Quinazoline Studies. Part XII.[1] Action of Acid and Alkali on Quinazoline

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Quinazoline was converted into 2-aminobenzaldehyde and its anhydro-polymers (the trimer, the tetramer, and the monoformyl-tetramer) by the action of hot dilute acid or alkali. The substance of high-molecular weight formed from quinazoline below pH 1·5 was found to be a polymer of the 3,4-adduct of the latter with 2-aminobenzaldehyde. The anhydro-dimer of 2-methylaminobenzaldehyde and the dimer of 2-aminobenzaldehyde methyl imide were found, on the evidence of the i.r., u.v., and n.m.r. spectra, to be 6,12-epoxy-5,11-dimethyldibenzo[*b,f*][1,5]diazocine (Va) and 6,12-methylimino-5*H*,11*H*-dibenzo[*b,f*][1,5]diazocine (Vc).

ALTHOUGH quinazoline (I) is well known to be stable in cold dilute acid and alkali (aqueous), the only observation of its behaviour in hot solution is that of Gabriel [2] who repeatedly evaporated it with hydrochloric acid on a steam-bath and observed that the residue was orange-red and contained ammonium chloride. He concluded that the quinazoline had partly decomposed to ammonia, formic acid, and 2-aminobenzaldehyde, the tetramer hydrochloride of which is reddish orange.[3,4]

In the present investigation, it was found that hot acid or alkali converted quinazoline into 2-aminobenzaldehyde and anhydro-polymers of the latter.[3-7] In detail, quinazoline, heated at 90° for 1 hour in aqueous solutions of graded hydrogen ion concentration, remained unchanged between pH 7 and 12; above and below this range it was destroyed to the extent shown in Figure 1.

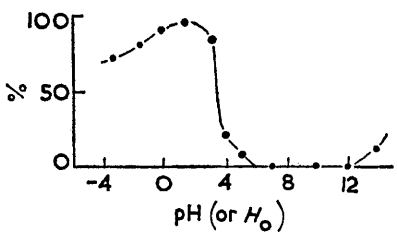


Figure 1 Destruction of quinazoline in 1 hr. at 90°

The ratio of 2-aminobenzaldehyde to quinazoline was determined, when no other product was formed, by measuring the intensities of the ^{1}H nuclear magnetic resonance (n.m.r.) signals (in aqueous buffer solutions as solvents) at τ 0·28 (due to the formyl group of the aldehyde) and 0·84 (due to H-4 of quinazoline,[8,9] which existed predominantly as the anhydrous neutral species in the above pH regions). The amounts of residual quinazoline in the more acidic solutions were found by extracting the neutralized reaction mixtures with dichloromethane.

In the pH range 4—5 and at pH 14, 2-aminobenzaldehyde was the only product (on the evidence of paper chromatography and n.m.r.). Between pH 1·5 and 3, 2-aminobenzaldehyde was partly converted into the anhydro-trimer (IIa),[3-7] the anhydro-tetramer (IIb),[3,4,6,7] and monoformyl-tetramer (IIc); [4] below pH 2, a new polymer was formed which will be referred to as substance Q. The Table gives the yields of degradation

Decomposition products from quinazoline after refluxing for 1 hour

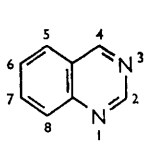
Products	pH 2·0	pH 1·5
2-Aminobenzaldehyde	30%	10%
Trimer	31	2
Tetramer	9	2
Monoformyl-tetramer	6	5·3
Substance Q (sulphate)	17	72

products obtained when quinazoline was refluxed for 1 hour in sodium hydrogen in sulphate buffer solutions at pH 2·0 and 1·5 (all the quinazoline was destroyed under these conditions). The Table also shows that, as the hydrogen ion concentration was increased, the yields of 2-aminobenzaldehyde and its anhydro-polymers decreased and that of substance Q increased proportionally. It had already been shown [3,4] that the anhydro-trimer was the sole product of the action of *cold* dilute acid (pH 1) on 2-aminobenzaldehyde. However, we found that when the amino-aldehyde was boiled with dilute hydrochloric acid (pH 1) for 1 hour, a small proportion of the tetramer was also formed. The tetramer is not likely to have been formed through the bright red hydrochloride of the isomeric tetramer [4] which is formed in concentrated acid. It was more likely formed by nucleophilic replacement of the hydroxy-group in the trimer with the amino-group of another molecule of 2-aminobenzaldehyde [cf. formulae (IIa) and (IIb)]. The monoformyl-tetramer is most likely derived from this tetramer and the formic acid produced during the above decomposition of quinazoline.

