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Thermal and Acid Dealkylation of Some Uracil Derivatives

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The dealkylation of *N*-alkyl-5-halo-6-methyluracils and *N*-alkyl-6-methyluracils was investigated. Heating these compounds at 240 to 250° resulted in the elimination of the alkyl groups at position 3 yielding 6-methyluracils and certain olefins. This indicated that there may be a reaction mechanism similar to the β-*cis*-elimination (Chugaev reaction). A systematic study of the effect of halogen in position 5 and of the nature of the alkyl group in position 3 on the reaction of dealkylation at elevated temperatures indicated that the reaction is affected by these two factors. In some compounds, the dealkylation by the action of concentrated HI was detected, but only *N*-*tert*-butyl-5-halo-6-methyluracil and *N*-*tert*-butyl-6-methyluracil dealkylated completely.

Uracil derivatives are commonly used as herbicides. However, little is known concerning their metabolism in plants. Gardiner *et al.* (1969) detected 5-bromo-3-*sec*-butyl-6-hydroxymethyluracil and several unknown metabolites in soil and orange seedlings treated with bromacil (5-bromo-3-*sec*-butyl-6-methyluracil).

According to Wegler (1970), for herbicidal activity of the uracils, it is necessary that position 1 remain unoccupied or be substituted by an easily detached group. There should also be an alkyl group at position 3. The methyl group in position 6 is particularly important for the activity of these compounds.

We believe that *in vitro* reactions may demonstrate possible changes *in vivo*. Our previous research (Tadić and Ries, 1971) demonstrated that hydrocarbon groups were eliminated from triazine herbicides by high temperature or sonication *in vitro*. These dealkylated triazines have been isolated from plants by Shimabukuro (1972). However, the mode of dealkylation in plants has not been elucidated.

It was postulated that the elimination of the alkyl group could proceed in a reaction similar to that described previously (Tadić and Ries, 1971). If a cyclic transition state occurs at all in the intermediate reaction, it would be accomplished by breaking of the N–C bond, with one of the two carbonyl oxygens being the proton acceptor (Figure 1).

Although the conclusions based on experiments performed under high temperature or acidic conditions at low temperature cannot be directly related to *in vivo* studies, these observations may elucidate the action in plants.

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MATERIALS AND METHODS

Chemicals. 3,6-Dimethyluracil, 3-ethyl-6-methyluracil, and 3-isopropyl-6-methyluracil were synthesized by the same method as 6-methyluracil (Donleavy and Kise, 1943). 3-*tert*-Butyl-6-methyluracil was synthesized by the same method as 3-cyclohexyl-6-methyluracil (Senda and Suzui, 1958). 5-Bromo-3,6-dimethyluracil was synthesized according to Schmedes (1925). 5-Bromo-3-ethyl-6-methyluracil and 5-bromo-3-isopropyl-6-methyluracil were obtained according to Bückendorff (1911). 5-Chloro-3-ethyl-6-methyluracil, 5-chloro-3-isopropyl-6-methyluracil, and 5-bromo-3-*tert*-butyl-6-methyluracil were products of E. I. du Pont de Nemours & Co. 5-Chloro-3-*tert*-butyl-6-methyluracil was obtained from terbacil (Sinbar) by chloroform extraction and recrystallization from ether; 5-iodo-3-isopropyl-6-methyluracil was prepared according to Loux and Luckenbaugh (1966). 5-Iodo-3,6-dimethyluracil and 5-iodo-3-ethyl-6-methyluracil were obtained by the same method as 5-iodo-6-methyluracil (Karlinskaya and Hromov-Borisov, 1960). Solutions of $Hg(ClO_4)_2$ and LiCl were prepared according to Young *et al.* (1952). Hydroiodic and hydrobromic acid were commercial products, manufactured by Fluka A.G., Buchs S.G. Hydroiodic acid was distilled before use in the presence of a small quantity of NaH_2PO_2. Silica gel G, according to Stahl (1965), was used for thin-layer chromatography. Ethylene, propylene, and isobutylene were products of Matheson Co., Joliet, Ill. Standards were prepared by adding 100 and 200 μl of olefin to 1.0 l. of air.

