A General and Practicable Synthesis of Polycyclic Heteroaromatic Compounds. Part 4.[1] A Rationale for the Mechanism of the Synthesis

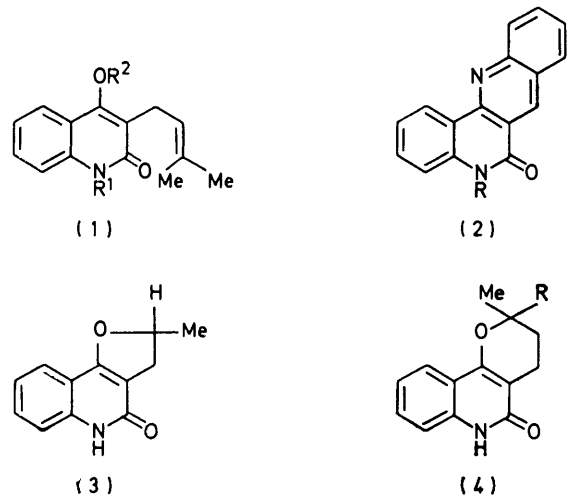
By **Janet L. Asherson, Orhan Bilgic,** and **Douglas W. Young,*** School of Molecular Sciences, University of Sussex, Falmer, Brighton BN1 9QJ

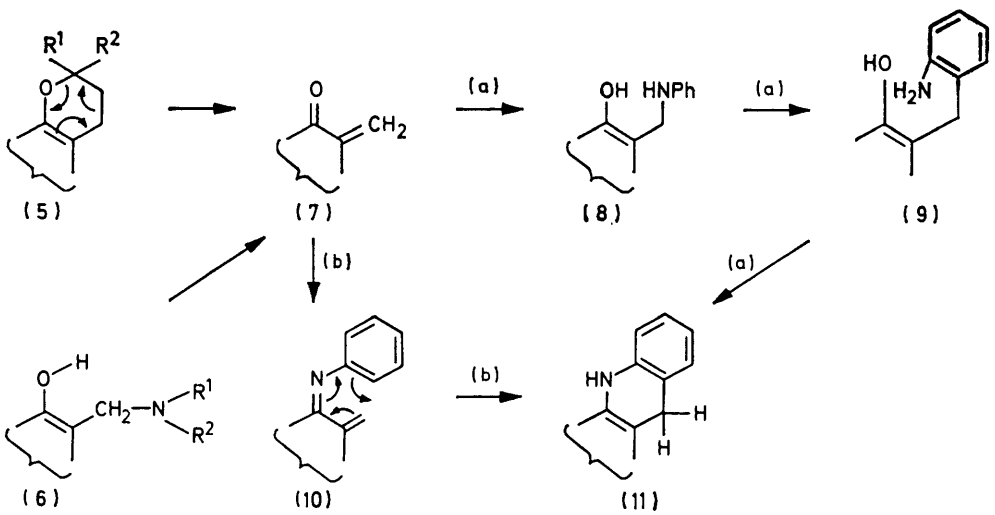
Studies on aspects of the mechanism of our general synthesis of polycyclic heteroaromatic compounds suggest that the reaction sequence outlined in Scheme 2 is followed. Under the conditions of our synthesis, the *ortho*-rearrangement (8) ⟶ (9) is preferred to the *para*-rearrangement which is known to occur in acid conditions. Aniline Mannich bases (29) are converted to benz[*a*]acridines (30) in an *inter*molecular reaction. The synthesis appears to be restricted to substrates where the putative intermediate (9) is not part of an amide group. In the course of these studies effective syntheses of the tricyclic compounds (24) and (25) have been discovered.

DURING studies on the synthesis of alkaloids of structural type (1) we noted [2] that reaction of 3-dimethylallyl-4-hydroxy-2-quinolones (1; R^2 = H) with aniline in refluxing diphenyl ether gave tetracyclic heteroaromatic compounds (2). Since 3-allyl-4-hydroxy-2-quinolone gave the product of Markownikoff addition (3),[2] we concluded that the synthesis of the compounds (2) had proceeded *via* the tricyclic compound (4; R = Me) as outlined in Scheme 1. Retro-Diels–Alder reaction would now yield a quinone methide (7) as shown. This might now add aniline either as shown in path (a) or path (b) to yield the polycyclic compounds (2) *via* the dihydro-intermediates (11).

We had no evidence that this scheme actually represented the reaction pathway but were able to use the idea to develop a very useful general synthesis of polycyclic heteroaromatic compounds.[1,3,4] The putative quinone methods of ' weakly aromatic ' compounds were found best to be generated by the retro-Diels–Alder approach,[3,4] whereas synthesis from ' more aromatic ' substrates required use of Mannich bases (6).[1] Although useful in synthetic planning, it seemed appropriate to test the reality of the proposed scheme.

