Thermolysis of 1,2,3-Benzotriazin-4(3*H*)-one

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The thermolysis of 1,2,3-benzotriazin-4(3*H*)-one gives quinazolino[3,2-*c*][1,2,3]benzotriazin-8-one, identified by hydrolysis and synthesis. Nucleophilic replacement reactions of the simple benzotriazinone readily provide substituted *o*-aminobenzoyl derivatives and ring-closed products resulting from these derivatives.

RECENT observations on the decomposition of 1,2,3-benzotriazinones [1-3] have prompted us to report our own observations on the thermal decomposition of 1,2,3-benzotriazin-4(3*H*)-one (I; R = H). When a solution of this triazinone in diethylene glycol dimethyl ether (b.p. 162—164°) was heated at reflux for periods of up to 2 hr. it yielded the previously unknown quinazolino-[3,2-*c*][1,2,3]benzotriazin-8-one (II) in 70% yield. Prolonged refluxing, or alternatively, prolonged heating of this product in aqueous alcohol afforded 2-phenylquinazolin-4(3*H*)-one (III; R′ = H); the same quinazolone was obtained by treating the tetracyclic product (II) with boiling titanium(III) chloride solution.[4] The assignment of structure (II) is consistent with analytical, i.r., and mass spectral data. Strong carbonyl absorption at 1720 cm.$^{-1}$ is characteristic of 3-acyl-1,2,3-benzotriazin-4-ones.[5] The fragmentation of the molecular ion (*m/e* 248) gives rise to an ion at *m/e* 220 as the base peak ($M - N_2$),[6] which loses carbon monoxide to give an ion at *m/e* 192.

Since compound (II) retains the masked diazonium system of a 1,2,3-benzotriazine it would be expected to react with reagents that ordinarily react with diazonium compounds.[4] Indeed treatment with β-naphthol in warm strongly acidic solution gave a bright red azo-dye, analysis of which agreed with structure (IV). Treatment of compound (II) with alcoholic sodium hydroxide yielded a small amount of the benzotriazinone (I; R = H) and anthraniloylanthranilic acid (VII). Prolonged treatment with alkali afforded anthranilic acid (VIII). Formation of these hydrolysis products is readily explained in terms of hydrolysis of the imino-linkage to generate the 3-(*o*-aminobenzoyl)benzotriazinone (V), which then suffers attack by hydroxide ion at the C-4 amide carbonyl group (*i.e.* cleavage at *a*) to produce the diazoamino-compound (VI). This can lose nitrogen [7,8] to yield anthraniloylanthranilic acid. Competing cleavage at *b* would yield the parent triazinone (I; R = H). The isomeric quinazolino[1,2-*c*]benzotriazine (IX) would be expected to yield *N*-(*o*-carboxyphenyl)anthranilamide (X), or the corresponding acid, under these conditions.

Finally, compound (II) was synthesised by diazotisation of 2-(*o*-aminophenyl)quinazolin-4(3*H*)-one (XI); it is well established [9] that N-3 of a quinazoline ring participates in intramolecular diazonium coupling.

An earlier investigation [3] demonstrated that 1,2,3-benzotriazin-4(3*H*)-one decomposes in boiling 1-methylnaphthalene (b.p. 245°) to give 2-(*o*-aminophenyl)-4*H*-3,1-benzoxazin-4-one (XIII), which is considered to arise by a Diels–Alder reaction involving the keten imine (XII) as a heterodiene and the carbonyl

