The Chemistry of Isatoic Anhydride Derivatives: Electrophilic Reactions of 2-Amino-3,1-benzoxazin-4-one

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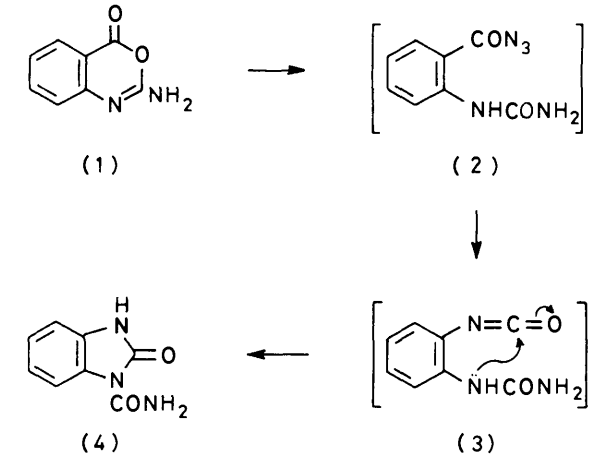
2-Amino-3,1-benzoxazin-4-one ('iminoisatoic anhydride') reacts with nucleophiles to yield 2-substituted phenylurea derivatives which undergo cyclisation to give a number of new quinazolone derivatives. With ethyl cyanoacetate, diethyl malonate, malononitrile, and acetoacetonitrile the corresponding quinazolones (6)—(9) are obtained. Sodium cyanamide yields the 3-*N*-cyano-derivative (21).

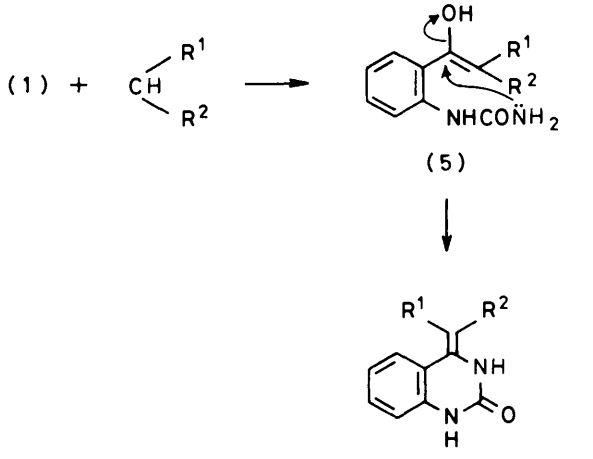
3,1-Benzoxazine-2,4(1*H*)-dione (isatoic anhydride) is a compound of wide synthetic utility and this has been emphasised in two recent reviews.[1,2] In spite of its ready availability,[3] the 'imino' derivative 2-amino-3,1-benzoxazin-4-one (1) however has aroused little interest. This is particularly surprising when it is realised that initial nucleophilic ring opening generates an *ortho*-substituted phenyl urea and the subsequent cyclisation reaction can involve either reaction at one of two nucleophilic centres or at an electrophilic centre, in contrast to isatoic anhydride where only a single nucleophilic centre is generated. This should lead to significant differences in chemistry and this paper describes investigations into the reactions of 'iminoisatoic anhydride' which gave rise to products involving all three active centres.

A facile reaction of compound (1) is its rearrangement to quinazoline-2,4-dione under relatively mild conditions.[3] It appeared quite feasible therefore that any attempt to open the hetero-ring with nucleophilic reagents would simply facilitate this rearrangement with concomitant regeneration of the original nucleophile. Thus a pilot reaction studied was chosen so as to reduce this possibility by permitting modification of the substituent *ortho* to the newly generated phenylurea group. This was achieved successfully with azide when the benzimidazol-2-one (4) was formed by rearrangement of the intermediate (2) to (3) and subsequent cyclisation (Scheme 1).



