[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE VIRGINIA POLYTECHNIC INSTITUTE]

The Synthesis of Some 10-(Substituted phenyl)-1,2-benzanthracenes[1,2]

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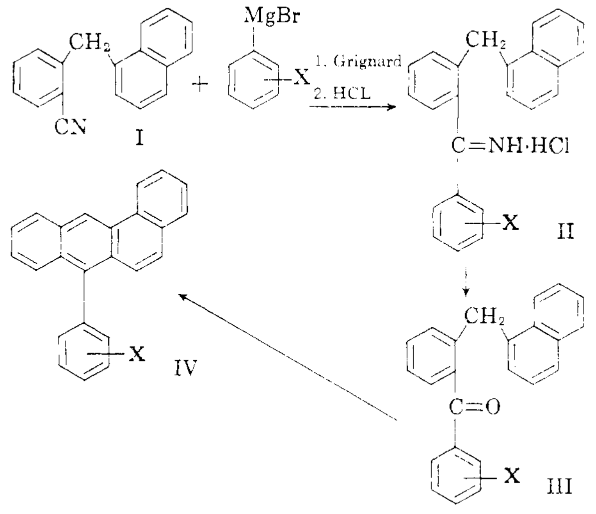
A series of new 10-(substituted phenyl)-1,2-benzanthracenes has been prepared. These compounds were prepared by applying a variety of techniques to the aromatic cyclodehydration of appropriate ketones.

In the last twenty years a tremendous amount of data has been collected on the chemistry of polynuclear hydrocarbons.[3] A systematic study by Cook[4] revealed that the most significant structural feature of the more potent carcinogens is the 1,2-benzanthracene ring system with a carbon substituent at either of the *meso* positions, 9 or 10. However, it has been only recently[5] that extensive research on the properties, reactions and syntheses of the *meso*-arylbenzanthracenes has been conducted. Since we have learned recently[6] of the physiological activity of 10-phenyl-1,2-benzanthracene, we thought it would be useful to prepare compounds in this series containing functional groups in the phenyl ring. Another interest in this work stems from the fact that the intermediate ketones lend themselves well to a study of the effects of various reagents on the aromatic cyclodehydration reaction.[7]

CHART I



The ketones III required in this study were prepared in good yield by the reaction of the appropriate Grignard reagent on 2-(1-naphthylmethyl)-benzonitrile.[8,9]

Aluminum oxide (alumina), hydrobromic acid–acetic acid mixture, phenyl acid phosphate, polyphosphoric acid and sulfuric acid were used to effect the aromatic cyclodehydration of the ketones III to the various substituted benzanthracenes (IV). The usual hydrobromic acid–acetic acid[7] mixture effected ring closure in the case of all ketones studied (see Table I); however, this reagent hydrolyzed the cyano group and cleaved the methoxy group.

Phenyl acid phosphate was used successfully to effect the cyclization of each of the ketones. This reagent did not cleave the methoxy group but it did hydrolyze the cyano group.

In view of the previous results obtained using alumina[10] this reagent proved rather disappointing. The methoxy ketone III, X = 4-OCH_3, was cyclized but split giving 1,2-benzanthracene in high yield and attempts to effect cyclization at lower temperatures resulting in recovery of starting material. The cyano ketone III, X = 4-CN, was unaffected. In the case of the halogen ketones III, X = 4-Cl and 4-Br, alumina gave fair yields of the corresponding aryl benzanthracenes.

Cold concentrated sulfuric acid was the only reagent we tried which effected cyclization of the cyano ketone III, X = 4-CN, without hydrolysis.[11] Under various conditions, 2-(1-naphthylmethyl)-2'-methoxybenzophenone (III, X = 2-OCH_3) gave 1,2-benzanthracene, 10-(2'-methoxyphenyl)-1,2-benzanthracene or starting material when treated with sulfuric acid.

Polyphosphoric acid apparently gave results which were inferior to phenyl acid phosphate.

As expected, the ultraviolet spectra of the new phenylbenzanthracenes were similar to the parent hydrocarbon.

Experimental[12,13]

2,1(Naphthylmethyl)-4'-chlorobenzophenone(III,X,4-Cl).—A Grignard reagent was prepared from 5.9 g. (0.28 mole) of magnesium and 48 g. (0.28 mole) of *p*-bromochlorobenzene in 300 ml. of dry ether. When the reaction was complete the ether was distilled while 30 g. (0.12 mole) of nitrile in 250 ml. of benzene was added. The mixture was heated under reflux and stirred for 18 hours, cooled to room temperature and decomposed with a solution of 20% ammonium chloride. The organic layer was separated,[14] washed with water, combined with 200 ml. of a solution of 25% sulfuric acid and heated under reflux for 20 hours. The organic layer was separated, the solvent removed, and the

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[1] Presented before the Division of Organic Chemistry at the 133rd Meeting of the American Chemical Society, San Francisco, Calif., April, 1958.

