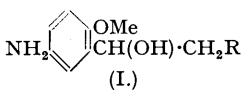
240. *Contributions to the Chemistry of Synthetic Antimalarials. Part VIII. Aromatic Carbinolamines.*

By D. W. Mathieson and (the late) G. Newbery.

The synthesis of some substituted phenylcarbinolamines is described. The products had no significant antimalarial activity.

The study by King and Work (*J.*, 1940, 1307) of quinoline derivatives bearing carbinolamine side chains suggested an investigation of some benzene derivatives containing similar side chains; various mono- and di-substituted phenylcarbinolamines have been prepared for testing against *Plasmodium gallinaceum*.

Compounds (I; R = morpholino and piperidino), (II; R = morpholino and piperidino), (III; R = NH·CHMe, morpholino, and piperidino), (IV; R = NEt_2, NBu^n_2, morpholino, and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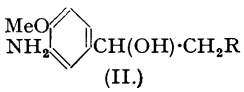
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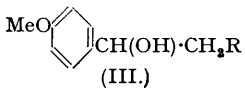
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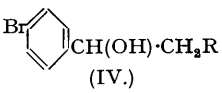
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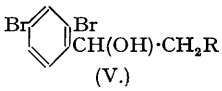

(V.)

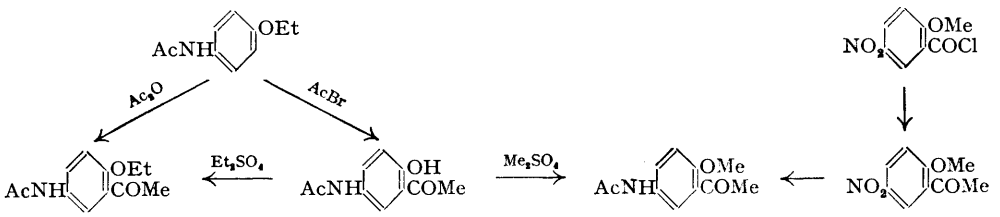
piperidino), and (V; R = morpholino) have been synthesised. Details of the first three examples of series (IV) have already been published by Drake and Goldman (*J. Org. Chem.*, 1946, **11**, 100) whilst Lutz *et al.* (*ibid.*, 1947, **12**, 617) have described the fourth member. Chemical work in these laboratories confirms the results of these authors. None of these compounds except (IV; R = NBu^n_2) and (IV; R = morpholino) showed any activity against *Pl. gallinaceum*.

Nitration of *o*-methoxybenzoic acid (Simonsen and Rau, *J.*, 1917, **111**, 228) gave 5-nitro-2-methoxybenzoic acid which was purified by successive crystallisation from acetic acid and methanol instead of the tedious fractionation of the barium and the calcium salts employed by these authors. Treatment of the corresponding acid chloride with ethereal diazomethane yielded *5-nitro-ω-diazo-2-methoxyacetophenone*. This with hydrogen bromide in chloroform gave an inseparable mixture, one constituent of which, obtained by handpicking, was shown to be the required *ω-bromo-5-nitro-2-methoxyacetophenone* identical with a sample synthesised as described below. The use of hydrogen chloride in ether gave a similar mixture, and the method was not investigated further. It is of interest that *m*-nitro-ω-diazoacetophenone reacts normally with bromine in chloroform to give the ω-bromo-derivative (Evans and Brook, *J. Amer. Chem. Soc.*, 1908, **30**, 406) whereas ω-diazo-*o*-methoxyacetophenone in our hands gave a mixture which could not be satisfactorily purified. 5-Nitro-2-methoxybenzoyl chloride was therefore condensed with ethoxymagnesium-malonic ester by Lund's method (*Ber.*, 1934, **67**, 935), and the resulting *ethyl 5-nitro-2-methoxybenzoylmalonate* hydrolysed to *5-nitro-2-methoxyacetophenone*. Reduction afforded 5-amino-2-methoxyacetophenone from which, by the action of acetic anhydride, *5-acetamido-2-methoxyacetophenone* was obtained. Treatment of *5-nitro-2-methoxyacetophenone* with bromine in chloroform gave ω-bromo-5-nitro-2-methoxyacetophenone.