It is more usual [5] for quinone methides to react with nucleophiles by 1,4-addition as in route (a) rather than by 1,2-addition as in route (b) and so the former route seemed the more likely. This route would require that the first-formed adduct (8) rearrange to the *ortho*-substituted aniline (9). Such rearrangements are known [6] but, although the Mannich base (12) is reported [7] to rearrange to the *ortho*-substituted product (13), a





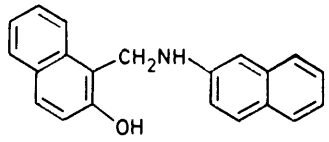
SCHEME 1

general review of aromatic rearrangements suggests [6] that alkyl migration from nitrogen usually results in *para*-substituted products. Acid-catalysed rearrangement of a variety of Mannich bases (14) has been shown [8-10] to lead to the *para*-substituted products and we felt that it would be of interest to re-investigate one of these rearrangements in the context of the Mannich base approach to our synthesis [Scheme 1, (6) ⟶ (7) ⟶ (8) ⟶ (9) ⟶ (11)]. We chose the Mannich base (16; $R^1 = R^2 = Me$) [11] as the starting point for the investigation, since acid-catalysed rearrangement of the suggested intermediate (16; $R^1 = H$, $R^2 = Ph$) resulted in the *para*-substituted product (17).[9,10] The Mannich base (16; $R^1 = R^2 = Me$) [11] was therefore heated with one molar equivalent of aniline in refluxing diphenyl ether, when two isomeric products were obtained. The minor isomer, obtained in 9% yield, was evidently the *para*-rearrangement product (17; $R^1 = H$) and, although it had a different melting point from that quoted, its spectra were identical to those of a sample prepared by the literature method.[10] Acetylation of both samples gave products which were identical in all respects. The major isomer, $C_{18}H_{19}N_3O$, which was obtained in 38% yield, was evidently the *ortho*-rearrangement product (18; R = H) since it could be converted into a monoacetate, $C_{20}H_{21}N_3O_2$. Acetylation is known [12] to result in a large downfield shift, in the ^1H n.m.r. spectrum, of the *ortho* protons of anilines, and in our product *one* proton had been deshielded by *ca.* 0.7 p.p.m., appearing as a broad doublet.

It is now evident that the proposed *ortho*-intermediate (9) can be formed under the reaction conditions of our synthesis. In the example we have chosen the reaction stops at the stage (18; R = H) rather than going on to cyclise to (19), and so the fact that the carbonyl group is part of an amide function seems to preclude further reaction. This represents a restriction to our general synthesis of polycyclic heteroaromatic compounds.

We now decided to investigate the possible intermediacy of the compound (8) in our synthesis and to this end prepared the imine (20) from the corresponding aldehyde.[13] Borohydride reduction, however, resulted in the formation of 4-hydroxy-3-methyl-2-quinolone (21) rather than the desired Mannich base (22; $R^1 = Ph$, $R^2 = H$). Although Mannich bases are known to undergo hydrogenolysis,[14] this reaction had occurred under very mild conditions and a mechanism similar to that proposed [15] for the reduction of the 3-acyl derivatives (23) to the corresponding 3-alkyl compounds may be implied. Hence protection of the 4-hydroxy-group might allow us to obtain the desired Mannich base. In endeavouring to protect this group, two interesting and useful cyclisation reactions were discovered.

When the imine (20) was reacted with acetic anhydride–pyridine, a product was obtained in 58% yield. This proved to be the tricyclic compound (24) which had been synthesised by more laborious methods.[13,16] This facile one-step reaction therefore represents an improved synthesis of the compound. Treatment of the imine (20) with diazomethane gave a compound $C_{17}H_{14}N_2O_2$ in *ca.* 20% yield. This was evidently the angular furoquinoline derivative (25; R = NHPh) from its i.r. and u.v.[17] spectral characteristics. The analogous compound (25; R = H) had already been synthesised [17] and we were able to obtain this compound in 38% yield by reacting the Mannich base (22; $R^1 = R^2 = Me$) with diazomethane. Cyclisation reactions using quaternised Mannich bases and diazomethane [18] or other reagents [19] have been used to prepare furan derivatives in other series but the reaction with the imine (20) is without precedent. Huffman [20] found that 3-acyl-4-hydroxy-2-quinolones (23) gave *linear* furano-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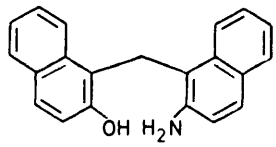
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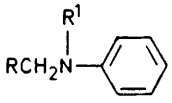
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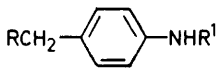
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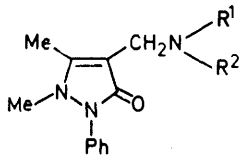
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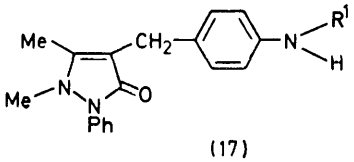
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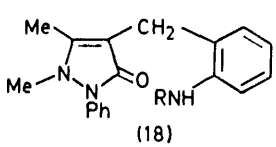
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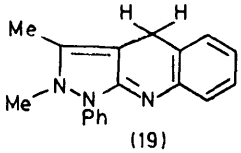
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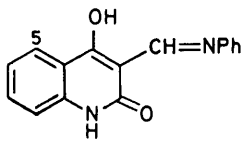
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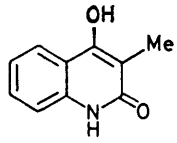
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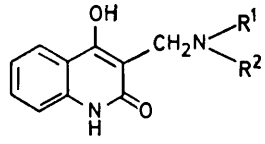
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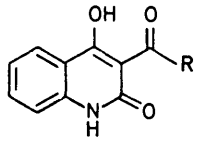
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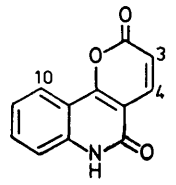
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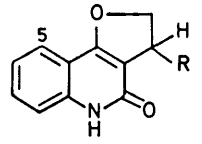
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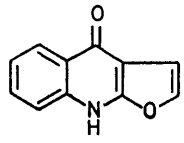
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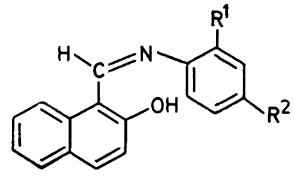
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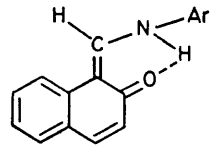
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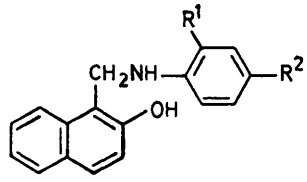
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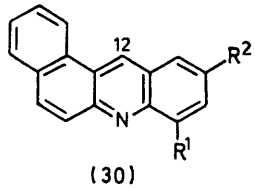
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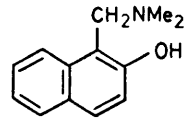
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quinolones (26) with diazomethane and his structural evidence seems unassailable. The evidence for our angular structures (25) is, however, equally good, the compounds having characteristic u.v.,[17] i.r.[17] and ^{1}H n.m.r.[21] spectra.

