

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

Derivatives of 10-Methyl-1,2-benzanthracene Related to the Nitrogen and Sulfur β -Chloroethyl Vesicants^{1a}

BY ORRIE M. FRIEDMAN AND ARNOLD M. SELIGMAN

In the course of research design to discover highly toxic vesicants suitable for tactical use in chemical warfare, methyl-bis-(β -chloroethyl)-amine and tris-(β -chloroethyl)-amine were found to exhibit lymphocidal activity.^{1,2} Clinical trials have indicated the substances to be toxic to certain malignant cells.^{2,3,4,5} They produced temporary regressions, consistent depression of the white count in chronic leukemia, and alleviation of the systemic symptoms of Hodgkin's disease. They simulate to a considerable extent the therapeutic effects of X-rays. The nitrogen mustards are systemic poisons, and until their selective toxicity for neoplastic cells is increased, considerable damage to normal hematopoietic tissue will result from their parenteral use.⁴ Mustard gas itself, β -dichloroethyl sulfide, has been little studied in human subjects because of its marked toxicity.^{2,6,7}

The limited specificity of the mustards for neoplastic cells is related to their rapid decomposition in body fluids⁸ and ready combination with cellular constituents.^{6,9} The problem of extending the application of compounds of the β -chloroethyl vesicant type to the point where they may be of real value in the treatment of neoplastic disease consists in finding a means not only of reducing their chemical reactivity and systemic toxicity but also of imparting to them a toxic action of greater specificity for neoplastic cells. The present state of knowledge makes such a search essentially empirical.

As a first step in this direction, it seemed of interest to prepare compounds which incorporate structures possessing special biological properties in addition to the structures of the β -chloroethyl vesicant type. The carcinogenic hydrocarbon was selected as a nucleus for this study because of its special carcinogenic influence on cells (indicating intimate and special reaction with cellular constituents) and because of its known ability to inhibit

the growth of tumors in rats and mice.^{10a,b,c,d,e,f} 10-Methyl-1,2-benzanthracene seemed a suitably potent carcinogen and tumor-growth inhibitor. The nitrogen and sulfur mustard moieties were attached to the 10-methyl group through the readily available 10-chloromethyl-1,2-benzanthracene.¹¹ In addition to direct nitrogen (III) and sulfur (V) linkages, amide (VIII), urea (XII) and urethan (XIV) linkages were used. These derivatives would be expected to afford variations in chemical and biological properties because of the effect of their structures on the basicity of the nitrogen and sulfur atoms, which would influence the ease of cyclization to ethylene immonium or ethylene sulfonium ions. In the view now generally held such cyclic compounds are produced prior to reaction.^{2,9,12} Although there are no precedent experimental data to suggest that the amide, urea and urethan linkages in compounds VIII, XII and XIV would be cleaved *in vivo*, such cleavage would release potent mustard derivatives at the site of such action.

Toxicity studies¹³ in mice by intraperitoneal injection of this series of compounds in oil showed about the same tolerance as for 10-methyl-1,2-benzanthracene. Determination of their tumor-growth inhibiting activity¹³ in mice and rats is in progress and reveals in order of potency among the compounds comparable with 10-methyl-1,2-benzanthracene. It is of interest that derivatives of 1,2-benzanthracene in which the 10-methyl group is replaced by a larger group such as isopropyl, amyl or methylpiperidinium hydrochloride (XV) were found by Haddow^{10f} to be completely devoid of tumor-growth inhibitory activity when tested in rats.

The first of the nitrogen mustard derivatives was prepared by way of the hydroxyethylamino intermediate (II) obtained directly from 10-chloromethyl-1,2-benzanthracene (I) by condensation with diethanolamine. The reaction was carried out in an excess of the amine and gave 1,2-benzanthranlyl-10-methyl-(diethanol)-amine (II) in almost quantitative yield. This material was readily converted to the bis-chloroethylamine derivative in the form of the amine hydrochloride by

(1a) Aided by a grant from the National Cancer Institute.

(1) Gilman, *Federation Proc.*, **5**, 285-292 (1946).

(2) Gilman and Philips, *Science*, **103**, 409-415 (1946).

