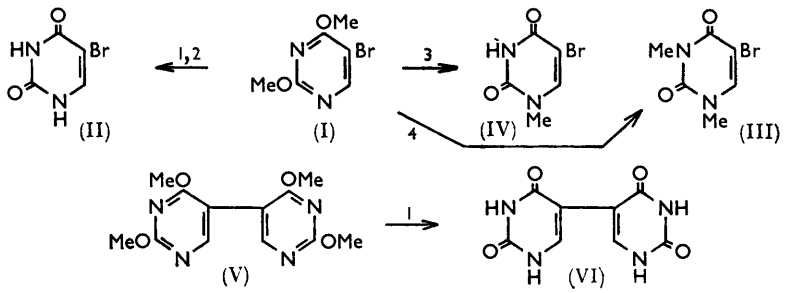
653. *Sodium Iodide in Acetic Acid as a Mild Dealkylating Agent.*

By T. L. V. Ulbricht.

Hydrogen bromide in acetic acid is the best of the strongly acidic reagents for dealkylating alkoxypyrimidines. The much milder reagent, sodium iodide in acetic acid, was found to dealkylate alkoxypyrimidines in 80—100% yield. 2-Methoxypyridine also reacted readily, but *p*-nitroanisole was unaffected, and 2,4-dinitroanisole and 4-methoxypyridine *N*-oxide reacted to only a small extent. With sodium iodide in acetonylacetone, a 2,4-dimethoxypyrimidine rearranged to the corresponding 1,3-dimethyluracil.

In connection with another problem, a method was required for dealkylating alkoxypyrimidines under relatively mild conditions. This reaction is usually accomplished with strong acids, for example, ethanolic hydrogen chloride [1] or concentrated hydrochloric acid.[2] In fact the most efficient reagent appears to be hydrogen bromide in glacial acetic acid; bromide is a stronger nucleophile than chloride ion, and acetic acid is an excellent solvent for alkoxypyrimidines, which are usually insoluble in water. 5-Bromo-2,4-dimethoxypyrimidine (I), available from other studies, was used as a test compound. It was converted into 5-bromouracil (II) by hydrogen bromide in acetic acid, in virtually quantitative yield in 2 hours at 70° and in 60% yield in 24 hours at room temperature (after being warmed for a few minutes at 50° to effect dissolution). Similarly, bi-(2,4-dimethoxypyrimidin-5-yl) [3] (V) was converted into biuracil-5-yl (VI).



Reagents: 1, HBr–AcOH. 2, NaI–AcOH. 3, NaI–AcOH–CH_2Ac_2. 4, NaI–CH_2Ac_2.

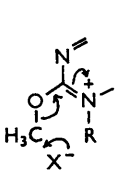
By using a more nucleophilic ion, it should be possible to effect the same reaction without resort to strong acid, and thus sodium iodide in acetic acid was tried. Conversion

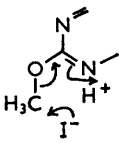
[1] Hilbert and Johnson, *J. Amer. Chem. Soc.*, 1930, **52**, 4489.
[2] Ulbricht, *Tetrahedron*, 1959, **6**, 225.
[3] Ulbricht, unpublished work.

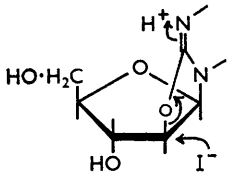
of the ether (I) into the uracil (II) by an excess of this reagent was 82% complete in 4 hours at 100° and 67% in 3 hours (all experiments were on a 500 mg. scale; working-up losses would be less, and the yields higher, on a larger scale). When exactly one molar equivalent of sodium iodide was used 40% of the uracil was obtained, together with unchanged ether; an intermediate was not isolated.

The mechanism of the reaction can be envisaged as involving two steps, protonation of nitrogen followed by attack by iodide ion (VII; R = H, X = I), as in the Hilbert–Johnson synthesis of glycosylpyrimidines [1] from alkoxypyrimidines and glycosyl halide RX; * alternatively, it might involve a concerted mechanism (VIII), analogous to the reaction of *O*,2′-cyclouridine with iodide ion in the presence of acetic acid [4] (cf. IX). In the latter case, no reaction takes place in the absence of acid; with the pyrimidine (I), a different reaction occurs with sodium iodide in a non-acidic solvent (see below).

