269. *The Chemotherapy of Amœbiasis. Some N-Substituted Dichloroacetamides.*

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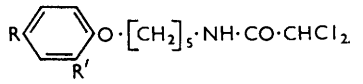
Some *N*-aryl-, *N*-alkyl-, and *N*-benzyl-dichloroacetamides have been prepared in the search for a new, non-toxic amœbicide. Certain *N*-(alkylsulphonylbenzyl)dichloroacetamides (*e.g.*, XVI; R = *p*-Me·SO_2) had marked activity *in vivo*. The effects of modifying the structures of these, and the synthesis of less active, analogues are described.

SEVERAL of the new compounds introduced recently for the treatment of amœbiasis contain the dichloroacetamide group. Activity against *Entamœba criceti* in hamsters was discovered [1] in 1954—1956 in a series of *N*-benzyldichloroacetamides, one of which, in particular, αα-dichloro-*N*-2,4-dichlorobenzyl-*N*-2-hydroxyethylacetamide (chlorbetamide), was useful in cases of chronic human intestinal amœbiasis.[2] αα-Dichloro-*p*-hydroxy-*N*-methylacetanilide (diloxanide), which first showed activity against *E. histolytica* in rats,[3] has found a similar clinical application.[4] In view of the low toxicity of this type of compound, we synthesised a variety of other dichloroacetamides in the hope of improving the activity. Meanwhile activity has been reported [5] also for the 4-*p*-nitrophenoxybenzyl analogue of chlorbetamide. Biological results for the compounds now described are to be reported elsewhere; compounds already covered by a patent [6] are mentioned here only in brief.

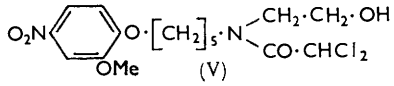
We first prepared some derivatives of phenoxyalkylamines. Dichloroacetylation

[1] Surrey and his co-workers, *J. Amer. Chem. Soc.*, 1954, **76**, 578, 2214; 1955, **77**, 3798, 5406; 1956, **78**, 2573, 3834.
[2] Loughlin and Mullin, *Antibiotics and Chemotherapy*, 1954, **4**, 570.
[3] Bristow, Oxley, Williams, and Woolfe, *Trans. Roy. Soc. Trop. Med. Hyg.*, 1956, **50**, 182.
[4] Woodruff, Bell, and Schofield, *Trans. Roy. Soc. Trop. Med. Hyg.*, 1956, **50**, 114.
[5] Logemann, Almirante, and De Carneri, *Il Farmaco*, 1958, **13**, 139.
[6] May & Baker, Ltd., B.P. 869,796.

of the nitro-compounds (I and II) was effected with chloral hydrate–sodium cyanide, a reagent first used in the chloramphenicol series.[7] A milder reagent, methyl dichloroacetate, was employed for the preferential dichloroacetylation of the aliphatic amino-group



(I : R = NO_2, R′ = H) (II : R = NO_2, R′ = OMe)
(III : R = NH_2, R′ = H) (IV : R = NH_2, R′ = OMe)



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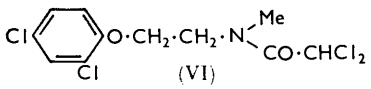
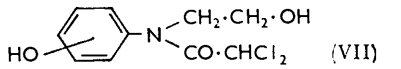


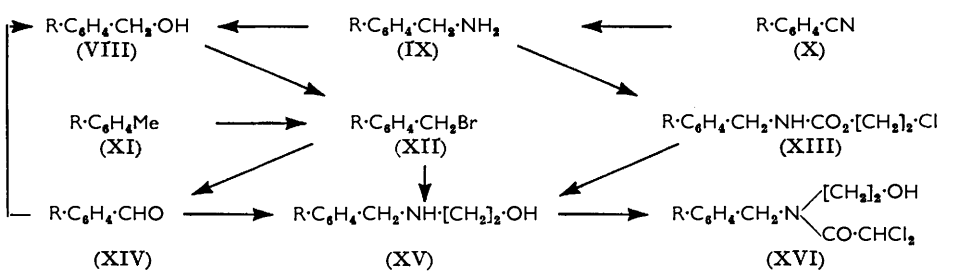
(VI)



(VII)

of 5-*p*-aminophenoxypentylamine and its 2-methoxy-analogue, to give the products (VI) and (VII), respectively. The pentylamine intermediate for the dichloroacetamide (V) was readily obtained by reaction of 5-(2-methoxy-4-nitrophenoxy)pentylamine with 2-chloroethyl chloroformate and alkaline hydrolysis of the resulting carbamate. This method, which involves an oxazolidone as intermediate, has been used for the synthesis of 2-arylaminoethanols [8] but apparently not previously in the aliphatic series. The 2,4-dichlorophenoxy-compound (VI) was prepared from *N*-methyl-2-(2,4-dichlorophenoxy)-ethylamine.

Moderate amœbicidal activity was found for some of these compounds and also in some of the type (VII), related to diloxanide and prepared conventionally, but much higher activity was shown by dichloroacetamides of the type (XVI). In particular, a *p*-methylsulphonyl substituent as R in (XVI) produced a compound greatly superior to chlorbetamide in its action *in vivo* against *E. histolytica*. These compounds were prepared by dichloroacetylation of the appropriate *N*-2-hydroxyethylbenzylamines (XV) by dichloroacetyl chloride or, better, methyl dichloroacetate. It has been suggested [1] that the reaction of the latter with this type of secondary amine under unusually mild conditions may be due to *O*-dichloroacetylation followed by *O*- ⟶ *N*-migration. A similar reaction has now been found to occur with ethyl cyanoacetate, to give α-cyano-*N*-2-hydroxyethyl--*N*-4-methylsulphonylbenzylacetamide.