(3) Spurr, Jacobson, Smith and Barron, "Approaches to Tumor Chemotherapy," Science Press Printing Co., Lancaster, Pa., 1947, pp. 306-318.

(4) Karnofsky, Craver, Rhoads and Abels, *ibid.*, pp. 319-338.

(5) Goodman, Wintrobe, McLennan, Dameshek, Goodman and Gilman, *ibid.*, pp. 338-346.

(6) Berenblum, *J. Path. and Bact.*, **40**, 549 (1935).

(7) Visser and Ten Seldam, *Geneesk tijdschr. v. Nederl.-Indie*, **77**, 3092 (1937).

(8) Golumbic, Fruton and Bergmann, *J. Org. Chem.*, **11**, 518 (1946); Golumbic and Bergmann, *ibid.*, **11**, 536 (1946); Fruton and Bergmann, *ibid.*, **11**, 543 (1946); Golumbic, Strahman and Bergmann, *ibid.*, **11**, 550 (1946).

(9) Fruton, Stein and Bergmann, *J. Org. Chem.*, **11**, 559 (1946); Fruton, Stein, Strahman and Bergmann, *ibid.*, **11**, 571 (1946).

(10) (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.*, **B127**, 277 (1939); (f) Badger, Elson, Haddow, Hewett and Robinson, *ibid.*, **B130**, 255 (1941).

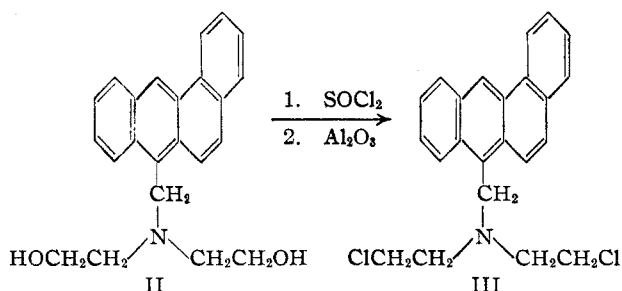
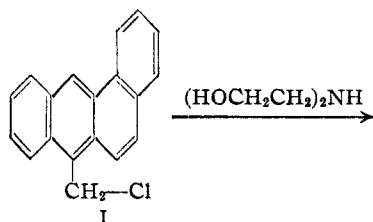
(11) Badger and Cook, *J. Chem. Soc.*, 802 (1939).

(12) Bartlett, Davis, Ross and Swain, *THIS JOURNAL*, **69**, 2971 (1948); Bartlett, Ross and Swain, *ibid.*, **69**, 2977 (1948).

(13) Seligman, Mildner and Friedman, to be published.

the action of an excess of thionyl chloride in chloroform. The free base, 10-methyl-bis-(β -chloroethyl)-amine (III), was liberated by passage of a solution of the hydrochloride in methanol or acetone through a bed of activated alumina.

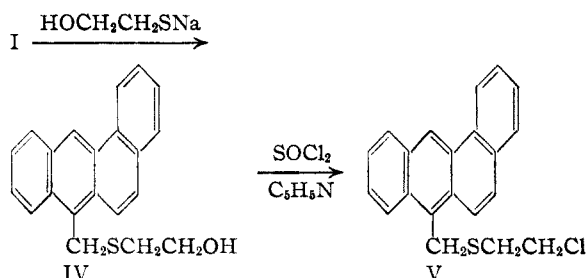
The sulfur-containing derivative (V) corresponding to the above compound was also prepared by way of the intermediate hydroxy com-



pound (IV) obtained by the interaction of 10-chloromethyl-1,2-benzanthracene with the sodium salt of monothioglycol. The product (IV) was not purified because of its intractable nature but converted directly to 1,2-benzanthranyl-10-methyl-(β -chloroethyl) sulfide (V) by the action of the required amount of thionyl chloride and a trace of pyridine in benzene. The over-all yield was good.

