The formation of this compound may be explained by the fact that diphenylhydrazine, at its boiling point, decomposes in part to form diphenylamine and other products.[8] Part of the arsenic chloride, in all probability, acts as a reducing agent and hastens the reaction at a lower temperature. The diphenylamine thus formed then condenses with arsenic trichloride to form 6-chloro-phenarsazin.

Subs., 0.2030, 0.2200: 30.80, 33.30 cc. of 0.0479 *N* iodine sol. Calc. for $C_{12}H_9NAsCl$: As, 27.02. Found: 27.29, 27.23.

Subs., 0.4053, 0.4207: 13.98, 13.94 cc. of 0.1 *N* HCl. Calc. for $C_{12}H_9NAsCl$: *N*, 5.04. Found: 4.83, 4.85.

Summary.

1. A brief summary of the chemistry of the nuclear heterocyclic arsenic compounds is presented.

2. The condensation of phenyl-α-naphthylamine with arsenic chloride, and the properties of the resulting 7-chloro-7,12-dihydro-γ-benzo-phenarsazin are described.

3. The methods of preparation and the properties of the following derivatives of 7-chloro-7,12-dihydro-γ-benzo-phenarsazin are given: 7-methoxy-7,12-dihydro-γ-benzo-phenarsazin; 7-ethoxy-7,12-dihydro-γ-benzo-phenarsazin; 7-*n*-propoxy-7,12-dihydro-γ-benzo-phenarsazin; 7-*n*-butoxy-7,12-dihydro-γ-benzo-phenarsazin; 7-phenoxy-7,12-dihydro-γ-benzo-phenarsazin; 7-benzyloxy-7,12-dihydro-γ-benzo-phenarsazin; γ-benzo-phenaz-arsinic acid; 7,12-dihydro-γ-benzo-phenarsazin-7-oxide; 7-bromo-7,12-dihydro-γ-benzo-phenarsazin; and 7,12-dihydro-γ-benzo-phenarsazin-7-sulfide.

EVANSTON, ILLINOIS.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS.]

β,β'-DICHLORO-DIETHYL ETHER. THE OXYGEN ANALOG OF MUSTARD GAS.[1]

BY OLIVER KAMM AND JOHN H. WALDO.

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The simple analog of mustard gas in which the sulfur atom has been replaced by oxygen apparently has not been described in the literature. We were therefore interested in studying this compound, not merely in order to compare its physiological action with that of its deadly relative, but also with a view aiming at the possible use of the compound as a new reagent in organic synthesis, particularly in the preparation of cyclic derivatives containing the polymethylene oxide structure.

[8] Stahel, *Ann.*, **258**, 244 (1890).

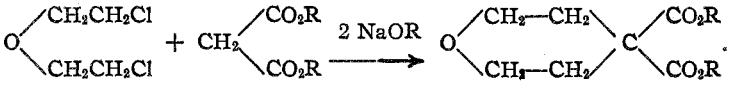
[1] Presented at the St. Louis Meeting of the American Chemical Society, March 1920.

It is not feasible to prepare β,β'-dichloro-diethyl ether by the chlorination of ethyl ether for the reason that such a reaction leads to the production of mixtures containing mainly *alpha* chlorination products; it may be prepared conveniently, however, by the general method for the preparation of ethers, *viz.*, by the dehydration of two molecules of the corresponding chloro alcohol. Since the sulfur analog can be prepared readily by the action of sulfur chloride upon ethylene, there is suggested also the possibility of obtaining the oxygen derivative by an analogous reaction:

$$2\ CH_2 = CH_2 + Cl_2O \longrightarrow Cl\text{-}CH_2CH_2\text{-}O\text{-}CH_2CH_2\text{-}Cl.$$

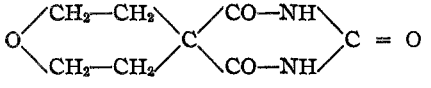
We are indebted to Dr. W. J. Hale, of the Dow Chemical Company for the information that a reaction similar to that expressed by the above equation actually takes place during the manufacture of ethylene chlorohydrin, and that a product identical in physical properties with the ether now characterized by us may be isolated from crude ethylene chlorohydrin.

In addition to the usual analysis, the dichloro-ether has been identified by its condensation with aniline, a reaction which yields an oxazine of known structure, 4-phenyl-morpholin. Because this derivative is a solid, it is well suited for identification purposes. By a slight modification of the usual tautomeric ester synthesis, the dichloro-ether (I) has been condensed with malonic ester to yield 4,4-dicarboxy-ethyl-pentamethylene oxide (II).

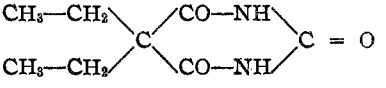


(I). (II).

This malonic ester derivative should condense readily with urea to yield a new *spiro* derivative of an unusual type, one ring consisting of a pyrimidine and the other of a cyclic oxide structure. This condensation occurs readily. The resultant barbituric acid derivative (III) is closely related in structure to the well-known hypnotic, barbital (IV).