[2] This paper has been abstracted from the Masters thesis of R. K. Stevens presented to the Virginia Polytechnic Institute in 1957.

[3] See, for example, E. Clar, "Aromatische Kohlenwasserstoffe Polycyclische System," Zweite Auflage, Springer-Verlag, Berlin, 1952.

[4] J. W. Cook, *J. Chem. Soc.*, 1037 (1930).

[5] See F. A. Vingiello and A. Bořkovec, THIS JOURNAL, **78**, 1240 (1956), and references listed there.

[6] Private communication from the Natl. Inst. Health, Bethesda, Md.

[7] C. K. Bradsher, THIS JOURNAL, **62**, 486 (1940).

[8] F. A. Vingiello, A. Bořkovec and J. Shulman, *ibid.*, **72**, 2320 (1955).

[9] Again it was found that yields of the ketones were 12–17% higher if the ketimine hydrochlorides were not isolated; see ref. 8.

[10] F. A. Vingiello and A. Bořkovec, THIS JOURNAL, **78**, 3295 (1956).

[11] For an analogous reaction see C. K. Bradsher, F. Brown and P. Leake, *ibid.*, **79**, 1471 (1957).

[12] All melting points were taken on a Fisher-Johns melting point block and are uncorrected.

[13] All analyses were carried out by the Micro-Tech Laboratories, Skokie, Ill.

[14] At this point the ketimine hydrochloride can be isolated by adding concentrated hydrochloric acid.

TABLE I

Ketones III cyclized, X =	Percentage yield, using various cyclizing agents, of IV, X = HBr–HOAc	Phenyl acid phosphate	Alumina	Concd. H_2SO_4	Polyphosphoric acid
4-OCH_3	4-OH(75)	4-OCH_3(54)	(80)[a]		
4-CN	4-COOH(60)	4-COOH(92)	(87)[b]	4-CN(60)	
4-Cl	4-Cl(76)	4-Cl(78)	4-Cl(61)		
4-Br	4-Br(92)	4-Br(65)	4-Br(60)		
2-OCH_3	2-OH(62)	2-OCH_3(72)		(15)[a]	2-OCH_3(33)

[a] Only 1,2-benzanthracene was isolated. [b] Only starting material was isolated.

resulting oil distilled *in vacuo*. The fraction distilling between 265–268° (1.5 mm.) was collected. This green, fluorescent, viscous oil was crystallized from 95% ethanol and then recrystallized three times yielding white microcrystals, m.p. 111–112°, yield 37 g. (92%).

Anal. Calcd. for $C_{24}H_{17}ClO$: C, 80.78; H, 4.80. Found: C, 80.47; H, 4.48.

The remaining new ketones were prepared in a similar way.

TABLE II

NEW KETONES III

X	Yield, %	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
4-OCH_3[a]	90	91–92	85.20	84.92	5.72	6.03
4-CN	57[b]	117–118	86.43	86.43	4.93	4.90
4-Cl[c]	92	111–112	80.78	80.47	4.80	4.84
4-Br[d]	72	106–107	71.85	72.07	4.27	4.51
2-OCH_3	80[e]	108–109	85.20	85.01	5.72	5.92

[a] B.p. 254–262° (3 mm.). [b] Prepared by a Rosenmund–von Braun reaction on the corresponding bromo ketone in 57% yield. A similar reaction on the chloro ketone gave only starting material. [c] B.p. 265–268° (1.5 mm.). [d] B.p. 275–278° (2 mm.). [e] Hydrolysis of the ketimine in the usual way with 20% H_2SO_4 gave only 1,2-benzanthracene. The desired product was obtained by using 20% HCl for the hydrolysis.

10-(4-Bromophenyl)-1,2-benzanthracene (IV, X = 4-Br).—A mixture of 1 g. of the corresponding ketone (III, X = 4-Br) and 10 g. of phenyl acid phosphate[15] was heated for 2 hours at 140°. The mixture was cooled and washed with water until all the phenyl acid phosphate was removed. The residual oil was dissolved in 95% ethanol and treated with charcoal. The ethanolic solution yielded 0.6 g. (65%) of light tan crystals, m.p. 164–168°.

Anal. Calcd. for $C_{24}H_{15}Br$: C, 75.20; H, 3.95. Found: C, 75.11; H, 4.05.

The other phenyl acid phosphate-catalyzed cyclizations were carried out in a similar way and the results are shown in Table I. The constants for the new products are shown in Table III.

