Synthesis of 5-Methylmercaptouracil

By Kentaro ANZAI and Saburo SUZUKI

*The Institute of Physical and Chemical Research,
Komagome, Bunkyo-ku, Tokyo*

Received January 6, 1966

5-Methylmercaptouracil was prepared by the reaction of uracil with dimethyl sulfoxide and monochloromethyl ether. At the same time the formation of methylal, methyl sulfide, methyl disulfide, methyl methanethiolsulfonate, methyl chloride and paraformaldehyde were observed. Acetyl chloride was successfully used instead of monochloromethyl ether. Uracil reacted with dimethyl sulfoxide and phenacyl bromides, resulting in the formation of 5-bromouracil. The mechanism of these reactions were discussed.

Chart 1

Burckhalter et al.¹⁾ have already prepared 5-chloromethyluracil by reacting uracil with formalin and hydrogen chloride. We attempted to synthesize it using monochloromethyl ether as a chloromethylating reagent. Because of a low solubility of uracil in most organic solvents the reaction was carried out in dimethyl sulfoxide (DMSO). However the product was, unexpectedly, identified as 5-methylmercaptouracil and the formation of any trace of 5-chloromethyluracil was not observed. We studied on this reaction and proposed the mechanism which involved the electrophilic attack of methanesulfenyl group to uracil.

Even in the absence of uracil monochloromethyl ether reacted with DMSO and the products obtained were methylal, methyl sulfide, methyl disulfide, methyl methanethiol-sulfonate, methyl chloride and paraformaldehyde. The occurrence of these compounds supported the reaction path outlined in Chart 1.

DMSO and monochloromethyl ether are a Lewis base and acid respectively, and one can hardly doubt that the sulfonium salt I was the first product. The following methyl migration was expected to give methylal (II) as well as methanesulfenyl chloride (III). The reactions of the latter compound with methanol,²⁾ water³⁾ and methylene oxide⁴⁾ were already studied by Douglass and his co-workers. They presumed that methanesulfenyl chloride successively attacked the intermediates and made the reaction entangled. Similarly we proposed such a mechanism that excess DMSO was attacked by methanesulfenyl chloride (III) resulting in the formation of another sulfonium salt IV. After liberation of methyl chloride (V), IV was altered to methyl methanethiol-sulfonate (VII) via an unstable intermediate VI. It was already known^{2,3)}

that VII was easily disproportionated into methyl methanethiol-sulfonate (VIII) and methyl disulfide (IX). Methanesulfenyl chloride (III) was also known to reduce VII to methyl disulfide, itself being altered to methane sulfinyl chloride²⁾. Methyl sulfide (X) might be derived directly from DMSO, the oxygen being transferred to III and/or VII.

The formation of paraformaldehyde (XII) was explicable if the intramolecular rearrangement of CH_3OCH_2- group in the sulfonium chloride I was postulated. Though the attempt to isolate the possible intermediate, 1-methylmercaptomethylal (XI), failed, and paraformaldehyde and methyl sulfide separated during the distillation even under the reduced pressure, the occurrence of the unstable intermediate was suggested by gas chromatography (See Exp.).

The electrophilic attack of the sulfonium chloride I (Chart 2) or, as another possibility, that of methanesulfenyl chloride (III) was considered to cause the introduction of methanesulfenyl group into uracil producing 5-methylmercaptouracil (XIII).

The structure of the product was supported by the disappearance of a NMR signal at $\delta 5.71\delta$ attributable to a proton at C-5 in uracil and the occurrence of a signal at $\delta 1.94$ (singlet) corresponding to three protons of the methylmercapto group in the product. The IR spectrum (Fig. 1) showed the absorptions at 1355 and 670cm^{-1} attributable to methylmercapto group.

1) J. H. Burckhalter, R. J. Seiwald, H. C. Scarborough, *J. Am. Chem. Soc.*, **82**, 991 (1960).

2) I. B. Douglass, D. A. Koop, *J. Org. Chem.*, **27**, 1398 (1962).

3) I. B. Douglass, *ibid.*, **24**, 2004 (1959).

4) I. B. Douglass, J. A. Douvolle, *ibid.*, **25**, 2221 (1960).

FIG. 1. The IR Spectrum of 5-Methylmercaptouracil (KBr pellet).

Thus it was clarified that splitting of methanesulphenyl group from DMSO was caused by the electrophilic attack of monochloromethyl ether, and other reagents having the same reactivity was searched.

Similar to the reaction between DMSO and monochloromethyl ether acetyl chloride reacted, though more vigorously, with DMSO producing methyl chloride, methyl sulfide, methyl disulfide, methylmethanethiolsulfonate, bismethylthiomethane and paraformaldehyde,

and the reaction path was proposed as shown in Chart 3.

