surface area measurements of Villalonga; these same authors speculate that the loss of coplanarity resulting from the repulsion interferes with resonance stabilization of the free radical. Such an explanation is consistent with the finding here that radicals with isopropyl or isobutyl moieties between the N atom at the 10 position and that in the 10-alkyl substituent are less stable than those radicals with *n*-propyl and *n*-butyl moieties. The slowly decaying radical which appears most appropriate for further study as an enzyme inhibitor is that of XX; one could not design a more stable radical, unless stability should continue to increase with progressive lengthening of the "inter-N" distance. An appropriate unstable free radical may be found among the radicals prepared from the promethazine derivatives.

It has been suggested that oxidation of chlorpromazine to a free radical is a transformation essential both to the activity and the metabolism of the drug.[16] That a ranking of phenothiazine tranquilizers by the usual antipsychotic dose[17] appears much different from the ranking of these same drugs according to the stability of the free radicals generated from them cannot be taken as evidence against an important role of the free radical in drug action. The therapeutic activity of a drug depends on many factors—*e.g.*, the rate at which the drug is absorbed from the gastrointestinal tract and the degree of binding to plasma and tissue proteins—in addition to the potency of the drug at its site of action. The demonstration by Tozer and his coworkers[18] that the activity of phenothiazine anthelmintics is related to the free radical concentration is of interest in this context. It now appears important to compare the radicals described in this present report for their potency as inhibitors of an appropriate oxidoreductase.

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Relative Carcinogenicity of Some Diethylbenz[*a*]anthracenes†

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Four novel diethyl derivatives of benz[*a*]anthracene, 6,8-, 7,8-, 7,9-, and 8,12-diethylbenz[*a*]-anthracenes, were synthesized and tested for sarcomagenic activity. The hypothesis that a dialkyl derivative of benz[*a*]anthracene would be active only if the thickness of either the convex side of the molecule (positions 6, 7, 8) or of the concave one (positions 1, 11, 12) did not exceed 4 Å, *i.e.*, the thickness of the methyl group, could not be confirmed.

7,12-Dimethylbenz[*a*]anthracene (7,12-DMBA) is the most potent of the known carcinogenic polynuclear aromatic hydrocarbons. Conversely, 7,12-diethylbenz[*a*]-anthracene (7,12-DEBA) is completely devoid of carcinogenic properties. The activity of 7-ethyl-12-methylbenz[*a*]-anthracene is comparable to that of the 7,12-dimethyl derivative and 7-methyl-12-ethylbenz[*a*]anthracene is a potent carcinogen, although somewhat less so. These observations suggested the hypothesis that molecular thickness may be an important factor in eliciting carcinogenic activity so that a dialkyl derivative of benz[*a*]anthracene would be active only if the thickness of either the convex side of the molecule (positions 6, 7, 8) or of the concave one (positions 1, 11, 12) did not exceed 4 Å, *i.e.*, the thickness of the methyl group.[1] In order to test the validity of this hypothesis, we synthesized 6,8-, 7,9-, and 8,12-diethylbenz[*a*]anthracenes for biological evaluation.‡

6,8-DEBA was synthesized, starting from *p*-bromopropiophenone (1) which reacted with benzylmagnesium chloride (2) to give 1-ethyl-1-(*p*-bromophenyl)-2-phenylethylene (3). The stilbene derivative 3 was photochemically cyclized in the presence of iodine[3] to 3-bromo-10-ethylphenanthrene (4). The Grignard derivative of 4 gave with succinic anhydride 4-oxo-4-[3-(10-ethyl)phenanthryl]-butyric acid (5), albeit in very poor yield. Wolff-Kishner reduction converted 5 to 4-[3-(10-ethyl)phenanthryl]-butyric acid (6). Cyclization of 6 with anhydrous HF led to 6-ethyl-8-oxo-8,9,10,11-tetrahydrobenz[*a*]anthracene (7). Reaction of the ketone with ethylmagnesium bromide afforded 6,8-diethyl-8-hydroxy-8,9,10,11-tetrahydrobenz[*a*]anthracene (8). Finally, 6,8-diethylbenz[*a*]anthracene (9) was obtained by simultaneous dehydrogenation-dehydration of the alcohol 8 with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.[4]

The starting material for the synthesis of 7,9-DEBA was 4-ethylaniline (10) which was first brominated[5] to 2-bromo-4-ethylaniline (11). The amino group was substituted by the cyano group[6] to give 3-bromo-4-cyanoethylbenzene (12). Treatment of 12 with 1-naphthylmagnesium bromide

