TABLE II

PHYSICAL PROPERTIES OF ALKYLBENZENES

Alkylbenzene	B. p., °C.	$n^{25}D$	Sp. gr. 25°
i-Propylbenzene	151	1.4885	0.8581
Diisopropylbenzene	204.5	1.4892	.8550
t-Amylbenzene	189	1.4860	.8550
t-Diamylbenzene	260	1.4841	.8491
s-Amylbenzene	193	1.4884	.8576
s-Diamylbenzene	265	1.4845	.8496
Benzylbenzene	261	1.5782	1.0000
Dibenzylbenzene	M. p. 84		
Ethylbenzene	135	1.4928	0.8603
Diethylbenzene	183	1.4949	0.8673

Derivatives of Alkylbenzenes.—The acetamido derivative of the various monoalkylbenzenes was prepared according to the procedure outlined by Ipatieff and Schmerling.[5] The compounds formed had melting points that agreed closely with those reported in the literature and are as follows: diacetaminoethylbenzene (m. p. 224°), monoacetaminoisopropylbenzene (m. p. 103°), diacetaminoisopropylbenzene (m. p. 114°), and monoacetamino-*t*-amylbenzene (m. p. 139°).

(5) Ipatieff and Schmerling, *ibid.*, **59**, 1056 (1937).

Summary

Benzene has been alkylated by various ethers in the presence of boron fluoride.

Normal ethers give secondary, while isoethers give tertiary alkylbenzenes.

The disubstituted products in the presence of boron fluoride were the para derivatives.

A mechanism has been proposed for the reaction of ethers with benzene.

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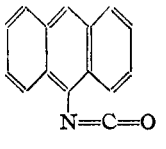
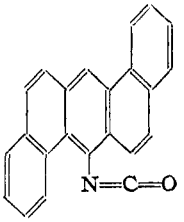
[CONTRIBUTION FROM THE DEPARTMENT OF MEDICAL RESEARCH OF THE UNIVERSITY OF TORONTO]

Anthranyl and 1,2,5,6-Dibenzanthranyl Isocyanates. I

BY HUGH J. CREECH AND W. R. FRANKS

The primary purpose behind the synthesis of anthranyl and 1,2,5,6-dibenzanthranyl isocyanates was the formation of artificial protein antigens[1] for an investigation of the possibility of immunization against the action of carcinogenic agents (i) applied experimentally and (ii) normally active in the organism.[2] Also, it has been found recently that some of the addition compounds of 1,2,5,6-dibenzanthranyl isocyanate possess carcinogenic activity. The water-soluble sodium salt of 1,2,5,6-dibenzanthranylcarbamidoacetic acid[1b] produces tumors rapidly in mice.

Anthranyl isocyanate (I) and 1,2,5,6-dibenzanthranyl isocyanate (II) were prepared by the action of phosgene on the 9-amino derivatives of anthracene and 1,2,5,6-dibenzanthracene according to the method used by Vittenet[3] for the preparation of naphthyl isocyanates.

(I)  (II) 

The well recognized instability of *meso*-substituted anthracenes together with the great reactivity of the isocyanate grouping seriously complicate the essentially simple syntheses of the isocyanates. The extent of the occurrence of the side reactions to which the isocyanates are subject has been summarized by Porter,[4] Franklin[5] and Shriner, Horne and Cox.[6]

The success of the syntheses depends to an unusual degree upon the purity of the reactants and solvents and the reduction to a minimum of the main side reactions in which quinones and disubstituted ureas result from an insufficient supply of phosgene, excessive heating, or exposure to dampness and oxygen. Solubility relationships and the instability of the isocyanates make extremely difficult the removal of side products. The amines and isocyanates must be stored in the dark under nitrogen. Consideration of these facts has allowed an increase of yield from 5 to 70% of the anthranyl isocyanate from anthranylamine.

The 1,2,5,6-dibenzanthranyl isocyanate is fairly stable. The work of Cook[7] supports this observation. The addition products of the isocyanates with alcohols are also quite stable.

The isocyanates react rapidly with amines to

(1) Creech and Franks, (a) *Can. Chem. Met.*, **21**, 50 (1937); (b) *Am. J. Cancer*, **30**, 555 (1937).

(2) Franks and Creech, unpublished.

(3) Vittenet, *Bull. soc. chim.*, [3] **21**, 586 and 957 (1899).

(4) Porter, "Molecular Rearrangements," Chemical Catalog Co., New York, 1928, pp. 13–30.

(5) Franklin, "The Nitrogen System of Compounds," Reinhold Publishing Corp., New York, 1936, pp. 108–127.

(6) Shriner, Horne and Cox, *Org. Syntheses*, **14**, 72 (1934).

(7) Cook, *J. Chem. Soc.*, 3273 (1931).

form disubstituted ureas. However, the ureas require further investigation because of technical difficulties encountered in their complete purification.

The authors wish to acknowledge the helpful criticisms of Professor J. W. Burns, of the University of Western Ontario.

