590. *Synthetical Methods for the Preparation of 3-Amino-2(1H)-quinolones.*[1]

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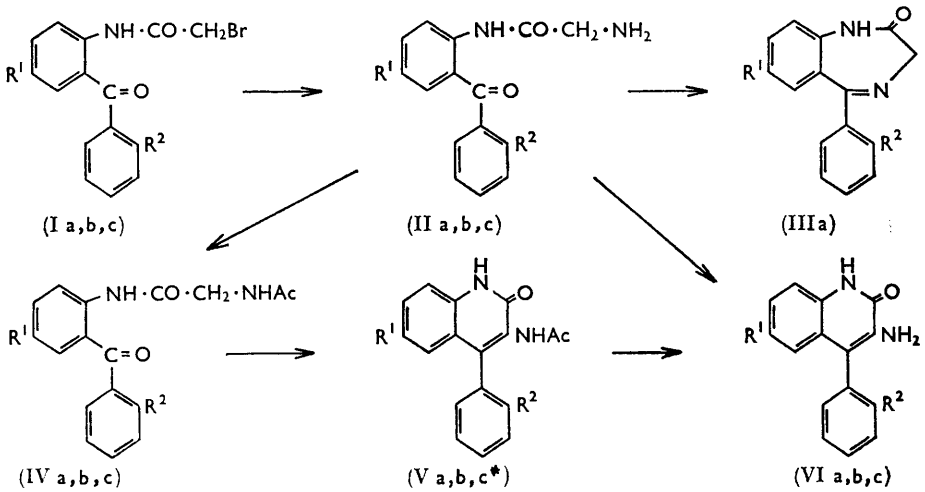
The preparation of substituted 1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones (III) from the appropriate 2-amino-2′-benzoylacetanilides (II) was often accompanied by the formation of small amounts of the corresponding substituted 3-amino-4-phenyl-2(1*H*)-quinolones (VI). These quinolones have now been synthesized in high yield by cyclization of 2-acetamido-2′-benzoylacetanilides (IV) followed by hydrolysis of the 3-acetamido-derivatives (V). Alkylation of the quinolones at the 1-position or at the 3-amino-group was effected by means of the appropriate alkylating agent. However, 3-alkylamino-derivatives (VIII) and 1-alkyl-3-alkylamino-derivatives (IX) were prepared more easily by cyclization of the corresponding alkylamino-acetanilides (VII).

In earlier publications concerning the synthesis of 1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones the isolation of 3-amino-4-phenylquinolones as by-products of the ring closure of 2-amino-2′-benzoylacetanilides was reported.[2,3]

In general the aminoquinolones (VI) had higher melting points than had the isomeric benzodiazepinones (III), while a comparison of their infrared (i.r.) spectra and ultraviolet (u.v.) spectra showed great differences. The i.r. spectrum of compound (VIa) in a potassium bromide pellet showed two NH bands at 3470 and 3370 cm.$^{-1}$ and a strong carbonyl band at 1656 cm.$^{-1}$, whereas compound (IIIa) in a potassium bromide pellet showed a single broad NH absorption band at 3240 cm.$^{-1}$ and the lactam carbonyl band at 1695 cm.$^{-1}$. The characteristic u.v. spectrum is shown in Fig. 1.



* Compound (Vc) was not isolated.

In some instances aminoquinolones could be obtained (i) by heating aminobenzoylacetanilides (II) at temperatures above that of the melting point of the product, and (ii) by heating, under reflux, concentrated solutions of compounds (II) in high-boiling solvents (*e.g.*, toluene). Neither of these methods gave results of practical value.

[1] Presented, in part, at the XIXth Congress, I.U.P.A.C., London, July 1963.
[2] Bell, Sulkowski, Gochman, and Childress, *J. Org. Chem.*, 1962, **27**, 562.
[3] Sternbach, Fryer, Metlesics, Reeder, Sach, Saucy, and Stempel, *J. Org. Chem.*, 1962, **27**, 3788.

3-Aminoquinolones were synthesized efficiently by protecting the amino-group of the aminobenzoylacetanilide (II) before cyclization. Acetylation of compound (IIa) gave the acetamido-compound (IVa) in excellent yield, and this was subsequently converted into the 3-acetamidoquinolone (Va) by heating it under reflux in pyridine–piperidine. Hydrolysis of the acetyl group with 70—90% sulphuric acid gave compound (VIa). This sequence of reactions constitutes the best known method for the preparation of 3-amino-4-phenyl-2(1*H*)-quinolones; compound (VIa) was obtained from compound (IIa) in an overall yield of 66%.