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[2] D. H. Hey, C. W. Rees, and A. R. Todd, *J. Chem. Soc.* (*C*), 1968, 1028.
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[4] H. Meyer, *Annalen*, 1907, **351**, 267.
[5] M. S. Gibson and A. W. Murray, *J. Org. Chem.*, 1962, **27**, 4083.
[6] J. C. Tou, L. A. Shadoff, and R. H. Rigterink, *Org. Mass Spectrometry*, 1969, **2**, 355.
[7] H. Mehner, *J. prakt. Chem.*, 1901, **63**, 241.
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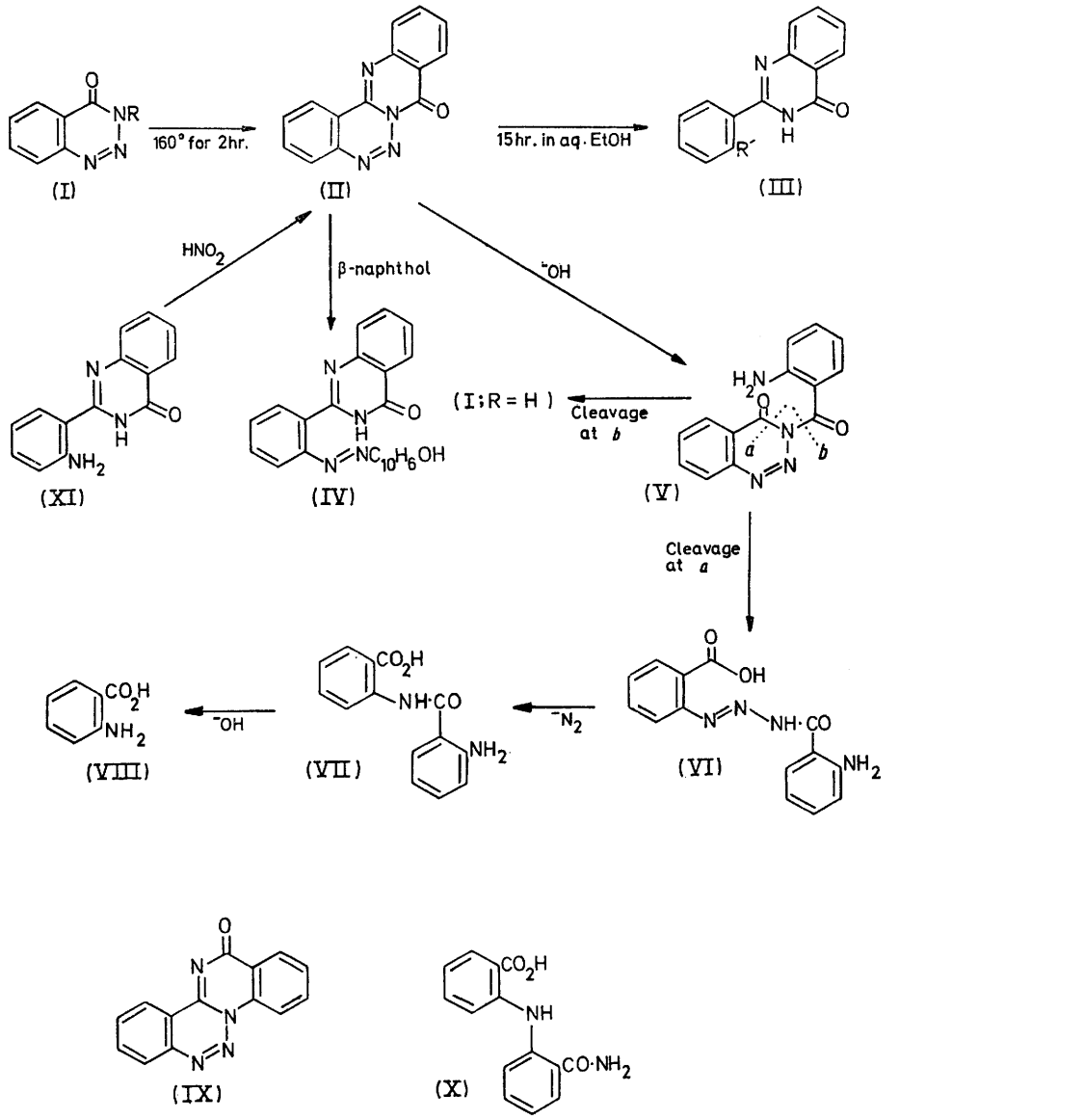
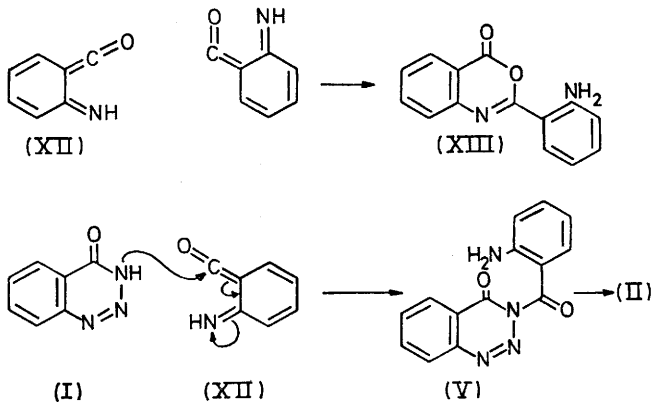


group as the dienophile. Such a keten imine has been postulated as an intermediate in the photolysis of benzotriazinones [10,11] and the mechanism of its formation has been substantiated by ^{15}N-labelling.[8] The i.r. spectrum of the photolysate shows absorption at 1830 cm.$^{-1}$, confirming the presence of a keten.

