679. *Sulphanilamide Derivatives: Compounds derived from 2- and 4-Aminoquinazoline and 1-Aminophthalazine.*

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The preparation and properties of 2- and 4-aminoquinazoline have been re-investigated and 1-aminophthalazine has been prepared. These compounds have been converted into their sulphanilyl derivatives.

In a preliminary note published some time ago [1] the preparation of 2- and 4-amino- and 2- and 4-sulphanilamido-quinazoline was reported and later 1-amino- and 1-sulphanilamido-phthalazine were prepared. Discrepancies between the results obtained in this work and other attempts to prepare some of these compounds make it desirable to record details.

Dewar [2] prepared 2-aminoquinazoline by amination of 2-chloroquinazoline in alcohol, having obtained very poor yields of the base by the condensation of *o*-aminobenzaldehyde and guanidine carbonate or cyanamide. It has now been found that refluxing guanidine carbonate and pure *o*-aminobenzaldehyde in a high-boiling solvent (*e.g.*, decalin) gives

[1] Macbeth and Rodda, *Nature*, 1945, **156**, 207.
[2] Dewar, *J.*, 1944, 619.

almost theoretical yields of 2-aminoquinazoline. The product with *p*-nitrobenzenesulphonyl chloride in anhydrous pyridine readily gives 2-*p*-nitrobenzenesulphonamidoquinazoline, which is reduced by iron powder and hydrochloric acid to 2-sulphanilamidoquinazoline.

There are several references to the preparation of 4-aminoquinazoline but there is some disagreement about its properties. Dewar [2] obtained a product, m. p. 259—260°, which is described as being practically non-basic and incapable of acylation. In the same manner Tomisek and Christensen [3] prepared a compound, designated also as 4-aminoquinazoline, m. p. 245—260°, which formed an acetyl derivative, m. p. 172°, with some difficulty. More recently, Morley and Simpson [4] prepared 4-aminoquinazoline by amination of the 4-chloro-compound with ammonia, or with ammonium carbonate in phenol, and by reaction of 4-phenoxyquinazoline with ammonium acetate. In each case, the product, m. p. 267° (decomp.), had pronounced basic properties and was readily acetylated, yielding 4-acetamidoquinazoline, m. p. 174—175°. Notwithstanding the evidence presented by the last authors, and confirmed subsequently by determination of pK_a values,[5] Naff and Christensen [6] reported that 4-aminoquinazoline has amide-like characteristics, thus confirming Dewar's [2] observations. In our hands alcoholic ammonia and 4-chloroquinazoline gave a basic product, m. p. 272—273°, crystallising readily from water. This material reacted readily with acid chlorides. Our results, therefore, agree with those of Morley and Simpson.[4]

Reaction of 4-aminoquinazoline with *p*-nitrobenzenesulphonyl chloride in anhydrous pyridine gave, normally, 4-*p*-nitrobenzenesulphonamidoquinazoline which is readily reduced (iron powder–hydrochloric acid) to 4-sulphanilamidoquinazoline.

1-Chlorophthalazine [7] with hot methanolic ammonia under pressure, smoothly gives 1-aminophthalazine hydrochloride. The free amino-compound, liberated by alkali, is a strong base which reacts readily with acyl halides, and forms crystalline salts with inorganic acids, including nitric acid. 1-Sulphanilamidophthalazine has been prepared in the usual manner *via* 1-*p*-nitrobenzenesulphonamido- or 1-*p*-acetamidobenzenesulphonamido-phthalazine.

Experimental

4-Aminoquinazoline.—4-Chloroquinazoline [8] aminated by a procedure similar to that described by Dewar [2] gave a product, m. p. 269—270°. Pure 4-aminoquinazoline, m. p. 272—273°, was obtained by repeated crystallisation from water (Found: C, 66·1; H, 4·8. Calc. for $C_8H_7N_3$: C, 66·2; H, 4·9%). 4-Acetamidoquinazoline crystallised from light petroleum (b. p. 100—120°) as fine white needles, m. p. 171° (Morley and Simpson [4] give m. p. 174—175°) (Found: C, 64·3; H, 4·7. Calc. for $C_{10}H_9ON_3$: C, 64·1; H, 4·9%). *4-Aminoquinazoline picrate*, crystallised from alcohol, had m. p. 292° (Found: C, 45·2; H, 2·8. $C_{10}H_{14}O_7N_6$ requires C, 44·9; H, 2·7%).