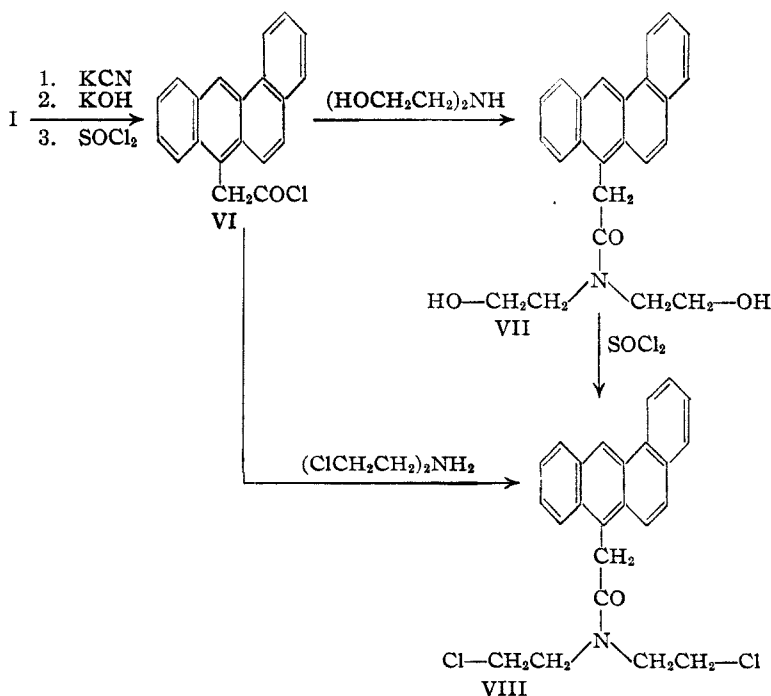
The preparation of the amide (VIII) was effected readily by condensation of the acid chloride of 10-benzanthranylacetic acid (VI) with bis- β -chloroethylamine. In an early preliminary attempt to synthesize this material, N,N-bis- β -hydroxyethyl-1,2-benzanthranyl-10-acetamide (VII) was prepared by an analogous condensation with diethanolamine but gave only a poor conversion to the bis- β -chloro compound (VIII) when treated with thionyl chloride. The replacement of hydroxyl by chlorine was tried under a variety of conditions but at best gave a relatively poor yield of a product difficult to purify.

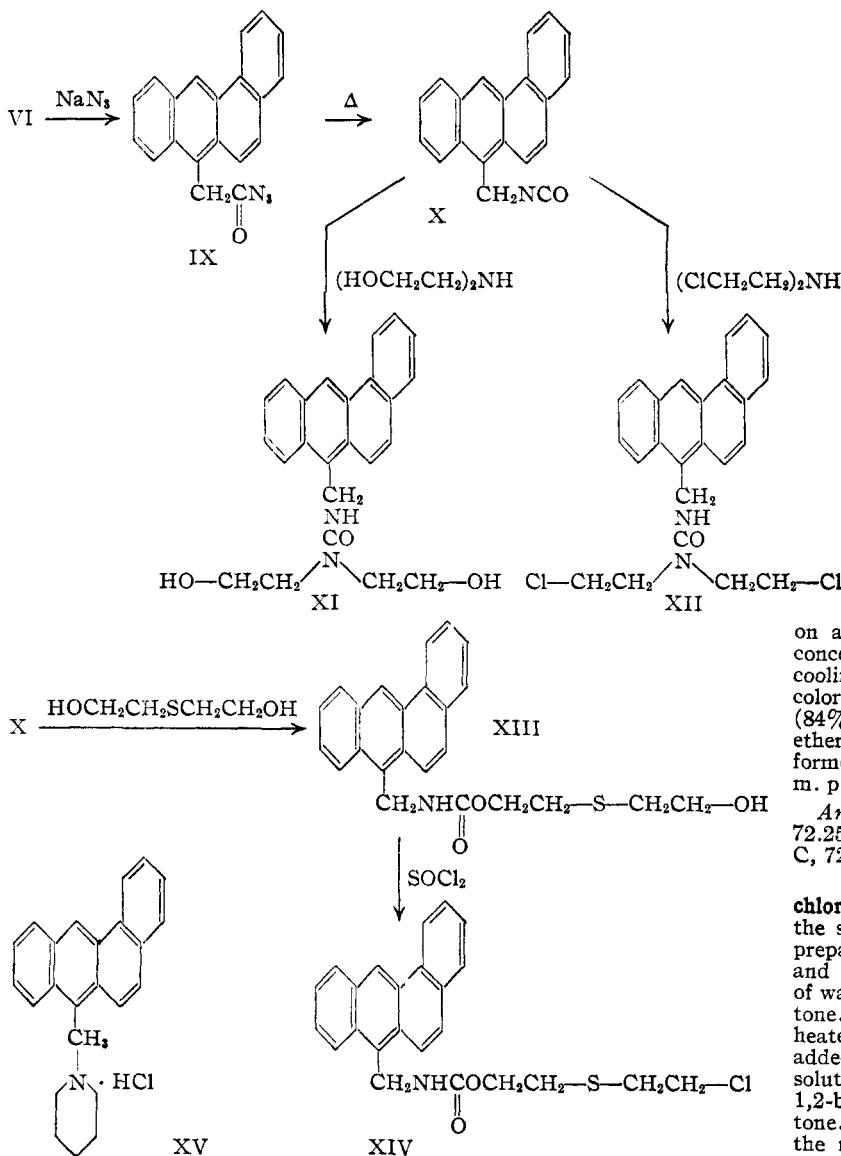
Preliminary attempts to prepare 10-benzanthranylmethyl-bis-(β -chloroethyl)-urea (XII) by replacement of hydroxyl groups by chlorine in the corresponding



