363. *Cytotoxic Compounds. Part IV.*[1] *Substituted Benzyl Halides.*

By R. Grice and L. N. Owen.

Syntheses of some acetoxy-, methylthio-, and acetamido-benzyl chlorides and bromides, and of 4-formylbenzyl chloride and its dimethyl acetal, are described. The rates of reaction of a number of substituted benzyl chlorides with 2-mercaptoethanol have been determined.

Previous papers in this series [1-3] have been concerned with compounds of the " nitrogen mustard " type. Other alkylating agents also show cytotoxic properties,[4] but apart from a brief reference [5] to some bishalogenoacetylbenzenes no attention appears to have been given to those which are commonly classified as lachrymators, including α-halogenocarbonyl compounds and benzyl halides. Lachrymators are known to attack enzyme systems which depend for their activity on the possession of thiol groups,[6] and one aim of the present work was to determine, for a range of substituted benzyl halides, whether any correlation exists between their toxicities *in vivo* * and their relative reactivities towards a thiol *in vitro*. Attention was directed particularly to the synthesis of halides carrying oxygen, sulphur, and nitrogen attached to the ring.

Although 2-, 3-, and 4-methoxybenzyl chloride are known, no free hydroxybenzyl chloride has been made and only the 2-acetoxy-derivative has been described. Early attempts by Gray [7] to convert saligenin into 2-hydroxybenzyl chloride by treatment of the diol with thionyl chloride in an excess of diethylaniline gave only tar, a result which is not surprising in view of the high reactivity to be expected of a chloromethylphenol. We find that even under milder conditions (reaction with thionyl chloride in chloroform or benzene containing a trace of pyridine) the product rapidly decomposes with evolution of hydrogen chloride. A similar result was obtained with 4-hydroxybenzyl alcohol.

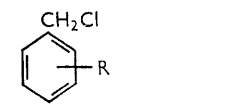
* The results of the biological tests, carried out by Professor J. F. Danielli, F.R.S., will be reported elsewhere.

[1] Part III, Creighton, Owen, and White, *J.*, 1961, 2375.
[2] Benn, Owen, and Creighton, *J.*, 1958, 2800.
[3] Benn, Creighton, Owen, and White, *J.*, 1961, 2365.
[4] Ross, " Biological Alkylating Agents," Butterworths Scientific Publns., London, 1962.
[5] Ross, *J.*, 1950, 752.
[6] Dixon, " Biochemical Society Symposia," Cambridge University Press, 1948, No. 2, p. 39; Bacq, *Experientia*, 1946, **2**, 1; Mackworth, *Biochem. J.*, 1948, **42**, 82.
[7] Gray, *J.*, 1925, **127**, 1155.

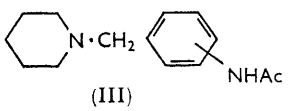
These observations are paralleled by the behaviour of simple phenols when subjected to chloromethylation.[8]

When the phenolic group is protected, formation of the halide can be effected without difficulty. Thus 2-,[9] 3-,[10] and 4-methoxybenzyl chloride [11] have been obtained from the methoxy-alcohols, and 2-acetoxybenzyl chloride [7] from saligenin monoacetate.* We have now prepared 3- and 4-acetoxybenzyl chloride from 3- and 4-acetoxybenzyl alcohol, these monoacetates being conveniently obtained by reaction of the diol, in aqueous solution containing one mol. of potassium hydroxide, with one mol. of acetic anhydride. 2-Acetoxybenzyl bromide was made by selective replacement, with hydrogen bromide in acetic acid, of the primary acetoxy-group in saligenin diacetate. With the 3-acetoxy-compound this procedure gave only a poor yield, and it failed completely with 4-acetoxybenzyl acetate. 4-Acetoxybenzyl bromide was therefore synthesised by treatment of 4-acetoxybenzyl alcohol with thionyl bromide; this was the only crystalline acetoxybenzyl halide obtained, but, like the liquid analogues, it decomposed on storage with evolution of hydrogen halide.

Thio-compounds corresponding to the oxygenated benzyl alcohols and halides are almost unknown. Only one (methylthio)benzyl alcohol (the 4-compound) and the corresponding chloride (I) have previously been synthesised,[13] whilst there is no record of any mercaptobenzyl alcohol. 3-(Methylthio)benzoic acid was prepared from benzoic acid by chlorosulphonation, reduction, and methylation,[14] and also from *m*-aminobenzoic acid by diazotisation, formation of the xanthate, conversion into thiol, and methylation. A better yield was obtained by the latter process, which was therefore used to prepare *p*-(methylthio)benzoic acid from *p*-aminobenzoic acid. *o*-(Methylthio)benzoic acid is readily available by methylation of commercial " thiosalicyclic acid," and the three methylthio-acids were then esterified and reduced with lithium aluminium hydride to give the three (methylthio)benzyl alcohols. With thionyl chloride in benzene, each of the alcohols was converted into the corresponding methylthiobenzyl chloride, whilst treatment of the alcohols with hydrogen bromide in benzene gave the three corresponding bromides.



