[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF MISSOURI]

The Reaction of Aryl Carbinols with Aluminum Chloride and Aromatic Hydrocarbons[1]

BY HERBERT E. UNGNADE AND ELBERT W. CRANDALL[2]

Benzyl alcohol and benzhydrol can react with benzene and aluminum chloride to give phenyl substituted methanes.[3,4] This reaction may be interpreted as an alkylation reaction in which these carbinols act as alkylating agents. In the presence of excess aluminum chloride this reaction is entirely suppressed and the same reactants furnish anthracene.

When toluene and diphenylmethane are used in the place of benzene, the two carbinols yield identical mixtures of dimethyl and dibenzylanthracenes, respectively, as the only products. Identical mixtures of such disubstituted anthracenes are also produced from benzaldehyde by reaction with aluminum chloride and the above hydrocarbons.

As an explanation for these reactions it is suggested that benzyl alcohol and benzhydrol can act as carbon monoxide donors when larger amounts of aluminum chloride are used. The hydrocarbon solvent provides the outside rings of the substituted anthracenes while the carbon monoxide from the carbinol furnishes the meso carbons.[5]

A similar explanation has been advanced for the formation of anthracene from aromatic aldehydes.[6]

The proposed mechanism is strengthened by the observation that benzyl alcohol and benzhydrol yield carbon monoxide when stirred with aluminum chloride at 60°, as is the case for benzaldehyde.

Triphenylcarbinol is a by-product in the reaction with benzhydrol only when benzene is used as a solvent. Its formation is favored by lower temperatures (Table I). It is also formed from various substituted aromatic aldehydes, aluminum chloride and benzene[7] and is possibly derived from a reaction between benzene and carbon monoxide. The yields of both anthracene and triphenylcarbinol are increased by adding carbon monoxide to the reaction mixture. Triphenylcarbinol remains unchanged when treated with benzene and aluminum chloride at 60°.

TABLE I

THE REACTION OF BENZHYDROL WITH BENZENE AND ALUMINUM CHLORIDE

Temp., °C.	Moles $AlCl_3$[a]	Triphenylmethane, g.	Triphenylcarbinol, g.	Anthracene, g.	Tar, g.
0	1.0	15.1	0	0	0
0	2.0	1.90	17.1	0	0
0	3.1	0	12.03	8.26	0
60	3.1	0	3.68	4.89	8.64
60[b]	3.1	0	5.94	7.95	9.05

[a] Per mole of benzhydrol. [b] With addition of carbon monoxide gas during the reaction.

Experimental[8]

The Reaction of Benzyl Alcohol with Aromatic Hydrocarbons and Aluminum Chloride.—Benzyl alcohol (19.5 g.), dissolved in 50 cc. of benzene, was added during fifteen minutes to a mixture of 100 cc. of benzene and 56 g. of aluminum chloride. The mixture was stirred for three and one half hours at 60°, then it was decomposed in the usual manner and steam-distilled. The dry non-volatile residue weighed 14.4 g. and gave 57% of crystalline material on vacuum sublimation. Chromatographic adsorption of the sublimate on aluminum oxide from Skellysolve C solution yielded 90.3% of pure anthracene, m. p. 212–214°.

When this reaction was carried out under identical conditions with toluene, the non-volatile product (25.5 g.) yielded 64.7% of sublimate which melted at 213–215° after crystallization from Skellysolve C. It depressed the melting point of anthracene, gave correct analytical values and identical absorption spectra as the mixture of dimethylanthracenes obtained from benzaldehyde, aluminum chloride and toluene.[7]

The non-volatile material from the reaction of benzyl alcohol (25 g.) with diphenylmethane (60 cc.) and aluminum chloride (67 g.) weighed 32.12 g. Vacuum distillation of the crude product at 180–210° (1×10^{-3} mm.) gave 35.5% of distillate which was chromatographically uniform and melted at 191–192° (from Skellysolve C). By analogy with the dimethylanthracenes, this substance may be a mixture of 2,6- and 2,7-dibenzylanthracenes.[9]

Anal. Calcd. for $C_{28}H_{22}$: C, 93.85; H, 6.15. Found: C, 93.99; H, 6.37

The Reaction of Benzhydrol with Aromatic Hydrocarbons and Aluminum Chloride.—The vigorous reaction between benzhydrol, benzene and aluminum chloride was moderated by adding benzhydrol (27.6 g.) slowly during two hours to a mixture of 150 cc. of benzene and aluminum chloride maintained at the specified temperature (Table I). Stirring was continued for one and one-half hours and the mixture was decomposed and steam-distilled. The residue from the steam-distillation was dried by distillation with benzene and weighed. The light colored residues from the reaction at 0° were used directly for the chromatographic separation. The other products were first sublimed at 2 mm.

