Covalent Hydrates as Intermediates in Heterocyclic Rearrangements. Part 3.[1] The Alkali-catalysed Transformations of 1,5-Diamino-1*H*-*s*-triazolo[1,5-*c*]quinazolinium Bromide

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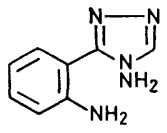
The action of alkali on 1,5-diamino-1*H*-*s*-triazolo[1,5-*c*]quinazolinium bromide leads to parallel reactions that obey the same unusual rate law: a rate that varies with the square of [OH^-] near pH 10, attenuating to the first power at high pH. The first reaction involves the generation of an anion believed to be the cyanamide (6) whose pK_a value lies below that of the original base, so that the neutral species is always metastable; a situation believed to be unique. This process is reversible. The second is the generation, *via* a covalently hydrated intermediate, of a basic species believed to be the amidine (9) which on acidification cyclises to the triazoloquinazolone (10) with loss of hydrazine. An unequivocal synthesis of this triazoloquinazolone is described. The rationale of these reactions is discussed in relation to factors known to influence the stability of covalent hydrates and the facility of cyclisation processes.

THE reaction of cyanogen bromide with the triazole (1) has been shown by *X*-ray crystallography to give 1,5-diamino-1*H*-*s*-triazolo[1,5-*c*]quinazolinium bromide (2), and not the expected triazepine (3).[2,3] Suspicion was originally aroused by the unmeasurably high pK_a value of (2), which feature would not be expected for (3),[2] and by the transformations that this compound undergoes in alkaline solution.[4] We present here the evidence for the



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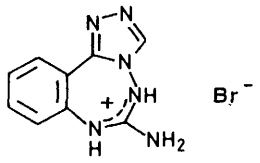


(3)

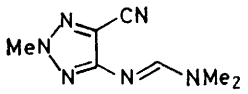
course of this reaction, its mechanism, and the structures of the reaction intermediates and products.

RESULTS

The Course of the Reaction.—We believe the course of the reaction in alkali to be that set out in Scheme 1. Extraction of the strongly alkaline solution with ethyl acetate yielded a solid of approximate composition $C_9H_{10}N_6O$, *i.e.* that of the hypothetical free base of (2) plus one molecule of water. It could therefore be a covalent hydrate of (2), or the result of ring-opening such a species. Titration from alkaline solution showed it to be a base of pK_a 4.85. We believe it to be the amidine (9), formed by fission of the covalent hydrate (7). Its pK_a is low for an amidine, but amidine pK_a values are unusually sensitive to electronegative substituents [5] and a similar base-weakening effect has been observed by Albert [6] for the heterocyclic amidine (11), pK_a 3.68. Its ^{1}H n.m.r. spectrum contains no aromatic resonance at field low enough for a triazole ring,[7] so whatever its structure, this ring has opened. The rest of the spectroscopic information (see Experimental section) is consistent with this structure, but not decisive.

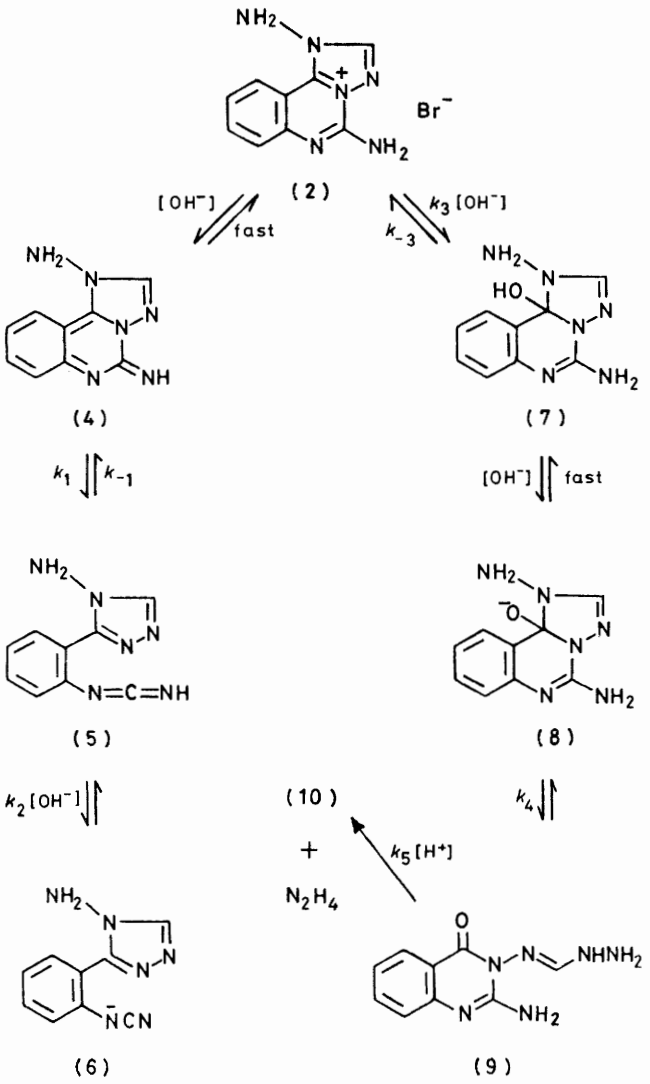
Dissolution of the amidine (9) in acid, followed after a period by titration with alkali, yields a titre of apparent pK_a *ca.* 7.7 corresponding to two equivalents of starting material. Two new species are therefore present. One of these has been identified as hydrazine, pK_a 8.11,[8] by precipitation from this solution as the azine of salicylaldehyde. The other was isolated by extracting with isopropyl alcohol either this freeze-dried solution, or one obtained by subjecting (2) to similar treatment. Evaporation of the extract yielded a solid of approximate composition $C_9H_6N_4O$, *i.e.* that of the amidine (9) minus one molecule of hydrazine. The identity of this product with the triazoloquinazolone (10) has been proved by its synthesis, as shown in Scheme 2. The only possible ambiguity in this sequence comes at the second step, where reaction of hydrazine with the cyanamide (12) could possibly, though implausibly, have led to the hydrazinoquinazolone (15) in place of the expected product (13). The identity of (13) has been proved in two ways. On treatment with nitrous acid it deaminates to give 2-aminoquinazol-4-one (14),[9] a reaction typical of 1,1-disubstituted hydrazines; [10] the isomer (15) is expected [11] to generate the azide. Also (13) does not possess an acid pK_a, whereas we find pK_a 10.62 for (14) in 50% aqueous acetone, and also 10.84 for (15), prepared by the method of Gupta *et al.*[12] This indicates that (13) unlike (14) and (15) possesses no ionisable ring NH, *i.e.* it must possess a 3-substituent, as is required by the structure shown.

