

6. Dibromo-pyrogallolsulfonephthalein is a tautomeric substance, having for itself and its ammonium salt the colored quinoid structure, and forming the colorless, dibromo-*sulfonegallein* tetrabenzoate, which has the lactoid structure.

7. Pyrogallolsulfonephthalin and its zinc salt have been made. They are colorless. Pyrogallolsulfonephthalin is very readily oxidized by the air to pyrogallolsulfonephthalein.

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## RING CLOSURE IN CHLORO-ALKYL PHENYLCARBAZATES. SIX- AND SEVEN-MEMBERED HYDRAZOLACTONES

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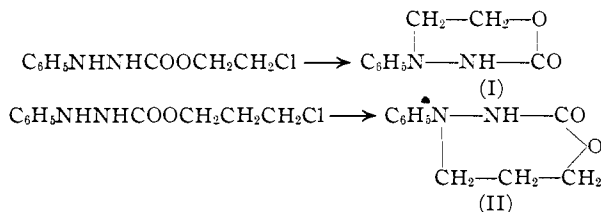
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The tendency of cyclic compounds to form when halogen and hydrogen are removed by simple treatment with alkali from the terminal atoms of a five- or six-membered open chain has made possible the synthesis of numerous new heterocyclic structures. In a previous paper<sup>1</sup> this reaction was applied to the synthesis of 1,3-oxazine derivatives from  $\gamma$ -chloropropyl carbanilates. It was shown that such ring closure took place only when the amide grouping was stabilized by the introduction of phenyl; otherwise, a decomposition occurred with formation of alkali cyanate.

A similar reaction should occur with chloro-alkyl phenylcarbazates, which are analogous to the carbanilates except for the presence of an additional NH group, and the ring closure should yield cyclic derivatives with two nitrogens and one oxygen as the hetero elements.

The two esters studied were the  $\beta$ -chloro-ethyl and the  $\gamma$ -chloropropyl. Assuming that the terminal NH of the phenylcarbazic acid group furnishes the hydrogen which is split out as hydrogen chloride, the resulting cyclic derivatives should contain six and seven members, respectively.



Such heterocycles containing an oxygen in the ring adjacent to a carbonyl may also be regarded as lactones and should be hydrolyzed easily by aqueous alkali. Hence, the yield is better when sodium ethoxide in absolute

<sup>1</sup> Dox and Yoder, THIS JOURNAL, 45, 723 (1923).

alcohol is used as the condensing agent, and only the calculated amount employed. A further advantage of this treatment is the greater solubility of the esters in alcohol than in water. The condensation product is, as a rule, less soluble than the ester, and often crystallizes without evaporation when a minimum amount of solvent is used.

### Experimental Part

**$\beta$ -Chloro-ethyl Phenylcarbazate.**—Fifty g. of phenylhydrazine was dissolved in 50 g. of pyridine and the solution diluted with 200 cc. of water. The flask was then immersed in cold water and the solution stirred continuously during the gradual addition of 66 g. of  $\beta$ -chloro-ethyl chlorocarbonate from a dropping funnel. The reaction was accompanied by a moderate evolution of heat. A red oil separated and soon solidified into crystalline lumps. These were filtered off, broken up and thoroughly washed with water until only a faint odor of pyridine remained. The crude product weighed 73.6 g. Recrystallization from benzene removed the color completely and the final product was obtained in white, needle-shaped crystals melting at 89°. It is practically insoluble in water, but soluble in the usual organic solvents.

*Anal.* Subs., 0.1612: AgCl, 0.1058. Calcd. for  $C_9H_{11}O_2N_2Cl$ : Cl, 16.55. Found: 16.23.