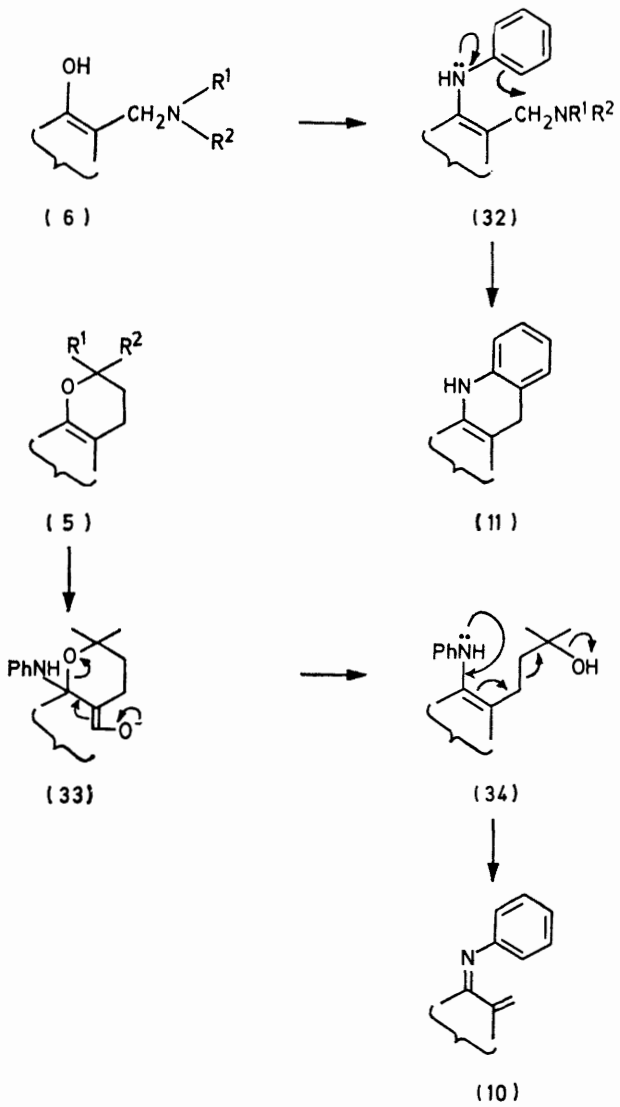
Since the aniline Mannich bases of 4-hydroxy-2-quinolone had proved so difficult to obtain, the more aromatic β-naphthol Mannich bases were investigated. A series of imines (27; $R^1 = R^2 = H$), (27; R^1 = OMe, $R_2 = H$), (27; $R^1 = H$, R^2 = OMe), and (27; $R^1 = H$, R^2 = Me) were prepared, and all exhibited evidence for the presence of the tautomeric form (28) in the ^{1}H n.m.r. spectrum,[22] the C*H*=N proton appearing as a doublet. Although borohydride reduction of the more electron-rich imines was accompanied by extensive over-reduction to 1-methyl-2-naphthol,[23] the aniline and *p*-toluidine imines (27; $R^1 = R^2 = H$) and (27; $R^1 = H$, R^2 = Me) reduced 'normally' to yield the Mannich bases (29; $R^1 = R^2 = H$) and (29; $R^1 = H$, R^2 = Me), respectively. We were now in a position not only to test for the intermediacy of compounds such as (8) in our synthesis, but also to examine the question of whether subsequent reaction would be intermolecular or intramolecular.

When the Mannich base (29; $R^1 = R^2 = H$) was heated in refluxing diphenyl ether for 24 h, the benzacridine (30; $R^1 = R^2 = H$) [1] was obtained in 50% yield. Similar treatment of (29; $R^1 = H$, R^2 = Me) resulted in a 23% yield of the benzacridine (30; $R^1 = H$, R^2 = Me) [1] together with the imine (27; $R^1 = H$, R^2 = Me) in 60% yield. Careful exclusion of air failed to increase the yield of the benzacridine (30; $R^1 = H$, R^2 = Me). The yields of the benzacridines were much lower than in the general synthesis from the Mannich base (31) [1] and this would argue against the *direct* involvement of the intermediate (8) in the synthetic scheme.

