Covalent Hydrates as Intermediates in Heterocyclic Rearrangements. Part II.[1] The Hydrolysis of 2-Amino-6-methyl-4-n-propyl-s-triazolo-[1,5-a]pyrimidin-5(4H)-one

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The title compound is hydrolysed in aqueous alkali to products, some of which have been isolated and identified. via an intermediate that has not. Circumstantial evidence (pK_a, u.v. spectrum) is presented for the structure (4) suggested for this intermediate, which if correct is formed in a mechanistically reasonable way. The rate of formation of this intermediate varies with $[OH^-]^2$. Comparisons are drawn with the stable compound (8).

COVALENT hydration as an equilibrium phenomenon has been well established by Albert and his school.[2] We have recently presented [1] kinetic evidence for its intermediacy in an acid-catalysed heterocyclic rearrangement; we now describe a more equivocal example in which, somewhat unusually,[2a] alkaline catalysis is involved.

In water at 60°, the hydrolysis of the title compound (1) [3] is a two-step process (see pH profile, Figure 1). The rate of the first step varies with $[OH^-]^2$ and leads to an intermediate the pH profile of whose decomposition is sigmoidal (pK_{app} 12·1). Consequently this intermediate is undetectable except in strong alkali (compare Figures

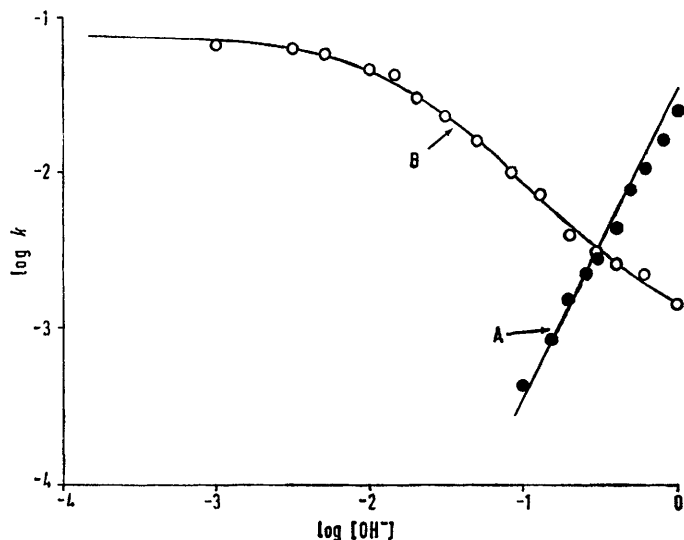

FIGURE 1   pH Profile at 60° in water. A, Disappearance of (1), line assumes $k_1 \propto [OH^-]^2$; B, disappearance of the intermediate, curve assumes $k_2 = 6\cdot6 \times 10^{-4}$ min^{-1}, $k_3 = 7\cdot5 \times 10^{-2}$ min^{-1}, and $pK_a = 12\cdot1$

2 and 3) and the problems posed by its isolation have proved insuperable (see Experimental section). However, since it will regenerate (1) if its neutral solution is freeze-dried, total fission of the molecule cannot have taken place at this stage.

The spent reaction mixture was scavenged to obtain

propionaldehyde as its 2,4-dinitrophenylhydrazone, and 3-amino-5-n-propylamino-s-triazole (6) as its carbamic
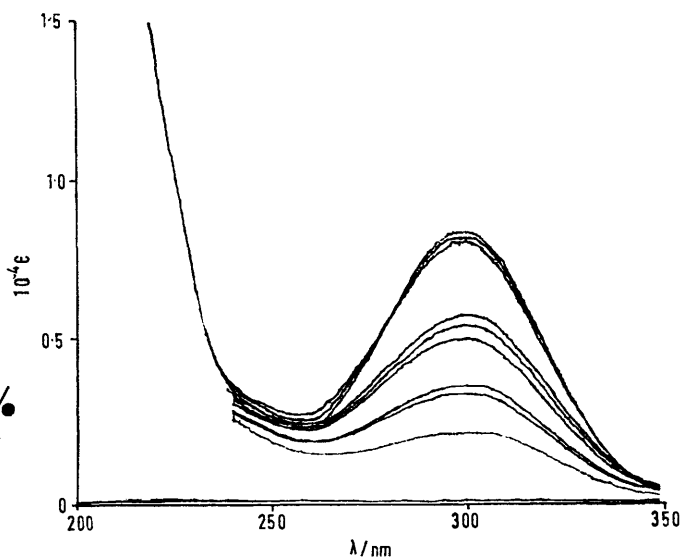