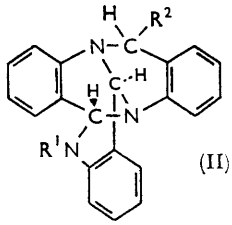
The Structure of Substance Q.—Substance Q, pale yellow and of high molecular weight, was obtained as a salt when quinazoline was boiled with partly neutralized sulphuric acid (pH 1·5) or 0·1N-hydrochloric acid. The neutral species, formed on basification with aqueous sodium carbonate, was readily converted into the hydrochloride, sulphate, and picrate. A formula, $(C_{15}H_{13}N_3O)_n$, calculated from the elemental analysis,

[1] Part XI, W. L. F. Armarego and J. I.C. Smith, *J. Chem. Soc.* (*B*), 1968, 407.
[2] S. Gabriel, *Ber.*, 1903, **36**, 800.
[3] F. Seidel, *Ber.*, 1926, **59**, 1894.
[4] A. Albert and H. Yamamoto, *J. Chem. Soc.* (*B*), 1966, 956.
[5] E. Bamberger, *Ber.*, 1927, **60**, 314.
[6] F. Seidel and W. Dick, *Ber.*, 1927, **60**, 2018.
[7] S. G. McGeachin, *Canad. J. Chem.*, 1966, **44**, 2323.
[8] W. L. F. Armarego and R. E. Willette, *J. Chem. Soc.*, 1965, 1258.
[9] A. R. Katritzky, R. E. Reavill, and F. J. Swinbourne, *J. Chem. Soc.* (*B*), 1966, 351.

was consistent with an equimolar adduct of quinazoline and 2-aminobenzaldehyde. The broadness of the peaks in the i.r. and the n.m.r. spectra suggested that substance Q would most likely be a polymer of high molecular weight. It possessed hydroxy- and, possibly, imino-groups ($\nu_{max.}$ 3300 cm.$^{-1}$, broad and strong), but no carbonyl group (no strong absorption at 1800—1630



(I)



(II)

a: $R^1 = H$, $R^2 = OH$
b: $R^1 = H$, $R^2 = NH{\cdot}C_6H_4{\cdot}CHO(o)$
c: $R^1 = CHO$, $R^2 = NH{\cdot}C_6H_4{\cdot}CHO(o)$

cm.$^{-1}$). The n.m.r. spectrum (Figure 2) showed only two broad multiplets at τ 4·2—4·8 and 2·5—3·5 (the ratio of the intensities was approximately 1 : 4).

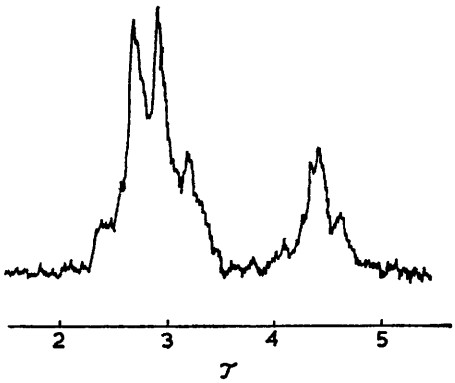


Figure 2 ^{1}H N.m.r. spectrum of substance Q in CD_3OD with a trace of D_2O

Because quinazoline is very reactive towards nucleophilic reagents [10-16] which attack position 4, it is suggested that substance Q is a polymer of the 1 : 1 adduct (IIIa) of quinazoline and 2-aminobenzaldehyde (the monomer is described below). Taking account of the known value τ 2·89 for the H-2 signal in the n.m.r. spectrum of 3,4-dihydroquinazoline in methanol,[17] the proton signal of the formamidino-group in (IVa) should be masked by the aromatic ring protons (at τ 2·5—3·5). Thus, the above spectroscopic results are compatible with the proposed structure (IVa).

Elemental analyses of the hydrochloride, sulphate, and picrate were compatible with their being mono-salts of structure (IVa); this assignment was supported by the i.r. (*e.g.* 3200, broad and medium, OH and NH; 1660 cm.$^{-1}$, strong, a formamidinium group) and the n.m.r. spectra [three broad multiplets at τ 1·3—1·8 (1H, formamidinium), 1·9—3·5 (8H, aromatic ring protons), and 3·4—4·2 (2H, aliphatic protons), in a mixture of pentadeuteriopyridine and deuterium oxide as solvent] of the above salts. Thus protonation takes place in the quinazoline ring.