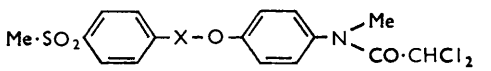
For the synthesis of *N*-2-hydroxyethyl-4-methylsulphonylbenzylamine (XV; R = *p*-Me·SO_2), *p*-methylsulphonylbenzonitrile (X; R = *p*-Me·SO_2), derived [9] from *p*-acetamidobenzenesulphonyl chloride, was catalytically reduced in the presence of ammonia, the benzylamine (IX; R = *p*-Me·SO_2) was treated with 2-chloroethyl chloroformate, and the carbamate (XIII) was hydrolysed in alkali as described above. However, formation of secondary amine as a by-product in the catalytic reduction could not be consistently

[7] Parke Davis & Co., B.P. 692,265.
[8] Adams and Segur, *J. Amer. Chem. Soc.*, 1923, **45**, 785.
[9] Fuller, Tonkins, and Walker, *J.*, 1945, 633.

suppressed in large-scale work, and a more direct route was established through 4-methylsulphonylbenzyl bromide (XII; R = *p*-Me·SO_2). Methyl *p*-tolyl sulphone, accessible from toluene-*p*-sulphonyl chloride,[10] when chlorinated at 125° under irradiation with ultraviolet light, gave an impure product with very low content of chlorine instead of the reported [11] 4-methylsulphonylbenzyl chloride; but bromination of the molten sulphone at 180° under ultraviolet irradiation gave the bromide (XII; R = *p*-Me·SO_2), m. p. 94—96° after recrystallisation, in a reproducible yield of about 63%. *N*-Bromosuccinimide, whose use for side-chain bromination in the presence of electronegative substituents has been reported,[12] gave a lower yield of the same product; 1,3-dibromo-5,5-dimethylhydantoin, earlier used for the bromination of benzoin compounds,[13] afforded a product which was difficult to purify. Ziegler and Connor [14] reported that methyl *p*-tolyl sulphone did not react with bromine under the milder conditions used earlier by themselves in the preparation of α-bromo-α-sulphonyl-amides, but that bromomethyl *p*-tolyl sulphone, m. p. 89—90°, was formed by the cold bromination of the bromomagnesium derivative of methyl *p*-tolyl sulphone. Although it was unlikely that our own product would be anything but a benzyl bromide, the proximity of melting points made confirmation essential. This was obtained by: (*a*) direct comparison with the compound prepared by Ziegler and Connor's method; (*b*) preparation of our bromide also from 4-methylsulphonylbenzyl alcohol (VIII; R = *p*-Me·SO_2), a new substance available both by reduction of the aldehyde (XIV; R = *p*-Me·SO_2) by the Meerwein–Ponndorf method and by treatment of 4-methylsulphonylbenzylamine with nitrous acid; and (*c*) conversion of our bromination product by the Sommelet reaction into *p*-methylsulphonylbenzaldehyde, identical with that derived from methyl *p*-tolyl sulphone by oxidation with chromium trioxide.[15]

4-Methylsulphonylbenzyl bromide condensed readily with ethanolamine, to give the required intermediate (XV; R = *p*-Me·SO_2) in 70% yield. *N*-2-Hydroxyethyl-2-methylsulphonylbenzylamine (XV; R = *o*-Me·SO_2) was similarly prepared from 2-methylsulphonylbenzyl bromide. For the *p*-ethylsulphonyl analogue (XV; R = *p*-Et·SO_2), however, a better method was catalytic hydrogenation of the Schiff base from *p*-ethylsulphonylbenzaldehyde and ethanolamine. The *N*-hydroxyethylbenzylamines (Table 1) were dichloroacetylated in the usual way (see Table 2).

The monochloroacetamide corresponding to the most active dichloroacetamide (XVI; R = *p*-Me·SO_2) had virtually no amœbicidal activity, but *O*-acylation of the latter did not greatly reduce activity. Derived ethers, also of biological interest, were obtained by using alkoxyalkylamines in the penultimate stage (see Table 3). Reaction of the *N*-2-hydroxyethyldichloroacetamide (XVI; R = *p*-Me·SO_2) with thionyl chloride afforded a 2-chloroethyl compound whose structure was confirmed by conversion with potassium acetate in acetic acid into the *O*-acetate of the dichloroacetamide (XVI; R = *p*-Me·SO_2). Two further compounds of amœbicidal interest (XVII) and (XVIII), which combine features of the active sulphones with the structure of diloxanide, were prepared by reaction of 4-methylsulphonylbenzyl bromide and *p*-methylsulphonylbenzoyl chloride, respectively, with diloxanide under standard conditions.



(XVII : −X− = −CH_2−)
(XVIII : −X− = −CO−)

The preparation of several other sulphones from *p*-methylsulphonylbenzaldehyde or 4-methylsulphonylbenzyl bromide is described in the Experimental section.