Trapping of Gases. Dealkylation reactions were performed by heating 1.0 mmol of substance in the apparatus of Tadić and Ries (1971). Releasing of trapped olefins

Table I. The Evolution of Olefins from Uracils with Different Halogens at Position 5, and with Different *N*-Alkyl Substituents in Position 3 by Heating at 240° for 1 Hr

Olefins	X				R
	H	Cl	Br	I	
ml/mmol	0.000	0.000	0.000	0.000	$-CH_3$
Ethylene (ml/mmol), %	0.000	0.0075	0.034 (0.247)[a]	0.000	$-CH_2-CH_3$
	0.000	0.033	0.153 (1.065)[a]	0.000 (decomposition)	
Propylene (ml/mmol), %	0.000	0.022	0.46	8.23	$-CH-(CH_3)_2$
	0.000	0.100	2.12	37.88	
Isobutylene (ml/mmol), %	9.79	21.52	22.31[b]		$-C-(CH_3)_3$
	43.72	96.50	100.00[b]		

[a]Heated at 280° for 1 hr. [b]Heated at 195–200° for 10 min.

from the $Hg(ClO_4)_2$-olefin complex by 4.0 *N* LiCl was performed as previously described.

Gas Chromatography. Released gases were analyzed on a Perkin-Elmer Fractometer F-7, using a flame ionization detector. The column was 100 cm × 2 mm i.d. and was packed with Al_2O_3 (Burrel Corp.). The temperature of the column for ethylene, propylene, and isobutylene analysis was 100, 100, and 120°, respectively. The temperature of injector was 35° and the detector was 150°. The nitrogen flow rate was 26 ml per min.

Qualitative detection of *tert*-butyliodide was made with a Perkin-Elmer Fractometer F-7, using a thermal detector. The column was 2 m × 4 mm i.d. and was filled with 5% silicon grease DC on Celite 545 60–100 mesh. The temperature of the column was 80°, the detector temperature was 150°, and the injector temperature was 100°, with a hydrogen flow rate of 32 ml per min.

Residue Analysis. After heating for 1 hr at 240°, residue analyses were made of the following uracil derivatives: 3,6-dimethyl-3-ethyl-6-methyl-, 3-isopropyl-6-methyl-, 3-*tert*-butyl-6-methyl-, 5-chloro-3-ethyl-6-methyl-, 5-chloro-3-isopropyl-6-methyl-, 5-iodo-3,6-dimethyl-, 5-iodo-3-ethyl-6-methyl-, 5-iodo-3-isopropyl-6-methyl-, 5-bromo-3,6-dimethyl-, 5-bromo-3-ethyl-6-methyl-, 5-bromo-3-isopropyl-6-methyl-, and 5-chloro-3-*tert*-butyl-6-methyluracils. After heating for 10 min at 200°, residue analyses of 5-bromo-3-*tert*-butyl-6-methyluracil were made.

Five-hundred milligrams of each uracil derivative were suspended in about 50 ml of mineral oil. After heating in an oil bath for 1 hr at 240–250° and cooling to room temperature, 70–80 ml of cyclohexane were added. The precipitated solid was filtered off on a G-3 gooch crucible and washed with cyclohexane and petroleum ether. Investigation of the solid reaction products was performed with tlc.

Dealkylation in Acid Media. Two grams of 5-chloro-3-*tert*-butyl-6-methyluracil were suspended in 40 ml of 57% HI (previously distilled over NaH_2PO_2). The mixture was stirred with a magnetic mixer and heated on a water bath. The substance was dissolved at 40° and immediately became opalescent. The stirring was continued at 45° for another 20 min, followed by cooling in an ice bath. The precipitated solid was filtered off, washed with distilled water, and recrystallized from methanol. The melting point of the substance was 328–330° (dec). Microanalysis data for C, H, and N, ir and mass spectra, and the melting point indicate that this substance is 5-chloro-6-methyluracil. A yield of 1.36 g (92%) of the substance was obtained. Analysis by gas chromatography established that *tert*-butyliodide was also present in the solution.

Treatment of 2 g of 5-chloro-3-*tert*-butyl-6-methyluracil with 50 ml of 63% HBr at 60° for 30 min yielded 1.32 g of 5-chloro-6-methyluracil (86% yield); the melting point was 328–330° (dec).

RESULTS AND DISCUSSION

Although the dealkylation reaction was postulated to proceed *via* the cyclic transition state, this mechanism has not been proven in the present paper. No reaction was detected in the 3-*N*-methyl derivatives, regardless of the halogen in position 5 (Tables I, II). Also no change occurred with compounds having hydrogen in position 5, regardless of the nature of alkyl group in position 3. The only exception was 3-*tert*-butyl-6-methyluracil, where the dealkylation of the very reactive tertiary butyl group gave 44% isobutylene. While the first phenomenon is logical and easily predicted, the question of the necessity of halogen in position 5, with the above mentioned exception, presents an interesting problem (Figure 1).

This transfer of a hydrogen from the alkyl substituent could occur to either the C-2 or C-4 oxygen (Figure 1).

