SHORT COMMUNICATIONS

THE DIMROTH REARRANGEMENT*

III.† FORMATION OF 2-HYDROXYPYRIMIDINE FROM 1,2-DIHYDRO-2-IMINO-1-METHYL-PYRIMIDINE

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Dimroth¹ suggested that the rearrangement of 5-amino-1-phenyl-1,2,3-triazole to 5-anilino-1,2,3-triazole proceeded through an open chain intermediate. Other apparent migrations of substituents in heterocyclic compounds, usually from nuclear to extranuclear nitrogen atoms, appear to involve similar mechanisms. For example, Brown,² and Goerdeler and Roth,³ have shown by isotopic labelling that during such a rearrangement in the pyrimidine series an exocyclic nitrogen atom changes places with one of the nitrogens in the pyrimidine ring; hence, a mechanism involving ring fission followed by rotation and recyclization has been proposed.²,³ Kinetic studies using spectroscopy give results consistent with this interpretation, because the rearrangement proceeds in two well-defined steps.⁵,⁶ Nevertheless, there is little chemical evidence as to the nature of the intermediates, probably because the ease of their conversion to initial or final materials makes it difficult to isolate them from solution or chemically characterize them.

The usual product of the rearrangement of 1,2-dihydro-2-imino-1-methylpyrimidine (I) is 2-methylaminopyrimidine (II). However, we have found that under certain conditions the reaction also involves a hydrolytic deamination to yield 2-hydroxypyrimidine (III) as a major product. Under the same conditions 2-methylaminopyrimidine is not detectably hydrolysed. Hence, 2-hydroxypyrimidine is

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¹ Dimroth, O., Liebigs Ann., 1910, 373, 336.
probably formed by a rearrangement in which methylamine is lost from an open chain intermediate prior to rotation and recyclization. Such a series of reactions is closely related to those postulated for the Dimroth rearrangement.

Experimental

Spectroscopic measurements involving 1,2-dihydro-2-imino-1-methylpyrimidine were made by adding solutions of its (stable) hydrochloride to sodium borate/sodium carbonate buffers (pH 9–11), sodium phosphate/sodium hydroxide buffers (pH 11–12), or sodium hydroxide solutions (pH 12–14), to give final amine concentrations around $10^{-4}$ M.

For the isolations of 2-hydroxypyrimidine and methylamine, 1,2-dihydro-2-imino-1-methylpyrimidine hydrochloride (3 g) was dissolved in water (750 ml) and the pH was adjusted to 11.5 with sodium hydroxide. The stoppered flask was left at 20° for 24 hr with occasional shaking and addition of further sodium hydroxide to maintain the pH at 11.5. (The pH fell as the reaction proceeded.) After adjustment to pH 5 with hydrochloric acid, the solution was evaporated under vacuum. The distillate contained 2-methyaminopyrimidine (identified by its picrate, m.p. and mixed m.p. 191°). The residue was freed from 2-methyaminopyrimidine by extraction (3 x 50 ml) with light petroleum (b.p. 60–100°). The total yield of 2-methyaminopyrimidine as picrate (3 g) was about 44% of theoretical. The residue gave positive carbylamine and Rimini tests for a primary amine, and produced a blue colour with an alkaline solution of phenol and sodium hypochlorite. Following dissolution of the residue in water (25 ml) and saturation with sodium chloride, the pH was adjusted to 12 with sodium hydroxide. Nitrogen was passed through the mixture warmed to 80° on a steam-bath, then into a saturated aqueous picric acid solution (100 ml). The methyamine picrate, precipitated in low yield, was filtered, washed with a little cold ethanol and benzene, and dried at 100° for 1 hr. Its m.p. (206°) was unchanged on admixture with authentic methyamine picrate, and the two materials had the same infrared spectrum. The solution was removed from the steam-bath and, after adjusting with hydrochloric acid to pH 7, was evaporated to dryness. After a 4-hr Soxhlet extraction of the residue with boiling ethyl acetate (100 ml), the crude 2-hydroxypyrimidine (0.48 g, 24% of theoretical) that crystallized out was washed with ethyl acetate (10 ml), then recrystallized from this solvent. Its identity was confirmed by melting point (182°), mixed melting point, ultraviolet spectrum, and infrared spectrum.

Results and Discussion

Repetitive spectral scans of aqueous solutions of 1,2-dihydro-2-imino-1-methylpyrimidine ($\lambda_{\text{max}}$ 237, 347 m$\mu$; $\log \epsilon$ 4·22, 3·45) above pH 13 showed a progressive conversion to 2-methyaminopyrimidine ($\lambda_{\text{max}}$ 234, 306–307 m$\mu$; $\log \epsilon$ 4·23, 3·43), together with lesser amounts of an unidentified material absorbing strongly at 270 m$\mu$ (and apparently identical with the product we observed to be formed by the irreversible breakdown in strong alkali of 1,2-dihydro-2-oxo-1-methylpyrimidine).

However, similar experiments in the pH range 9–12 showed the final products to be a roughly 2 : 3 mixture of 2-hydroxypyrimidine ($\lambda_{\text{max}}$ 220, 292 m$\mu$; $\log \epsilon$ 4·07, 3·66, for anion$^9$) and 2-methyaminopyrimidine. The spectra became constant after about 24 hr. Both of these substances were demonstrated to be present by paper chromatography [(a) aqueous ammonium chloride, and (b) butanol/acetic acid] against authentic material, followed by elution of the spots and determination of their


ultraviolet spectra. The reaction was also carried out on a preparative scale. Control experiments showed that 2-methylaminopyrimidine is not hydrolysed to 2-hydroxy-pyrimidine under the experimental conditions. (Quantitative conversion of 2-amino-pyrimidine to 2-hydroxy-pyrimidine required 12 hr heating under reflux in 10N sodium hydroxide.10)

We believe that the formation of methylamine and 2-hydroxy-pyrimidine from the dihydropyrimidine under our mild experimental conditions provides further compelling evidence that the reaction proceeds through an open-chain intermediate such as the substituted guanidine (IV). By analogy with guanidine which, in aqueous alkaline solutions at room temperature, is hydrolysed slowly to urea,11 substance (IV) would be expected to be converted slowly to the substituted urea (V) and methylamine. (Some formation of the N-methylated urea and ammonia probably also occurs.)

This reaction competes with the ring-closing processes which lead to the starting material (I) or 2-methylaminopyrimidine (II). The open chain intermediate from 5-bromo-1,2-dihydro-2-imino-1-methylpyrimidine cyclizes much more rapidly than the species derived from the parent (non-brominated) substance.* This may account for the failure to observe bromohydroxy-pyrimidine formation in the former case.

Elimination of water between the amine and aldehyde groups in substance (V) gives 2-hydroxy-pyrimidine (III) which, because of its acidic nature, is responsible for the progressive fall in pH of the alkaline reaction mixture. It is also likely that further decomposition of the guanidine group in (IV) at higher pH values gives the material having its absorption maximum at 270 mp.

The results indicate that in studies of rearrangements belonging to this class, deaminating reactions of the type (I)⇌(III) must also be considered.

* Based on a comparison of the respective values of the composite rate constants, Y,
(see ref. 6).