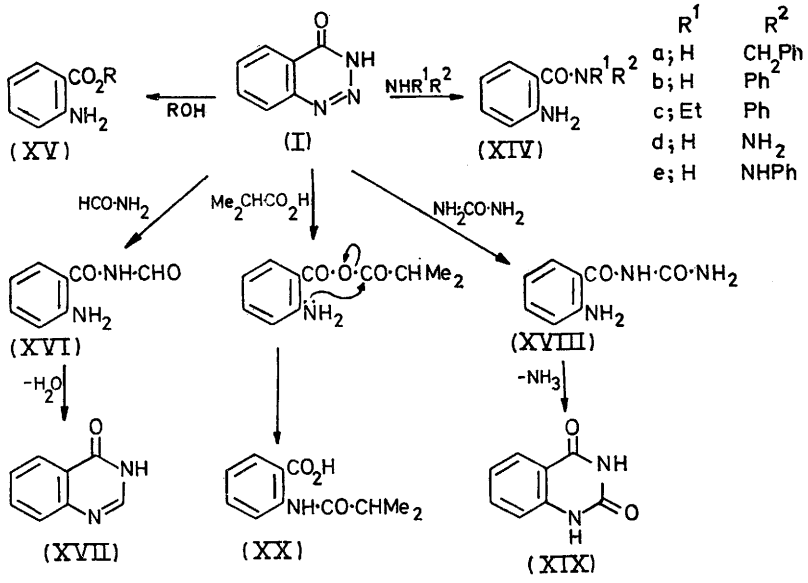
Although the benzoxazinone (XIII) has not been isolated under the conditions used in this laboratory, the formation of (II) can likewise be explained in terms of an intermediate keten imine, which reacts with a second molecule of the triazinone [see (I) + (XII) ⟶ (V) ⟶ (II)]. Alternatively, one molecule of the triazinone, acting as a nucleophile, could attack a second molecule at the amide carbonyl group, in a manner similar to the attack of hydroxide ion at C-4 in (V). Subsequent loss of nitrogen would yield the 3-(*o*-aminobenzoyl)benzotriazinone (V), and cyclodehydration of this amino-compound would lead to (II). Such a scheme involves anionic or nucleophilic attack at the amide carbonyl group in a benzotriazinone. Such attack is



[10] G. Ege, *Angew. Chem. Internat. Edn.*, 1965, **4**, 699.
[11] E. M. Burgess and G. Milne, *Tetrahedron Letters*, 1966, **1**, 93.

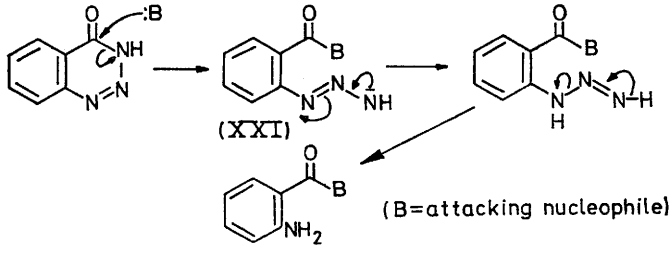
not nearly as easy as it is in isatoic anhydride, where nucleophilic attack at the 4-position is the normal mode of reaction;[3,12] however, we have found that nucleophiles do react with compound (I; R = H) at elevated temperatures to produce *o*-aminobenzoyl derivatives. Thus, when 1,2,3-benzotriazin-4(3*H*)-one was heated with high-boiling amines, loss of nitrogen occurred and anthranilamide derivatives (XIV) were isolated in almost quantitative yield. Use of primary amines gave mono-*N*-substituted anthranilamides, *e.g.* (XIVa) and (XIVb); use of *N*-ethylaniline afforded the *NN*-disubstituted anthranilamide (XIVc), and use of hydrazine and phenylhydrazine yielded the *o*-aminobenzoylhydrazines (XIVd and e respectively). In a similar manner, reaction of (I; R = H) with high-boiling alcohols gave anthranilate esters (XV); reaction with phenol afforded phenyl anthranilate (XV; R = Ph) and reaction with benzenethiol yielded *S*-phenyl thioanthranilate (XV; CO·SPh for CO_2R). All these products were either shown to be identical with authentic material or identified by m.p., analytical, and spectral data. The benzotriazinone (I; R = H) also reacted with formamide at 200°, to give quinazolin-4(3*H*)-one (XVII). This product probably arises by cyclisation [13] of the first formed *N*-formylanthranilamide (XVI), the formamide acting as a weak nucleophile in the initial reaction. When urea was used quinazoline-2,4-dione (XIX) was obtained, presumably, by analogy with the formamide reaction, *via* formation and cyclisation of *N*-(*o*-aminobenzoyl)urea (XVIII). A reaction was also observed when the triazinone was refluxed in isobutyric acid. The n.m.r. spectrum of the product and the fact that its alkaline hydrolysis afforded anthranilic acid established that it was *N*-(isobutyryl)anthranilic acid (XX). Its formation from the triazinone can be accounted for by the sequence shown in Scheme 1, involving formation of the anhydride and subsequent rearrangement.