It is reasonable to consider that the reaction started with the electrophilic attack of acetyl group to the oxygen in DMSO and the resultant sulfonium chloride XIV was altered to methanesulphenyl acetate (XV) with liberation of methyl chloride (V). If XV is rearranged intermolecularly to methyl methanethiolsulfinate (VII), the formation of methyl sulfide, methyl disulfide and methyl methane-

Chart 3

thiolsulfonate is explicable as in the case of the reaction between DMSO and monochloromethyl ether (See also Chart 1, VIII). Similar to the reaction between methanesulfenyl chloride (III) and methyl methanethiolsulfinate²⁾ (VII, Chart 1), methanesulfenyl acetate might reduce DMSO as well as methyl methanethiolsulfinate (VII) producing methyl sulfide and methyl disulfide (X and IX, Chart 3) respectively.

As paraformaldehyde and bismethylthiomethane (XVII) were isolated from the reaction mixture, the formation of methylacetoxymethyl sulfide (XVI) was considered to be involved in the reaction path. Horner et al.⁵⁾ already observed the occurrence of this rearrangement when DMSO was treated with acetic anhydride. Traynelis et al.⁶⁾ obtained, though in a low yield (3.7% volatile matter), methyl sulfide, methyl disulfide, paraformaldehyde and bismethylthiomethane (XVII), when DMSO was refluxed for 3 days. The mechanism proposed by them (Chart 3), however, could not explain the occurrence of methyl chloride (V) and methyl methanethiolsulfonate (VIII) observed in our experiment.

5-Methylmercaptouracil (XIII) was also obtained quantitatively when acetyl chloride was added to a DMSO solution of uracil (Chart 4).

Chart 4

Because any trace of methyl acetate was not detected by gas chromatography, the mechanism involving methyl migration as was observed in the reaction between DMSO and monochloromethyl ether was excluded in this case.

When monochloroacetyl chloride was used

5) L. Horner, P. Laiser, *Ann. Chem.*, **626**, 19 (1959).

6) V. J. Traynelis, W. L. Heagenrother, *J. Org. Chem.*, **29**, 221 (1964).

instead of acetyl chloride, methyl sulfide once formed, reacted with excess monochloroacetyl chloride and, after hydrolysis of the unstable product XVIII (Chart 5), dimethylcarboxymethylenesulfonium chloride (XIX) was obtained. A study on NMR spectrum showed that hydrogens of the methylene group in XIX were gradually replaced by deuteriums in deuterium oxide.

Chart 5

Kornblum et al.⁷⁾ reported that DMSO oxidized phenacyl bromides to their corresponding α -ketoaldehyds (Chart 6, XXI) and the sulfonium compounds XX were postulated as intermediates. We expected that the electrophilic attack of XX also caused the introduction of methanesulfenyl group to uracil.

Chart 6

However the product was, in this case, 5-bromouracil (XXII) and this peculiarity was explained as follows. Hydrogen bromide, once formed, was oxidized to bromine with DMSO and the bromination of uracil occurred. An unusual reaction of 2,3-bis-(bromomethyl)-quinoxaline with DMSO involving the oxidation of hydrogen bromide to bromine among

7) N. Kornblum et al., *J. Am. Chem. Soc.*, **79**, 6562 (1957).

the reaction path was also reported by Moriconi et al.⁸⁾

Geothals et al.⁹⁾ prepared dimethylhydroxyarylsulfonium chlorides, $(\text{ArSMe}^+)\text{Cl}^-$, by condensing DMSO and phenols with hydrogen chloride. The pyrolysis of these compounds yielded quantitatively the corresponding methylmercapto compounds, ArSMe . We attempted to synthesize 5-methylmercaptouracil by reacting uracil with DMSO and dry hydrogen chloride. Methyl chloride, methyl sulfide and methyl disulfide were also formed when dry hydrogen chloride was introduced into DMSO at an elevated temperature. The path was presumed to involve the formation of methanesulfenic acid (Chart 7, XXIII), and the following reaction seemed to pass a somewhat similar course as the reaction of DMSO with monochloromethyl ether or acetyl chloride.

Chart 7

Douglas³⁾ had already postulated the methanesulfenic acid as the intermediate product of the reaction between methanesulfonyl chloride and water. Hydrogen chloride and DMSO altered uracil to a compound which was easily soluble in water. The analytical data were found to be almost consistent with that of the expected structure, dimethyl-(2, 4-dioxypyrimidyl-5)-sulfonium chloride (XXIV). However the product was unstable and lost its sulfur and chloride rapidly even in aqueous solvents. The attempts to prepare 5-methylmercaptouracil from this unstable compound

failed. The reaction path will be clarified later.