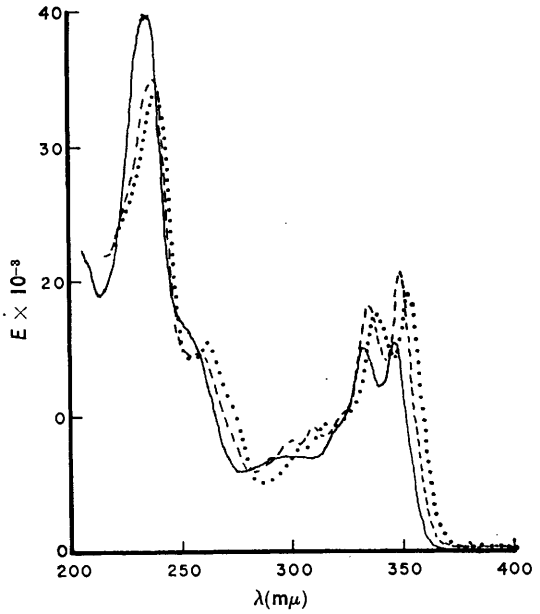


FIG. 1.

———, 3-Amino-6-chloro-4-phenyl-2(1*H*)-quinolone.
— — —, 6-Chloro-3-methylamino-4-phenyl-2(1*H*)-quinolone.
. . . . . 6-Chloro-1-methyl-3-methylamino-4-phenyl-2(1*H*)-quinolone.

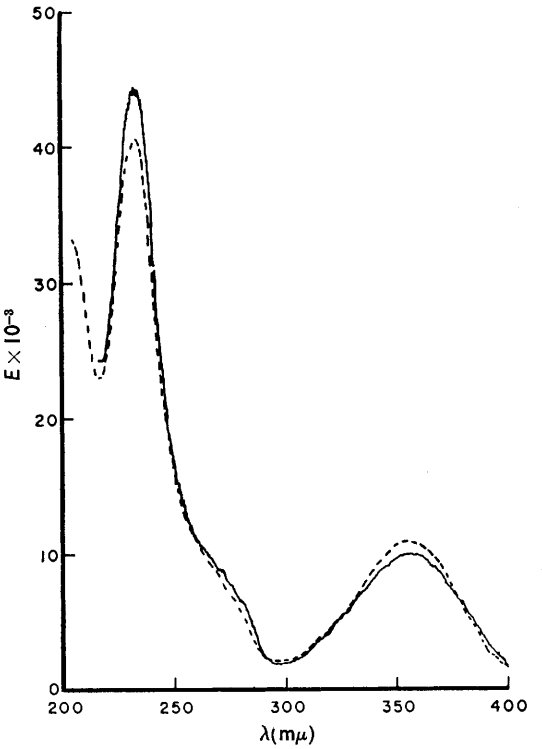


FIG. 2.

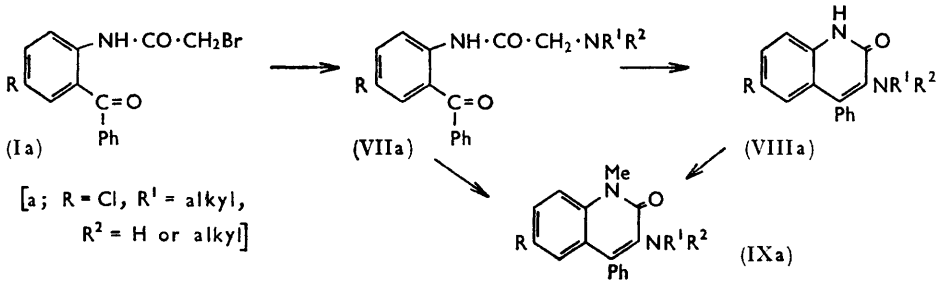
———, 6-Chloro-3-dimethylamino-1-methyl-4-phenyl-2(1*H*)-quinolone.
— — —, 6-Chloro-3-dimethylamino-4-phenyl-2(1*H*)-quinolone.

Two other aminoquinolones (VIb) and (VIc), were also synthesized as outlined above. The acetylation of compounds (IIb) and (IIc) proceeded again with excellent yield. The yield of compound (Vb) was, however, lower than in the previous case and the overall yield [(IIb) to (VIb)] was 30%. Cyclization of compound (IVc) gave two products, a small amount of the expected acetamidoquinolone (Vc) (identified by its i.r. spectrum), and the hydrolysed compound (VIc). Hydrolysis of compound (Vc) gave a combined yield of compound (VI) (from IIc) of 46%.