4-p-*Nitrobenzenesulphonamidoquinazoline.*—Recrystallised *p*-nitrobenzenesulphonyl chloride (9·2 g.) was added slowly to a cold (0°), stirred solution of 4-aminoquinazoline (6 g.) in anhydrous pyridine (40 c.c.). The mixture was heated at 60° for 1 hr., then poured with stirring into cold water (400 c.c.), and the stirring continued for several hours. The moist solid was extracted with 2% aqueous ammonia (400 c.c.) for 30 min. Acidification (hydrochloric acid) of the extract gave 4-*p*-nitrobenzenesulphonamidoquinazoline as a buff solid of satisfactory purity for subsequent reduction. Purification was difficult, repeated crystallisation from 50% aqueous alcohol giving the compound as pale yellow plates, m. p. 214—219° and for which analyses were not very satisfactory (Found, *e.g.*: C, 49·4; H, 3·0. Calc. for $C_{14}H_{10}O_4N_4S$: C, 50·9; H, 3·1%).

4-Sulphanilamidoquinazoline.—Reduced iron powder (4 g.) was added slowly to a warm (60°) stirred suspension of 4-*p*-nitrobenzenesulphonamidoquinazoline in water (120 c.c.), ethanol (40 c.c.), and concentrated hydrochloric acid (1·6 c.c.). The temperature was then raised to 75° and kept thereat for 30 min. The end of the reduction was indicated by the development

[3] Tomisek and Christensen, *J. Amer. Chem. Soc.*, 1945, **67**, 2112.
[4] Morley and Simpson, *J.*, 1949, 1354.
[5] Keneford, Morley, Simpson, and Wright, *J.*, 1949, 1356.
[6] Naff and Christensen, *J. Amer. Chem. Soc.*, 1951, **73**, 1372.
[7] Gabriel and Neumann, *Ber.*, 1893, **26**, 523.
[8] Bogert, *J. Amer. Chem. Soc.*, 1909, **31**, 509.

of a chocolate-brown colour. 10% Sodium hydroxide solution (12 c.c.) was added and the alkaline solution filtered, acidified with hydrochloric acid, treated with charcoal, made alkaline with ammonia, treated again with charcoal, and neutralised. 4-*Sulphanilamidoquinazoline* (2·4 g.) was precipitated as a cream-coloured powder, m. p. 253—255°. A sample crystallised from 50% aqueous alcohol for analysis had m. p. 255° (Found : C, 56·2; H, 3·9. $C_{14}H_{12}O_2N_4S$ requires C, 56·0; H, 4·0%).

2-*Aminoquinazoline.*—(a) *From* o-*aminobenzaldehyde.* Pure *o*-aminobenzaldehyde (12 g.) was thoroughly ground with guanidine nitrate (19 g.) and sodium carbonate (8 g.), suspended in dry decalin (200 c.c.), and stirred under reflux with stirring and removal of water, while heated successively at 180° (10 min.), 220°, 180°, the total heating time being 30 min. The hot decalin solution was decanted through a filter and cooled; crude 2-aminoquinazoline was deposited. A second extraction of the residual solids yielded a further quantity (total yield 13·6 g.; m. p. 194—200°). Precipitation with ammonia from a solution in 10% hydrochloric acid, followed by vacuum-sublimation, yielded 2-aminoquinazoline, m. p. 203—204° (Dewar [2] gives m. p. 198°) (Found : C, 66·2; H, 4·9. Calc. for $C_8H_7N_3$: C, 66·2; H, 4·9%).

(b) *From* 2-*chloroquinazoline.* 2-Chloroquinazoline (2 g.) was heated with 25% aqueous ammonia (75 c.c.) at 250° for 2 hr. The cooled mixture deposited 2-aminoquinazoline as yellow crystals (10 g.), m. p. 198°. Purified by sublimation the product had m. p. 203—204° undepressed by a sample prepared from *o*-aminobenzaldehyde.

