-2-ALKYLNAPHTH[1,2-*d*]IMIDAZOLE-4,5-DIONES (IV)

Compound IV[a]	R	Mp, °C	% yield[b]	Molecular formula[c]
a	CH_3	143–147	66	$C_{19}H_{23}N_3O_2$
b	$CH_3(CH_2)_4$	138–141	72	$C_{23}H_{31}N_3O_2$
c	$C_6H_5CH_2$	141–143	12[d]	$C_{25}H_{27}N_3O_2$
d	3,4,5-$(CH_3O)_3$-$C_6H_2CH_2$	176–179	40[d]	$C_{28}H_{33}N_3O_5$
e	$C_6H_5CH{=}CH$	193–196	24	$C_{26}H_{27}N_3O_2$
f	$C_6H_{11}(CH_2)_3$	119–121	60	$C_{27}H_{37}N_3O_2$
g	C_6H_{11}	121–124	53	$C_{24}H_{31}N_3O_2$

[a] A typical procedure is given in the Experimental Section. [b] Based on pure compound isolated. [c] Analyzed for C, H, N (see ref 11). [d] The intermediate 3-alkylamino-3-acylamino-1,2-naphthoquinone was not isolated in these cases and the yield is based on starting 3-acylamino-1,2-naphthoquinone.

SCHEME I



c and IVa–f were also evaluated for activity against chicks infected with *Plasmodium gallinaceum*.[7,8] None of the structures prepared in this study were considered active in either the forementioned rodent or avian screen.[9,10]

(9) Test results were supplied through the courtesy of Dr. B. T. Poon, Dr. T. R. Sweeney, and Dr. David P. Jacobus, Walter Reed Army Institute of Research, Washington, D. C.

(10) In addition to the compounds prepared in this report, several 3-acylamino-1,2-naphthoquinones, 4-alkylamino-3-acylamino-1,2-naphthoquinones, and 1,2-disubstituted naphth[1,2-*d*]imidazole-4,5-diones described in an earlier publication (ref 6) were also screened against *P. berghei* and *P. gallinaceum*. These classes of compounds were uniformly inactive in these tests.

Experimental Section[11]

Melting points were determined on a Kofler hot stage microscope using a calibrated thermometer. Uv and visible spectra were measured on a Cary Model 14 spectrophotometer. The visible spectra were obtained only in MeOH. Nmr spectra were recorded on a Varian Model A-60 (Me_4Si). Ir spectra were measured with a Perkin-Elmer 221 spectrophotometer (KBr). Mass spectra were determined on an AEI MS-902 spectrometer. Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Ill. All uv, ir, nmr, and mass spectra are in agreement with the assigned structures.

3-Amino-1,2-naphthohydroquinone hydrochloride (V) was prepared according to the procedure of Groves.[12] A 150-g sample of V as well as 3-diethylaminopropylamine was supplied through the courtesy of Dr. B. T. Poon of the Walter Reed Army Institute of Research. 3-Acetamino-, 3-(3,4,5-trimethoxyphenylacetamino)-, 3-cinnamoylamino-, and 3-(4-cyclohexylbutanonylamino)-1,2-naphthoquinone were prepared as reported in an earlier publication.[6]

3-Hexanoylamino-1,2-naphthoquinone.—To a suspension of 4.24 g (20 mmol) of 3-amino-1,2-naphthalenediol·HCl and 20 mmol of the appropriate carboxylic acid in 80 ml of EtOAc was added 2.02 g (20 mmol) of Et_3N followed by 4.14 g (20 mmol) of DCI. The mixture was stirred at 25° under N_2 for 6 hr and filtered, and the filtrate concentrated on a rotary evaporator. The residue was dissolved in 100 ml of EtOH, cooled in an ice bath, and treated with a cold solution of 12 g of $FeCl_3 \cdot 6H_2O$ in 100 ml of H_2O containing 1 ml of concentrated HCl. The mixture was extracted with $CHCl_3$. The $CHCl_3$ extracts were dried (Na_2SO_4) and concentrated to give the 3-acylamino-1,2-naphthoquinones as dark solids. The products were purified by recrystallization (EtOH). The new 3-acylamino-1,2-naphthoquiones prepared are listed in Table III.

