441. *Compounds containing the 3-Chloroallyl Group.*

By A. F. Childs, S. G. P. Plant, A. L. L. Tompsett, and G. A. Weeks.

As part of an investigation of vesicant compounds and in view of reports that 3-chloroallyl alcohol has a powerful effect on the skin, several substances containing the 3-chloroallyl group have been prepared for examination. These include a number which are analogous to well known 2-chloroethyl compounds and contain the group attached to sulphur or nitrogen. Some substances containing the 3-chloroallyl group attached to oxygen in esters, urethanes, and acetals have been made, and 3-*chloroallyldichloroarsine* has been included.

Several authors have emphasised the vesicant properties of 3-chloroallyl alcohol, $CHCl{:}CH{\cdot}CH_2{\cdot}OH$ (van Romburgh, *Bull. Soc. chim.*, 1881, **36**, 555; Henry, *Compt. rend.*, 1882, **95**, 851; Kirrmann, Pacaud, and Dosque, *Bull. Soc. chim.*, 1934, **1**, 860). As part of an investigation into vesicant substances, it appeared of importance therefore to prepare certain compounds containing the 3-chloroallyl group, and related to known toxic types. For this purpose 3-chloroallyl chloride $CHCl{:}CH{\cdot}CH_2Cl$, was obtained by dehydraton of glycerol 1 : 3-dichlorohydrin, $CH_2Cl{\cdot}CH(OH){\cdot}CH_2Cl$, with phosphorus oxychloride as described by Hill and Fischer (*J. Amer. Chem. Soc.*, 1922, **44**, 2582). When treated with alcoholic sodium sulphide, the chloride gave 3 : 3′-*dichlorodiallyl sulphide*, $(CHCl{:}CH{\cdot}CH_2)_2S$, while 2-*hydroxyethyl* 3-*chloroallyl sulphide*, $CH_2(OH){\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot}CH{:}CHCl$, was obtained by the action of the sodium salt of monothioethylene glycol. This hydroxy-compound, which was also prepared from the thiol, $CHCl{:}CH{\cdot}CH_2{\cdot}SH$, and ethylene chlorohydrin, was converted by thionyl chloride into 2-*chloroethyl* 3-*chloroallyl sulphide*, $CH_2Cl{\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot}CH{:}CHCl$, whence by a similar sequence of reactions with monothioethylene glycol 1-(2 -*hydroxyethylthio*)- and 1-(2′-*chloroethylthio*)-2-(3′-*chloroallylthio*)*ethane*, $CH_2R{\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot}CH{:}CHCl$ ($R = OH$ or Cl), were obtained. 1 : 2-*Di*-(3 -*chloroallylthio*)*ethane*, $(CHCl{:}CH{\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot})_2$, was prepared from the above thiol and ethylene dibromide, and *methyl* 3-*chloroallyl sulphide*, $CH_3{\cdot}S{\cdot}CH_2{\cdot}CH{:}CHCl$, from the chloride and methylthiol.

Di-(3-*chloroallyl*)*amine*, $(CHCl{:}CH{\cdot}CH_2)_2NH$, and *tri*-(3-*chloroallyl*)*amine*, $(CHCl{:}CH{\cdot}CH_2)_3N$, have been isolated from the product of the action of alcoholic ammonia on 3-chloroallyl chloride, while the tertiary base has also been obtained in a similar way from the corresponding iodide. The secondary base was methylated by heating its formate with paraformaldehyde (compare Clarke, Gillespie, and Weisshaus, *J. Amer. Chem. Soc.*, 1933, **55**, 4571; see also this vol., p. 2174) with the formation of methyldi-(3-chloroallyl)amine, which has been described by von Braun, Kühn, and Weismantel (*Annalen*, 1926 **449**, 249) as one of the products of the action of methylamine on 3-chloroallyl chloride.