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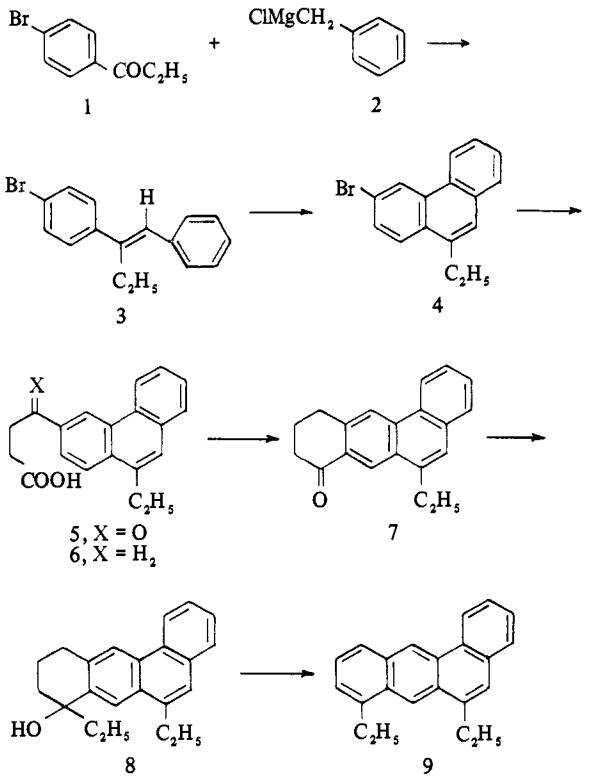
‡We included 7, 9-DEBA because in the trimethyl series, an additional methyl in position 9 seems to enhance sarcomagenic potency.[2]



gave 3-bromo-4-(1-naphthoyl)ethylbenzene (13). 3-Cyano-4-(1-naphthoyl)ethylbenzene (14) was obtained from 13 by treating it with cuprous cyanide in dimethyl formamide. Hydrolysis of the nitrile group led to 2-(1-naphthoyl)-5-ethylbenzoic acid (15). The keto group in 15 was reduced with zinc and alkali, affording 2-(1-naphthylmethyl-5-ethylbenzoic acid (16). Treatment of 16 with anhydrous HF gave a mixture of the anthrone 17 and the phenol 17a as seen in the infrared spectrum of the crude mixture. The latter was treated with ethylmagnesium bromide without further purification. Pure 7,9-DEBA (18) was secured from the products after chromatography. Considering the great susceptibility of the Grignard reactions to steric hindrance,[7] we expected that 1-naphthylmagnesium bromide would react preferentially with the unhindered carbonyl group of 3-ethylphthalic anhydride (19). In fact, from the reaction mixture, only one product was isolated in 75% yield, and the structure of 1-(1-naphthoyl)-6-ethylbenzoic acid (20) was assigned to it. Reduction of the keto group in 20 with zinc-copper couple in alkaline solution afforded 2-(1-naphthylmethyl)-6-ethylbenzoic acid (21) which did not crystallize. The crude acid was cyclized with anhydrous HF to the crystalline anthrone 22; 7,8-DEBA (23) was obtained from 22 by reaction with ethyllithium.

The keto acid 20 also served as starting material for the synthesis of 8,12-DEBA. Grignard reaction with ethylmagnesium bromide gave the lactone 24 which could not be obtained in crystalline form, probably due to contamination with the reduction product of 20, 2-(1-hydroxy-1-naphthylmethyl)-6-ethylbenzoic acid lactone. The mixture was submitted to reduction with zinc and alkali to give 2-(1-naphthylpropyl)-6-ethylbenzoic acid (25) in 40% yield from 20. The acid 25 was cyclized to 8,12-diethylbenz[*a*]-anthr-7-one (26) with anhydrous HF. This product, which did not crystallize, was reduced to the anthrol 27 with zinc-copper couple in alkaline medium. Finally, 8,12-DEBA (28) was obtained on dehydration of 27 with TSOH in benzene solution.

Table I. Induction of Spindle-Cell Sarcoma[a]

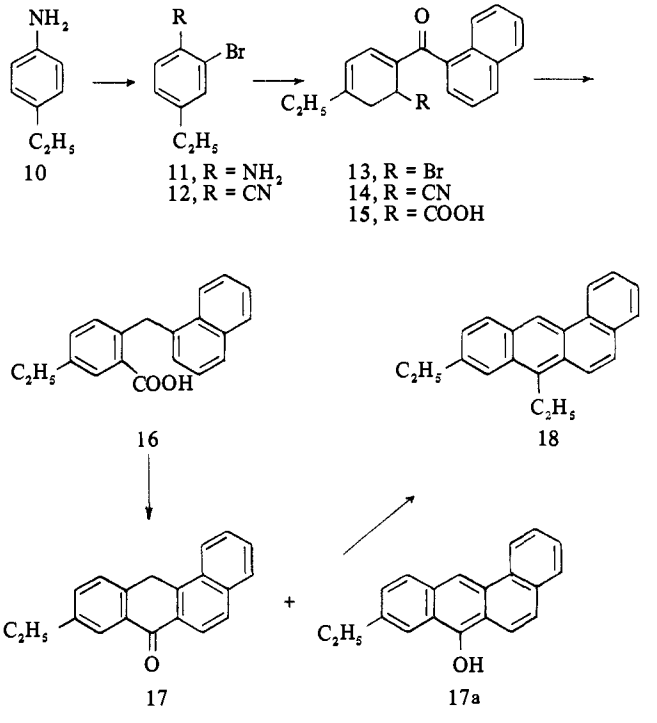
Compound	No. of rats	No. with sarcoma	Range, days
7, 12-DMBA[b]	20	20	67-116
7-Et-12-MeBA[b]	15	15	68-95
7-Me-12-EtBA[b]	7	4	162-182
7, 12-DEBA[b]	24	0	
6, 8-DMBA[c]	8	8	95-123
6, 8-DEBA (9)	16	15	41-199
7, 8-DMBA[c]	7	7	82-137
7, 8-DEBA (23)	16	0	
7, 9-DEBA (18)	16	0	
8, 12-DMBA[c]	8	8	85-109
8, 12-DEBA (24)	8	6	102-197

