Synthesis of Heterocyclic Compounds. Part XXX.[1] Reactions of *o*-Alkylamino- and *o*-Dialkylamino-anilines with Some αβ-Unsaturated Carbonyl Compounds

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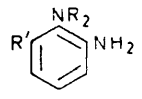
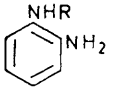
The condensation of *o*-alkylamino- and *o*-dialkylamino-anilines with diethyl ethoxymethylenemalonate gave intermediates which could be cyclised to 4-quinolone derivatives. In phosphoryl chloride, the intermediate from *N*-(*o*-aminophenyl)pyrrole gave pyrrolo[1,2-*a*]quinoxaline. 4-Quinolones were also prepared by the reaction of *o*-dialkylaminoanilines with dimethyl acetylenedicarboxylate, followed by thermal cyclisation. The intermediate from *N*-(*o*-aminophenyl)pyrrole gave a pyrrolo[1.2-*a*]quinoxaline derivative. *o*-Dialkylaminoanilines attacked the β-carbon atom of methyl acrylate but the resulting intermediates could not be cyclised. The corresponding reactions with methyl methacrylate and methyl crotonate gave amides, *via* attack at the ester carbonyl group. With acetylacetone, the intermediate imine was formed, but failed to cyclise in polyphosphoric acid or its ethyl ester.

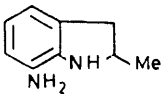
o-PHENYLENEDIAMINE and its *N*-monosubstituted derivatives react with dimethyl acetylenedicarboxylate to give quinoxaline derivatives.[2] We now describe



(1) $R_2 = [CH_2]_4$, R' = H
(2) $R_2 = [CH_2]_5$, R' = H
(3) $R_2 = [CH_2]_2 \cdot O \cdot [CH_2]$, R' = H
(4) $R_2 = [CH_2]_4$, R' = Cl
(5) $R_2 = [CH_2]_5$, R' = Cl
(6) $R_2 = [CH_2]_2 \cdot O \cdot [CH_2]_2$, R' = Cl



(7) R = Pr
(8) $R = CH_2CH{:}CH_2$



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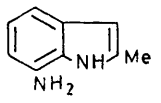

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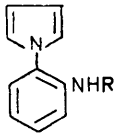
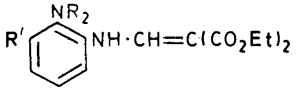


(11) R = H
(22) $R = CH{:}C(CO_2Et)_2$
(47) R = COMe



(12) $R_2 = [CH_2]_4$, R' = H
(13) $R_2 = [CH_2]_5$, R' = H
(14) $R_2 = [CH_2]_2 \cdot O \cdot [CH_2]_2$, R' = H
(15) $R_2 = [CH_2]_4$, R' = Cl
(16) $R_2 = [CH_2]_5$, R' = Cl
(17) $R_2 = [CH_2]_2 \cdot O \cdot [CH_2]_2$, R' = Cl

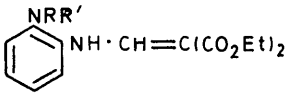
some related reactions of *N*-monosubstituted and *NN*-disubstituted *o*-phenylenediamines with αβ-unsaturated compounds, to give intermediates which either fail to cyclise, or do so by attack on the aromatic ring, to give 4-quinolone derivatives. In view of their structural similarity to known antibacterial and anticoccidial ethoxycarbonylquinolines,[3] several of the cyclised products were tested but no significant degree of activity was observed.[4]

Reactions with Diethyl Ethoxymethylenemalonate (DEMM).—Compounds (1)—(11) reacted smoothly with DEMM (*cf.* ref. 5) to give the expected products (12)—(22) in good yields. When the intermediates (12)—(21) were heated in polyphosphoric acid (PPA), hydrolysis to the parent amine occurred, and no cyclisation products were obtained. Compounds (12)—(17) behaved similarly in the ethyl ester of polyphosphoric acid (PPEt). On the other hand, when the intermediates (12)—(17) and (21) were heated under reflux in biphenyl, the cyclisation products (23)—(29) were obtained. Both the intermediates and the products are heat-sensitive, but by careful attention to the period of heating (*cf.* ref. 6), moderate to good yields could be obtained (see Table 1). The malonate intermediates (18)—(20) did not cyclise on heating in biphenyl but when they were initially tosylated the quinolones (30)—(32) were obtained. The location of the tosyl groups in the intermediates (33)—(35) was established by their n.m.r. spectra, in which the NH,CH coupling was still observed.