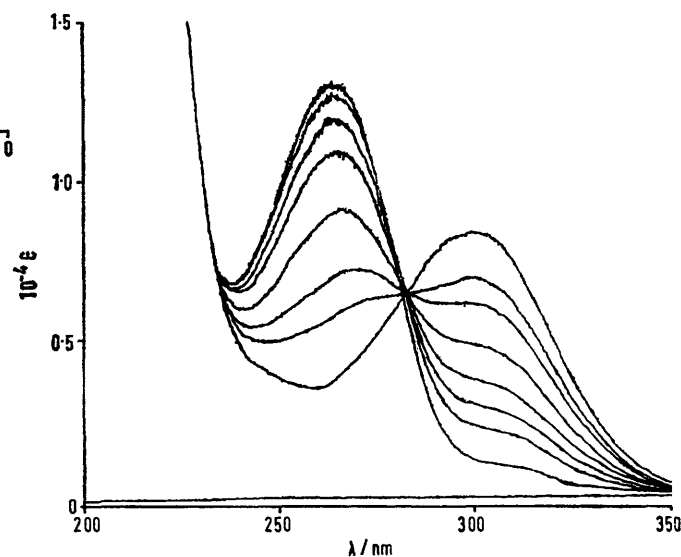FIGURE 2   Decline in the u.v. spectrum of (1) as a function of time at 60° in 0·1M-NaOH at $I = 1\cdot0$


FIGURE 3   Decline in the u.v spectrum of (1) and appearance of the intermediate, as a function of time in M-NaOH at 60°

[1] Part I, S. Nicholson, G. J. Stacey, and P. J. Taylor, J.C.S. Perkin II, 1972, 4.

[2] (a) A. Albert and W. L. F. Armarego, Adv. Heterocyclic Chem., 1965, 4, 1; (b) A. Albert, Angew. Chem. Internat. Edn., 1967, 6, 919.

[3] B.P. 1,234,635.

acid complex. If the former is derived from methylmalonaldehydic acid (5) by decarboxylation, then (5) and (6) together possess the necessary structural features to complete the structure of (1). Their isolation was far from quantitative, so other final products cannot be excluded. However, an aliquot portion taken from the spent reaction mixture revealed sufficient weak base (pK_a ca. 5) by potentiometric titration to account for most of the product [guanazole (7) has pK_a 4·71 (lit.,[4] 4·43) and, like the above solution, no u.v. absorption].

A reaction sequence consistent with the kinetics is shown in the Scheme. The intermediate (4) formed by
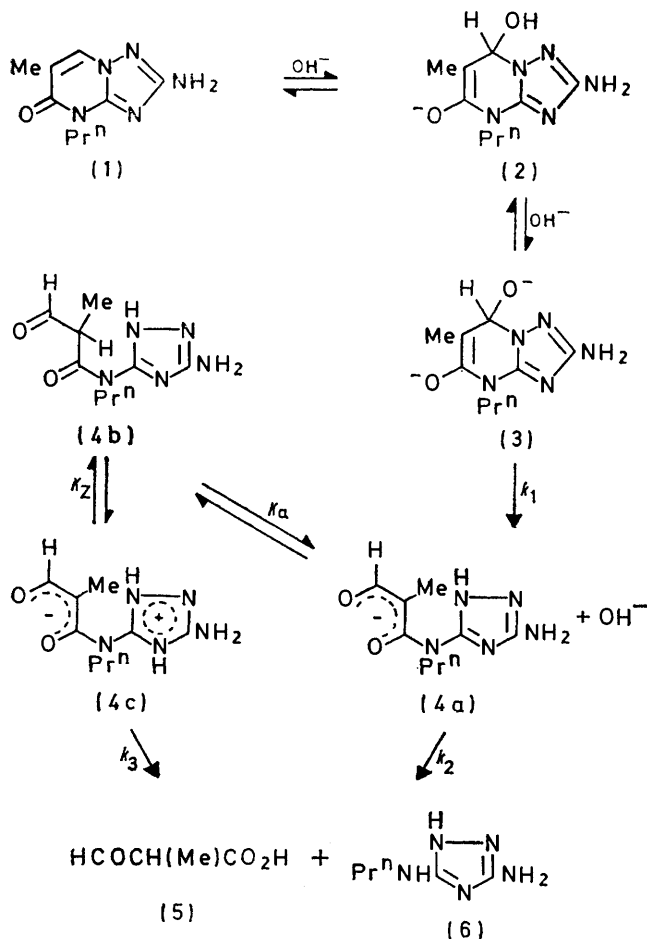
SCHEME