(I: R = 4-SMe)
(II: R = NHAc)
(IV: R = 4-CHO)
[VI: R = 4-CH(OMe)$_2$]



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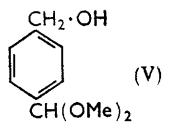

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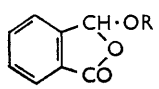
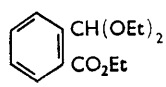


(VII: R = Me)
(IX: R = Et)



(VIII)

The three mercaptobenzyl alcohols were synthesised by reduction of methyl *o*-, *m*-, and *p*-mercaptobenzoate with lithium aluminium hydride, but reaction of each alcohol with thionyl chloride gave only resinous products; it therefore appears that the free mercaptobenzyl chlorides are as inaccessible as their phenolic analogues. 3-Mercaptobenzyl alcohol was also obtained by esterification, followed by reduction with lithium

* It is claimed by Hart and Hirschfelder [12] that this monoacetate can be prepared from monopotassium saligenate either by treatment with one mol. of acetic anhydride in ether or by reaction with an excess of boiling acetic anhydride. The analysis (acetyl value) reported by these authors presumably refers to the product obtained by the former method, since in our hands the latter procedure gave, as would be expected, the diacetate.

[8] Fuson and McKeever, *Organic Reactions*, 1942, **1**, 63.
[9] Cragoe and Pietruszkiewicz, *J. Org. Chem.*, 1957, **22**, 1338.
[10] Tsukamoto, Yoshimura, and Toki, *Pharm. Bull.* (*Japan*), 1955, **3**, 239.
[11] Shriner and Hull, *J. Org. Chem.*, 1945, **10**, 228.
[12] Hart and Hirschfelder, *J. Amer. Chem. Soc.*, 1921, **43**, 1688.
[13] Goldberg and Jampolsky, U.S.P. 2,624,738/1953.
[14] Smiles and Stewart, *J.*, 1921, **119**, 1792.

aluminium hydride, of di-(*m*-carboxyphenyl) disulphide, a procedure which avoids the separate reduction of the disulphide which is necessary when it is used as the source of methyl *m*-mercaptobenzoate. In the *p*-series, the intermediate mercapto-acid was synthesised from *p*-aminobenzoic acid by the same route as for *p*-(methylthio)benzoic acid, but without the methylation stage.

It is improbable that a free aminobenzyl halide would be sufficiently stable to be isolated, although both 2-aminobenzyl chloride and the bromide have been prepared in the form of the hydrochloride and hydrobromide, respectively.[15] Kühn [16] obtained all three *N*-acetamidobenzyl chlorides (II), in unspecified yields, by treatment of the three *N*-(*N'*-acetamidobenzyl)piperidines (III) with carbonyl chloride, but more direct methods of synthesis have now been investigated, based on the aminobenzyl alcohols. These were prepared quantitatively by hydrogenation of the nitrobenzyl alcohols over Adams catalyst at atmospheric pressure; the polymer which Phillips and Maggiolo [17] obtained on hydrogenation of the *p*-compound was not encountered. Selective *N*-acetylation furnished the three *N*-acetamidobenzyl alcohols, which on treatment with thionyl chloride gave the three *N*-acetamidobenzyl chlorides, though in poor yield. 3-*N*-Acetamidobenzyl bromide, and the 4-isomer, were obtained by reaction of the corresponding alcohol with thionyl bromide, the yields being better than for the chlorides; the 2-isomer could not be obtained pure.

The formyl group is a substituent of particular interest in that its electron-attracting properties can be easily masked by conversion into an acetal, and a comparison of these two types chemically and biologically might provide information on the possible reconversion of acetal into aldehyde *in vivo*. 4-Formylbenzyl chloride (IV) had been synthesised earlier [18] by reduction of 4-cyanobenzyl chloride, but an alternative route was used in the present work. *p*-Methoxycarbonylbenzaldehyde dimethyl acetal,[19, 20] prepared from methyl *p*-aminobenzoate, was reduced by lithium aluminium hydride to give an almost quantitative yield of 4-formylbenzyl alcohol dimethyl acetal (V). When this was treated with hydrogen chloride in ether, followed by thionyl chloride, it gave 4-formylbenzyl chloride, from which the dimethyl acetal (VI) was obtained by treatment with methyl orthoformate. Attempts to convert the alcohol (V) directly into the chloride (VI) were unsuccessful, the acetal group being attacked during the reaction with thionyl chloride.

