was repeated twice; yield practically quantitative; m. p. 213–215° decompn.

Anal. Calcd. for $C_{13}H_9O_5N_2AsBr_2$: As, 14.75; Br, 31.46. Found: As, 14.83; Br, 31.30.

Methyldi-(3-nitro-4-hydroxyphenyl)-arsine Oxide.—A suspension of 4.0 g. of methyldi-(3-nitro-4-bromophenyl)-arsine oxide in 600 cc. of water, which contained 4.0 g. of potassium hydroxide, was boiled for one hour, a solution of 10 g. of potassium hydroxide in 20 cc. of water added, the clear orange solution boiled two hours longer, concentrated on a steam-bath to a volume of 250 cc., cooled and neutralized with sulfuric acid (1:1). The pale yellow, crystalline precipitate was recrystallized from 40% acetic acid; yield 2.9 g.; m. p. 239–240° decompn.

Anal. Calcd. for $C_{13}H_{11}O_7N_2As$: As, 19.60. Found: As, 19.50.

Tri-(4-bromophenyl)-arsine Oxide.—A solution of 1.6 g. of tri-(4-bromophenyl)-arsine in 75 cc. of acetone was oxidized with 0.4 g. of potassium permanganate in the manner described above. The crude oxide was dissolved in benzene and petroleum ether (30–40°) added; the oxide separated slowly in the form of colorless needles; yield 1.3 g. (79%); m. p. 190–193°.

Anal. Calcd. for $C_{18}H_{12}OAsBr_3$: As, 13.41; Br, 42.91. Found: As, 13.44; Br, 42.70.

Tri-(3-nitro-4-bromophenyl)-arsine Oxide.—One gram of finely powdered tri-(4-bromophenyl)-arsine oxide was added, in portions, to a mixture of 0.6 cc. of nitric acid (sp. gr. 1.60) and 1.5 cc. of concd. sulfuric acid. The material was heated for two hours on a steam-bath, poured into ice water, the precipitated yellow oxide heated with 75 cc. of acetone and the mixture filtered; the treatment of the filtrate is described below. The colorless, undissolved portion (0.5 g.) was dissolved in 500 cc. of acetone and an equal volume of water added; the oxide separated in the form of colorless, glistening crystals; m. p. 252–254° decompn.

An equal volume of water was added to the yellow, acetone filtrate; 0.5 g. of yellow, sparkling crystals precipitated. The material was dissolved in the smallest possible amount of hot acetone and water added to effect precipitation; the process was repeated until the oxide was obtained in colorless form; this portion of the oxide also melted at 252–254° decompn.

Anal. Calcd. for $C_{18}H_9O_7N_3AsBr_3$: As, 10.80; Br, 34.56. Found: As, 10.87; Br, 34.37.

Summary

A number of new arsines and arsine oxides have been described.

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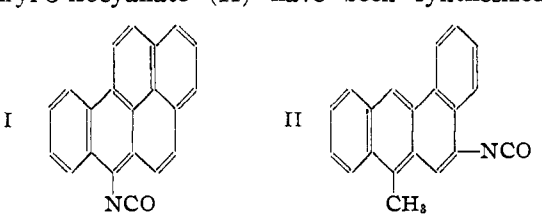
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Isocyanates of 3,4-Benzpyrene and 10-Methyl-1,2-benzanthracene

BY HUGH J. CREECH

In a continuation of a program of research on the conjugation of carcinogenic hydrocarbons with proteins[1,2] and amino acids[3], 3,4-benzpyrenyl-5-isocyanate (I) and 10-methyl-1,2-benzanthryl-3-isocyanate (II) have been synthesized.



The recent observation[4] of the pronounced carcinogenic activity of 1,2,5,6-dibenzanthryl-9-isocyanate[5] makes the tests on the present compounds of considerable significance. The 3- and 10-isocyanates[3] of 1,2-benzanthracene and their amino acid conjugates[3] have displayed no outstanding tumor-producing properties to date. The latter isocyanates are derivatives of the inactive hydrocarbon 1,2-benzanthracene, whereas the dibenzanthryl isocyanate is derived from an active parent hydrocarbon and a slightly active amine. The isocyanates described in this article are derivatives of very active hydrocarbons and thus also may be capable of causing tumors rapidly. Since it has been demonstrated[2] that isocyanates couple readily with proteins "*in vitro*,"

(1) Creech and Franks, *Am. J. Cancer*, **30**, 555 (1937).

(2) Creech and Jones, THIS JOURNAL, **62**, 1970 (1940).