[10] Field and Clark, *Org. Synth.*, 1958, **38**, 62.
[11] Tanaka and Anmo, *J. Pharm. Soc. Japan*, 1957, **77**, 311.
[12] Buu-Hoï, *Annalen*, 1944, **556**, 1.
[13] Orazi and Meseri, *Anales Asoc. quím. argentina*, 1950, **38**, 307.
[14] Ziegler and Connor, *J. Amer. Chem. Soc.*, 1940, **62**, 2596.
[15] Momose, Japanese Pat. 3073/1951.

Experimental

Light petroleum refers to the fraction of b. p. 60—80° unless otherwise stated.

αα-*Dichloro*-N-(5-p-*nitrophenoxypentyl*)*acetamide* (I).—A solution of 5-*p*-nitrophenoxypentylamine [16] (67·5 g.) in dioxan (150 ml.) was stirred during addition of chloral hydrate (66 g.) followed by sodium cyanide (21 g.). When the exothermic reaction had subsided, the mixture was stirred on the steam-bath for a further 5 hr., kept at room temperature for 16 hr., and poured into water (1·5 l.). The precipitate was collected, ground with 2N-hydrochloric acid, collected, and washed with water. Recrystallisation from ethanol and then benzene afforded needles of the *acetamide* (35·8 g., 36%), m. p. 91—94° (Found: N, 8·55; Cl, 20·7. $C_{13}H_{16}Cl_2N_2O_4$ requires N, 8·4; Cl, 21·15%).

αα-*Dichloro*-N-5-(2-*methoxy*-4-*nitrophenoxy*)*pentylacetamide* (II), pale yellow needles, m. p. 94—98° (Found: N, 7·7; Cl, 18·8. $C_{14}H_{18}Cl_2N_2O_5$ requires N, 7·6; Cl, 19·4%), was obtained similarly.

5-p-*Aminophenoxypentylamine*.—This had been prepared previously [16] from the phthalimido-derivative. Reduced iron powder (182 g.) was added during 10 min. to a boiling solution of 5-*p*-nitrophenoxypentylamine (183 g.) in 50% aqueous acetic acid (2·5 l.). After a further 10 min., the mixture was cooled, filtered, treated with chloroform (1 l.), and stirred at 10° while 50% aqueous sodium hydroxide (1·4 l.) was slowly added. The emulsion was filtered through kieselguhr and the product isolated with chloroform as a red syrup which slowly crystallised. Extraction with boiling light petroleum (b. p. 80—100°) followed by recrystallisation from ethyl acetate gave pink prisms of the amine (36 g., 26%), m. p. 74—78° (Found: N, 14·0. Calc. for $C_{11}H_{18}N_2O$: N, 14·4%).

Similar reduction of 5-(2-methoxy-4-nitrophenoxy)pentylamine (3 g.) and addition of concentrated hydrochloric acid to the filtered reaction mixture gave 5-(4-*amino*-2-*methoxyphenoxy*)*pentylamine dihydrochloride* (2·1 g., 60%), m. p. 268° (decomp.) (Found: N, 9·5; Cl, 23·4. $C_{12}H_{20}N_2O_2$,2HCl requires N, 9·4; Cl, 23·9%).

αα-*Dichloro*-N-5-(4-*amino*-2-*methoxyphenoxy*)*pentylacetamide*.—A solution of the above diamine (22 g.) in methanol (110 ml.) was refluxed with methyl dichloroacetate (15 g.) for 15 min., and the cooled solution poured into water (1 l.). The oil solidified and was filtered off, dried, and recrystallised from benzene–light petroleum; the *dichloroacetamide* separated in needles (10 g. ,31%), m. p. 80—82° (Found: N, 8·4; Cl, 21·05. $C_{14}H_{20}Cl_2N_2O_3$ requires N, 8·4; Cl, 21·15%).

αα-Dichloro-*N*-5-*p*-aminophenoxypentylacetamide [16] was prepared similarly.

2-[5-(2-*Methoxy*-4-*nitrophenoxy*)*pentylamino*]*ethanol*.—A suspension of 5-(2-methoxy-4-nitrophenoxy)pentylamine (12·7 g.) in acetone (25 ml.) and 2N-sodium hydroxide (25 ml.) was stirred at 25° during dropwise addition of 2-chloroethyl chloroformate (7·2 g.). After a further 1·5 hr., the acetone was distilled off *in vacuo* and the oil isolated with chloroform and triturated with light petroleum, giving a yellow solid (17·8 g., 99%), m. p. 62°, which, on recrystallisation from the same solvent, gave 2-*chloroethyl* N-[5-(2-*methoxy*-4-*nitrophenoxy*)*pentyl*]*carbamate*, m. p. 70—71° (Found: N, 7·6; Cl, 9·7. $C_{15}H_{21}ClN_2O_6$ requires N, 7·7; Cl, 9·7%). A mixture of the carbamate (17·3 g.), aqueous sodium hydroxide (8·5 g. in 28 ml.), ethanol (50 ml.), and 2-ethoxyethanol (50 ml.) was refluxed for 1 hr., the filtered solution diluted with water, and the product collected and recrystallised from benzene–light petroleum, to give pale yellow 2-[5-(2-*methoxy*-4-*nitrophenoxy*)*pentylamino*]*ethanol* (8 g., 56%), m. p. 89—90° (Found: C, 56·3; H, 6·9; N, 9·3. $C_{14}H_{22}N_2O_5$ requires C, 56·4; H, 7·4; N, 9·4%).