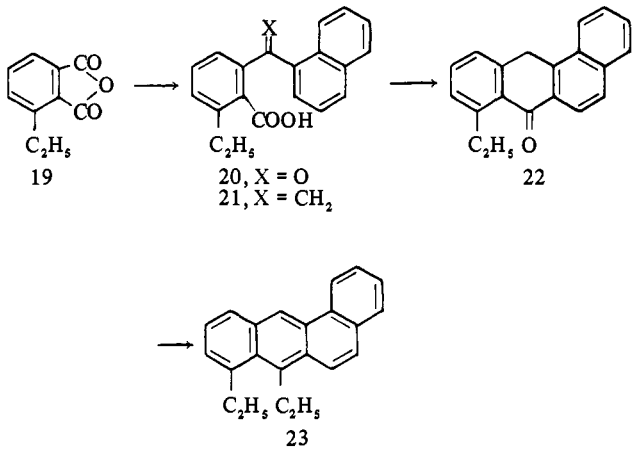
[a] It should be noted that there are instances in which a polynuclear aromatic hydrocarbon has induced tumors by skin painting, but not by single injection, and *vice versa*. However, our results strictly hold for sarcomagenic activity. [b] Ref 1. [c] Ref 2.

Biological Activity. There were 8 to 16 male rats, Long-Evans strain, 24-25 days old, in each experiment. On day 0, the rats were injected intramuscularly in a hind leg with the solution of 2.5 mg of hydrocarbon in sesame oil. The animals were sacrificed on day 270 unless sarcomas were detected by palpation earlier. Necropsy was performed on every rat. The sarcomagenic activities of the diethylbenz[*a*]-anthracenes are summarized in Table I. For comparison's sake, data for 6,8-, 7,8-, 7,12-, and 8,12-DMBA, 7-ethyl-12-methylbenz[*a*]anthracene, 7-methyl-12-ethylbenz[*a*]-anthracene, and 7,12-DEBA are also included.[1,8]

The results indicate no simple correlation between position of the ethyl groups and carcinogenic activity of the diethylbenz[*a*]anthracenes tested. Though 6,8-DEBA is a strong carcinogen and its concave side is not thicker than 4.0 Å, 7,8-DEBA and 7,9-DEBA, which also fulfill this prerequisite, are inactive. On the other hand, 8,12-DEBA, which is thicker than 4 Å on both sides and was consequently expected to lack carcinogenic properties, was found to be active.

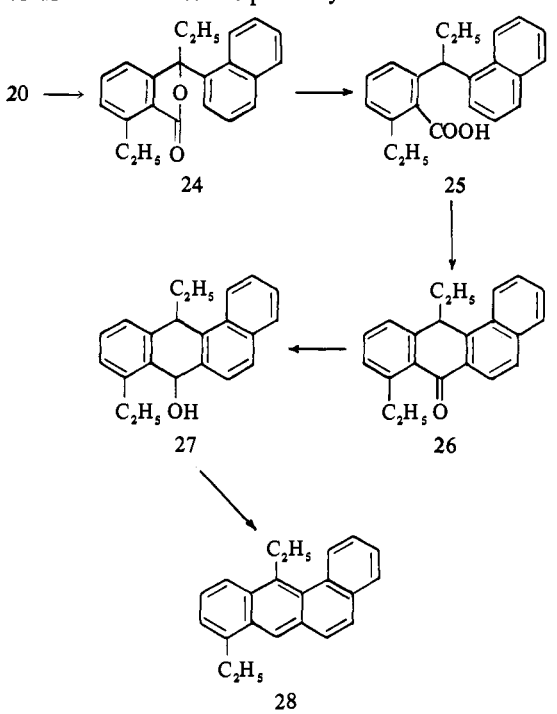
It is generally accepted that to be carcinogenic, polycyclic aromatic hydrocarbons undergo metabolic activation.[9]





19 20, X = O 21, X = CH_2 22 23

Boyland proposed involvement of reactive epoxides.[10] Brookes and coworkers suggested that methylated hydrocarbons are metabolically activated by formation of carbonium ions.[11] Mono- and dimethyl substituents activate the benz[*a*]anthracene moiety, especially in the "critical" region (*i.e.*, 6, 7, 8, 12 positions).[1,8] In the case of diethyl derivatives, no analogous region seems to exist, 7,8-DEBA being inactive. Moreover, sarcomagenic inactivation, the overriding consequence of alkyl interference, occurs in derivatives having an ethyl group at position 7 of the compounds tested in our system. It appears that ethyl substituents can affect the formation of obligatory intermediates in the transformation process to the proximate carcinogen. The difference in activity between dimethyl- and diethylbenz[*a*]anthracenes might also be due to different metabolic pathways.