The triazoloquinazolone (10) is an acid of pK_a 7.26. An



(11)

equimolar mixture of hydrazine with (10) possesses an apparent pK_a of *ca.* 7.7 which, because the individual values overlap, appears as a single titre. This fact has been used in the quantitative reaction following (see below). Qualitatively however, it was found that, when (2) is digested with alkali, acidified, and titrated as above, the actual titre never corresponded to anything approaching 100% reaction. As determined by titration, the ultimate yield of (10) plus hydrazine varies from 30 to 79% according to the pH and temperature (see Tables 1 and 2). Since the reaction rate measured in terms of this yield follows simple first-order kinetics, a second reaction of (2) in parallel to



Scheme 1

that which gives the amidine (9) must be involved. We believe this reaction to consist in the reversible sequence (2) ⇌ (6), the forward reaction taking place in alkali and the reverse reaction in acid. Direct evidence for the structure of (6) has proved unobtainable; as an anion stable only in strong alkali it cannot be extracted from its solutions, and their evaporation has led in our hands only to an intractable mixture of products.

There is, however, unequivocal evidence for the reversible

Table 1

Rates (min^{-1}) and product balance for the reaction of compound (2) in water at 25 °C

pH	10.00	10.00	10.25	10.50	10.79
10^2k_{obs}	0.0945	0.1085	0.2935	0.727	2.22
% [Q] [a]	30	30	32	31	45
pH	11.00	11.20	11.50	11.67	12.00
10^2k_{obs}	2.97	5.76	13.52	18.72	48.4
% [Q] [a]	46	54	60	65	65
pH	12.16	12.43	12.55		
10^2k_{obs}	68.9	127	166		
% [Q] [a]	64	67	65		

[a] % Yield of amidine (9) based on infinity titre (see text).

Table 2

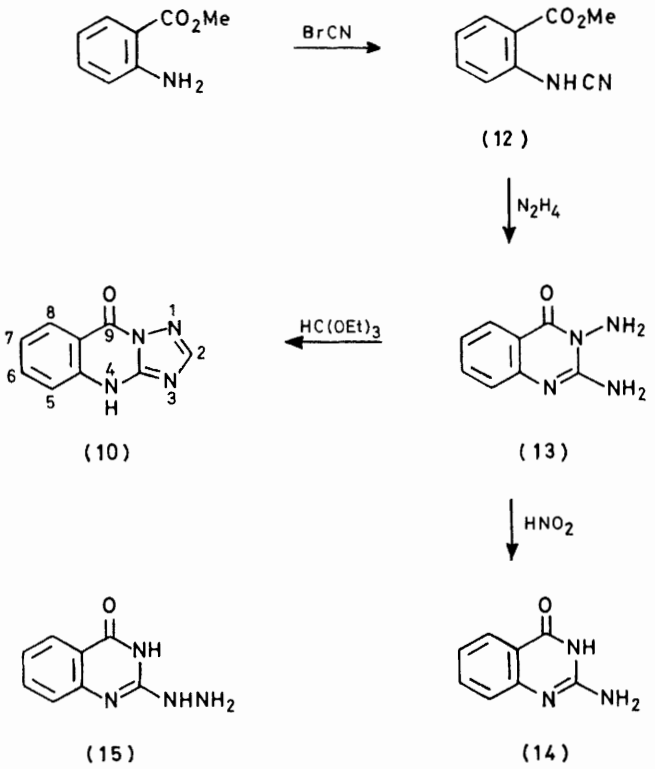
Rates (min^{-1}) and product balance for the reaction of (2) in water at $[OH^-]$ = 0.028M as a function of temperature

t/°C	6	10.2	14.8	18.6
10^2k_{obs}	15.3	23.2	37.1	51.5
% [Q] [a]	72	76	79	75

[a] See note to Table 1.

formation of an anion directly from the cation (2). In 50% aqueous acetone, where this reaction path predominates, slow titration leads to a titration curve of anomalous shape in which almost two equivalents of alkali are absorbed (Figure 1). The abnormal titre means that acid is being liberated from within the system; [13] the anomalous plateau pH is that at which liberation of acid just keeps pace with addition of alkali. Both the position of this 'apparent pK_a', and the titre itself, have been found to be sensitive to titration speed and solvent composition. The true basic pK_a must lie above this plateau. This phenomenon is invisible in water since the apparent, and therefore the true, pK_a values are too high to be accessible to potentiometric titration [14] ($pK_a > 12$).