EXPERIMENTAL

Reaction of monochloromethyl ether with DMSO. Monochloromethyl ether (105 g, 1.3 M) was added at once into DMSO (220 g, 2.8 M) and the mixture was stirred. A moderate exothermal reaction occurred and the temperature was adjusted between 30°C to 40°C. Through a reflux condenser a tube was led into a trap cooled with a dry ice-acetone bath. After 5 hrs. a small amount of evolved gas was found to condense. After redistillation the liquefied gas was vaporized and its IR spectrum was measured on vapor phase. The result showed that the evolved gas was methyl chloride contaminated with a slight amount of methylal.

When the reaction mixture was allowed to stand over-night at the room temperature, it separated into two layers. Water (100 ml) was added and, as an exothermal reaction occurred, the mixture was cooled with tap water. The upper layer was washed with cold water, dried with calcium chloride, and fractionated by distillation.

The first fraction (60 ml) was distilled at 37°C to 40°C and its IR spectrum and gas chromatography showed that it was a mixture of methylal and methyl sulfide at the ratio of about 1:2. The former was much more volatile than the latter in spite of the higher boiling point and, when the mixture was allowed to vaporize at the room temperature into a gas cell for the IR measurement, the spectrum was found to be essentially the same to that of an authentic sample of methylal.

The boiling point of the distillate gradually raised and reached about 70°C. However at the same time much white powder separated during distillation and accumulated on the inside of the whole distillation system. It was collected and washed with ethanol. The IR spectrum showed that it was paraformaldehyde. C, 39.65; H, 6.64%. Calcd. for $(\text{CH}_2\text{O})_n$: C, 40.00; H, 6.71%. The yield reached throughout several experiments at most 26 g (40%). The attempt to obtain the compound from which paraformaldehyde had been separated was not successful when the distillation was carried out under the reduced pressure, and the eluate (b.p. 32~36°C at 60 mmHg; yield 3 g) showed an IR spectrum which had absorptions ascribing both to methyl sulfide and to paraformaldehyde.

8) E. J. Moriconi, A. J. Fritschy, *J. Org. Chem.*, **30**, 1542 (1965).

9) E. Geothals, P. Padzitzky, *Bull. Soc. Chim. Belges*, **73**, 546 (1964); *C. A.*, **61**, 19614a (1964).

After the volatile matters were removed at 150°, the distillation was continued in vacuo. Another product, b.p. 111~113°C at 3 mmHg, was obtained; yield 25 g. It was identified as methyl methanethiol-sulfonate (VIII) from its IR spectrum. C, 19.26; H, 4.79; S, 50.82%. Calcd. for $C_2H_6S_2O_2$: C, 19.03; H, 4.51; S, 50.79%.

The reaction mixture was also applied to gas chromatography: a polyethylene glycol column, 3 m; the temperature, 100°C; the carrier gas flow rate, 1 kg/cm². Two main peaks were found to correspond to methylal (2.2 min) and methyl sulfide (2.3 min) respectively. A small peak was found to correspond to methyl disulfide by comparison of the retention time with that of an authentic sample (9.6 min). Another small peak (7.2 min) possibly could be ascribed to the unstable compound, 1-methylmercaptomethylal (XI), from which paraformaldehyde and methyl sulfide were liberated.

Preparation of 5-methylmercaptouracil (XIII) in DMSO and monochloromethyl ether. Uracil (1 g) was dissolved in DMSO (20 ml), and monochloromethyl ether (10 ml) was added. The mixture was stirred at the room temperature for 24 hrs. The paperchromatogram of the mixture using the solvent system of butanol, acetic acid and water (4:1:2) showed that the spot corresponding to uracil (R_F 0.5) completely disappeared and a new spot was observed (R_F 0.65) by inspecting the fluorescence under ultraviolet light.

Ethanol (50 ml) was added and the volatile matters were evaporated. The amorphous residue, thus obtained, was crystallized from dimethylformamide and ethanol; yield 1 g (70%). C, 37.91; H, 3.69; N, 17.71; S, 20.08%. Calcd. for $C_5H_6N_2O_2S$: C, 37.96; H, 3.82; N, 17.71; S, 20.27%. The UV spectrum showed a shoulder at about 280 m μ (ϵ , 4100) in either 0.1N HCl or water, and the maximum at 293 m μ (ϵ , 7000) in 0.1N NaOH. The NMR spectrum showed two singlets at δ 1.94 (3 H) and δ 7.56 (1 H). It sublimated at about 290°C and did not decompose at 300°C.