20 24 25 27 26 28

Experimental Section§

1-Ethyl-1-(*p*-bromophenyl)-2-phenylethylene (3). To a stirred soln of 100 g (0.47 mole) of *p*-bromopropiophenone (1) in 300 ml of anhyd C_6H_6 900 ml (0.9 mole) of a 1 *M* soln of benzylmagnesium chloride (2) in Et_2O was slowly added. The soln was then refluxed for 3 hr with stirring. After cooling, the mixture was decomposed with 500 ml of a 15% HCl soln. The organic layer was washed with H_2O and dried (Na_2SO_4). The solvents were evapd. The residue was dissolved in 400 ml of dry C_6H_6, 4.0 g of TsOH was added, and the soln was heated to reflux for 2 hr. The soln was washed twice with H_2O and dried (Na_2SO_4). After the solvent was removed, the residue (135.7 g) was distilled *in vacuo*. The bulk, 74.4 g, distilled between 140 and 145° (0.65 mm). After standing in the cold room for several days, most of the product crystd. A small amount of hexane was added and the cryst material separated by filtration: yield 56.1 g (41.6%); mp 74–75°. The analytical sample melted at 76–77° (from hexane). *Anal.* ($C_{16}H_{15}Br$) C, H, Br.

3-Bromo-10-ethylphenanthrene (4). To a soln of 13.5 g (0.047 mole) of 3 in 4 l. of cyclohexane, 0.275 g of I_2 was added and the soln was stirred and irradiated for 48 hr with a 200-W photochemical lamp, Hanovia No. 654A-36, contained in a water-cooled quartz immersion well. The soln was passed through a short column of alumina, and the solvent was evapd *in vacuo*. The residue was crystd from hexane: yield 7.55 g (55.9%); mp 88.5–89.5°. The analytical sample melted at 90–91°. *Anal.* ($C_{16}H_{13}Br$) C, H, Br.

4-Oxo-4-[3-(10-ethyl)phenanthryl]butyric Acid (5). To a stirred suspension of 5.84 g (0.24 g-atom) of Mg turnings in 25 ml of Et_2O, a soln of 34.20 g (0.12 mole) of 4 and 18.78 g (8.65 ml, 0.10 mole) of CH_2Br_2 in 50 ml of C_6H_6 and 30 ml of Et_2O was added over a period of 70 min, while the soln was gently boiled. The mixture was then refluxed for 4.5 hr. Most of the Mg remained undissolved. The mixture was diluted with 100 ml of C_6H_6 and filtered under nitrogen into a well-stirred suspension of 12.0 g (0.12 mole) of succinic anhydride in 150 ml of C_6H_6. The mixture was stirred at reflux temp for 3 hr. After cooling in an ice bath, the reaction mixture was decomposed with 250 ml of a 10% HCl soln. The organic layer was extracted 3 times with a 5% soln of Na_2CO_3. The aqueous soln was acidified with HCl and the amorphous product which separated was filtered off, washed with H_2O, and dried (Na_2SO_4). The product, 6.52 g, crystd from C_6H_6, giving 1.96 g (8.5%) of 5: mp 146.5–148.5°. Twice recrystd, the analytical sample melted at 150–151°. *Anal.* ($C_{20}H_{18}O_3$) C, H. From the neutral soln 12.90 g of starting material was recovered.

6-Ethyl-8-oxo-8,9,10,11-tetrahydrobenz[*a*]anthracene (7). A mixture of 1.82 g (6 mmoles) of 5, 1.40 g of NaOH, and 1.0 ml of 85% hydrazine hydrate in 15 ml of diethylene glycol was refluxed for 1 hr at a bath temp of 163–170°. The temp of the oil bath was then raised to 203–205° in 35 min, H_2O and excess reagent being allowed to evaporate. The soln was stirred at 200° interior temp for 4 hr. After cooling, the soln was poured into H_2O and made acid with 2 *N* HCl, and the mixture was allowed to stand 48 hr in the cold room. The amorphous precipitate was filtered off, washed well with H_2O, and dried. The crude 4-[3-(10-ethyl)phenanthryl]-butyric acid (6) weighed 1.71 g.

