Base-promoted Reactions of α-Halogeno-alkylanilides

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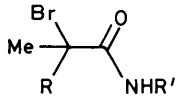
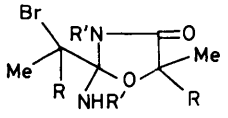
Hydride-promoted reactions of 2-halogeno-alkylcarboxanilides afford heterocyclic and acyclic condensation products, some of the latter compounds arising upon hydrolysis and/or rearrangement of the former ones. Competitive formation of dioxopiperazines *versus* oxazolidinone derivatives or their transformation products depends mainly upon the nature (primary, secondary or tertiary) of the halide moiety. Concurrent dehydrohalogenation of 2-bromo-isobutyranilides leads to unsaturated condensation products.

In order to explore the synthetic value of 2-halogeno-amides, we recently investigated hydride-promoted reactions of the 2-bromo-propionamide (1a) and -isobutyramide (1b). Both self-condensations to 2-amino-2-bromoalkyl-oxazolidinones (2),[1] and cross-condensations with a variety of amides to produce 2-alkyl- or 2-aryl-2-amino-oxazolidinones (3),[2] were observed. A dioxopiperazine (4a) and the rearranged, hydrolytically ring-opened derivative (5a) were present as secondary products from (1a) or (1b), their production possibly depending on the halide moiety.[1]† Analogous reactions of the 2-bromo-anilides (6a—e) and related amide derivatives shed light on the influence of the halide moiety and the group linked to the amide nitrogen on the reaction pattern.

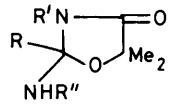


(1)

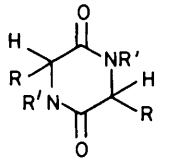
a; R = H, R′ = CH_2Ph
b; R = Me, R′ = CH_2Ph



(2) R = H or Me

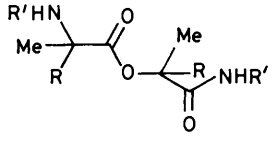


(3)



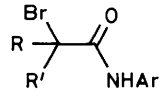
(4)

a; R = Me, R′ = CH_2Ph
b; R = H, R′ = Ph
c; R = H, R′ = CH_2Ph
d; R = Me, R′ = Ph



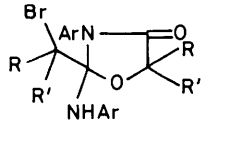
(5)

a; R = Me, R′ = CH_2Ph
b; R = H, R′ = Ph
c; R = Me, R′ = Ph
d; R = Me, R′ = C_6H_4OMe-*p*



(6)

a; R = R′ = H, Ar = Ph
b; R = H, R′ = Me, Ar = Ph
c; R = R′ = Me, Ar = Ph
d; R = R′ = Me, Ar = C_6H_4OMe-*p*
e; R = R′ = Me, Ar = C_6H_4Cl-*p*



(7)

a; R = R′ = H, Ar = Ph
b; R = H, R′ = Me, Ar = Ph
c; R = R′ = Me, Ar = Ph

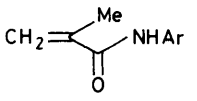
Results and Discussion

Amides carrying a vicinal primary halide function, such as 2-bromoacetanilide (6a) and 2-chloro- or 2-bromo-*N*-benzyl-acetamide, react in the presence of sodium hydride, yielding only the pertinent dioxopiperazines (4b) and (4c);[3] no oxazolidinone (7a) or other derivatives are observed. 2-Bromopropionanilide (6b) reacts, in turn, with sodium hydride yielding (i) *cis*- and *trans*-dioxopiperazines (4d), and (ii) 1-phenylcarbamoylethyl 2-anilinopropionate (5b, two diastereoisomers); the formation of this rearranged amino-ester derivative is discussed below for (5c) (see also the Scheme).