Since all the reactions described, including the proposed generation of (V), occur below the decomposition temperature of 2,3-benzotriazin-4(3*H*)-one, they are unlikely to involve the intermediacy of the heterodiene (XII). Moreover, although cleavage between N-2 and N-3 in the photolytic decomposition of the 3-phenylbenzotriazinone (I; R = Ph) is likely on the basis of ^{15}N-labelling,[8] we feel that a valid mechanism for the reaction of nucleophiles with the parent benzotriazinone, and for the reaction of benzotriazinone with itself in refluxing diethylene glycol dimethyl ether, is that shown in Scheme 2, where the intermediate (XXI) is the *N*-analogue of the intermediate suggested [14] for the



SCHEME 1

Huang-Minlon modification of the Wolff–Kishner reduction.



SCHEME 2

In an attempt to synthesise compound (V) unambiguously, the 3-(*o*-nitrobenzoyl) compound (I; R = $CO{\cdot}C_6H_4{\cdot}NO_2$-*o*) was prepared from the sodium salt of (I; R = H) and *o*-nitrobenzoyl chloride, and subjected

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[14] K. Alexander, 'Ionic Organic Reactions,' Wiley, New York, 1950, p. 275.

to various methods of reduction. In no case, however, was the amino-compound isolated. The *N*-acyl linkage was usually cleaved to regenerate the benzotriazinone (I; R = H). Cleavage of the *N*-acyl bond in 3-acyl- and 3-aroyl-1,2,3-benzotriazines under similar conditions has been observed previously.[15]

EXPERIMENTAL

I.r. spectra were measured for Nujol mulls with a Perkin-Elmer 137 spectrometer. N.m.r. spectra were recorded for solutions in carbon tetrachloride with a Perkin-Elmer R10 spectrometer (60 MHz), with tetramethylsilane as internal standard. Mass spectra were determined with an A.E.I. MS9 instrument. Microanalyses were conducted by Drs. Weiler and Strauss (Oxford) and m.p.s were determined with a Kofler hot-stage apparatus.

Thermolysis of 1,2,3-*Benzotriazin*-4(3H)-*one*.—The benzotriazinone (5·0 g.) was refluxed in diethylene glycol dimethyl ether (200 ml.) for 1 hr. The resulting orange solution, on evaporation to dryness, *in vacuo*, yielded a bright yellow precipitate which afforded *quinazolino*[3,2-c][1,2,3]*benzotriazin*-8-*one* (3·0 g.) as yellow prisms, m.p. 214—216° (decomp.) (from benzene), $\nu_{max.}$ 1720, 1660, and 1605 cm.$^{-1}$, $\lambda_{max.}$ (EtOH) 213 (log ε 4·29), 232 (4·36), 249 (4·42), 275 (4·26), 287 (4·23), 311 (4·02), and 325 (3·99) nm., *m/e* 220 ($C_{14}H_8N_2O$) and 192 ($C_{13}H_8N_2$) [Found: C, 67·7; H, 3·4; N, 22·5%; *M* (mass spec.) 248·070. $C_{14}H_8N_4O$ requires C, 67·6; H, 3·2; N, 22·6%; *M*, 248·070].