hydroxyethyl compounds (XI) were unsuccessful. Thionyl chloride and phosphorus pentachloride were tried under a variety of conditions. Three different unidentified products were isolated in small amounts, none of which had the expected analysis. The desired compound was finally obtained in reasonably good yield by condensation of bis- β -chloroethylamine with 1,2-benzanthranyl-10-methyl isocyanate (X). The isocyanate was prepared smoothly by a Curtius rearrangement of the azide (IX) obtained from 1,2-benzanthranyl-10-acetyl chloride and sodium azide. The benzanthranyl-10-methyl-N',N'-bis- β -hydroxyethyl-urea (XI) had been prepared in an analogous manner by the condensation of the isocyanate with diethanolamine.

The 1,2-benzanthranyl-10-methyl isocyanate (X) also condenses readily with thiodiglycol to give a product presumed to be 1,2-benzanthranyl-10-methylcarbamic acid (β -hydroxyethyl-thio)-ethyl ester (XIII). This material, an amorphous granular solid, was converted without purification to the corresponding β -chloroethyl compound (XIV) by the use of thionyl chloride.





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Experimental¹⁴

1,2-Benzanthranil-10-methyl-bis-(β -hydroxyethyl)-amine (II).—The 10-chloromethyl-1,2-benzanthracene was prepared according to Badger and Cook¹⁵ from 1,2-benzanthracene, trioxymethylene and hydrogen chloride in acetic acid and crystallized twice from benzene, m. p. 190.5–191.5°. A suspension of 2.0 g. of the halide in 20 cc. of diethanolamine was heated on the steam-bath for twelve hours. The reaction mixture was allowed to stand in the cold after it had been diluted with 80 cc. of water and the crude product was collected and washed with water. It was then treated with Norit in a solution in methanol. The hot solution was diluted to cloudiness with water and on cooling feathery white needles were obtained, m. p. 141–142°, 2.3 g. (96%).

(14) Microanalysis by Miss Shirley Katz; all melting points are corrected.

Anal. Calcd. for $\text{C}_{22}\text{H}_{21}\text{O}_2\text{N}$: C, 79.75; H, 6.39. Found: C, 79.91; H, 6.72.

The hydrochloride was obtained as a white powder, m. p. 217–218°, on cooling a hot solution of the amine in 50% hydrochloric acid.

1,2-Benzanthranil-10-methyl-bis-(β -chloroethyl)-amine (III).

—A solution of 1.5 g. of the diethanolamine (II) in 40 cc. of chloroform was added over a period of five minutes to a solution of 5 cc. of purified thionyl chloride in 18 cc. of chloroform. The mixture was refluxed for one-half hour. The chloroform and excess thionyl chloride were removed by distillation under reduced pressure. The residue, presumably the crude hydrochloride when crystallized from chloroform gave a white amorphous powder, m. p. 163–164°.