When the Mannich base (29; $R^1 = H$, R^2 = Me) was heated with one molar equivalent of aniline in refluxing diphenyl ether for 24 h, the crude reaction product showed two singlets characteristic of H-12 in the benzacridines (30; $R^1 = R^2 = H$) and (30; $R^1 = H$, R^2 = Me). Integration of these peaks indicated the ratio of these two compounds to be *ca.* 2 : 1 in favour of the *inter*molecular product (30; $R^1 = R^2 = H$). When the reaction was repeated using ten molar equivalents of aniline, the crude reaction product was evidently contaminated with 5,12-dihydrobenzacridine(s) but oxidation using acetic anhydride [1] gave a cleaner product where the ratio of the benzacridines (30) was *ca.* 4 : 1 in favour of the *inter*molecular product.

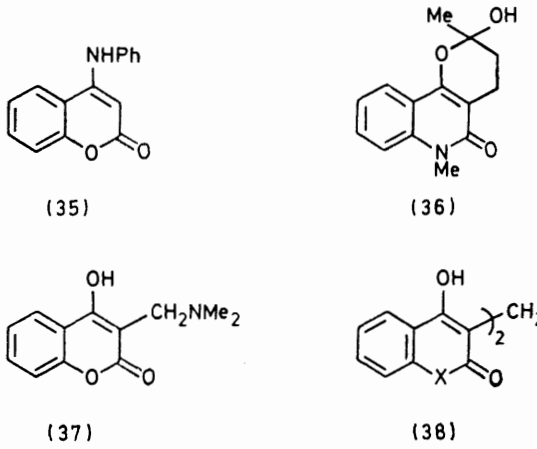
The Mannich base (29; $R^1 = R^2 = H$) was now heated with one molar equivalent of *para*-toluidine in refluxing diphenyl ether. The product was contaminated with the imine (27; $R^1 = H$, $R^2 = Me$) which was removed by preparative t.l.c. yielding a mixture of benzacridines (30) in which the ratio was *ca.* 4 : 1 in favour of the *inter*molecular product (30; $R^1 = H$, $R^2 = Me$). Finally the Mannich base (29; $R^1 = R^2 = H$) was heated with *ortho*-anisidine when the two compounds (30; $R^1 = R^2 = H$) and (30; $R^1 = OMe$, $R^2 = H$) could be separated by preparative t.l.c. The isolated ratio was 5 : 1 in favour of the *inter*molecular product (30; $R^1 = OMe$, $R^2 = H$).

We have now shown that the reaction sequence (8) ⟶ (11) of Scheme 1 is feasible under the conditions of our synthesis and that it is *inter*molecular. The yields, however, make it unlikely that this sequence plays a large part in our synthetic scheme. An alternative route for the synthesis is suggested in Scheme 2.



SCHEME 2

An intermediate (32) might be formed either from the quinone methide (7) or as shown in Scheme 2. The finding of the anilinocoumarin (35) as a biproduct in one heterocyclic synthesis [4] may support the existence of such an intermediate and the fact that the amide (16) does not proceed to the polycyclic product (19) may be due to its inability to form such an intermediate so that reaction proceeds to (18) by an alternative pathway.



In an attempt to provide support for the intermediacy of quinone methides (7) in our synthesis, the pyranoquinolone (36) was heated successively in refluxing diphenyl ether with the dienophiles ethyl vinyl ether, dihydropyran, and maleic anhydride. In all cases starting material was recovered unchanged whereas, in a control experiment using aniline, an 80% yield of the heterocyclic compound (2; R = Me) was obtained. When the Mannich bases (22; $R^1 = R^2 = Me$) and (37) were heated with maleic anhydride, again no adduct of the quinone methide was obtained, the products of the reaction being the adducts (38; X = NH) and (38; X = O), respectively, together with an amide of maleic or fumaric acid. Control experiments in the presence of aniline again gave the expected heterocyclic products.

It would seem, therefore, that although we have found the quinone methide rationale of Scheme 1 useful in planning syntheses,[1-4] there is no evidence for the existence of a quinone methide intermediate under the conditions of our reaction. Indeed it would seem that the presence of aniline is necessary to initiate the breakdown of the compound (36). This and the other evidence would tend to support the route outlined in Scheme 2 as a rationale for our generalised synthesis of polycyclic heteroaromatic compounds.

EXPERIMENTAL

General details are as for Part 1.[3]

Reaction of 1-*Phenyl*-2,3-*dimethyl*-4-(NN-*dimethylaminomethyl*)-*pyrazol*-5-*one* (16; $R^1 = R^2 = Me$) *with Aniline.*—1-Phenyl-2,3-dimethyl-4-(*NN*-dimethylaminomethyl)-pyrazol-5-one [11] (2.45 g, 10 mmol) and aniline (930 mg, 10 mmol) were heated to reflux in diphenyl ether (25 ml) under nitrogen for 70 h. The solvents were removed *in vacuo* to