Reaction of acetyl chloride with DMSO. Acetyl chloride (220 g) was added slowly into DMSO (440 g). A vigorous reaction occurred and the reaction mixture was cooled with ice-water to keep the temperature below 50°C. Water (700 m) was added and the mixture was refluxed on a water bath of 80°C for 1 hr. It gradually separated into two layers. During these processes the evolved gas was introduced

into a trap cooled with a dry ice-acetone bath. After the liquefied gas was redistilled and left to stand at the room temperature, 10 g of the distillate which boiled at -24°C was caught. Its IR spectrum on vapour phase was found to be identical with that of methyl chloride.

The lower layer was, after evaporating water and acetic acid, attempted to fractionate under a reduced pressure. However paraformaldehyde accumulated inside the distillation column and any other product was obtained in good yield.

The upper layer was washed with water, dried with calcium chloride and fractionated by distillation under the atmospheric pressure. The first fraction boiling at 38°C was identified as methyl sulfide by comparison of its IR spectrum with that of an authentic sample; yield 88 g. The second fraction boiling at 109°C was identified as methyl disulfide by its IR spectrum; yield 42 g. C, 25.47; H, 6.42; S, 68.07%. Calcd. for $C_2H_6O_2$: C, 25.46; H, 6.43; S, 68.08%.

After methyl sulfide and methyl disulfide were removed, the distillation was continued under a reduced pressure. Two minor fractions distilled at 35~40°C at 14 mmHg and 112~114°C at 13 mmHg respectively were obtained. The former component boiled at 145°C and the analytical data (C, 32.40; H, 6.93; S, 60.45%. Calcd. for $C_3H_6S_2$: C, 33.29; H, 7.45; S, 59.26%) and the NMR spectrum (two singlets at δ 2.08 and δ 3.55 corresponding to two methyl and one methylene groups) showed that it was bismethylthiomethane (XVII); yield 4 g. The latter component was identified as methyl methanethiol-sulfonate (VIII) from its IR spectrum; yield 8 g.

Preparation of 5-methylmercaptouracil (XIII) in DMSO and acetyl chloride. Uracil (1 g) was dissolved in DMSO (20 ml) and acetyl chloride was added dropwise slowly. A vigorous exothermal reaction occurred and the reaction mixture was cooled with an ice-water bath to keep the temperature at about 50°C. After acetyl chloride was added, the mixture was left to stand at the room temperature overnight. The paperchromatogram showed that the reaction proceeded quantitatively. Water (50 ml) was added and the mixture was refluxed for a short time, resulting in separation into two layers. After volatile matters were removed by vacuum evaporation, ethanol (30 ml) was added to the residue, and the solution was left in a refrigerator overnight. The resultant precipitate was recrystallized from dimethylformamide and ethanol, or dimethylformamide and water.

The IR spectrum was identical with that of 5-methylmercaptouracil prepared from uracil by reacting with DMSO and monochloromethyl ether; yield 300 mg.

Preparation of 5-methylmercaptouracil (XIII) and dimethylcarboxymethylenesulfonium chloride (XIX) in DMSO and monochloroacetyl chloride. Uracil (300 mg) was dissolved in DMSO (6 ml) and monochloroacetyl chloride (1.8 g) was added dropwise. A vigorous exothermal reaction occurred and the reaction mixture was cooled with ice-water to keep the temperature at about 50°C. After it was left to stand overnight at the room temperature, much amount of precipitate was formed. It was extracted with hot water and, on addition of excess cold ethanol, crystals of dimethylcarboxymethylenesulfonium chloride (XIX) were obtained. After recrystallization from water and ethanol, the yield was 1.7 g; m.p. 139–139.5°C. C, 30.61; H, 5.74; S, 19.56; Cl, 21.53%. Calcd. for $C_4H_9O_2SCl$: C, 30.62; H, 5.79; S, 20.47; Cl, 22.64. The IR spectrum was identical with that of dimethylcarboxymethylenesulfonium chloride (XIX) obtained from methyl sulfide and monochloroacetic acid by leaving the mixture overnight at the room temperature followed by recrystallizing the resultant precipitate from water and ethanol.

Its NMR spectrum showed two singlets at δ 3.0 (6 H) and δ 4.43 (2 H) in deuterium oxide. Their relative strength was observed to change with time, indicating the replacement of hydrogens of the methylene group with deuteriums; after 5 min, 1:1/3.5; after 5 hrs, 1:1/11; after 5 days, 1:0.