cleavage of the dianion (3) * may either undergo irreversible fission to (5) and (6), or regenerate (1) by removal of solvent at neutral pH. Its structure, if correct, resembles a β-diketone. Data for ethyl acetoacetate and this intermediate are given in Table 1; they compare very closely, especially in the profound u.v. changes brought about by ionisation. The $\Delta S^{\ddagger}$ values for the two reactions (Table 2) are consistent respectively with the formation of a highly charged transition state, and with simple fission.[5]

* Kinetically, all that can be proved is that the transition state is dianionic; the second and third steps may be telescoped.

TABLE 1

U.v. and pK data for ethyl acetoacetate (A) and the reaction intermediate (B)

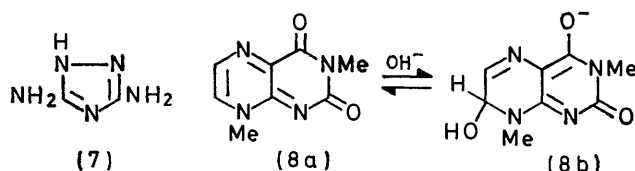|	(A)	(B)
Neutral species $\lambda_{max.}$/nm	255[a]	215inf
log ε	2·1	3·95[e]
Anion $\lambda_{max.}$/nm	272[b]	264
log ε	4·34	4·09[e]
pK_a (25°)	10·79[b]	11·4

[a] B. A. Arbuzov and V. S. Vinogradova, *Doklady Acad. Nauk S.S.S.R.*, 1956, **106**, 465. [b] W. Walisch and H. A. Ruppersberg, *Chem. Ber.*, 1959, **92**, 2622. [e] Apparent log ε based on work at pH 14.

TABLE 2

Activation parameters for the decomposition of (1) in water

	$\Delta H^{\ddagger}$/ cal mol^{-1}	$\Delta S^{\ddagger}$/ cal mol^{-1} K^{-1}
First step [OH$^-$] = 1·0M	11,600	−39·5
Second step [OH$^-$] = 1·0M	25,700	−2·5
Second step pH ca. 9	24,500	+1·4

Species (2) is a sort of covalent hydrate. The closest analogue we can find is (8).[6] This like (1) has no ionis-

able protons; both form anions by adding hydroxide ion across a carbon double bond. Since (8b) is a mesomeric anion, the pK_a value (10·4)[6] of (8) is measurable. However, generation of mesomerism in the present case involves fission to (4a), so accounting for their difference in stability.

EXPERIMENTAL

Materials.—The synthesis of (1) has been described.[3] Water was distilled and de-ionised; other materials were of analytical reagent grade.

Kinetics.—The first step of the reaction was investigated for NaOH–NaCl mixtures at $I = 1·0$, the second step similarly except that carbonate and borate buffers were used to extend the pH range downwards to [OH$^-$] < 10^{-3}M. Since $k_3 = 9·52 \times 10^{-2}$ min^{-1} at pH 2 whereas the plateau value indicated by Figure 1 is ca. 7·5 × 10^{-2} min^{-1}, the rate of the second step remains roughly a constant at pH values below those shown.

Reaction mixtures were held in thermostat baths whose temperatures did not vary by more than ±0·2° as measured by N.P.L.-calibrated thermometers. Aliquots were extracted, cooled rapidly, and examined at once with a Perkin-Elmer 137 u.v. spectrophotometer. Stock solutions of the intermediate were prepared by digesting compound (1) in M-sodium hydroxide solution. Rates were measured by Swinbourne's method[7] by taking readings at an appropriate

[4] C. F. Kroeger and W. Freiburg, *Z. Chem.*, 1965, **5**, 381.