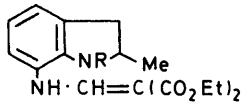
The cyclisation products have been represented as quinolones, and spectroscopic evidence suggests that these are the true structures in solution in chloroform. Thus, the n.m.r. signals due to the pyridone ring proton are doublets, owing to coupling with NH [except in the cases of compounds (23), (24), and (29)] and two carbonyl stretching peaks (amide and ester) occur in the i.r. spectrum in each case. On the other hand, the Nujol mull i.r. spectra showed in each case only one carbonyl stretching vibration, and broad absorption from 3 300 to below 3 000 cm^{-1}, indicating the presence of a hydrogen-bonded hydroxy-group. Apparently, the hydroxy-quinoline forms predominate in the solid state. An

[1] Part XXIX, J. A. L. Herbert and H. Suschitzky, *J.C.S. Perkin I*, 1974, 2657.
[2] H. Suschitzky, B. J. Wakefield, and R. A. Whittaker, *J.C.S. Perkin I*, 1975, 401.
[3] C. K. Cain, *Ann. Reports Medicin. Chem.*, 1969, 87, 121.
[4] W. Hoyle, personal communication.
[5] R. E. Gould and W. A. Jacobs, *J. Amer. Chem. Soc.*, 1939, **61**, 2890.
[6] J. Egri, J. Halmos, and J. Rakoczi, *Acta Chim. Acad. Sci. Hung.*, 1972, **73**, 469.

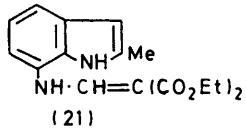
attempt to distinguish between the tautomeric forms by comparison of alkylated derivatives [7] was unsuccessful, as alkylation of the quinolones under various conditions gave only *O*-alkylated products, *e.g.* compounds (36)—(38), and the malonate intermediate (39) (from 1-ethylamino-2-piperidinobenzene and DEMM) failed to cyclise.



(18) R = Pr, R′ = H
(19) R = CH_2·CH : CH_2, R′ = H
(33) R = Pr, R′ = *p*-MeC_6H_4·SO_2
(34) R = CH_2·CH : CH_2, R′ = *p*-MeC_6H_4·SO_2



(20) R = H
(35) R = *p*-MeC_6H_4·SO_2



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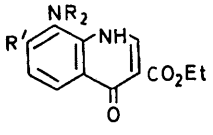
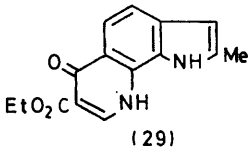


(23) R_2 = $[CH_2]_4$, R′ = H
(24) R_2 = $[CH_2]_5$, R′ = H
(25) R_2 = $[CH_2]_2$·O·$[CH_2]_2$, R′ = H
(26) R_2 = $[CH_2]_4$, R′ = Cl
(27) R_2 = $[CH_2]_5$, R′ = Cl
(28) R_2 = $[CH_2]_2$·O·$[CH_2]_2$, R′ = Cl



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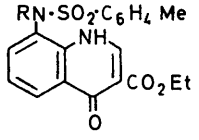
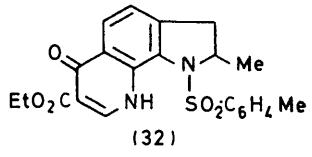


(30) R = Pr
(31) R = CH_2·CH : CH_2



(32)

When the intermediate (22) from *N*-(*o*-aminophenyl)pyrrole (11) was heated in phosphoryl chloride cyclisation occurred, as expected, by attack on the pyrrole ring, and was accompanied by hydrolysis and decarboxylation, giving the known pyrrolo[1,2-*a*]quinoxaline (40).[8] On the other hand when the intermediate (22) was heated in biphenyl, the quinolone (41) was obtained. This reaction is noteworthy in involving electrophilic attack on the benzene rather than the pyrrole ring (*cf.* ref. 9 and refs. cited therein); it is even more remarkable that it should occur in an inert solvent which apparently would not interact with the pyrrole nitrogen atom to reduce the electron density on the pyrrole ring.