Nitration of *p*-methoxyacetophenone yielded 3-nitro-4-methoxyacetophenone (Harding, *J.*, 1914, **105**, 2794) which on bromination gave *ω-bromo-3-nitro-4-methoxyacetophenone*.

In early experiments the direct synthesis of the intermediate ω-halogenoacetophenones by the Friedel–Crafts reaction was contemplated, and, in view of the unreactivity of nitro-compounds with aluminium chloride under normal conditions, the substituted acetamido-derivatives were used. *p*-Methoxyacetanilide with acetyl chloride and aluminium chloride gave a complex mixture, partly ketonic in nature, and in view of Kunckell's work (*Ber.*, 1901, **34**, 124; *Ber. deut. pharm. Ges.*, 1913, **23**, 472) attention was turned to *p*-ethoxyacetanilide. This author has described the reaction of acetyl bromide with phenacetin without, however, offering rigorous

proof of the structure of the resulting compound. Repetition of this work yielded a phenolic ketone the methyl ether of which was identical with 5-acetamido-2-methoxyacetophenone. Use of acetic anhydride in place of acetyl bromide gave *5-acetamido-2-ethoxyacetophenone* identical with the product of ethylation of the corresponding 2-hydroxy-compound; thus:



The products, however, were always contaminated by a second substance, ketonic in nature, which was not readily removed and was present in varying proportions in various apparently identical experiments; this method therefore was not further pursued. It is interesting that nitration of phenacetin (Reverdin, *Ber.*, 1876, **29**, 2595; *Rec. Trav. chim.*, 1929, **48**, 838; Hinsberg, *Annalen*, 1896, **292**, 249; Erp, *J. pr. Chem.*, 1931, **129**, 327) yields 2-nitro-4-ethoxyacetanilide, suggesting that the relative orienting power of these two groups is NHAc>OEt. Ingold (*J.*, 1926, 1310) reports that nitration of 2-methoxyacetanilide yields 4-nitro- (74%), 5-nitro- (13%), and 6-nitro-2-methoxyacetanilide (1·5%); again establishing the relative directing powers, in nitration at least, as NHAc>OMe. With the Friedel–Crafts reaction the opposite appears to be the case though, in view of the second fraction reported above, the possibility of the other isomer being present is not excluded. Further work will be reported later.

m-Bromonitrobenzene with iron dust in presence of calcium chloride gave *m*-bromoaniline from which *m*-dibromobenzene was obtained by a Sandmeyer reaction (Holleman, *Rec. Trav. chim.*, 1906, **25**, 186). Contrary to the evidence of Lutz *et al.* (*loc. cit.*) treatment of this with acetyl chloride and aluminium chloride gave 2 : 4-*dibromoacetophenone* in good yield; this constitution being initially assigned by analogy with the work of Montagne and van Charante (*Rec. Trav. chim.*, 1912, **31**, 298) and Böeseken (*ibid.*, 1908, **27**, 15) who similarly synthesised 2 : 4-dichlorobenzophenone. Proof was obtained by oxidation with dilute nitric acid which gave 2 : 4-dibromobenzoic acid, m. p. 167—168° (Cohen and Dutt, *J.*, 1914, **105**, 502, give m. p. 168—169°), from which 2 : 4-dibromobenzamide, m. p. 197°, was obtained (Montagne and van Charante, *Rec. Trav. chim.*, 1912, **31**, 329).

p-Methoxyacetophenone, *p*-bromoacetophenone, and 2 : 4-dibromoacetophenone with bromine in chloroform gave ω-bromo-p-methoxyacetophenone, ω : *p*-dibromoacetophenone and ω : 2 : 4-*tribromoacetophenone*, respectively.