αα-*Dichloro*-N-2-*hydroxyethyl*-N-[5-(2-*methoxy*-4-*nitrophenoxy*)*pentyl*]*acetamide* (V).—A mixture of the above-mentioned ethanol (42 g.) and methyl dichloroacetate (21 g.) was kept at 65—70° for 4 hr., cooled, and poured into water. The oily product solidified after 3 weeks and was recrystallised from aqueous methanol, giving the pure *dichloroacetamide* (30 g., 52%), m. p. 78—79° (Found: N, 6·5; Cl, 17·2. $C_{16}H_{22}Cl_2N_2O_6$ requires N, 6·8; Cl, 17·3%).

αα-*Dichloro*-N-2,4-*dichlorophenoxyethyl*-N-*methylacetamide* (VI).—A solution of *N*-methyl-2-(2,4-dichlorophenoxy)ethylamine [17] (11 g.) and triethylamine (5·2 g.) in chloroform (100 ml.) was stirred and cooled in ice during dropwise addition of dichloroacetyl chloride (7·4 g.) in chloroform (50 ml.). After a further 2 hr. at room temperature, water was added and the product isolated from the chloroform layer as an oil which crystallised from benzene–light

[16] Ashley, Collins, Davis, and Sirett, *J.*, 1959, 3880.
[17] Jones, Metcalfe, and Sexton, *Biochem. J.*, 1949, **45**, 143.

petroleum and then recrystallised from ethanol to give cream-coloured prisms of the *dichloroacetamide* (11·3 g., 69%), m. p. 110—111° (Found: N, 4·2; Cl, 42·3. $C_{11}H_{11}Cl_4NO_2$ requires N, 4·2; Cl, 42·8%).

αα-Dichloro-o-hydroxy-N-2-hydroxyethylacetanilide.— *o*-(2-Hydroxyethylamino)phenol sulphate (20·2 g.) was added to sodium acetate trihydrate (40 g.) and sodium pyrosulphite (1 g.) in water (120 ml.). Benzene (180 ml.) was added and the slurry stirred and cooled in ice during slow addition of dichloroacetyl chloride (15 g.) in benzene (50 ml.). After a further 5 hr. at room temperature, the solid was collected, washed with 2N-hydrochloric acid, and water, and recrystallised from benzene to give the *acetanilide* (11·1 g., 42%), m. p. 91—92° (rapid heating), 119—120° with softening at 92° (slow heating). When recrystallised from water, a sample had m. p. 119—120° with no previous softening. Both forms gave similar analytical results (Found: N, 5·3; Cl, 26·6. $C_{10}H_{11}Cl_2NO_3$ requires N, 5·3; Cl, 26·85%).

αα-Dichloro-p-hydroxy-N-2-hydroxyethylacetanilide, similarly prepared from *p*-(2-hydroxyethylamino)phenol,[18] separated from acetone in prisms, m. p. 136—137° (Found: N, 5·2; Cl, 27·0. $C_{10}H_{11}Cl_2NO_3$ requires N, 5·3; Cl, 26·85%).

N-p-*Hydroxyphenyl-N-methylmethanesulphonamide.*—This *amide* was prepared similarly from *p*-methylaminophenol and methanesulphonyl chloride; it formed colourless needles, m. p. 130—131°, from water (Found: N, 7·1; S, 15·75. $C_8H_{11}NO_3S$ requires N, 7·0; S, 15·9%).

p-*Methylsulphonylbenzonitrile.*—This intermediate is described by Sikdar and Basu [19] and by Fuller, Tonkins, and Walker; [9] the following improved procedure reduces the liberation of cyanide fumes in large-scale work. The cooled suspension obtained after hydrolysis of *p*-methylsulphonylacetanilide (1·29 kg.) with dilute hydrochloric acid (2·6 l. of concentrated acid in 10 l. of water) at 95° was diazotised with sodium nitrite (420 g.). The diazonium solution was efficiently stirred during addition of saturated aqueous sodium carbonate (1·3 kg.) until the pH was 5—6. The clear solution was then added rapidly (45 min.) to a mixture of cuprous cyanide (540 g.) and aqueous sodium cyanide (450 g. in 5 l.) at 50—55°. The temperature was raised to 75° for a further 45 min. and, after cooling, the precipitate was collected, washed with water, and stirred with cold acetone (3 × 4 l.), each extract being decanted through a filter. The combined extracts were concentrated to 2 l., treated with water (500 ml.) while hot, and left to crystallise. The nitrile (795 g., 72%), m. p. 134—135°, was washed with 50% aqueous acetone.

4-*Methylsulphonylbenzylamine.*—The above nitrile was catalytically reduced in presence of ammonia,[20] the residue after removal of solvent being heated with 5N-hydrochloric acid and filtered while hot to remove any secondary amine hydrochloride. Addition of acetone to the filtrate gave 4-methylsulphonylbenzylamine hydrochloride, m. p. 279—280° (from 90% ethanol).