(III).



(IV).

It will be noted that the new compound differs from barbital (veronal) only in the fact that an oxygen atom may be considered as having replaced one hydrogen atom from each of the two methyl groups. The observations made in respect to the difference in physiological action between these two barbituric acid derivatives ultimately should prove of aid in the interpretation of the underlying principles concerning the action of such drugs in the animal body.

Experimental Part.

β,β'-Dichloro-diethyl Ether.—This compound was prepared by the action of conc. sulfuric acid upon ethylene chlorohydrin. When, by direct analogy, the usual continuous method for the preparation of ethyl ether, was employed, a very poor, almost negligible, yield was obtained. When the alcohol was refluxed with $^1/_5$ its weight of conc. sulfuric acid, followed subsequently by direct distillation, the yield was 10% to 15% of the desired product. A further modification of the method consisted in the gradual removal of water during the period of refluxing, this resulted in a yield of about 20% to 25%. Based upon the amount of chlorohydrin actually lost in the process, the yield amounted to about 75%.

A mixture of 200 g. of ethylene chlorohydrin and 35 g. of conc. sulfuric acid was placed in a round-bottom boiling flask and heated under a reflux condenser for 6 hours. During this refluxing period, the water in the condenser was maintained at 90° to 100° and the heating regulated so that a very slow but continuous removal of water and chlorohydrin was effected. This distillate consisted mainly of the constant-boiling mixture of the alcohol and water,[1] and was saved, together with the subsequent distillate, for recovery of chlorohydrin. About ⅓ the volume of the reaction mixture was removed during the refluxing period, after which the liquid was distilled directly through a horizontal condenser. This distillation, in spite of the formation of sulfur dioxide, was continued until only a charred mass remained in the fractionating flask. The distillate was washed with sodium carbonate solution, dried with sodium sulfate, and then subjected to careful fractionation, with the aid of an efficient column.

The β,β'-dichloro-diethyl ether is a colorless oil with a pleasant ethereal odor; b. p., 177–8° (corr.); d_{20}^{20}, 1.213; n^{20}, 1.457.

Analysis. Subs., 0.2417, 0.1910: 33.24 cc., 26.27 cc. of 0.1 *N* $AgNO_3$. Calc. for $C_4H_8OCl_2$: Cl, 49.6. Found: 48.8, 48.8.

4-Phenyl-morpholin.—A mixture of 72 g. of the dichloro ether and 47 g. of aniline was heated for about 10 hours under a reflux condenser with sufficient 10% aqueous sodium hydroxide to remove the hydrochloric acid liberated in the reaction. The oily reaction product was extracted with ether and the solvent layer washed with several small portions of 1% hydrochloric acid in order to remove those impurities more basic than the desired oxazine. Upon evaporation of the ether, an oily mass of crystals remained, from which the residual oil was removed by pressing the crystals on a porous clay plate. The remaining solid was then crystallized from 50% aqueous alcohol and obtained in the form of almost white flakes melting at 57° to 58°. Upon distillation, a pure white product was obtained boiling at 259° to 260°, at 745 mm. These constants, together with the chlorine analyses recorded above, establish the constitution of the dichloro-diethyl ether.

4,4-Dicarboxyethyl-tetrahydro-pyran.—One-half mole of sodium was dissolved in 200 cc. of absolute ethyl alcohol. To the sodium ethylate solution, ½ mole of malonic ester and 72 g. (½ mole) of the dichloro-diethyl ether were added, and the mixture was refluxed on the water-bath for an hour. The flask containing the reaction mixture was then cooled, an alcoholic solution of a second ½ mole of sodium ethylate added, and the mixture was refluxed again during an hour. After cooling the reaction mixture, the sodium chloride was separated by filtration, the major portion of the alcohol removed by distillation, and the remaining product treated with water. The oil which separated was extracted with ether. The ether solution was dried over anhydrous sodium sulfate and subjected to distillation with the use of a short but fairly efficient fractionating column. Yield 30 g. (26%).

[1] THIS JOURNAL, **41**, 1422 (1919).

The 4,4-dicarboxyethyl-tetrahydro-pyran is a liquid boiling at 260° (740–745 mm.); d_{20}^{20}, 1.107. It was not subjected to analysis, but its condensation product with urea served for its analytical identification. Its physical and chemical properties agree with the assigned formula (II).

In one experiment, the above directions were modified and the total quantity of sodium ethylate was used at one time. This variation resulted in the formation of an appreciable quantity of a higher-boiling product consisting partly, no doubt, of the ethyoxy derivative, C_2H_5-O-CH_2-CH_2-O-CH_2-CH_2-$CH<(C(O)OC_2H_5)_2$.

Tetrahydro-pyran-4,5-spiro-2,4,6-triketo-hexahydro-pyrimidine.[3]—This barbituric acid derivative was prepared by the well-known condensation of malonic ester derivatives with urea in the presence of sodium ethylate.