However, the crude residue was dissolved in methanol and passed through a bed of active alumina on a Hirsch funnel. The filtrate was concentrated to small volume and on cooling the product crystallized as fine colorless needles, 1.45 g.; m. p. 103–104° (84%). After recrystallization from ether-petroleum ether the substance formed clusters of colorless crystals, m. p. 106–107°.

Anal. Calcd. for $\text{C}_{22}\text{H}_{21}\text{NCl}_2$: C, 72.25; H, 5.54; Cl, 18.55. Found: C, 72.26; H, 5.33; Cl, 18.66.

1,2-Benzanthranil-10-methyl-(β -chloroethyl) Sulfide (V).—A solution of the sodium salt of β -mercaptoethanol, prepared from 4.8 cc. of the mercaptan and 2.8 g. sodium hydroxide in 50 cc. of water, was mixed with 50 cc. of acetone. To the stirred two-layer mixture heated under reflux there was slowly added over a period of two hours a warm solution of 5.0 g. of 10-chloromethyl-1,2-benzanthracene in 250 cc. of acetone. The stirring was continued and the refluxing maintained for an additional twenty-four hours after the addition was complete.

The reaction mixture was reduced to half volume by removal of acetone by distillation and diluted to a volume of 2 l. with water. The amorphous white powder that precipitated, presumably the crude hydroxyethyl sulfide (IV), was separated on a filter and dried by subjecting a solution of the material to 150 cc. of benzene to azeotropic distillation. Purified thionyl chloride (1.3 cc.) and a trace of pyridine (4 drops) were added and the solution refluxed overnight. The reaction mixture was concentrated to small volume and upon the addition of ligroin and cooling there was obtained 4.25 g. of crystalline product, m. p. 135.5–136.5°. A second crop, 1.0 g., m. p. 134–136°, was obtained from the mother liquors on further concentration. The combined product after four crystallizations from benzene-ligroin was obtained as fluffy white needles, 3.6 g. (60%), m. p. 139–140°.

Anal. Calcd. for $\text{C}_{22}\text{H}_{27}\text{ClS}$: C, 74.87; H, 5.09; Cl, 10.53. Found: C, 74.81; H, 5.14; Cl, 10.48.

N,N-bis- β -Hydroxyethyl-1,2-benzanthranil-10-acetamide (VII).—The 1,2-benzanthranil-10-acetic acid was prepared according to Badger and Cook¹⁵ from 10-chloromethyl-1,2-benzanthracene by way of the nitrile, ob-

(15) Badger and Cook, *J. Chem. Soc.*, 411 (1940).

tained by condensing the halide with potassium cyanide in acetone-water. The nitrile was converted to the acid by hydrolysis in alcoholic caustic potash and the acid crystallized from dioxane-water as a white powder, m. p. 280–281° (with previous softening). A suspension of 1.5 g. of the acid in 5 cc. of purified thionyl chloride was warmed on the steam-bath for a few minutes when the substance dissolved and the solution refluxed for five to ten minutes. The excess thionyl chloride was removed by distillation under reduced pressure. The crude light brown semicrystalline residue, washed by decantation with 5 cc. of dry ether, afforded 1.4 g. of the acid chloride. This was refluxed for five hours with a mixture of 10 cc. of diethanolamine and 20 cc. of sodium-dried dioxane. When cooled, the reaction mixture was poured into 200 cc. of water and after standing for two days in the cold room the product was separated and crystallized from methanol-water, m. p. 168–171°; 1.35 g. (69%). After two recrystallizations from a mixture of chloroform and methanol the substance was obtained as fine granular crystals, m. p. 179–180°.

Anal. Calcd. for $C_{24}H_{20}O_2N$: C, 77.21; H, 6.21. Found: C, 77.25; H, 6.48.

N,N-bis- β -Chloroethyl-1,2-benzanthranil-10-acetamide (VIII). (a) **From the Amide VII.**—A solution of 0.2 g. of the amide in an excess of thionyl chloride was warmed on the steam-bath for ten minutes. The excess thionyl chloride was removed by distillation under reduced pressure. The residue was crystallized by cooling a solution of the material in chloroform-benzene in Dry Ice-acetone for a few hours. There was obtained 0.14 g. of brownish granular material, m. p. 177–179° (previous softening). After repeated crystallization from chloroform-benzene the substance formed light tan granules, m. p. 181–183°. This material gave a positive Beilstein test and no depression in melting point when mixed with a sample prepared as in (b).