Meyer [21] claimed to have obtained methyl *o*-formylbenzoate by heating phthalaldehydic acid with methanol and sulphuric acid. This was later disputed,[22,23] and we find that reaction of the acid with methanolic hydrogen chloride leads only to the pseudo-ester (VII). In the hope of avoiding this lactonisation an attempt was made to prepare the ester-acetal (VIII) directly by reaction of the aldehydo-acid with ethyl orthoformate, but again only a pseudo-ester (IX) was obtained.

The reactivities of substituted benzyl halides towards a variety of reagents have been extensively studied, and it has been shown that the mechanism, according to the conditions used, may be of the S_N1 or the S_N2 type, or a combination of the two.[24–26]

[15] Gabriel and Posner, *Ber.*, 1894, **27**, 3509.
[16] Kühn, *Ber.*, 1900, **33**, 2900.
[17] Phillips and Maggiolo, *J. Org. Chem.*, 1950, **15**, 659.
[18] Baker, Brieux, and Saunders, *J.*, 1956, 404.
[19] Slotta and Kethur, *Ber.*, 1938, **71**, 335.
[20] Wegscheider and Suida, *Monatsh.*, 1912, **33**, 999.
[21] Meyer, *Monatsh.*, 1904, **25**, 496.
[22] Gabriel, *Ber.*, 1916, **49**, 1608.
[23] Auwers and Heinze, *Ber.*, 1919, **52**, 584.
[24] Swain and Langsdorf, *J. Amer. Chem. Soc.*, 1951, **73**, 2813; Ingold, "Structure and Mechanism in Organic Chemistry," Bell and Sons, London, 1953, pp. 325 *et seq.*; Streitwieser, *Chem. Rev.*, 1956, **56**, 571.
[25] Hine, "Physical Organic Chemistry," McGraw-Hill, New York, 1st edn., 1956, p. 153.
[26] Kohnstam, Queen, and Ribar, *Chem. and Ind.*, 1962, 1287.

Comparatively little attention has been given to reactions involving thiol groups, but second-order kinetics have been observed with thiourea,[27] sodium thiosulphate,[28,29] and substituted thiophenols,[30] as would be expected for such powerful nucleophiles. In the present work, rate measurements were carried out on a selection of the chlorides with 2-mercaptoethanol in aqueous dioxan at 30°. Since the nucleophilic strength of a thiol depends on the degree of ionisation, control of the latter is essential. The simple way to achieve this, by ensuring that ionisation is complete, is to add one equivalent of sodium hydroxide, but the rates of reaction were then inconveniently high. Satisfactory results were obtained however, by the use of an excess of sodium carbonate as buffer; the thiol was then only partly ionised, and these conditions also had the advantage of providing a closer approach to a physiological pH. The second-order rate constants so obtained are given in the Table, and it is clear that substitution, even by groups of widely different electronic character, has only a relatively small effect. This is in accord with the usual behaviour of substituted benzyl halides towards other good nucleophiles. The greater reactivity of 4-, compared with 2- and 3-substituted compounds, shown in both the methoxy- and the methylthio-series, is also characteristic; earlier investigations involving attack by anions under S_N2 conditions have shown that 4-substitution invariably increases the reactivity, irrespective of the nature of the substituent.[25,29,30]

Reaction of $R{\cdot}C_6H_4{\cdot}CH_2Cl$ with 2-mercaptoethanol.
(k in l. mole^{-1} min.$^{-1}$.)

R	H	3-OAc	3-NHAc	4-NO_2	4-$CH(OMe)_2$	4-CHO
k	0·044	0·075	0·092	0·082	0·070	0·149
R	2-OMe	3-OMe	4-OMe	2-SMe	3-SMe	4-SMe
k	0·034	0·028	0·159	0·050	0·041	0·188

Experimental

2-Methoxybenzyl Alcohol.—*o*-Methoxybenzaldehyde (30 g.) in dry ether (200 c.c.) was slowly added (2 hr.) to a stirred suspension of lithium aluminium hydride (8·5 g.) in dry ether (200 c.c.). The mixture was then boiled under reflux for 6 hr. and worked up to give 2-methoxybenzyl alcohol (26 g., 85%), b. p. 80—82°/10^{-2} mm., n_D^{21} 1·5470 (cf. Tadros *et al.*[31]).

3-Methoxybenzyl Alcohol.—Prepared similarly (yield 90%), this had b. p. 86—87°/10^{-3} mm., n_D^{25} 1·5418.

Methoxybenzyl Chlorides.—A solution of 2-methoxybenzyl alcohol (10 g.), thionyl chloride (15 g.), and pyridine (0·2 g.) in dry benzene (80 c.c.) was boiled under reflux for 2 hr., then concentrated, and diluted with ether. The solution was washed with water, dried, and distilled to give 2-methoxybenzyl chloride (7·5 g.), b. p. 52—54°/10^{-1} mm., n_D^{22} 1·5478 (lit.,[9] b. p. 110—114°/14 mm.).

