Synthesis of Diamino-*s*-Triazinyl Ketones

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In connection with the continuing program concerning diamino-*s*-triazines as potential insect chemosterilants (1, 2), the synthesis of previously unreported 4,6-diamino-*s*-triazin-2-yl ketones (3) was undertaken. The convenient preparation of triazinyl methanols by the condensation of appropriate α-hydroxy esters with biguanides (4, 5) or by the reaction of α-cyanoacetals with dicyandiamide followed by acid hydrolysis (6) made these alcohols attractive precursors for the ketones. Several new triazinyl methanols (Table I) have been prepared by these methods and subsequently oxidized to the corresponding ketones.

The preparation of pyrimidinyl ketones by the treatment of the corresponding alcohols with chromium trioxide in pyridine and active manganese dioxide in benzene has been reported (7). Although these methods were suitable for the oxidation of pyrimidinyl methanols, the extremely low solubility of diamino-*s*-triazines in pyridine and benzene restricted the direct application of these procedures to the triazines. Treatment of III with chromium trioxide in a more polar solvent (acetic acid) provided only a 20% yield of the corresponding ketone. Despite this marginal success, isolation of the product from the reaction mixture was difficult.

The problem of low solubility of the triazinyl methanols was alleviated by the use of dimethylformamide. Thus, yields of the triazinyl ketones ranging from 61 to 99% were obtained by heating the corresponding alcohols in this solvent with active manganese dioxide. The various conditions for the oxidations and physical data for these ketones are reported in Table II. A mixture of acetic anhydride in dimethyl sulfoxide (8) provided an alternate but less effective method for the oxidation of II and III.

Carbonyl stretching bands of moderate intensity were observed for the ketones in the 5.83-6.00 μ region of the infrared spectrum. With the exception of XIV (5.91 μ) aromatic substituted triazinyl ketones XI-XVI absorbed in a narrow range between 5.97 and 6.00 μ.

EXPERIMENTAL

Melting points (capillary tubes) were determined on a Büchi apparatus and are uncorrected. Infrared spectra (potassium bromide discs) were measured with a Perkin-Elmer Model 137 sodium chloride prism spectrophotometer. Glpc analyses were made on a Micro-Tek Model 220 instrument. Mention of a proprietary product or company does not necessarily imply endorsement of the product or company by the U. S. Department of Agriculture.

Materials.

Methyl mandelate and *p*-chloromandelic acid were obtained from Aldrich Chemical Company. Methyl 2-furylglycolate (10) and methyl 2-pyridylglycolate hydrochloride (11) were synthesized according to published procedures. Filtration of the freshly prepared active manganese dioxide (12) through large glass-fritted funnels (medium porosity) rather than collection by centrifugation greatly facilitated large-scale production of this oxidant.

4,6-Diamino-*s*-triazine-2-methanols. (Table I).

All of the triazinyl methanols except II were prepared by the biguanide-ester condensation method (4, 5). The biguanides were obtained commercially in the form of hydrochloride or sulfate salts. The free biguanide bases were obtained by treating the corresponding salts with sodium methoxide in methanol. In most cases the bases were not isolated, but rather a slurry of the salt in methanol was treated with an equivalent of sodium methoxide, the mixture was filtered, and the filtrate was reacted with the appropriate α-hydroxy ester. Yields of the alcohols were improved by addition of excess sodium methoxide.

Isobutyraldehyde Cyanohydrin.

The cyanohydrin was prepared according to the procedure used by Roberts, *et al.* (13) for pivaldehyde cyanohydrin. The crude oil was used without purification.

Acetaldehyde Butyl 1-Cyano-2-methylpropyl Acetal.