If an anion is formed reversibly from (2) by titration with alkali, back-titration with acid should reveal this anion directly. In fact, there are two titres (Figure 2): the amidine (9) of pK_a *ca.* 4.8, and another species of pK_a *ca.* 6.5. At any given alkaline pH these titres increase with time and in constant proportion to a maximum. They therefore result from parallel reactions. The titration curve for the species of apparent pK_a *ca.* 6.5 shows similar anomalies in shape to that for (2), and arguably for the same reason. Furthermore its titre corresponds, at the end of the reaction, approximately to what would be expected if its value is similarly doubled by taking up an extra mole



Scheme 2

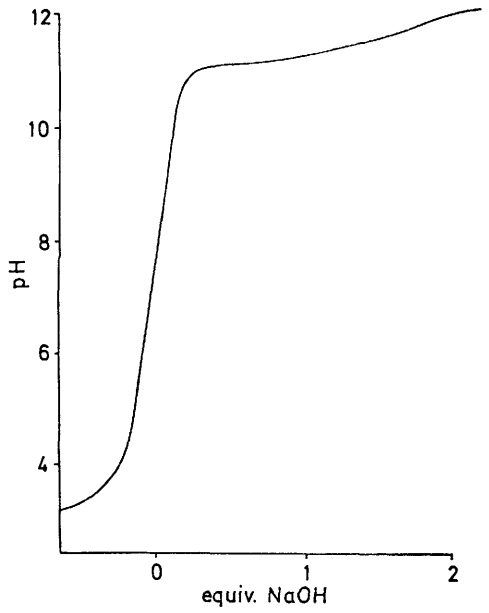


FIGURE 1 The titration curve (acid→alkali) of (2) in 50% acetone

of acid. Its identity cannot be established as (6), but it may be noted that (12), a related cyanamide, possesses pK_a 7.85 in 13% aqueous acetonitrile, a value which would probably be lower but for a strong intramolecular hydrogen bond (ν_{NH} 3 230, $\nu_{C=O}$ 1 692 cm^{-1}). This is circumstantial evidence at best, but the sequence of Scheme 1 appears plausible in the light of the subsequent discussion.

According to Scheme 1, the apparent equilibrium between the two reaction pathways found in alkali should be displaced by acid, since (10) is formed irreversibly. This is found: if the reaction mixture at equilibrium in alkali is acidified and the whole process is repeated, the combined

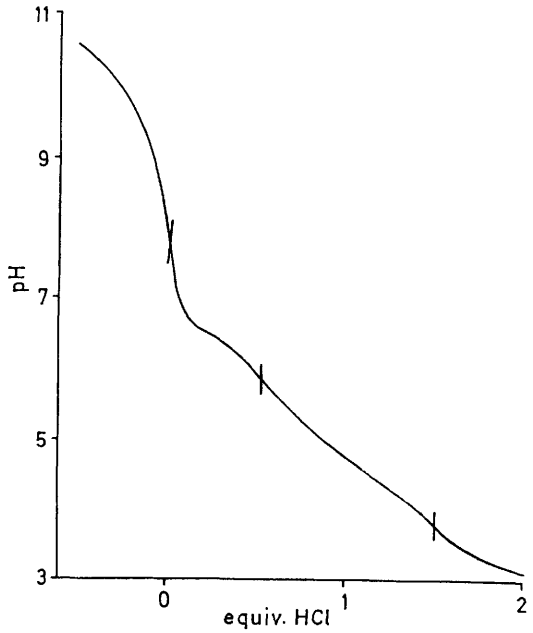


FIGURE 2 The titration curve (alkali→acid) of (2) in water after standing to apparent equilibrium in alkali

titre for (10) plus hydrazine increases, and after several such re-cyclings it rises to its theoretical maximum value.

Kinetics.—Preliminary attempts to follow the reaction in alkali by spectrophotometric means proved fruitless, probably because there are parallel reactions and all species possess closely similar u.v. spectra. A potentiometric technique based on the above observations was therefore devised. A pH-stat procedure was used to control the solution pH; aliquot portions were acidified to pH *ca.* 2 and the titre corresponding to (10) plus hydrazine (Figure 3)

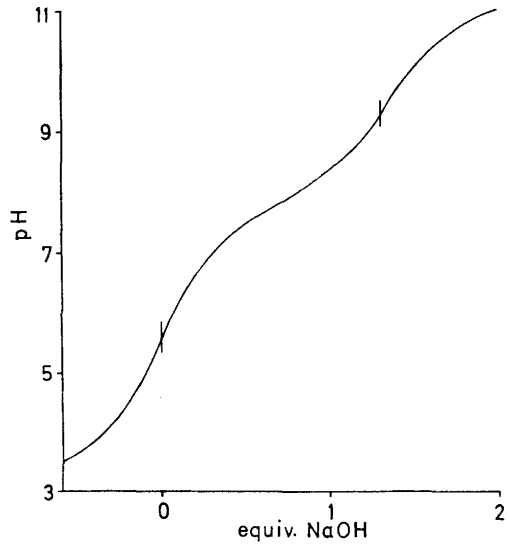


FIGURE 3 The titration curve (acid→alkali) of (2) in water after standing to apparent equilibrium in alkali

was measured after a period of time sufficient to complete the conversion of the amidine (9) and remove dissolved carbon dioxide; 10 min proved such a period. The alternative possible procedure, direct titration of these aliquots with acid (*cf.* Figure 2), was found to be less satisfactory since (a) the initial alkaline conditions are not instantly quenched and (b) absorbed carbon dioxide can affect the titre for the species of apparent pK_a 6.5. The method employed avoids these imprecisions in (a) pH and (b) titre, and has proved reasonably accurate (s.e. ±5%).