The crude product was dissolved in about 20 ml of anhyd HF, and the HF was allowed to evaporate. The solid residue was dissolved in CH_2Cl_2 and the soln was washed with Na_2CO_3 soln and with H_2O. After drying (Na_2SO_4), the solvent was evaporated, and the residue was dissolved in Et_2O and filtered through a column of 20 g of alumina. The filtrate was evapd and the residue, 1.26 g, was crystd from Me_2CO–hexane: yield 0.98 g of 7; mp 145.5–147.5°. The analytical sample melted at 147–148.5°. *Anal.* ($C_{20}H_{18}O$) C, H.

6,8-Diethylbenz[*a*]anthracene (9). To a soln of 4 ml of 3 *M* EtMgBr in 10 ml of C_6H_6 and 20 ml of Et_2O, 0.90 g of 7 was added at once. The soln was stirred in a nitrogen atm for 2.5 hr at room temp. The reaction mixture was decomposed with a 5% HCl soln, and after the usual work-up, 1.02 g of crude 6,8-diethyl-8-hydroxy-8,9,10,11-tetrahydrozenz[*a*]anthracene (8) was obtained as a colorless foam.

The foam was dissolved in 30 ml of anhyd C_6H_6 and refluxed with 0.874 g (1.1 mole equiv) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone for 3 hr under nitrogen. The mixture was allowed to stand at room temp overnight. The hydroquinone which separated was filtered off (weight 0.74 g), and the filtrate was diluted with Et_2O and washed with a 2% NaOH soln and with H_2O. After drying (Na_2SO_4), the solvents were evapd. The residue, 0.85 g, was chromatographed on 30 g of alumina. The petroleum ether–20% Et_2O eluates (0.51 g) gave from hexane 0.33 g (35.5%) of 9: mp 99–102°. One additional crystn gave 0.29 g of pure hydrocarbon: mp 102–104°; nmr δ1.45 (m, 6), 3.21 (m, 4). *Anal.* ($C_{22}H_{20}$) C, H.

2-Bromo-4-ethylaniline (11). A soln of 484.7 g (4.0 moles) of *p*-ethylaniline in 1600 ml of glacial AcOH was heated at reflux for 2 hr. The soln was cooled to 45°, and 650 g (204 ml; 4.06 moles) of bromine was added at such a rate that the temp of the soln was

§ All mp were determined on a Buchi capillary mp apparatus and are uncorr. The structures of the compounds were supported by ir and nmr spectra, obtained on a Perkin-Elmer Model 137 Infracord Spectrometer and a Varian A-60 Spectrometer, respectively. Where analyses are indicated only by symbols of the element, analytical results obtained for these elements were within ±0.4% of the theoretical values.

maintained at 50–55° (duration 2.25 hr). The soln was stirred for 30 min more and was set aside at room temp overnight. The soln was run into 16 l. of H_2O containing 50 g of $NaHSO_3$. The precipitate was filtered off, washed well with H_2O, and dried at room temp for 48 hr. The crude product was dissolved in 1 l. of warm EtOH and 1 l. of concd HCl was added. The soln was refluxed for 3 hr. After cooling, the cryst hydrochloride was filtered off and washed with two 200-ml portions of ice-cold EtOH. The product was air-dried for 24 hr.

The hydrochloride (418.0 g) was suspended in 1500 ml of H_2O, a soln of 280 g of NaOH in 1000 ml of H_2O was added, and the mixture was stirred for 15 min. The aqueous layer was decanted, and the remaining brownish oil was dried with NaOH pellets and was then distilled *in vacuo*. 2-Bromo-4-ethylaniline distilled at 149–151° (25 mm): yield 277.8 g (34.7%). *Anal.* ($C_8H_{10}BrN$) C, H, Br, N.

3-Bromo-4-cyanoethylbenzene (12). 2-Bromo-4-ethylaniline (200.8 g; 1.0 mole) was mixed with 200 ml of concd HCl and 50 ml of H_2O. Cracked ice was added to lower the temp to 0°. A soln of 70.5 g (1.02 moles) of $NaNO_2$ in 200 ml of H_2O was added slowly, maintaining the temp at 0–5°. After the addition was complete, a small excess of $NaNO_2$ was added to dissolve all of the hydrochloride. The soln was then neutralized with solid Na_2CO_3. Toluene (250 ml), followed by the diazo soln, was added to a soln of cuprous cyanide prepared from 312.5 g (1.25 moles) of $CuSO_4 \cdot 6H_2O$ according to the lit.[6] The temp was maintained at 5–15°. The thick mixture was then stirred for 5 hr, warmed to 50°, and kept overnight at room temp. The mixture was filtered through a Celite pad which was washed with 100 ml of toluene. The organic layer was separated and washed with a saturated NaCl soln. The toluene was distilled off from the dried (Na_2SO_4) soln, and the residue was distilled in high vacuum: yield 138.80 g (65.8%); bp 109–110° (0.45 mm). The product crystd from hexane; first crop 61.08 g, mp 37.5–39°, second crop 24.47 g, mp 37–38°. The analytical sample had a mp of 38.5–39.5°. *Anal.* (C_9H_8BrN) C, H, Br, N.

