New Psychotropic Agents.[1] III. Derivatives of 6,11-Dihydrodibenz[b,e]oxepine and 6,11-Dihydrodibenzo[b,e]thiepine

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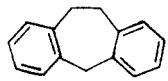
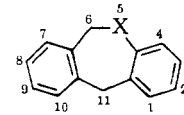
Cyclodehydrations were carried out successfully on 2-carboxybenzyl phenyl ether (IVa), 2-carboxybenzyl 4-chlorophenyl ether and 2-carboxybenzyl phenyl thioether (IVb) to yield, respectively, 11-keto-6,11-dihydrodibenz[b,e]oxepine (Va), 2-chloro-11-keto-6,11-dihydrodibenz[b,e]oxepine and 11-keto-6,11-dihydrodibenzo[b,e]thiepine (Vb). Alkylation with 3-dimethylaminopropylmagnesium chloride gave the somewhat unstable 11-(3-dimethylaminopropyl)-11-hydroxy compounds which under dehydrating conditions unexpectedly rearranged to anthracene-like products. In contrast, 11-keto-6,11-dihydrodibenzo[b,e]-thiepine-5,5-dioxide (Vc) produced an 11-(3-dimethylaminopropyl)-11-hydroxy compound (VIc) which underwent dehydration without rearrangement and yielded the expected olefin (VII). The pharmacological activity of this latter compound is discussed briefly.

In continuing our investigation of derivatives of tricyclic ring systems as potential psychotropic agents, we have prepared a number of compounds containing the 6,11-dihydrodibenz[b,e]oxepine, -thiepine and -thiepine-5,5-dioxide rings (IIa,b,c). These may be considered as analogs of the dibenzo[a,d][1,4]cycloheptadiene ring (I) in which the carbon atom at position 10 has been replaced by oxygen or sulfur.



I



IIa, X = O
b, X = S
c, X = SO_2

A search of the chemical literature discloses only two instances where the synthesis of a dibenz[b,e]oxepine ring has been carried out.

(1) Paper II in this series: S. O. Winthrop, M. A. Davis, F. Herr, J. Stewart, and R. Gaudry, *J. Med. Pharm. Chem.*, **5**, 1199 (1962).
(2) Department of Chemistry.
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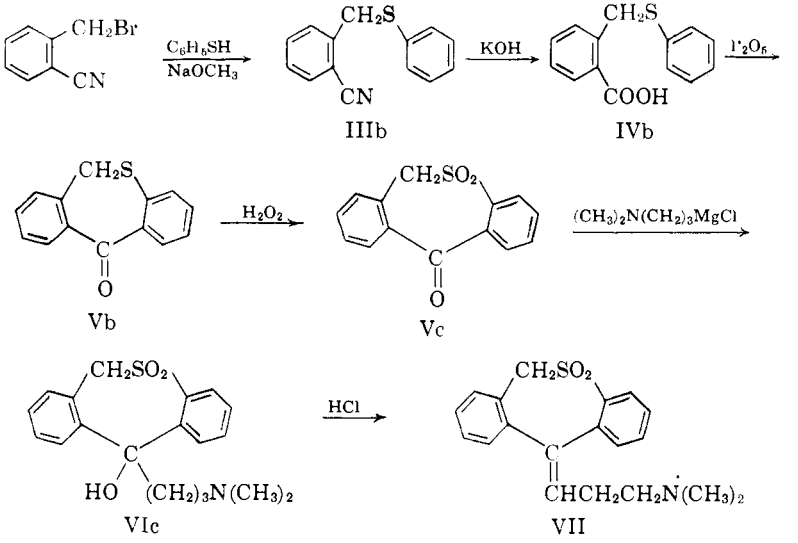
Hubacher[4] has prepared an ϵ-lactone, 3-hydroxy-6-keto-11-phenyl-6,11-dihydrodibenz[b,e]oxepine, by the dehydration of α-(2,4-dihydroxyphenyl)-α-phenyl-*o*-toluic acid. The monoacetyl and monomethyl ether derivatives were also reported. In a similar manner, Baker and co-workers[5] have cyclized 2-carboxy-2′-hydroxybenzophenones and 2-carboxy-2′-hydroxydiphenylmethanes to yield 6,11-diketo-6,11-dihydrodibenz[b,e]oxepines and 6-keto-6,11-dihydrodibenz[b,e]oxepines, respectively. As all of the reported compounds are lactones they could not be easily used as starting materials for the synthesis of the 11-substituted compounds desired for the present investigation. No synthesis of a dibenzo[b,e]thiepine ring has been reported to date.