[5] L. L. Schaleger and F. A. Long, *Adv. Phys. Org. Chem.*, 1963, **1**, 1.

[6] W. Pfleiderer, personal communication quoted in ref. 2a.

[7] E. S. Swinbourne, *J. Chem. Soc.*, 1960, 2371.

wavelength. Three temperatures were used for each determination of the activation parameters,[8] which are estimated[9] as accurate to ± 1.5 kcal mol⁻¹.

p*K* Determinations.—The pK_a value of the intermediate at 25° was measured by adding aliquot portions of the stock solution described above to buffer solutions at various pH values, and measuring their u.v. spectra at once. A plot of absorbance *vs* pH. gave a smooth sigmoidal curve from which pK_a 11.4 ± 0.1 was calculated.[10] Since the calculated half-life for its decomposition at 25° exceeds 10 h, no compensation for this was necessary. The pK_a of guanazole (7) was determined similarly.

Isolation of the Final Products.—A solution of compound (1) in hot aqueous methanolic barium hydroxide, after standing at 60° for 2.5 h, neutralising, and cooling, was added to aqueous 2,4-dinitrophenylhydrazine and the resulting precipitate was centrifuged, washed with water, recrystallised from aqueous ethanol, and dried, to yield propionaldehyde dinitrophenylhydrazone, m.p. 146—149° (decomp.) (lit.,[11] 155°) (Found: C, 45.8; H, 4.4; N, 22.7. Calc. for $C_9H_{10}N_4O_4$: C, 45.4; H, 4.2; N, 23.5%), i.r. spectrum identical with that published.[12] A repeat experiment was carried as far as acidification (pH 1) which was followed by extraction with ethyl acetate. After making strongly alkaline the aqueous layer was again extracted, and the

ethyl acetate after drying (K_2CO_3) was evaporated to yield a crystalline precipitate which was filtered and vacuum dried to give the *carbamate complex* of 3-*amino*-5-n-*propyl*-*amino*-s-*triazole* (6), m.p. 134—137° (Found: C, 40.1; H, 7.1; N, 43.3. $C_5H_{11}N_5,0.5CO_2$ requires C, 40.5; H, 6.8; N, 43.0%), δ [$(CD_3)_2SO$] 5.6br (s, H exchangeable, NH), 5.2 (s, 2H exchangeable, NH_2), 2.95 (t, 2H, CH_2), 1.7—1.2 (m, 2H, CH_2), and 0.84 p.p.m. (t, 3H, Me), ν_{max} 1620s (NH_2) with shoulder at 1655 cm⁻¹ (CO_2H [13]).

Attempted Isolation of the Intermediate.—The reaction was carried as far as maximum intermediate formation in strong alkali. Problems encountered were (a) extraction from neutral, acid, or alkaline solution, yields no product. (b) At least a 10-fold excess by weight of inorganic material (sodium or barium hydroxide or chloride) over the reactant (1) has to be present; most of this can be removed using ion-exchange resins only at the cost of replacing it in part by resinous materials. (c) Even though solutions prepared in this way show the u.v. spectrum of the intermediate and appear to be stable for 24 h at 0°, freeze-drying yields a solid, mostly inorganic in nature, whose u.v. spectrum is that of (1). (d) Wholly non-aqueous fission techniques, such as that of Gassman *et al.*[14] effect no reaction.

[8] K. J. Laidler and H. Eyring, *Ann. New York Acad. Sci.,* 1940, **89**, 303.

[9] E. L. Purlee, R. W. Taft, and C. A. De Fazio, *J. Amer. Chem. Soc.,* 1955, **77**, 837.

[10] A. Albert and E. P. Serjeant, 'Ionisation Constants of Acids and Bases,' Methuen, London, 1962.

[11] C. F. H. Allen, *J. Amer. Chem. Soc.,* 1930, **52**, 2955.

[12] Sadtler prism spectrum no. 2076.

[13] G. F. Beattie, J. M. Pryce, and P. J. Taylor, *Chem. Comm.,* 1971, 793.

[14] P. G. Gassman, J. T. Lumb, and F. V. Zalar, *J. Amer. Chem. Soc.,* 1967, **89**, 946.