3-Methoxybenzyl chloride, b. p. 58°/10^{-1} mm., n_D^{21} 1·5445 (lit.,[10] b. p. 92·5—95°/5 mm.), and 4-methoxybenzyl chloride, b. p. 59—60°/10^{-2} mm., n_D^{19} 1·5492 (lit.,[11] b. p. 101—103°/8—10 mm.), were obtained similarly (yields, 66—68%).

Reaction of Potassium Saligenate with Acetic Anhydride.—Addition of 3·5N-ethanolic potassium hydroxide (50 c.c.) to saligenin (20 g.) in acetone (300 c.c.) precipitated the potassium salt,[12] which was dried *in vacuo* (yield, 25 g.) and boiled with acetic anhydride (50 c.c.) for 30 min. The excess of anhydride was removed under reduced pressure and ether was added to precipitate potassium acetate. Evaporation and distillation of the filtered solution then gave saligenin diacetate (15·8 g.), b. p. 104°/10^{-3} mm., n_D^{22} 1·4955, $\nu_{max.}$ (liquid film) 1770 and 1745 cm.$^{-1}$ (diacetate) (Found: Ac, 42·0. Calc. for $C_{11}H_{12}O_4$: Ac, 41·3%).

3-Acetoxybenzyl Chloride.—Acetic anhydride (7 g.) was slowly added (10 min.) to a cooled and stirred solution of 3-hydroxybenzyl alcohol (8·4 g.) in 5·45N-potassium hydroxide (11 c.c.). The mixture was extracted with ether (2 × 10 c.c.), and the extracts were washed with aqueous

[27] Pearson, Langer, Williams, and McGuire, *J. Amer. Chem. Soc.*, 1952, **74**, 5130.
[28] Slaytor and Twiss, *J.*, 1909, **95**, 93.
[29] Fuchs, *J. Amer. Chem. Soc.*, 1957, **79**, 6531; Fuchs and Nisbet, *ibid.*, 1959, **81**, 2371; Fuchs and Carlton, *J. Org. Chem.*, 1962, **27**, 1520.
[30] Hudson and Klopman, *J.*, 1962, 1062.
[31] Tadros, Ekladius, and Sakla, *J.*, 1954, 2351.

sodium hydrogen carbonate, then dried, and distilled to give crude 3-acetoxybenzyl alcohol (7·0 g.), b. p. 95—99°/10^{-3} mm., n_D^{19} 1·5240, characterised as the *α-naphthylurethane*, needles (from methanol), m. p. 102—103° (Found: C, 71·8; H, 5·3. $C_{20}H_{17}NO_4$ requires C, 71·6; H, 5·1%).

Thionyl chloride (4 g.) in benzene (8 c.c.) was added (5 min.) to a stirred solution of the above monoacetate (3·5 g.) in benzene (8 c.c.) containing a drop of pyridine. After 2 hr., the solution was concentrated under reduced pressure, and the residual oil was dissolved in ether, washed with water, dried, and distilled to give 3-*acetoxybenzyl chloride* (2·7 g.), b. p. 95—98°/10^{-3} mm., n_D^{21} 1·5272 (Found: C, 58·4; H, 5·0. $C_9H_9ClO_2$ requires C, 58·5; H, 4·9%). The S-*alkylthiouronium picrate* crystallised from methanol as yellow rhombs, m. p. 184—187° (decomp.) (Found: C, 42·7; H, 3·8; N, 15·1. $C_{16}H_{15}N_5O_9S$ requires C, 42·4; H, 3·3; N, 15·45%).

4-*Acetoxybenzyl Chloride*.—Reaction of 4-hydroxybenzyl alcohol with acetic anhydride and aqueous potassium hydroxide, as described above for the 3-isomer, gave 4-*acetoxybenzyl alcohol* (29%), b. p. 110°/10^{-3} mm., n_D^{21} 1·5289 (Found: C, 65·2; H, 5·9. $C_9H_{10}O_3$ requires C, 65·05; H, 6·02%). The *α-naphthylurethane*, needles from benzene, had m. p. 134° (Found: C, 71·2; H, 5·2. $C_{20}H_{17}NO_4$ requires C, 71·6; H, 5·1%).

This monoacetate (4·2 g.), treated as above with thionyl chloride (5 g.) in benzene, except that the mixture was boiled under reflux for 1 hr., gave 4-*acetoxybenzyl chloride* (3·5 g.), b. p. 82°/10^{-2} mm., n_D^{21} 1·5315 (Found: Cl, 19·2. $C_9H_9ClO_2$ requires Cl, 19·2%). The S-*alkylthiouronium picrate* formed yellow plates (from ethanol), m. p. 194—195° (Found: C, 42·45; H, 3·2. $C_{16}H_{15}N_5O_9S$ requires C, 42·4; H, 3·3%).