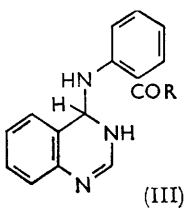
Acetylation of substance Q (in acetic anhydride–pyridine mixture at 25°) gave a diacetyl derivative on the evidence of elemental analysis. The i.r. spectrum showed the presence of *O*-Ac and *N*-Ac groups (at 1720 and 1690—1660) but no hydroxy-group (no absorption at 3500—3100 cm.$^{-1}$); all peaks in the spectrum were unusually broad like those of the starting material and its salts. The n.m.r. spectrum in hexadeuteriodimethyl sulphoxide consisted of broad multiplets at τ 7·5—8·3 (two acetyl groups), 2·0—3·6 (*ca.* 10H, aromatic ring and aliphatic protons), and 1·3 (1H, the formamidino-group), supporting structure (IVb) for the diacetyl derivative. The molecular weight of the diacetyl compound was found to be about 1400, which led to $n = 4$ for the molecular formula of (IVb). Although substance Q and its salts were too poorly soluble to permit molecular weight determination, it is unlikely that any skeletal change took place during the gentle acetylation. Hence, the most likely structure for substance Q is a tetramer of the monomeric unit (IIIa). Unusual broadness of the i.r. absorption peaks suggests a population of polymers, in which one species (the tetramer) is predominant. Although a medium—weak absorption peak was present at 1655 cm.$^{-1}$ in the i.r. spectrum, absence of a (terminal) formyl group was indicated by the lack of any change in the spectrum after the specimen had been submitted to the standard process for conversion into an acetal with triethyl orthoformate. This result suggests that the polymer is cyclic.

The mass spectrum of substance Q sulphate was measured by Dr. J. A. Wunderlich, C.S.I.R.O., Melbourne. It showed mainly the intense peaks due to quinazoline and its fragments, all below *m/e* 130 (for quinazoline, see ref. 18). Although there were weak peaks even above *m/e* 500, the molecular ion peaks could not be confirmed.

A reaction pathway for the formation of substance Q was sought by periodical chromatographic sampling of an acidic solution of quinazoline (pH 1) maintained at 87°. This exhibited first an intense blue fluorescent spot (under u.v. light) which was replaced in later samplings by the dark spot due to substance Q (see Experimental part). In stronger acid (*e.g.* 10N-hydrochloric acid) the proportion of the initial product to substance Q seemed to be higher than at pH 1. The same blue spot gradually

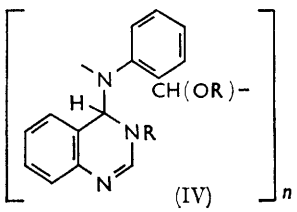
[10] T. Higashino, *J. Pharm. Soc. Japan*, 1960, **80**, 245.
[11] W. L. F. Armarego and J. I. C. Smith, *J. Chem. Soc.*, 1965, 5360.
[12] A. Albert, W. L. F. Armarego, and E. Spinner, *J. Chem. Soc.*, 1961, 2689.
[13] T. Teshigawara, E. Hayashi, and T. Tono, *Jap. Pat.*, 8133 (1963) (*Chem. Abs.*, 1963, **59**, 11527).
[14] E. Hayashi and T. Higashino, *Chem. and Pharm. Bull.* (*Japan*), 1964, **12**, 1111.
[15] E. Hayashi and T. Higashino, *Chem. and Pharm. Bull.* (*Japan*), 1965, **13**, 291.
[16] T. Higashino, *Chem. and Pharm. Bull.* (*Japan*), 1962, **10**, 1043.
[17] A. Albert, *J. Chem. Soc.* (*B*), 1966, 427.
[18] T. J. Batterham, A. C. K. Triffett, and J. A. Wunderlich, *J. Chem. Soc.* (*B*), 1967, 892.

appeared when quinazoline was stirred with one molecular equivalent of 2-aminobenzaldehyde (but not with the anhydro-trimer) in dilute hydrochloric acid (pH 0·2) at 3°; after 1 day a considerable amount of substance Q was obtained together with the anhydro-trimer. [On dissolving substance Q in a large amount of 1N-hydrochloric acid, the blue fluorescing substance (amongst



(III)

a: R = H
b: R = Me



(IV)

a: R = H
b: R = Ac

others) was produced]. The fact that the spot due to the initial product appeared only after heating the acidified solution of quinazoline distinguished this product from the quinazoline hydrochloride monohydrate obtained by the action of hydrogen chloride on quinazoline in ether [12] (different also from 2-formamidobenzaldehyde,[19] which gave a dark spot on paper chromatograms). Because quinazoline is stable and 2-aminobenzaldehyde gives only the anhydro-trimer in dilute acid at 25°, the initial product is, most likely, the adduct (IIIa) formed by a reaction between the amino-aldehyde and quinazoline under the above conditions. The blue fluorescent spot on a paper chromatogram which had been developed two-dimensionally with 3% aqueous ammonium chloride and light petroleum–methanol as solvents (see Experimental part) was cut off and eluted with water. The ultraviolet spectrum of the solution (pH 5·0; $\lambda_{max.}$ 216, 258sh, 275, and 373 mμ; E 1·05, 0·368, 0·363, and 0·108) closely resembled that of the adduct (IIIb) (at pH 4·2; see below), thus supporting the above assumption. Several attempts were made to isolate this intermediate, but it always polymerized during the separation.