2-Acetamidoquinazoline crystallised from acetone as long needles, m. p. 177° (Found : C, 63·9; H, 4·7. Calc. for $C_{10}H_9ON_3$: C, 64·1; H, 4·9%). 2-Aminoquinazoline picrate formed needles (from acetone), m. p. 253° (Found : C, 44·8; H, 2·6. $C_{14}H_{10}O_7N_6$ requires C, 44·9; H, 2·7%).

2-*Aminoquinazoline* p-*nitrobenzenesulphonate*, crystallised from 50% ethanol, had m. p. 249—250° (Found : C, 48·5; H, 3·6. $C_{14}H_{12}O_5N_4S$ requires C, 48·3; H, 3·5%).

2-p-*Nitrobenzenesulphonamidoquinazoline.*—*p*-Nitrobenzenesulphonyl chloride (4·4 g.) was added slowly to a stirred solution of 2-aminoquinazoline (3 g.) in anhydrous pyridine (10 c.c.); the mixture was heated on a water-bath for 1 hr., then poured into cold water (100 c.c.). The oil which separated slowly solidified and was washed to remove pyridine. The brown amorphous product (5·5 g.), although impure, was suitable for reduction. Purification was effected by extracting the crude solid with 2% sodium hydroxide solution (3 × 50 c.c.). Acidification (pH 6·5) of the extract gave 2-p-*nitrobenzenesulphonamidoquinazoline* as a pale yellow powder, m. p. 234—238°. From acetone–light petroleum (1 : 1) the compound crystallised as fine cream-coloured needles but the melting point was not improved (Found : C, 50·9; H, 3·2. $C_{14}H_{10}O_4N_4S$ requires C, 50·9; H, 3·1%).

2-*Sulphanilamidoquinazoline.*—Crude 2-*p*-nitrobenzenesulphonamidoquinazoline (5·6 g.) was stirred vigorously in a mixture of water (90 c.c.), ethanol (30 c.c.), and concentrated hydrochloric acid (3 c.c.) at 65° and reduced iron powder (3 g.) was added during 10 min. The temperature was raised to 75° for a further 35 min. during which the mixture changed from dark-grey to reddish-brown. The mixture was cooled to 50° before 50% sodium hydroxide solution (25 c.c.) was added. The insoluble material was removed and the filtrate made acid with hydrochloric acid; most of the solid, initially precipitated, redissolved, leaving a red gelatinous material in suspension. This was removed by filtration (Supercel) and the clarified filtrate neutralised with ammonia. The precipitated cream-coloured, gelatinous solid became granular at 0° overnight. Crystallisation from 50% ethanol gave 2-*sulphanilamidoquinazoline* as feathery white crystals, m. p. 286° (Found : C, 56·1; H, 4·0. $C_{14}H_{12}O_2N_4S$ requires C, 56·0; H, 4·0%).

1-*Aminophthalazine.*—1-Chlorophthalazine (30 g.) was heated at 160° for 8 hr. with methanolic ammonia (300 c.c., *ca.* 10N). The alcoholic solution was then evaporated under reduced pressure and the pale brown residue of hydrochloride was extracted with boiling water (200 c.c.). The aqueous solution was taken to dryness, finally in a vacuum desiccator over sulphuric acid. The solid was extracted with absolute alcohol and the extract again taken to dryness. Slightly more than the theoretical quantity of sodium hydroxide dissolved in the minimum of hot alcohol was added to the residue, and the mixture heated to boiling and filtered from sodium chloride. Evaporation of the alcoholic solution gave the amine slightly contaminated with sodium chloride. Crystallisation from water gave 1-*aminophthalazine* (17 g.) as cream-coloured needles, m. p. 210—211°. A sample was further purified by sublimation at 190°/0·5 mm. and then had m. p. 211° (Found : C, 66·4; H, 4·8. $C_8H_7N_3$ requires C, 66·2; H, 4·9%).