By treating the 3-aminoquinolones with sodium methoxide, followed by the appropriate alkyl halide, 1-alkylation was readily effected. The primary amino-group, however, was not so easily alkylated. Prolonged treatment, even at high temperatures, with such alkylating agents as dimethyl sulphate gave only small yields of the 3-dimethylamino-1-methylquinolones. 3-Alkylamino- and 3-dialkylamino-quinolones (VIII) were synthesized by

cyclization of the corresponding alkylaminobenzoylacetanilides (VII). These intermediates were, in turn, prepared by treatment of the bromobenzoylacetanilides (I) with primary or secondary amines. Cyclizations were by use of a molar equivalent of acetic anhydride in toluene, and yields of 60—90% were obtained.

By treating the dialkylaminobenzoylacetanilides (VII) with sodium methoxide and then with methyl iodide, 1-alkylation and ring closure occurred simultaneously, giving 1-methyl-3-dialkylaminoquinolones (IX) directly. Alkylation of the 3-mono- or di-alkylaminoquinolones (VIII) by the above procedure gave the corresponding 1-alkyl derivative (IX). All five methyl derivatives of compound (VIa) were obtained.



The characteristic u.v. spectra are retained only when the 3-amino-group bears at least one hydrogen atom (Fig. 1). 3-Dialkylaminoquinolones which cannot exist in the imino-form no longer exhibit the two sharp absorption peaks in the 330—360 mμ region and, in addition to the strong band at 238 mμ, show only a broad absorption band in the 360 mμ region (Fig. 2).

Experimental

All melting points were determined microscopically on a hot-stage apparatus and are corrected. Ultraviolet spectra were determined in isopropyl alcohol on a Carey model 14 spectrophotometer.

2-Acetamido-2′-benzoyl-4′-chloroacetanilide (VIa).—A mixture of 2-amino-2′-benzoyl-4′-chloroacetanilide (IIa) [3] (6·8 g.), acetic anhydide (9·54 g.), and sodium acetate hydrate (8·7 g.) was warmed on a steam-bath for 3 hr. Hot water (500 ml.) was added and the crystalline product was filtered off, washed with water, and recrystallized from acetone–hexane to give *compound* (IVa) (6·4 g., 81%), white rods, m. p. 137—139° (Found: C, 61·5; H, 4·7. $C_{17}H_{15}ClN_2O_3$ requires C, 61·7; H, 4·6%).

3-Acetamido-6-chloro-4-phenyl-2(1H)-quinolone (Va).—A solution of compound (IVa) (2·0 g.) in a mixture of piperidine (15 ml.) and pyridine (5 ml.) was refluxed for 6 hr., then concentrated *in vacuo* to an oil. Crystallization from methanol–water gave compound (Va) (1·7 g., 90%) as the *hemihydrate*, white rods, m. p. 210—214°, reset m. p. 276—284° (Found: C, 63·5; H, 4·6. $C_{17}H_{13}ClN_2O_2,\frac{1}{2}H_2O$ requires C, 63·5; H, 4·1%).

3-Amino-6-chloro-4-phenyl-2(1H)-quinolone (VIa).[2]—A solution of compound (Va) (2·7 g.) in a mixture of 70% (v/v) sulphuric acid (40 ml.) and acetic acid (5 ml.) was refluxed for 5 hr. The reaction mixture was poured on ice (100 g.), diluted to 250 ml. with water, and adjusted to pH 9 with sodium carbonate solution (30 g./100 ml.). The crude precipitate was separated by filtration and recrystallized from acetone to give *compound* (VIa) (2·02 g., 88%), white needles, m. p. 239—242° (Found: C, 66·6; H, 3·8. $C_{15}H_{11}ClN_2O$ requires C, 66·55; H, 4·1%).

2-Amino-4′-chloro-2′-o-methoxybenzoylacetanilide (IIb).—A solution of 2-bromo-4′-chloro-2′-*o*-methoxybenzoylacetanilide (Ib) [3] (1·55 g.) in dichloromethane (20 ml.) was poured into liquid ammonia (50 ml.). After 15 min. the ammonia was evaporated on the steam-bath. The organic layer was washed with water, dried (Na_2SO_4), and concentrated to an oil. Crystallisation from ether–light petroleum gave *compound* (IIb) (1·05 g., 82%), white needles, m. p. 109·5—111·5° (Found: C, 60·3; H, 5·1. $C_{16}H_{15}ClN_2O_3$ requires C, 60·2; H, 4·7%).