(3) Fieser and Creech, *ibid.*, **61**, 3502 (1939).

(4) I am indebted to Drs. Shields Warren and Charles E. Dunlap of the Huntington Memorial Hospital for permission to quote the following results. The subcutaneous injection of 2 mg. of 1,2,5,6-dibenzanthryl-9-isocyanate, m. p. 179–179.5° cor., dissolved in 0.2 cc. of tricaprylin produced tumors at the site of injection in all of the fourteen C3H mice under test within 125 days, the earliest tumors being observed at 92 days. The average latent period was 111 days and the carcinogenic index was 90. It is noteworthy that this compound appears to be somewhat more active than the parent hydrocarbon [Fieser, *Am. J. Cancer*, **34**, 37 (1938); Shimkin and Andervont, *J. Natl. Cancer Inst.*, **1**, 57 (1940)]. In earlier tests [Franks and Creech, *Am. J. Cancer*, **35**, 203 (1939)] which were rendered indecisive by animal mortality due to other causes, an aqueous suspension of the dibenzanthryl isocyanate (2 mg.) produced one tumor at 159 days in an effective total of four stock white mice; the remaining three mice had not developed tumors at one year. The present observation offers one explanation of the erratic carcinogenic action of some of the dibenzanthrylcarbamido casein preparations which were known to contain adsorbed isocyanate but it does not necessarily invalidate the observations of the activity of the amino acid conjugate.[1,3]

(5) Creech and Franks, THIS JOURNAL, **60**, 127 (1938).

the possibility that they may combine with tissue proteins "*in vivo*" is worthy of consideration.

The isocyanates of 3,4-benzpyrene and 10-methyl-1,2-benzanthracene were synthesized in excellent condition and in good yield by the action of phosgene on the corresponding amines and were characterized by the formation of the usual derivatives. Difficulties were again encountered with the crystallization of the substituted urea derivatives which, however, were obtained eventually in a satisfactory condition and were found to possess the usual characteristic properties. Glycine ethyl ester has been coupled with the isocyanates to form conjugates required for carcinogenic tests and for the calibration[2] of the ultraviolet absorption intensities of the conjugated proteins whose preparation is in progress.

Experimental Part[6]

Nitration of 3,4-benzpyrene.—3,4-Benzpyrene, m. p. 177–178°, was obtained in 35% yield from 3-benzoylperinaphthane by a fully described method.[7] Nitration of the hydrocarbon (6.5 g.) was conducted in three lots according to the procedure of Fieser and Hershberg[8] using, however, only 1.15 moles of nitric acid (sp. gr. 1.42). A total of 6.4 g. (83%) of crystalline material, m. p. 252–253°, separated from the nitrating solutions. This product apparently did not contain the appreciable amounts of dinitro compound reported by other investigators.[8,9] One crystallization from benzene–ligroin gave 5.72 g. (75%) of orange-yellow nitrobenzpyrene, m. p. 254.5–255.5°.

5-Amino-3,4-benzpyrene.—The nitro compound (5.0 g.) was reduced by the stannous chloride procedure giving 4.17 g. (93%) of the amine in the form of golden yellow plates, m. p. 236–238° dec. (245.5–246.5° in an evacuated capillary). This method proved as satisfactory as hydrogenation[8] and better than reduction with phenylhydrazine.[9] In a typical experiment, a suspension of 1.6 g. of nitrobenzpyrene in 250 cc. of hot glacial acetic acid was treated with 20 g. of stannous chloride in 25 cc. of concentrated hydrochloric acid and the mixture was refluxed for twenty minutes. During this period the orange-yellow suspension changed to a pale yellow solution. The addition of 25 cc. of concentrated hydrochloric acid caused the formation of a voluminous faintly yellow precipitate. When the flask had been cooled to 40°, water was added to complete the precipitation. After being washed with a mixture of dilute hydrochloric and acetic acids, the complex was stirred at room temperature with 100 cc. of normal ammonium hydroxide for ten minutes. Benzene (800 cc.) was added and the dark yellow solid rapidly went into solution in the benzene layer which was separated, washed and dried. The solution was concentrated, ligroin was added and upon being cooled it deposited 1.35 g. of amine with the above characteristics. A sample after two recrystallizations from benzene–ligroin melted at 239–241° dec. (246.5–247.5° vac.).