$$\ln x_e/(x_e - x) = k_{obs}t \quad (1)$$

$$k_{obs} = k_C + k_Q \quad (2)$$

$$k_Q/k_{obs} = x_e/a \quad (3)$$

The overall rate constant k_{obs} (Tables 1 and 2) was calculated from equation (1), where x_e is the titre obtained at infinite time (10 half-lives). Good kinetics resulted to above 3 half-lives on the assumption of parallel first-order reactions that this treatment implies. The individual rate constants k_C and k_Q for the anion and amidine formation reactions were then derived from k_{obs} by means of equations (2) and (3), where a is the calculated initial titre of the reactant (2); as explained above, this titre cannot be measured in water. The effect of this procedure is to concentrate errors into k_C, so that the values for k_Q are more accurately known; hence activation parameters [15] for the reaction at high pH (Table 3) have been calculated only for k_Q. Even so they must be regarded as approximate.

The pH profile for both reactions is shown on Figure 4. Each reaction separately obeys the rate law of equation

(4), according to which a reaction second-order in hydroxide ion concentration under moderately alkaline conditions becomes first-order as the pH rises. At each end of the pH profile the product balance settles down to a constant value,

$$k_{C(Q)} = \frac{k_{1(3)}k_{2(4)}[OH^-]^2}{k_{-1(-3)} + k_{2(4)}[OH^-]} \quad (4)$$

so that at pH <10 and >12 each reaction must possess the same order. However, the transitional pH which defines the change in slope with $[OH^-]$ is slightly higher for amidine than for anion formation, resulting in a higher yield for the former above this value. The % yield of amidine varies at 25 °C from 30 to 65 over the pH range studied and may show some tendency to fall as the temperature rises, but this is uncertain.

For both pathways this change in slope with pH is

TABLE 3

Microscopic rates (25 °C) and activation parameters

For k_C	For k_Q
$k_1 = 16.4$ l mol^{-1} min^{-1}	$k_3 = 32.4$ l mol^{-1} min^{-1}
$k_{-1}/k_2 = 2.31 \times 10^{-4}$ mol l^{-1}	$k_{-3}/k_4 = 1.08 \times 10^3$ mol l^{-1}
pH_{tr} [a] = 10.36	pH_{tr} [a] = 11.03
	$\Delta H^{\ddagger} = 15.09$ kcal mol^{-1}
	$\Delta S^{\ddagger} = -6.5$ cal mol^{-1} K^{-1}

[a] Transitional pH; see text.

evidence for reaction *via* a steady-state intermediate, the rate-determining step changing from its destruction to its formation as the pH rises, and both steps being catalysed by hydroxide ion.[16,17] Alternatively it might have been due to an ionisation step,[18,19] but that possibility is precluded here by the high pK_a value of (2); a value of *ca.* 10.7

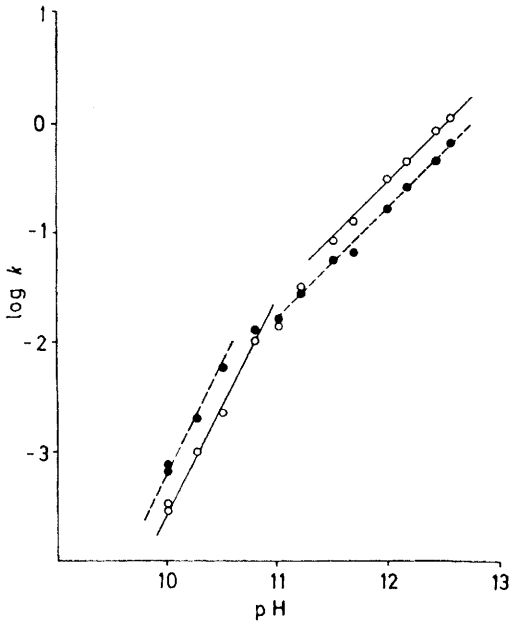


FIGURE 4 pH Profile (k/min^{-1}) for the reactions of (2) in water at 25 °C: full circles and dotted lines, k_C; open circles and full lines, k_Q. The lower lines are drawn with a slope of 2 and the upper lines with a slope of unity

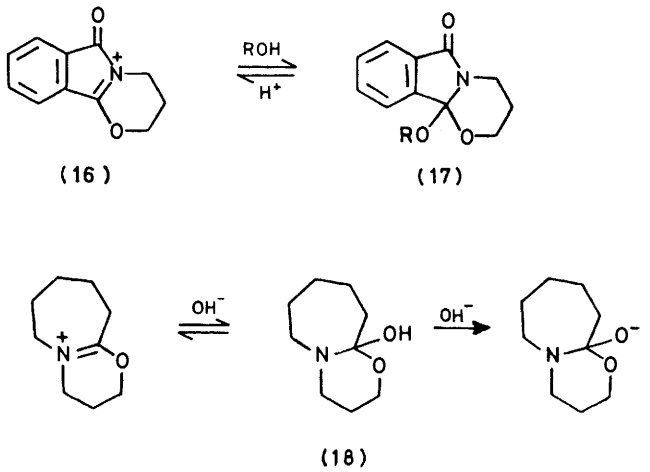
would be required to fit the pH profile. In fact, this pK_a value can be stated as >13 and probably >14 from the total absence of curvature in strong alkali (Figure 4).

Equation (4) can be solved by a double reciprocal plot [16] to yield the kinetic parameters given in Table 3. The non-identity of the two transitional pH values is evidence that these reactions do *not* go through a common steady-state intermediate which then partitions to different products; [20] their pathways are quite independent. This is consistent with the qualitative observations already recorded. The nature of these pathways is considered below.