To prevent this polymerization, a condensation of quinazoline and 2-aminobenzaldehyde methyl imide was attempted in hot, aqueous triethylamine. But the imide gave the dimeric compound (Vc) (75% yield) (see below) and the quinazoline remained unchanged.

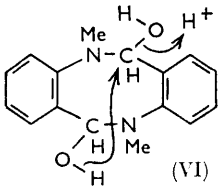
The condensing properties of 2-aminoacetophenone were then examined in the belief that it would prove less reactive than 2-aminobenzaldehyde. 2-Aminoacetophenone was stable in dilute acid under the conditions which convert 2-aminobenzaldehyde into the trimer. Accordingly, when molar equivalents of quinazoline and the ketone were stirred in acid (pH 1·5) at 25°, the 1 : 1 adduct (IIIb) was obtained as the main product. On a paper chromatogram with various developing solvents, this material gave an intense blue fluorescent spot. The adduct (IIIb) showed a characteristic i.r. absorption at 3400, 3300 (both medium, 2 NH), and 1650 cm.$^{-1}$ (strong, C=O). The n.m.r. spectrum in hexadeuteriodimethyl sulphoxide with a trace of deuterium oxide was consistent with the structure (IIIb); *i.e.*, singlets at τ 7·53 and 4·42 (the acetyl and H-4 groups, respectively), a doublet at 2·34 (J 1·5 c./sec., the N=C*H*–N), and a multiplet at 2·5—3·4 (8H, aromatic ring protons). The ultraviolet spectra at various pH values and the two cationic pK_a values are consistent with the structure (IIIb), taking into account those of 3,4-hydrated quinazoline [12,20] and 2-aminoacetophenone.[21–23] Polymerization of this adduct in dilute acid is probably prevented by the steric hindrance which the acetyl methyl group exerts.

As the adduct (IIIa) is an analogue of 2-methylaminobenzaldehyde, the action of acid on the latter was examined. It was found that the action of 1N-hydrochloric acid on the aldehyde at room temperature gave the anhydro-dimer (Va) (see below). However, when 2-methylaminobenzaldehyde was refluxed with this acid for 1 hour, a substance of higher melting point (above 220°, gradually decomposing) was formed; although a considerable amount of the starting material remained unchanged at the end of the above period, no dimer was detected. Very broad absorption bands in the i.r. spectrum suggested that the product would probably be a polymer of higher molecular weight; the determination of the structure of the substance has not been sought. The polymerization of the adduct (IIIa) in hot, dilute acid to give substance Q may have taken place in a manner similar to that of 2-methylaminobenzaldehyde under almost the same conditions.

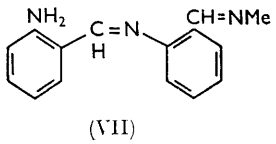
Structures of the Dimers of 2-Methylaminobenzaldehyde and 2-Aminobenzaldehyde Alkyl Imide.—Bamberger [24] obtained an anhydro-dimer ($C_{16}H_{16}N_2O$) of 2-methylaminobenzaldehyde as a by-product (8% yield) during the preparation of the monomer (66% yield) by the action of dimethyl sulphate on anthranil. He determined the molecular weight of the dimer ebullioscopically in acetone, but formulated no structure. In the present reinvestigation, the same dimer was obtained by the action of 1N-hydrochloric acid on 2-methylaminobenzaldehyde at room temperature as mentioned above. The lack of absorption at 3500—3100 and 1800—1620 cm.$^{-1}$ in the i.r. spectrum indicated that the dimer possessed neither a hydroxy- nor a carbonyl group. The n.m.r. spectrum in deuteriochloroform showed a singlet (6H) at τ 6·90 due to two equivalent *N*-methyl groups, a singlet (2H) at 4·41, and a complicated multiplet (8H) at 2·8—3·5 arising from aromatic ring protons. The singlet at τ 4·41 is most likely due to two equivalent methine protons similar to the aliphatic protons of both the trimer (IIa) and the tetramer (IIb) of 2-aminobenzaldehyde (for the n.m.r. spectra of the trimer and the tetramer, see ref. 4). The above spectral results led