Cyclization of 2-(1-Naphthylmethyl)-4′-cyanobenzophenone (III, X = 4-CN).—A. To 6 ml. of cooled (−15°) concentrated sulfuric acid there was added 0.5 g. of the ketone III, X = 4-CN. This mixture was stirred for two hours while the temperature was maintained between −20 and −15°. The mixture was poured over a small amount of crushed ice and the resulting solution was extracted with ether. The ethereal solution was concentrated, yielding 0.3 g. (60%) of a yellow solid. Four recrystallizations from ethanol gave slightly yellow needles, m.p. 197–198°.

Anal. Calcd. for $C_{25}H_{15}N$: C, 91.16; H, 4.59. Found: C, 91.20; H, 4.67.

B. Cyclization of 1.0 g. of the ketone using phenyl acid phosphate gave 0.9 g. (92%) of 10-(4-carboxyphenyl)-1,2-benzanthracene (IV, X = 4-COOH), m.p. 298–300° (with sublimation).

Anal. Calcd. for $C_{25}H_{16}O_2$: C, 86.18; H, 4.63; neut. equiv., 348. Found: C, 85.81; H, 5.23; neut. equiv., 351.

C. A mixture of 0.5 g. of the ketone, 15 ml. of 48% hydrobromic acid and 30 ml. of glacial acetic acid was heated for 24 hours under reflux. On cooling, sand-colored crystals formed, 0.3 g. (60%). Recrystallization from ethanol gave white crystals, m.p. 298–300° (with sublimation). A mixture of this product with that from "B" above showed no depression of the melting point.

D. Attempted cyclization of the ketone using the recently developed alumina procedure[10] gave only an 87% recovery of starting material.

TABLE III

NEW 10-PHENYL-1,2-BENZANTHRACENES (IV)[a]

X	Yield, %	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
4-Cl	78	168.5–169	85.07	85.17	4.46	4.51
4-Br	92	163 –163.5	75.20	75.11	3.95	4.05
4-OCH_3[c]	54	188 –189	89.79	89.30	5.42	5.50
4-OH	75	218 –220	89.97	90.19	5.04	4.96
4-$OCOCH_3$[b]	55	163 –164.5	86.16	86.00	5.01	5.08
4-CN	60	197 –198	91.16	91.20	4.59	4.67
4-COOH	92	298 –300	86.18	85.81	4.63	5.23
2-OCH_3	72	132 –134.5	89.79	89.63	5.42	5.66
2-OH	62	181 –182	89.97	89.81	5.04	5.01

[a] The ultraviolet spectra of all the new compounds were determined with a Beckman spectrophotometer (model DU, 1-cm. silica cell) using 95% ethanol as the solvent. The curves for all nine compounds are very similar. [b] Prepared from the corresponding hydroxy compound using acetic anhydride and trifluoroacetic acid. [c] The wave length maxima for IV, X = 4-OCH_3, are λ 223, 230, 260, 272, 282, 293, 320 and 335 mμ.

Cyclization of 2-(1-Naphthylmethyl)-2′-methoxybenzophenone (III, X = 2-OCH_3).—A. Cyclization of the ketone with phenyl acid phosphate using essentially the procedure described earlier gave 72% of 10-(2′-methoxyphenyl)-1,2-benzanthracene (IV, X = 2-OCH_3), m.p. 132–134.5°.

Anal. Calcd. for $C_{25}H_{18}O$: C, 89.79; H, 5.42. Found: C, 89.63; H, 5.66.

B. Cyclization in polyphosphoric acid for 24 hours at 100° gave only a 33% yield, while 80% sulfuric acid at 100° appeared without effect (67% recovery).

C. Cyclization using 85% sulfuric acid at 100° gave a 30% yield, while concentrated sulfuric acid at room temperature gave a 25% yield of 1,2-benzanthracene.

D. A mixture of 2.0 g. of the ketone, 40 ml. of 48% hydrobromic acid and 60 ml. of glacial acetic acid was heated under reflux for 18 hours, under a nitrogen atmosphere. The mixture was cooled and the white crystals separated, washed with water, dissolved in ethanol, treated with charcoal and cooled. There was obtained 1.0 g. (62%) of 10-(2-hydroxyphenyl)-1,2-benzanthracene (IV, X = 2-OH), m.p. 181–182°.

Anal. Calcd. for $C_{24}H_{16}O$: C, 89.97; H, 5.04. Found: C, 89.81; H, 5.01.

This product was methylated in the usual way with dimethyl sulfate to give 77% of a product identical with that obtained in "A" above.

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[15] This was kindly given to us by the Virginia–Carolina Chemical Corp., Richmond, Va. This material is a mixture of mono- and dihydrogen phosphate esters containing varying amounts of polyphosphates.