355. *The Preparation of some αω-Di-2-quinazolinylalkanes.*

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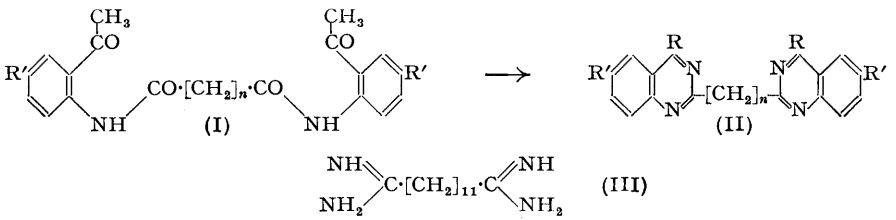
A number of the compounds named in the title have been synthesised by Bischler's cyclisation (*Ber.*, 1891, **24**, 506) of *NN'*-di-*o*-acetylphenyl-adipo- and -sebaco-diamides. The use of high pressure in this reaction has been avoided by effecting cyclisation in molten ammonium acetate. The same conditions applied to 2-formamidoacetophenone give 4-methylquinazoline.

For a number of reasons we were interested in compounds of type (II). Thus, substances of this class bear an obvious relation to numerous therapeutically effective diamidines, *e.g.* (III) (King, Lourie, and Yorke, *Ann. Trop. Med.*, 1938, **32**, 177), and it has recently been stressed that quinazoline should be regarded as a cyclic amidine (Elderfield, Williamson, Gensler, and Kremer, *J. Org. Chem.*, 1947, **12**, 405; Morley and Simpson, *J.*, 1948, 360). Further, we are aiming at the synthesis of αω-diquinazolinylpolyenes, and methods suitable for the synthesis of (II) promised to have limited application in this series also.



Only one compound of type (II) has hitherto been described, König (*J. pr. Chem.*, 1904, **69**, 23) having obtained (II; R = OH; R' = H; $n = 2$) from anthranilic acid and succinonitrile at 150°. The availability of various substituted *o*-aminoacetophenones rendered Bischler's method (*loc. cit.*), involving the cyclisation of an *o*-acylamino-ketone with ammonia under pressure, immediately feasible [I ⟶ II (R = Me)].

The readily available adipic and sebacic acids have so far served as the source of the polymethylene chain, and the related dianilides (I; R' = H, Cl, NO_2, or CN; $n = 4$ or 8) have been prepared from adipoyl or sebacoyl chloride and the relevant *o*-aminoacetophenone. The ease of anilide formation depended decidedly on the nature of the substituent, R', *para* to the amino-group. *o*-Aminoacetophenone reacted violently with both adipoyl and sebacoyl chloride in ethereal solution. 2-Amino-5-chloroacetophenone condensed noticeably less vigorously under these conditions, but the change nevertheless went to completion. A nitro-group however made the amine so weakly basic that, even in boiling pyridine, adipoyl chloride and 2-amino-5-nitroacetophenone reacted only to the extent

of 30%, although the corresponding sebacoyl derivative gave a good yield in boiling toluene. 2-Amino-5-cyanoacetophenone reacted readily with both the acid chlorides in ether, but, in contrast to the other derivatives, the cyano-anilides (I; R′ = CN; $n = 4$ or 8) were appreciably soluble in this medium.

The cyclisation of the anilides, when heated, with aqueous alcoholic ammonia under pressure, was almost quantitative in all cases except that of the adipoyl nitroanilide (I; R′ = NO_2; $n = 4$). This behaviour was at first attributed to the deactivating influence of the nitro-group, but since the corresponding sebacanilide (I; R′ = NO_2; $n = 8$) cyclised quantitatively it is now believed to be due merely to the unusually small solubility of the compound in the reaction medium. Despite sharp melting points, analysis (see Experimental) suggests that the two cyano-quinazolines were not entirely pure.

Clearly, in the absence of large-scale pressure equipment, Bischler's quinazoline synthesis is limited severely in its scale of application. To remove this handicap we have sought new conditions for the reaction, and have effected the cyclisations of this type by passing ammonia through a solution or suspension of the anilides in molten ammonium acetate. In all the cases so far examined, including the adipoyl-nitroanilide which previously presented difficulty, this method resulted in quantitative production of the quinazoline. Quinazolines of the present type are therefore available in any desired quantity.

Our interest in 4-methylquinazoline (Schofield and Swain, *J.*, 1949, **1367**, and unpublished work) prompted the application of the new conditions to *o*-formamidoacetophenone. 4-Methylquinazoline was originally obtained by Bogert and Nabenhauer (*J. Amer. Chem. Soc.*, 1924, **46**, 1932) from 4-methylquinazoline-2-carboxyamide, and by Schofield and Swain (*loc. cit.*) by cyclisation of *o*-formamidoacetophenone with ammonia under pressure. Application of our new conditions to the latter intermediate has now provided 4-methylquinazoline in high yield.