A 2.5 g. portion of sodium was dissolved in 35 cc. of absolute ethyl alcohol. This sodium ethylate solution, together with 10 g. of 4,4-dicarboxyethyl-tetrahydro-pyran and 3.3 g. of finely powdered urea, was heated in a sealed tube for 5 hours at 100° to 105°. The reaction mixture was then filtered, the mass of sodium salts treated with dil. hydrochloric acid, and the insoluble barbituric acid derivative separated by filtration. The product was purified by crystallization from hot water. Yield, 41%.

This barbituric acid derivative is a white crystalline product melting at 218°. It crystallizes with one molecule of water which, however, is gradually lost if it is dried at 110°, as may be seen from the following data.

Subs., 0.6170: heated at 110°. Calc. loss, 0.0510: Found: 0.0514. Loss in weight with time: 1st. hour, 0.0302; 2nd. hour, 0.0206; 3rd. hour, 0.0004; 4th. hour, 0.0002.

Analysis. Subs., 0.2034: N_2, 25.40 cc. (727.5 mm. and 29°).

Subs., 0.2336: H_2O, 0.1148; CO_2, 0.3767. Calc. for $C_8H_{10}O_4N_2.H_2O$: C, 44.4; H, 5.60; N, 12.96. Found: C, 43.9; H, 5.49; N, 12.9.

Physiological Behavior of β,β'-Dichloro-diethyl Ether and of Tetrahydro-pyran-4,5-spiro-2,4,6-triketo-hexahydro-pyrimidine.

The explanation appears to be generally accepted that β,β'-dichloro-diethyl sulfide exerts its highly toxic influence upon the tissues because of the liberation of hydrochloric acid within the body cells. The physical properties of the compound are apparently such as to yield exactly the requisite relationship between the rate of penetration of the compound and its rate of hydrolysis to produce the well-known toxic effect. It was therefore of interest to test the corresponding oxygen ether for the possibility of a related effect; it was found, however, that β,β'-dichloro-diethyl ether exerted no similar deleterious action upon the tissues; in fact, liberal quantities of the ether were applied directly to the skin without a noticeable effect.

The close structural relationship between the well-known hypnotic, barbital, and the new barbituric acid derivative, tetrahydro-pyran-4,5 *spiro*-2,4,6-triketo-hexahydro-pyrimidine, has been briefly referred to above. The *spiro* compound was found to possess no hypnotic and no toxic effect when administered orally to a rabbit of about 1.5 kg. weight in

[3] This system of nomenclature has been proposed recently by Dox and Yoder, THIS JOURNAL, 43, 678 (1921). The numerals preceding the word *spiro* mean that the *spiro* carbon corresponds to Position 4 in the pyran ring and Position 5 in the pyrimidine ring.

1g. doses. Barbital, on the other hand, is effective[4] even in considerably smaller amounts, the fatal dose for rabbits being about 0.35 g. per kg. body weight.

The above difference in physiological effect is unusual for the reason that di-alkyl derivatives of barbituric acid are practically all effective unless, of course, the alkyl groups are sufficiently high in molecular weight, as in the dibenzyl compound, to produce compounds of limited solubility. The new derivative, in which we may consider that the two alkyl groups have been united through an oxygen atom, does not differ greatly from barbital in its physical properties; therefore one must seek elsewhere an explanation for its lack of activity.

The observation that the new derivative is in combination with water to form a monohydrate suggests one possible explanation for its non-activity, particularly so, since barbital does not crystallize as a hydrate under similar experimental conditions. We are inclined, however, to a different explanation.

It is known that when barbital is administered to an animal a considerable percentage of the drug is eliminated unchanged. The *spiro* derivative appeared, however, in the urine in the form of fine needles melting in the neighborhood of 150° to 160°. Unfortunately, because of the limited physiological study, we neglected to seek an identification of the transformation product as eliminated from the animal body. There is a possibility that in this instance, because of the *spiro* structure, the compound is more susceptible to hydrolysis *in vivo*. Whether or not this view is correct may be determined when reports are available concerning the physiological behavior of related cyclic derivatives.

Summary.

1. β,β′-Dichloro-diethyl ether has been prepared by the dehydration of ethylene chlorohydrin.

2. The new dichloro ether was condensed with malonic ester and yielded 4,4-dicarboxyethyl-tetrahydro-pyran. This di-substituted malonic ester derivative was condensed with carbamide and yielded a substituted barbituric acid of the *spiro* type.

3. β,β′-Dichloro-diethyl ether possesses no baneful effect upon the tissues of the animal body, an action which is so striking in the case of the sulfur analog known as *mustard gas*.

4. Tetrahydro-pyran 4,5-*spiro*-2,4,6-triketo-hexahydro-pyrimidine, although closely related in structure to barbital, possesses no marked hypnotic properties. In contrast to the latter compound, it is modified within the animal body. The ready formation of an inert hydrolytic product probably accounts for its physiological behavior.

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[4] *Biochem. Z.*, **31**, 1 (1911).