(b) **From 1,2-Benzanthranil-10-acetyl Chloride and 2,2'-Dichlorodiethylamine.**—The required 2,2'-dichlorodiethylamine was prepared according to the method of Laselle and Sundet¹⁶ by treatment of 5.0 g. of the amine hydrochloride¹⁷ in cold aqueous solution with 1.6 g. of sodium hydroxide. The free base was quickly extracted with three 5-cc. portions of benzene and one 5-cc. portion of chloroform. The combined extract was dried over calcium chloride and stored in the cold. A mixture of 8.0 cc. of this stock solution of the amine (about 1.5 g.) and a solution of 1.5 g. of 1,2-benzanthranil-10-acetyl chloride in 60 cc. of dry benzene was heated under reflux for ten hours. When the reaction mixture cooled it was filtered to remove a suspended solid. The residue, a fine flaky white crystalline material, was shown to be 2,2'-dichlorodiethylamine hydrochloride by a mixed melting point determination. The filtrate after treatment with Norit was concentrated by distillation and diluted with ligroin. After the solution had stood in the cold there was obtained a slightly discolored white crystalline solid which was washed with a little methanol to remove the color, m. p. 183–185°. The product weighed 1.65 g. (82%). After recrystallization from benzene-ligroin it was obtained as fine hard granules, m. p. 184–185°.

Anal. Calcd. for $C_{24}H_{22}ONCl_2$: C, 70.25; H, 5.16; Cl, 17.39. Found: C, 70.41; H, 5.31; Cl, 17.70.

N,N-bis- β -Hydroxyethyl-1,2-benzanthranil-10-methylurea (XI).—A solution of 0.3 g. of sodium azide in 0.8 cc. of water was slowly added to a solution of 1.25 g. of 1,2-benzanthranil-10-acetyl chloride (VI) in 15 cc. of reagent acetone cooled in ice and vigorously agitated. The azide formed as a precipitate during the addition. After the mixture was allowed to stand in an ice-bath for an additional twenty minutes, 30 cc. of water was added to complete the precipitation. The precipitate, collected on a filter and washed with a small amount of cold water, was obtained as a pale yellow granular solid, which was

dried in a vacuum desiccator, 1.1 g., m. p. 96° (dec.). To prepare the isocyanate a solution of this material in 15 cc. of dry benzene was warmed gently on the steam-bath for fifteen minutes until the evolution of nitrogen had ceased. Diethanolamine (5 cc.) was added and the mixture heated under reflux for twenty-four hours. The benzene was completely removed by distillation at reduced pressure. The undistilled residual solution was heated on the steam-bath for one hour and the product separated from the excess diethanolamine by dilution with water. The crude product collected on a filter, dried and washed with a little dry ether, weighed 1.4 g., (78%). After repeated crystallization from chloroform-benzene and methanol-water it was obtained as a pale yellow granular powder, m. p. 198–199°.

Anal. Calcd. for $C_{24}H_{24}N_2O_3$: C, 74.20; H, 6.23; N, 7.23. Found: C, 73.96; H, 6.12; N, 7.41.

N,N-bis- β -Chloroethyl-1,2-benzanthranil-10-methylurea (XII).—A solution of 1,2-benzanthranil-10-methyl isocyanate (X) was prepared by warming 1.5 g. of the azide in 20 cc. of dry benzene for ten minutes, when the evolution of nitrogen had ceased. To this was added 4.5 cc. of the stock solution (see preparation of (VIII)) of dichloroethylamine in benzene-chloroform and the mixture heated under reflux for five hours. The reaction mixture after treatment with Norit was diluted with 20 cc. of ligroin and concentrated by distillation to about half volume. On cooling a white solid crust formed. The crude product, separated on a filter and washed with a small amount of methanol, weighed 1.15 g. (72%), m. p. 155–157°. After recrystallization from acetone-ligroin granular crystals were obtained, m. p. 162–163°.