Experimental Part[8]

Anthranyl Isocyanate.—Anthranylamine, prepared according to Meisenheimer and Connerade[9] from 9-nitroanthracene,[10] was converted to anthranyl isocyanate by a slight modification of methods used by Vittenet[3] and Shriner, Horne and Cox.[6]

The necessary alterations include a greater excess of phosgene,[6,11] the use of nitrogen to protect the products from oxidation, extensive purification of the anthranylamine, careful refluxing of the flocculent red precipitate of the amine hydrochloride at pressures and temperatures not exceeding 75 mm. and 70°. When the volume of the benzene–toluene solution of anthranyl isocyanate had been reduced (80%) by vacuum distillation to 35 cc., it was transferred to a vacuum desiccator where crystallization occurred when the volume was further reduced to 10 cc. The crystals were dissolved in 25 cc. of carbon tetrachloride. After filtration to remove the very insoluble disubstituted urea, the solution was placed in a vacuum desiccator in the dark. Dark green needles of anthranyl isocyanate, m. p. 75.5–76.5° separated. Tests for anthraquinone were negative. Anthranylamine, m. p. 147–148°, (5.7 g.) gave 4.0 g. of isocyanate.

Anal. Calcd. for $C_{15}H_9ON$: C, 82.12; H, 4.14. Found: C, 81.40, 81.21; H, 4.14, 4.01.

Anthranyl Carbamates.—A nitrogen stirred solution of anthranyl isocyanate (added either as a solid or in an inert solvent) in absolute alcohol was refluxed for ten minutes. Slow evaporation under nitrogen gave the carbamates, which were recrystallized from the alcohol and from carbon tetrachloride.

(a) **N-Anthranyl-O-ethyl Carbamate.**—Yellow needles; m. p. 236.5–237°.

Anal. Calcd. for $C_{17}H_{16}O_2N$: C, 76.92; H, 5.70. Found: C, 76.78, 77.00; H, 5.69, 5.85.

(b) **N-Anthranyl-O-methyl Carbamate.**—Green crystals; m. p. 265–266°.

Anal. Calcd. for $C_{16}H_{13}O_2N$: C, 76.43; H, 5.21. Found: C, 76.62, 76.72; H, 5.17, 5.37.

Anthranyl Carbamido Ethanol, $C_{14}H_9NHCONHCH_2CH_2OH$.—Equivalent amounts of β-aminoethanol and anthranyl isocyanate in chloroform solution react immediately at room temperature to give a yellow precipitate which was washed thoroughly with chloroform and crystallized from ethanol, m. p. 263–264°.

Anal. Calcd. for $C_{17}H_{16}O_2N_2$: C, 72.81; H, 5.72. Found: C, 72.65, 72.79; H, 5.85, 5.96.

Excess isocyanate and refluxing failed to cause an additional reaction with the hydroxyl group as was found by Knorr and Rössler[12] with phenyl isocyanate.

Oxidation.—Anthranyl isocyanate and its addition products oxidize readily to anthraquinone by refluxing with potassium dichromate.

1,2,5,6-Dibenzanthranyl Isocyanate.—This synthesis from 1,2,5,6-dibenzanthranylamine, m. p. 277–278°, prepared according to Cook,[7] was essentially similar to that of Vittenet.[3] The solvents required less concentration to allow the crystallization of 1,2,5,6-dibenzanthranyl isocyanate in fine light green needles. Recrystallized from carbon tetrachloride, m. p. 181–181.5°; yield 75%.

Anal. Calcd. for $C_{23}H_{13}ON$: C, 86.50; H, 4.11. Found: C, 86.51, 87.06; H, 4.07, 4.35.

N-1,2,5,6-Dibenzanthranyl-O-ethyl Carbamate was prepared by refluxing the isocyanate with absolute ethanol for an hour under nitrogen. The product crystallized on cooling in slender, bright green needles; recrystallized from ethanol–dioxane; m. p. 224–224.5°.

Anal. Calcd. for $C_{25}H_{19}O_2N$: C, 82.15; H, 5.24. Found: C, 82.21, 82.33; H, 5.23, 5.56.

N-1,2,5,6-Dibenzanthranyl-O-methyl Carbamate separated as a white powder after half an hour refluxing of the isocyanate with methanol; crystallized from methanol–dioxane in tiny white crystals, m. p. 264–265°.

Anal. Calcd. for $C_{24}H_{17}O_2N$: C, 82.03; H, 4.88. Found: C, 82.13; H, 5.16.

1,2,5,6-Dibenzanthranyl Carbamido Ethanol.—Equivalent quantities of β-aminoethanol and 1,2,5,6-dibenzanthranyl isocyanate in carbon tetrachloride reacted immediately on slight warming under nitrogen to give a brown flocculent precipitate which was washed with carbon tetrachloride and crystallized from ethanol as greenish white needles, m. p. 308–309°.

Anal. Calcd. for $C_{25}H_{20}O_2N_2$: C, 78.86, H, 5.30. Found: C, 78.58, 78.27; H, 4.97, 5.45.

Oxidation.—The 1,2,5,6-dibenzanthranyl isocyanate and its addition products were converted readily to 1,2,5,6-dibenzanthraquinone by the method of Clar.[13]

Summary

The synthesis of anthranyl and 1,2,5,6-dibenzanthranyl isocyanates and their identification by reactions with alcohols have been described. The 1,2,5,6-dibenzanthranyl isocyanate and its addition compounds are being tested for carcinogenic activity.

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(8) All melting points are corrected. The microanalyses were kindly done by Dr. Helen Stantial, of the Department of Chemistry, University of Toronto.

(9) Meisenheimer and Connerade, (a) *Ber.*, **33**, 3548 (1900); (b) *Ann.*, **330**, 165 (1904).

(10) Dimroth, *Ber.*, **34**, 219 (1901).

(11) Cumming, Hopper and Wheeler, "Systematic Organic Chemistry," Constable and Co. Ltd., London, 1931, p. 521.

(12) Knorr and Rössler, *Ber.*, **36**, 1280 (1903).

(13) Clar, *Ibid.* **62**, 350 (1929).