Adsorption of the mixtures on alumina from Skellysolve C solution permitted a nearly quantitative separation of the constituents. The experimental results are given in Table I.

The reaction of benzhydrol (0.09 mole) with aluminum chloride (0.28 mole) and 150 cc. of toluene yielded 14.96 g. of non-volatile residue which contained 39.7% tar.

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(1) Presented in part before the division of Organic Chemistry of the American Chemical Society, Chicago, April, 1948.

(2) In part from the Ph.D. thesis of E. W. Crandall.

(3) Huston and Friedemann, THIS JOURNAL, **38,** 2528 (1916).

(4) Huston and Friedemann, *ibid.*, **40,** 791 (1918).

(5) An alternative explanation is possible for the formation of dimethylanthracenes from benzyl alcohol and toluene, as was pointed out by the referee. Direct condensation of two moles of benzyl alcohol could produce anthracene which could then be methylated by methyl groups from the toluene. An attempt to methylate anthracene with toluene in this manner under the conditions of the reaction, however, yielded only unchanged anthracene and tar.

(6) Hey, *J. Chem. Soc.*, 72 (1935).

(7) Ungnade and Crandall, THIS JOURNAL, **71,** 2209 (1949).

(8) All temperatures uncorrected.

(9) NOTE ADDED IN PROOF.—Oxidation of the mixture of dibenzylanthracenes (1 g.) with chromic oxide (4 g.) in acetic acid (30 cc.) and water (4 cc.) yielded 1.14 g. (98%) of dibenzoylanthraquinone, m. p. 241–242° (from 95% alcohol). *Anal.* Calcd. for $C_{28}H_{16}O_4$: C, 80.70; H, 3.85. Found: C, 80.50; H, 4.04.

The sublimate melted at 215-217° (from Skellysolve C) and was identical with the mixture of dimethylanthracenes obtained previously.

A mixture of benzhydrol (25 g.), diphenylmethane (60 cc.) and aluminum chloride (56 g.) maintained for three hours at 60° yielded 40.43 g. of non-volatile product. Vacuum distillation at 180-210° (1×10^{-3} mm.) yielded 16.0% of dibenzylanthracene, m. p. 191-192°, which was spectroscopically identical with the substance isolated from the benzyl alcohol reaction (Table II).

The Reaction of Benzaldehyde with Diphenylmethane.—Benzaldehyde (25 g.), aluminum chloride (67 g.) and diphenylmethane (70 cc.) gave 55.7 g. of non-volatile product under the same conditions. Dibenzylanthracene, m. p. 190-191°, was obtained from this residue as the only distillable substance. It proved to be identical in all respects with the dibenzylanthracenes described above.

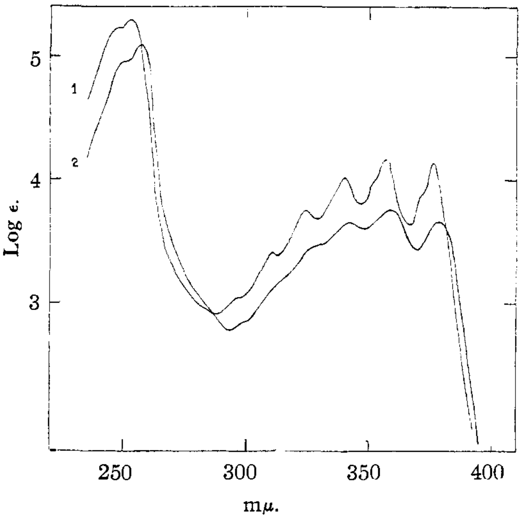

Fig. 1.—Ultraviolet absorption spectra: curve 1, dibenzylanthracenes; curve 2, dimethylanthracenes.