2-Acetamido-4′-chloro-2′-o-methoxybenzoylacetanilide (IVb).—Compound (IIb) (15·0 g.) was treated as described for compound (IVa) to give *compound* (IVb) (13·65 g., 81%), white

needles, m. p. 190—192°, from dichloromethane–ether (Found: C, 56·8; H, 4·8. $C_{18}H_{17}ClN_2O_4,H_2O$ requires C, 57·1; H, 5·1%).

2-*Acetamido*-2′-*benzoyl*-4′-*nitroacetanilide* (IVc).—2-Amino-2′-benzoyl-4′-nitroacetanilide (IIc) [4] (2·94 g.) was treated as described for compound (IVa) to give *compound* (IVc) (2·63 g., 79%), white rods, m. p. 160—162°, from acetone–light petroleum (Found: C, 59·6; H, 4·4. $C_{17}H_{15}N_3O_5$ requires C, 59·8; H, 4·4%).

3-*Acetamido*-6-*chloro*-4-o-*methoxyphenyl*-2(1*H*)-*quinolone* (Vb).—Compound (IVb) was cyclized as described for compound (Va) to give, after crystallization from methanol–ether, *compound* (Vb) (5·65 g., 58%), white prisms, m. p. 268—274° (Found: C, 63·3; H, 3·8. $C_{18}H_{15}ClN_2O_3$ requires C, 63·1; H, 4·4%).

3-*Amino*-6-*chloro*-4-o-*methoxyphenyl*-2(1*H*)-*quinolone* (VIb).—A suspension of compound (Vb) (1 g.) in hydrochloric acid (25 ml.) was heated under reflux for 120 hr. The mixture was cooled, diluted to 100 ml. with water, and filtered. The precipitate was washed until acid-free, and recrystallized from acetone to give *compound* (VIb) (0·65 g., 75%), white prisms, m. p. 248—250° (Found: C, 64·1; H, 4·4. $C_{16}H_{13}ClN_2O_2$ requires C, 63·9; H, 4·4%).

3-*Amino*-6-*nitro*-4-*phenyl*-2(1*H*)-*quinolone* (VIc).—Compound (IVc) (2·5 g.) was cyclized as already described, and on recrystallization from dilute acetic acid gave compound (VIc) (0·90 g.), yellow prisms, m. p. 330—332·5°. Concentration of the mother-liquors and filtration through activated neutral alumina with dichloromethane gave 1·14 g. of material identified by its i.r. spectra as 3-acetamido-6-nitro-4-phenyl-2(1*H*)-quinolone (Vc). This crude material was then hydrolysed in ethanolic 3N-sodium hydroxide for 3 hr. Neutralization of the mixture with 3N-hydrochloric acid gave an additional 0·30 g. of *compound* (VIc), m. p. and mixed m. p. 330—332° (total yield 58%) (Found: C, 64·25; H, 4·1. $C_{15}H_{11}N_3O_3$ requires C, 64·05; H, 3·9%).

3-*Amino*-6-*chloro*-1-*methyl*-4-*phenyl*-2(1*H*)-*quinolone* (IXa; $R^1 = R^2 = H$).—A mixture of compound (VIa) (0·40 g.), methanol (30 ml.), and a solution of sodium methoxide (0·097 g.) in methanol was stirred at room temperature for 30 min. and then cooled in ice. Methyl iodide (2·13 g.) was added, and the solution was stirred at room temperature for 3 hr. and concentrated *in vacuo* to an oil. A solution of the oil in dichloromethane (50 ml.) was washed with water and then brine, dried (Na_2SO_4), and filtered over a small amount of alumina. [Starting material (0·18 g.) was recovered by further elution of the alumina with methanol.] Concentration of the filtrate and crystallization of the residual oil from acetone–light petroleum gave *compound* (IXa; $R^1 = R^2 = H$) (0·21 g., 50%), white rods, m. p. 130—133° (Found: C, 67·8; H, 4·6. $C_{16}H_{13}ClN_2O$ requires C, 67·5; H, 4·6%).

2′-*Benzoyl*-4-*chloro*-2-*methylaminoacetanilide* (VIIa; $R^1 = H$, $R^2 = Me$).—A solution of 2′-benzoyl-2-bromo-4′-chloroacetanilide (Ia) [2] (25 g.) in dichloromethane (250 ml.) was saturated with methylamine for 30 min. at 5—10°. The reaction mixture was kept overnight at room temperature, then washed with water, dried (Na_2SO_4), and concentrated to an oil. Crystallization from ether–light petroleum gave *compound* (VIIa; $R^1 = H$, $R^2 = Me$) (15·5 g., 73%) as white prisms, m. p. 89—92° (Found: C, 63·6; H, 5·3. $C_{16}H_{15}ClN_2O_2$ requires C, 63·5; H, 5·0%).