yield a gum which was purified by preparative t.l.c. (SiO_2; Et_2O). The upper layer was recrystallised from ethyl acetate and was the ortho-*product* (18; R = H) (1.121 g, 38%), m.p. 192—193 °C (Found: C, 73.8; H, 6.6; N, 14.3; $C_{18}H_{19}N_3O$ requires C, 73.7; H, 6.5; N, 14.3%); *m/e* 293 (M^+); $\nu_{max.}$ ($CHCl_3$) 3 380 (NH) and 1 650 (C=O) cm^{-1}; $\lambda_{max.}$ (MeOH) 230 and 277 nm; τ ($CDCl_3$) 2.6—3.45 (9 H, m, aromatics), 5.44 (2 H, br s, NH_2), 6.5 (2 H, s, CH_2), 7.06 (3 H, s, NMe), and 7.78 (3 H, s, CMe). The lower layer from the plate was recrystallised from ethanol and was the para-*adduct* (17; R^1 = H) (275 mg, 9%), m.p. 118—120 °C (lit.,[10] m.p. 140—145 °C); *m/e* 293 (M^+) $\nu_{max.}$ (KBr) 3 420, 3 340 (NH), 1 615 (C=O), and 1 600 (aromatic) cm^{-1}; $\lambda_{max.}$ (MeOH) 237, and 274 nm; τ ($CDCl_3$) 2.6—2.8 (5 H, m, aromatics), 2.95 and 3.45 (4 H, 2 × AB, J_{AB} 8 Hz, aromatics), 6.51 (2 H, s, CH_2), 7.1 (3 H, s, NMe), and 7.92 (3 H, s, CMe).

Monoacetylation of the Adduct (18; R = H).—The *ortho*-product (18; R = H) from the above reaction (100 mg, 0.34 mmol) was dissolved in pyridine (1 ml) with acetic anhydride (1 ml) and left overnight at room temperature. The solvents were removed *in vacuo* to give a gum which was crystallised from ether (105 mg, 92%), m.p. 151—152 °C (Found: C, 71.15; H, 6.4; N, 12.6. $C_{20}H_{21}N_3O_2$ requires C, 71.6; H, 6.3; N, 12.5%); *m/e* 335 (M^+), 334 and 277 (M^+ − MeCONH); $\lambda_{max.}$ (MeOH) 230 (sh), 245 and 270 nm; $\nu_{max.}$ ($CHCl_3$) 3 242 (NH), 1 675 and 1 630 cm^{-1}; τ ($CDCl_3$) 2.03 (1 H, br d, *J* 8 Hz, aromatic), 2.5—3.0 (8 H, m, aromatics), 6.4 (2 H, s, CH_2), 6.99 (3 H, s, NMe), 7.67 (3 H, s, COMe), and 7.76 (3 H, s, CMe).

Monoacetylation of the Adduct (17; R^1 = H).—The *para*-product (17; R^1 = H) (100 mg, 0.34 mmol) from the above reaction was dissolved in pyridine (1 ml) with acetic anhydride (1 ml) and left overnight at room temperature. The solvent was removed *in vacuo* to yield a yellow gum which was crystallised from ethanol (74 mg, 65%), m.p. 223—225 °C (lit.,[10] m.p. 220—226 °C) (Found: C, 71.3; H, 6.5; N, 12.3. $C_{20}H_{21}N_3O_2$ requires C, 71.6; H, 6.3; N, 12.5%); *m/e* 292 (M^+ − COMe); $\lambda_{max.}$ (MeOH) 246 and 275 (sh) nm; $\nu_{max.}$ (KBr) 3 240, 3 170 (NH), 1 675, and 1 630 cm^{-1}; τ ($CDCl_3$) 1.7 (1 H, br s, aromatic), 2.52—2.72 (8 H, m, aromatics), 6.36 (2 H, br s, CH_2), 6.98 (3 H, s, NMe), 7.8 (3 H, s, NCOMe), and 7.98 (3 H, s, CMe). An identical product was obtained using the method of Bodendorf and Raaf.[10]

3-Phenyliminomethyl-4-hydroxy-2-quinolone (20).— 3-Formyl-4-hydroxy-2-quinolone [13] (950 mg, 5 mmol) and aniline (490 mg, 5 mmol) were added to dry dioxan (50 ml) and the reaction was refluxed for 3 h under a Soxhlet containing CaH. The solvent was partially removed to yield a yellow precipitate which was washed with ether and recrystallised from ethanol (1.19 g, 90%), m.p. 264 °C (Found: C, 72.3; H, 4.5; N, 10.3. $C_{16}H_{12}N_2O_2$ requires C, 72.7; H, 4.5; N, 10.6%); *m/e* 264 (M^+); $\lambda_{max.}$ (MeOH) 228, 252, and 373 nm (log ε 4.50, 4.53, and 4.59); $\lambda_{max.}$ (OH^-) 250 (sh), 278 (sh), and 366 nm (log ε 4.48, 4.20, and 4.51); $\nu_{max.}$ (Nujol) 3 200 (NH) and 1 690 cm^{-1}; τ ([$^2H_6$]DMSO) 1.08 and 1.22 (1 H, 2 × s, *syn*- and *anti*-C*H*–N), 2.07 (1 H dd, *J* 8 and 1 Hz, H-5) and 2.4—2.9 (8 H, m, aromatics).

Reduction of the Imine (20).—3-Phenyliminomethyl-4-hydroxy-2-quinolone (500 mg, 1.9 mmol) was suspended in dry ethanol (50 ml) and $NaBH_4$ (120 mg, 3 mmol) was added in portions. The solution was stirred for 15 h at room temperature, water (30 ml) was added, and the mixture was extracted with chloroform. The extracts were dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield a solid which was recrystallised from methanol as needles of 4-hydroxy-3-methyl-2-quinolone (120 mg, 36%), m.p. 300—305 °C (decomp.) (lit.,[24] m.p. >270 °C) (Found: C, 68.3; H, 5.1; N, 8.0. $C_{10}H_9NO_2$ requires C, 68.6; H, 5.1; N, 8.0); *m/e* 175 (M^+); $\lambda_{max.}$ (MeOH) 229, 273, 282, 314, and 327 nm; $\lambda_{max.}$ (OH^-) 220 and 308 nm; $\nu_{max.}$ (Nujol) 3 300 (NH or OH) and 1 630 cm^{-1} (amide); τ ([$^2H_6$]DMSO) 2.15 (1 H, dd, *J* 8 and 1 Hz, H-5), 2.8—3.3 (>3 H, m, aromatics), and 8.20 (3 H, s, CMe).