Treatment of a warm acid solution of the product with alkaline β-naphthol produced a precipitate of the azo-dye, which yielded fine red needles, m.p. 315° (from benzene) (Found: C, 73·3; H, 4·4; N, 14·0. $C_{24}H_{16}N_4O_2$ requires C, 73·5; H, 4·1; N, 14·3%).

2-*Phenylquinazolin*-4(3H)-*one*.—The quinazolinobenzotriazinone (II) (0·1 g.) was refluxed in 70% aqueous ethanol for 15 hr. The pale yellow solution was concentrated and cooled to afford 2-phenylquinazolin-4(3*H*)-one (750 mg.) as needles, m.p. 239—240° (from ethanol), identical with an authentic sample.[16] The same quinazolone was obtained by treatment of compound (II) (0·1 g.) in ethanol with a drop of dilute hydrochloric acid and 15% titanium(III) chloride solution (5 ml.) followed by boiling for 2 hr. The cooled mixture was made alkaline to litmus and filtered, and the residue was thoroughly washed with alcohol. Concentration of the filtrate yielded the quinazolinone (48 mg.).

Hydrolysis of the Quinazolinobenzotriazine (II).—Compound (II) (1·5 g.) in ethanol (30 ml.) was refluxed with 10% sodium hydroxide solution (30 ml.) for 40 min. Concentration of the mixture caused precipitation of a yellow solid which on treatment with dilute hydrochloric acid yielded anthraniloylanthranilic acid (1·0 g.), m.p. 207—208° (from ethanol) (Found: *M*, 256·0851. Calc. for $C_{14}H_{12}N_2O_3$: *M*, 256·0848). This acid and its acetyl derivative (m.p. 226°) were identical with authentic samples. Acidification of the mother liquor from the reaction mixture afforded buff-coloured material (0·3 g.) identical with 1,2,3-benzotriazin-4(3*H*)-one.

Compound (II) (1 g.) was refluxed in 10% sodium hydroxide solution for 4 hr. The solution was neutralised (to litmus) with hydrochloric acid, reduced to one-third of its original volume, and cooled in an ice-bath. Addition of hydrochloric acid until the solution was just acid to litmus yielded a white precipitate of anthranilic acid, m.p. 143—145° (from water) (Found: *M*, 137·0475. Calc. for $C_7H_7NO_2$: *M*, 137·0477), identical with an authentic sample.

N-*Benzylanthranilamide*.— 1,2,3-Benzotriazin-4(3*H*)-one (0·5 g.) was refluxed in benzylamine (10 ml.) for 1 hr. The resulting yellow solution was evaporated to dryness *in vacuo* and the residual gummy solid was triturated with ether to afford *N*-benzylanthranilamide (0·56 g.) as plates, m.p. 124—125° (from benzene), $\nu_{max.}$ 3400, 3300, 3250, and 1640 cm.$^{-1}$ (Found: C, 74·2; H, 6·2; N, 12·4. Calc. for $C_{14}H_{14}N_2O$: C, 74·3; H, 6·25; N, 12·4%).

Similarly, refluxing 1,2,3-benzotriazin-4(3*H*)-one (0·5 g.) in aniline (20 ml.) for 1 hr., evaporation of the resulting red solution to dryness, and trituration of the residue with light petroleum (b.p. 80—100°) afforded *N*-phenylanthranilamide (0·58 g.) as needles, m.p. 130° (from benzene), $\nu_{max.}$ 3370, 3275, 3200, and 1635 cm.$^{-1}$ (Found: C, 73·5; H, 5·8; N, 13·4. Calc. for $C_{13}H_{12}N_2O$: C, 73·5; H, 5·7; N, 13·2%).

In the same way *N*-ethyl-*N*-phenylanthranilamide was prepared (85%) from *N*-ethylaniline as needles, m.p. 102—104° [from light petroleum (b.p. 80—100°)] (Found: C, 75·0; H, 6·6; N, 11·6. Calc. for $C_{15}H_{16}N_2O$: C, 75·0; H, 6·7; N, 11·7%).

o-*Aminobenzoylhydrazine*.— 1,2,3-Benzotriazin-4(3*H*)-one (0·5 g.) was refluxed in hydrazine hydrate (20 ml.) for 9 hr. The solution was evaporated to dryness and the residue was triturated with benzene to afford *o*-aminobenzoylhydrazine (0·49 g.) as plates, m.p. and mixed m.p.[17] 119—121° (from ethanol).