A composite pattern resulted from anilides carrying a tertiary halide moiety. By treating 2-bromoisobutyranilide (6c) with sodium hydride in tetrahydrofuran (THF) at −20 °C, followed by fractionation on silica gel, the rearranged ring-opened 1-phenylcarbamoyl-1-methylethyl 2-anilinoisobutyrate (5c) was isolated as the major product. Identical runs starting from compounds (6c, d) at or above room temperature yielded again the pertinent rearranged ring-opened derivatives (5c,d) and several unsaturated products. Among the latter, we identified: (i) traces of methacrylanilide (8a) [more consistent amounts of the *p*-anisidide (8b) resulted from (6d)]; (ii) 1-phenylcarbamoyl-1-methylethyl methacrylate (9a); (iii) *N*-(1-phenylcarbamoyl-1-methylethyl)methacrylanilide (10a); a minor product, having possibly the molecular formula $(C_{10}H_{11}NO)_3$, is still under investigation.

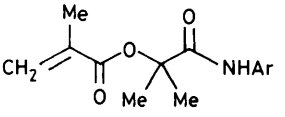
By fractionating on alumina some of the reaction mixture obtained at 20 °C, an additional unsaturated derivative was obtained. It consists of the 2-arylamino-2-isopropenyl-3-aryl-oxazolidinone (11a), which undergoes hydrolytic ring-opening on silica gel to produce the ester derivative (9a). In spite of the fact that in no case has a 2-arylamino-2-bromoalkyl-3-aryl-oxazolidinone (7) been isolated, we think that two equivalents of the α-bromo-amidate anion (12) undergoes self-condensation (see Scheme) to produce the anionic intermediate (13) and then its cyclic isomer (14). Whereas quench-

† Formation of aziridinones is subject to the presence of bulky aliphatic groups at the nitrogen, and eventually at the sp^3 carbon of 2-halogeno-amides (*cf.* I. Lengyel and J. C. Sheehan, *Angew. Chem., Int. Ed. Engl.*, 1968, **7**, 25).



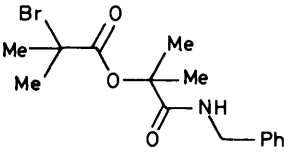
(8)

a; Ar = Ph
b; Ar = C_6H_4OMe-*p*
c; Ar = C_6H_4Cl-*p*

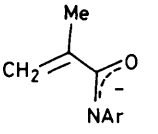


(9)

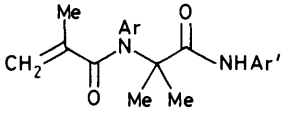
a; Ar = Ph
b; Ar = C_6H_4OMe-*p*



(16)

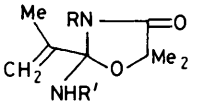


(17)



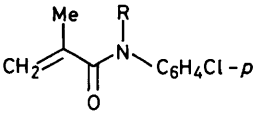
(10)

a; Ar = Ar' = Ph
b; Ar = Ph, Ar' = C_6H_4Cl-*p*
c; Ar = Ar' = C_6H_4OMe-*p*



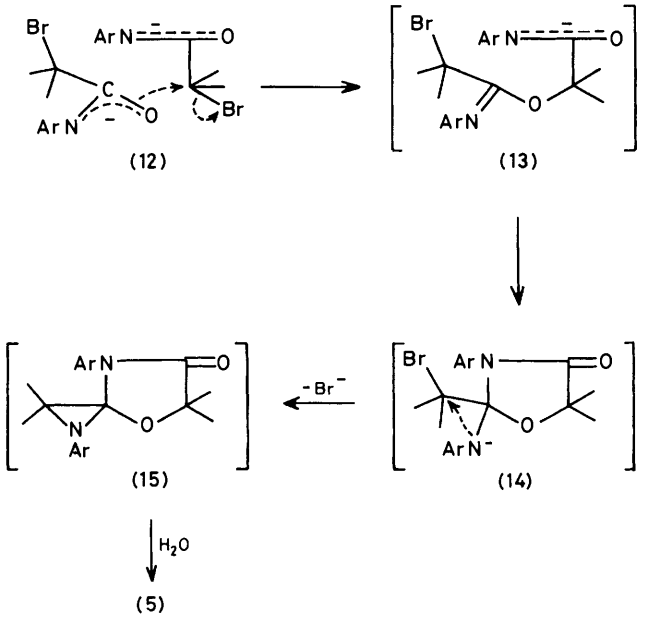
(11)