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA

Wave length	$\log \epsilon\ \lambda_{\max.}$ I	II	III	Wave length	$\log \epsilon\ \lambda_{\min.}$ I	II	III
			Dimethylanthracenes[a]				
257.5	5.029	5.134	5.097	292.5	2.775	2.810	2.790
341.3	3.640	3.655	3.654	349	3.593	3.608	3.594
359	3.751	3.766	3.765	369	3.423	3.444	3.431
379	3.667	3.679	3.673				
			Dibenzylanthracenes[a]				
254	5.312	5.638	5.689	287.5	2.924	2.834	2.997
311	3.423	3.379	3.416	312.5	3.386	3.376	3.412
324	3.769	3.736	3.749	330	3.691	3.664	3.683
340	4.037	4.003	4.012	346	3.822	3.790	3.804
356	4.173	4.146	4.157	367.5	3.654	3.634	3.648
376	4.161	4.130	4.136	380	...	3.756	3.774
381	...[b]	3.895	3.906				

[a] I, product from benzaldehyde, II from benzhydrol, III from benzyl alcohol. [b] This small maximum, which is not present in anthracene, was probably overlooked in the first curve.

Absorption Spectra.—The ultraviolet absorption spectra of the dimethyl and dibenzylanthracenes were determined in cyclohexane in 0.00128 and 0.00073 molar solutions with a Beckmann spectrophotometer.[10]

One curve each is shown in Fig. 1. Extinction values for maxima and minima of all six substances are listed in Table II. The spectral characteristics of the compounds are in good agreement with the proposed structures. The methylanthracenes exhibit a small hypsochromic effect, slight bathochromic effect and loss of fine structure as compared to anthracene[11] while the benzyl substituents cause general hyperchromic effect, no bathochromic effect and no loss in fine structure.

Summary

Evidence has been presented to show that benzyl alcohol and benzhydrol can act as carbon monoxide donors in the presence of excess aluminum chloride.

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[10] Absorption spectra by Dr. E. E. Pickett, University of Missouri.

[11] Jones, *Chem. Rev.*, **41**, 368 (1947); **32**, 11 (1943).

[12] The first draft of this article was received October 25, 1948.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY, THE DEPARTMENT OF SURGERY OF THE BETH ISRAEL HOSPITAL, BOSTON, AND THE HARVARD MEDICAL SCHOOL]

Preparation of Azo Compounds for the Study of Inhibition of Tumor Growth*

BY ORRIE M. FRIEDMAN, RALPH M. GOFSTEIN AND ARNOLD M. SELIGMAN

Following the demonstration by Haddow[1] that certain carcinogenic hydrocarbons are able to inhibit the growth of certain tumors in animals, many compounds with a structural resemblance to carcinogenic substances were subjected to this type of bioassay.[2] Isolated instances of inhibition of tumor growth with non-carcinogenic substances were observed, for example, with the unsymmetrical azonaphthalene (I).[2] Haddow suggested that this compound bears a superficial resemblance to the carcinogen, 1,2,5,6-dibenzanthracene (II). However, the only forms in which the unsymmetrical azonaphthalene (I) has features in common with the polynuclear carcinogenic hydrocarbons are the *cis* structures (III) and (IV) which resemble benz- derivatives of both 1,2-benzanthracene and chrysene. The hydrocarbon 1,2,5,6-dibenzphenanthrene, suggested by formula (IV), was found to be an inhibitor of tumor growth.[2] In order to explore further possible relationships between structure of azo compounds and their activity as inhibitors

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[1] (a) Haddow, *Nature*, **136**, 868 (1935); (b) Haddow and Robinson, *Proc. Roy. Soc.* (*London*), **B122**, 442 (1937); (c) Haddow, Scott and Scott, *ibid.*, **B122**, 477 (1937); (d) Haddow, *J. Path. Bact.*, **47**, 567 (1938); (e) Haddow and Robinson, *Proc. Roy. Soc.* (*London*) **B127**, 277 (1939).

[2] Badger, Elson, Haddow, Hewett and Robinson, *Proc. Roy. Soc.* (*London*), **B130**, 255 (1941).