2-Methoxypyridine is readily converted into 2-pyridone by sodium iodide in acetic acid; but 4-methoxypyridine *N*-oxide, for the demethylation of which a strictly analogous mechanism cannot be written, was recovered unchanged, though some reaction must have occurred, since free iodine was liberated. No reaction took place with *p*-nitroanisole, and 2,4-dinitroanisole was demethylated only to the extent of 8% in 3 hours at 100°. The much greater activating effect of a ring-nitrogen atom than of two *op*-nitro-groups in a benzene ring is noteworthy, and is undoubtedly due to the fact that the nitro-compounds are much weaker bases.


(VII)


(VIII)


(IX)

With sodium iodide in acetonylacetone, the pyrimidine (I) undergoes *O* ⟶ *N* alkyl rearrangement. As is to be expected, this reaction is slower than demethylation, and the yield of 5-bromo-1,3-dimethyluracil (III) was 35% after 3 hours at 100° and 75% after 6 hours. Hilbert and Johnson [1] found that alkyl iodides readily effected the rearrangement of the 2-alkoxy-group in such compounds; for example, 2,4-dimethoxypyrimidine gave 4-methoxy-1-methylpyrimid-2-one, but that heating to 220—240° was necessary to rearrange both groups.[6] It would be of interest to see whether sodium iodide (or lithium bromide) in a suitable solvent could be used to effect the rearrangement of *O*-glycosyl- to *N*-glycosyl-pyrimidines.

When the pyrimidine (I) was heated with sodium iodide in acetonylacetone containing 10% of acetic acid, 5-bromo-1-methyluracil (IV) was isolated.

Experimental

Light petroleum refers to the fraction of b. p. 60—80°.

Demethylations with Hydrogen Bromide.—(1) *5-Bromo-2,4-dimethoxypyrimidine* (I). (*a*) The pyrimidine [7] (I) (500 mg.) was refluxed for 30 min. in a 50% w/v solution of hydrogen bromide in glacial acetic acid (5 c.c.). Water (5 c.c.) was added, and the solution cooled to 0°. The yield of 5-bromouracil was 355 mg. (81%), and the m. p. and mixed m. p. (insertion at 290°)

* Ionisation of the glycosyl halide proceeds by neighbouring-group participation of the 2-acyloxy-group.[5]

[4] Brown, Parihar, and Sir Alexander Todd, *J.*, 1958, 4242.
[5] Baker, Joseph, Schaub, and Williams, *J. Org. Chem.*, 1954, **19**, 1786.
[6] Hilbert and Johnson, *J. Amer. Chem. Soc.*, 1930, **52**, 2001.
[7] Hilbert and Jansen, *J. Amer. Chem. Soc.*, 1934, **56**, 134.

310° (lit.,[7] m. p. 312°). (*b*) A similar experiment in which the reactants were left at room temperature for 24 hr., then heated at 50—60° for 1 hr. and 60—70° for 1 hr., and finally evaporated to dryness gave 402 mg. (92%) of the uracil. (*c*) In a third experiment the reactants were warmed, with shaking, at 50° until the pyrimidine dissolved (8 min.), then left for 24 hr. at room temperature. The yield was 260 mg. (60%).

(2) *Bi-(2,4-dimethoxypyrimidin-5-yl)* (V). The bipyrimidinyl[3] (150 mg.) was heated in 50% w/v hydrogen bromide–acetic acid (5 c.c.) on a steam-bath for 3 hr. The solvent was removed under reduced pressure, and the product warmed with water, cooled, filtered off, and washed with ethanol. The yield of *biuracil-5-yl* (VI) was 120 mg. (99%). Recrystallisation from water gave pale buff needles, no m. p. <300° (Found: C, 41·8; H, 2·9; N, 23·8. $C_8H_8N_4O_4,\frac{1}{2}H_2O$ requires C, 41·6; H, 3·0; N, 24·2%).