Initial experiments were directed toward the preparation of 11-keto-6,11-dihydrodibenz[b,e]oxepine (Va) and the corresponding thiepine (Vb) from 2-benzyloxy- and 2-benzylthiobenzoic acids. These intermediates were readily available from salicylic and thiosalicylic acids, respectively. Attempted cyclodehydrations using polyphosphoric acid, phosphorus pentoxide or liquid hydrogen fluoride gave, however, unchanged material together with some anhydride and polymeric by-products. An examination of the infrared spectra of the reaction products did not reveal the presence of any ketonic materials.

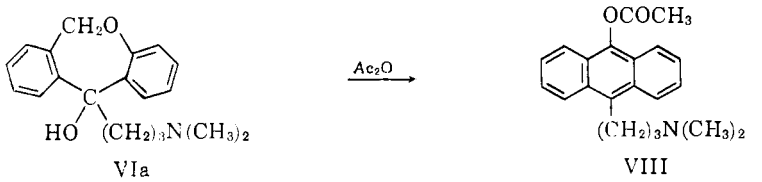
The ketones were synthesized successfully by the cyclization of 2-carboxybenzyl phenyl ether (IVa) and the corresponding thioether (IVb). In these compounds the benzene ring is activated by the presence of an electron-releasing *ortho* substituent. The intermediates not previously described in the literature were prepared by treating *o*-cyanobenzyl bromide with the appropriate phenol in the presence of sodium methoxide. Alkaline hydrolysis of the nitriles was effected by heating with potassium hydroxide in ethylene glycol. The carboxylic acids thus produced were then heated with a suspension of phosphorus pentoxide and Celite in xylene giving the desired ketones in satisfactory yields. Other methods of cyclodehydration such as polyphosphoric acid at 95°, concentrated sulfuric acid at room temperature or liquid hydrogen fluoride gave mainly the anhydride of the starting acid. The chemistry involved is illustrated by the reaction sequence employed for the preparation of the 11-keto-6,11-dihydrodibenzo[b,e]thiepine (Vb). The corresponding oxepine (Va) and its 2-chloro derivative were prepared in analogous manner. The ketones are listed in Table I and represented by formula A.

(4) M. H. Hubacher, *J. Org. Chem.*, **23**, 1400 (1959).
(5) W. Baker, D. Clark, W. D. Ollis and T. Z. Zealley, *J. Chem. Soc.*, 1452 (1952).



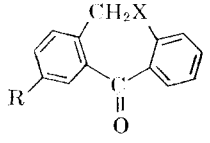
Interaction of ketones Va and Vc with the Grignard reagent derived from 3-dimethylaminopropylmagnesium chloride in tetrahydrofuran solution gave the carbinols VIa and VIc. When VIa was subjected to the action of boiling acetic anhydride none of the expected olefin could be isolated from the reaction mixture. Instead a compound resulted in good yield, which on the basis of infrared, ultraviolet and analytical data, was presumed to be 10-acetoxy-9-(3-dimethylaminopropyl)anthracene (VIII).

A comparison with 10-acetoxyanthracene revealed similarities in the infrared spectra and only slight differences in the position and intensity of the ultraviolet absorption bands. The latter may be explained by the presence of an additional substituent at position 9. Hydrolysis of VIII by dilute hydrochloric acid gave only anthraquinone and none of the desired 9-(3-dimethylaminopropyl)-anthrone could be isolated. This compound might be expected to be short-lived under the hydrolysis conditions. Anthrones substituted in the 9-position have been reported by Julian and co-workers[6] to add at-

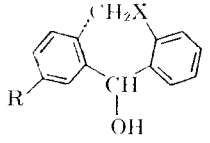


(6) P. L. Julian, W. Cole and G. Diemer, *J. Am. Chem. Soc.*, **67**, 1721 (1945).