3-Bromo-4-(1-naphthoyl)ethylbenzene (13). To a stirred soln of 62.08 g (0.3 mole) of 12 in 450 ml of anhyd C_6H_6, the Grignard reagent prepared from 8.76 g (0.36 g-atom) of Mg turnings and 68.34 g (0.33 mole) of 1-bromonaphthalene in 150 ml of Et_2O and 60 ml of C_6H_6 was added within 5 min. About 250 ml of solvent was distilled off and the remaining soln was then refluxed for 6.5 hr. After standing overnight at room temp, the complex was then decomposed by slowly adding 450 ml of a 6 *N* HCl soln. The yellow solid which separated was filtered off and washed, successively, with C_6H_6 and H_2O. The product was dissolved in 450 ml of EtOH, 75 ml of concd HCl and 75 ml of H_2O were added, and the soln was heated under reflux for 2 hr. The soln was cooled and the cryst precipitate was filtered off and washed with 70% EtOH. Recrystn from EtOH gave 65.59 g of the title compound: mp 82–83.5°. From the mother liquors, additional material, 6.58 g, mp 81–82.5°, was isolated: yield 71%. Mp of the analytical sample was 83–84°. *Anal.* ($C_{19}H_{15}BrO$) C, H, Br.

3-Cyano-4-(1-naphthoyl)ethylbenzene (14). Compd 13 (75 g; 0.22 mole) and 23.80 g (0.37 mole) of CuCN in 120 ml of DMF were heated at reflux temp for 6 hr with stirring. The mixture was poured into a soln of 46.0 g of NaCN in 160 ml of warm H_2O. After stirring for 5 min, the soln was diluted with 500 ml of H_2O and extracted with 700 ml of C_6H_6. The organic layer was washed with 50 ml of a 15% NaCN soln, then 3 times with H_2O. The C_6H_6 soln was dried (Na_2SO_4) and concentrated to about 60 ml. The soln was filtered through a column of 150 g of alumina and the column was rinsed with 1200 ml of Et_2O. The solvents were evapd. The residue, 55.60 g of a slightly yellow resinous material, did not crystallize and was used in the next step without further purification.

2-(1-Naphthoyl)-5-ethylbenzoic Acid (15). To the soln of 55.60 g of crude nitrile 14 in 220 ml of ethylene glycol monoethyl ether, a soln of 55.0 g of KOH in 27 ml of H_2O was added. The soln was refluxed for 6 hr with stirring. It was then poured into 1500 ml of ice water and made acid with concd HCl. After standing overnight, the precipitate was filtered off, washed with H_2O, and dissolved in EtOAc. The soln was extracted with a 5% Na_2CO_3 soln. The aqueous extracts were acidified, and the precipitate was filtered off and washed well with H_2O. The slightly wet product was crystd from AcOH to give 18.56 g of 15: mp 176–177°. From the mother liquors, an additional 9.68 g, mp 172–175°, was obtained. The yield was 42% based on 14. The analytical sample, mp 176–177°, was crystd from C_6H_6. *Anal.* ($C_{20}H_{16}O_3$) C, H.

2-(1-Naphthylmethyl)-5-ethylbenzoic Acid (16). Keto acid 15, 11.14 g (0.037 mole) was dissolved in 390 ml of warm H_2O containing 29 g of NaOH. Zn dust (26 g) was added and the mixture was refluxed with stirring for 42 hr. The mixture was filtered, and the filtrate was acidified. The precipitate was dissolved in EtOAc and the soln was extracted with a 5% Na_2CO_3 soln. The extract was made acidic and the precipitate was again taken up in EtOAc. The soln was washed with H_2O and dried (Na_2SO_4), and the solvent removed *in vacuo*. The cryst residue, 9.98 g, was recrystd from AcOH–H_2O and afforded 9.66 g (91%) of acid 16: mp 123.5–124.5°. The analytical sample melted at 124–125°: nmr δ 1.41 (m, 6) 2.92 (q, 2), 3.62 (q, 2). *Anal.* ($C_{20}H_{18}O_2$) C, H.

7,9-Diethylbenz[*a*]anthracene (18). Six g (0.021 mole) of 16 was dissolved in about 50 ml of anhyd HF. The reagent was allowed to evaporate overnight. The residue was taken up in CH_2Cl_2, and the soln was washed twice with a 5% Na_2CO_3 soln, then with H_2O. After drying (Na_2SO_4), the solvent was evapd. The spectrum of the crude material indicated that it was a mixture of the expected anthrone 17 and its enolized form, 7-hydroxy-9-ethylbenz[*a*]anthracene, 17a. The cryst crude product was used in the next step without further purification.