4-*Methylsulphonylbenzyl Alcohol* (By Dr. R. F. Collins).—(*a*) 4-Methylsulphonylbenzylamine (4·4 g.) in 2N-hydrochloric acid (50 ml.) was mixed with aqueous sodium nitrite (2 g. in 10 ml.) and, after 15 min., heated to 100° for 30 min. The product was extracted with chloroform, and recrystallisation from ether gave the *alcohol*, m. p. 82—84° (Found: C, 51·7; H, 5·4; S, 17·5. $C_8H_{10}O_3S$ requires C, 51·6; H, 5·4; S, 17·2%). (*b*) A mixture of aluminium isopropoxide (6·1 g.) and *p*-methylsulphonylbenzaldehyde [15] (5·5 g.) in propan-2-ol (100 ml.) was slowly distilled until no further acetone was detected, and the propan-2-ol was then distilled off *in vacuo*. Extraction of the product with chloroform after addition of 2N-hydrochloric acid and sodium chloride gave the alcohol (3·25 g., 59%), m. p. 82—84°, undepressed by the product from (*a*).

4-*Methylsulphonylbenzyl Bromide* (*Methods* A *and* B *by* Dr. R. F. Collins).—(*A*) A mixture of 4-methylsulphonylbenzyl alcohol (3·25 g.) and 50% aqueous hydrogen bromide (30 ml.) was heated on the steam-bath for 2 hr., cooled, and the crystalline product collected, washed with water and recrystallised from aqueous ethanol, giving the *bromide* (3·55 g., 82%), m. p. 94—96° (Found: Br, 31·9. $C_8H_9BrO_2S$ requires Br, 32·2%). (*B*) A mixture of methyl *p*-tolyl sulphone [10] (7 g.) and *N*-bromosuccinimide (7·2 g.) in carbon tetrachloride (120 ml.) was refluxed for 2 hr., then filtered and evaporated, and the residue recrystallised from methanol and then from benzene–light petroleum, giving the bromide (3·4 g., 33%), m. p. 85—88° (Found: Br, 32·1%). Further recrystallisation from methanol raised the m. p. to 93—94°. (*C*) Methyl *p*-tolyl sulphone (300 g.) was heated under reflux at 180° and stirred whilst irradiated with

[18] I.G. Farbenindustrie, G.P. 501,280.
[19] Sikdar and Basu, *J. Indian Chem. Soc.*, 1945, **22**, 343.
[20] Boots Pure Drug Co., B.P. 583,585.

ultraviolet light during slow addition of bromine (96 ml.) under the surface of the liquid. Dissolved hydrogen bromide was then removed with a stream of dry nitrogen, and the liquid was cooled to about 120° and poured into ethanol (800 ml.). The dark solution was boiled (charcoal), filtered, and cooled rapidly. The bromide was ground with ice-cold ethanol, filtered off, and dried, giving material (298 g., 63%), m. p. 83—84°, suitable for further use. The spectrum of this material showed no strong band at 675 or 840 cm.$^{-1}$ which helped to characterise the spectrum of bromomethyl *p*-tolyl sulphone. Further recrystallisation of a sample from ethanol raised the m. p. to 94°, and it was undepressed by the product from (*A*) but depressed to ~58° by bromomethyl *p*-tolyl sulphone. (*D*) A suspension of methyl *p*-tolyl sulphone (4·25 g.) and 1,3-dibromo-5,5-dimethylhydantoin (3·6 g.) in carbon tetrachloride (100 ml.) was refluxed in the light of a 200-w tungsten lamp for 6 hr., the hot mixture was filtered, and, after cooling, the crystals (3·9 g.; m. p. 75°) were collected and recrystallised twice from methanol, giving prisms, m. p. 79—80° (Found: Br, 33·85%). A mixture with pure 4-methylsulphonylbenzyl bromide melted at 84—85°.

2-*Methylsulphonylbenzyl Bromide.*—Bromination of methyl *o*-tolyl sulphone by method (*C*) gave the vesicant *bromide* (49%), m. p. 104—105° (Found: Br, 32·0. $C_8H_9BrO_2S$ requires Br, 32·2%).

4-*Ethylsulphonylbenzyl Bromide.*—This *sulphone* was similarly prepared (54%) from ethyl *p*-tolyl sulphone and separated from ethanol in prisms, m. p. 94—95° (Found: Br, 30·3. $C_9H_{11}BrO_2S$ requires Br, 30·4%).

p-*Methylsulphonylbenzaldehyde.*—Solutions of 4-methylsulphonylbenzyl bromide (300 g.) and of hexamethylenetetramine (336 g.) in chloroform (total, 3·5 l.) were mixed and the mixture was refluxed for 1 hr. When cool, the solid (400 g., 85%), m. p. 187—190°, was collected. A sample of the *hexamethylenetetramine salt* crystallised from methanol in needles, m. p. 191—192° (decomp.) (Found: N, 14·2. $C_{14}H_{21}BrN_4O_2S$ requires N, 14·4%). The remainder was refluxed with 50% aqueous acetic acid for 3 hr., charcoal was added, and the solution was filtered and diluted with water. *p*-Methylsulphonylbenzaldehyde (118 g., 62%), m. p. 156—158°, which crystallised did not depress the m. p. of authentic aldehyde prepared by oxidation of methyl *p*-tolyl sulphone.

p-*Ethylsulphonylbenzaldehyde*, m. p. 101—103°, was prepared (50%) analogously from *p*-ethylsulphonylbenzyl bromide and crystallised from ethanol (Found: C, 54·3; H, 5·0. $C_9H_{10}O_3S$ requires C, 54·5; H, 5·1%).

Substituted 2-Benzylamino-ethanols (XV).—The *compounds* summarised in Table 1 were prepared by two methods.[6] In method A, the appropriate aldehyde was condensed with

TABLE 1.