Experimental

M. p.s are uncorrected. Cyclisations in molten ammonium acetate were all carried out (except for the cyano-compounds) as described below for 1 : 4-di-(4-methyl-6-nitro-2-quinazolinyl)-butane, and in all cases gave substantially quantitative yields.

NN′-*Di*-o-*acetylphenyladipodiamide*.—Adipoyl chloride, from adipic acid (1·35 g.) (*Org. Synth.*, 1943, Coll. Vol. 2, 169), was dissolved in dry ether (10 c.c.), and added slowly to a solution of *o*-aminoacetophenone (5 g.) in ether (10 c.c.); a vigorous reaction occurred and a white solid separated. The mixture was set aside for 12 hours, and the product (3·17 g.) was then collected, washed with water, and dried. Recrystallisation from alcohol afforded silky white needles, m. p. 151—152°, of the *diamide* (Found: C, 69·3; H, 7·1. $C_{22}H_{24}O_4N_2$ requires C, 69·5; H, 6·3%).

1 : 4-*Di*-(4-*methyl*-2-*quinazolinyl*)*butane*.—The powdered anilide (0·5 g.), aqueous ammonia (1 c.c.; *d* 0·88), and alcohol (10 c.c.) were heated in a sealed tube at 140° for 6 hours. The resulting solution was evaporated to dryness and the residue (0·4 g.; m. p. 109—111°) was crystallised from dilute ethanol, giving the *diquinazolinylbutane*, m. p. 116—117° (Found: C, 76·9; H, 6·2; N, 16·5. $C_{22}H_{22}N_4$ requires C, 77·2; H, 6·3; N, 16·4%).

NN′-*Di*-o-*acetylphenylsebacodiamide*.—Sebacoyl chloride [prepared from the acid (1·87 g.) in a similar manner to adipoyl chloride] in dry ether (25 c.c.) was added to *o*-aminoacetophenone (5 g.) in the same solvent (25 c.c.). The *anilide* (1·7 g.; m. p. 76—78°), isolated as above, crystallised from alcohol in colourless needles, m. p. 89—90° (Found: C, 71·3; H, 7·4. $C_{26}H_{32}O_4N_2$ requires C, 71·6; H, 7·3%).

1 : 8-*Di*-(4-*methyl*-2-*quinazolinyl*)*octane*.—The above anilide (1·5 g.), alcohol (10 c.c.), and aqueous ammonia (2 c.c.) were treated as described for the butane, and provided on concentration to half-volume a yellow solid (1·15 g.; m. p. 99—100°). The pure *product*, obtained by crystallisation from dilute alcohol, formed pale yellow needles, m. p. 101—102° (Found: C, 77·7; H, 7·1. $C_{26}H_{30}N_4$ requires C, 78·3; H, 7·5%).

NN′-*Di*-(2-*acetyl*-4-*chlorophenyl*)*adipodiamide*.—Adipoyl chloride (from 0·22 g. of the acid) in dry ether (10 c.c.) was added to 2-amino-5-chloroacetophenone (1 g.) in ether (10 c.c.). After being shaken for a few minutes the solution became turbid, and a flocculent precipitate separated. Crystallisation of this from chloroform gave a white solid (0·62 g.; m. p. 219—221°), and further crystallisation gave the pure *anilide* as small white crystals, m. p. 220—221° (Found: C, 58·3; H, 4·8. $C_{22}H_{22}O_4N_2Cl_2$ requires C, 58·8; H, 4·9%).

1 : 4-*Di*-(6-*chloro*-4-*methyl*-2-*quinazolinyl*)*butane*.—From the anilide (0·5 g.), alcohol (9 c.c.), and concentrated ammonia (1 c.c.) there was obtained in the usual way a yellowish solid (0·41 g.). The *quinazoline* separated from alcohol as fine white needles, m. p. 166—167° (Found : C, 64·0; H, 4·9. $C_{22}H_{20}N_4Cl_2$ requires C, 64·2; H, 4·9%).

NN′-*Di*-(2-*acetyl*-4-*chlorophenyl*)*sebacodiamide*.—Prepared as in previous examples, from sebacic acid (1·49 g.) and 2-amino-5-chloroacetophenone (5 g.), the crude compound (1·65 g.) was crystallised several times from alcohol, giving a white crystalline *anilide*, m. p. 137—138° (Found : C, 62·0; H, 6·4. $C_{26}H_{30}O_4N_2Cl_2$ requires C, 61·8; H, 5·9%).

1 : 8-*Di*-(6-*chloro*-4-*methyl*-2-*quinazolinyl*)*octane*.—The chloro-anilide (1·5 g.) gave, by the usual procedure, a product (1·17 g.), m. p. 146—147°, after one crystallisation. The *quinazoline* separated from alcohol as pale yellow needles, m. p. 147—148° (Found : C, 66·1; H, 6·1; N, 12·9. $C_{26}H_{28}N_4Cl_2$ requires C, 66·8; H, 6·0; N, 12·0%).