Several substances containing the 3-chloroallyl group attached to oxygen have been prepared. The action of silver chloroacetate on 3-chloroallyl iodide gave the expected *ester*, from which 3-*chloroallyl iodoacetate*, $CH_2I{\cdot}CO_2CH_2{\cdot}CH{:}CHCl$, was obtained by treatment with sodium iodide in acetone. Addition of 3-chloroallyl alcohol to carbonyl chloride led to the *chloroformate* $Cl{\cdot}CO_2CH_2{\cdot}CH{:}CHCl$, which was converted by aniline into 3-*chloroallyl carbanilate* $NHPh{\cdot}CO_2CH_2{\cdot}CH{:}CHCl$, also obtained from the alcohol and phenyl *iso*cyanate, and by 2-chloroethylamine into the corresponding 2-*chloroethylcarbamate*, $CH_2Cl{\cdot}CH_2{\cdot}NH{\cdot}CO_2CH_2{\cdot}CH{:}CHCl$. Attempts to obtain a nitrosourethane from the latter gave products which could not be purified. Condensation of 3-chloroallyl alcohol with the appropriate aldehydes gave the *acetals* $CHR(O{\cdot}CH_2{\cdot}CH{:}CHCl)_2$ ($R = H$ or CH_3), while the sulphur-containing *analogue* $CH_3{\cdot}CH(S{\cdot}CH_2{\cdot}CH{:}CHCl)_2$ was obtained from the corresponding thiol.

3-*Chloroallyl thiocyanate* was prepared from the chloride with potassium thiocyanate, and its identity was confirmed by its conversion into 3-*chloroallyl acetyldithiocarbamate*, $CHCl{:}CH{\cdot}CH_2{\cdot}S{\cdot}CS{\cdot}NHAc$, on treatment with ethanethioic acid (see Wheeler and Merriam, *J. Amer. Chem. Soc.*, 1901, **23**, 283), but when heated in attempts to obtain a mustard oil, it suffered profound decomposition. 3-*Chloroallyldichloroarsine*, $CHCl{:}CH{\cdot}CH_2AsCl_2$, has been made from the chloride through the corresponding arsonic acid.

The presence of the 3-chloroallyl group in a compound leads to the possibility of geometrical isomerism, and frequent reference to this feature was made by us in 1943—1944 in Extra Mural Reports of the Ministry of Supply. In this connexion it is of interest that Hatch and Moore (*J. Amer. Chem. Soc.*, 1944, **66**, 285) have isolated two forms of 3-chloroallyl chloride, b. p.s 104·3° and 112°, by careful fractionation of a residue obtained from the distillation of crude allyl chloride prepared by the chlorination of propylene, and have converted them into the corresponding forms of 3-chloroallyl alcohol, both of which have delayed vesicant action.

EXPERIMENTAL.

The preparation of 3-chloroallyl chloride by the method of Hill and Fischer (*loc. cit.*) was carriec out several times, but the yield of material, b. p. 106—109·5°, never exceeded 40% of the theoretical Hill and Fischer claim a 75% yield, but Hurd and Webb (*J. Amer. Chem. Soc.*, 1936, **58**, 2190) reportec only 34%.

3 : 3′-*Dichlorodiallyl Sulphide*.—When 3-chloroallyl chloride (22·2 g.) was slowly added to a solutior of sodium sulphide crystals (24 g.) in hot alcohol (100 c.c.) under reflux, the mixture boiled withou external heating. The whole was boiled for a further ½ hour, and most of the alcohol was removed by distillation. The oil which separated when the residue was poured into water was extracted with ether, washed with aqueous sodium hydroxide, and dried. After removal of the ether, the product was distilled and 3 : 3′-*dichlorodiallyl sulphide* (14·9 g.) collected as an almost colourless liquid, b. p. 116—117°/19 mm. (Found : C, 39·0; H, 4·5. $C_6H_8Cl_2S$ requires C, 39·3; H, 4·4%).

2-*Hydroxyethyl* 3-*Chloroallyl Sulphide*.—(A) Monothioethylene glycol (24·6 g.) was added to a solution of sodium (8·3 g.) in alcohol (150 c.c.), the mixture heated to boiling on a water-bath, and the flame removed while 3-chloroallyl chloride (35 g.) was slowly added with mechanical stirring. After the whole had been stirred for a further hour, the sodium chloride was filtered off and washed with alcohol. When the united alcoholic solutions were fractionated, 2-*hydroxyethyl* 3-*chloroallyl sulphide* (34·2 g.) was obtained as a colourless oil, b. p. 136—139°/20 mm. (Found : C, 39·2; H, 6·1. C_5H_9OClS requires C, 39·3; H, 5·9%).