DISCUSSION

Reactions whose rates vary with the square of the hydroxide ion concentration are rare; [1,16-19,21] for two to take place in parallel must defy all precedent. The overall sequence we propose is set out as Scheme 1. We discuss each pathway separately.

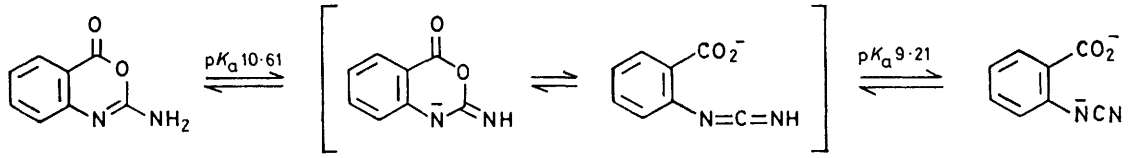
Addition of hydroxide ion to the cation (2) is expected to take place at the most electron-deficient carbon atom.[22] For (2) the dominant canonical form has been shown to possess the pseudo-quaternary structure written,[23] and covalent hydration should accordingly give (7). In one distantly analogous case, Gravitz and Jencks [24] have shown that the cation (16) can be trapped as the adduct (17); the latter is sufficiently stable to be visible as a fugitive species even when R = H. No trapping experiments have been carried out in the present case. Similarly, Coller *et al.*[16] have shown the adduct (18) to be stable against breakdown except through



further attack of hydroxide ion, with kinetic consequences that precisely parallel our own. In all three cases, resonance stabilisation of the cation may facilitate hydroxide ion loss in the reverse to the addition step (here k_{-3}), making further attack of hydroxide ion mandatory if the hydrolysis is to proceed. In Scheme 2, this further attack has been dissected into two steps, ionisation to (8) followed by the fission step k_4. In fact these steps need not be discrete: proton removal may be only partial and synchronous with fission, *i.e.* this step may be catalysed by general bases.[19] No experiments to check that possibility have been carried out.

As an alternative to addition, hydroxide ion could abstract a proton from the cation (2). The resulting free base (4) is of a tautomerically disfavoured type [25] and fission could occur to the carbodi-imide (5), which

would then give the anion (6) either directly, or through prior rearrangement to the tautomerically favoured cyanamide (step k_2). Given that the ionisation and tautomerisation steps subsumed under k_2 must both be very fast, the condensation step k_{-1} must also be fast even though *ca.* 10^4 times slower (Table 3). Cyanamide intermediates are postulated as transient species in a number of intramolecular heterocyclic condensations and rearrangements,[26] but no rates have been reported.



(19) (20)

The reversible formation of (6) from (2) is paralleled by the process (19) ⇌ (20) [27] in which the anion of a weak acid rearranges; if acid its second pK_a is *lower* than the first. In the present case, a cation of pK_a >12 gives an anion of pK_a <6.5. Like the covalent hydrate (7), the neutral species (4) ⇌ (5) functions solely as a steady-state intermediate. So far as we are aware, this interconversion of a cation with an anion, such that the neutral species is at all times metastable, is unique.*

At high pH, the initial step of both reactions becomes rate-limiting. Step k_3 for the addition of hydroxide ion at 25 °C is some seven times slower than the addition of *water* at 20 °C to the quinazolinium cation,[28] indicating a far greater resistance to hydration than in that case. Possibly this is because the adduct (7) fails to satisfy the second of Albert's criteria: [22] while excessive electronegativity is relieved, no cation is available to it whose resonance stabilisation approaches that of (2). We have encountered previous examples of this kind.[29] It may be noted that $\Delta S^{\ddagger}$ for k_3 is more negative than would normally be expected for a reaction between charged species of opposite sign,[30] presumably because the cationic charge is somewhat dispersed. For the other pathway, there are no published data with which k_1 can be compared. In any case this step is composite, and cannot be interpreted quantitatively without knowledge of the pK_a for (2).

It is unclear whether the balance between anion and amidine in alkali is subject to kinetic or thermodynamic control. If the latter, step k_4 must be reversible. Alternatively, the anion is trapped by the alkaline conditions ($K_a > [H^+]$ by 10^4—10^6) such that step k_2 is effectively irreversible on the time-scale of the kinetic experiments. On acidification, divergent pathways appear. The amidine (9) is presented, in step k_5, with an alternative, irreversible, and in any case much more favourable cyclisation route than the reverse of k_4. This step is analogous to the intermolecular synthetic route by which, for example, amidines can be used to build the triazole ring of purines,[31] and is likely to be fast since subject to the ' intramolecular advantage ' of 10^5 or more in rate.[32] This same advantage will account for the rapidity of step k_{-1}, which is probably rate-determining in the retrogression of anion to cation since all other steps are proton transfers and therefore, by comparison, very fast. The above considerations will satisfactorily account both for the pseudo-equilibrium in alkali which the kinetics reveal, and its ' freezing ' in acid without happy accident no quantitative study would have been possible.

* A referee has drawn attention to the reversible hydrolysis of the 1-methoxypyridinium cation (R. Eisenthal and A. R. Katritzky, *Tetrahedron*, 1965, **21**, 2205.

EXPERIMENTAL

2-Aminoquinazol-4-one (14) was prepared by the method of Lempert and Breuer; [9] methyl anthranilate was a commercial sample. Water was distilled de-ionised; other materials were of analytical reagent grade. I.r. spectra (Perkin-Elmer 457 i.r. spectrophotometer) are reported for Nujol mulls, n.m.r. spectra (Varian HA-100 n.m.r. spectrometer) for deuteriated dimethyl sulphoxide solution, and mass spectra for a Perkin-Elmer–Hitachi RMV 6 E mass spectrometer.