Attempted condensation of ω-bromo-5-nitro-2-methoxyacetophenone and ω-bromo-3-nitro-4-methoxyacetophenone with diethylamine and di-*n*-butylamine yielded uncrystallisable oils which rapidly decomposed in presence of hydrochloric acid. With piperidine and morpholine, however, crystalline *hydrobromides* of 5-nitro-ω-piperidino-2-methoxyacetophenone, 5-nitro-ω-morpholino-2-methoxyacetophenone, 3-nitro-ω-piperidino-4-methoxyacetophenone, and 3-nitro-ω-morpholino-4-methoxyacetophenone were obtained. Treatment of these with hydrogen in the presence of Adams's catalyst led to a smooth uptake in two distinct steps, corresponding to the reduction (*a*) of NO_2 to NH_2 and (*b*) of C:O to CH·OH in this order. 2-*Piperidino*-1-(5′-*amino*-2′-*methoxyphenyl*)*ethanol hydrobromide*, 2-*morpholino*-1-(5′-*amino*-2′-*methoxyphenyl*)*ethanol hydrobromide*, 2-*morpholino*-1-(3′-*amino*-4′-*methoxyphenyl*)*ethanol*, and 2-*piperidino*-1-(3′-*amino*-4′-*methoxyphenyl*)*ethanol* were so obtained.

Reaction of the corresponding ω-bromoacetophenone with the requisite secondary amines, followed by reduction with aluminium *iso*propoxide of the salts of the products yielded 2-diethylamino-1-*p*-bromophenylethanol hydrobromide, 2-di-*n*-butylamino-1-*p*-bromophenylethanol hydrobromide and 2-piperidino-1-*p*-bromophenylethanol hydrochloride, as described by Drake and Goldman (*loc. cit.*). In addition 2-*morpholino*-1-p-*bromophenylethanol hydrobromide*, 2-*morpholino*-1-(2′ : 4′-*dibromophenyl*)*ethanol hydrobromide*, 2-iso*propylamino*-1-p-*methoxyphenylethanol hydrobromide*, 2-*piperidino*-1-p-*methoxyphenylethanol hydrobromide* and 2-*morpholino*-1-p-*methoxyphenylethanol hydrobromide* were similarly obtained.

Experimental.

5-Nitro-2-methoxybenzoyl Chloride.—5-Nitro-2-methoxybenzoic acid (Simonsen and Rau, *J.*, 1917, **111**, 228) (15 g.) and thionyl chloride (25 c.c.) were heated under reflux for 4 hours on the steam-bath.

Excess of thionyl chloride was removed under reduced pressure; the residual solid crystallised from dry benzene in colourless needles (16 g., 95%), m. p. 90—91° (Found: Cl, 16·35. $C_8H_6O_4NCl$ requires Cl, 16·48%).

5-Nitro-ω-diazo-2-methoxyacetophenone.—Treatment of 5-nitro-2-methoxybenzoyl chloride (4·4 g.) in dry benzene (30 c.c.) with excess of ethereal diazomethane yielded, on partial evaporation of the solvent, *5-nitro-ω-diazo-2-methoxyacetophenone* (3·2 g., 72%), m. p. 158—160° (decomp.) (Found: N, 18·8. $C_9H_7O_4N_3$ requires N, 18·9%).

5-Nitro-ω-diazo-2-methoxyacetophenone (3·1 g.) in chloroform (120 c.c.) was treated with 50% aqueous hydrobromic acid, and after 1 hour the aqueous layer was removed and the solvent evaporated from the chloroform layer. Crystallisation of the product from benzene–light petroleum gave a mixture of two crystalline substances which were separated by handpicking; (*A*), m. p. 124—128° (softening at 120°) and (*B*), m. p. 117—118°, which was shown to be *ω-bromo-5-nitro-2-methoxyacetophenone* by mixed m. p. with a synthetic sample described below. In view of the small amount available (*A*) was not further investigated.