(B) After a solution of sodium (6·9 g.) in alcohol (120 c.c.) had been saturated with dry hydrogen sulphide at 0°, 3-chloroallyl chloride (27·7 g.) was added, and the mixture heated in pressure bottles at 60° for 6 hours. The oily thiol which separated when the whole was poured into water was extracted with ether, dried, and distilled. It was obtained as a colourless liquid (12·2 g.), b. p. 43—45°/27 mm., and was then added to a solution of sodium (3 g.) in alcohol (65 c.c.). After the mixture had been heated to the boiling point, ethylene chlorohydrin (10·4 g.) was added during 40 minutes with mechanical stirring, the whole was refluxed for ½ hour, the sodium chloride removed by filtration, and the alcoholic solution fractionated. 2-Hydroxyethyl 3-chloroallyl sulphide (7·9 g.) was collected at 135—137·5°/16 mm. (Found : C, 38·7; H, 5·8%).

2-*Chloroethyl* 3-*Chloroallyl Sulphide*.—Thionyl chloride (16·4 g.) in chloroform (20 c.c.) was slowly added with mechanical stirring to a solution of the above hydroxy-compound (20 g.) in hot chloroform (30 c.c.), and the whole was gently refluxed for 2 hours. When the solution was then fractionated, 2-*chloroethyl* 3-*chloroallyl sulphide* (18·6 g.) was obtained as a colourless oil, b. p. 113—114°/17 mm. (Found : C, 35·2; H, 4·5. $C_5H_8Cl_2S$ requires C, 35·1; H, 4·7%).

1 : 2-*Di*-(3′-*chloroallylthio*)*ethane*.—After the above thiol (21·5 g.), from 3-chloroallyl chloride, had been added to sodium (4·6 g.) in alcohol (150 c.c.), and the whole raised to the boiling point under reflux, ethylene dibromide (19 g.) was added during ½ hour with stirring. When the mixture had been refluxed for 5 hours with continued stirring, and cooled, the sodium bromide was filtered off, and the filtrate fractionated. 1 : 2-*Di*-(3′-*chloroallylthio*)*ethane* (8·1 g.) was collected as a yellow oil, b. p. 192—194°/19 mm., which solidified on standing. After redistillation, the product was crystallised from alcohol and obtained in colourless plates, m. p. 45—49° (Found : C, 39·3; H, 4·8. $C_8H_{12}Cl_2S_2$ requires C, 39·5; H, 4·9%).

1-(2′-*Chloroethylthio*)-2-(3′-*chloroallylthio*)*ethane*.—Obtained from 2-chloroethyl 3-chloroallyl sulphide by a process similar to the first method described above for the preparation of 2-hydroxyethyl 3-chloroallyl sulphide, 1-(2′-*hydroxyethylthio*)-2-(3′-*chloroallylthio*)*ethane* was isolated as a pale brown oil, b. p. 195—200°/27 mm. (Found: C, 39·3; H, 6·1. $C_7H_{13}OClS_2$ requires C, 39·5; H, 6·1%). After its solution in chloroform had been refluxed for an hour in an all glass apparatus with a small excess of thionyl chloride, all volatile material was removed under reduced pressure at 40°, and 1-(2′-*chloroethylthio*)-2-(3′-*chloroallyl thio*)*ethane* remained as a dark brown oil (Found : C, 36·8; H, 5·5. $C_7H_{12}Cl_2S_2$ requires C, 36·4; H, 5·2%). No attempt was made to distil the product since substances of this type readily change into derivatives of 1 : 4-dithian.

Methyl 3-*Chloroallyl Sulphide*.—Prepared from 3-chloroallyl chloride and the sodium salt of methylthiol under conditions similar to those used for 2-hydroxyethyl 3-chloroallyl sulphide (method A), this *sulphide* was obtained as a colourless oil, b. p. 55°/21 mm. (Found : C, 39·0; H, 6·0. C_4H_7ClS requires C, 39·2; H, 5·7%).