Reactions with Dimethyl Acetylenedicarboxylate (DMAD).—Compounds (1)—(3), reacted smoothly with DMAD to give the enamines (42)—(44) in high yield (*cf.* refs. 10—12); the chemical shift for the olefinic proton (τ *ca.* 4.7) was consistent with the fumarate geometry depicted.[11,12] In the case of the pyrrole (11), the enamine (45) was accompanied by a compound whose spectroscopic properties (see Experimental section) indicated it to be the pyrrolo[1,2-*a*]quinoxaline (46). Compound (46) could have been formed by cyclisation of the intermediate (45), followed by a hydrogen shift. This conversion was indeed observed, but took 1 week in boiling $CHCl_3$ for completion. As some compound (46) was detectable after only a short reaction time, it could have been formed at least in part by the route shown in the Scheme (or an analogous concerted process). On the other hand, *N*-(2-acetamidophenyl)pyrrole (47) failed to react with DMAD.

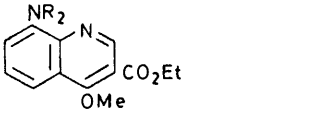
When the enamines (43) and (44) were heated in biphenyl, the quinolones (48) and (49) were obtained,

[7] A. R. Katritzky and J. M. Lagowski, *Adv. Heterocyclic Chem.*, **1963**, **1**, 339.
[8] G. W. H. Cheeseman and B. Tuck, *J. Chem. Soc.*, 1965, 3678.
[9] G. W. H. Cheeseman and M. Rafiq, *J. Chem. Soc.* (*C*), 1971, 2732.
[10] J. B. Hendrickson, R. Rees, and J. Templeton, *J. Amer. Chem. Soc.*, 1964, **86**, 107.
[11] R. Huisgen, K. Herbig, A. Siegel, and H. Huber, *Chem. Ber.*, 1966, **99**, 2526.
[12] E. C. Taylor and N. D. Heindel, *J. Org. Chem.*, 1967, **32**, 3339.

showing appropriate analytical and spectroscopic data (*cf.* ref. 12) including two carbonyl stretching vibrations (ester and 4-quinolone).

Reactions with αβ-Unsaturated Monoesters.—It has been reported [13] that 2,3-dihydro-4(1*H*)-quinolones may be prepared by the reaction of aromatic amines with αβ-unsaturated esters (methyl acrylate, methyl methacrylate, methyl crotonate) in PPA. However, although the reaction of the *o*-dialkylaminoanilines (2) and (3) with methyl acrylate gave the appropriate intermediates (50) and (51), cyclisation was not observed. Moreover, the reactions of compounds (2) and (3) with methyl methacrylate and of compounds (1)—(3) with methyl crotonate proceeded by attack at the ester carbonyl groups, rather than at the β-carbon atom, leading to the amides (52)—(56).

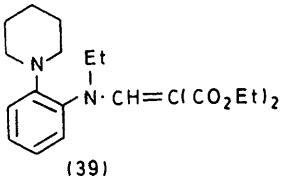
Reactions with Acetylacetone.—The amines (2) and (3) reacted with acetylacetone to give products which we formulate as the enols (57) and (58). The ^{1}H n.m.r. spectra (solvent C_6D_6) showed signals attributable to two methyl groups (in CCl_4 these were coincident), one olefinic proton, and an exchangeable proton, at very low



(36) $R_2 = [CH_2]_4$

(37) $R_2 = [CH_2]_5$

(38) $R_2 = [CH_2]_2 \cdot O \cdot [CH_2]_2$



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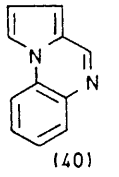

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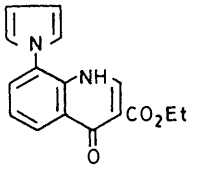

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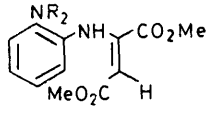
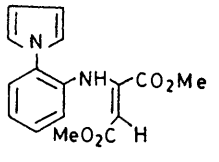


(42) $R_2 = [CH_2]_4$

(43) $R_2 = [CH_2]_5$

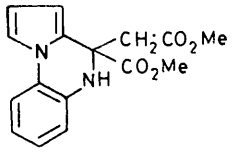
(44) $R_2 = [CH_2]_2 \cdot O \cdot [CH_2]_2$



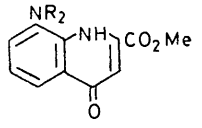
(45)

field, corresponding to a hydrogen-bonded hydroxy-proton. The i.r. spectra showed no carbonyl stretching absorption (and any hydroxy-stretching absorption was so broad as to be unrecognisable).