Reaction of the Imine (20) *with Acetic Anhydride*.—3-Phenyliminomethyl-4-hydroxy-2-quinolone (83 mg, 0.3 mmol) was dissolved in acetic anhydride (3 g) and dry pyridine (3 g) and left for 15 h at room temperature before refluxing for 1 h. The solvents were removed *in vacuo* and the resultant gum was triturated with ether–methanol to yield a solid which sublimed *in vacuo* at 300 °C as *pyrano*-[3,2-c]*quinoline*-2,5(6H)-*dione* (24) (39 mg, 61%), m.p. 345 °C (lit.,[16] m.p. 345 °C) (Found: C, 67.6; H, 3.5; N, 6.8; $C_{12}H_7NO_3$ requires C, 67.6; H, 3.3; N, 6.6%); *m/e* 213 (M^+); $\lambda_{max.}$ (MeOH) 228, 248, 267 (sh), 278 (sh), 314 (sh), 330 (sh), 358 (sh), and 368 nm; $\lambda_{max.}$ (OH^-) 220, 294, 330 (sh), and 352 nm; $\nu_{max.}$ (Nujol) 1 740 (C=O), and 1 655 (amide) cm^{-1}; τ ([$^2H_6$]DMSO) 1.96 (1 H, d, *J* 10 Hz, H-3), 2.06 (1 H, dd, *J* 7 and 1 Hz, H-10), 2.4—2.8 (>3 H, m, aromatics), and 3.54 (1 H, d, *J* 10 Hz, H-4).

Reaction of the Imine (20) *with Diazomethane*.—3-Phenyliminomethyl-4-hydroxy-2-quinolone (35 mg, 0.13 mmol) was suspended in ethanol (20 ml) and treated with an excess of etheral diazomethane.[25] The reaction was stirred overnight at room temperature and the solvent was removed *in vacuo*. The product recrystallised as white needles of 3-*anilino*-2,3-*dihydrofuro*[3,2-c]*quinolin*-4(5H)-*one* (25; R = NHPh) (7 mg, 19%), m.p. 252 °C (Found: C, 73.3; H, 5.4; N, 9.9. $C_{17}H_{14}N_2O_2$ requires C, 73.4; H, 5.0; N, 10.1%); $\lambda_{max.}$ (MeOH) 232, 283, 293, 320, and 332 (sh); $\nu_{max.}$ (Nujol) 3 280 (NH) and 1 650 (amide) cm^{-1}; τ ([$^2H_6$]DMSO) 2.4—3.1 and 3.3—3.6 (9 H, 2 × m, aromatics), 3.98 (1 H, t, *J* 7 Hz, NH, exchanges with D_2O), 5.27 (2 H, m, CH_2), and 6.70 (1 H, m, C*H*–NHPh).

Reaction of the Mannich Base (22; R^1 = R^2 = Me) *with Diazomethane*.—3-(*NN*-Dimethylaminomethyl)-4-hydroxy-2-quinolone (22; R^1 = R^2 = Me) (52 mg, 0.24 mmol) was suspended in methanol (50 ml) and an excess of ethereal diazomethane [25] was added. The mixture was stirred at room temperature for 15 h and the solvent was removed *in vacuo* to yield a brown gum. This solidified on trituration with acetone and was recrystallised from methanol as 2,3-*dihydrofuro*[3,2-c]*quinolin*-4(5H)-*one* (25; R = H) (17 mg, 38%), m.p. 260 °C (decomp.) (lit.,[17] m.p. 272—275 °C); *m/e* 187 (M^+), $\lambda_{max.}$ (MeOH) 219, 230, 282, 292, 319, and 330 nm; $\nu_{max.}$ (Nujol) 1 655 (amide), 1 630, and 1 605 cm^{-1}; τ (CF_3CO_2H) 1.91 (1 H, d, *J* 8 Hz, H-5), 2.0—2.45 (3 H, m, aromatics), 4.82 (2 H, t, *J* 10 Hz, α-dihydrofuran CH_2) and 6.52 (2 H, t, *J* 10 Hz, β-dihydrofuran CH_2).

Preparation of the Imines (27).—*General*. A solution of the substituted aniline (0.01 mol) in ethanol (10 ml) was added slowly over 1 h to an ice-cooled solution of 2-hydroxy-1-naphthaldehyde (1.72 g, 0.01 mol) in ethanol (20 ml). The reaction was stirred for 30 min in an ice-bath when the imine precipitated. The reactions with *para*-methoxyaniline and *para*-toluidine were conducted in methanol. The imines had the following properties:

(*a*) (27; R^1 = R^2 = H), m.p. 105—107 °C (Found: C, 82.3; H, 5.6; N, 5.4. $C_{17}H_{13}NO$ requires C, 82.6; H, 5.3; N, 5.7%); *m/e* 247 (M^+); $\lambda_{max.}$ (MeOH) 232, 253 (sh),