The acetal was prepared by the method of Sims, *et al.* (6) in 75% yield, b.p. 77-85° (2.4 mm.). Glpc analysis of the distillate on a 4 ft. x 0.25 in. glass column packed with 10% DEGS (LAC-728) on acid washed Chromosorb W, 60-80 mesh (column temp., 130°, nitrogen flow rate, 70 ml. per minute) indicated two products having retention times of 1.25 minutes (67%) and 1.77 minutes (33%). Further distillation did not change the product ratio (14) and the material was used directly in the next step.

Acetaldehyde Butyl 1-(4,6-Diamino-*s*-triazin-2-yl)-2-methylpropyl Acetal.

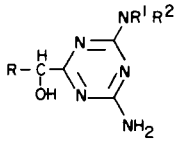
The title compound was prepared in 44% yield according to the method of Sims, *et al.* (6). Recrystallization from ethanol-water gave the analytical sample, m.p. 133.5-135°.

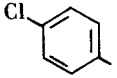
Anal. Calcd. for $C_{13}H_{25}N_5O_2$: C, 55.10; H, 8.89; N, 24.71. Found: C, 55.08; H, 9.38; N, 24.61.

4,6-Diamino-α-isopropyl-*s*-triazine-2-methanol (II).

Acid hydrolysis of the previously mentioned triazinyl acetal according to the procedure of Sims, *et al.* (6) gave II in 86% yield (Table I).

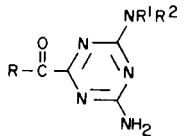
TABLE I

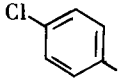


Compound	R	R^1	R^2	Yield, % (a)	M.p., °C	Recrystallization Solvent	Formula	Elemental Analysis Calcd., % C	H	N	Found, % C	H	N
I	CH_3	H	H	32	261.5-263 (b)	Water	$C_5H_9N_5O$						
II	i-C_3H_7	H	H		204-205.5	Ethanol-water	$C_7H_{13}N_5O$	45.89	7.15	38.23	46.10	7.19	38.03
III		H	H	43	218-224 (c)	Ethanol-water	$C_{10}H_{11}N_5O$	55.29	5.11	32.24	55.43	5.27	32.41
IV		H	H	55	234.5-242	Ethanol	$C_{10}H_{10}ClN_5O$	47.72	4.01	27.82	48.07	4.22	27.82
V		H	H	39	199.5-202	Methanol	$C_8H_9N_5O_2$	46.38	4.38	33.80	46.02	4.40	33.65
VI		H	H	34	227-231.5	Water	$C_9H_{10}N_6O$	49.54	4.62		49.64	4.62	
VII		H		34	232-233.5 (d)	Dimethyl= formamide-water	$C_{16}H_{15}N_5O$	65.53	5.16	23.88	65.72	5.31	23.90
VIII		CH_3	CH_3	46	157-157.5	Ethanol	$C_{12}H_{15}N_5O$	58.74	6.16		58.98	6.21	

(a) Percentages reported are based on crude product. (b) Lit. (6) m.p. 254°. (c) Lit. (6) m.p. 182-190°. (d) Lit. (9) m.p. 210-215°.