a; R = R' = Ph
b; R = C_6H_4Cl-*p*, R' = Ph
c; R = R' = CH_2Ph



(18)

a; R = Me
b; R = CH_2Ph



Scheme

ing of (14) by a proton would give the expected oxazolidinone derivatives (7b,c), a rearrangement based on a fast intramolecular nucleophilic substitution may afford the hypothetical oxazolidine-2,2'-spiroaziridin-4-one (15): hydrolysis by environmental water of the orthoester-aminal compound (15) [4] will finally give the observed major products (5b,c).* The failure to isolate 2-arylamino-2-bromoalkyl-oxazolidinones (7), in contrast with the 2-benzylamino-analogues (2), may be ascribed to the aromatic *versus* aliphatic character of the amine moieties. ^{1}H N.m.r. spectra of representative oxazolidinone derivatives (2), (3), (11c),[1,2] and (11a,b) show that a 2-anilino- is more acidic than a 2-benzylamino-substituent at the orthoester-aminal function: the relatively more stable conjugate anion (14) would consequently be favoured in the attack on the adjacent halogenated carbon.

A parallel finding, that the α-halogeno-ester amide (16) [1] does not undergo aminolysis to the pertinent α-amino-ester amide (5a), even under forcing conditions, adds indirect support to the proposed rearrangement.

The presence of the unsaturated products (9), (10), and (11) is subject, in turn, to a competitive, temperature-dependent dehydrohalogenation of the bromo-isobutyranilides (6c—e); [5] the resulting methacrylamide anion (17) would react with the parent halogenoamide to yield (i) the oxazolidinone derivative (11a) [2] and its open-chain derivative (9a), or (ii) the *N*-alkylation derivative (10a), possibly an O ⟶ N rearrangement product.† The formation of unsaturated products (10), (11), or (9) increases, in fact, in the presence of methacrylanilide anion (17), formed *in situ* from added (8a).

In order to rationalize the distribution of dioxopiperazines (4b,d) as opposed to substituted oxazolidinones (7b,c) and their open-chain substituted derivatives, we propose the following hypotheses, in agreement with Kornblum's postulate.[6] (i) α-Halogeno-amides carrying a primary halide function undergo self-condensation to dioxopiperazines through regiospecific substitutions by the soft end(s) (N) of the ambifunctional amide anions (12) onto the (soft) primary halide moieties. (ii) α-Halogeno-anilides carrying a tertiary halide function undergo substitution by the hard end (O) of an amide anion: the development of positive charge at the tertiary carbon of the bromo-anion (12) occurs despite the adverse influence of the neighbouring carbonyl and may be favoured by the presence of the anionic charge.[7] (iii)α-Halogeno-amides carrying a secondary halide moiety react less regioselectively, giving both types of products.

Further research, aimed at isolating spiro-heterocycles related to the postulated rearrangement intermediates (15), is in progress.

* A related rearrangement was observed in the nucleophilic addition of RO^- to α-chloroaldimines, R. De Kimpe, R. Verhe, L. De Buyck, H. Hasma, and N. Schamp, *Tetrahedron*, 1976, **32**, 2457.

† For work concerning *O- versus N*-alkylation of amide anions, and rearrangements of intermediate *O*-alkylimidates, see B. C. Challis and J. A. Challis in 'The Chemistry of Amides,' ed. J. Zabicky, Interscience, London, 1970, p. 748. Gas-phase enthalpy differences of *ca.* 17 kcal mol^{-1} (1 cal = 4.184 J) have been measured for amide–imidate pairs in equilibration studies by P. Beak, J. Lee, and J. M. Ziegler, *J. Org. Chem.*, 1978, **43**, 1536. Two examples of *N*-alkylation of the methacrylamide anion (17) by simple halides are reported (see Experimental section).