The mixture of 17 and 17a (5.74 g) was added to 120 ml (0.12 mole) of a 1 *M* EtMgBr soln in Et_2O–C_6H_6. The soln was stirred at room temp for 2 hr, then heated at reflux for another 2 hr. The chilled soln was decomposed with 100 ml of 15% HCl. The organic layer was washed with 2 *N* NaOH and with H_2O and dried (Na_2SO_4), and the solvents were removed under reduced pressure. The residue, 7.80 g, was chromatographed on 300 g of alumina. 7,9-Diethylbenz[*a*]anthracene, 2.99 g, was eluted with petroleum ether–20% Et_2O. Recrystn from hexane gave 2.20 g, mp 70.5–72°, and 0.37 g, mp 70–70.5, of 18: yield 43.7%. Analytical sample had mp 71–72.5°. *Anal.* ($C_{22}H_{20}$) C, H.

2-(1-Naphthoyl)-6-ethylbenzoic Acid (20). A Grignard soln, prepared from 5.36 g (0.22 g-atom) of Mg turnings and 41.54 g (0.20 mole) of 1-bromonaphthalene in 90 ml of Et_2O and 30 ml of C_6H_6, was added to a stirred soln of 32.10 g (0.182 mole) of 3-ethylphthalic anhydride[12] in 250 ml of C_6H_6 at room temp. The mixture was refluxed with stirring for 3 hr. The cold reaction mixture was decomposed with 250 ml of a 15% HCl soln. The organic layer was extracted 3 times with 200-ml portions of a 5% Na_2CO_3 soln. The alkaline extracts were acidified with concd HCl. The oily product was taken up in C_6H_6, and the soln was washed with H_2O and with satd NaCl soln. After drying (Na_2SO_4), the soln was concentrated to a small volume to afford 40.84 g of 2-(1-naphthoyl)-6-ethylbenzoic acid (20): mp 155–157°. From the mother liquors, 0.84 g of material melting at 155–156.5° was isolated: yield 75.2%. Mp of the analytical sample was 157–158°. *Anal.* ($C_{20}H_{16}O_3$) C, H.

2-(1-Naphthylmethyl)-6-ethylbenzoic Acid (21). Twelve g (0.04 mole) of 20 was dissolved in 400 ml of H_2O containing 30 g (0.75 mole) of NaOH. The soln was stirred and heated to reflux temp with 24 g of Zn–Cu couple for 31 hr. The mixture was cooled and filtered, and the filtrate was acidified with concd HCl. The amorphous precipitate was filtered off and washed with H_2O. The solid was dissolved in C_6H_6 and the soln was extracted 3 times with a 2.5% soln of Na_2CO_3. The extracts were acidified and the precipitate was redissolved in C_6H_6. The soln was washed with H_2O, dried (Na_2SO_4), and evaporated. The residue, 9.20 g, could not be crystd.

8-Ethylbenz[*a*]anthr-7-one (22). The crude acid 21 was dissolved in about 100 ml of anhyd HF. The reagent was allowed to evaporate overnight. The residue was dissolved in CH_2Cl_2, the soln was washed with a 5% Na_2CO_3 soln and with H_2O. After drying (Na_2SO_4), the solvent was evaporated. The residue was crystd from C_6H_6 and yielded 4.39 g of 22, mp 162–165°, and 1.22 g, mp 158–163°: yield 52.4% based on 20. The analytical sample melted at 163–165°. *Anal.* ($C_{20}H_{16}O$) C, H.

7,8-Diethylbenz[*a*]anthracene (23). To a stirred suspension of 5.0 g (0.018 mole) of 22 in 200 ml of C_6H_6, 100 ml (0.14 mole) of a 5% LiEt soln in C_6H_6 was added. The mixture was refluxed in a nitrogen atmosphere for 6 hr. The chilled soln was decomposed with a 15% soln of HCl. The organic layer was washed with H_2O and dried (Na_2SO_4). The evaporation residue, 5.21 g, was chromatographed on 160 g of alumina. Petroleum ether–20% Et_2O eluted 3.52 g of material which crystd from hexane to give 3.04 g of 23, mp 105.5–107°, and 0.30 g, mp 102.5–105°: yield 64.2%. Mp of the analytical sample was 106–107.5°: nmr δ 1.31 (m, 6), 3.21 (q, 2), 3.54 (q, 2). *Anal.* ($C_{22}H_{20}$) C, H.

2-(1-Naphthylpropyl)-6-ethylbenzoic Acid (25). To a stirred suspension of 24.0 g (0.078 mole) of 2-(1-naphthoyl)-6-ethylbenzoic acid (20) in 300 ml of C_6H_6 105 ml (0.315 mole) of 3 *M* EtMgBr was added in 25 min. The soln was stirred 30 min at room temp, then refluxed for 2 hr. The soln, cooled in an ice bath, was decomposed

with 200 ml of 10% HCl. The organic layer was washed twice with a 5% soln of Na_2CO_3 and dried (Na_2SO_4), and the solvent removed. The residue, 20.18 g, did not crystallize.