TABLE I
KETONES AND ALCOHOLS



A



B

Cpd.	R	X	M.p., °C.	Recryst. soln.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
A	H	O	69–70	[a]	68	$C_{14}H_{10}O_2$	79.98	80.13	4.79	4.81		
B	H	O	88–89	[b]	70	$C_{14}H_{12}O_2$	79.22	79.41	5.70	5.85		
A	Cl	O	130–131	[a]	51	$C_{14}H_9ClO_2$	68.72	69,04	3.71	3.84	14.50[f]	14.58
B	Cl	O	140	[c]	62	$C_{14}H_{11}ClO_2$	68.18	67.88	4.50	4.44	14.38[f]	14.33
A	H	S	89–90	[b]	61	$C_{14}H_{10}OS$	74.30	74.20	4.45	4.56	14.17	14.09
B	H	S	108–109	[b,d]	76	$C_{14}H_{12}OS$	73.67	72.95	5.30	5.11	14.02	14.02
A	H	SO_2	122–124	[e]	66	$C_{14}H_{10}O_3S$	65.10	65.51	3.93	3.87	12.41	12.18
B	H	SO_2	157	[c]	36	$C_{14}H_{12}O_3S$	64.61	64.71	4.65	4.84	12.30	12.37

[a] Petroleum ether (b.p. 80–100). [b] Hexane. [c] 2-Propanol. [d] Ethyl acetate. [e] Ethanol. [f] Chlorine.

mospheric oxygen rapidly and then undergo thermal decomposition to give an alcohol and anthraquinone.

Other dehydrating agents were equally unsuccessful in producing the desired olefin from VIa. Methanolic hydrogen chloride, phosphorus pentoxide, acetyl chloride in pyridine, alkaline alumina and even sublimation *in vacuo* gave in all cases reaction products containing varying amounts of anthracene-like materials whose presence was indicated by the characteristic absorption bands in the ultraviolet spectra. Heating under reflux in amyl alcohol did not change the compound. The carbinols derived from ketone Vb and the 2-chloro derivative of ketone Va were found not sufficiently stable to be easily purified and were not characterized as such. In these two cases dehydrations were attempted on the impure materials but again the crude reaction products showed the anthracene-like ultraviolet spectra. They were not otherwise characterized.

In contrast to the results obtained with carbinols VIa, VIb and the 2-chloro derivative of VIa, the sulfone-containing carbinol VIc proved to be stable toward the action of boiling acetic anhydride. On heating, however, with a mixture of concentrated hydrochloric and acetic acids, the ring remained intact and dehydration proceeded in the normal manner to yield the desired 11-(3-dimethylaminopropylidene) compound (VII).

In connection with other studies being carried out in these laboratories, it was of interest to reduce the novel ketones to their corresponding alcohols. These are listed in Table I and represented by formula B. Lithium aluminum hydride in ether was found to be the preferred reagent since sodium borohydride in aqueous methanol gave with ketones Va and Vb, carbinols which could not be satisfactorily purified.

Pharmacological Activity.—Compounds VIa and VII were studied in the series of pharmacological tests used in this laboratory to screen for antidepressant and other central nervous system activity.[7] The tests included in this work have been outlined in the preceding paper.[1] The activity of the two compounds studied is compared to that of amitriptyline in Table II. It can be seen that compound VIa had very little activity in both the central and peripheral tests. Compound VII had some central activity (see the potentiation of narcosis and the effect on a conditioned response, runway test) and considerable antispasmodic activity. In all respects, however, it was less potent than amitriptyline.

(7) F. Herr, J. Stewart, and M. P. Charest, *Arch. Int. Pharmacodyn.*, **134**, 388 (1961).

TABLE II

RESULTS OF THE PHARMACOLOGICAL INVESTIGATIONS

Compound number	VIa	VII	Amitryptyline
LD_{50} (approx.) mg./kg. mice, i.p.	300–350	210–230	83 ± 2.5
Potentiation of narcosis, ED_{50} mg./kg. mice, i.p.	110 ± 13	21 ± 2.2	7.9 ± 0.8
MES ED_{50} mg./kg. mice, i.p.	>100[c]	>55[c]	10 ± 0.8
Mydriasis caused by 0.25 LD_{50}[a] mice, i.p.	0	+10	+19
% difference in motility 0.25 LD_{50} rats, i.p.	—	0	−37
Ataxia approx. ED_{50} mg./kg. rats, i.p.	>200[c]	>100[c] (death)	53
Runway approx. ED_{50} mg./kg. rats, i.p.	70	27	8
Antiacetylcholine EC_{50} μg./ml.[b]	>2[c]	0.078 ± 0.01	0.038 ± 0.003
Antihistamine EC_{50} μg./ml.[b]	0.1–0.2	0.02 ± 0.006	0.004 ± 0.001

[a] The numbers represent unit increases over control pupil diameter. +40 is approximately the maximal dilation. [b] EC_{50} is the concentration which inhibited the normal response to 0.1 μg./ml. of either acetylcholine or histamine by 50%. [c] > means that the compound was inactive up to the dose indicated in the table.