It is not possible to conclude whether the resonance or inductive effect or both are the reason for the evident influence of halogen in position 5 on the dealkylation reaction. When the series of compounds with the *N*-isopropyl group in position 3 was subjected to dealkylation, the ratio of evolved propylene was in the order chlorine–bromine–iodine (1:21:379).

The dominant influence of halogen in the dealkylation reaction remains a problem which we intend to study further in forthcoming investigations. The effect of the alkyl group in position 3 on the dealkylation reaction is predictable. For example, with bromine at position 5, the ratio of evolved olefins increases in this order: ethylene–propylene–isobutylene (1:14:654).

5-Iodo-3-*tert*-butyl-6-methyluracil could not be synthesized, but dealkylation of 5-chloro-3-*tert*-butyl-6-methyluracil at temperatures of 240–250° was almost quantitative. The molar quantities of the dealkylation products isobutylene (96%) and 5-chloro-6-methyluracil (95%) were approximately equivalent; 5-chloro-6-methyluracil was identified by its melting point (328–330° dec), C, H, N analysis, and ir and mass spectra. The mass spectrum had a

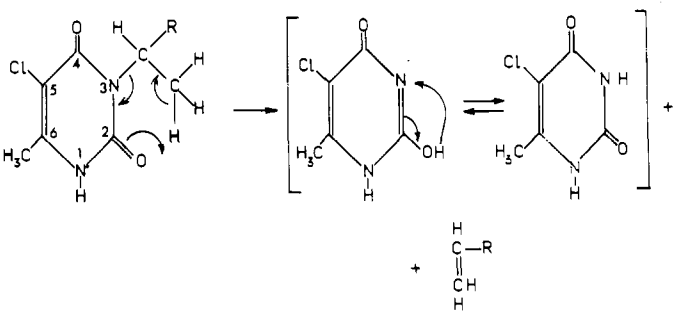

Figure 1. Proposed mechanism for the dealkylation of selected uracil derivatives.

Table II. R_f Values from Thin-Layer Chromatography of Residual Compounds after Heating *N*-Alkyl Derivatives of Uracil at 240° for 1 Hr

Solvent system[a]	Starting compound and reaction products	R_f values	R_f values of residual compounds
A	3,6-Dimethyluracil	0.42	0.42
B		0.37	0.37
A	3-Ethyl-6-methyluracil	0.53	0.53
B		0.34	0.34
A	3-Isopropyl-6-methyluracil	0.60	0.60
B		0.51	0.51
A	5-Bromo-3,6-dimethyluracil[b]	0.60	0.60, 0.42
A	3,6-Dimethyluracil	0.42	
B	5-Bromo-3,6-dimethyluracil[b]	0.53	0.53, 0.37
B	3,6-Dimethyluracil	0.37	
A	5-Chloro-3-ethyl-6-methyluracil	0.60	
A	3-Ethyl-6-methyluracil	0.53	0.60, 0.53, 0.37 in traces
A	6-Methyluracil	0.37	
B	5-Chloro-3-ethyl-6-methyluracil	0.42	
B	3-Ethyl-6-methyluracil	0.34	0.42, 0.34, 0.11 in traces
B	6-Methyluracil	0.11	
A	5-Bromo-3-ethyl-6-methyluracil	0.62	
A	3-Ethyl-6-methyluracil	0.53	0.62, 0.53, 0.37
A	6-Methyluracil	0.37	
B	5-Bromo-3-ethyl-6-methyluracil	0.45	
B	3-Ethyl-6-methyluracil	0.34	0.45, 0.34, 0.11
B	6-Methyluracil	0.11	
A	5-Iodo-3-ethyl-6-methyluracil	0.65	0.65 in traces, 0.53
A	3-Ethyl-6-methyluracil	0.52	
B	5-Iodo-3-ethyl-6-methyluracil	0.47	0.47 in traces, 0.34
B	3-Ethyl-6-methyluracil	0.34	
A	5-Chloro-3-isopropyl-6-methyluracil	0.68	
A	3-Isopropyl-6-methyluracil	0.60	0.68, 0.60, 0.37 in traces
A	6-Methyluracil	0.37	
B	5-Chloro-3-isopropyl-6-methyluracil	0.54	
B	3-Isopropyl-6-methyluracil	0.51	0.54, 0.51, 0.11 in traces
B	6-Methyluracil	0.11	
A	5-Bromo-3-isopropyl-6-methyluracil	0.70	
A	3-Isopropyl-6-methyluracil	0.60	0.70, 0.60, 0.37
A	6-Methyluracil	0.37	
B	5-Bromo-3-isopropyl-6-methyluracil	0.56	
B	3-Isopropyl-6-methyluracil	0.51	0.56, 0.51, 0.11
B	6-Methyluracil	0.11	
A	5-Iodo-3-isopropyl-6-methyluracil	0.73	
A	3-Isopropyl-6-methyluracil	0.60	0.73 in traces, 0.60, 0.37
A	6-Methyluracil	0.37	
B	5-Iodo-3-isopropyl-6-methyluracil	0.59	
B	3-Isopropyl-6-methyluracil	0.51	0.59 in traces, 0.51, 0.11
B	6-Methyluracil	0.11	
A	3-*tert*-Butyl-6-methyluracil	0.63	0.63, 0.37
A	6-Methyluracil	0.37	
B	3-*tert*-Butyl-6-methyluracil	0.53	0.53, 0.11
B	6-Methyluracil	0.11	
C	5-Chloro-3-*tert*-butyl-6-methyluracil	0.69	0.45 (mp 328–330°)
		0.57	0.25 (mp 328–330°)
A	5-Bromo-3-*tert*-butyl-6-methyluracil[c]	0.73	0.47
A	5-Bromo-6-methyluracil	0.47	
B	5-Bromo-3-*tert*-butyl-6-methyluracil[c]	0.62	0.28
B	5-Bromo-6-methyluracil	0.28	