Ethyl 5-Nitro-2-methoxybenzoylmalonate.—Magnesium (3·35 g.) was treated with half of a mixture of ethyl malonate (25 g.) and ethanol (19 c.c.) in the presence of carbon tetrachloride (0·5 c.c.). After the initial reaction, moderated by cooling in an ice-bath, had subsided, the second half was added, and when reaction had again ceased, dry ether (100 c.c.) was added and the whole heated under reflux for 1 hour, then filtered. 5-Nitro-2-methoxybenzoyl chloride (25 g.) in dry benzene (40 c.c.) was added and heating under reflux continued for 2 hours. Water (150 c.c.) was next added and the whole shaken vigorously; the benzene layer was separated off, the aqueous layer extracted well with ether, and the combined extracts dried (Na_2SO_4). Evaporation of the solvent gave an oil which rapidly solidified and was crystallised from ethanol. The resultant *ethyl 5-nitro-2-methoxybenzoylmalonate* (37·4 g., 83%) had m. p. 78—79° (Found: C, 53·0; H, 5·3; N, 4·2. $C_{15}H_{17}O_8N$ requires C, 53·1; H, 5·0; N, 4·15%).

5-Nitro-2-methoxyacetophenone.—Hydrolysis of the above ester with boiling 6N-sulphuric acid (400 c.c.) in alcohol (50 c.c.) for 6 hours yielded *5-nitro-2-methoxyacetophenone* (60%), m. p. 98° (Found: N, 7·2; OMe, 15·9. $C_9H_9O_4N$ requires N, 7·2; OMe, 15·9%). The *semicarbazone* crystallised in colourless needles, m. p. 215—216°, from alcohol (Found: N, 22·0. $C_{10}H_{12}O_4N_4$ requires N, 22·1%). The 2 : 4-*dinitrophenylhydrazone*, m. p. 239°, separated in orange clusters from acetic acid (Found: N, 18·6. $C_{15}H_{13}O_7N_5$ requires N, 18·65%).

5-Amino-2-methoxyacetophenone.—5-Nitro-2-methoxyacetophenone (4 g.), ethanol (50 c.c.), and granulated tin (4 g.) were treated with hydrochloric acid (*d* 1·18; 18 c.c.) added portionwise at 25°. The nitro-compound and the tin gradually dissolved during 4 hours. After being left for 12 hours the liquid was concentrated to half bulk. The stannichloride which separated was dissolved in water (100 c.c.), and the solution basified with 25% sodium hydroxide (phenolphthalein) and then extracted with ether. Evaporation of the dried (Na_2SO_4) extract gave 5-amino-2-methoxyacetophenone (2·14 g., 65%), b. p. 125—127°/0·25 mm., characterised as the *hydrochloride*, m. p. 186° (decomp.) (Found: N, 7·0; Cl, 17·8. $C_9H_{11}O_2N$,HCl requires N, 6·95; Cl, 17·6%). The N-*acetyl* derivative crystallised from ethanol in needles, m. p. 186—187° (Found: C, 63·9; H, 6·5; N, 6·8; OMe, 15·3. $C_{11}H_{13}O_3N$ requires C, 63·7; H, 6·3; N, 6·8; OMe, 15·0%). *5-Acetamido-2-methoxyacetophenone* 2 : 4-*dinitrophenylhydrazone*, m. p. 205—206°, crystallised in fine rosettes of scarlet needles from acetic acid (Found: N, 15·7. $C_{17}H_{17}O_6N_5,C_2H_4O_2$ requires N, 15·7%). Similarly the *semicarbazone*, m. p. 216—217°, formed cream micro-needles from ethanol (Found: N, 21·2. $C_{12}H_{16}O_3N_4$ requires N, 21·2%).

