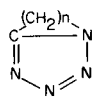
Synthesis of Some Dihalotetrazolopyridines, Azepines, and Azocines (1)

Frank M. D'Itri (2) and Alexander I. Popov

Department of Chemistry, Michigan State University

We recently reported on the preparation and the complexing abilities of some 1,5-(polymethylene)-1,*H*-tetrazoles (3).



Pharmacological studies of these compounds showed a remarkable gradation of stimulating activity on the central nervous system with the length of the polymethylene chain (4). It was of interest to us, therefore, to study the influence of halogen substitution in the polymethylene chain on the physiological and complexing abilities of tetrazoles as well as those properties in compounds containing two tetrazole rings.

Literature search seems to indicate only one previous reference to 9,9-dichloro-6,7,8,9-tetrahydro-5*H*-tetrazolo-[1,5-*a*]azepine and 9,9-dichloro-ω,ω-dialkyl-6,7,8,9-tetrahydro-5*H*-tetrazolo[1,5-*a*]azepine (5). Since these compounds were prepared as intermediates for the lactam method of preparing the respective alkyl substituted 6,7,8,9-tetrahydro-5*H*-tetrazoloazepine, they were not isolated or characterized.

In this work the dihalotetrazolopyridines, azepines and azocines were all prepared by reacting the respective 3,3-dihaloazacycloalkan-2-one first with phosphorus pentachloride and then with hydrazoic acid. The chlorination of hexahydro-2*H*-azepin-2-one to produce 3,3-dichlorohexahydro-2*H*-azepin-2-one was first reported by von Braun and Heymons (6) with the reaction conditions improved by Wineman *et al.* (7). When treated with additional phosphorus pentachloride, the 3,3-dihaloazacycloalkan-2-ones form the imidyl chloride intermediates which add in the azido group when they are reacted with hydrazoic acid. This unstable intermediate quickly rearranges to produce the desired 1,5-(ω,ω-dichloropolymethylene)-1*H*-tetrazole.

EXPERIMENTAL

Reagents.

All chemicals, commercially available, were obtained from either Aldrich Chemical Company, Eastman Organic Chemicals, or Fisher Scientific Company; and they were used without further purification.

Hydrazoic Acid.

The method outlined by von Braun (8) was used to prepare solutions of hydrazoic acid in benzene. Since hydrazoic acid vapors are very toxic, all reactions involving its use were performed in a hood.

3,3-Dibromo-2-piperidone.

A stirred solution of 58 g. (0.58 mole) of 2-piperidone in 400 ml. of dry chloroform was prepared in a 1-liter, three-necked, round-bottom flask equipped with a mechanical stirrer and thermometer. A small Erlenmeyer flask was attached to the third opening by means of a large diameter rubber tubing slipped over the opening. Phosphorus pentachloride (242 g., 1.16 moles) was quickly weighed into the Erlenmeyer flask which was then attached to the apparatus. The phosphorus pentachloride was then added to the reaction flask in about one or two g. portions during a period of one hour. Throughout this addition the reaction mixture was maintained between 3° and 10° by external cooling. After all the phosphorus pentachloride was added, the resulting slurry was allowed to return to room temperature. Then 1.5 g. of zinc (II) chloride were added, followed by 96 g. (0.6 mole) of bromine. The stirring was continued for five hours before the solvent was removed by vacuum distillation at 40° and 20 mm. The residue was poured into an ice-water mixture. The solid product was dissolved in chloroform, and the solution was treated with 10% aqueous sodium bisulfite solution to remove the last traces of bromine. Evaporation of the chloroform solution left a solid residue which was recrystallized from ethanol to yield 80 g. of well-formed prisms of 3,3-dibromo-2-piperidone, m.p. 186°. The yield, based on 2-piperidone, was 53.7%.

3,3-Dichlorohexahydro-2(1*H*)-azocinone (9).

This compound was prepared in 75.8% yield from 25 g. (0.197 mole) of hexahydro-2(1*H*)-azocinone and phosphorus pentachloride following the procedure described for the preparation of 3,3-dibromo-2-piperidone. The product was recrystallized from boiling ethanol and dried *in vacuo* to give 29.2 g. of well-formed prisms of 3,3-dichlorohexahydro-2(1*H*)-azocinone, m.p. 96-97°.

8,8-Dichloro-5,6,7,8-tetrahydrotetrazolo[1,5-*a*]pyridine.