[19] P. Friedländer and C. F. Göhring, *Ber.*, 1884, **17**, 456.
[20] A. Albert, W. L. F. Armarego, and E. Spinner, *J. Chem. Soc.*, 1961, 5267.
[21] A. E. Lutskii and V. V. Dorofeev, *Zhur. obshchei Khim.*, 1957, **27**, 1064.
[22] W. F. Forbes and I. R. Leckie, *Canad. J. Chem.*, 1958, **36**, 1371.
[23] J. M. Vandenbelt, C. Henrich, and S. G. Vanden Berg, *Analyt. Chem.*, 1954, **26**, 726.
[24] E. Bamberger, *Ber.*, 1904, **37**, 966.

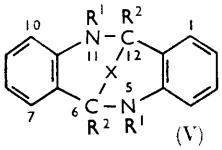
to the only possible structure (Va) for the anhydro-dimer of 2-methylaminobenzaldehyde. Another compound with this ring system has been reported,[25] namely the acid (Vb) obtained by refluxing isatin with aqueous potassium hydroxide, followed by acidification. The ultraviolet spectrum of the dimer (Va) in ethanol (see Experimental part) resembled that of *N*-methyl-*o*-toluidine in the same solvent ($\lambda_{max.}$ 242 and 292 mμ; log ε 3·96 and 3·27),[26-28] and the extinction coefficients of the former were (as expected) approximately twice as large as those of the toluidine. The singlet at τ 4·41 in the n.m.r. spectrum is assigned to H-12 and H-6. The dimer could be formed in cold dilute acid from a simpler cyclic dimer, shown in formula (VI), by acid-catalysed elimination of a hydroxy-group, followed by internal ether formation (or both reactions may take place concertedly) as shown by the arrows in the formula.



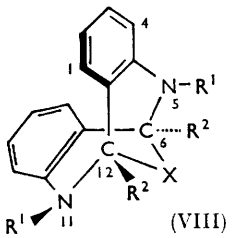
(VI)



(VII)



(V)



(VIII)

a: R^1 = Me, R^2 = H, X = O
b: R^1 = H, R^2 = CO_2H, X = O
c: R^1 = R^2 = H, X = NMe
d: R^1 = R^2 = H, X = NEt
e: R^1 = CHO, R^2 = H, X = N·C_6H_4·CHO(*o*)

Gabriel and Colman [29] reported a compound ($C_{15}H_{15}N_3$) which was formed, along with formic acid and 2-aminobenzaldehyde, on distillation of 3-methylquinazolinium hydroxide with aqueous potassium hydroxide. They determined the molecular weight ebullioscopically (in acetone) and assigned the structure (VII) on the evidence of the elemental analysis. On setting aside 2-aminobenzaldehyde methyl imide in the air or, more quickly, upon treatment of the imide with concentrated hydrochloric acid, the same compound was formed together with one molecular proportion of methylamine. Also the ethyl analogue ($C_{16}H_{17}N_3$) was obtained from 2-aminobenzaldehyde ethyl imide by similar treatment. Substances with the same melting points as these were obtained in the present reinvestigation and will be referred to as the anhydro-dimers of 2-aminobenzaldehyde methyl imide and ethyl imide (as indicated by the analytical figures). 2-Aminobenzaldehyde methyl imide itself had characteristic i.r. absorption bands at 3440 and 3280 (strong, NH_2), and at 1640 cm.$^{-1}$ (strong; C=N). However, the dimers had imino-groups but no carbonyl or imido-group [3370 and 3310 (medium) for the methyl, and 3380 and 3290 (medium) for the ethyl analogue; no absorption at 1800—1610 cm.$^{-1}$ for either compound]. The n.m.r. spectrum of the methylamino-dimer in perdeuteriodimethyl sulphoxide–deuteriochloroform (1 : 2) consisted of a singlet at τ 7·62 (3H, an aliphatic *N*-Me), a slightly broadened doublet at 5·25 (*J* 2 c./sec., 2H), a very broad doublet at 3·97 (*J* *ca.* 2, 2H), and a complicated multiplet from the aromatic ring protons at 2·8—3·6. After deuterium exchange the doublet at τ 5·25 collapsed to a sharp singlet with simultaneous disappearance of the doublet at 3·97. These spectral results led to the only possible structure (Vc) for the methylamino-anhydro-dimer of 2-aminobenzaldehyde. The doublets at τ 5·25 and 3·97 in the n.m.r. spectrum are assigned to two equivalent aliphatic (H-6 and H-12) and imino- (NH-11 and NH-5)protons, respectively. The ethyl analogue obviously has the structure (Vd). The n.m.r. data are recorded in the Experimental part. These are, most likely, formed by a similar reaction mechanism to that of the formation of the dimer (Va) [see formula (VI)]. The u.v. spectra of both dimers (Vc) and (Vd) are, as expected, almost identical with that of (Va) in the same solvent (see the Experimental part). The diformyl-trimer of 2-aminobenzaldehyde [4] (Ve) is the only reported compound which has the same ring system as those of the above dimers. A steric model of the dimers (Va—e) is shown in formula (VIII).