TABLE III
3-ACYLAMINO-1,2-NAPHTHOQUINONES

Compound[a] VI	R	Mp, °C	% yield[b]	Molecular formula[c]
b	$CH_3(CH_2)_4$	156–158	32	$C_{16}H_{17}NO_3$
c	$C_6H_5CH_2$[d]	174–176 dec	37	$C_{18}H_{13}NO_3$
g	C_6H_{11}	153–156	16	$C_{17}H_{17}NO_3$

[a] A general procedure is given in the Experimental Section. [b] Based on pure compound isolated. [b] Analyzed for C, H, N (see ref 11). [d] A solution of 6 g of $Na_2Cr_2O_7$ in 140 ml of 2 *N* H_2SO_4 was used in place of $FeCl_3$ as the oxidant.

4-(3-*N*,*N*-Diethylaminopropylamino)-3-hexanoylamino-1,2-naphthoquinone (IIIb).—A solution of 4.58 g (16.9 mmol) of 3-hexanoylamino-1,2-naphthoquinone and 2.20 g (16.9 mmol) of $Et_2N(CH_2)_3NH_2$ in 200 ml of $CHCl_3$ was stirred for 7 hr at 25°. It was concentrated on a rotary evaporator and the remaining dark residue was dried under high vacuum. Recrystallization of this solid from a CH_2Cl_2 and EtOAc mixture gave 3.01 g (46%) of IIIb, mp 149–151°. The analytical sample prepared

(11) Where analyses are indicated only by symbols of the elements, analytical results obtained for those functions were within ±0.4% of the theoretical values.

(12) C. E. Groves *J. Chem. Soc.*, 291 (1884).

by recrystallization from the same solvent systems had mp 150–152°; ν_{max}^{KBr} 3265 (NH), 1690 (amide I), 1665 (C=O), 1615 and 1590 (C=C), and 1530 cm^{-1} (amide II); $\lambda_{max}^{CH_3OH}$ 239 mμ (ε × 10^{-3} = 17.8), 278 (18.6), and 455 (3.7).

The 4-(3-*N*,*N*-diethylaminopropylamino)-3-acylamino-1,2-naphthoquinones listed in Table I were synthesized by an analogous procedure.

1-(3′-*N*,*N*-Diethylaminopropyl)-2-pentylnaphth[1,2-*d*]imidazole-4,5-dione (IVb).—A solution of 2.51 g, 6.1 mmol, of IIIb in 200 ml of AcOH was refluxed for 0.5 hr. It was concentrated by freeze-drying and the remaining residue was chromatographed on 400 g of Al_2O_3 using $CHCl_3$ as the eluent. A red band was collected. Removal of the $CHCl_3$ on a rotary evaporator followed by recrystallization of the remaining red crystals from EtOAc gave 1.69 g (72%) of IVb, mp 138–141°. The analytical sample prepared by recrystallization from EtOAc had mp 140–142°, ν_{max}^{KBr} 1670 cm^{-1} (C=O); λ_{max}^{MeOH} 261 mμ (ε × 10^{-3} 22.6), 269 (22.2), and 449 (1.4); $\lambda_s^{CH_3OH}$ 253 (20.2); $\lambda_{max}^{0.1\ N\ HCl}$ 254 (24.0); λ_{max}^{pH7} 261 (22.8) and 268 (21.8); λ_s^{pH7} 253 (19.6); $\lambda_{max}^{0.1\ N\ NaOH}$ 240 (17.9) and 260 (14.6); $\lambda_s^{0.1\ N\ NaOH}$ 267 (13.1).

The 1-(3′-*N*,*N*-diethylaminopropyl)-2-alkylnaphth[1,2-*d*]imidazole-4,5-diones listed in Table II were synthesized by an analogous procedure.

Acknowledgment.—We thank Dr. Monroe E. Wall, Director of this laboratory, for his kind encouragement and support of this work.