2-Benzylaminoethanols, $R{\cdot}C_6H_4{\cdot}CH_2{\cdot}NH{\cdot}[CH_2]_2{\cdot}OH$.

R	Method	Yield (%)	M. p.	Formula	Found (%) N	Found (%) S	Reqd. (%) N	Reqd. (%) S
p-CN	B [a]	48	70—71 [b]	$C_{10}H_{12}N_2O$	16·15	—	15·9	—
p-SMe	B [c]	44	B. p. 140—145°/0·2 mm.	$C_{10}H_{15}NOS$	6·8	16·2	7·1	16·3
p-Me·SO_2...	A, B [d]	64, 70	137—138 [e]	$C_{10}H_{15}NO_3S$	5·9	14·1	6·1	14·0
o-Me·SO_2...	B	44	108—109 [e]	$C_{10}H_{15}NO_3S$	5·9	14·0	6·1	14·0
p-Et·SO_2...	A	87	87—90 [f]	$C_{11}H_{17}NO_3S$	5·8	—	5·8	—
p-CO_2Me ...	A	19	59—61 [e]	$C_{11}H_{15}NO_3$	6·75	—	6·7	—
p-NHAc ...	A	63	127—128 [e]	$C_{11}H_{16}N_2O_2$ [g]	13·5	—	13·45	—

[a] 4-Cyanobenzyl bromide (Case, *J. Amer. Chem. Soc.*, 1925, **47**, 1143) was used. [b] Purified by distillation; b. p. 168—172°/0·2 mm. [c] 4-Methylthiobenzyl chloride (Buu-Hoï and Hoan, *J. Org. Chem.*, 1952, **17**, 350) was used. [d] Also prepared [7] from 4-methylsulphonylbenzylamine. [e] Recryst. from ethanol. [f] Recryst. from benzene. [g] Found: C, 63·25; H, 7·8. Reqd.: C, 63·4; H, 7·7%.

ethanolamine in hot ethanol, and catalytic reduction over Raney nickel followed; in method B, the requisite benzyl halide was treated with 2 equiv. of ethanolamine in cold chloroform or in absence of a solvent.

Substituted N-*Benzyl-αα-dichloro*-N-2-*hydroxyethylacetamides.*—These *compounds* are described in Table 2.

α-*Cyano*-N-2-*hydroxyethyl*-N-4-*methylsulphonylbenzylacetamide.*—*N*-2-Hydroxyethyl-*N*-4-methylsulphonylbenzylamine (12·3 g.) was heated with ethyl cyanoacetate (6·5 ml.) at 100—110°, then at 110—120° for 4 hr., cooled, and triturated with light petroleum, and the solid

TABLE 2.

N-Benzyl-αα-dichloro-*N*-2-hydroxyethylacetamides (XVI).

R	Yield (%)	M. p.	Formula	Found (%) N	Cl	S	Reqd. (%) N	Cl	S
p-CN	91 [a]	136°	$C_{12}H_{12}Cl_2N_2O_2$	9·55	24·5	—	9·8	24·7	—
p-SMe	50 [a]	Syrup [b]	$C_{12}H_{15}Cl_2NO_2S$	4·4	—	10·35	4·5	—	10·4
p-SO_2Me	66,[c] 34 [a]	112	$C_{12}H_{15}Cl_2NO_4S$	4·1	20·7	—	4·1	20·85	—
o-SO_2Me	43 [c]	117—118	$C_{12}H_{15}Cl_2NO_4S$ [g]	—	20·9	9·4	—	20·85	9·4
p-SO_2Et	[d]								
p-Me	36 [c, e]	Syrup [f]	$C_{12}H_{15}Cl_2NO_2$	5·2	—	—	5·2	—	—

[a] With dichloroacetylchloride in ethylene dichloride in presence of aqueous sodium hydroxide at about 5°. [b] Decomp. if distilled. [c] With methyl dichloroacetate (1 equiv.) at ~80—85° in absence of solvent. [d] Did not crystallise; *acetate*, m. p. 89—90° (Found: C, 45·1; H, 5·0; N, 3·55. $C_{15}H_{19}Cl_2NO_5S$ requires C, 45·5; H, 4·8; N, 3·55%). [e] From 2-*p*-methylbenzylaminoethanol (Campbell and Ullyot, U.S.P. 2,640,828). [f] B. p. 150—160° (bath-temp.)/0·06 mm. [g] Found: C, 42·8; H, 4·5. Reqd.: C, 42·3; H, 4·5%.

TABLE 3.

Derivatives *p*-Me·SO_2·C_6H_4·CH_2·N(CO·$CHCl_2$)·[CH_2]$_2$·OR.

R	Yield (%)	M. p.	Formula	Found (%) N	Cl	S	Reqd. (%) N	Cl	S
Ac	92 [a]	105—106° [b]	$C_{14}H_{17}Cl_2NO_5S$	3·45	—	8·4	3·7	—	8·4
CO·Pr^n	85 [a]	120 [b]	$C_{16}H_{21}Cl_2NO_5S$	—	17·0	7·7	—	17·3	7·8
CO·$CHCl_2$	35 [c]	90—91 [b]	$C_{14}H_{15}Cl_4NO_5S$	2·9	30·8	—	3·1	31·4	—
Bz	89 [c]	117—119 [b]	$C_{19}H_{19}Cl_2NO_5S$	3·2	15·9	—	3·2	16·0	—
CO·[CH_2]$_2$·CO_2H...	36 [a]	138—139 [d]	$C_{16}H_{19}Cl_2NO_7S$	3·2	16·4	—	3·2	16·1	—
CO·CH_2Br	65 [c]	110—112 [b]	$C_{14}H_{16}BrCl_2NO_5S$	—	32·35 [g]	—	—	32·35 [g]	—
Et	47 [e]	94—95 [f]	$C_{14}H_{19}Cl_2NO_4S$	—	19·2	9·0	—	19·25	8·7
CH_2Pr^i	83 [e]	120—121·5 [b]	$C_{16}H_{23}Cl_2NO_4S$	—	17·6	8·35	—	17·9	8·1

