Mannich Reaction Studies in the Theophylline Series

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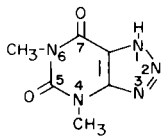
Theophylline and several of its analogs have already been subjected to Mannich reactions (1-3), but there is no report in the literature on the Mannich reaction studies of 4,6-dimethyl-1*H*-*v*-triazolo[4,5-*d*]pyrimidine-5,7-(4*H*,6*H*)-dione (8-azatheophylline, I) (4) and 8-chlorotheophylline (II). In this present publication, Mannich reaction studies on compounds I and II are described.

The compounds I and II undergo the Mannich reaction easily when equimolar amounts of either I or II, 37% aqueous formaldehyde and a secondary amine are mixed in alcoholic solution at room temperature, giving the corresponding Mannich bases (III-VII, Table I and VIII-XI, Table II).



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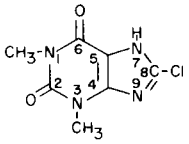
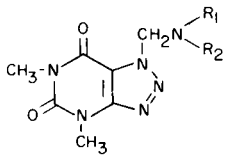
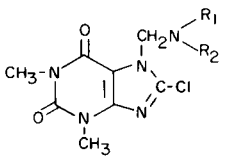


II



III - VII



VIII - XI

The Mannich bases IX and X decomposed during attempted crystallization from polar solvents such as alcohol. Previous workers have reported that Mannich bases of theophylline and several of its analogs decompose on crystallization to give the original purines (1,2). In the present studies, it was found that recrystallization of IX and X from alcohol yielded water soluble crystalline products. These products were shown by microanalysis and NMR spectral data to be salts of 8-chlorotheophylline and the secondary amine. These salts were prepared separately and found to be identical with the products obtained from the recrystallization. There seems to be no earlier report in the literature of the isolation of a salt of the acidic and amine component of a Mannich base as the decomposition product in this series. The Mannich bases of 8-azatheophylline (III-VII) were relatively stable compounds and could be recrystallized from common solvents without decomposition. The methylation studies of 8-azatheophylline by Nübel and Pfleiderer (5) indicate that the acidic hydrogen of 8-azatheophylline I is at N-1 and not at N-3. In order to confirm the structures of compounds III-VII, the catalytic reduction of compounds III and IV using platinum oxide and palladium on carbon to get the known N-1-methyl derivative of 8-azatheophylline (5) was attempted. However, the Mannich bases III and IV decomposed and gave a mixture of products.

The Mannich bases of 8-chlorotheophylline (VIII-XI) were given the above structures in accordance with the work of the previous workers in analogous cases (1,2).

EXPERIMENTAL

All melting points were taken with the Thomas-Hoover Capillary melting point apparatus. Infrared spectra were recorded on a Beckman IR-8 infrared spectrophotometer. Microanalyses were performed at the Microanalytical Laboratories at Abbott Laboratories, North Chicago, Illinois. The NMR spectra were obtained using a Varian A-60 spectrophotometer at the Physics Laboratory, Abbott Laboratories, North Chicago, Illinois.

General Procedure for the Mannich Reaction on 8-Chlorotheophylline and 8-Azatheophylline.

To a suspension of 8-chlorotheophylline or 8-azatheophylline in alcohol was added equimolecular amounts of a secondary amine and 38% formaldehyde solution. The reaction mixture was stirred while heat was evolved in the solution. The solution was filtered at once and the solvent was removed under vacuum. The residue was washed with dry ether and recrystallized. For physical data, see Tables I and II.

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TABLE I

4,6-Dimethyl-1-(dialkylaminomethyl)-1*H*-*v*-triazolo[4,5-*d*]-pyrimidine-5,7-(4*H*,6*H*)diones (III-VII)

Compound No.	NR_2	Mp, °C	Yield, %	Formula	Analysis Calculated C	H	N	Found C	H	N
III	piperidine (b)	117-118	50	$C_{12}H_{18}N_6O_2$	51.78	6.52	30.20	51.71	6.36	30.18
IV	morpholine (a)	172-173	70	$C_{11}H_{16}N_6O_3$	47.13	5.75	29.99	47.41	5.75	29.81
V	4-*N*-phenylpiperazine (c)	206-207	50	$C_{17}H_{21}N_7O_2$	57.45	5.96	27.59	57.21	5.67	27.70
VI	2-methylpiperidine (d)	97-98	35	$C_{13}H_{20}N_6O_2$	53.41	6.90	28.75	53.64	7.11	28.92
VII	3-methylpiperidine (e)	112-114	30	$C_{13}H_{20}N_6O_2$	53.41	6.90	28.75	53.70	6.93	28.76

(a) Recrystallized from ether and acetone mixture. (b) Recrystallized from acetone. (c) Recrystallized from a mixture of DMF and methanol. (d) Recrystallized from a mixture of methanol and ether. (e) Recrystallized from 95% alcohol.

TABLE II

8-Chloro-7-(dialkylaminomethyl)theophyllines (VIII-XI).

Compound No.	NR_2	Mp, °C	Yield, %	Formula	Analysis Calculated C	H	N	Found C	H	N
VIII	piperidine (a)	119-121	32	$C_{13}H_{18}ClN_5O_2$	50.09	5.82	22.46	49.94	5.95	22.29
IX	morpholine (a)	135-137	20	$C_{12}H_{16}ClN_5O_3$	45.94	5.14	22.31	45.95	5.05	22.25
X	pyrrolidine (b)	120-122	30	$C_{12}H_{16}ClN_5O_2$	48.40	5.41	23.52	48.64	5.63	23.74
XI	3-methylpiperidine (a)	144-146	30	$C_{14}H_{20}ClN_5O_2$	51.61	6.19	21.50	51.26	6.65	21.85

(a) Recrystallized from ether and acetone mixture. (b) Recrystallized from acetone.

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