3,4-Benzpyrenyl-5-isocyanate.—The addition of an excess of phosgene (25 g.) in 100 cc. of toluene to a solution of the amine (3.65 g.) in a liter of warm benzene produced an immediate flocculent precipitate which disappeared upon refluxing for ten minutes. Approximately a liter of solvent was removed by distillation at atmospheric pressure, ligroin was added and upon cooling 3.7 g. (92%) of the isocyanate, m. p. 183.5–184°, separated as shining yellow needles. Recrystallization from benzene–ligroin did not alter the melting point.

Anal. Calcd. for $C_{21}H_{11}ON$: N, 4.78; C, 85.99; H, 3.78. Found: N, 4.75; C, 85.75; H, 3.81.

Ethyl 3,4-benzpyrenyl-5-carbamate was prepared by refluxing the isocyanate with absolute ethanol for one-half hour. The product crystallized from benzene–ligroin as pale yellow needles, m. p. 249–249.5°.

Anal. Calcd. for $C_{23}H_{17}ON$: N, 4.13. Found: N, 4.04.

3,4-Benzpyrenyl-5-urea.—The isocyanate in cold dioxane solution underwent an instantaneous reaction with concentrated ammonium hydroxide giving a flocculent precipitate. The material was obtained from dioxane–ligroin as fluffy yellow needles which melted with decomposition in an evacuated capillary at about 370° after darkening at 300°.

Anal. Calcd. for $C_{21}H_{14}ON_2$: N, 9.03. Found: N, 8.77.

3,4-Benzpyrenyl-5-carbamidoethanol.—An immediate precipitate was formed upon mixing solutions of the isocyanate and β-aminoethanol in chloroform. The product was washed with warm chloroform and crystallized from dioxane–ligroin as slender fluffy yellow needles which darkened at 290° and melted with decomposition in an evacuated capillary at about 310°. As was the case with the urea derivative, the crystals lost their character on the collecting funnel.

Anal. Calcd. for $C_{23}H_{18}O_2N_2$: N, 7.89. Found: N, 7.48.

3,4-Benzpyrenyl-5-carbamidoacetic Acid.—The addition of the isocyanate in dioxane solution to glycine in carbonate–bicarbonate solution caused the immediate formation of a yellow precipitate. This was dissolved in 0.02 *N* carbonate–bicarbonate solution and precipitated by the addition of enough 2 *N* hydrochloric acid to bring the *p*H to 3. The flocculent precipitate was redissolved and reprecipitated. It was dried in a vacuum desiccator to a dark powder which was washed with ether to give a brownish-yellow powder (calcd.: N, 7.59; found: N, 7.42) which melted with decomposition at about 320°. Attempted crystallization of the compound from organic solvents invariably caused decomposition.[3]

The ethyl ester was obtained by the reaction of glycine ethyl ester (100 mg.) with the isocyanate (200 mg.) in cold benzene solution. The flocculent material was dissolved in dioxane at 70°, ligroin was added and upon slow cooling clusters of fine yellow needles (180 mg.) were obtained.

(6) All melting points are corrected; those above 275° were determined with a metal block. Microanalyses by Lyon Southworth.

(7) Fieser and Hershberg, THIS JOURNAL, 60, 1658 (1938).

(8) Fieser and Hershberg, *ibid.*, 61, 1565 (1939).

(9) Windaus and Rennhak, *Z. physiol. Chem.*, 249, 256 (1937).

The compound also could be obtained in an analytically pure but non-crystalline condition by rapidly precipitating it from dioxane solution with ligroin. The substance after darkening and partially melting at 265° melted with decomposition at about 330°.

Anal. Calcd. for $C_{25}H_{20}O_2N_2$: N, 7.06; C, 75.74; H, 5.07. Found: N, 7.12; C, 75.50; H, 5.18.

3 - Amino - 10 - methyl - 1,2 - benzanthracene.—3-Hydroxy-10-methyl-1,2-benzanthracene, m. p. 192.5–193.5° vac., was synthesized by the method of Fieser and Hershberg[10] in 11% yield from 2-(4'-methoxy-1'-naphthylmethyl)-benzoic acid by way of 3-methoxy-1,2-benzanthrone prepared by hydrogen fluoride ring closure.[11] It was found expedient to conduct small-scale syntheses and it may be noted that some of the 3-methoxy-10-methyl-1,2-benzanthracene preparations required purification through the picrate. A mixture of 2.1 g. of the hydroxy compound, 12 cc. of dioxane, 20 cc. of concentrated ammonia solution and 10 g. of sodium bisulfite in 20 cc. of water was heated in a sealed tube at 175–185° for sixteen hours. The yellow, remarkably clean, crystalline product was dissolved in hot ethanol. After concentration and dilution with water, 1.59 g. (70%) of yellow needles, m. p. 185–187° vac., were obtained. One portion (1.09 g.) on recrystallization from benzene–hexane gave 0.90 g. of amine, m. p. 188–189° in an evacuated capillary. The remainder was purified through the sulfate and crystallized from ether-petroleum ether as yellow needles (265 mg.), m. p. 187.5–188.5° vac. A sample after several recrystallizations melted at 189–189.5° vac. (188–189° in an open capillary).