EXPERIMENTAL

Microanalyses were performed by Dr J. E. Fildes and her staff. Compounds for analysis were dried over P_2O_5 at 80°/0·01 mm. for 1 hr., unless otherwise specified.

Paper chromatography was carried out on Whatman No. 1 (or sometimes No. 4 for quicker sampling of easily resolving mixtures) sheets which were developed with 3% aqueous ammonium chloride or light petroleum (b.p. 80—100°) saturated with methanol. Thin-layer chromatography on silica gel (Kieselgel G) (0·2 or 0·5 mm. in thickness) was used with chloroform–acetone (9 : 1) as developer. Chromatograms were examined under two u.v. lamps with principal emission at 365 and 254 mμ respectively.

Ultraviolet spectra were measured on a Shimadzu model RS 27 recording spectrophotometer or a Perkin-Elmer Spectracord model 4000A, and the wavelength and intensity of each maximum checked with an Optical manual instrument. Infrared spectra of solids (Nujol mulls) were taken with a Unicam SP 200 spectrophotometer. ^{1}H n.m.r. measurements were made at 33·3° with a 60 Mc./sec. Perkin-Elmer spectrometer R 10.

Action of Sodium Hydrogen Sulphate Buffer on Quinazoline.—(*a*) At pH 2·0. A solution of quinazoline [30] (0·45 g.) in 1N-sodium hydrogen sulphate (31 ml.) was refluxed for 1 hr. After cooling, the gummy deposit was transformed

[25] G. Stefanovic, L. Lorenc, R. I. Mamuzić, and M. L. Mihailović, *Tetrahedron*, 1959, **6**, 304.
[26] A. Wohl, *Bull. Soc. chim. France*, 1939, **6**, 1312.
[27] P. Grammaticakis, *Bull. Soc. chim. France*, 1949, **16**, 134.
[28] P. Ramart-Lucas and J. Klein, *Bull. Soc. chim. France*, 1949, **16**, 454.
[29] S. Gabriel and J. Colman, *Ber.*, 1904, **47**, 3643.
[30] W. L. F. Armarego, *J. Appl. Chem.*, 1961, **11**, 70.

to a powder by scratching; the suspension was stirred for 5 hr. and set aside for 12 hr., then chilled. The precipitate, filtered off and washed with a little cold water, was stirred with chloroform (20 ml.) for 0·5 hr. at 25°. The substance Q sulphate (see below) was obtained on filtration and washing with chloroform. The filtrate was passed through a silica gel column and eluted with chloroform. Removal of the solvent *in vacuo* gave a yellow powder (0·29 g.), which consisted of 2-aminobenzaldehyde and its anhydro-polymers (chromatography; for R_F values, see ref. 4). The powder, warmed with ethanol (1 ml.) then chilled, deposited the trimer as a pale yellow powder, m.p. 233—234° after one recrystallization from acetone. The filtrate was subjected to thin-layer silica gel chromatography, the three bands, R_F 0·6—0·7, 0·8, and 0·9, which exhibited respectively a dark, green, and blue (fluorescent) colour under 356 mμ light, were collected, eluted with chloroform, and afforded respectively the trimer, the tetramer (m.p. 233—235°), and the monoformyl-tetramer (m.p. 269—271°). The yields of the above products are recorded in the Table. Although 2-aminobenzaldehyde was not isolated as a pure material, the approximate yield was calculated by subtracting the amounts of the anhydro-polymers from that of the above yellow powder (*i.e.* the chloroform-soluble part).

(*b*) *At* pH 1·5 (partly neutralised 1N-sulphuric acid). The same procedures as above were followed, and the results are recorded in the Table.

Substance Q.—Quinazoline (2·6 g.) in 0·1N-hydrochloric acid (150 ml.; the solution, pH 1·1) was refluxed for 1 hr. and set aside overnight at 5°, depositing *substance Q hydrochloride* (55%) as a pale yellow powder which after two recrystallizations from 0·01N-hydrochloric acid had m.p. 281—283° (decomp.) [Found, for material dried over KOH–$CaCl_2$ at 5°/20 mm. for 4 days: C, 59·65; H, 5·0; Cl, 14·95; N, 13·75. $(C_{15}H_{13}N_3O,1{\cdot}3HCl)_n$ requires C, 60·3; H, 4·85; Cl, 15·4; N, 14·05%]. The hydrochloride was hygroscopic and decomposed on drying at a temperature higher than 5°.