The crude 2-(1-hydroxy-1-naphthylpropyl)-6-ethylbenzoic acid lactone (24) was dissolved in 300 ml of EtOH, 70 ml of a 30% aqueous soln of NaOH was added, and the EtOH was removed under reduced pressure. To the residue, 400 ml of H_2O, 70 ml of concd NH_4OH, and 70 g of Zn dust were added, and the mixture was refluxed with stirring for 47 hr. The mixture was filtered and the cold filtrate was acidified with HCl. The precipitate was filtered off and washed with H_2O. The dried product (17.00 g), crystd from C_6H_6–hexane: first crop 6.18 g, mp 133–134.5°, second crop 2.25 g, mp 131–133°: yield 33.6%. Mp of the analytical sample was 139–139.5°. *Anal.* ($C_{22}H_{22}O_2$) C, H.

8,12-Diethylbenz[*a*]anthr-7-one (26). Ten g (0.031 mole) of 25 was dissolved in 50 ml of anhyd HF. The excess reagent was allowed to evaporate overnight. The residue was dissolved in Et_2O, the soln was washed with a 5% Na_2CO_3 soln and with H_2O. The dried (Na_2SO_4) soln was evaporated. The remaining material (7.72 g) did not crystallize.

8,12-Diethylbenz[*a*]anthr-7-ol (27). The crude anthrone 26 was dissolved in 50 ml of toluene. To the soln, 125 ml of a 15% NaOH soln and 28 g of Zn–Cu couple were added, and the mixture was boiled for 48 hr with stirring. The organic layer was washed twice with H_2O and dried (Na_2SO_4). After evaporation of the solvent, a cryst residue (6.39 g) was obtained. For analysis, a sample was recrystd twice from hexane: mp 121–123°. *Anal.* ($C_{22}H_{22}O$) C, H.

8,12-Diethylbenz[*a*]anthracene (28). The soln of the crude anthrol (5.0 g) in 75 ml of C_6H_6 was refluxed with 0.75 g of TsOH for 1 hr. The cooled soln was washed with a 5% Na_2CO_3 soln and with H_2O. After drying (Na_2SO_4), the solvent was evaporated, and the residue (4.47 g) was crystd from hexane: yield 1.19 g, mp 104–105° and 1.84 g, mp 100–102.5°. Yield was 34% based on 25. The analytical sample melted at 104–105°: nmr δ 1.45 (t, 3), 1.82 (t, 3), 3.24 (q, 2), 3.81 (q, 2). *Anal.* ($C_{22}H_{20}$) C, H.

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14α,17α-Alkylidenedioxyprogesterone Derivatives

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14α,17α-Alkylidenedioxyprogesterone derivatives, having interesting progestational and anticonceptive activities, were prepared by reaction of 14α,17α-dihydroxyprogesterone derivatives with aldehydes and orthoformates. Reaction with ketones did not yield the corresponding alkylidenedioxy compounds because of steric hindrance. The structure–activity relationship of the new compounds is discussed.

In the past there have been several attempts to enhance the pharmacological activity of steroids by attaching a new ring to the D ring of the steroid molecule. In the field of progestational hormones this has been carried out by Solo, *et al.*,[1] who synthesized 14α,17α-etheno derivatives by means of a Diels–Alder reaction and by Fried, *et al.*,[2a] who found that 16α,17α-alkylidenedioxy groups, normally used as protecting groups or for characterization purposes, showed an enhancing effect on certain pharmacological activities. Steroids with alkylidenedioxy groups in various positions, in most cases 16 and 17 or 17 and 21, have been described.[2] 14α,17α-Dihydroxy steroids have hydroxyl groups in a suitable position for condensation with carbonyl compounds and the bridging alkylidenedioxy group, together with carbon atoms 13, 14, and 17, would incorporate a new six-membered ring on the α side of the molecule. 14α,17α-Dihydroxy steroids were readily available to us and it was of interest to determine whether such compounds possessed biological activity. This communication describes the preparation and biological activity of a number of new 14α,17α-alkylidenedioxyprogesterone derivatives.

Chemistry. Most of the products were derived from the parent compound 14α,17α-dihydroxyprogesterone (**1**)[3] which was obtained from the 21-hydroxy analog according to the method described by Cooley, *et al.*[3] Some of the initially prepared products had promising progestational properties. Therefore the influence on activity of variation in the alkylidenedioxy moiety was investigated by the synthesis of a series of derivatives of the general formula I (Chart I), in which R_1 is an alkyl or aryl group or in some cases an alkoxy group. Also studied was the influence of substituents in the steroid skeleton such as double bonds, halogens, hydroxyl, or alkyl groups. The compounds of general formula II or III (Chart I) resulted. These compounds were, in some cases, synthesized from two other parent compounds, 11β,14α,-17α-trihydroxypregn-4-ene-3,20-dione (**2**)[4] and 6α-fluoro-16α-methyl-14α,17α-dihydroxypregn-4-ene-3,20-dione (**3**),[5] which were also derived from the corresponding 21-hydroxy analogs.[3] The key reaction for the preparation of these products is condensation of the parent compounds with aldehydes[2a] or ortho esters[2b] as shown in Schemes I and II.

Consideration of Dreiding models shows that the most

Chart I