Experimental

For reagents and spectroscopic details, see ref. 1. Column chromatography was performed on silica (KG-60) or on alumina. R_Fs refer to t.l.c. on silica, with ethyl acetate–toluene (1 : 4). M.p.s were determined with a Reichert Köfler block and are uncorrected.

Reactions of 2-*Bromoacetanilide* (6a) *or* 2-*Chloro- and* 2-*Bromo*-N-*benzylacetamide with Sodium Hydride*.—Reactions were carried out as described below for (6b—e); the pertinent 1,4-diphenyl- (78%) and 1,4-dibenzyl-2,5-dioxopiperazines (4b,c) [3] (74%; 81%) were isolated along with minor amounts of starting materials; no other product could be detected.

Reaction of 2-*Bromopropionanilide* (6b) *with Sodium Hydride*.—1-*Phenylcarbamoylethyl* 2-*anilinopropionate* (5b, *two diastereoisomers*) *and* cis- *and* trans-1,4-*diphenyl*-3,6-*dimethyl*-2,5-*dioxopiperazines* (4b). A solution of the 2-bromo-propionanilide (6b) [8] [ν(KBr) 3 310, 1 665 cm^{-1}; δ($CDCl_3$) 1.39 (3 H, d, *J* 7 Hz, Me), 4.55 (1 H, q, *J* 7 Hz, MeC*H*), 7.1—7.7 (5 H, m, Ph), and 8.52br (CONH)] (3.4 g, 0.015 mol) in anhydrous THF (20 ml) was added during 70 min at 20 °C with stirring to a suspension of sodium hydride (0.54 g, 0.022 mol) in THF (10 ml), and hydrogen was evolved uniformly. Stirring was continued overnight and centrifugation then yielded a solution. The solvent was evaporated off and the crude oily mixture (2.2 g) was fractionated by chromatography on a column of silica, under low pressure (4 atm), using ethyl acetate–toluene (1 : 4) as solvent. A few fractions containing only the slower moving diastereoisomer (5b) were concentrated; the resulting oil was dissolved in methylene dichloride, washed with 1M-HCl, dried (Na_2SO_4), and the solvent evaporated off to give an oil (5.5%), brown single spot (I_2–NaN_3), R_F 0.39; $\nu_{max.}$ ($CHCl_3$) 1 750 (ester CO) and 1 680 cm^{-1} (amide CO); δ($CDCl_3$) 1.55 (3 H, d, *J* 7 Hz, MeCN), 1.65 (3 H, d, *J* 7 Hz, MeCO), 2.0br (1 H, NH), 4.52 (1 H, q, *J* 7 Hz, MeCHN), 5.11 (1 H, q, *J* 7 Hz, MeCHO), 6.7br (CONH), and 7.3 (10 H, m, 2 Ph) (Found: C, 68.9; H, 6.45; N, 8.8. $C_{18}H_{20}N_2O_3$ requires C, 69.21; H, 6.45; N, 8.97%). Concentration to dryness of the fractions containing both diastereoisomers also gave an oil (15%), R_F 0.39, single spot with I_2–NaN_3; for the faster moving diastereoisomer (5b), $\nu_{max.}$ ($CHCl_3$) 1 750 (ester CO) and 1 680 cm^{-1} (amide CO); δ($CDCl_3$) 1.05 (3 H, d, *J* 7 Hz, MeCN), 1.56 (3 H, d, *J* 7 Hz, MeCO), *ca.* 2.0br (1 H, NH), 4.09 (1 H, q, *J* 7 Hz, MeCHN), 4.75 (1 H, q, *J* 7 Hz, MeCHO), 6.7br (CONH), 7.3 (10 H, m, 2 Ph) [overall yield of the diastereoisomeric pair (5b) 20.5%].