**2-Keto-4-phenyl-tetrahydro-1,3,4-oxidazine (lactone of  $\beta$ -hydroxyethylphenylcarbazic acid).**—A solution containing 25 g. of  $\beta$ -chloro-ethyl phenylcarbazate in 200 cc. of absolute alcohol was treated with the exact equivalent of sodium ethoxide in absolute alcohol (73.3 cc. of 1.59 *N* solution). A slight evolution of heat occurred and an almost immediate separation of sodium chloride. Within five minutes the reaction mass had become neutral to litmus, without the application of heat. The sodium chloride was filtered off and the yellow filtrate carefully evaporated. Yellow crystals were obtained, together with some oily impurity which was removed by absorption on a porcelain tile. Recrystallization from benzene gave a pure white product consisting of scaly crystals melting at 120°. The yield of pure substance was 9.89 g. It is sparingly soluble in hot water from which it crystallizes in flat prisms on cooling, but more readily soluble in alcohol, benzene and ether.

*Anal.* Subs., 0.2252:  $CO_2$ , 0.5035;  $H_2O$ , 0.1185. Subs., 0.1486:  $N_2$ , 22.0 cc. (25°, 729 mm.). Calcd. for  $C_9H_{10}O_2N_2$ : C, 60.68; H, 5.62; N, 15.73. Found: C, 60.98; H, 5.85; N, 15.82.

**$\gamma$ -Chloropropyl Phenylcarbazate.**—This was obtained from phenylhydrazine and  $\gamma$ -chloropropyl chlorocarbonate in dil. pyridine in exactly the same manner as that described above for the chloro-ethyl ester. The product separated at first as an oil which solidified when cooled in an ice-bath. Recrystallization from benzene gave white, scaly crystals melting at 72°. From 36 g. of phenylhydrazine and 52 g. of chlorocarbonate the yield was 44.2 g. of pure product.

*Anal.* Subs., 0.2042: AgCl, 0.1269. Calcd. for  $C_{10}H_{13}O_2N_2Cl$ : Cl, 15.54. Found: 15.37.

**Lactone of  $\gamma$ -hydroxypropyl-phenylcarbazic acid.**—Twenty g. of the ester just described was dissolved in 100 cc. of absolute alcohol and the solution treated with the exact equivalent of sodium ethoxide in absolute alcohol (42.0 cc. of 3.92 *N* solution). Sodium chloride began to separate immediately, and in a few minutes the mixture had become neutral. The filtrate began to deposit crystals of the lactone before evaporation of the solvent. After recrystallizing from benzene the yield was 7.53 g. of white, scaly crystals; m. p. 146°. The substance is somewhat less soluble in alcohol than the

analogous oxadiazone, but is readily soluble in benzene and ether. The nomenclature of ring systems has not yet been extended to include seven-membered heterocycles, but this type might provisionally be designated a homo-oxdiazine.

*Anal.* Subs., 0.2028: CO<sub>2</sub>, 0.4699; H<sub>2</sub>O, 0.1177. Subs., 0.1704: N<sub>2</sub>, 22.8 cc. (25°, 740 mm.). Calcd. for C<sub>10</sub>H<sub>12</sub>O<sub>2</sub>N<sub>2</sub>: C, 62.50; H, 6.25; N, 14.58. Found: C, 63.19; H, 6.45; N, 14.53.

Attempts to alkylate the two hydrazolactones described above were unsuccessful. When refluxed in alcoholic solution with sodium ethoxide and ethyl bromide, the mixture eventually became neutral, but the lactones were recovered for the most part unchanged. Neutrality resulted apparently by removal of hydrogen bromide from the ethyl bromide to form ethylene or ethyl ether as indicated by the separation of sodium bromide, or possibly in part by formation of the sodium salt of the acid corresponding to the lactone. The free acid, however, could not be obtained in sufficient yield or purity for identification. This failure to form alkyl derivatives supports the assumption that the ring closure occurred as indicated in Formulas I and II, since the hydrogen to be replaced is present in an amide grouping. On the other hand, the isomeric five- and six-membered rings with aniline groupings as side chains would be expected to react without difficulty.