Anal. Calcd. for $C_{19}H_{15}N$: N, 5.44. Found: N, 5.25.

10 - Methyl - 1,2 - benzanthryl - 3 - isocyanate.—Following the described procedure, 1.02 g. of amine gave 0.76 g. (68%) of isocyanate as yellow needles, m. p. 149.5–150°, from ether–petroleum ether.

Anal. Calcd. for $C_{20}H_{13}ON$: N, 4.94; C, 84.78; H, 4.62. Found: N, 4.79; C, 84.96; H, 4.65.

The isocyanate was characterized by the formation of the ethyl carbamate which was obtained as colorless needles, m. p. 201–201.5°, from ether.

Anal. Calcd. for $C_{22}H_{19}O_2N$: N, 4.25. Found: N, 4.12.

10-Methyl-1,2-benzanthryl-3-urea was prepared in the usual manner and was crystallized with difficulty from dioxane as poorly formed needles, m. p. 348–350° vac.

Anal. Calcd. for $C_{20}H_{16}ON_2$: N, 9.30. Found: N, 8.89.

The **ethyl ester of 10-methyl-1,2-benzanthryl-3-carbamidoacetic acid** was synthesized by the described procedure and obtained from dioxane–ligroin as almost colorless needles, m. p. 213–214° vac.

Anal. Calcd. for $C_{24}H_{22}O_4N_2$: N, 7.24; C, 74.59; H, 5.72. Found: N, 7.24; C, 74.53; H, 5.70.

Acknowledgments.—The author wishes to thank the International Cancer Research Foundation for a grant supporting the research and to express his appreciation of the interest and advice of Professor L. F. Fieser.

Summary

3,4-Benzpyrenyl-5-isocyanate and 10-methyl-1,2-benzanthryl-3-isocyanate have been synthesized from the corresponding amines and characterized by the formation of ethyl carbamates and substituted urea derivatives. The isocyanates were coupled with glycine ethyl ester to form compounds required for studies of the protein conjugates prepared from the isocyanates. The isocyanates, amino acid conjugates and the newly synthesized 3-amino-10-methyl-1,2-benzanthracene are being tested for carcinogenic activity.

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(10) Fieser and Hershberg, THIS JOURNAL, **59**, 1028 (1937).
(11) Fieser and Hershberg, *ibid.*, **61**, 1272 (1939).

[CONTRIBUTION FROM THE MEDICAL-RESEARCH DIVISION, SHARP AND DOHME, INC.]

Sulfonamido Derivatives of Thiazoles

BY JAMES M. SPRAGUE AND L. W. KISSINGER

The success of sulfapyridine in combating bacterial infections, particularly pneumococcal infections, has led to the preparation and study of other heterocyclic derivatives of sulfanilamide. The recent interest in thiazole derivatives[1] prompts us to report on a series of sulfonamidothiazoles which we have prepared and tested for their chemotherapeutic activity.[2]

(1) Fosbinder and Walter, THIS JOURNAL, **61**, 2032 (1939); Lott, *et al.*, *ibid.*, **61**, 3593 (1939); **62**, 1873 (1940); Roblin, *et al.*, *ibid.*, **62**, 2002 (1940); Barlow and Homburger, *Proc. Soc. Exptl. Biol. Med.*, **43**, 317 (1940); Long, *et al.*, *ibid.*, **43**, 324–328 (1940).
(2) *Cf.* Northey, *Chem. Rev.*, **27**, 85 (1940).

Experimental Part[3]

The 2-aminothiazoles were prepared by procedures reported in the literature; 2-amino-4-ethyl-5-methylthiazole and 2-amino-4,5,6,7-tetrahydrobenzothiazole, which were prepared from α-bromo-diethyl ketone and α-bromocyclohexanone, respectively, do not appear in the literature previously. The properties and analyses of these compounds are recorded in Table I.

2-Sulfonamidothiazoles.—In general, these compounds were prepared by the slow addition of a slight excess of the appropriate sulfonyl chloride to a solution of a 2-aminothiazole in pyridine. After the addition was com-

(3) All melting points are uncorrected.