ω-Bromo-5-nitro-2-methoxyacetophenone.—5-Nitro-2-methoxyacetophenone (2·5 g.) in chloroform (35 c.c.) was treated with bromine (2 g.) in sunlight. After 30 minutes the solution became colourless and hydrogen bromide was evolved. Evaporation gave *ω-bromo-5-nitro-2-methoxyacetophenone*, which crystallised from benzene in colourless needles (1·15 g.), m. p. 119° (Found: N, 5·25; Br, 29·0. $C_9H_8O_4NBr$ requires N, 5·15; Br, 29·2%). The *benzoate*, m. p. 142°, crystallised in colourless plates from ethanol (Found: N, 4·5. $C_{16}H_{13}O_6N$ requires N, 4·45%).

ω-Bromo-3-nitro-4-methoxyacetophenone.—3-Nitro-4-methoxyacetophenone (3 g.) (cf. Harding, *J.*, 1914, **105**, 2794) in dry chloroform (35 c.c.) was treated, as described above, with dry bromine (2·1 g.) in chloroform (8 c.c.). The *product* (2·5 g.) crystallised from ethanol in pale buff needles, m. p. 96° (Found: N, 5·3; Br, 29·2. $C_9H_8O_4NBr$ requires N, 5·15; Br, 29·2%).

Acylation of Phenacetin.—(*a*) *With acetyl bromide* (cf. Kunckell, *Ber. deut. pharm. Ges.*, 1913, **23**, 472). Phenacetin (20 g.) and acetyl bromide (40 g.) in carbon disulphide (60 c.c.) were stirred with anhydrous aluminium chloride (60 g.). After the mixture had been heated under reflux for 1 hour on the steam-bath the solvent was distilled off and the residue treated with ice, giving 5-acetamido-2-hydroxyacetophenone (16 g., 65%) as yellow cubes, m. p. 165°, from ethanol. The 2 : 4-*dinitrophenylhydrazone*, m. p. 290° (decomp.), crystallised in orange needles from acetic acid (Found: N, 18·6. $C_{16}H_{15}O_6N_5$ requires N, 18·75%). 5-Acetamido-2-hydroxyacetophenone (1·8 g.) in water (10 c.c.) containing sodium hydroxide (0·4 g.) was shaken with ethyl sulphate (1 g.) for 2 hours. The precipitate, on recrystallisation from ethanol, gave 5-acetamido-2-ethoxyacetophenone (1·4 g.) m. p. 155—156°. Methylation with methyl toluene-*p*-sulphonate similarly gave 5-acetamido-2-methoxyacetophenone, m. p. 186—188°. The 2 : 4-dinitrophenylhydrazone had m. p. 205°. Neither gave any depression in m. p. on admixture with the synthetic samples described above.

(*b*) *With acetic anhydride.* Phenacetin (20 g.) and acetic anhydride (12 g.) in carbon disulphide (150 c.c.) were stirred with anhydrous aluminium chloride (30 g.). After being left overnight at room temperature the solution was concentrated by removal of the solvent and the residue decomposed with ice-water. After four recrystallisations from ethanol and two from benzene, 5-acetamido-2-ethoxyacetophenone (3 g.) was obtained, m. p. 155° (Kunckell, *loc. cit.*, gives m. p. 155°), identical with the sample above (Found: C, 65·3; H, 6·6; N, 6·45; OEt, 20·5. Calc. for $C_{12}H_{15}O_3N$: C, 65·2; H, 6·75; N, 6·35; OEt, 20·4%). The 2 : 4-*dinitrophenylhydrazone*, m. p. 232—233° (decomp.), separated in golden-orange needles from acetic acid (Found: N, 15·25. $C_{18}H_{19}O_6N_5,C_2H_4O_2$ requires N, 15·2%). The *semicarbazone*, m. p. 238—239°, formed colourless needles from ethanol (Found: C, 55·8; H, 6·5; N, 19·9. $C_{13}H_{18}O_3N_4$ requires C, 56·1; H, 6·5; N, 20·0%).

Fractionation of the residue left after evaporation of the mother liquors from the above recrystallisations gave an unidentified product (0·25 g.), m. p. 111—112°.