[a]Solvent systems: (A) benzene–isopropyl alcohol (50:50); (B) chloroform–acetone (80:20); (C) benzene–methanol (60:40). [b]5-Bromo-3,6-dimethyluracil (mp 239–241°) was heated at 255 to 260°. [c]5-Bromo-3-*tert*-butyl-6-methyluracil was heated at 200° for 10 min.

base peak of m/e 42 ($NCO\cdot^+$). A molecular ion was observed at m/e 160. Fragments were at m/e 117 ($HN{=}CCH_3CCl{=}C{=}O\cdot^+$) and m/e 76 ($CHCl{=}C{=}O\cdot^+$). 5-Bromo-*tert*-butyl-6-methyluracil was completely dealkylated at a temperature considerably lower and in much shorter time than the chlorine derivative (Tables I, II).

An attempt was made to determine the effect of the type of halogen in position 5 in 5-halo-6-methyl-3-alkyl-

Table III. Dealkylation and Dehalogenation in Acid Media with HI

3,6-Dimethyluracil	No changes
5-Bromo-3,6-dimethyluracil	Dehalogenation
3-Ethyl-6-methyluracil	No changes
5-Bromo-3-ethyl-6-methyluracil	Dehalogenation
3-Isopropyl-6-methyluracil	No changes
5-Chloro-3-isopropyl-6-methyluracil	Incomplete dehalogenation
5-Bromo-3-isopropyl-6-methyluracil	Dehalogenation
3-*tert*-Butyl-6-methyluracil	Dealkylation
5-Chloro-3-*tert*-butyl-6-methyluracil	Dealkylation
5-Bromo-3-*tert*-butyl-6-methyluracil	Dehalogenation and dealkylation

uracils on the dealkylation reaction. However, there were two different results from the treatment with HI. In the case of the 3,6-dimethyl-, 3-ethyl-6-methyl-, and 3-isopropyl-6-methyluracils, the starting compound remained unchanged, reflecting the decrease in stability of the proposed carbonium ion intermediates. For example, the 5-chloro-3-*tert*-butyl derivative was completely dealkylated at room temperature, and the 5-chloro-6-methyluracil was formed in about 20 min and its structure was established by mass spectroscopy.

By treating 3-*tert*-butyl-6-methyl- and 5-bromo-3-*tert*-butyl-6-methyluracil with 57% HI, dealkylation occurred and complete dealkylation and dehalogenation took place, with 6-methyluracil being the only product. Treatment of 5-bromo-3,6-dimethyl-, 5-bromo-3-ethyl-6-methyl-, and 5-bromo-3-isopropyl-6-methyluracil with HI produced the corresponding 3-alkyl-6-methyluracils. This indicates that only the dehalogenation reaction occurred. By treating 5-chloro-3-isopropyl-6-methyluracil with HI, a mixture of the starting compound and 3-isopropyl-6-methyluracil was obtained (Table III).

Since this reaction occurs readily at room temperature, we postulate that these uracils may be dealkylated *in vivo* by an ionic mechanism having intermediates similar to those which may exist under the acidic reaction conditions.

The mechanism of the thermal reaction may be similar to the Herzig–Meyer reaction, which also occurs (Krauch and Kunz, 1964) with HI. Evidence for this was the detection of *tert*-butyliodide in the filtrate, although this was only qualitative. This is not absolute proof for the reaction mechanism because the *tert*-butyliodide could also have been formed in a secondary reaction from isobutylene.

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