Kinetics.—A solution of (2) (1—2 mmol) in water (100 ml) was placed in an E.I.L. jacketted titration vessel and allowed to equilibrate to 25.0 ± 0.2 °C (temperatures measured with a N.P.L. calibrated thermometer). The titration vessel was equipped with a Radiometer type G202B glass electrode, and the salt bridge of a standard calomel electrode, both leading from a Radiometer model 28 pH meter. Also immersed in the solution was the tip of a 10-ml burette charged with 0.1N-aqueous sodium hydroxide carrying a CaO guard tube and operated by a Radiometer type MNV 1 magnetic valve. This magnetic valve was controlled by a Radiometer Titration model 11 to which the pH-meter was also attached. The solution also incorporated a fast magnetic stirrer.

For each run the solution pH was controlled by appropriate adjustment of the pH-meter, but before the run actually began the required pH was approximately attained by addition of a very small volume of strong alkali; the magnetic valve was then immediately activated. This device ensures that the amount of alkali which needs to be added by the automatic burette to hold the pH constant is too small to affect appreciably the solution volume. At pH 12 and above, pH-stat methods were not used; a known volume (p ml) of N-aqueous sodium hydroxide representing a considerable excess (above two-fold) of alkali was added to (100 − p) ml reaction solution, and the actual pH value was monitored as the reaction proceeded. These reactions have half-lives of 2 min down to 35 s, and

conventional pH-stat methods could not have established a steady solution pH rapidly enough. In practice, there was an *upwards* drift of 0.02—0.07 pH units between 10 and 99% reaction; the ultimate reading was taken as correct. This upwards drift [it may be caused by the formation of compound (9)] is sufficient evidence that the incursion of atmospheric carbon dioxide is unimportant, over the time-span concerned, into the lidded reaction vessel.

Aliquot portions (10 ml) were extracted from the reaction mixture and added to an equal volume of an excess of dilute hydrochloric acid solution. This procedure is satisfactory for the slower reactions (half-lives greater than 10 min); for the faster ones, aliquots were taken with carefully calibrated rapid-action Froud pipettes. These solutions were stirred 10 min before titration, partly to complete the conversion of amidine (9), but mostly to expel carbon dioxide from the solution. We have found this a very satisfactory technique for obtaining carbon dioxide titres that are small and reproducible; [33] since the carbon dioxide blank amounted to *ca.* 0.05 ml in a titre of up to 4 ml, no important error is introduced by what remains (no attempt was made to measure titres corresponding to less than 10% reaction). The rate was measured by following the titre of the species of apparent pK_a 7.7; the infinity titre was taken as that after 10 half-lives. Good first-order plots were obtained, even for the fastest runs, to 3 half-lives or better. The separate rate constants k_C and k_Q were obtained from k_{obs} by means of equations (1)—(3) using the procedure described above. This involves a precise knowledge of *a*, *i.e.* of the theoretical titre for (2), which is readily obtained from the known concentration of reactant, the volume taken, and the strength of the titrant (0.05M carbonate-free aqueous potassium hydroxide, calibrated regularly). These titrations were performed on a Metrohm Potentiograph, which was also used for the pK_a determinations [14] and for the preliminary experiments as, *e.g.*, illustrated on Figures 1—3.

The temperature coefficient was measured for solutions of known alkali (p = 4.00 ml; see above). It therefore refers to standard hydroxide ion concentration, not standard hydrogen ion activity. The measured solution pH was 12.55 at 25 °C. Data are in Table 2. These rates were used to calculate activation parameters for step k_3 (see above) by means of the Eyring equation.[15]

Isolation of the Amidine (9).—Compound (2) (1.12 g) was dissolved in hot 20% aqueous methanol (100 ml), aqueous N-sodium hydroxide (12 ml) was added, and the solution was at once extracted with ethyl acetate (500 ml). After drying with anhydrous magnesium sulphate for 0.5 h, this solution was evaporated to dryness to yield a solid (0.3 g) some of which was recrystallised from benzene–methanol to give a crystalline *product* (Found: C, 49.6; H, 4.7; N, 37.9; no chloride ion. $C_9H_{10}N_6O$ requires C, 49.6; H, 4.6; N, 39.5%); $\nu_{max.}$ 3 485m, 3 370w, 3 340w, 3 280mw, 3 230m,br, 1 676s, 1 624sh, 1 616ms, 1 608ms, and 1 582w cm^{-1}; δ 8.4br (s, 1 H, NH), 7.9 (s, 1 H, amidine CH), 7.85 (d, 1 H, aromatic), 7.6—7.0 (m, 3 H, aromatic), and 6.9br (4 H, 2 × NH_2); those peaks assigned to NH were removed by deuteriation. Its mass spectrum was identical with that of the triazoloquinazolone (10), showing that cyclisation must have taken place in the mass spectrometer. Titration of the crude material from high pH showed it to be a base of pK_a 4.85.

Isolation of Hydrazine as an Azine.—Some of the crude solid prepared as described above was dissolved in aqueous methanol and added to a solution of 2-hydroxybenzaldehyde in methanolic hydrochloric acid. Yellow crystals were precipitated and these were washed with methanol but not otherwise purified to give 2,2′-dihydroxybenzaldehyde azine, m.p. 211 °C (lit.,[34] 214 °C), i.r. spectrum identical with that of an authentic [35] specimen.