Concentration of the slower moving fractions yielded the following: (i) colourless prisms (from toluene–light petroleum, b.p. 40—70 °C), m.p. 161—163 °C (212 mg, 10%) corresponding to *cis*-(4d); [9] R_F 0.14; δ($CDCl_3$) 1.42 (6 H, d, *J* 7 Hz, 2 Me), 4.54 (2 H, q, *J* 7 Hz, 2 *H*CMe), and 7.3 (10 H, m, 2 Ph); (ii) colourless needles (from toluene–light petroleum), b.p. 40—70 °C), m.p. 180—182 °C (738 mg, 34%), corresponding to *trans*-(4d); [9] R_F 0.10; δ($CDCl_3$) 1.58 (6 H, d, *J* 7 Hz, 2 Me), 4.45 (2 H, q, *J* 7 Hz, 2 *H*CMe), and 7.3 (10 H, m, 2 Ph).

Reactions of 2-*Bromoisobutyranilide* (6c) *with Sodium Hydride*.—(a) *At* −20 °C. 1-*Phenylcarbamoyl*-1-*methylethyl* 2-*anilinoisobutyrate* (5c). A solution of the bromo-anilide (6c) [10] (0.24 g, 0.001 mol) [$\nu_{max.}$ (KBr) 3 300br, and 1 655 cm^{-1}; δ($CDCl_3$) 2.02 (6 H, s, 2 Me), 7.07—7.77 (5 H, m, Ph), 8.47br (CONH)], in anhydrous THF (4 ml) was added during 40 min to sodium hydride (48 mg, 0.002 mol) covered with THF (3 ml) at −20 °C and the mixture was stirred for 2 h at the same temperature under nitrogen. After centrifugation of the mixture, the solution was concentrated to give a crude oil. Chromatography on a column of silica gel gave a pure oily product (136 mg, 80%).

(*b*) An identical run gave a crude oil which was purified on alumina, yielding the same product. Colourless prisms were obtained from diethyl ether–light petroleum; m.p. 113—114 °C, R_F 0.47, brown with I_2–NaN_3; $\nu_{max.}$ ($CHCl_3$) 1 740 (ester CO) and 1 695 cm^{-1} (amide CO); δ($CDCl_3$) 1.53 (6 H, s, Me_2), 1.67 (6 H, s, Me_2), 6.6—7.4 (10 H, m, 2 Ph), 7.77 (1 H, br, NHCO), 4.0 (1 H, br, NH) (Found: C, 70.65; H, 7.1; N, 8.05. $C_{20}H_{24}N_2O_3$ requires C, 70.56; H, 7.10; N, 8.23%).

(*c*) *At room temperature*. A reaction mixture identical with the one described in (*a*), but using ten-fold amounts of reagents, was kept for 80 min at room temperature and then centrifuged and the solution concentrated to dryness. The thick oil was dissolved in ethyl acetate–toluene (1 : 4) and separated using a silica column and the same solvent mixture. Upon concentration of the pertinent fractions we obtained the following: (i) compound (5c) (44%); (ii) 1-*phenylcarbamoyl*-1-*methylethyl methacrylate* (9a); this product was absent in the crude reaction mixture but was produced on the silica column. The oil (R_F 0.52) was crystallized from ethyl acetate–light petroleum (b.p. 40—70 °C) to yield colourless prisms (15%), m.p. 98—99 °C, R_F 0.52, brown with I_2–NaN_3; $\nu_{max.}$ ($CHCl_3$) 3 500 (amide NH) and 1 725 (unsaturated ester CO) and 1 695 cm^{-1} (amide CO); δ($CDCl_3$) 1.72 (6 H, s, Me_2), 1.95 (3 H, m, =CMe), 5.65, 6.15 (2 H, 2 m, $=CH_2$), 7.4 (5 H, m, Ph), and 8.0br (1 H, s, NHCO) (Found: C, 68.1; H, 7.0; N, 5.55. $C_{14}H_{17}NO_3$ requires C, 68.0; H, 6.93; N, 5.66%). The same compound (61% yield) was obtained by cross-condensation of (8a) with (6c) (see below), followed by hydrolysis on silica. (iii) N-(1-*Phenylcarbamoyl*-1-*methylethyl*)*methacrylanilide* (10a). The crude solid (4% yield) was recrystallized from ethanol–water (1:1) to give colourless prisms, m.p. 192—193 °C, brown with I_2–NaN_3; R_F 0.2; $\nu_{max.}$ ($CHCl_3$) 3 450 (amide NH), 1 690 (amide CO), and 1 655 cm^{-1} (conj. amide CO); δ($CDCl_3$) 1.48 (6 H, s, Me_2), 1.65 (3 H, m, =CMe), 4.91 (2 H, br, $=CH_2$), 7.4 (10 H, m, 2 Ph), and 8.16 (1 H, s, NHCO) (Found: C, 74.3; H, 7.1; N, 8.6. $C_{20}H_{22}N_2O_2$ requires C, 74.51; H, 6.88; N, 8.69%). (iv) Unidentified colourless product, m.p. 168—169 °C, probably $(C_{10}H_{11}NO)_3$.