The intermediates (57) and (58) failed to cyclise in

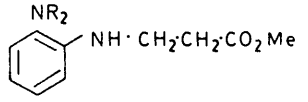


(46)



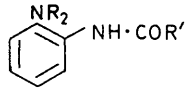
(48) $R_2 = [CH_2]_5$

(49) $R_2 = [CH_2]_2 \cdot O \cdot [CH_2]_2$



(50) $R_2 = [CH_2]_5$

(51) $R_2 = [CH_2]_2 \cdot O \cdot [CH_2]_2$



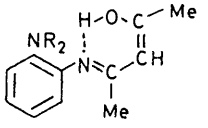
(52) $R_2 = [CH_2]_5$, $R' = CMe : CH_2$

(53) $R_2 = [CH_2]_2 \cdot O \cdot [CH_2]_2$, $R' = CMe : CH_2$

(54) $R_2 = [CH_2]_4$, $R' = CH : CHMe$

(55) $R_2 = [CH_2]_5$, $R' = CH : CHMe$

(56) $R_2 = [CH_2]_2 \cdot O \cdot [CH_2]_2$, $R' = CH : CHMe$



(57) $R_2 = [CH_2]_5$

(58) $R_2 = [CH_2]_2 \cdot O \cdot [CH_2]_2$

PPA or PPEt. This type of cyclisation (Combes synthesis [14]) is often inhibited by electron-donating groups in the *o*- or *p*-position.[15]

EXPERIMENTAL

Analytical and selected spectroscopic data for compounds marked with an asterisk are given in Supplementary Publication SUP 21540 (14 pp., 1 microfiche).†

o-Dialkylaminoanilines (1)—(6) were prepared by the reaction of the appropriate chloronitrobenzene with the amine,[16] followed by reduction.[17] The known compounds had physical constants in agreement with the literature values; 3-*chloro*-2-*pyrrolidinoaniline* (4) * had b.p. 145—147° at 2 mmHg, 3-*chloro*-2-*piperidinoaniline* (5) * had b.p. 133° at 1 mmHg, and 3-*chloro*-2-*morpholinoaniline* (6) * had m.p. 156—157°.

o-Alkylaminoanilines (7)—(10) were prepared as previously described.[2]

N-(*o*-Aminophenyl)pyrrole (11) was prepared essentially

† For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1974, Index issue.

[13] J. R. Merchant and D. S. Chothia, *Indian J. Chem.*, 1972, **10**, 243.

[14] A. F. Campbell and A. F. Temple, *J. Chem. Soc.*, 1957, 207.

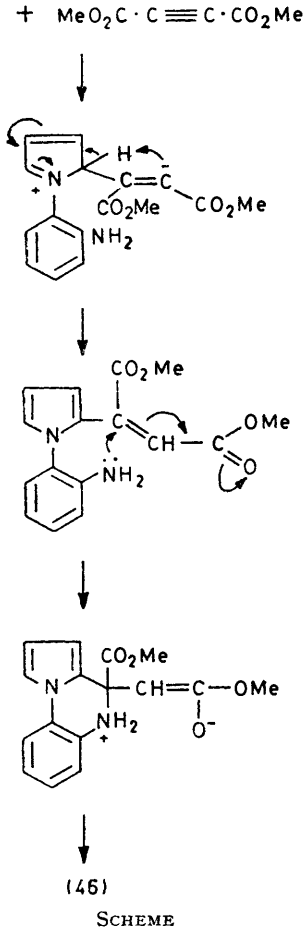
[15] E. Roberts and E. E. Turner, *J. Chem. Soc.*, 1927, 1832.

[16] R. Fielden, Ph.D. Thesis, Salford, 1971.

[17] O. Meth-Cohn, Ph.D. Thesis, Salford, 1967.

as described,[8,9] but the reduction was conveniently accomplished by use of Raney nickel and hydrazine hydrate in ethanol.