ω-Bromo-p-methoxyacetophenone and ω: p-*dibromoacetophenone.*—These were prepared by bromination of *p*-methoxy- and *p*-bromo-acetophenone (*Org. Synth.*, Coll. Vol. I, p. 109).

2 : 4-*Dibromoacetophenone.*—*m*-Bromonitrobenzene (*Org. Synth.*, Coll. Vol. I, p. 123) (10 g.) in ethanol (30 c.c.) was boiled with calcium chloride (0·6 g.) in water (12 c.c.). After removal from the steam-bath, reduced iron (10 g.) was added slowly in 1 g. portions at such a rate that the heat of reaction kept the solution boiling gently under reflux. The mixture was then heated under reflux for 30 minutes and filtered, and the alcohol distilled off. After addition of hydrochloric acid (*d* 1·16, 20 c.c.) the non-basic substances were extracted with ether. The aqueous layer yielded *m*-bromoaniline, b. p. 122—124°/10 mm. (Holleman, *Rec. Trav. chim.*, 1906, **25**, 186, cites b. p. 130°/12 mm.) (6·4 g., 80%; on the scale of 120 g. of *m*-bromonitrobenzene however the yield fell to 68%).

m-Bromoaniline (68 g.) in sulphuric acid (*d* 1·84, 44 c.c.) and water (2 l.) was diazotised at 5° with sodium nitrite (27 g.) in water (50 c.c.). Cuprous bromide (*Org. Synth.*, Coll. Vol. I, p. 136) was then added at 75° with vigorous stirring. Steam distillation of the mixture followed by ether extraction of the distillate gave *m*-dibromobenzene (23 g.), a colourless oil, b. p. 94°/15 mm., characterised as 2 : 4-dibromobenzenesulphonyl chloride, m. p. 81—82°, and as 2 : 4-dibromobenzenesulphonamide, m. p. 191—192° (Huntress and Carten, *J. Amer. Chem. Soc.*, 1940, **62**, 511, give m. p. 78—79° and m. p. 188—189°, respectively, for these two compounds). *m*-Dibromobenzene (46 g.) and acetyl chloride (33 g.) in dry carbon disulphide (500 c.c.) were heated under reflux with anhydrous aluminium chloride (140 g.) for 6 hours. After decomposition of the product with ice-water and extraction with benzene, 2 : 4-*dibromoacetophenone* (38·25 g., 71%) was obtained, which crystallised from light petroleum (b. p. 60—80°), m. p. 61—62° (Found : C, 34·9; H, 2·5; Br, 57·1. $C_8H_6OBr_2$ requires C, 34·6; H, 2·2; Br, 57·5%). The 2 : 4-*dinitrophenylhydrazone* had m. p. 175° (Found : N, 12·4; Br, 35·4. $C_{14}H_{10}O_4N_4Br_2$ requires N, 12·2; Br, 35·0%).

2 : 4 : *ω-Tribromoacetophenone.*—2 : 4-Dibromoacetophenone (36 g.) in dry chloroform (200 c.c.) was treated with bromine (20·6 g.). The yellow *product* (43 g., 93%) had m. p. 34—35° and b. p. 193—195°/10 mm. (Found : Br, 66·7. $C_8H_5OBr_3$ requires Br, 67·2%).

ω-Dialkylaminoacetophenones.—General procedure. The ω-bromoacetophenone (1 mol.) in dry ether was treated with the requisite amine (2 mols.) and left for 2—24 hours by which time 1 mol. of amine hydrobromide had been precipitated. This was filtered off and the filtrate treated with hydrogen chloride or bromide to precipitate the ω-amino-ketone salt which was then recrystallised from ethanol–ether. Excess of hydrogen halide was avoided as this tended to precipitate the products as gums which slowly decomposed. If an oil was formed trituration with dry ether reversed the change where this had not proceeded too far. The compounds listed in the table were so obtained.

