Preparation of 1,2,4-Triazole Derivatives of *S*-Triazines

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Eleven symmetrical triazine derivatives containing 1,2,4-triazole and 3-amino-1,2,4-triazole substituents have been prepared. The derivatives with 1,2,4-triazole substituents were synthesized by reacting *N,N'*-diformylhydrazine with certain amine derivatives of cyanuric chloride. The derivatives with 3-amino-1,2,4-triazole substituents were synthesized by reacting 3-amino-1,2,4-triazole with cyanuric chloride *per se*. Five of the derivatives were screened for anticarcinogenic and herbicidal properties. No anticarcinogenic or herbicidal effects were detected. Mouse behavior studies showed that three of the five were weak central nervous system depressants.

THE PURPOSE of this investigation was to prepare a number of compounds containing both the *S*-triazine and the 1,2,4-triazole heterocycles in a single nonfused ring system for biological testing.

Compounds containing either of these rings have shown a variety of biological activities. Among *S*-triazine derivatives are compounds that have shown activity as anticarcinogens (1), trypanocides (2), antihistamines (3, 4) curarimimetics (5), fungicides (6), diuretics (7), and antimalarials (8). Among 1,2,4-triazole derivatives are compounds which inhibit cholinesterase activity (9), exert a pressor effect (10), and act as central nervous system stimulants (11–13) and depressants (13–15). Both *S*-triazine and 1,2,4-triazole derivatives have found use also as herbicides (16).

The compounds prepared in this investigation containing both *S*-triazine and 1,2,4-triazole in a single nonfused ring system are shown in Table I. All of the compounds are new.

Attempts were made to obtain a melting point for each of the compounds by means of a Fisher-Johns apparatus. The apparatus was limited to a 300° thermometer. None of the compounds melted when heated to 300°.

Some difficulty was experienced with elemental analyses of the compounds. Nitrogen values generally approximated the theoretical; carbon and hydrogen values were irregular. Some *S*-triazine derivatives, however, have presented difficulties in elemental analyses (17–19). Walker and coworkers (18) attribute irregular carbon and hydrogen values to a combination of poor combustion and/or the formation of cyanogen compounds which can then react with copper oxide to give stable salts.

Infrared spectra of the compounds in Table I were compared with spectra of known compounds which contain the 1,2,4-triazole or *S*-triazine rings. The presence of both rings was demonstrated in all of the compounds.

EXPERIMENTAL

The preparation of compounds *1–5* in Table I was based on the method of Pellizarri (11) in which *N,N'*-diformylhydrazine is reacted with a primary amine. The primary amines in this investigation were essentially derivatives of cyanuric chloride. A general procedure for synthesizing compounds *1–5* was followed, using appropriately substituted *S*-triazines as the primary amine. The following synthesis of compound *1* is typical of the procedure.

2,4 - Dihydroxy - 6[4 - (1,2,4 - triazolyl)] - S-triazine (Compound 1).—*N,N'*-Diformylhydrazine, 4.4 Gm. (0.05 mole), was melted on an oil bath maintained at 180–200°. To this was added 2-amino-4,6-dihydroxy-*S*-triazine, 12.8 Gm. (0.10 mole), in small portions. The oil bath was maintained at the above temperature until the water was completely removed from the reaction mixture. Upon cooling to room temperature, the solid residue was extracted successively with water, dilute sodium hydroxide solution, water, dilute hydrochloric acid, and water. The resulting product was a white powder.[1] It did not melt when heated to 300°. The yield was 5.7 Gm. (63.3%).

Anal.—Calcd. for $C_5H_4N_6O_2$: N, 46.66. Found: N, 45.40.

Compounds *6–11* in Table I were prepared by reacting 3-amino-1,2,4-triazole with cyanuric chloride *per se*. Here a general procedure was also followed. For the introduction of a single triazolyl group into the *S*-triazine ring, a temperature of 0–5° was maintained; for the introduction of two triazolyl groups, a temperature of 40–45° was maintained. Amino or hydroxy substituents were formed by treating the resulting triazolyl-amino-*S*-triazines with either ammonia or potassium hydroxide. The preparation of compound *6* illustrates the general procedure for compounds *6–11*.

2 - Amino - 4 - chloro - 6 - [3 - (1,2,4 - triazolyl)-amino]-S-triazine (Compound 6).—A methanol solution of 16.8 Gm. (0.15 mole) of 3-amino-1,2,4-triazole was added to an acetone solution of cyanuric chloride, 18.4 Gm. (0.10 mole), at a temperature of 0–5°. After 2 hr. at this temperature, the mixture was heated to 45°, and 13.6 ml. of 28% ammonium hydroxide solution (0.20 mole NH_3) was added. The suspension formed was allowed to stand for 2 hr., then filtered with suction. The light yellow precipitate obtained was washed free of the chloride ion. The product did not melt when heated to 300°. The yield was 17.9 Gm. (84.0%).

Anal.—Calcd. for $C_5H_5ClN_8$: N, 52.71. Found: N, 51.80.

BIOLOGICAL RESULTS

Compounds *1*, *3*, *4*, *5*, and *6* in Table I were screened for anticarcinogenic effects and for herbicidal activity.[2] No anticarcinogenic effects were

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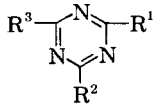
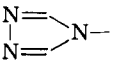
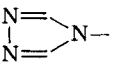
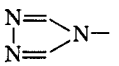
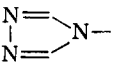
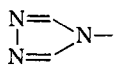
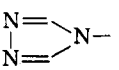
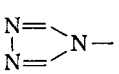
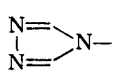
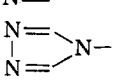
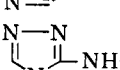
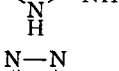
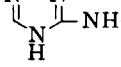
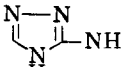
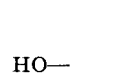
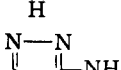
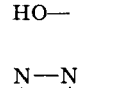
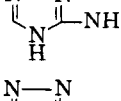
[1] A suitable recrystallization procedure for the compounds in Table I was not achieved.

[2] The authors are indebted to Eli Lilly and Co. Research Laboratories for carrying out the biological screening tests.

TABLE I.—1,2,4-TRIAZOLYL-TRIAZINES



Compd.	R^1	R^2	R^3	Yield, %	Formula	N[a] Calcd.	N[a] Found
1	HO—	HO—		63.3	$C_5H_4N_6O_2$	46.66	45.40
2	NH_2—	C_6H_5—		11.7	$C_{11}H_9N_7$	43.28	43.90
3	NH_2—			47.0	$C_7H_6N_{10}$	60.85	60.02
4	C_6H_5—			32.6	$C_{13}H_9N_9$	43.28	43.90
5				33.7	$C_9H_6N_{12}$	59.56	59.90
6	NH_2—	Cl—		84.0	$C_5H_5ClN_8$	52.71	51.80
7	Cl—	Cl—		99.1	$C_5H_3Cl_2N_7$	42.26	42.50
8	HO—	HO—		88.3	$C_5H_5N_7O_2$	50.26	50.70
9	NH_2—	HO—		87.8	$C_5H_6N_8O$	57.73	57.28
10	Cl—			97.9	$C_7H_6ClN_{11}$	55.10	55.20
11	HO—			78.2	$C_7H_7N_{11}O$	59.00	58.40

[a] Analyses by Weiler and Strauss, Oxford, England.

detected and no meaningful herbicidal activity noted. A mouse behavior study on the same compounds revealed that *1*, *3*, and *6* were weak central nervous system depressants.

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