CHEMISTRY OF 1,2,4-TRIAZINE. IV.*

METHYLATION OF 2,3,4,5-TETRAHYDRO-1,2,4-TRIAZINE-3,5-DIONE WITH DIMETHYL SULFATE IN NEUTRAL MEDIA

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Received July 26th, 1972

Methylation of 2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione (*I*) with dimethyl sulfate afforded anhydro-3-hydroxy-1-methyl-2,5(4,5)-dihydro-5-oxo-1,2,4-triazinium hydroxide (*II*), the structure of which was established by NMR spectra and chemical evidence consisting in hydrogenation to 1-methylhexahydro-1,2,4-triazine-3,5-dione (*IV*).

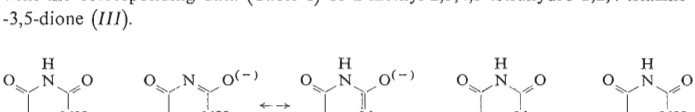
Alkylations of 2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione (6-azauracil; *I*) with alkyl iodides, dialkyl sulfates[1] or benzyl chloride[2] in aqueous alkali or of the corresponding salts in nonpolar solvents[1] afford depending on reaction conditions the 2- and 4-monoalkyl or 2,4-dialkyl derivatives. Reaction of compound *I* with diazoalkanes leads to a mixture in which the 4-alkyl derivatives highly predominate[1,3]. Alkylations of the thio analogues of compound *I* with alkyl iodides in alkaline media results in a primary formation of the corresponding alkylthio derivatives and then in the subsequent alkylation on the nitrogen atoms at positions 2 or 4 (*cf.*[4,5]). Similar products are obtained on methylation with diazomethane[4,5] along with a lesser amount of the O-methyl derivatives[6].

All the above alkylations involve substitution of acidic hydrogen atoms of the lactam or tautomeric lactim form of compound *I* or its thio analogues. We have now observed that the course of the reaction between the triazinedione *I* and dimethylsulfate is different when alkali is absent. The reaction mixture obtained on heating the two components at 135–145° was chromatographed on an anion exchange resin in carbonate cycle (procedure *B*) or on cellulose (procedure *C*) to afford a monomethyl derivative *II* which was not identical with the known alkylation products in alkaline media[1], namely, with 2- or 4-methyl-2,3,4,5-tetrahydro-1,2,4-triazine-3,5-dione.

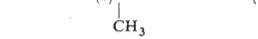
The yield of the reaction is about 40%. When the reaction mixture is diluted with water and the precipitate crystallised from water, a molecular compound is obtained containing the substances *I* and *II* in the ratio of 1 : 1 (procedure *A*). Longer reaction periods of time do not considerably increase the yield of the methylation product. Elevated temperatures lead to decomposition.

* Part III: This Journal *38*, 592 (1973).

The polar character of the product and its stability towards hydrolysis exclude the structure of a O-methyl derivative. On the other hand, the behaviour of the product and reaction conditions which make possible quaternisation on the nitrogen atom at position 1, favour the structure of anhydro-3-hydroxy-1-methyl-2,5(4,5)-dihydro-5-oxo-1,2,4-triazinium hydroxide (*II*). The betain character of compound *II* is confirmed by the frequency shift of the carbonyl maximum and the 6-CH bond at position 6 in infrared spectra and the remarkable chemical shift of the signal of the methyl group and the proton at position 6 in NMR spectra, when compared with the corresponding data (Table I) of 2-methyl-2,3,4,5-tetrahydro-1,2,4-triazine--3,5-dione (*III*).



I *II* *III* *IV*



V

VI

The structure of the betain *II* is also supported by the unequivocal synthesis of the corresponding hydrogenation product, namely, 1-methylhexahydro-1,2,4-triazine--3,5-dione (*IV*). Thus, 1-methylhydrazinoacetic acid[7] as the starting compound was converted to the ethyl ester hydrochloride *V* which afforded ethyl 1-methylsemicarbazidoacetate (*VI*) by reaction with cyanic acid. Cyclisation of compound *VI* in ethanolic sodium ethoxide led to the identical hexahydrotriazine *IV*.

To our knowledge, compound *II* represents the first betain in the 1,2,4-triazine series.

EXPERIMENTAL

Melting points were taken on a heated microscope stage (Kofler block). Analytical samples were dried at 0·1 Torr and 20°C for 10 h.

Anhydro-3-hydroxy-1-methyl-2,5(4,5)dihydro-5-oxo-1,2,4-triazinium Hydroxide (*II*)

A. A mixture of the triazinedione *I* (4·52 g; 40 mmol) and dimethyl sulfate (5 ml) was heated at 135—145°C for 30 min, the melt cooled down, triturated with water (10 ml), set aside for several hours, and the solid molecular compound of substances *I* and *II* finally collected with suction. Yield, 4·3 g (89%); m.p. 235—236°C (decomposition). The analytical sample was recrystallised from water. For $C_3H_3N_3O_2 \cdot C_4H_5N_3O_2$ (240·2) calculated: 35·00% C, 3·36% H, 34·99% N; found: 35·15% C, 3·45% H, 34·86% N. *B*. The molecular compound (2 g) obtained by procedure *A*