More conclusive proof of the structure indicated by Formula II was obtained by hydrolysis and reduction. One g. of the seven-membered lactone was treated with 20 cc. of hydrochloric acid, in which it dissolved completely, and 2 g. of tin foil. After the tin had dissolved, the mixture was diluted with water, made strongly alkaline with sodium hydroxide and distilled to half its volume. The distillate was slightly alkaline to litmus (ammonia), but showed no cloudiness, and hence could not have contained any significant amount of aniline. On the other hand, the residue contained oily drops possessing a faintly basic odor. This non-volatile amine was extracted with ether and the solvent evaporated, leaving 0.5 g. of a yellow basic oil which was readily soluble in hydrochloric acid. When treated with sodium hydroxide and benzene sulfochloride, this oil yielded a red oil which was insoluble in both acid and alkali. The condensation product could not be solidified in a freezing mixture. The formation of a secondary amine thus establishes the fact that ring closure has occurred with substitution of the end nitrogen of the phenylcarbamic acid. The isomeric six-membered oxazine should yield aniline when subjected to this treatment.

The sulfur analog of Formula I, with two sulfurs in place of the two oxygens, has been described by Busch<sup>2</sup> and designated phenylpentathio-diazthine. The synthesis was, in this case, by an altogether different method, and consisted in the condensation of potassium phenylthiocarbamate with ethylene bromide. The product thus obtained differed from

<sup>2</sup> Busch, *Ber.*, **27**, 2516 (1894).

both of the above lactones in that the alcoholic solution gave a blue violet color with ferric chloride, whereas the lactones gave no color whatever.

In order to test further the applicability of pyridine as a condensing agent in the reaction between hydrazines and alkyl chlorocarbonates, the butyl esters of phenylcarbamic acid and hydrazodicarboxylic acid were prepared.

***n*-Butyl Phenylcarbazate.**—A solution of 3.1 g. of phenylhydrazine and 3.1 g. of pyridine in 15 cc. of water was treated with 3.9 g. of *n*-butyl chlorocarbonate. A yellow oil separated and solidified on cooling. After being thoroughly washed with water and recrystallized from benzene, the product was obtained in white, scaly crystals melting at 70°.

*Anal.* Subs., 0.1973: N<sub>2</sub>, 25.2 cc. (25°, 745 mm.). Calcd. for C<sub>11</sub>H<sub>18</sub>O<sub>2</sub>N<sub>2</sub>: N, 13.46. Found: 13.95.

***n*-Butyl Bicarbamate.**—A solution of 34 g. of hydrazine hydrate (40%) and 25 g. of pyridine in 100 cc. of water was treated with 18.5 g. of butyl chlorocarbonate. The oil which separated was thoroughly washed by shaking with water and dil. acetic acid, and allowed to stand in an ice box overnight. A mass of scaly crystals was thus obtained which after recrystallization from benzene melted at 47°.

*Anal.* Subs., 0.1600: CO<sub>2</sub>, 0.3036; H<sub>2</sub>O, 0.1314. Subs., 0.2087: N<sub>2</sub>, 22.9 cc. (24°, 753 mm.). Calcd. for C<sub>10</sub>H<sub>20</sub>O<sub>4</sub>N<sub>2</sub>: C, 51.73; H, 8.62; N, 12.07. Found: C, 51.74; H, 8.92; N, 12.08.

The two cyclic derivatives, I and II, representing as they do new types of ring structures, were of interest as possible pharmacological agents. Preliminary tests, however, failed to reveal any noteworthy physiological action. When administered orally in 1g. doses to normal dogs of about 10 kg. weight, no marked symptoms were observed, either of gastric or intestinal disturbance, or of narcotic or toxic action. The hydrazine grouping present might, however, lead one to expect a certain degree of antipyretic action, and it is planned to perform a suitable test of this effect in the near future.

### Summary

Heterocycles containing two nitrogens and one oxygen, and representing six- and seven-membered ring structures, respectively, were prepared by removal of hydrogen chloride from the  $\beta$ -chloro-ethyl and the  $\gamma$ -chloro-propyl esters of phenylcarbamic acid. These hydrazolactones represent new types, the first of which may be designated a 1,3,4-oxdiazine, but for the second our present system of cyclic nomenclature is inadequate. Provisionally, the latter may be designated a homo-1,3,4-oxdiazine. No noteworthy pharmacological action was observed when these derivatives were administered orally in 1g. doses to normal dogs.

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