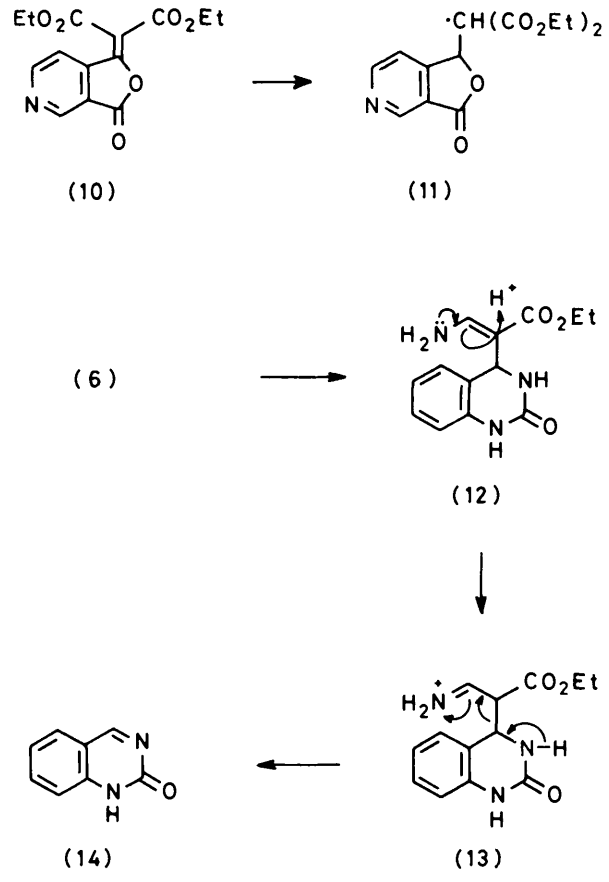
Scheme 1

Having thus established that (1) is capable of undergoing transformations other than rearrangement, the reaction with carbanions derived from active methylene compounds was investigated. Hereby it was found that in the reaction with the anions from diethyl malonate and ethyl cyanoacetate ring cleavage and recyclisation did occur, but in these cases N-3 of the urea group participated in the reaction, not N-1 as with azide (Scheme 2). The products from these transformations were identified as the quinazolones (6) and (7). The infrared frequencies of compound (7) support the structure whereby one ester carbonyl group is in plane as a *cis*-enamino carbonyl system, with its inherent high carbonyl frequency [4] at 1 655 cm^{-1}, whereas the other ester group is twisted out of plane and more closely resembles a saturated ester with a frequency at 1 720 cm^{-1}. Similarly the ester group of the cyano-derivative (6) is in a similar in-plane environment with a carbonyl frequency at 1 664 cm^{-1}. In neither case was the intermediate (5) isolated. With the anion derived from malononitrile, however, the urea (5; $R^1 = R^2 = CN$) was isolated in good yield. This underwent cyclisation to compound (8) when treated with acetic anhydride. The enolic urea (5; $R^1 = R^2 = CN$) is highly acidic, its pK_a being of the order of -5 to -7, *i.e.* similar to hydrochloric acid. This is in agreement with published data [5] which show that the pH of 0.01M-solutions of acylmalononitriles lies in the range 2.03—2.07.