On stirring substance Q hydrochloride (50 mg.) with 1N-sodium hydrogen sulphate (pH 1·8) (7·5 ml.) at 25° for 1 hr., the *substance Q hemisulphate* was obtained as a pale yellow powder after two recrystallizations of the precipitate from boiling water, m.p. *ca.* 270° (gradual decomp.) [Found, for material dried at 105°/0·01 mm.: C, 59·8; H, 5·25; N, 13·45; S, 5·3. $(C_{15}H_{13}N_3O,\frac{1}{2}H_2SO_4)_n$ requires C, 60·0; H, 4·7; N, 14·0; S, 5·35%].

Substance Q *picrate* was obtained as a crystalline powder by stirring substance Q hydrochloride with a saturated aqueous solution of picric acid (together with a trace of hydrochloric acid) at 25° for 1 hr., then recrystallizing the deposit from ethylene glycol monomethyl ether–ethanol, m.p. 200—210° (gradually foaming) [Found: C, 53·25; H, 3·85; N, 16·95. $(C_{15}H_{13}N_3O,C_6H_3N_3O_7)_n$ requires C, 52·5; H, 3·35; N, 17·5%].

A suspension of the above hydrochloride or sulphate in 10% aqueous sodium carbonate was stirred at 25° for 2 hr.; the precipitate was filtered off and recrystallized twice from ethanol–water, giving *substance Q* as a pale yellow powder (85—90%), m.p. *ca.* 260° (gradual decomp.) [Found, for material dried at 105°/0·01 mm.: C, 71·8; H, 5·25; N, 16·2. $(C_{15}H_{13}N_3O)_n$ requires C, 71·7; H, 5·2; N, 16·7%].

Acetylation of Substance Q.—The substance (0·10 g.), dissolved in a mixture of acetic anhydride and pyridine (1 : 1) (2 ml.), was set aside at 25° for 2 days. The solvent was removed by repeatedly taking the preparation to dryness *in vacuo* in the presence of ethanol. The residue, after two recrystallizations from propan-2-ol, gave the *diacetyl derivative* as an almost colourless crystalline powder (68%), m.p. 210—215° (gradually foaming) [Found: C, 68·3; H, 5·2; N, 12·0%; *M*, 1400, 1410 (chloroform in a vapour pressure osmometer Mechrolab model 301A at 37°). $(C_{19}H_{17}N_3O_3)_4$ requires C, 68·05; H, 5·1; N, 12·5%; *M* 1340].

Chromatographic Study of the Degradation of Quinazoline.—Quinazoline (50 mg.), dissolved in 0·1N-hydrochloric acid (20 ml.; pH 1), was heated at 87° (bath), and the contents were periodically checked by paper chromatography with 3% aqueous ammonium chloride. The sky-blue fluorescent spot (R_F 0·65) was gradually seen after 30 min. heating; then a dark elongated spot (R_F 0·2—0·4) due to substance Q appeared after 60 min., when a large amount of quinazoline was still present (R_F 0·75, dark spot).

Quinazoline and 2-Aminobenzaldehyde.—The powdered aldehyde (0·24 g.) was added at 3° to a solution of quinazoline (0·26 g., 1 equiv.) in 1N-hydrochloric acid (15 ml.; pH 0·2), and the mixture was vigorously stirred for 7·5 hr. and set aside overnight at 3°. The precipitate, which consisted mainly of the amino-aldehyde and its anhydro-trimer (chromatography) was filtered off and recrystallized from ethanol, giving the trimer (46%) (identified by i.r.). To the above filtrate, diluted to 40 ml. with water, solid potassium hydrogen sulphate (2·0 g.) was added, and the mixture, after stirring at 25° for 1 hr. deposited substance Q as sulphate (30%).