Isolation of Compound (10).—Compound (2) (1.12 g) was dissolved in hot 20% aqueous methanol (100 ml), aqueous N-sodium hydroxide (12 ml) was added, and after 15 min the solution was acidified with aqueous N-hydrochloric acid (13 ml). This solution was freeze-dried to give a solid which was extracted with isopropyl alcohol (3 × 20 ml). The combined extracts were evaporated to yield a solid which, after drying at 80 °C for 24 h to remove traces of solvent, was shaken with water, filtered, and dried at 80 °C for 1.5 h to yield 190 mg of *product* (Found: C, 56.8; H, 3.5; N, 28.9. $C_9H_6N_4O$ requires C, 58.0; H, 3.23; N, 30.1%), one spot on two t.l.c. systems (chloroform–ethanol; toluene–ethyl acetate–ethanol–ammonia). It behaves as a crude sample of compound (10) (acid pK_a 7.3 in water, 7.45 in 50% aqueous acetone); $\nu_{max.}$ *ca.* 2 800vbr, 1 722s, 1 650s, 1 618mw, 1 570ms, and 1 524ms cm^{-1}; δ 14—10br (1 H, NH), 8.31 (s, 1 H, 2-CH), 8.23 (d, 1 H, 8-CH), 7.91 (t, 1 H, 6-CH), 7.61 (d, 1 H, 5-CH), and 7.44 (t, 1 H, 7-CH); *m/e* 186, base peak 158 (M − CO). The solid remaining after the above multiple extraction with isopropyl alcohol appeared to consist, by i.r. examination, of a mixture of hydrazine dihydrochloride [36] and compound (2).

Conversion of Compound (2) *to Compound* (10).—The above procedure for isolating compound (10) was taken as far as the acidification step. The whole process of adding excess of alkali and re-acidification after a period, was then thrice repeated. Titration of an aliquot portion of this solution revealed the conversion process to be complete to within the limits of error; on the basis of the data in Table 1, *ca.* 98.5% conversion is expected. The extraction procedures were now repeated as above, to yield a solid from isopropyl alcohol whose i.r. spectrum was almost identical with that of the triazoloquinazolone (10). The solid remaining after extraction appeared from its i.r. spectrum to be hydrazine dihydrochloride (see above), this time contaminated with only a trace of the starting material (2).

Preparation of 9-Oxo-4,9-dihydro-s-triazolo[5,1-b]*quinazoline* (10).—Sodium acetate (7.8 g) was added to a stirred solution of methyl anthranilate (10 g) in glacial acetic acid (30 ml) and water (30 ml). After the mixture had been cooled to 0—5 °C excess of cyanogen bromide (8.2 g) was added; the mixture was then stirred for 18 h and finally poured into water. The solid deposited was filtered off, washed with dilute acetic acid and water, and dried *in vacuo* over phosphorus pentoxide to yield 7.0 g of *methyl 2-cyanoaminobenzoate* (12), m.p. 96—98 °C (Found: C, 61.1; H, 4.8; N, 15.6. $C_9H_8N_2O_2$ requires C, 61.35; H, 4.6; N, 15.9%); $\nu_{max.}$ 3 230ms, 2 250ms, 1 692s, 1 603m, 1 587m, and 1 501ms cm^{-1}; δ 10.2br (1 H, NH), 8.06 (d of d, 1 H, 6-CH), 7.7—6.9 (m, 3 H, aromatic), and 4.0 (s, 3 H, CH_3); *m/e* 176; acidic pK_a 7.85 in 13% aqueous acetonitrile.

A sample of (12) (5.0 g) was heated under reflux with 100% hydrazine hydrate (5 ml) and ethanol (15 ml) for 1 h and the mixture was then allowed to cool. The solid deposited was filtered off and recrystallised from n-butanol to yield white crystals (4.25 g) of *2,3-diaminoquinazol-4-one* (13), m.p. 289—290 °C (Found: C, 54.4; H, 4.5; N, 32.0. $C_8H_8N_4O$ requires C, 54.55; H, 4.6; N, 31.8%); $\nu_{max.}$

3 450m, 3 320mw, 3 280w, 3 220mw, 1 688ms, 1 636s, 1 616ms, 1 576mw, 1 557mw, and 1 482ms cm^{-1}; δ 8.00 (d of d, 1 H, 5-CH), 7.8—7.0 (m, 3 H, aromatic), 7.12 (s, 2 H, NH_2), and 5.54 (s, 2 H, NH_2); *m/e* 176; no acidic pK_a visible by potentiometric titration in 50% aqueous acetone at pH <13.

A sample (2.0 g) of (13) was heated under reflux with triethyl orthoformate (50 ml) for 12 h. The solid precipitated on cooling was filtered off and recrystallised from ethanol to give white crystals (yield 1.3 g) of 9-*oxo*-4,9-*dihydro*-s-*triazolo*[5,1-b]*quinazoline* (10), m.p. 325—326 °C (Found: C, 57.9; H, 3.1; N, 30.3. $C_9H_6N_4O$ requires C, 58.05; H, 3.25; N, 30.1%); $\nu_{max.}$ 3 100—2 600mw, br, 1 722s, 1 649vs, 1 614w, 1 577m, 1 518m, and 1 481m cm^{-1}; δ 14—11br (1 H, NH), 8.30 (s, 1 H, 2-CH), 8.25 (d, 1 H, 8-CH), 7.90 (t, 1 H, 6-CH), 7.60 (d, 1 H, 5-CH), and 7.42 (t, 1 H, 7-CH); *m/e* 186, base peak 158 (*M* − CO); acid pK_a 7.26 by potentiometric titration in water.