TABLE II



Compound	R	R^1	R^2	Yield, % (a)	M.p., °C	Recrystallization Solvent	Reaction Conditions (a) Time, hours (Temp., °C)	Formula		Elemental Analysis %C	%H	%N
IX	CH_3	H	H	61	264 dec.	Dimethyl= formamide	2.5 (65)	$C_5H_7N_5O$	Calcd.	39.24	4.61	45.74
									Found	39.28	4.68	45.91
X	i-C_3H_7	H	H	18 (b)	206.5-208.5	Dimethyl= formamide-water		$C_7H_{11}N_5O$	Calcd.	46.40	6.12	38.64
									Found	46.49	6.22	38.85
XI		H	H	70, 55 (b)	243.5-245	Ethanol-water	2.5 (85)	$C_{10}H_9N_5O$	Calcd.	55.81	4.21	32.54
									Found	56.07	4.28	32.42
XII		H	H	73	272-274.5	Dimethyl= formamide-water	2.5 (65) (c)	$C_{10}H_8ClN_5O$	Calcd.	48.10	3.15	28.04
									Found	48.39	3.24	28.13
XIII		H	H	61	265.5-266.5	Dimethyl= formamide-water	2.5 (65) (c)	$C_8H_7N_5O_2$	Calcd.	46.83	3.36	34.13
									Found	46.99	3.53	34.35
XIV		H	H	73	250.5-251.5	Water	2.25 (85)	$C_9H_8N_6O$	Calcd.	50.00	3.73	38.87
									Found	50.11	3.73	38.95
XV		H		99	168-169	Ethanol	2.5 (65) (c)	$C_{16}H_{13}N_5O$	Calcd.	65.98	4.50	24.04
									Found	65.83	4.55	24.06
XVI		CH_3	CH_3	61	178.5-180	Ethanol	2.5 (65) (c)	$C_{12}H_{13}N_5O$	Calcd.	59.23	5.38	28.78
									Found	59.22	5.36	28.68

(a) Manganese dioxide oxidation procedure. (b) **Dimethyl sulfoxide-acetic anhydride oxidation procedure.** (c) Reaction was heated for an additional 0.5 hour at 85° prior to work-up.

Manganese Dioxide Oxidation of Diamino-*s*-triazine-2-methanols.

Although oxidation of the triazinyl methanols were routinely run at 65° with 5 g. of active manganese dioxide and 20 ml. of dimethylformamide per gram of the alcohol, additional solvent and increased temperatures were employed when low solubility of certain alcohols was encountered. Undesirable side reactions and lower yields frequently resulted when reaction conditions more severe than those reported in Table II were used. Additional solvent was generally added during the remaining few minutes of reaction to insure maximum solubility of the ketone prior to filtration. A detailed procedure for the preparation of XI follows.

4,6-Diamino-*s*-triazin-2-yl Phenyl Ketone (XI). Manganese Dioxide Procedure.

Compound III (1.00 g., 4.60 mmoles) and finely pulverized active manganese dioxide (5 g.) were stirred in 30 ml. of dimethylformamide for 2.5 hours at 85°. The hot mixture was filtered and the solid was washed with warm dimethylformamide. Evaporation of the filtrate and recrystallization of the solid residue from ethanol-water gave 686 mg. (70%) of XI (Table II).

Dimethyl Sulfoxide-Acetic Anhydride Procedure.

A mixture of III (5.86 g., 27 mmoles), acetic anhydride (12 ml.), and anhydrous dimethyl sulfoxide (120 ml.) was stirred at room temperature for 25 hours. The violet solution was cooled in an ice-water bath and made alkaline with concentrated ammonium hydroxide. The product was isolated by pouring the mixture into water (300 ml.), cooling, and collecting the solid by filtration. Recrystallization from ethanol-water gave 3.18 g., (55%) of pure XI.

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(1) A. B. Borkovec and P. H. Terry, U. S. Patent 3,189,521 (1965).

(2) A. B. Borkovec, "Insect Chemosterilants," Interscience Publishers, Inc., New York, New York, 1966, pp. 33-36.

(3) Several erroneous entries of the triazinyl ketones appear in *Chem. Abstr.* Errors involved structure interpretation of the commonly used terms aceto- and benzoguanamine which are synonymous for 2,4-diamino-6-methyl and 6-phenyl-*s*-triazine, respectively.

(4) J. T. Thurston, U. S. Patent 2,394,526 (1946); *Chem. Abstr.*, **40**, 5776 (1946).

(5) For related methods see E. M. Smolin and L. Rapoport, "*s*-Triazines and Derivatives," Interscience Publishers, Inc., New York, New York, 1959, pp. 226-229.

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(14) The products are probably diastereomers. M. Schwarz of these laboratories has observed similar distributions of diastereoisomeric products derived from reactions of other closely related cyanohydrins with alkyl vinyl ethers (unpublished results).

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