2-*Acetoxybenzyl Bromide*.—A solution of saligenin diacetate (4·0 g.) in a mixture of acetic anhydride (4·0 g.) and 50% hydrogen bromide in acetic acid (20 g.) was kept for 4 days at 0° and then distilled to give 2-*acetoxybenzyl bromide* (3·2 g.), b. p. 94°/10^{-4} mm., n_D^{19} 1·5519 (Found: C, 47·4; H, 4·4. $C_9H_9BrO_2$ requires C, 47·2; H, 4·0%). The S-*alkylthiouronium picrate*, yellow needles from ethanol, had m. p. 172—174° (Found: C, 42·4; H, 3·2; N, 15·0. $C_{16}H_{15}N_5O_9S$ requires C, 42·4; H, 3·3; N, 15·45%).

3-*Acetoxybenzyl Bromide*.—*m*-Acetoxybenzyl acetate (4·0 g.), treated in the same way, gave an oil which on distillation left a polymeric residue and gave only a small amount of 3-*acetoxybenzyl bromide*, b. p. 90—93°/10^{-3} mm., n_D^{22} 1·5538 (Found: C, 46·65; H, 4·4%). This gave the same *S*-alkylthiouronium picrate, m. p. 185—188°, as obtained from the corresponding chloride (see above).

4-*Acetoxybenzyl Bromide*.—4-Acetoxybenzyl alcohol (2 g.) in benzene (2 c.c.) was added to thionyl bromide (4 g.) in benzene (7 c.c.) containing a drop of pyridine. The mixture was boiled under reflux for 3 hr. and worked up to give a brown solid, which on recrystallisation from light petroleum (b. p. 60—80°) gave white prisms of 4-*acetoxybenzyl bromide* (1 g.), m. p. 54—55° (Found: C, 46·8; H, 4·3%). The *S*-alkylthiouronium picrate derived from it had m p. 194°, and was identical with that obtained from the chloride (see above).

2-*Methylthiobenzyl Alcohol*.—Methyl *o*-(methylthio)benzoate [32] in ether (250 c.c.) was slowly added to a suspension of lithium aluminium hydride (4 g.) in ether (200 c.c.). The mixture was boiled under reflux for 6 hr., and worked up to give 2-(*methylthio*)*benzyl alcohol* (6·4 g.), b. p. 88°/10^{-3} mm., n_D^{20} 1·6060 (Found: C, 62·0; H, 6·4. $C_8H_{10}OS$ requires C, 62·3; H, 6·5%).

2-*Methylthiobenzyl Chloride*.—The preceding alcohol (1 g.), with thionyl chloride (1·4 g.) in benzene (7 c.c.) and pyridine (0·1 c.c.), heated under reflux for 1 hr., gave 2-*methylthiobenzyl chloride* (0·8 g.), b. p. 75—76°/10^{-2} mm., n_D^{21} 1·6045 (Found: C, 55·3; H, 5·5. C_8H_9ClS requires C, 55·6; H, 5·25%).

2-*Methylthiobenzyl Bromide*.—Dry hydrogen bromide was passed through a solution of 2-(methylthio)benzyl alcohol (2·6 g.) in benzene (10 c.c.) for 1 hr. at 0°. Two layers were formed; the lower (aqueous) was discarded, and the upper portion was dried and distilled to give 2-*methylthiobenzyl bromide* (2·0 g.), b. p. 89°/10^{-3} mm., n_D^{20} 1·6350, which crystallised. From light petroleum (b. p. 30—40°) it formed needles, m. p. 43—44° (Found: C, 44·4; H, 4·2. C_8H_9BrS requires C, 44·25; H, 4·2%).

Methyl m-(*Methylthio*)*benzoate*.—*m*-Aminobenzoic acid (48 g.), suspended in 2N-hydrochloric acid (360 c.c.), was diazotised at 0° by addition of sodium nitrite (25 g.) in water (100 c.c.).

[32] Friedlander, *Annalen*, 1907, **351**, 390.

A solution of potassium ethyl xanthate (60 g.) in water (200 c.c.) was then added, and next day the precipitate was collected, washed with water, and dried (yield, 59 g.). This xanthate (33 g.) was heated with a solution of potassium hydroxide (35 g.) in water (250 c.c.) for 1 hr. on a steam-bath, then the solution was cooled, treated with methyl sulphate (20 g.), and shaken for 3 hr.; acidification then gave *m*-(methylthio)benzoic acid (12 g.), m. p. 128°. Esterification with boiling methanol, saturated with hydrogen chloride, gave the methyl ester, b. p. 83°/10^{-3} mm., n_D^{20} 1·5767 (lit.,[33] b. p. 132°/4 mm.).

3-(*Methylthio*)*benzyl Alcohol*.—Reduction of the preceding ester (10·6 g.) with lithium aluminium hydride (2·6 g.) in boiling ether gave the *alcohol* (7·0 g.), b. p. 98°/10^{-4} mm., n_D^{24} 1·5987 (Found: C, 62·3; H, 6·6%).