261 (sh), 269 (sh), 316, 334, 358, 437, and 458 nm (log ε 4.559, 4.179, 4.128, 3.959, 3.980, 3.822, 3.811, 4.081, and 4.069); $\lambda_{max.}$ (H^+) 221, 236, 255, 264 (sh), 290, 318, and 360 nm (log ε 4.643, 4.131, 3.816, 3.666, 3.270, 3.693, and 3.530), $\lambda_{max.}$ (OH^-) 235, 240, 261, 316, and 407 nm (log ε 4.510, 4.462, 4.274, 3.974, and 4.086); $\nu_{max.}$ ($CHCl_3$) 1 630 cm^{-1}; τ ($CDCl_3$) −5.83 (1 H, d, *J* 5 Hz, phenolic OH, exchangeable in D_2O) 0.60 (1 H, d, *J* 5 Hz, CH=N, becomes s on addition of D_2O), and 1.75—2.88 (11 H, aromatics).

(*b*) (27; R^1 = OMe, R^2 = H), m.p. 167—168 °C; *m/e* 277 (M^+); $\lambda_{max.}$ (MeOH) 235, 260 (sh), 270 (sh), 320, 350, 446, and 468 nm (log ε 3.965, 3.682, 3.442, 3.363, 3.266, 3.794, and 3.778); $\nu_{max.}$ ($CHCl_3$) 3 340 (OH) and 1 625 (C=N) cm^{-1}; τ ($CDCl_3$) 0.73 (1 H, d, *J* 8 Hz, CH=N, becomes s on addition of D_2O); 1.99—3.18 (10 H, m, aromatics), and 5.99 (3 H, s, OMe).

(*c*) (27; R^1 = H, R^2 = OMe), m.p. 109—110 °C, *m/e* 277 (M^+); $\lambda_{max.}$ (MeOH) 233, 265, 274 (sh), 315 (sh), 323, 340, 360, 392, 442, and 464 nm (log ε 4.345, 3.830, 3.731, 3.718, 3.755, 3.606, 3.718, 3.743, 3.935, and 3.789); $\nu_{max.}$ (Nujol) 1 617 cm^{-1} (C=N); τ ($CDCl_3$) 0.75 (1 H, s, CH=N), 1.90—3.16 (10 H, m, aromatics), and 6.18 (3 H, s, OMe).

(*d*) (27; R^1 = H, R^2 = Me), m.p. 130—131 °C (Found: C, 82.9; H, 5.8; N, 5.4. $C_{18}H_{15}NO$ requires C, 82.8; H, 5.75; N, 5.4%); *m/e* 261 (M^+); $\nu_{max.}$ (KBr) 3 400 cm^{-1} (OH); τ ($CDCl_3$) 0.74 (1 H, br d, *J* 4 Hz, CH, becomes s on addition of D_2O), 1.92—3.02 (10 H, m, aromatics), and 7.66 (3 H, s, CMe).

The Mannich bases (29).—*General.*—A solution of the corresponding imine (1 mmol) in dry methanol (105 ml) was added slowly to an ice-cooled suspension of sodium borohydride (500 mg, 13 mmol) in dry methanol (10 ml) over 1 h. The reaction was kept at this temperature for a further 2 h and then stirred at room temperature for 24 h. Water (20 ml) was added and the solvents were removed *in vacuo*. The residue was dissolved in water (50 ml), neutralised with 1M HCl, and extracted with chloroform. The extracts were dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield a gum.

(*a*) (29; R^1 = R^2 = H) was crystallised from ethanol in 83% yield, m.p. 118—120 °C (Found: C, 81.4; H, 6.2; N, 5.3. $C_{17}H_{15}NO$ requires C, 81.9; H, 6.0; N, 5.6%); *m/e* 249 (M^+); $\lambda_{max.}$ (MeOH) 228, 268, 279, 291, 323, and 335 nm (log ε 4.616, 3.919, 3.979, 3.940, 3.572, and 3.639); $\lambda_{max.}$ (OH^-) 243, 286, 296 (sh), and 350 nm (log ε 4.716, 4.136, 4.045, and 3.794); $\nu_{max.}$ ($CHCl_3$) 3 580 (OH) cm^{-1}; τ ($CDCl_3$) 2.08—3.21 (12 H, m, aromatics and NH) and 5.17 (2 H, s, CH_2).

(*b*) (29; R^1 = H, R^2 = Me) was crystallised from methanol in 79% yield, m.p. 140—141 °C (Found: C, 82.1; H, 6.6; N, 5.3. $C_{18}H_{17}NO$ requires C, 82.1; H, 6.5; N, 5.3%); *m/e* 263 (M^+); $\lambda_{max.}$ (MeOH) 228, 265, 278, 291, 323, and 336 nm (log ε 4.787, 3.738, 3.738, 3.715, 3.420, and 3.455); $\lambda_{max.}$ (OH^-) 242, 273, 286, 296, and 354 nm (log ε 4.891, 3.953, 3.993, 3.908, and 3.663); $\nu_{max.}$ (KBr) 3 420 and 3 240 cm^{-1} (OH, NH); τ ($CDCl_3$) 2.15—3.36 (11 H, m, aromatics), 5.28 (2 H, s, CH_2), and 7.89 (3 H, s, CMe).