Reaction of 2,3-*Diaminoquinazol*-4-*one* (13) *with Nitrous Acid*.—A sample of compound (13) (1 g) was dissolved in concentrated sulphuric acid (10 ml) cooled in an ice–ethanol bath, and sodium nitrite (0.39 g) was added in small portions over 45 min at <5 °C. The mixture was stirred for 4 h the temperature being allowed to rise slowly to ambient; the mixture was then poured into ice–water and the white precipitate was filtered off. Recrystallisation of the product from water gave the *sulphate* (yield 0.9 g), m.p. 317—318 °C (Found: C, 44.1; H, 4.2; N, 19.1; S, 7.3. $C_8H_7N_3O\cdot\frac{1}{2}H_2SO_4\cdot\frac{1}{2}H_2O$ requires C, 43.8; H, 4.1; N, 19.2; S, 7.3%). This material, heated with aqueous sodium carbonate, yielded a solid whose i.r. spectrum was identical with that of an authentic specimen [14] of 2-aminoquinazol-4-one (14).

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REFERENCES

[1] Part 2; M. Dukes, S. Nicholson, and P. J. Taylor, *J.C.S. Perkin II*, 1972, 1695.
[2] R. A. Bowie, D. A. Thomason, and J. A. J. Jarvis, *Tetrahedron Letters*, 1973, 1643.
[3] J. A. J. Jarvis and P. J. Taylor, *J.C.S. Perkin II*, 1979, 420.
[4] P. J. Taylor, paper presented at the Autumn Meeting of the Chemical Society, Norwich, September 1973.
[5] M. Charton, *J. Org. Chem.*, 1965, **30**, 969.
[6] A. Albert, *J.C.S. Perkin I*, 1972, 461.
[7] R. A. Bowie and D. A. Thomason, *J.C.S. Perkin I*, 1972, 1842.
[8] G. Schwarzenbach, *Helv. Chim. Acta*, 1936, **19**, 178.
[9] K. Lempert and J. Breuer, *Magy. Kem. Folyoirat*, 1962, **68**, 452; *C.A.*, **58**, 11355.
[10] M. N. Sheng and A. R. Day, *J. Org. Chem.*, 1963, **28**, 736.
[11] K. Klusius and K. Schwarzenbach, *Helv. Chim. Acta*, 1959, **42**, 739; T. Taguchi, T. Matsuo, and M. Kojima, *J. Org. Chem.*, 1964, **29**, 1104.
[12] C. M. Gupta, A. P. Bhaduri, and N. M. Khanna, *J. Medicin. Chem.*, 1968, **11**, 392.
[13] G. A. Cockayne and P. J. Taylor, *J.C.S. Perkin II*, 1972, 2173.
[14] A. Albert and E. P. Serjeant, ' Ionisation Constants of Acids and Bases,' Methuen, London, 1962.
[15] K. J. Laidler and H. Eyring, *Ann. N.Y. Acad. Sci.*, 1940, **39**, 302.
[16] B. A. W. Coller, F. W. Eastwood, L. Y. Foo, and N. C. G. H. Y. Ho, *Chem. Comm.*, 1970, 900.
[17] E. G. Sander, *J. Amer. Chem. Soc.*, 1969, **91**, 3629; S. O. Eriksson and C. Holst, *Acta Chem. Scand.*, 1966, **20**, 1892; R. M. Pollak and T. C. Dumsha, *J. Amer. Chem. Soc.*, 1973, **95**, 4463.
[18] B. Hansen, *Acta Chem. Scand.*, 1963, **17**, 1307.
[19] T. H. Fife and B. R. De Mark, *J. Amer. Chem. Soc.*, 1976, **98**, 6978.
[20] G. L. Schmir and B. A. Cunningham, *J. Amer. Chem. Soc.*, 1965, **87**, 5692.
[21] R. L. Schowen, H. Jayaraman, and L. Kerschner, *Tetrahedron Letters*, 1966, 497; M. T. Behme and E. H. Cordes, *J. Org. Chem.*, 1964, **29**, 1255; I. Blagoeva, B. J. Kurtev, and I. G. Pojarlieff, *J. Chem. Soc.* (*B*), 1970, 232; R. B. Homer and K. W. Alwis, *J.C.S. Perkin II*, 1976, 781.
[22] A. Albert, *Adv. Heterocyclic Chem.*, 1976, **20**, 117.
[23] See ref. 3 for a more precise discussion of this point.
[24] N. Gravitz and W. P. Jencks, *J. Amer. Chem. Soc.*, 1974, **96**, 489.
[25] J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, ' The Tautomerism of Heterocycles,' Academic Press, New York, 1976.
[26] H. C. Van den Plas, ' Ring Transformations of Heterocycles,' Vol. 2, Academic Press, London, 1973.
[27] A. F. Hegarty and T. C. Bruice, *J. Amer. Chem. Soc.*, 1970, **92**, 6561, 6568.
[28] J. W. Bunting and D. D. Perrin, *J. Chem. Soc.* (*B*), 1967, 950.
[29] S. Nicholson, G. J. Stacey, and P. J. Taylor, *J.C.S. Perkin II*, 1972, 4.
[30] L. L. Schaleger and F. A. Long, *Adv. Phys. Org. Chem.*, 1963, **1**, 1.
[31] J. H. Lister, in ' The Chemistry of Heterocyclic Compounds,' Vol. 24, part 2, ch. 2, Wiley–Interscience, New York, 1971.
[32] M. I. Page, in *Chem. Soc. Rev.*, 1973, **2**, 295.
[33] P. J. Taylor, *J.C.S. Perkin II*, 1972, 1077.
[34] W. Borsche, *Chem. Ber.*, 1901, **34**, 4297.
[35] Sadtler Prism Spectrum No. 5705.
[36] Sadtler Prism Spectrum No. 8674.