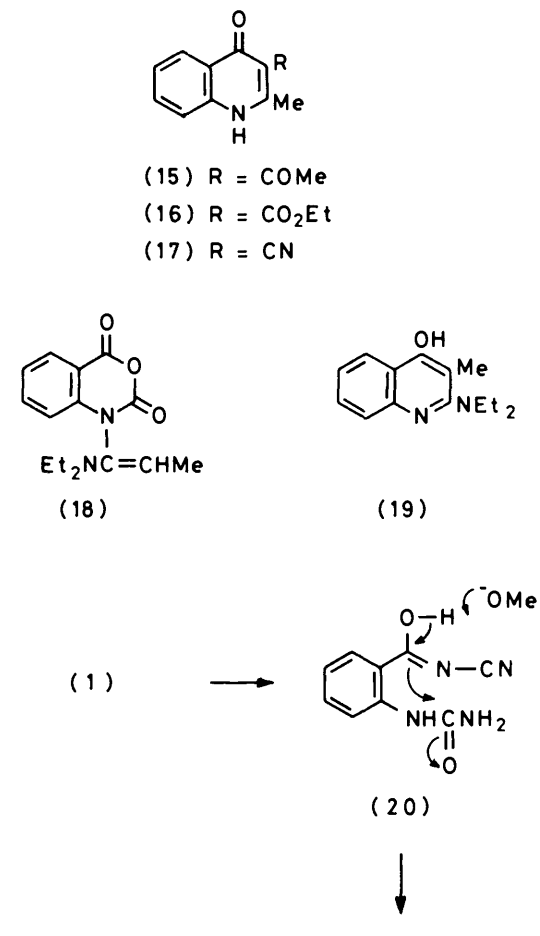


Scheme 2

To help confirm the structure of the quinazolines thus prepared, compound (6) was subjected to catalytic hydrogenation. Binder has shown [6] that the related compound (10) is hydrogenated smoothly to the dihydro-derivative (11). With the quinazolone (6), however, the reaction was complex, the volume of hydrogen absorbed exceeding that required for one molar equivalent, but upon acidification of the reaction solution the known [7] quinazolone (14) was isolated. The formation



Scheme 3



Scheme 4

of (14) can be rationalised by the mechanism shown in Scheme 3. This mechanism was confirmed when, by careful control of the reaction, the enamine (12) was isolated and this generated (14) upon treatment with acid.

The reaction of the anions of enolisable compounds proceeded differently. The main product with both acetylacetone and ethyl acetoacetate was quinazoline-2,4-dione, thus confirming that a reacting nucleophile could indeed act as a 'catalyst' in promoting the rearrangement of the amine (1). However, from each reaction small amounts of the quinolones (15) and (16) were isolated. An exception to this reaction pathway was found with acetoacetonitrile. In place of the potentially hazardous compound itself the anion was generated from 5-methylisoxazole; [8] however the product isolated was not the expected quinolone (17), but the quinazolone (9).

It had been our intention to study the reactions of compound (1) with enamines and ynamines, but it was found that no reaction took place with 1-diethylaminoprop-1-yne. The reaction failed also with *N*-methylisatoic anhydride and with isatoic anhydride itself, *N*-alkylation was the only reaction observed, yielding the dione (18). However, as nucleophilic attack at C-4 by an enolisable anion facilitates intramolecular rearrangement, this approach was applied to compound (18) using the anion derived from ethyl acetoacetate. The reaction product was indeed the quinoline (19), identical with the product theoretically obtainable by direct reaction of the propyne with isatoic anhydride.

The reactions discussed thus far have involved initial ring cleavage of the amine (1) by an anion followed by cyclisation involving one or other of the two ureido nitrogen atoms. With cyanamide a third transformation is observed involving the ureido carbonyl group. The initial product of the reaction of compound (1) with cyanamide in the presence of base was one for which the spectroscopic data indicated the structure (20) (Scheme 4), although hydration of the product precluded exact characterisation. However, when this product was heated at reflux in methanol a glass was produced which upon treatment with water yielded the 3-cyanoquinazoline-2,4-dione (21) in moderate yield. The structure of compound (21) was based upon spectroscopic evidence. The infrared spectrum (Nujol) showed carbonyl absorptions at 1 705 and 1 722 cm^{-1} and a nitrile absorption at 2 300 cm^{-1}. Elementary analysis gave data for the empirical formula $C_9H_5N_3O_2$, supported by the mass spectrum with a molecular ion at 187. The most conclusive evidence, however, came from the ^{13}C n.m.r. spectrum which exhibited an absorption at δ 104.0 p.p.m., assignable to the >N–CN system. *N*-Cyanophthalimide exhibits a similar signal at δ 104.5 p.p.m. and a nitrile absorption at 2 270 cm^{-1}.