Quinazoline and 2-Aminoacetophenone.—This acetophenone [31,32] (135 mg.) and quinazoline (130 mg., 1 equiv.) were stirred in 1N-sulphuric acid (2·5 ml.; pH 1·8) at 25° for 3 days; the contents were brought to pH 11 with 10% aqueous sodium carbonate–sodium hydrogen carbonate (1 : 1) and extracted thoroughly with chloroform. After being washed with cold water, the extract was evaporated to dryness *in vacuo*, and the residue was twice recrystallized from chloroform–benzene, giving 4-o-*acetylanilino*-3,4-*dihydroquinazoline* as pale yellow prisms (45%), m.p. 193—195° (Found: C, 72·6; H, 5·7; N, 15·7. $C_{16}H_{15}N_3O$ requires C, 72·45; H, 5·7; N, 15·85%), R_F 0·65 (paper/3% aqueous NH_4Cl; a sky-blue fluorescent spot), $\lambda_{max.}$ (pH 11·0) 234, 256sh, 290sh, and 363 mμ (log ε 4·46, 4·07, 3·84, and 3·59), $\lambda_{max.}$ (pH 4·2), 226, 252sh, 270sh, and 362 mμ (log ε 4·47, 4·11, 4·00, and 3·60), $\lambda_{max.}$ (H_0 −0·5) 222, 244sh, and 282 mμ (log ε 4·46, 4·06, and 3·77), pK_a (spectrophotometric) *ca.* 8·8 and 1·1.

The Anhydro-dimer of 2-Methylaminobenzaldehyde.—The methylaminoaldehyde [33] (0·45 g.) was stirred with 1N-hydrochloric acid (3 ml.) at 25—30° for 2 days. The precipitate was filtered off, washed with cold water, and dried over $CaCl_2$ at 25°/20 mm., giving the crude dimer (94%). Two recrystallizations from ethanol gave analytically pure material (88%), m.p. 138—139·5° (lit.,[20] 139·5—140° from ligroin) [Found: C, 76·2; H, 6·1; N, 11·2%; *M*, 273, 278 (by vapour pressure osmometer in chloroform at 37°). Calc. for $C_{16}H_{16}N_2O$: C, 76·15; H, 6·4; N, 11·1%; *M*. 252·3], $\lambda_{max.}$ (95% EtOH) 246 and 299 mμ (log ε 4·26 and 3·51).

2-Aminobenzaldehyde and Methylamine.—The freshly pre-

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[32] J. C. E. Simpson, C. M. Atkinson, K. Schofield, and O. Stephenson, *J. Chem. Soc.*, 1945, 646.
[33] G. B. Barlin, *J. Appl. Chem.*, 1962, **12**, 148.

pared aldehyde (3·5 g.) and aqueous methylamine (40%; 6 ml.) were shaken for 2 hr. at 20°, then heated on a steam-bath for 15 min. The lower layer (a pale yellow oil) was separated and, after drying over K_2CO_3, distilled, giving 2-aminobenzaldehyde methyl imide (40%) as a pale yellow oil, b.p. 80°/2·0 mm. The material should be kept in a refrigerator (5°). The residue of the above distillation, after two recrystallizations from benzene, gave the anhydro-dimer of the 2-aminobenzaldehyde methyl imide as prisms (6%), m.p. 192—194° (lit.,[25] 189—190°) [Found, for material dried at 30°/0·01 mm. for 1·5 hr.: C, 75·9; H, 6·45; N, 17·5%; *M* (osmometer), 268. Calc. for $C_{15}H_{15}N_3$: C, 75·9; H, 6·35; N, 17·7%; *M*, 237·4], $\lambda_{max.}$ (95% EtOH) 243, 257sh, and 296 mμ (log ε 4·27, 3·74, and 3·58).

Anhydro-dimer of 2-Aminobenzaldehyde Ethyl Imide.—Freshly prepared 2-aminobenzaldehyde (1·0 g.) and aqueous ethylamine (33%; 2 ml.) were vigorously stirred at 30° for 2 hr., then warmed on a steam-bath for 30 min. The cooled contents were thoroughly extracted with ether and the extract (dried over Na_2SO_4) was evaporated to dryness. The oily residue solidified after setting aside at about 30° in a watch glass for 1 day, and gave, on two recrystallizations from benzene, the dimer as prisms (59%), m.p. 152·5—154° (lit.,[25] 152—153°) [Found, for material dried at 30°/0·01 mm. for 2 hr.: C, 76·65; H, 6·7; N, 16·5%; *M* (osmometer), 282. Calc. for $C_{16}H_{17}N_3$: C, 76·45; H, 6·8; N, 16·7%; *M*, 251·3], $\lambda_{max.}$ (95% EtOH) 243, 257sh, and 297 mμ (log ε 4·27, 4·76, and 3·59), τ ([$^2H_6$]DMSO–$CDCl_3$, 1 : 3) 8·88t (*J* 7 c./sec., CH_3), 7·47q (*J* 7, CH_2), 5·14d* [*J* 2, H-6,12], 4·23m* (H-11 and NH-5), and 2·8—3·6m (the aromatic protons).

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* Deuterium exchange caused the disappearance of the multiplet with simultaneous collapse of the doublet to a singlet.