Diethyl Arylaminomethylenemalonates (12)—(22).—Equimolar quantities of diethyl ethoxymethylenemalonate and



SCHEME

the arylamine were heated at *ca.* 100 °C during 1 h [in the cases of the amines (7) and (8) only 30 min at room temperature required]. The resulting solids were recrystallised from suitable solvents, to give *compounds* (12),* m.p. 30—32° (60%); (13),* m.p. 50—51° (84%); (14),* m.p. 96—97° (87%); (15),* m.p. 94.5—96.5° (83%); (16),* m.p. 86—87° (82%); (17),* m.p. 131.5—133° (91%); (18),* m.p. 123.5—124.5° (82%); (19),* m.p. 97—97.5° (79%); (20),* m.p. 108.5—110° (75%); (21),* m.p. 183—184° (83%); and (22),* m.p. 121—122° (76%).

Compounds (18)—(20) gave the *p-tolylsulphonyl derivatives* (33),* m.p. 151—152° (64%); (34),* m.p. 108—109° (66%); and (35),* m.p. 141—143° (73%), with toluene-*p*-sulphonyl chloride in pyridine.

Ethyl 1,4-Dihydro-4-oxoquinoline-3-carboxylates.—The diethyl arylaminomethylenemalonate (2.0 g) was heated under reflux in biphenyl (10 g). The mixture was cooled, light petroleum (b.p. 60—80°) was added, and the resulting suspension was filtered. The solid was washed several times with light petroleum and recrystallised from a suitable solvent to give the *compounds* listed in the Table.

Pyrrolo[1,2-a]*quinoxaline* (40).—Diethyl [2-(pyrrol-1-yl)-anilino]methylenemalonate (2.0 g) and phosphoryl chloride (15 ml) were heated under reflux during 15 min. The mixture was evaporated *in vacuo* and the residue dissolved in chloroform. Conventional work-up of the solution gave pyrrolo[1,2-*a*]quinoxaline (0.80 g, 76%), m.p. 131—132° (from light petroleum) (lit.,[8] 131—132°).

Alkylation of Ethyl 1,4-Dihydro-4-oxoquinoline-3-carboxylates.—A typical procedure is described; other reagents used were ethyl iodide, dimethyl sulphate, diazomethane, and methyl fluorosulphonate.

Ethyl 1,4-dihydro-4-oxoquinoline-3-carboxylates

Compd.	Reaction time (min)	Yield (%)	M.p. (°C)
(23) *	8	56	180 [a]
(24) *	8	63	199—201 [a,b]
(25) *	8	65	221—223 [a]
(26) *	5	71	131—133 [a]
(27) *	5	70	197 [a]
(28) *	5	81	240 [a]
(29) *	5	53	290—292
(30) *	13	77	235—237
(31) *	13	72	218—220
(32) *	13	44	234—235 [a]
(41) *	8	23	235—237 [a]

[a] Decomp. [b] Two crystalline forms observed, depending on the rate of crystallisation. Both had the same m.p. and n.m.r. spectrum and both showed a single carbonyl stretching absorption at ν_{max} 1 700 cm^{-1}, but they differed markedly in the fingerprint region of their Nujol mull spectra.

To the 4-oxo-quinoline (2.0 g) in ethanol (20 ml) were added 2M-sodium hydroxide (5 ml) and methyl iodide (1.0 ml). The mixture was heated under reflux during 1—2 h. The *4-methoxyquinoline-3-carboxylates* (36),* m.p. 109—111°; (37),* m.p. 133—134°; and (38),* m.p. 152—154°, were isolated by conventional means and recrystallised from aqueous ethanol.

Diethyl (N-*Ethyl-2-piperidinoanilino*)*methylenemalonate*.—*o*-Piperidinoaniline (4.0 g), Raney nickel (10 g), and ethanol (50 ml) were heated under reflux during 24 h. Conventional work-up, chromatography on alumina (light petroleum–benzene), and distillation gave *1-ethylamino-2-piperidinobenzene* * (2.6 g, 56%), b.p. 101—103° at 2 mmHg. 1-Ethylamino-2-piperidinobenzene (2.0 g) and diethyl ethoxymethylenemalonate (2.2 g) were heated at 120—130 °C during 3 h. Chromatography on alumina (light petroleum) gave *diethyl* (N-*ethyl-2-piperidinoanilino*)*methylenemalonate* (39) * (2.4 g, 66%), b.p. 120—122° at 0.3 mmHg.