[a] From the acid anhydride with pyridine. [b] Recryst. from ethanol. [c] From the acid chloride with pyridine. [d] Recryst. from ethyl acetate. [e] Prepared by dichloroacetylation of the amine. [f] Recryst. from benzene. [g] Total halogen. Found: C, 36·7; H, 3·6. Reqd.: C, 36·45; H, 3·5%.

product was washed with 2N-hydrochloric acid and recrystallised from ethanol, giving the *product* (6·3 g., 40%), m. p. 109° (Found: N, 9·15; S, 10·9. $C_{13}H_{16}N_2O_4S$ requires N, 9·5; S, 10·8%).

α-Chloro-N-2-*hydroxyethyl*-N-4-*methylsulphonylbenzylacetamide*.—This was prepared from *N*-2-hydroxyethyl-*N*-4-methylsulphonylbenzylamine and chloroacetyl chloride in ethylene dichloride in presence of 2N-sodium hydroxide. The syrupy product crystallised from benzene–ethyl acetate and recrystallised from ethanol, giving the pure *chloroacetamide* (29%), m. p. 93—95° (Found: Cl, 11·7. $C_{12}H_{16}ClNO_4S$ requires Cl, 11·6%).

Derivatives of αα-Dichloro-N-2-*hydroxyethyl*-N-4-*methylsulphonylbenzylacetamide*.—These *products* are summarised in Table 3.

N-2-*Ethoxyethyl*-N-4-*methylsulphonylbenzylamine*, b. p. 195—200° (bath-temp.)/0·04 mm. (Found: N, 4·9. $C_{12}H_{19}NO_3S$ requires N, 5·4%), was obtained by heating 2-ethoxyethyl chloride with 4-methylsulphonylbenzylamine (2 equiv.) at 140—150°. N-2-*Isobutoxyethyl*-N-4-*methylsulphonylbenzylamine*, b. p. 205—210°/0·2 mm., n_D^{18} 1·5195 (Found: N, 5·2; S, 11·25. $C_{14}H_{23}NO_3S$ requires N, 4·9; S, 11·2%), was prepared by catalytic hydrogenation of the condensation product of *p*-methylsulphonylbenzaldehyde with 2-isobutoxyethylamine, b. p. 136—142°, n_D^{21} 1·4160 (Found: C, 61·4; H, 12·6; N, 11·7. $C_6H_{15}NO$ requires C, 61·5; H, 12·9; N, 12·0%) [(−)-*di*-p-*toluoyltartrate*, m. p. 177° (Found: C, 62·45; H, 6·85. $C_6H_5NO,C_{20}H_{18}O_8$ requires C, 62·05; H, 6·6%)], the last-named amine being the hydrogenation product of isobutoxyacetonitrile.[21]

N-3-*Methoxypropyl*-N-4-*methylsulphonylbenzylamine*.—*p*-Methylsulphonylbenzaldehyde (36·8 g.), suspended in ethanol (200 ml.) was refluxed with 3-methoxypropylamine (17·8 g.) for 1 hr., and the cooled solution was hydrogenated over Raney nickel at 34°/385 lb. per sq. in. Evaporation of the filtrate gave an oil which, on distillation, afforded the *amine* (43·3 g., 84%), b. p. 198—210°/0·1 mm., n_D^{25} 1·5318 (Found: C, 55·8; H, 7·5; N, 5·5. $C_{12}H_{19}NO_2S$ requires C, 56·0; H, 7·45; N, 5·45%).

αα-*Dichloro*-N-3-*methoxypropyl*-N-4-*methylsulphonylbenzylacetamide*.—The preceding amine (20 g.) in ethylene dichloride (150 ml.) was stirred at 0° with N-sodium hydroxide (85 ml.) during dropwise addition of dichloroacetyl chloride (12·6 g.). After being stirred at room

[21] Spurlock, U.S.P. 2,591,103.

temperature for a further 3 hr., the product was isolated from the organic layer and recrystallised from ethanol, giving the *dichloroacetamide* as prisms (22·5 g., 79%), m. p. 98—99° (Found: N, 3·7; Cl, 19·45. $C_{14}H_{19}Cl_2NO_4S$ requires N, 3·8; Cl, 19·3%).

*αα-Dichloro-*N*-2-chloroethyl-*N*-4-methylsulphonylbenzylacetamide.*—Thionyl chloride (10 ml.; redistilled from quinoline) was added to the amide (XV; R = *p*-Me·SO_2) (5 g.) at 0°. When the exothermic reaction had abated, the solution was briefly heated and the excess of thionyl chloride removed by distillation. A portion of the solid residue (5 g., 95%), m. p. 118—122°, was recrystallised from benzene–light petroleum, giving the *compound*, m. p. 122° (Found: N, 3·8; Cl, 29·9. $C_{12}H_{14}Cl_3NO_3S$ requires N, 3·9; Cl, 29·65%). This, when dissolved in acetic acid and refluxed with potassium acetate for 1 hr., gave *N*-2-acetoxyethyl-αα-dichloro-*N*-4-methylsulphonylbenzylacetamide, m. p. and mixed m. p. with authentic material (m. p. 105—106°) 102—103°.