				Analysis. Found, %.		Required, %.	
Acetophenone.	No.	Formula of salt.	M. p.	N.	Br.	N.	Br.
5-Nitro-ω-piperidino-2-methoxy-	1	$C_{14}H_{18}O_4N_2$,HBr	195—196° (decomp.)	7·8	22·2	7·8	22·25
5-Nitro-ω-morpholino-2-methoxy-	2	$C_{13}H_{16}O_5N_2$,HBr	197—198 (decomp.)	7·8	22·4	7·76	22·2
3-Nitro-ω-piperidino-4-methoxy-	3	$C_{14}H_{18}O_4N_2$,HBr	186—187 (decomp.)	7·75	22·3	7·8	22·25
3-Nitro-ω-morpholino-4-methoxy-	4	$C_{13}H_{16}O_5N_2$,HBr	210 (decomp.)	7·6	21·9	7·76	22·2
p-Bromo-ω-diethylamino-	5	$C_{12}H_{16}ONBr$,HCl	170—171	—	—	—	—
p-Bromo-ω-di-*n*-butylamino-	6	$C_{16}H_{24}ONBr$,HBr	176—177	—	—	—	—
p-Bromo-ω-piperidino-.....	7	$C_{13}H_{16}ONBr$,HCl	224—225	—	—	—	—
p-Bromo-ω-morpholino-	8	$C_{12}H_{14}O_2NBr$,HBr	248—249	4·0	43·75	3·8	43·8
p-Bromo-ω-*iso*propylamino-	9	$C_{11}H_{14}ONBr$,HBr	246—248	4·2	47·5	4·15	47·5
2 : 4-Dibromo-ω-morpholino-	10	$C_{12}H_{12}O_2NBr$,HBr	223	3·2	54·0	3·2	54·0
ω-Diethylamino-*p*-methoxy-	11	$C_{13}H_{19}O_2N$,HBr	111—112	4·6	(C, 52·0) (H, 6·8)	4·6	(C, 5·7) (H, 6·6)
ω-Piperidino-*p*-methoxy-.....	12	$C_{14}H_{19}O_2N$,HBr	188—189	4·4	25·3	4·5	25·4
ω-*iso*Propylamino-*p*-methoxy- ...	13	$C_{12}H_{17}O_2N$,HBr	171—172	4·9	27·9	4·9	27·8
ω-Morpholino-*p*-methoxy-	14	$C_{13}H_{17}O_3N$,HBr	210	4·36	25·4	4·43	25·3

Reduction of compounds 5, 6, 7, 8, and 10 was carried out with aluminium *iso*propoxide as described by Drake and Goldman (*loc. cit.*) except that the salts were reduced directly instead of as the free base. There were thus obtained 2-diethylamino-1-*p*-bromophenylethanol hydrobromide (64%), m. p. 135—136° (Found : C, 40·5; H, 5·5; N, 4·0; active H, 2. Calc. for $C_{12}H_{18}ONBr$,HBr : C, 40·8; H, 5·4; N, 4·0%; active H, 2); 2-di-*n*-butylamino-1-*p*-bromophenylethanol hydrobromide (68%), m. p. 110—112° (lit. 112—113°) (Found : C, 46·9; H, 6·5; N, 3·6; active H, 2. Calc. for $C_{16}H_{26}ONBr$,HBr : C, 46·9; H, 6·6; N, 3·4%; active H, 2); 2-piperidino-1-*p*-bromophenylethanol hydrochloride (89%), m. p. 236° (lit. 237—238°) (Found : C, 48·6; H, 5·7; N, 4·4; active H, 2. Calc. for $C_{13}H_{18}ONBr$,HCl : C, 48·7; H, 5·9; N, 4·4%; active H, 2); 2-*morpholino*-1-p-*bromophenylethanol hydrobromide* (75%), m. p. 232° (Found : C, 39·0; H, 4·6; active H, 1·8. $C_{12}H_{16}O_2NBr$,HBr requires C, 39·2; H, 4·6%; active H, 2); 2-*morpholino*-1-(2′ : 4′-*dibromophenyl*)*ethanol hydrobromide* (56%), m. p. 215—218° (Found : C, 32·6; H, 3·6; active H, 2. $C_{12}H_{15}O_2NBr_2$,HBr requires C, 32·3; H, 3·6%; active H, 2). Compound 9 could not be reduced to a pure alcohol either by the use of aluminium *iso*propoxide or by hydrogenation under the conditions described below.