Analogs of Steroid Hormones. III. Benz[*e*]indene Derivatives[1,2]

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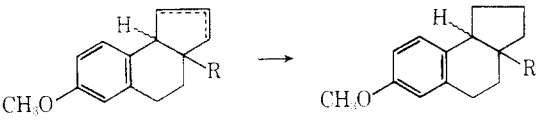
In view of the reported antiandrogenic activity of a 7-acetyl-2(3H)-phenanthrene derivative,[3] we became interested in preparing benz[*e*]indene analogs for purposes of comparison. We were also interested in developing methods for preparing compounds having angular carboalkoxy and carbinol groups. Starting with 3,4-dihydro-6-methoxy-1(2H)-naphthalenone (**2**), suitably substituted benz[*e*]inden-2-one derivatives were first prepared using Scheme I. Alkylation of the starting ketone with propargyl bromide followed by hydration of the product alkyne appeared to be the most convenient approach for the introduction of a propanone side chain. The method has been used by Islam,[4] Dauben,[5] and coworkers, but only on β-keto esters using alkoxide catalysts. We also wished to use the method on ketones such as **4**, which require more basic conditions for alkylation.

Catalytic hydrogenation of **9** and **10** produced mixtures from which both *cis* and *trans* isomers could be isolated and compared. All attempts to obtain both isomers of **11** from **8**, however, were unsuccessful, although five different methods involving catalytic and chemical were used, including one reduction in which the double bond was shifted to the *endo* position.[6]

These hydrogenation results are intermediate between those of simple hydrindenones and 16-keto steroid analogs. Augustine[7] found that the former formed only *cis* isomers even when an angular carbomethoxy group was present. Wilds[8] and ourselves[9] have found both *cis* and *trans* isomers formed from the hydrogenation of Δ^{14}-16-keto steroids, even when no angular group was present. Augustine[10] proposed a multistep process in which the catalyst–substrate complex is less hindered in the *cis* configuration. Wilds attributed some of his results to steric inhibition of adsorption on the catalyst by the angular group, thus resulting in the formation of *trans* isomers. This could explain the results from the hydrogenation of **9** and **10**, but the failure to obtain any *trans* isomer of **11** by any of the above methods could be explained by thermodynamic control of the reduction to give the more stable *cis* isomer with the hydrogenations occurring by some multistep process.

In an attempt to change the isomer ratios obtained, the hydroborations of **8** and **9** were studied. The boron residues were removed by acetolysis to produce mixtures of the alkenes, **14** and **15**. It proved impossible



14, R = H
15, R = CH$_3$

16, R = H
17, R = CH$_3$

to remove B without loss of the O functions. Analysis of **14** and **15** by glpc showed that all four possible isomers were present in substantial amounts in each case. Analysis showed that **16** contained about equal amounts of the *cis* and *trans* isomers, while **17** was 70% *trans*. Conversion of **11** into **16** produced a single isomer, corresponding to the faster moving isomer on glpc, and thus may be assigned the *cis* configuration.

The *cis* and *trans* isomers of **12** and **13** were distinguished by the following method. Since the *trans* isomers are more highly strained than the *cis*, the carbonyl stretch bands in the ir spectra should have the higher frequency.[11] The actual frequencies were 1747 and 1741 cm^{-1} for the presumed *trans* isomers and 1742 and 1737 cm^{-1} for the *cis* isomers, respectively. The half-height width of the angular methyl peak in the nmr spectrum of the presumed *trans* isomer of **12** was also greater than the *cis* by 0.2 cps.[12,13] The configura-

(1) Supported, in part, by Grant CA-05077, National Cancer Institute, National Institutes of Health.

(2) For the previous paper of this series, see R. E. Juday, L. Cubbage, J. Mazur, and B. Bukwa, *J. Med. Chem.*, **11**, 872 (1968).

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(10) For more complete discussion of the stereochemistry of the reduction of cyclic ketones, see: (a) R. L. Augustine, "Catalytic Hydrogenation," Marcel Dekker, Inc., New York, N. Y., 1965, pp 61–62; (b) R. L. Augustine and J. Van Peppen, *Ann. N. Y. Acad. Sci.*, **158**, 482 (1969); (c) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, pp 16–22.

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