Pyrolysis of the Mannich Base (29; R^1 = R^2 = H) *in Diphenyl Ether.*—(a) *Alone.* 1-(*N*-Phenylaminomethyl)-2-naphthol (249 mg, 1 mmol) was refluxed in diphenyl ether (25 ml) under nitrogen for 24 h. The solvent was removed *in vacuo* to yield a black gum which was purified by preparative t.l.c. (SiO_2; $CHCl_3$). Benz[*a*]acridine (30; R^1 = R^2 = H) was recrystallised from ethanol (113 mg, 50%), identical in all respects with an authentic sample.[1]

(b) *With One Molar Equivalent of* para-*Toluidine.* 1-(*N*-Phenylaminomethyl)-2-naphthol (249 mg, 1 mmol) and *para*-toluidine (105 mg, 1 mmol) were refluxed in diphenyl ether (20 ml) under nitrogen for 24 h. The solvents were removed *in vacuo* to yield a red gum which was a mixture of three compounds by t.l.c. (SiO_2; $CHCl_3$). The imine (27; R^1 = H, R^2 = Me) (20 mg, 8%) could be separated by preparative t.l.c. (SiO_2; $CHCl_3$) but the other two compounds ran too close for effective separation. Integration of the protons corresponding to H-12 indicated the ratio of (30; R^1 = R^2 = H) : (30; R^1 = H, R^2 = Me) to be 1 : 4.

(c) *With* ortho-*anisidine.* 1-(*N*-Phenylaminomethyl)-2-naphthol (178 mg, 0.7 mmol) and *ortho*-anisidine (86 mg, 0.7 mmol) were refluxed in diphenyl ether (10 ml) under nitrogen for 24 h. The solvents were removed *in vacuo* to yield a black gum which was purified by preparative t.l.c. (SiO_2; $CHCl_3$) to yield benz[*a*]acridine (7 mg, 4%) and 8-methoxybenz[*a*]acridine (40 mg, 22%). These compounds were identical in all respects with authentic samples.[1]

Pyrolysis of the Mannich Base (29; R^1 = H, R^2 = Me) *in Diphenyl Ether.*—(a) *Alone.* 1-(*N*-*para*-Methylphenylaminomethyl)-2-naphthol (112 mg, 0.42 mmol) was heated at 200 °C in diphenyl ether (10 ml) for 24 h under nitrogen. The solvent was removed *in vacuo* to yield a red gum which was purified by preparative t.l.c. giving 10-methylbenz[*a*]acridine (26 mg, 25%) and the imine (27; R^1 = H, R^2 = Me) (62 mg, 56%). Both compounds were identical in all respects with authentic compounds.[1]

(b) *With one molar equivalent of aniline.* 1-(*N*-*para*-Methylphenylaminomethyl)-2-naphthol (132 mg, 0.5 mmol) and aniline (47 mg, 0.5 mmol), were refluxed in diphenyl ether (20 ml) for 24 h under nitrogen. The solvents were removed to yield a black gum (122 mg). From integration of the singlets for H-12, the ratio of (30; R^1 = R^2 = H) : (30, R^1 = H, R^2 = Me) was *ca.* 2 : 1.

(c) *With ten equivalents of aniline.* 1-(*para*-Methylphenylaminomethyl)-2-naphthol (263 mg, 1 mmol) and aniline (910 mg, 10 mmol) were refluxed in diphenyl ether (25 ml) for 24 h under nitrogen. Removal of the solvents *in vacuo* gave a gum which showed the CH_2 protons of (11). The gum was therefore dissolved in dry pyridine (10 ml) with acetic anhydride (5 ml) and the reaction was stirred overnight at room temperature. The solvents were removed *in vacuo* to yield a gum which now showed the characteristic H-12 protons of (30; R^1 = R^2 = H) and (30; R^1 = H, R^2 = Me) in the ratio 4 : 1.

Reaction of 3-(NN-*Dimethylaminomethyl*)-4-*hydroxy*-2-*quinolone with Maleic Anhydride.*—3-(*NN*-Dimethylaminomethyl)-4-hydroxy-2-quinolone (102 mg, 0.47 mmol) and maleic anhydride (60 mg, 0.6 mmol) were heated at 250 °C in diphenyl ether (10 ml) for 15 h under nitrogen. The solvent was removed *in vacuo* to yield a solid which was triturated with methanol and sublimed *in vacuo* at 300 °C to give 3,3′-methylenebis-(4-hydroxy-2-quinolone) (38; X = NH) (52 mg, 67%), identical in all respects with an authentic sample.[2] Preparative t.l.c. on the residues gave a white crystalline solid, m.p. 126 °C (Found: C, 56.5; H, 7.55; N, 16.0. $C_8H_{14}N_2O_2$ requires C, 56.5; H, 8.2; N, 16.5%); *m/e* 170 (M^+); $\nu_{max.}$ (Nujol) 1 610 cm^{-1} (amide); τ ($CDCl_3$) 2.65 (2 H, s, olefinic), 6.91 (6 H, s, NMe), and 7.0 (6 H, s, NMe).

Reaction of 3-(NN-*Dimethylaminomethyl*)-4-*hydroxy-coumarin* (37) *with Maleic Anhydride.*—This reaction was conducted under the above conditions using the coumarin derivative (37), when a 73% yield of 3,3′-methylenebis-(4-

hydroxycoumarin) (38; X = O) [26] and a 1% yield of the above amide were obtained. Both compounds were identical in all respects with authentic samples.

We thank Mr. and Mrs. A. G. Olney for the microanalyses, Mr. A. Greenway for the mass spectra and the S.R.C. (J. L. A.) and the Turkish Government (O. B.) for scholarships.

[1/499 *Received*, 30*th March*, 1981]

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