*αα-Dichloro-*N*-methyl-*p*-(4-methylsulphonylbenzyloxy)acetanilide* (XVII).—A mixture of αα-dichloro-*p*-hydroxy-*N*-methylacetanilide (18·8 g.), 4-methylsulphonylbenzyl bromide (20 g.), anhydrous potassium carbonate (8 g.), and acetone (200 ml.) was refluxed for 24 hr., filtered, and evaporated. The residue was stirred with 0·5N-sodium hydroxide, and the product was collected and recrystallised from ethanol, giving the *anilide* (XVII) (18 g., 60%), m. p. 144—145° (Found: N, 3·4; Cl, 17·6. $C_{17}H_{17}Cl_2NO_4S$ requires N, 3·5; Cl, 17·6%).

*αα-Dichloro-*N*-methyl-*p*-(4-methylsulphonylbenzoyloxy)acetanilide* (XVIII).—*p*-Methylsulphonylbenzoyl chloride [9] (22 g.) was added during 15 min. to a stirred solution of αα-dichloro-*p*-hydroxy-*N*-methylacetanilide (23·5 g.) in dry pyridine (175 ml.). After 6 hr., the solvent was distilled off *in vacuo* and the residue treated with water, giving a solid which, when recrystallised from ethanol, afforded the *product* (XVIII) (21·1 g., 50%), m. p. 162—164° (Found: C, 49·1; H, 3·8. $C_{17}H_{15}Cl_2NO_5S$ requires C, 49·0; H, 3·6%).

4-Methylsulphonylbenzylidenerhodanine.—*p*-Methylsulphonylbenzaldehyde (20·2 g.), rhodanine (14·6 g.), and anhydrous sodium acetate (27·5 g.) in acetic acid (220 ml.) were refluxed for 2 hr., then poured into water. The yellow solid recrystallised from dimethylformamide to give the *rhodanine* (27 g., 85%), m. p. 262—264° (Found: N, 4·4; S, 31·9. $C_{11}H_9NO_3S_3$ requires N, 4·7; S, 32·1%).

4-4′-Methylsulphonylbenzylmorpholine.—A solution of 4-methylsulphonylbenzyl bromide (20 g.) in chloroform (50 ml.) was slowly added with stirring to a similar solution of morpholine (20 g.) at 5°. After 2 hr., the filtered solution was washed with water and evaporated. The residue was treated with 4N-hydrochloric acid, the mixture filtered, and the filtrate made alkaline. Recrystallisation of the precipitate from benzene–light petroleum afforded the *product* (14·5 g., 71%), m. p. 110—112° (Found: N, 5·6; S, 12·4. $C_{12}H_{17}NO_3S$ requires N, 5·5; S, 12·55%).

4-Methylsulphonylbenzylthiouronium Bromide.—A solution of bromomethyl *p*-tolyl sulphone (12·5 g.) and thiourea (3·8 g.) in ethanol (50 ml.) was refluxed for 15 hr., cooled, and treated with ether. The *thiouronium salt* (10·6 g., 65%), recrystallised from ethanol, had m. p. 213—214° (Found: N, 8·4; Br, 24·3. $C_9H_{13}BrN_2O_2S_2$ requires N, 8·6; Br, 24·55%).

Amides Derived from N*-Methyl-*p*-methylsulphonylaniline.*—(*a*) *N*-Methyl-*p*-methylsulphonylaniline [22] with acetic anhydride at 100° gave N*-methyl-*p*-methylsulphonylacetanilide* (76%), prisms (from water), m. p. 124—125° (Found: N, 6·0; S, 14·1. $C_{10}H_{13}NO_3S$ requires N, 6·2; S, 14·1%).

(*b*) Methanesulphonyl chloride (3·35 g.) in acetone (15 ml.) was slowly added to the amine (4·2 g.) in acetone (30 ml.) and pyridine (10 ml.) at 0°. After being stirred overnight, the acetone was evaporated *in vacuo*, and the residual solution poured into water, to give an oil which solidified under 2N-hydrochloric acid. Recrystallisation from ethanol gave N*-methyl-*N*-methylsulphonyl-*p*-methylsulphonylaniline* (3·1 g., 52%), m. p. 134—135° (Found: N, 5·2; S, 24·15. $C_9H_{13}NO_4S_2$ requires N, 5·3; S, 24·3%).

(*c*) *αα-Dichloro-*N*-methyl-4-methylsulphonylacetanilide*, needles, m. p. 173—174°, from ethanol (Found: N, 4·6; Cl, 23·8. $C_{10}H_{11}Cl_2NO_3S$ requires N, 4·7; Cl, 23·9%), was similarly prepared by using dichloroacetyl chloride.

We thank Drs. H. J. Barber and J. N. Ashley, for help and encouragement, Mr. S. Bance, for the micro-analyses, Mr. G. H. Smith for amœbicidal tests, and Dr. D. F. Muggleton for the infrared spectra.

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[*Received, October 9th*, 1961.]

[22] I.G. Farbenindustrie, French P. 829,926.