Reactions of 2-*Bromo*-N-p-*methoxyisobutyranilide* (6d) *with Sodium Hydride*.—A solution of the halogenoanilide (6d) [10] (1.36 g, 0.005 mol) in anhydrous THF (4 ml), was added at 0 °C to sodium hydride (0.24 g, 0.01 mol) covered with THF (3.5 ml), and the mixture was stirred at 0 °C for 1 h. Work-up and column chromatography as indicated for (6c) gave a corresponding set of products, namely: (5d) (30%), (8b) (7%), (9b) (13%), (10c) (9%), and an unidentified product $(C_{11}H_{13}NO_2)_3$ (8%). The i.r. and n.m.r. data match those reported for the products from (6c), with the additional absorptions due to the methoxy-group; data are omitted for brevity. Contamination by *p*-methoxyaniline and easy air-oxidation of the reaction products were observed throughout.

Reactions of Methacrylanilide (8a) *with* 2-*Bromoisobutyranilide* (6c) *in the Presence of Sodium Hydride*.—A solution of methacrylanilide (8a) [11] (0.47 g, 2.9 mmol) in THF (12 ml) was added to sodium hydride (210 mg, 7 mmol) covered with THF (10 ml) with stirring; when the production of hydrogen ceased, the mixture was cooled to 0 °C and a solution of 2-bromoisobutyranilide (6c) (0.68 g, 2.8 mmol) in THF (8 ml) was added during 1 h and stirring continued for 2 h. The mixture was left overnight at 0 °C, centrifuged and concentrated to dryness; the resulting oil was fractionated on a column of neutral alumina, with ethyl acetate–toluene (1 : 4). The fast moving fractions yielded 2-*anilino*-2-*isopropenyl*-3-*phenyl*-5,5-*dimethyloxazolidin*-4-*one* (11a). Work-up and

recrystallization of the crude product from diethyl ether–light petroleum (b.p. 40—70 °C) gave compound (11a) as colourless prisms (0.5 g, 56%), m.p. 109—112 °C, R_F 0.6; $\nu_{max.}$ ($CHCl_3$) 3 405 (NH) and 1 710 cm^{-1} (CO); δ($CDCl_3$) 1.22, 1.49 (6 H, 2 s, 2 Me), 1.78 (3 H, m, =CMe), 4.67br (1 H, NH), 5.32, 5.22 (2 H, 2 m, $=CH_2$), 7.63—6.73 (10 H, m, 2 Ph) (Found: C, 73.8; H, 7.15; N, 8.9. $C_{20}H_{22}N_2O_2$ requires C, 74.51; H, 6.88; N, 8.69%). Slower moving fractions yielded compound (10a) (0.16 g, 18%), identical with the sample described above.