Experimental

2-Cyanobenzyl 4-Chlorophenyl Ether.—Sodium methoxide (38.6 g., 0.72 mole) was added to ethanol (200 ml.) containing *p*-chlorophenol (91 g., 0.72 mole) and the solution stirred and warmed for a few min. 2-Cyanobenzyl bromide (137 g., 0.7 mole) then was added dropwise with stirring. The addition was completed in 30 min. and the reaction mixture then was heated under reflux for an additional 2 hr. After removing the precipitated solid, the filtrate was evaporated *in vacuo*. A residue was combined with the original precipitate which then was triturated with water (2 l.), filtered, and crystallized from 2-propanol to give 127 g. of product, m.p. 70–72° (73% yield). One recrystallization from 2-propanol gave an analytical sample, m.p. 72–73°.

Anal. Calcd. for $C_{14}H_{10}ClNO$: N, 5.75; Cl, 14.55. Found: N, 5.51; Cl, 14.49.

2-Cyanobenzyl Phenyl Thioether.—In the same manner as described in the preceding paragraph, sodium methoxide (38.6 g., 0.72 mole), thiophenol (78 g., 0.72 mole) and 2-cyanobenzyl bromide (137 g., 0.7 mole) gave 117 g. (75% yield) of product after distillation, b.p. 148–150° (0.35 mm.), $n^{25}D$ 1.6195.

Anal. Calcd. for $C_{14}H_{11}NS$: C, 74.64; H, 4.92; N, 6.22. Found: C, 74.15; H, 4.77; N, 6.37.

2-Carboxybenzyl 4-Chlorophenyl Ether.—2-Cyanobenzyl 4-chlorophenyl ether (126 g., 0.52 mole) was hydrolyzed by heating under reflux for 24 hr. in a solution of sodium hydroxide (160 g., 4 moles) in ethanol (240 ml.) and water (730 ml.). After cooling, the reaction mixture was extracted with ether. The ethereal extracts were then back-extracted with water. On neutralizing the original aqueous layer together with the water washings with dilute hydrochloric acid, the product precipitated. After drying, it weighed 126 g. (92% yield), m.p. 166–177°.

One recrystallization from 2-propanol gave an analytically pure sample with m.p. 167–168°.

Anal. Calcd. for $C_{14}H_{11}ClO_3$: C, 64.02; H, 4.22; Cl, 13.50. Found: C, 64.30; H, 4.12; Cl, 13.35.

2-Carboxybenzyl Phenyl Thioether.—2-Cyanobenzyl phenyl thioether (11.3 g., 0.05 mole) was hydrolyzed by heating under reflux for 24 hr. with a solution of potassium hydroxide (15 g.) in ethylene glycol (150 ml.) and water (50 ml.). The reaction mixture then was diluted with water (400 ml.) and neutralized with dilute hydrochloric acid, causing the product to precipitate as a solid, m.p. 107–111° (9.1 g., 75% yield). One recrystallization from ethanol raised the melting point to 109–111° (lit.[8] m.p. 112°).

11-Keto-6,11-dihydrodibenzo[b,e]thiepine (Vb).—2-Carboxybenzyl phenyl thioether (45.7 g., 0.187 mole) was cyclized by heating at reflux in 1,200 ml. of xylene for 16 hr. with 138 g. of phosphorus pentoxide and 138 g. of Celite. The reaction mixture then was filtered and the filtrate evaporated *in vacuo* to yield 33 g. of a crude product as an oil. This was triturated with a small amount of hexane which caused it to crystallize giving 26 g., m.p. 85–88° (61% yield). Two recrystallizations from hexane raised the melting point to 89–90° (see Table I).