TABLE I

IR Spectra (KBr) and NMR Spectra (hexadeuteriodimethyl sulfoxide) of Compounds *II* and *III*

Compound	IR spectrum	NMR spectrum	
II	ν(C—H) 3 105 m, sh	$N_{(1)}$—CH_3	δ 3·92 (s)
	ν(C=O) 1 701 s	$C_{(6)}$—H	8·03 (s)
	ν(C—O$^-$) ν(C—N$^+$) } 1 642 s, br	N—H	11·72 (m)
III	ν(C—H) 3 040	$N_{(2)}$—CH_3	3·45 (s)
	ν(C=O) 1 724 i, 1 713 i, 1 690	$C_{(6)}$—H	7·36 (s)
		$N_{(4)}$—H	12·09 (m)

was dissolved in water (50 ml) and mixed with 90 ml of the ion exchange resin Dowex 1 (CO_3^{2-}). After 10 min, the suspension was applied to the top of a column packed with the same resin (60 ml). The column was eluted with total 1 500 ml of water, the eluate evaporated, and the residue crystallised from water to afford the betain *II* in 35% overall yield; m.p. 230—233°C (decomposition). For $C_4H_5N_3O_2$ (127·1) calculated: 37·53% C, 4·07% H, 32·89% N; found: 37·58% C, 3·98% H, 32·82% N. *C.* The molecular compound (4·8 g) obtained by procedure *A* was chromatographed on a column of cellulose (800 g) in a 43 : 7 mixture (8 000 ml) of 1-butanol and water, the chromatographically homogeneous fractions combined, evaporated, and the residue crystallised from water–propanol to afford 17% overall yield of the betain *II*, identical with the specimen obtained by procedure *B*.

Ethyl 1-Methylhydrazinoacetate Hydrochloride (*V*)

A solution of 1-methylhydrazinoacetic acid[7] (2·08 g; 20 mmol) in ethanol (50 ml) was saturated with hydrogen chloride, refluxed for 30 min, resaturated with hydrogen chloride, and kept at room temperature for 12 h. The reaction mixture was evaporated under diminished pressure and the residue crystallised from an ethanol–ether mixture to afford 2 g (59%) of compound *V*, m.p. 95—97°C. For $C_5H_{13}ClN_2O_2$ (168·6) calculated: 35·61% C, 7·77% H, 21·03% Cl, 16·62% N; found: 35·32% C, 7·78% H, 21·00% Cl, 16·70% N.

Ethyl 1-Methylsemicarbazidoacetate (*VI*)

A solution of the hydrochloride *V* (0·42 g; 2·5 mmol) in ethanol (6 ml) was treated with 1M-HCl (2·5 ml) and potassium cyanate (0·406 g; 5 mmol). The mixture was kept at room temperature for 2 h, heated at 40°C for additional 2 h, and evaporated under diminished pressure. The residue was extracted with five 20 ml portions of hot ethanol, the extracts combined, evaporated, and the residue chromatographed on a column of silica gel (20 g; previously deactivated by the addition of 12% of water) in an 1 : 20 methanol–ethyl acetate mixture. The eluate was evaporated and the residue crystallised from a benzene–light petroleum mixture to afford 0·41 g (94%) of the ester *VI*, m.p. 81—85°C. For $C_6H_{13}N_3O_2$ (175·2) calculated: 41·14% C, 7·78% H, 23·99% N; found: 40·95% C, 7·55% H, 23·64% N.

1-Methylhexahydro-1,2,4-triazine-3,5-dione (*IV*)

A. A solution of compound *II* (0·70 g; 5·5 mmol) in water (80 ml) was hydrogenated over the Adams catalyst (0·1 g of PtO_2) at room temperature and ordinary pressure until the hydrogen uptake ceased (for about 45 min). The catalyst was filtered off, the filtrate evaporated under diminished pressure, and the residue crystallised from ethanol to afford 0·59 g (83%) of compound *IV*, m.p. 189—190°C. NMR spectra (dimethyl-d_6-sulfoxide): δ 2·55 (s, N_1—CH_3), 3·48 (s, 2 × C_6—H), 9·10 (m, N_2—H), and 10·36 p.p.m. (m, N_4—H). For $C_4H_7N_3O_2$ (129·1) calculated: 37·21% C, 5·46% H, 32·54% N; found: 37·50% C, 5·40% H, 32·33% N. *B*. A mixture of 1-methylsemicarbazidoacetic acid (*VI*; 0·35 g; 2·0 mmol) and 0·5M ethanolic sodium ethoxide (4 ml) was refluxed for 1 h, evaporated, and the residue applied to a column of Dowex 50 (H^+) ion exchange resin. The column was eluted with water (150 ml) and the eluate evaporated under diminished pressure. The residue was chromatographed on a column of silica gel (20 g; previously deactivated by the addition of 12% of water) in ethyl acetate. The corresponding fractions were combined and processed as usual to afford 0·22 g (85%) of the hexahydro compound *VI*, m.p. undepressed on admixture with the specimen obtained by procedure *A*. The identity of both specimens was also confirmed by NMR spectra.

The authors wish to thank Dr P. Fiedler for infrared spectra and Dr M. Synáčková for NMR spectra. Analyses were performed in the Analytical department (Dr J. Horáček, Head) of our Institute.

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Translated by J. Pliml.