Similarly, heating 1,2,3-benzotriazin-4(3*H*)-one (0·5 g.) in phenylhydrazine (10 ml.) at 200° for 1 hr., evaporation of the resulting solution, and trituration of the orange residue with ether produced *N*-phenyl-*N'*-(*o*-aminobenzoyl)-hydrazine (0·53 g.) as needles, m.p. 172—174° (from ethanol), $\nu_{max.}$ 3400, 3250, 3150, and 1635 cm.$^{-1}$ (Found: C, 68·4; H, 6·0; N, 18·4. Calc. for $C_{13}H_{13}N_3O$: C, 68·7; H, 5·8; N, 18·5%).

Alkyl Anthranilates (XV; R = 1-*methylheptyl*, *n-hexyl*, *or n-pentyl*).—1,2,3-Benzotriazin-4(3*H*)-one (0·5 g.) was refluxed in the appropriate alcohol (20 ml.) for 1—6 hr. and the solution was then evaporated to dryness *in vacuo*. Unchanged starting material was recovered by washing the residue with benzene followed by filtration. Evaporation of the filtrate gave yellow oils which were purified by column chromatography on alumina with benzene as eluant. The following alkyl anthranilates were obtained (alkyl group, reaction temperature, reaction time, yield, spectra data): R = CHMe·$[CH_2]_5$Me, 180°, 1 hr., 100%, $\nu_{max.}$ 3400, 3300, and 1690 cm.$^{-1}$, τ (CCl_4) 2·1—3·6 (4H, m, aromatic), 4·1 (2H, s, NH_2), 4·7—5·1(1H, m, O·CH), 8·4—8·9 (13H, m, $[CH_2]_5$ and Me) and 9·1 (3H, t, *J* 5 Hz, Me); R = $[CH_2]_4$Me, 138°, 6 hr., 12%, $\nu_{max.}$ 3400, 3300, and 1690 cm.$^{-1}$, τ (CCl_4) 2·0—3·6 (4H, m, aromatic), 3·9 (2H, s, NH_2), 5·8 (2H, t, *J* 6 Hz, O·CH_2), 8·4—8·8 (6H, m, $[CH_2]_3$), and 9·0 (3H, t, *J* 6 Hz, Me); R = $[CH_2]_5$Me, 156°, 1 hr., 44%. $\nu_{max.}$ 3400, 3300, and 1690 cm.$^{-1}$, τ (CCl_4) 2·1—3·6 (4H, m, aromatic), 4·1 (2H, s, NH_2), 5·8 (2H, t, *J* 6 Hz, O·CH_2), 8·4—8·9 (8H, m, $[CH_2]_4$), and 9·1 (3H, t, *J* 5 Hz, Me).

Phenyl Anthranilate.—1,2,3-Benzotriazin-4(3*H*)-one (0·5

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[16] M. M. Endicott, E. Wick, M. L. Mercury, and M. L. Sherrill, *J. Amer. Chem. Soc.*, 1946, **68**, 1299.

[17] H. H. Fox and J. T. Gibas, *J. Org. Chem.*, 1952, **17**, 1653.

g.) and phenol (2 g.) were heated at 180° for 15 min., after which time effervescence had ceased. The mixture was cooled and treated with 2N-sodium hydroxide to yield phenyl anthranilate (0·28 g.) which gave needles, m.p. and mixed m.p. 70° (from ethanol), $\nu_{max.}$ 3400, 3300, and 1695 cm.$^{-1}$, identical with an authentic sample.[12]

S-*Phenyl Thioanthranilate*.—1,2,3-Benzotriazin-4(3*H*)-one (1·0 g.) was refluxed in benzenethiol (20 ml.) for 2 hr. The excess of thiol was removed under vacuum and the residue was triturated with light petroleum (b.p. 60—80°) to give phenyl thioanthranilate (1·1 g.) as yellow prisms, m.p. 103—105° [from light petroleum (b.p. 80—100°)] (lit.,[12] 104—105°).