3-*Methylthiobenzyl Chloride*.—Prepared from the alcohol (4·6 g.) and thionyl chloride (5 g.), as described for the *o*-isomer, the *chloride* (4·9 g.) had b. p. 78°/10^{-3} mm., n_D^{24} 1·5987 (Found: C, 55·6; H, 5·2%).

3-*Methylthiobenzyl Bromide*.—Reaction of dry hydrogen bromide with the alcohol (3·8 g.) (see the 2-isomer, above) gave the *bromide* (2·9 g.), b. p. 89°/10^{-4} mm., n_D^{20} 1·6298 (Found: C, 44·2; H, 4·0%).

Methyl p-(*Methylthio*)*benzoate*.—As described for the *m*-compound, *p*-aminobenzoic acid (10 g.) was converted into the crude xanthate (16·5 g.). A portion of this (3·0 g.) treated with alkali and then with methyl sulphate gave *p*-(methylthio)benzoic acid (1·5 g.), m. p. 187—190°, from which the methyl ester (1·5 g.), m. p. 78—80°, was obtained (lit.,[34] m. p. 82°).

4-(*Methylthio*)*benzyl Alcohol*.—Reduction of the above ester (8·2 g.) with lithium aluminium hydride (4·5 g.) in boiling ether gave the alcohol (4·1 g.), b. p. 100°/10^{-3} mm., m. p. 37—39° (lit.,[13] b. p. 108—109°/0·4 mm., m. p. 41—42°).

4-(*Methylthio*)*benzyl Chloride*.—The alcohol (5 g.) on treatment with thionyl chloride (10 g.) as for the 2-compound gave the chloride (4·1 g.), b. p. 77—78°/10^{-2} mm., n_D^{19} 1·6075 (lit.,[13] b. p. 83°/0·3 mm., n_D^{27} 1·6034).

4-(*Methylthio*)*benzyl Bromide*.—By the method used for the 2-compound, the alcohol (2·6 g.) with hydrogen bromide gave the *bromide* (2·2 g.), which crystallised from light petroleum (b. p. 60—80°) in plates, m. p. 44° (Found: C, 44·3; H, 4·2%).

Di-(m-*methoxycarbonylphenyl*) *Disulphide*.—Di-(*m*-carboxyphenyl) disulphide [14] (4 g.) in methanol (70 c.c.), saturated with hydrogen chloride, was boiled for 12 hr. and gave the *dimethyl ester* (2·5 g.), b. p. 185—190°/10^{-3} mm., m. p. 45—47° (plates from aqueous methanol) (Found: C, 57·6; H, 4·5. $C_{16}H_{14}O_4S_2$ requires C, 57·5; H, 4·2%).

Methyl p-*Mercaptobenzoate*.—The xanthate from *p*-aminobenzoic acid (10 g.) was boiled under reflux with potassium hydroxide (13 g.) in ethanol for 1 hr.; after dilution with water (150 c.c.) the solution was heated on the steam-bath for a further hour and then concentrated under reduced pressure to remove ethanol. Acidification of the cooled solution in the presence of zinc dust (5 g.) gave *p*-mercaptobenzoic acid (5·2 g.), m. p. 220° (decomp.). Esterification with methanolic hydrogen chloride gave the methyl ester (5·6 g.), m. p. 49—50° (lit.,[35] m. p. 50°). On oxidation with aqueous iodine it gave *di*-(p-*methoxycarbonylphenyl*) *disulphide*, m. p. 127—128° (from methanol) (Found: C, 57·4; H, 4·3. $C_{16}H_{14}O_4S_2$ requires C, 57·5; H, 4·2%).

2-*Mercaptobenzyl Alcohol*.—Reduction of methyl *o*-mercaptobenzoate [35] (18·3 g.) with lithium aluminium hydride (6·8 g.) in ether (200 c.c.) gave the *alcohol* (13·6 g.), b. p. 85°/10^{-3} mm., m. p. 30—31°, n_D^{22} 1·6080 (Found: C, 59·8; H, 5·9. C_7H_8OS requires C, 60·0; H, 5·75%). Oxidation with aqueous iodine gave the disulphide, m. p. 141—142° (lit.,[36] 141—142°).

3-*Mercaptobenzyl Alcohol*.—(i) Reduction of methyl *m*-mercaptobenzoate (6·5 g.) similarly gave the *alcohol* (2·4 g.), b. p. 88°/10^{-4} mm., n_D^{22} 1·6044 (Found: C, 59·5; H, 5·6%).

(ii) Reduction of di-(*m*-methoxycarbonylphenyl) disulphide (11 g.) with lithium aluminium hydride (6 g.) in ether (200 c.c.) gave the same alcohol (3·8 g.), b. p. 92°/10^{-3} mm. (Found: thiol-S, 22·3. C_7H_8OS requires S, 22·9%). Oxidation with aqueous iodine gave *di*-(m-*hydroxymethylphenyl*) *disulphide*, prisms [from ether–light petroleum (b. p. 40—60°)] (Found: C, 60·5; H, 5·4. $C_{14}H_{14}O_2S_2$ requires C, 60·4; H, 5·1%).