NN′-*Di*-(2-*acetyl*-4-*nitrophenyl*)*adipodiamide*.—Adipoyl chloride (from 0·4 g. of acid), 2-amino-5-nitroacetophenone (1 g.), and pyridine (10 c.c.) were refluxed for 1 hour, and the product (0·3 g.), collected after cooling, was recrystallised from pyridine, giving the pure *anilide*, m. p. 287—288° (Found : C, 56·2; H, 4·7. $C_{22}H_{22}O_8N_4$ requires C, 56·2; H, 4·7%).

1 : 4-*Di*-(4-*methyl*-6-*nitro*-2-*quinazolinyl*)*butane*.—A suspension of the nitroanilide (0·5 g.) in molten ammonium acetate (5 g.) was heated for 4 hours at 160° with dry ammonia, the mixture was then diluted with water, and the product (0·45 g.; m. p. 218—219°) collected. The *quinazoline* crystallised from alcohol as a white crystalline solid, m. p. 219—220° (Found : C, 60·0; H, 4·7. $C_{22}H_{20}O_4N_6$ requires C, 61·1; H, 4·6%). The bomb-tube method gave 0·4 g. of this product together with 1·1 g. of unchanged material from 1·5 g. of the anilide.

NN′-*Di*-(2-*acetyl*-4-*nitrophenyl*)*sebacodiamide*.—Sebacoyl chloride (from 1·4 g. of acid), 2-amino-5-nitroacetophenone (5 g.), and dry toluene (40 c.c.) were refluxed for 1 hour, and the grey solid was collected and triturated with concentrated hydrochloric acid, giving a product (2·5 g.), m. p. 178—182°. The *anilide* formed lustreless filaments, m. p. 183—184° (Found : C, 58·1; H, 5·6. $C_{26}H_{30}O_8N_4$ requires C, 59·3; H, 5·7%), from chloroform.

NN′-*Di*-(2-*acetyl*-4-*cyanophenyl*)*adipodiamide*.—Adipoyl chloride (from 0·34 g. of acid) in dry ether (10 c.c.) was added to 2-amino-5-cyanoacetophenone (1·5 g.) also in ether (100 c.c.). After 12 hours the precipitate of amine hydrochloride was removed and the solution was concentrated, giving the crude product (1·15 g.). Trituration with concentrated hydrochloric acid, followed by washing with water and crystallisation from chloroform, afforded a pale yellow *diamide*, m. p. 246—247° (Found : C, 66·3; H, 5·4. $C_{24}H_{22}O_4N_4$ requires C, 66·9; H, 5·1%).

1 : 4-*Di*-(6-*cyano*-4-*methyl*-2-*quinazolinyl*)*butane*.—The anilide (0·5 g.), treated as usual in a sealed tube, gave the *quinazoline* (0·25 g. after one crystallisation), which separated from alcohol as a buff solid, m. p. 238—239° (Found : C, 72·4; H, 5·4. $C_{24}H_{20}N_6$ requires C, 73·4; H, 5·1%).

NN′-*Di*-(2-*acetyl*-4-*cyanophenyl*)*sebacodiamide*.—Sebacoyl chloride (from 0·48 g. of acid) in dry ether (10 c.c.) was added to 2-amino-5-cyanoacetophenone (1·5 g.) in the same solvent (100 c.c.). The *anilide* (1·55 g.), isolated as before, separated from alcohol as a yellow solid, m. p. 179—180° (Found : C, 68·5; H, 6·3. $C_{28}H_{30}O_4N_4$ requires C, 69·1; H, 6·2%).

1 : 8-*Di*-(6-*cyano*-4-*methyl*-2-*quinazolinyl*)*octane*.—The anilide (0·5 g.), cyclised under pressure, gave the *quinazoline* (0·23 g. after one crystallisation from dilute ethanol), which was a cream-coloured solid, m. p. 197—198° (Found : C, 73·4; H, 6·6. $C_{28}H_{28}N_6$ required C, 74·9; H, 6·3%).

4-*Methylquinazoline*.—A suspension of *o*-formamidoacetophenone (8·9 g.) in molten ammonium acetate (90 g.) was maintained at 155—160° for 3 hours, during the passage of a vigorous stream of ammonia. The resulting yellow solution was diluted with water and extracted with ether, and the ethereal solution was washed with dilute sodium hydroxide solution and dried (Na_2CO_3). Removal of the ether and distillation of the residue (7·2 g.) gave a clear pale yellow oil (6·9 g.), b. p. 140—142°/20 mm. The product was characterised as 4-methylquinazoline by conversion into the picrate (Schofield and Swain, *loc. cit.*).

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