Further supportive evidence comes from an examination of the aqueous solution from which (21) was crystallised. Acidification regenerated the monocyclic compound (20) in *ca.* 50% yield, suggesting that it was present as its ammonium salt.

Indeed, upon making the acidified solution alkaline, ammonia was detected.

The structure (22) has been proposed [9] for an isomeric product isolated from the pyrolysis of 3,3-diazido-6-chloro-1*H*,3*H*-quinoline-2,4-dione. Here too significant emphasis was placed upon the ^{13}C n.m.r. evidence for the strcutural proof, in particular the assignment of a signal at δ 119.8 p.p.m. to the N–CN group by analogy with *N*-cyanopyrrolidine (δ 117.2 p.p.m.). No signals were reported at δ *ca.* 104 p.p.m. Further, the signals at δ 184.5 and 174.7 p.p.m. are incompatible with structure (22). This evidence together with that submitted in support of compound (21) suggests that the structure for (22) is incorrect. Unfortunately, it has not been found possible to repeat the published pyrolysis to permit a more exact comparison of (21) and (22). Using the published conditions intractable tars have been the only products.

Experimental

1-*Carbamoylbenzimidazol-2-one* (4).—A solution of 2-amino-3,1-benzoxazin-4-one (3 g) and sodium azide (1.2 g) in acetic acid (50 ml) was heated under reflux for 2 h. The solution was then evaporated to *ca.* 10 ml and diluted with water (50 ml). The resulting solid was collected and recrystallisation from aqueous dimethylformamide yielded 1-*carbamoylbenzimidazol-2-one* (2.5 g), m.p. 306 °C (Found: C, 54.1; H, 4.0; N, 23.4. $C_8H_7N_3O_2$ requires C, 54.3; H, 4.0; N, 23.7%); $\nu_{max.}$ 1 710 (CO) and 1 755 cm^{-1} (CO); $\delta_H[(CD_3)_2SO]$ 7.2 (3 H, m), 7.83 (1 H, s), 8.05 (1 H, m), 8.3 (1 H, s), and 11.4 (1 H, s).

Reaction of Compound (1) *with Active Methylene Compounds.*—(*a*) *Ethyl cyanoacetate.* Ethyl cyanoacetate (2.3 g) was added dropwise to a suspension of sodium hydride (0.5 g) in dimethylformamide (50 ml). To the resulting solution was added the benzoxazine (1) (3.2 g) and the mixture was stirred at ambient temperature for 4 h. The solution was then diluted with water (50 ml), filtered and, with ice-cooling, acidified with 3M-HCl. The resulting solid was collected, washed with hot isopropyl alcohol (75 ml) and recrystallised from dimethylformamide–diethyl ether to yield *ethyl cyano*(1,2,3,4-*tetrahydro-2-oxoquinazolin-4-ylidene*)*acetate* (6) (4 g), m.p. 296—297 °C (Found: C, 60.8; H, 4.3; N, 16.3. $C_{13}H_{11}N_3O_3$ requires C, 60.7; H, 4.3; N, 16.3%); $\nu_{max.}$ (Nujol) 2 215 (C≡N), 1 710 (ring CO), 1 664 (ester CO), 1 600 (Ph), 1 568 (C=C), 1 264 cm^{-1} (C–O), $\delta_H[(CD_3)_2SO]$ 1.37 (3 H, t), 4.4 (2 H, q), 7.5 (3 H, m), and 8.75 (1 H, d, *J* 6 Hz).