In the series of *p*-methoxy-compounds reduction was effected by hydrogenating the amino-ketone in

alcohol at normal temperature and pressure in the presence of (10%) Adams's catalyst. From compounds 12, 13, and 14 were obtained 2-*piperidino*-1-p-*methoxyphenylethanol hydrobromide* (75%), m. p. 164—165° (Found : C, 53·2; H, 6·8; N, 4·5; Br, 25·3; OMe, 9·8. $C_{14}H_{21}O_2N$,HBr requires C, 53·2; H, 7·0; N, 4·4; Br, 25·3; OMe, 9·8%); 2-iso*propylamino*-1-p-*methoxyphenylethanol hydrobromide*, m. p. 110—111° (Found : C, 49·4; H, 6·8; OMe, 10·7; active H, 2·6. $C_{12}H_{19}O_2N$,HBr requires C, 49·65; H, 6·9; OMe, 10·7%; active H, 3); and 2-*morpholino*-1-p-*methoxyphenylethanol hydrobromide* (75%), m. p. 170—171° (Found : C, 49·2; H, 6·3; active H, 2. $C_{13}H_{19}O_3N$,HBr requires C, 49·0; H, 6·3%; active H, 2).

Compounds 1, 2, 3, and 4 were similarly reduced, and gave, respectively, 2-*piperidino*-1-(5′-*amino*-2′-*methoxyphenyl*)*ethanol hydrobromide*, m. p. 151—152° (Found : C, 50·4; H, 7·3; N, 8·3; OMe, 9·4; active H, 3·04. $C_{14}H_{22}O_2N_2$,HBr requires C, 50·7; H, 7·0; N, 8·3; OMe, 9·4%; active H, 3) [the free *base* had m. p. 115° and b. p. 155° (bath temp.)/0·05 mm. (Found : C, 67·7; H, 8·5; active H, 2. $C_{14}H_{22}O_2N_2$ requires C, 67·2; H, 8·8%; active H, 2)]; 2-*morpholino*-1-(5′-*amino*-2′-*methoxyphenyl*)*ethanol hydrobromide*, m. p. 184—185° (Found : C, 46·2; H, 6·0; active H, 2·2. $C_{13}H_{20}O_3N_2$,HBr requires C, 46·9; H, 6·3%; active H, 2); 2-*piperidino*-1-(3′-*amino*-4′-*methoxyphenyl*)*ethanol*, b. p. 175—185°(bath temp.)/0·1 mm. (Found : C, 67·2; H, 8·8; N, 11·2; OMe, 12·3; active H, 1·7. $C_{14}H_{22}O_2N_2$ requires C, 67·2; H, 8·8; N, 11·2; OMe, 12·4%; active H, 2); and 2-*morpholino*-1-(3′-*amino*-4′-*methoxyphenyl*)-*ethanol*, m. p. 66—67°, b. p. 85—90°/10^{-6} mm. (Found : C, 61·95; H, 7·4; active H, 1·75. $C_{13}H_{20}O_3N_2$ requires C, 61·9; H, 7·9%; active H, 2).

The authors thank Mr. S. Bance, B.Sc., A.R.I.C., for the semi-micro-analyses, Mr. G. J. Hill for help with the experimental work, and the Directors of May and Baker Ltd. for permission to publish these results.

Research Laboratories, May and Baker Ltd.,
Dagenham.

[*Received, July 30th,* 1948.]