4-*Mercaptobenzyl Alcohol*.—Methyl *p*-mercaptobenzoate [35] (7 g.) on similar reduction gave the *alcohol* (2·8 g.), which crystallised from carbon tetrachloride–light petroleum (b. p. 60—80°)

[33] Brand, Gabel, and Rosenkranz, *Ber.*, 1937, **70**, 296.
[34] Brand and Stallmann, *J. prakt. Chem.*, 1924, **107**, 358.
[35] Schwarzenbach and Rudin, *Helv. Chim. Acta*, 1939, **22**, 360.
[36] Reissert and Cramer, *Ber.*, 1928, **61**, 2555.

in plates, m. p. 52—54° (Found: C, 60·2; H, 6·0. C_7H_8OS requires C, 60·0; H, 5·75%). Oxidation with aqueous iodine gave *di-(p-hydroxymethylphenyl) disulphide*, needles (from aqueous acetone), m. p. 130—132° (Found: C, 60·1; H, 5·2. $C_{14}H_{14}O_2S_2$ requires C, 60·4; H, 5·1%).

Aminobenzyl Alcohols.—2-Nitrobenzyl alcohol (20 g.), ethanol (100 c.c.), and Adams platinum catalyst (0·2 g.) were shaken in hydrogen at atmospheric pressure. The calculated uptake was reached in about 3 hr., and absorption of gas then ceased. Evaporation of the filtered solution gave 2-aminobenzyl alcohol (16 g.), m. p. 83—84°. The 3- (m. p. 89—91°) and the 4-amino-compound (m. p. 58—61°) were similarly obtained.

N-*Acetamidobenzyl Alcohols.*—Acetic anhydride (5 g.) was added to a stirred suspension of the amino-alcohol (5 g.) in ethyl acetate (25 c.c.). Heat was evolved and the mixture became homogeneous. After 30 min. it was cooled to 0°, whereupon the acetyl derivative crystallised from the solution. 2-*N*-Acetamidobenzyl alcohol (5·2 g.) had m. p. 116° (lit.,[37] m. p. 114°); the 3-compound (6·6 g.), m. p. 106—108° (lit.,[38] m. p. 106—107°); and 4-N-*acetamidobenzyl alcohol* (5·0 g.), m. p. 120—121° (prisms from nitromethane) (Found: C, 65·3; H, 6·8. $C_9H_{11}NO_2$ requires C, 65·35; H, 6·7%).

N-*Acetamidobenzyl Chlorides.*—Thionyl chloride (1·6 g.) in benzene (5 c.c.) was slowly added (15 min.) to a stirred suspension of the *N*-acetamido-alcohol (2·0 g.) in benzene (10 c.c.). The mixture was heated at 80—90° for 3 hr. (but for only 10 min. with the 4-compound, which then began to decompose), and then concentrated to an oily solid. This was triturated with benzene and recrystallised from benzene–light petroleum (b. p. 60—80°). 2-*N*-Acetamidobenzyl chloride (0·3 g.) had m. p. 116—119° (lit.,[16] m. p. 114°); the 3-compound (0·5 g.), m. p. 86—88° (lit.,[16] m. p. 89°); and the 4-compound (0·5 g.), m. p. 151—154° (lit.,[16] m. p. 155°).

3-N-*Acetamidobenzyl Bromide.*—Thionyl bromide (4 g.) in benzene (10 c.c.) was added to 3-*N*-acetamidobenzyl alcohol (1·1 g.) in benzene (50 c.c.). The mixture was stirred and heated at 90° for 2 hr., with formation of an oily layer; when cooled, the latter solidified and was the *bromide* (1·1 g.), which after being triturated with ethyl acetate and dried had m. p. 119—120° (Found: C, 47·4; H, 4·5. $C_9H_{10}BrNO$ requires C, 47·4; H, 4·4%). Attempts to recrystallise it led to decomposition.

4-N-*Acetamidobenzyl Bromide.*—In a similar way the 4-acetamido-alcohol (1·0 g.) gave the *bromide* (0·8 g.) which on recrystallisation from ethyl acetate formed plates, m. p. 162° (Found: C, 47·8; H, 4·3%).

p-*Methoxycarbonylbenzaldehyde Dimethyl Acetal.*—*p*-Methoxycarbonylbenzaldehyde [19] (9·6 g.), methyl orthoformate (10 g.), ammonium chloride (0·1 g.), and dry methanol (60 c.c.) were boiled under reflux for 1 hr. Removal of solvent and distillation of the residue gave the dimethyl acetal (10·1 g.), b. p. 90°/10^{-2} mm., m. p. 32—33°, $\nu_{max.}$ (in CCl_4) 2933, 2825 (acetal), and 1724 cm.$^{-1}$ (ester) (lit.,[20] m. p. 30°).