2′-*Benzoyl*-4′-*chloro*-2-*dimethylaminoacetanilide* (VIIa; $R^1 = R^2 = Me$).—On substitution of dimethylamine for methylamine in the above reaction, compound (Ia) (25·0 g.) gave *compound* (VIIa; $R^1 = R^2 = Me$) (21·2 g., 94·5%) as white prisms (from ether), m. p. 120—122° (Found: C, 64·2; H, 5·15. $C_{17}H_{17}ClN_2O_2$ requires C, 64·45; H, 5·4%).

6-*Chloro*-3-*methylamino*-4-*phenyl*-2(1*H*)-*quinolone* (VIIIa; $R^1 = H$, $R^2 = Me$).—A mixture of compound (VIIa; $R^1 = H$, $R^2 = Me$) (6·05 g.), 0·1N-sodium hydroxide (105 ml.), and ethanol (100 ml.) was refluxed for 2 hr., and then cooled. The precipitate was filtered off and washed free from alkali with water. Crystallization from acetone gave *compound* (VIIIa; $R^1 = R^2 =$ Me) (4·8 g., 84%), white rods, m. p. 271—275° (Found: C, 67·8; H, 4·6. $C_{16}H_{13}ClN_2O$ requires C, 67·5; H, 4·6%). [Some hydrolysis product, 2-amino-5-chlorobenzophenone (0·5 g.), was obtained from the filtrate.]

6-*Chloro*-3-*dimethylamino*-4-*phenyl*-2(1*H*)-*quinolone* (VIIIa; $R^1 = R^2 = Me$).—A mixture of compound (VIIa; $R^1 = R^2 = Me$) (6·3 g.), toluene (75 ml.), and acetic anhydride (2·04 g.) was refluxed for 26 hr. and then concentrated under reduced pressure. The oil was crystallized from acetone to give *compound* (VIIIa; $R^1 = R^2 = Me$) (5·1 g., 85·5%), pale yellow prisms, m. p. 295—296° (Found: C, 68·4; H, 5·3. $C_{17}H_{15}ClN_2O$ requires C, 68·3; H, 5·1%).

[4] Sternbach, Fryer, Keller, Metlesics, Sach, and Steiger, *J. Medicin. Chem.*, 1963, **6**, 261.

6-*Chloro*-1-*methyl*-3-*methylamino*-4-*phenyl*-2(1*H*)-*quinolone* (IXa; R^1 = H, R^2 = Me).—A mixture of compound (VIIIa; R^1 = H; R^2 = Me) (2·85 g.), a solution of sodium methoxide (0·648 g.) in methanol, and *NN*-dimethylformamide (15 ml.) was stirred at room temperature for 20 min. and then cooled to 10°. Methyl iodide (1·99 g.) was added, the solution was stirred at room temperature for 3 hr., and the product was precipitated by slow addition of water (75 ml.). The precipitate was separated by filtration, washed with water, and crystallized from ether to give *compound* (IXa; R^1 = H, R^2 = Me) (2·7 g., 90%) as prisms, m. p. 184—185° (Found: C, 68·6; H, 5·1. $C_{17}H_{15}ClN_2O$ requires C, 68·3; H, 5·1%).

6-*Chloro*-3-*dimethylamino*-1-*methyl*-4-*phenyl*-2(1*H*)-*quinolone* (IXa; R^1 = R^2 = Me).—(*a*) A mixture of compound (VIIa; R^1 = R^2 = Me) (6·32 g.), *NN*-dimethylformamide (20 ml.), and a solution of sodium methoxide (1·32 g.) in methanol was stirred at room temperature for 15 min. Methyl iodide (7·1 g., 50 mmole) was added (a vigorous heat of reaction elevated the temperature to 61°), the mixture was stirred for 30 min., and the product was obtained as described in the preceding example. Recrystallization from hexane gave *compound* (IXa; R^1 = R^2 = Me) (4·6 g., 74%) as pale yellow prisms, m. p. 143—147° (Found: C, 69·65; H, 5·6. $C_{18}H_{17}ClN_2O$ requires C, 70·0; H, 5·55%).

(*b*) A mixture of compound (VIIIa; R^1 = R^2 = Me) (1·0 g.), *NN*-dimethylformamide (5 ml.), and sodium methoxide (0·218 g.) in methanol, was stirred at room temperature for 20 min. and then cooled. Methyl iodide (0·686 g., 4·83 mmole) was added, and after 3 hr. compound (IXa; R^1 = R^2 = Me) (0·95 g., 90%) was isolated as described above; it had m. p. and mixed m. p. 143—147°.

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