Similarly prepared were *diethyl* 1,2,3,4-*tetrahydro-2-oxoquinazolin-4-ylidenemalonate* (7) (1.7 g), m.p. 226—228 °C (from methanol) (Found: C, 59.4; H, 5.3; N, 9.4. $C_{15}H_{16}N_2O_5$ requires C, 59.2; H, 5.3; N, 9.2%); $\nu_{max.}$ (Nujol) 1 720 (ester CO), 1 698 (ring CO), 1 655 (ester CO), 1 605 (Ph), 1 571 cm^{-1} (C=C); $\delta_H[(CD_3)_2SO]$ 1.2 (3 H, t), 4.24 (2 H, q), 7.33 (4 H, m); and 4-*acetylcyanomethylene*-3,4-*dihydroquinazolin*-2(1H)-*one* (9) (3.2 g), m.p. 274 °C (from acetonitrile) (Found: C, 63.4; H, 3.9; N, 18.6. $C_{12}H_9N_3O_2$ requires C, 63.4; H, 4.0; N, 18.5%); $\nu_{max.}$ 2 205 (C≡N), 1 695 (ring CO), 1 610 (CO) and 1 595 cm^{-1} (Ph); $\delta_H[(CD_3)_2SO]$ 2.5 (3 H, s), 7.56 (3 H, m), and 8.95 (1 H, d, *J* 6 Hz).

(*b*) *Malononitrile.* Malononitrile (1.3 g) was added in portions to a suspension of sodium hydride (0.54 g) in dimethylformamide. To the resulting solution was added compound (1) (3.2 g) and the mixture stirred at ambient temperature overnight. Sufficient 3M-HCl was added to discharge the deep blue colour of the solution which was evaporated to dryness. Addition of ethyl acetate to the residue yielded a solid which was collected, dissolved in water and the solution treated with 3M-HCl to yield 1-(2,2-*dicyano*-1-*hydroxyvinyl*)-2-*ureidobenzene* (5; R^1 = R^2 = CN) (2.5 g), m.p. 141—142 °C (from acetone–light petroleum, b.p. 60—80 °C) (Found: C, 57.9; H, 3.8; N, 24.2. $C_{11}H_8N_4O_2$ requires C, 57.9; H, 3.5; N, 24.2%).

(*c*) *Acetylacetone.* The anion of acetylacetone (2 g) was prepared as in (*a*), and compound (1) (3.2 g) was added in portions to the clear solution. After standing for 3 days at ambient temperature, the mixture was evaporated to dryness and the residue extracted with hot acetonitrile (2 × 200 ml). The acetonitrile extracts were combined, evaporated to dryness and the residue recrystallised from ethanol to yield 3-*acetyl*-2-*methylquinolin*-4(1H)-*one* (15) (1 g), m.p. 259—260 °C (Found: C, 71.8; H, 5.5; N, 7.0. $C_{12}N_{11}NO_2$ requires C, 71.6; H, 5.5; N, 7.0%); $\delta_H[(CD_3)_2SO]$ 2.55 (3 H, s), 2.65 (3 H, s), 7.6 (3 H, m), and 8.28 (1 H, d, *J* 6 Hz).

Similarly prepared from ethyl acetoacetate was 3-carboxyethyl-2-methylquinolin-4-one, identical with authentic material.[10]

The cyclisation of the Ureido-compound (5; R^1 = R^2 = CN).—A solution of (5; R^1 = R^2 = CN) (5 g) in acetic anhydride (15 ml) and pyridine (10 ml) was allowed to stand at ambient temperature overnight. The solid which separated was crystallised from acetonitrile then acetic acid to yield 4-*dicyanomethylene*-3,4-*dihydroquinazolin*-2(1H)-*one* (8) (2.5 g), m.p. > 300 °C (Found: C, 62.6; H, 2.8; N, 26.3. $C_{11}H_6N_4O$ requires C, 62.9; H, 2.8; N, 26.6%); $\nu_{max.}$ (Nujol) 2 225 (C≡N), 1 704 (CO), 1 596 (Ph), 1 542 cm^{-1} (C=C); $\delta_H[(CD_3)_2SO]$ 7.50 (m, 3 H) 8.61 (d, 1 H, *J* 6 Hz), and 11.2 (2 H).