4-*Formylbenzyl Alcohol Dimethyl Acetal.*—The preceding ester (10·1 g.) was reduced with lithium aluminium hydride (4 g.) in ether (100 c.c.) to give the corresponding *alcohol* (8·6 g.), prisms [from carbon tetrachloride–light petroleum (b. p. 60—80°)], m. p. 42—43° (Found: C, 65·8; H, 7·7. $C_{10}H_{14}O_3$ requires C, 65·9; H, 7·7%).

4-*Formylbenzyl Chloride.*—A solution of the preceding alcohol (5·2 g.) in ether (30 c.c.) was saturated with hydrogen chloride, set aside for 12 hr., and evaporated to an oil, which was dissolved in benzene (30 c.c.) and treated with thionyl chloride (8 g.). After 2 hr., the solution was evaporated and the residue distilled; the main fraction (2·2 g.), b. p. 100°/0·1 mm., solidified. Recrystallisation from light petroleum (b. p. 60—80°) gave needles, m. p. 74°, $\nu_{max.}$ (in CCl_4) 1704 cm.$^{-1}$ (CHO) (Found: C, 62·2; H, 4·6. Calc. for C_8H_7ClO: C, 62·15; H, 4·6%) (lit.,[18] m. p. 74°).

4-*Formylbenzyl Chloride Dimethyl Acetal.*—The chloride (1 g.), methyl orthoformate (0·8 g.), dry methanol (12 c.c.), and ammonium chloride (0·5 g.) were boiled under reflux for 1 hr. The solvent was removed under reduced pressure and the residue was diluted with ether and washed with water. Distillation of the dried ethereal solution then gave the *dimethyl acetal* (1·0 g.), b. p. 78—80°/10^{-4} mm., n_D^{21} 1·5189, $\nu_{max.}$ (liquid film) 2907 and 2801 cm.$^{-1}$ (acetal) (Found: C, 59·5; H, 6·5. $C_{10}H_{13}ClO_2$ requires C, 59·9; H, 6·5%).

Pseudo-esters from Phthalaldehydic Acid.—(i) A solution of the acid (4·0 g.) in methanol

[37] Soderbaum and Widman, *Ber.*, 1889, **22**, 1665.
[38] Lutter, *Ber.*, 1897, **30**, 1065.

(50 c.c.), saturated with hydrogen chloride, was boiled under reflux for 20 hr. Evaporation gave the pseudo-methyl ester (3·8 g.), m. p. 44°, $\nu_{max.}$ (in CCl_4) 1786 cm.$^{-1}$ (lactone) (Found: C, 65·9; H, 4·9. Calc. for $C_9H_8O_3$: C, 65·85; H, 4·9%) (lit.,[22] m. p. 44°).

(ii) The acid (3·0 g.), ethyl orthoformate (3·5 g.), dry ethanol (5 c.c.), and ammonium chloride (0·1 g.) were boiled under reflux for 15 min. Evaporation gave a solid which was extracted with ether. Removal of solvent from the washed extract gave the pseudo-ethyl ester (2·8 g.), m. p. 68° (Found: C, 67·6; H, 5·75. Calc. for $C_{10}H_{10}O_3$: C, 67·4; H, 5·7%) (lit.,[21, 39] m. p. 64°, 66°).

Kinetic Experiments.—These were carried out in a flask (fitted with a stirrer, thermometer, and nitrogen inlet) immersed in a thermostat-bath at 30°. Stirring, and a flow of nitrogen (previously saturated with aqueous dioxan of the same composition as used in the reactions), were maintained throughout each run. The flask initially contained 0·9M-sodium carbonate (60 c.c.) to which was added dioxan (100 c.c.), causing some of the carbonate to be thrown out as a fine suspension which persisted during the subsequent reaction; the aqueous dioxan thus remained saturated with sodium carbonate throughout. After 30 min., the internal temperature then being 29·8°, 2-mercaptoethanol (0·02 mole) was added and washed in with dioxan (total, 14 c.c.), followed 10 min. later by the benzyl halide (0·02 mole) and dioxan washings (26 c.c.). Portions (10 c.c.) were periodically withdrawn and run into 2N-hydrochloric acid (10 c.c.), and the free thiol content was determined by titration with iodine, with starch as indicator. A control experiment, identical except for the absence of benzyl halide, established that the thiol itself was stable under the reaction conditions, no significant diminution in the titration value being recorded during a time greater than the duration of any kinetic run. Based on the second-order equation $k = x/ta(a - x)$, plots of $x/(a - x)$ against t approximated to straight lines for about 70% of the total reaction. The rate constants recorded in the Table were calculated from the slopes of these lines.

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[39] Racine, *Annalen*, 1887, **239**, 83.