After removal of dimethylcarboxymethylenesulfonium chloride by extracting with hot water, the remaining precipitate was dissolved in dimethylformamide (5 ml), and excess ethanol was added. The crystals, thus obtained, were recrystallized from dimethylformamide and water; yield 200 mg. The IR spectrum was identical with that of 5-methylmercaptouracil prepared by reacting uracil with DMSO and monochloromethyl ether.

Reaction of uracil with DMSO and *p*-bromophenacyl bromide. Preliminary experiments using paperchromatography showed that uracil reacted with DMSO and phenacyl bromide or its *p*-chloro and *p*-bromo derivatives. Because the R_F value (0.48) was found to be slightly lower than that of 5-methylmercaptouracil (0.50: butanol, acetic acid, water; 4:1:2), further isolation of the product was attempted.

Uracil (500 mg) and *p*-bromophenacyl bromide (3 g) were dissolved in DMSO (10 ml), and the solution was shaken in a water bath at 30°C. After 2 hrs. the mixture separated into two layers. Ethanol (50 ml) was added and the volatile matters including methyl sulfide were removed by evaporation. *p*-Bromophenylglyoxal (XXI, X=Br) and unaltered *p*-bromophenacyl bromide were removed by washing the residue with ether repeatedly and the ether layer was discarded. The lower layer was dissolved in ethyl acetate (30 ml), and the precipitate, which occurred instantly and showed no UV absorption, was removed by filtration. The ethyl acetate solution was extracted repeatedly with a small amount of water. The aqueous layers were combined and, after leaving the solution in a refrigerator overnight, 5-bromouracil (XXII) was found to crystallize; yield 350 mg; recrystallized from dimethylformamide and ethanol. C, 25.28; H, 1.59; N, 14.62; Br, 42.08%. Calcd. for $C_4H_5N_2O_2Br$: C, 25.15; H, 1.58; N, 14.67; Br, 41.84%. The IR and UV spectra were identical with those of an authentic sample of 5-bromouracil.

Reaction of uracil with DMSO and hydrogen chloride. Uracil (10 g) was dissolved in DMSO (220 g), and dry hydrogen chloride was introduced into the solution. The temperature was allowed to raise up to about 70°C. After the solution had been left to stand overnight at the room temperature, a large quantity of crystalline mass precipitated. When it was heated on a water bath at 80°C, the precipitate dissolved and a vigorous exothermal reaction started. The temperature rapidly raised (over 100°C) and the reaction vessel was cooled with tap water. After the primary vigorous reaction had completed, the reaction mixture was further heated on a water bath at 80°C. After 1 hr water (600 ml) was added and the reflux was continued for 3 hrs.

The mixture gradually began to separate into two layers. During these processes the evolved gas was introduced into a trap cooled with a dry ice-acetone bath. The liquefied material was, after being redistilled, introduced into a gas cell for the IR measurement by leaving at the room temperature, and its spectrum was found to be identical with that of an authentic sample of methyl chloride.

The upper layer was separated, washed with water, dried with calcium chloride and fractionated by distillation. Two fractions distilled at 38–40°C and 109°C were obtained and identified as methyl sulfide (yield 40 g), and methyl disulfide, yield 10 g, respec-

tively. From the lower layer 37 g of methyl sulfide was recovered.

The lower layer was condensed until the amorphous residue was free from volatile matters. Acetone (400 ml) was added and the mixture was left to stand overnight in a refrigerator. Then acetone layer was discarded by decantation. The residue was solidified when excess ethanol saturated with hydrogen chloride was added; yield 4 g. The analytical data was consistent with that of the expected structure, dimethyl-(2-4-dioxypyrimidyl-5-)sulfonium chloride (XXIV). C, 36.48; H, 4.74; N, 11.43; S, 13.86; Cl, 14.46%. Calcd. for $C_7H_{12}O_2N_2SCl$: C, 37.58; H, 5.41; N, 12.52; S, 14.33; Cl, 15.85%. When it was dissolved in a sodium bicarbonate solution and gently warmed, it rapidly decomposed with odor of a mercaptan and

the product, though it was difficult to purify, was found to have no sulfur and chlorine. The decomposition was observed even in aqueous acetone in a refrigerator. It softened or melted at about 190°C and solidified again on further heating. No more decomposition was observed until 300°C. The heat decomposition product at 250°C was insoluble in water and in most organic solvents, and, though the purification was impossible, it was clearly different from the expected compound, 5-methylmercaptouracil.

Acknowledgment. The authors wish to express their hearty thanks to Dr. S. Emoto, this institute, for his valuable suggestions and discussions.