Quinazolin-4(3H)-*one*.—1,2,3-Benzotriazin-4(3*H*)-one (0·5 g.) was heated with formamide (20 ml.) at 200° for 1 hr., after which time effervescence had ceased. The orange mixture was concentrated under reduced pressure and the gummy residue was triturated with water to afford quinazolin-4(3*H*)-one (0·12 g.) as needles (from ethanol), m.p. and mixed m.p. 216—217°, $\nu_{max.}$ 3100sh and 1695 cm.$^{-1}$, identical with an authentic sample.[16]

Quinazoline-2(1H),4(3H)-*dione*.— 1,2,3-Benzotriazin-4(3*H*)-one (0·5 g.) and urea (5 g.) were heated at 200° for 0·5 hr. The cooled mixture was crystallised from ethanol. The product was added to material obtained by evaporation of the ethanolic mother liquor and the combined residue was triturated with benzene to yield the quinazolinedione (0·41 g.) as prisms, m.p. and mixed m.p. >350°, $\nu_{max.}$ 3150, 3050, 1705, and 1680 cm.$^{-1}$, identical with an authentic sample.[18]

N-*Isobutyrylanthranilic Acid*.—1,2,3-Benzotrazin-4(3*H*)-one (0·5 g.) was refluxed in isobutyric acid (20 ml.) for 6 hr. The excess of acid was then removed under vacuum at 100° leaving a yellow oil which solidified when cool. Trituration of the resulting solid with light petroleum (b.p. 60—80°) yielded *N*-isobutyrylanthranilic acid (0·6 g.) as needles, m.p. 125—127° (from benzene–light petroleum), $\nu_{max.}$ 3300, 1695, and 1675 cm.$^{-1}$, τ ($CDCl_3$) −1·2br (2H, s, CO_2H and NH), 1·1—3·0 (4H, m, aromatic), 7·3 (1H, heptet, *J* 7 Hz, CH·CO), and 8·65 (6H, d, *J* 7 Hz, 2 × Me) (Found: C, 63·6; H, 6·2. Calc. for $C_{11}H_{13}NO_3$: C, 63·7; H, 6·3%). This product, on refluxing with aqueous 2N-sodium hydroxide for 1 hr. yielded anthranilic acid.

Diazotisation of 2-(o-*Aminophenyl*)*quinazolin*-4(3H)-*one*.—A solution of 2-(*o*-aminophenyl)quinazolin-4(3*H*)-one [19] (0·6 g.) in 2N-hydrochloric acid (10 ml.) was cooled to 0°. Sodium nitrite (0·3 g.) in water (5 ml.) was added dropwise, with stirring, during 15 min. The yellow precipitate (from benzene) afforded the quinazolinobenzotriazinone (II) (0·42 g.), m.p. and mixed m.p. 214—216° with the product obtained previously $\nu_{max.}$ 1720, 1660, and 1605 cm.$^{-1}$ (Found: C, 67·8; H, 3·5; N, 22·6. Calc. for $C_{14}H_8N_4O$: C, 67·6; H, 3·2; N, 22·6%).

3-(o-*Nitrobenzoyl*)-1,2,3-*benzotriazin*-4(3H)-*one*.— The sodium salt of 1,2,3-benzotriazin-4(3*H*)-one (3·5 g.) was suspended in anhydrous toluene (40 ml.) and freshly distilled *o*-nitrobenzoyl chloride (4 g.) was added. The mixture was refluxed for 2 hr., the solution was filtered to remove sodium chloride, and the filtrate was evaporated to dryness *in vacuo*. Trituration of the residue with benzene afforded 3-(o-*nitrobenzoyl*)-1,2,3-*benzotriazin*-4(3H)-*one* (4·5 g.) as buff-coloured needles, m.p. 195—197° (decomp.) (from benzene), $\nu_{max.}$ 1760, 1700, 1530, and 1350 cm.$^{-1}$ (Found: C, 56·6; H, 2·9; N, 18·9. $C_{14}H_8N_4O_4$ requires C, 56·8; H, 2·7; N, 18·95%). All attempts to reduce this compound to the amine (with palladium–charcoal and hydrogen, palladium–charcoal and sodium borohydride, hydrazine hydrate–Raney nickel, iron(II) sulphate–ammonia, or cyclohexene and palladium–charcoal) failed; the products were 1,2,3-benzotriazin-4(3*H*)-one, anthranilic acid, or an intractable red oil.

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