A stirred solution of 16.8 g. of 3,3-dichloro-2-piperidone (0.10 mole) in 300 ml. of dry benzene was prepared in a 1-liter, three-necked, round-bottom flask fitted with a stirrer, reflux condenser, and surmounted by a calcium chloride drying tube. The third opening was connected to a 500 ml. Erlenmeyer flask containing 22.88 g. (0.11 mole) of phosphorus pentachloride. The benzene solution was stirred and heated to 40° while the phosphorus pentachloride was added in 0.5 g. portions over a period of one hour. The reaction was accompanied by the vigorous evolution of hydrogen chloride. When the formation of the imidyl chloride was com-

plete, as evidenced by the disappearance of solid phosphorus pentachloride, the reaction mixture was cooled to 20°. The Erlenmeyer flask was then replaced by a dropping-funnel through which 10 g. of hydrazoic acid (0.233 mole, 137 ml. of 1.7 *N* hydrazoic acid-benzene solution) was added, maintaining the temperature of the reaction mixture between 20 and 30° by means of external cooling. After the addition of the hydrazoic acid, the reaction mixture was allowed to stand at room temperature for two hours. It was gradually warmed to the boiling point on a steam bath and maintained at this temperature until hydrogen chloride evolution ceased in about three hours. The solvent was removed by air evaporation, and the residue was treated with ice and water (100 g. each) to decompose any phosphorus oxychloride that was present. Dry sodium carbonate was then carefully added to neutralize any acid, the presence of which caused the oily residue to solidify. The product was extracted from the mixture with four 100 ml. portions of chloroform. It was then evaporated to dryness and recrystallized twice from ethanol. On cooling, 13.5 g. (70% yield, based on the 3,3-dichloro-2-piperidone) of 8,8-dichloro-5,6,7,8-tetrahydrotetrazolo[1,5-*a*]pyridine precipitated. The colorless crystals that were obtained melted at 84°. The infrared and nmr spectra of this compound are in complete agreement with the proposed structure of this compound.

Anal. Calcd. for $C_5H_6Cl_2N_4$: C, 31.11; H, 3.13; Cl, 36.73; N, 29.02. Found: C, 31.77; H, 3.26; Cl, 36.90; N, 28.86.

8,8-Dibromo-5,6,7,8-tetrahydrotetrazolo[1,5-*a*]pyridine.

This compound was prepared in the manner previously described for the preparation of 8,8-dichloro-5,6,7,8-tetrahydrotetrazolo[1,5-*a*]pyridine. Starting with 25.69 g. of 3,3-dibromo-2-piperidone (0.1 mole), 12 g. of crude product was obtained and recrystallized twice from boiling ethanol. On cooling 10 g. (36.5% yield) of 8,8-dibromo-5,6,7,8-tetrahydrotetrazolo[1,5-a]pyridine precipitated. These colorless crystals melted at 91°.

Anal. Calcd. for $C_5H_6Br_2N_4$: C, 21.30; H, 2.15; Br, 56.68; N, 19.87. Found: C, 21.30; H, 2.19; Br, 56.48; N, 20.08.

9,9-Dichloro-6,7,8,9-tetrahydro-5*H*-tetrazolo[1,5-*a*]azepine.

This compound was prepared starting with 18.2 g. of 3,3-dichlorohexahydro-2*H*-azepin-2-one (0.10 mole) in the manner previously described for the preparation of 8,8-dichloro-5,6,7,8-tetrahydrotetrazolo[1,5-*a*]pyridine. The crude product was recrystallized from boiling ethanol twice. The resulting colorless crystals melted at 81-82°. The yield (total 17.48 g.) based on 3,3-dichlorohexahydro-2*H*-azepin-2-one was 84.5%. The infrared and nmr spectra of this compound are in complete agreement with the proposed structure of this compound.

Anal. Calcd. for $C_6H_8Cl_2N_4$: C, 34.80; H, 3.94; Cl, 34.24; N, 27.06. Found: C, 34.77; H, 3.81; Cl, 34.22; N, 27.11.

9,9-Dibromo-6,7,8,9-tetrahydro-5*H*-tetrazolo[1,5-*a*]azepine.

The preparation of this compound started with 27.10 g. of 3,3-dibromohexahydro-2*H*-azepin-2-one (0.10 mole) in the manner previously described to prepare 8,8-dichloro-5,6,7,8-tetrahydrotetrazolo[1,5-*a*]pyridine. The crude product was recrystallized from boiling ethanol. Upon cooling, 22.35 g. (75.4% yield) of 9,9-dibromo-6,7,8,9-tetrahydro-5*H*-tetrazolo[1,5-*a*]azepine precipitated. The colorless crystals thus obtained melted at 117-119°.

Anal. Calcd. for $C_6H_8Br_2N_4$: C, 24.35; H, 2.73; Br, 54.00; N. 18.93. Found: C, 24.38; H, 2.72; Br, 54.00; N, 18.95.

10,10-Dichloro-5,6,7,8,9,10-hexahydrotetrazolo[1,5-*a*]azocine.

Starting with 19.6 g. of 3,3-dichlorohexahydro-2(1*H*)-azocinone (0.10 mole), this compound was prepared in the manner described for the preparation of 8,8-dichloro-5,6,7,8-tetrahydrotetrazolo[1,5-*a*]pyridine. The crude product, recovered by evaporating the chloroform, was purified by two recrystallizations from ethanol. On cooling 12,20 g. (55.2% yield) of colorless crystals of 10,10-dichloro-5,6,7,8,9,10-hexahydrotetrazolo[1,5-*a*]azocine (m.p. 63-64°) precipitated.

Anal. Calcd. for $C_7H_{10}Cl_2N_4$: C, 38.03; H, 4.56; Cl, 32.97; N, 25.34. Found: C, 38.56; H, 4.61; Cl, 31.23; N, 25.10.

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