11-Keto-6,11-dihydrodibenzo[b,e]thiepine-5,5-dioxide (Vc).—The sulfide ketone (Vb, 78 g., 0.35 mole) was added to a solution of 150 ml. of glacial acetic acid and 150 ml. of acetic anhydride. Hydrogen peroxide (30%, 95 ml.), was added dropwise while the temperature was maintained at approximately 4°, by means of an ice-water bath. The reaction mixture then was allowed to warm to room temperature and stand for 72 hr. The product precipitated and was filtered off to yield 59 g., m.p. 111–114° (66% yield). Two recrystallizations from ethanol raised the m.p. to 122–124° (see Table I).

11-Hydroxy-6,11-dihydrodibenz[b,e]oxepine.—A solution of 11-keto-6,11-dihydrodibenz[b,e]oxepine (Va, 3.55 g., 0.017 mole) in dry ether (75 ml.) was added dropwise to a stirred suspension of lithium aluminum hydride (1.90 g., 0.050 mole) in ether (60 ml.). The reaction mixture was heated under reflux for 3 hr. during which time a green color developed. Hydrolysis was effected by the successive addition of water (1.9 ml.), 20% aqueous sodium hydroxide solution (1.4 ml.) and water (6.7 ml.). The precipitate was filtered off, washed well with ether and the combined ethereal solutions were dried and evaporated. The residue thus obtained was recrystallized once from hexane to give 2.5 g. (70% yield) of product as white needles, m.p. 88–89° (see Table I).

11-Hydroxy-6,11-dihydrodibenzo[b,e]thiepine-5,5-dioxide.—A solution of sodium borohydride (2.9 g., 0.08 mole) in water (15 ml.) containing 10% aqueous sodium hydroxide (0.5 ml.) was added dropwise to a stirred suspension of ketone Vc (5.0 g., 0.02 mole) in methanol (300 ml.). An exothermic reaction took place and then complete dissolution of the starting material. The reaction mixture was stirred at room temperature for 6 hr. and the bulk of the methanol was then removed *in vacuo*. The residue was added to cold water and the mixture was neutralized by the careful addition of acetic acid. The precipitate was collected, dried and recrystallized repeatedly from 2-propanol or ethyl acetate to furnish 1.8 g. (36% yield) of pure product, m.p. 157° (see Table I).

11-Hydroxy-11-(3-dimethylaminopropyl)-6,11-dihydrodibenz[b,e]oxepine

(8) This compound has been prepared from 2-hydroxymethylbenzoic acid and thiophenol: Henkel et Cie., G.m.b.H., British Patent 773,594, May 1, 1957.

(**VIa**).—11-Keto-6,11-dihydrodibenz[b,e]oxepine (Va, 15 g., 0.075 mole), dissolved in tetrahydrofuran (20 ml.) was added dropwise to 3-dimethylaminopropylmagnesium chloride prepared from magnesium (5.16 g., 0.225 mole) and 3-dimethylaminopropyl chloride (27.2 g., 0.225 mole) in tetrahydrofuran (100 ml.). The addition was complete in 30 min. and the reaction mixture was heated under reflux for an additional 16 hr. The Grignard complex then was hydrolyzed with approximately 1 l. of aqueous ammonium chloride solution, causing the product to precipitate as a solid, 19 g., m.p. 206–209° (89% yield). Two recrystallizations from acetone–methanol raised the melting point to 219–220°.

Anal. Calcd. for $C_{19}H_{23}NO$: C, 76.73; H, 7.71; N, 4.70. Found: C, 76.65; H, 7.65; N, 4.83.

Attempted Dehydration of Tertiary Carbinol VIa.—The tertiary carbinol VIa (11.6 g.) was heated under reflux in acetic anhydride (200 ml.) for 4 hr. The reaction mixture was then evaporated *in vacuo* and the residue triturated with aqueous sodium hydroxide solution and extracted with ether. The ethereal extract was dried over sodium sulfate and then evaporated *in vacuo* to give 12 g. of a crystalline solid, m.p. 82–85° (VIII). Two recrystallizations from benzene–hexane gave material with a constant m.p. of 95–96°. Infrared, ultraviolet and microanalytical data indicated a 10-acetoxyanthracene derivative. The product was presumed to be 10-acetoxy-9-(3-dimethylaminopropyl)-anthracene; $\lambda_{max.}$ (ethanol) were: 252, 258, 339, 356, 376, 397; ϵ = 97,000, 112,000, 231,000, 3430, 7530, 12,400, 11,900; $\nu_{max.}$ ($CHCl_3$) 1765, 1195 (phenolic acetate).