Reactions of Methacrylanilide (8a) *with* 2-*Bromo*-N-p-*chlorophenylisobutyramide* (6e) *in the Presence of Sodium Hydride.*—2-*Anilino*-2-*isopropenyl*-3-p-*chlorophenyl*-5,5-*dimethyl-oxazolidin*-4-*one* (11b) was obtained by an identical way to the analogue (11a), by treating (8a) with sodium hydride and then with 2-bromo-*N*-*p*-chlorophenylisobutyramide (6e) [m.p. 115—116 °C (lit.,[10] m.p. 110—111 °C)]. Chromatography on neutral alumina and recrystallization from diethyl ether of the crude product (47%) gave colourless prisms of (11b), m.p. 147—150 °C; R_F 0.57; δ($CDCl_3$) 1.14, 1.43 (6 H, 2 s, 2 Me), 1.74 (3 H, unresolved m, =CMe), 4.67 (1 H, s, NH), 5.07, 5.28 (2 H, two unresolved m, $=CH_2$), 6.7—7.6 (9 H, m, Ph and C_6H_4) (Found: C, 66.8; H, 6.0; Cl, 10.2; N, 7.75. $C_{20}H_{21}ClN_2O_2$ requires C, 67.32; H, 5.93; Cl, 9.93; N, 7.8%). The slower moving fractions yielded a second solid product, N-[1-(p-*chlorophenylcarbamoyl*)-1-*methylethyl*]-*methacrylanilide* (10b) (17%) as colourless prisms [from ethanol–water (1 : 1)], m.p. 194—196 °C, R_F 0.48; δ($CDCl_3$) 1.5 (6 H, s, Me_2), 1.68 (3 H, m, =CMe), 4.95 (2 H, m, $=CH_2$), 7.2—7.6 (9 H, m, Ar), 7.85br (1 H, NH) (Found: C, 67.4; H, 5.9; Cl, 10.15; N, 7.65. $C_{20}H_{21}ClN_2O_2$ requires C, 67.32; H, 5.94; Cl, 9.93; N, 7.85%).

N-*Methyl*-p-*chloromethacrylanilide* (18a).—A sample of *p*-chloromethacrylanilide (8c) [11] (197 mg, 1 mmol) in THF (2 ml) was added with stirring during 2 h to a suspension of sodium hydride (96 mg, 2 mmol) in THF (3 ml). When the evolution of hydrogen ended, methyl iodide (142 mg, 1 mmol) in THF (3 ml) was added during 0.5 h. After additional stirring at 20 °C (2 h), the solution was centrifuged and concentrated to yield a chromatographically pure solid (80%), m.p. 60—61 °C; R_F 0.4; $\nu_{max.}$ ($CHCl_3$) 1 650 (CO) and 1 620 cm^{-1} (C=C); δ($CDCl_3$) 1.78 (3 H, s, =CMe), 3.44 (3 H, s, NMe), 4.96, 5.14 (2 H, unresolved m, $=CH_2$), 7.09, 7.35 (4 H, A_2B_2, C_6H_4) (Found: C, 62.85; H, 5.75; Cl, 16.75; N, 6.55. $C_{11}H_{12}ClNO$ requires C, 63.01; H, 5.77; Cl, 16.91; N, 6.68%).

N-*Benzyl*-p-*chloromethacrylanilide* (18b) (80%) was obtained in the same way as the above compound, using benzyl chloride, as colourless prisms (from aqueous ethanol); m.p. 79—80 °C, R_F 0.35; $\nu_{max.}$ ($CHCl_3$) 1 660 (CO) and 1 640 (C=C) cm^{-1}; δ($CDCl_3$) 1.8 (3 H, s, =CMe), 5.0 (2 H, s, CH_2Ph), 5.02, 5.04 (2 H, m, $=CH_2$), 6.9, 7.2 (4 H, A_2B_2, C_6H_4) (Found: C, 71.35; H, 5.8; Cl, 12.6; N, 4.75. $C_{17}H_{16}ClNO$ requires C, 71.45; H, 5.64; Cl, 12.4; N, 4.9%).

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