Anal. Calcd. for $C_{24}H_{22}N_2OCl_2$: C, 67.73; H, 5.21; Cl, 16.67. Found: C, 67.75; H, 5.37; Cl, 16.40.

1,2-Benzanthranil-10-methylcarbamic Acid-(β -chloroethylthio)ethyl-ester (XIV).—A solution of 1,2-benzanthranil-10-methyl isocyanate (X) was prepared by warming a solution of 2.0 g. of the azide in 20 cc. of dry benzene for ten minutes when the evolution of nitrogen ceased. A solution of 4.0 cc. of thiodiglycol in 30 cc. of chloroform was added, and after the mixture was allowed to stand at room temperature for two hours it was heated under reflux for twelve hours. The chloroform and benzene were removed by distillation and the sirupy residue diluted with excess of water. The precipitate that formed was separated by filtration, and after air-drying was obtained as a light brown amorphous powder. The crude material was taken up in 100 cc. of benzene, the solution treated with Norit and then boiled until anhydrous. Purified thionyl chloride (0.45 cc.) and a trace of pyridine were added, and the mixture heated under reflux for twelve hours. After treatment with Norit the reaction mixture was concentrated by distillation and diluted with ligroin. There was obtained 1.7 g. (63%) of product, m. p. 141–144°. Recrystallization from chloroform-ligroin gave an almost white granular powder, m. p. 143–144°.

Anal. Calcd. for $C_{27}H_{28}O_3NSCl$: C, 68.00; H, 5.23; Cl, 8.36. Found: C, 68.19; H, 5.43; Cl, 8.09.

Summary

On reaction with diethanolamine and with sodium mercaptoethanol, followed by reaction of the resulting hydroxyethyl compounds with thionyl chloride, 10-chloromethyl-1,2-benzanthracene gives a bis- β -chloroethylamine and a β -chloroethylthio derivative, respectively. Benzanthranil-10-acetyl chloride when condensed either with diethanolamine or with dichlorodiethylamine gives the corresponding hydroxyethyl or chloroethyl amide. The 1,2-benzanthranil-10-methyl isocyanate, obtained by a Curtius rearrangement of the azide prepared by condensation of the acid chloride with sodium azide, will undergo condensation

(16) Laselle and Sundet, *THIS JOURNAL*, **63**, 2374 (1941).

(17) Ward, *ibid.*, **57**, 914 (1935).

with diethanolamine and with dichlorodiethylamine to give the corresponding urea derivatives, and also with thiodiglycol to give a product which after treatment with thionyl chloride yields chloroethylthio substituted benzanthranylmethylurethane.

Certain rationalizations are presented with regard to the interest in the β -chloroethyl substituted derivatives as possible agents in a study of chemotherapy of cancer.

CAMBRIDGE 38, MASSACHUSETTS

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

Plant Insecticides. I. Ryanodine, A New Alkaloid from *Ryania Speciosa* Vahl.

BY EDWARD F. ROGERS, FRANK R. KONIUSZY, JOHN SHAVEL, JR., AND KARL FOLKERS

In a survey of plant materials for new insecticides, which has been conducted in coöperation with the Department of Entomology of Rutgers University, it was found that extracts of the stem and root of *Ryania* spp. (family, *Flacourtiaceae*) showed insecticidal activity.¹ Extracts of *Ryania speciosa* Vahl. (*Ryania pyrifera* [L. C. Rich.] Vitt.) were very active and promising.

Entomological tests on stem wood dusts of *Ryania speciosa* Vahl. have been reported by Pepper and Carruth,² and other investigators.³

Chemical studies of *Ryania* constituents have been reported by Quintero Serra and Gomez,⁴ who examined *Ryania speciosa* Vahl. and by Nakarai and Sano,⁵ Le Cointe,⁶ Bret⁷ and Merz,⁸ who all worked with root material of *Ryania acuminata* Spruce (*Patrisia acuminata*). These investigators attempted to isolate the principle or principles responsible for the mammalian toxicity of *Ryania* extracts. Various toxic preparations were secured, but these were amorphous and were not analyzed or otherwise characterized. Nakarai and Sano, and Le Cointe and Bret named their toxic fractions "ryanine" and "ryanetine," respectively. It was suggested that these materials were glycosides.