Dimethyl Arylaminofumarates (42)—(45).—(*a*) Dimethyl acetylenedicarboxylate (0.01 mol) was added to an ice-cold-solution of the *o*-dialkylaminoaniline (0.01 mol) in chloroform. After 15 min the solution was allowed to warm to room temperature, and the chloroform was evaporated off. The *products* (42),* m.p. 70—71° (80%); (43),* m.p. 79—81° (85%); and (44),* m.p. 85—86° (92%), were recrystallised from light petroleum.

(*b*) *N*-(2-aminophenyl)pyrrole (2.0 g) and dimethyl acetylenedicarboxylate (1.9 g) in chloroform (20 ml) were heated under reflux during 36 h. The solvent was evaporated off. Chromatography of the residue (alumina; 5% ethyl acetate–light petroleum) gave (i) *dimethyl* [2-(*pyrrol-1-yl*)*anilino*]*fumarate* (45) * (1.5 g, 40%), b.p. 110° at 1 mmHg; and (ii) *methyl 4,5-dihydro-4-methoxycarbonyl-pyrrolo*[1,2-a]*quinoxalin-4-ylacetate* (46) (1.7 g, 45%), m.p. 72.5—74°, $\nu_{max.}$ 3 490 (NH str.) and 1 730 cm^{-1} (C=O str.), τ 2.5—3.3 (5 H, m, ArH and pyrrole α-H), 3.5—3.9 (2 H, m, pyrrole β-H), 4.5 (exch. 1 H, s, NH), 6.2 and 6.3 (2 × 3 H,

s, CO_2Me), and 6.35 and 7.05 (2 × 1 H, d, J 17 Hz, CH_2) (Found: C, 63.6; H, 5.45; N, 9.1%; M^+, 300. $C_{16}H_{16}N_2O_4$ requires C, 64.0; H, 5.4; N, 9.3%; M^+, 300).

Methyl 1,4-Dihydro-4-oxoquinoline-2-carboxylates.—The anilinofumarate (2.0 g) and biphenyl (10 g) were heated under reflux during 5 min and cooled. Light petroleum (50 ml) was added and the brown solid was collected, washed with light petroleum, and recrystallised from benzene–light petroleum to give compounds (48),* m.p. 156—157.5° (62%), and (49),* m.p. 179.5—180.5° (65%).

Reactions of o-Dialkylaminoanilines with αβ-Unsaturated Esters.—The amine (0.01 mol), the ester (0.01 mol), and PPA (20 g) were heated at 100 °C during 5 h. The cooled mixture was diluted with ice–water and extracted with chloroform. Conventional work-up and chromatography on alumina gave the products noted below. The aqueous solution was basified to pH 8 with concentrated ammonia and extracted with chloroform; the extract yielded the amine starting material in each case.

The reaction of compound (2) with methyl acrylate gave *methyl 3-(2-piperidinoanilino)propionate* (50) (53%), b.p. 102° at 0.5 mmHg; $\nu_{max.}$ 3 360 (NH str.) and 1 745 cm^{-1} (CO str.); τ (CCl_4), 2.9—3.7 (4 H, m, ArH), 5.0 (exch. 1 H, s, NH), and other signals as expected (Found: C, 68.7; H, 8.45; N, 10.6%; M^+, 262. $C_{15}H_{22}N_2O_2$ requires C, 68.5; H, 8.5; N, 10.6%; M, 262). A similar reaction of compound (3) gave the *morpholino-derivative* (51).*

The reaction of compound (2) with methyl methacrylate gave *N-(2-piperidinophenyl)methacrylamide* (52) * (36%), b.p. 155° at 0.5 mmHg. Analogous reactions with methyl methacrylate and methyl crotonate gave *compounds* (53)—(56).*

Reactions of o-Dialkylaminoanilines with Acetylacetone.—The amine (2) or (3) (0.01 mol), acetylacetone (0.01 mol), and benzene (30 ml) were heated in a Dean–Stark apparatus during 4 h. The benzene was evaporated off and the residue purified by chromatography on alumina and recrystallisation from light petroleum, to give *compounds* (57),* m.p. 72—73° (64%); and (58),* m.p. 81.5—82° (57%).

We thank the S.R.C. for a CASE award (to R. A. W.) and Drs. B. Tuck and H. F. Ridley, CIBA-GEIGY (U.K.) Ltd., for discussions.

[5/352 *Received*, 19*th February*, 1975]