Anal. Calcd. for $C_{21}H_{23}NO_2$: N, 4.29. Found: N, 4.09.

A hydrochloride was prepared in the usual manner and purified by two recrystallizations from acetone–methanol. It analyzed for a monohydrate.

Anal. Calcd. for $C_{21}H_{24}ClNO_2 \cdot H_2O$: C, 67.11; H, 6.97; N, 3.73; Cl, 9.44; H_2O: 4.79. Found: C, 66.74; H, 7.21; N, 3.78; Cl, 9.89; H_2O, 4.40.

For comparison purposes 10-acetoxyanthracene[9] was prepared and its infrared and ultraviolet spectra were determined: $\lambda_{max.}$ (ethanol); 247, 253, 331, 346, 363, 394; ϵ = 103,500, 197,000, 3140, 6100, 9250, 8550; $\nu_{max.}$ ($CHCl_3$) 1761, 1193.

Hydrolysis of Compound VIII.—10-Acetoxy-9-(3-dimethylaminopropyl)-anthracene (VIII, 300 mg.) was dissolved in 20 ml. of 6 *N* hydrochloric acid and heated on a steam bath for 1 hr. The solution was neutralized with aqueous sodium bicarbonate and then cooled, causing a product to precipitate as a solid, 100 mg., m.p. 275° dec. This was identified as anthraquinone by its ultraviolet and infrared spectra as well as by a mixture melting point.

11-Hydroxy-11-(3-dimethylaminopropyl)-6,11-dihydrodibenzo[b,e]thiepine-5,5-dioxide (VIc).—The sulfone ketone (Vç, 17.3 g., 0.067 mole) in 50 ml. of tetrahydrofuran was added dropwise to 200 ml. of tetrahydrofuran containing the Grignard reagent prepared from 3-dimethylaminopropyl chloride (16.3 g., 0.134 mole) and magnesium (3.2 g., 0.134 mole). During the addition, the temperature was maintained at approximately 5°, by means of an ice–water bath. The addition was completed in 20 min. The reaction mixture then was stirred for an additional 16 hr. at room temperature. It was hydrolyzed with an aqueous solution of ammonium chloride and the hydrolysis mixture was extracted with chloroform. The chloroform extract was dried over sodium sulfate and evaporated, leaving an oil residue which on trituration with ether gave 8.3 g. of solid product, m.p. 142–144° (33% yield). One recrystallization from ethanol did not change the melting point.

(9) E. B. Barnett and M. A. Matthews, *J. Chem. Soc.*, **123**, 389 (1923).

Anal. Calcd. for $C_{19}H_{23}NO_3S$: N, 4.06; S, 9.28. Found: N, 4.10; S, 9.27.

11-(3-Dimethylaminopropylidene)-6,11-dihydrodibenzo[b,e]thiepine-5,5-dioxide (VII).—The tertiary carbinol (VIc 2.7 g.) was added to a solution of 15 ml. of concd. hydrochloric acid and 40 ml. of glacial acetic acid, and heated under reflux for 3 hr. The reaction mixture then was filtered, neutralized with aqueous sodium hydroxide solution and extracted with ether. The ethereal extract was dried over sodium sulfate and then treated with hydrogen chloride gas, causing the product hydrochloride to precipitate as a solid (2.3 g.), m.p. 249–252°. One recrystallization from 2-propanol ether did not change the melting point; $\lambda_{max.}$ (ethanol), 236; $\epsilon = 11{,}100$.

Anal. Calcd. for $C_{19}H_{22}ClNO_2S$: S, 8.82; Cl, 9.74. Found: S, 8.82; Cl, 9.92.

NOTE ADDED IN PROOF.—Since this manuscript was submitted, three publications have come to our attention which disclose some of the compounds described above. In contrast to our findings the authors report the dehydration of the tertiary carbinols as giving the expected corresponding basic propylidene compounds and not anthracene derivatives: ((1) Sandoz, S. A., Belgian Patent 607,503; Derwent Report No. 87A, Feb. 28, 1962. (2) K. Stack and H. Spingler, *Angew. Chem.* internat. edit., **1**, 50 (1962). (3) M. Protiva, M. Rajsner, V. Seidlova, E. Adlerova and Z. J. Vejdelek, *Experientia*, **18**, 326 (1962).

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