Hydrogenation of Compound (6).—A solution of (6) (2 g) in ethanol (50 ml) was shaken in an atmosphere of hydrogen in the presence of 10% palladium-on-charcoal (2 g). After the absorption of 2 moles of hydrogen the catalyst was removed and the solution evaporated to dryness. The residue was recrystallised from methanol to give *diethyl aminomethylene*-(1,2,3,4-*tetrahydro-2-oxoquinazolin-4-yl*)*acetate* (12) (1.3 g), m.p. 157—158 °C (Found: C, 59.7; H, 5.9; N, 15.9. $C_{13}H_{15}N_3O_3$ requires C, 59.8; H, 5.8; N, 16.1%); $\nu_{max.}$ (Nujol) 1 681 (ring CO), 1 660 (ester CO), and 1 560 cm^{-1} (C=C); $\delta_H[(CD_3)_2SO]$ 1.1 (3 H, t), 3.2 (1 H, d, *J* 4.5 Hz), 4.0 (2 H, q), 5.2 (1 H, s), 6.9 (7 H, m), and 9.15 (1 H, s).

Treatment of (12) in methanol (20 ml) with ethereal hydrogen chloride yielded yellow crystals of quinazolin-2(1*H*)-one hydrochloride,[7] m.p. 243—245 °C.

1-(1-*Diethylaminoprop*-1-*en*-1-*yl*)-3,1-*benzoxazine*-2,4(1H)-*dione* (18).—A solution of isatoic anhydride (1.6 g) and 2-diethylaminoprop-2-yne (1.4 ml) in acetonitrile (25 ml) was heated under reflux for 2 h. After addition of water (100 ml), the *product* (18) (3 g) was collected and recrystallised from cyclohexane, m.p. 120 °C (Found: C, 65.5; H, 6.5; N, 10.1. $C_{15}H_{18}N_2O_3$ requires C, 65.7; H, 6.6; N, 10.2%); $\delta_H(CDCl_3)$ 1.1 (6 H, t), 1.5 (3 H, d, *J* 10 Hz), 3.07 (4 H, q), 4.82 (1 H, q), 7.45 (3 H, m), and 8.17 (1 H, d, *J* 6 Hz).

2-*Diethylamino*-4-*hydroxy*-3-*methylquinoline* (19).—The anion from ethyl acetoacetate (1.3 g) in dimethylformamide (25 ml) was treated with compound (18) (2.7 g) and the mixture stirred at ambient temperature for 3 days. Water (100 ml) was added and the *product* (19) collected and recrystallised from methanol (1.2 g), m.p. 276—278 °C (Found: C, 73.0; H, 8.1; N, 12.1. $C_{14}H_{18}N_2O$ requires C, 73.0; H, 7.9; N, 12.2%). δ[$(CD_3)_2SO$ + TFA] 1.2 (6 H, t), 2.23 (3 H, s), 3.61 (4 H, q), and 7.85 (4 H, m).

3-*Cyanoquinazoline*-2,4(1H,3H)-*dione* (21).—To a suspension of sodium hydride (1 g) in dimethylformamide (50 ml) was added cyanamide (1.7 g) and compound (1) (6.6 g). After being left overnight at ambient temperature, the mixture was

poured into water (500 ml) and acidified with 3M-HCl. The resulting solid was collected and heated under reflux in methanol (50 ml) for 4 h. Evaporation of the solution and treatment of the residue with water yielded compound (21) (1.8 g), m.p. 258—260 °C (from ethanol) (Found: C, 57.8; H, 2.5; N, 22.4. $C_9H_5N_3O_2$ requires C, 57.8; H, 2.7; N, 22.5%); $\nu_{max.}$ (Nujol) 2 310 (C≡N), 1 720 (CO), and 1 710 cm^{-1} (CO); δ_C [$(CD_3)_2SO$] 104.03, 112.61, 116.51, 123.98, 127.95, 137.18, 139.64, 146.86, and 160.18.

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