1-*Aminophthalazine hydrochloride*, crystallised from *iso*pentyl alcohol or aqueous dioxan, had m. p. 205—206° (Found : C, 52·6; H, 4·4. $C_8H_8N_3Cl$ requires C, 52·9; H, 4·4%). The

nitrate recrystallised from 10% nitric acid as long, flat needles, m. p. 220° (decomp.) (Found: C, 46·1; H, 3·7. $C_8H_8O_3N_4$ requires C, 46·1; H, 3·9%), the *picrate* as yellow needles (from water), m. p. 301° (Found: C, 45·1; H, 2·6. $C_{14}H_{10}O_7N_6$ requires C, 44·9; H, 2·7%), and the p-*nitrobenzenesulphonate* (from water) had m. p. 226° (Found: C, 48·8; H, 3·5. $C_{14}H_{12}O_5N_4S$ requires C, 48·3; H, 3·5%).

1-*Acetamidophthalazine*, prepared by use of acetic anhydride–glacial acetic acid and precipitated therefrom by light petroleum, crystallised from acetone as needles, m. p. 185° (Found: C, 64·1; H, 4·7. $C_{10}H_9ON_3$ requires C, 64·1; H, 4·9%).

1-*Benzamidophthalazine* crystallised from 40% aqueous pyridine as yellow prisms, m. p. 146° (Found: C, 72·2; H, 4·2. $C_{15}H_{11}ON_3$ requires C, 72·3; H, 4·5%).

1-p-*Nitrobenzenesulphonamidophthalazine.*—*p*-Nitrobenzenesulphonyl chloride (11 g.) was added to a stirred suspension of 1-aminophthalazine (7·2 g.) in anhydrous pyridine (20 c.c.) at 0°. The mixture was heated to 80° in 30 min. The dark brown solution was poured, with vigorous stirring, into ice-water (100 c.c.) and after several hours the precipitated solid was removed and washed with water to remove pyridine. The solid, after drying, was extracted with boiling acetone, the required product being relatively insoluble. The residue of 1-*p*-nitrobenzenesulphonamidophthalazine (6 g.) was a yellow, crystalline powder, m. p. 223—225°. This was suitable for reduction. Crystallisation from a large volume of acetone followed by sublimation at 175°/0·05 mm. gave a material, m. p. 229—230°, but analyses were unsatisfactory (Found: C, 49·4; H, 3·0. Calc. for $C_{14}H_{10}O_4N_4S$: C, 50·9; H, 3·1%).

1-*Sulphanilamidophthalazine.*—(a) *From the nitro-compound.* 1-*p*-Nitrobenzenesulphonamidophthalazine (3·2 g.) in aqueous-ethanolic hydrochloric acid was reduced with iron as described above. The 1-*sulphanilamidophthalazine*, crystallised from alcohol (1 g. in 500 c.c.), had m. p. 242° (Found: C, 56·1; H, 3·9. $C_{14}H_{12}O_2N_4S$ requires C, 56·0; H, 4·0%).

(b) Via 1-p-*acetamidobenzenesulphonamidophthalazine*. 1-Aminophthalazine (1·4 g.), suspended in anhydrous pyridine (10 c.c.), was treated with *p*-acetamidobenzenesulphonyl chloride (2·3 g.), heated on a water-bath for 1 hr., cooled, and poured into ice-water (100 c.c.). The viscous oil, which separated, solidified at 0° in several hours. The crude sulphonamide was extracted with 1% sodium hydroxide solution (100 c.c.), and the clarified extract made acid (Congo-red) with hydrochloric acid. The precipitated 1-*p*-acetamidobenzenesulphonamidophthalazine (2·1 g.), crystallised from dioxan, had m. p. 236—237°.

The acetyl compound (2 g.) was heated on a water-bath for 1 hr. with alcohol (20 c.c.) containing concentrated hydrochloric acid (8 c.c.). The mixture was diluted with water (80 c.c.) and neutralised with ammonia. The solid obtained was crystallised from alcohol, giving 1-sulphanilamidophthalazine, m. p. and mixed m. p. 242°.

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