Insecticidal preparations are obtained from the stem and root material of *Ryania speciosa* Vahl. by extraction with water and many organic solvents.

Quantitative extraction of the insecticidal principles can be secured by the use of water, methanol or chloroform. Chloroform extraction is much more effective with wet wood than with dry. Thus, in the time required for quantitative extraction of wet wood by chloroform, extraction of dry wood is only about 25% completed. That these methods of extraction are quantitative was proved in two ways. Firstly, bioassay⁹ results showed that a constant amount of insecticidal activity was obtained by the three extraction methods; secondly, the marcs obtained were non-insecticidal and subsequent extraction with other solvents yielded non-insecticidal material. The extractives which were secured with methanol, water and chloroform contained considerable amounts of inactive substances. In practice, the chloroform and water extractives are favored for further purification procedures. A concentrated aqueous solution of crude material can be extracted with either ether or amyl acetate to remove the insecticidal principles from the water solution. The distribution coefficients of the insecticidal principles have been determined by bioassay⁹ to be approximately 0.6 for ether/water and approximately 7.5 for amyl acetate/water. Alternatively, the active principles in a concentrated chloroform extract can be transferred to water, since the distribution coefficient for water/chloroform is approximately 9.0, and then extracted from the water by ether or amyl acetate. Ether or acetone solutions of the ether and amyl acetate extractives gave crude crystalline material which melted between 140° and 160°. By repeated crystallization of this product from ether, a pure compound was obtained; m. p. 219–220°, $[\alpha]^{25}_D + 26^\circ$ (methanol). This compound has been designated ryanodine. It is highly insecticidal and possesses approximately 700 times the potency of the stem wood of *Ryania speciosa* Vahl.

Ryanodine is neutral to litmus and forms no salts. It does not give precipitates with the common alkaloid reagents, such as the Mayer, Scheibler, Sonnenschein and Wagner reagents. The presence of a pyrrole-like ring system, which may explain the lack of basicity, is suggested by

(9) The bioassay employed measures protection against clothes moth larvae damage. This method was developed by Dr. Ralph E. Heal of these Laboratories.

(1) Folkers, Rogers and Heal, U. S. Patent 2,400,295, May 14, 1946.

(2) Pepper and Carruth, *J. Econ. Entomol.*, **38**, 59 (1945).

(3) Wheeler and La Plante, *ibid.*, **39**, 211 (1945); Wheeler, *ibid.*, **38**, 281 (1945); Hockett, *ibid.*, **39**, 184 (1946); Bishopp, *ibid.*, **39**, 449 (1946); Dills and Odland, *Vegetable Growers News* (Pennsylvania State College), July, 1946; Dugas and Concienne, *Sugar Cane Investigations in 1946*, Part I (Louisiana Agricultural Experiment Station); Rainwater and Bondy, *J. Econ. Entomol.*, **40**, 371 (1947); Decker, Apple, Wright and Petty, *ibid.*, **40**, 395 (1947); Bigger, Decker, Wright and Petty, *ibid.*, **40**, 401 (1947); Carruth, *Farm Research* (New York Agricultural Experiment Station), **13**, 11 (1947); Polivka, *Farm and Home Research* (Ohio Agricultural Experiment Station), **33**, 107 (1947); Turner, Connecticut Agricultural Experiment Station Circular 164, April, 1947; Ivy and Ewing, *J. Econ. Entomol.*, **40**, 568 (1947); Ingram, Bynum and Charpentier, *ibid.*, **40**, 779 (1947); Kulash, *ibid.*, **40**, 927 (1947).

(4) Quintero Serra and Gomez, Thesis of R. Quintero Serra, Central University of Venezuela, Caracas, May 15, 1939.

(5) Nakarai and Sano, *J. Pharm. Soc. Japan*, **48**, 157 (1928); *Arch. Pharm.*, **272**, 1 (1934).

(6) Le Cointe, *Bol. Esc. Chim. Ind. (Belem)*, **1**, 43 (1930).

(7) Bret, *ibid.*, **1**, 48 (1930).

(8) Merz, *Arch. Pharm.*, **268**, 592 (1934).