Demethylations with Sodium Iodide in Acetic Acid.—(1) *Pyrimidine* (I). (*a*) The pyrimidine (I) (500 mg.) was heated with sodium iodide (1·0 g.) in glacial acetic acid (5 c.c.) on a steam-bath for 4 hr. The solvent was removed under reduced pressure, and the residue washed with benzene, then boiled with water (5 c.c.) and a little sodium thiosulphate, to give a colourless solution, which was cooled to 0°. The yield of 5-bromouracil was 291 mg. (82%). After 3 hr. the yield was 67%. (*b*) Reaction as in (*a*), but with 342 mg. (1·0 mol.) of sodium iodide, gave a product that was washed with light petroleum, leaving 175 mg. (40%) of 5-bromouracil. From the filtrate, unchanged ether, m. p. and mixed m. p. 62—64°, was isolated.

(2) *2-Methoxypyridine.* 2-Methoxypyridine (100 mg.) and sodium iodide (250 mg.) were heated in glacial acetic acid (5 c.c.) on a steam-bath for 3 hr. The solvent was evaporated, ethanol and benzene were added, and the whole was evaporated. The residue was extracted with hot benzene, and the greenish solid obtained on evaporation of the extract was again extracted with benzene; this extract was concentrated, giving colourless 2-pyridone (correct infrared spectrum).

(3) *4-Methoxypyridine N-oxide.* The *N*-oxide (330 mg.) and sodium iodide (1·0 g.) were heated in glacial acetic acid (10 c.c.) on a steam-bath for 3 hr. The solvent was removed from the dark brown solution under reduced pressure, and sodium thiosulphate solution and chloroform were added. The residue obtained from the chloroform extract was recrystallised from benzene, giving the unchanged oxide, m. p. and mixed m. p. 81—82°.

(4) *p-Nitroanisole.* *p*-Nitroanisole (1·0 g.) and sodium iodide (2·0 g.) were heated in glacial acetic acid (10 c.c.) on a steam-bath for 3 hr. There was almost quantitative recovery of *p*-nitroanisole, m. p. and mixed m. p. 52—53°.

(5) *2,4-Dinitroanisole.* 2,4-Dinitroanisole (5 g.) and sodium iodide (10 g.) were heated in glacial acetic acid (50 c.c.) on a steam-bath for 3 hr. The solvent was removed under pressure, and ethyl acetate and dilute sodium hydroxide solution containing a little sodium thiosulphate were added to the residue. After being washed with ethyl acetate, the aqueous layer was acidified with hydrochloric acid, heated until the product dissolved, treated with charcoal, and filtered, giving, on cooling, 2,4-dinitrophenol (400 mg.), m. p. 111—113°, mixed m. p. 112—114°. The ethyl acetate layer gave 4·4 g. of unchanged dinitroanisole, m. p. 86° (from ethanol).

Rearrangement with Sodium Iodide in Acetonylacetone.—The pyrimidine (I) (500 mg.) was heated with sodium iodide (1·0 g.) in acetonylacetone (5 c.c.) on a steam-bath for 6 hr. The solvent was removed under reduced pressure, a little water added, and the product filtered off. After washing with light petroleum there remained 5-bromo-1,3-dimethyluracil (III) (375 mg., 75%), m. p. and mixed m. p. 184—185° (corr.) (from benzene) (lit.,[8] 181—182°). The yield after 3 hr. was 35%. No reaction took place in acetonylacetone without sodium iodide in 6 hr. at 100°.

Reaction with Sodium Iodide and Acetic Acid in Acetonylacetone.—The pyrimidine (I) (500 mg.) and sodium iodide (1·0 g.) were heated with acetic acid (0·5 c.c.) in acetonylacetone (5 c.c.) on a steam-bath for 6 hr. The solvent was removed under reduced pressure, and the residue extracted with light petroleum (discarded) and crystallised from water, to give a product (288 mg., 60%) of indefinite m. p. 200—230°. After several recrystallisations from aqueous ethanol it had m. p. 264—266° (Found: C, 29·7; H, 2·7; N, 13·9. Calc. for $C_5H_5BrN_2O_2$: C, 29·3; H, 2·5; N, 13·7%). Comparison with 5-bromo-1-methyluracil[9] showed that the compounds were identical (mixed m. p. 265—267°).

[8] Johnson and Clapp, *J. Biol. Chem.*, 1908, **5**, 49.
[9] Benitez, Ross, Goodman, and Baker, *J. Amer. Chem. Soc.*, 1960, **82**, 4585.

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