Di- and Tri-(3-*chloroallyl*)*amine*. (A) When dry ammonia was passed into 3-chloroallyl chloride (96 g.), dissolved in alcohol (600 c.c.), until the solution had gained 25 g. in weight, and the whole left for a fortnight at room temperature, a considerable quantity of ammonium chloride separated. After filtration, the filtrate was evaporated to dryness under reduced pressure on a steam bath, and the residue made alkaline with the least possible quantity of concentrated aqueous potassium hydroxide. The oily product was extracted with ether, and the extract was dried ($MgSO_4$) and fractionated. Three fractions were collected at (i) 40—70°/21 mm., (ii) 105—115°/21 mm., and (iii) 157—159°/21 mm. When the first of these was redistilled at atmospheric pressure, a liquid (3·5 g.), b. p. 95—119°, was collected, and this appeared to consist largely of 3-chloroallylamine, but the primary base has not been obtained in a pure condition. Further distillation of the middle fraction gave *di*-(3-*chloroallyl*)*amine* (9·7 g.) as a pale yellow oil, b. p. 103·5—104°/17 mm. (Found : C, 43·3; H, 5·7; N, 8·5. $C_6H_9NCl_2$ requires C, 43·4; H, 5·4; N, 8·4%). The third fraction (23 g.) was *tri*-(3-*chloroallyl*)*amine*, and on redistillation it was collected as an almost colourless oil at 145—147°/15 mm. (Found : C, 44·5; H, 5·3; N, 6·1. $C_9H_{12}NCl_3$ requires C, 44·9; H, 5·0; N, 5·8%).

(B) When 3-chloroallyl chloride (77·8 g.) was added to a solution of sodium iodide (116 g.) in acetone (600 c.c.), there was an immediate precipitation of sodium chloride. After the whole had been refluxed for 2 hours, some of the acetone (300 c.c.) was distilled off, and the residue treated with water (600 c.c.). When the oily 3-chloroallyl iodide was shaken with aqueous sodium thiosulphate until colourless, dried, and distilled (yield 104·6 g.), it boiled at 69—70°/32 mm. This iodide has been obtained by the use of other reactions (van Romburgh, *Rec. Trav. chim.*, 1882, **1**, 233; Kirrmann, Pacaud, and Dosque, *loc.*

cit.; Bert and Andor, *Compt. rend.*, 1932, **194**, 722). Dry ammonia was passed into a solution of the iodide (100 g.) in alcohol (200 c.c.), cooled in ice-water, until an increase in weight of 14 g. had been attained, and the whole was heated at 60° for 8 hours. When the alcohol was distilled off under reduced pressure and the residue treated as described under (A), tri-(3-chloroallyl)amine (24·5 g.) was obtained at 154—155·5°/17 mm., and the amounts of the lower-boiling fractions were less than from 3-chloroallyl chloride.

Methyldi-(3-*chloroallyl*)*amine*.—When a mixture of di-(3-chloroallyl)amine (9·5 g.), anhydrous formic acid (2·65 g.), and paraformaldehyde (1·7 g.) was slowly heated under reflux, the evolution of carbon dioxide began at about 60° and was exceedingly brisk for a few moments. After being kept at 100—120° for ½ hour, the liquid, in ether (50 c.c.), was shaken with toluene-*p*-sulphonyl chloride (1·5 g.) and potassium hydroxide (2 g.), in water (15 c.c.), to ensure removal of any secondary base, the ether washed with water, and the tertiary base extracted with dilute hydrochloric acid. Methyldi-(3-chloroallyl)amine, recovered by the addition of alkali, was extracted with ether, dried, and distilled, and was collected as a colourless oil (7·0 g.), b. p. 95—97°/10 mm. (Found : C, 47·3; H, 6·2. Calc. for $C_7H_{11}NCl_2$: C, 46·7; H, 6·1%).

3-*Chloroallyl Chloro- and Iodo-acetate*.—When a suspension of dry, freshly prepared silver chloroacetate (85·5 g.) in ether (50 c.c.) was treated with a solution of 3-chloroallyl iodide (45·3 g.) in ether (50 c.c.) under reflux, a steady reaction ensued, the ether boiled without external heating, and the solid became yellow. After the reaction had subsided, the whole was refluxed for 2 hours, cooled, and filtered. The filtrate was fractionated, and 3-*chloroallyl chloroacetate* obtained as a colourless oil (17 g.), b. p. 95—100·5°/13 mm. (Found : C, 35·1; H, 3·6. $C_5H_6O_2Cl_2$ requires C, 35·5; H, 3·6%). A mixture of the ester (16·2 g.), sodium iodide (16·2 g.), and acetone (100 c.c.) was refluxed for 2 hours, and filtered from the precipitated sodium chloride. After the precipitate had been washed with acetone, the solvent was distilled from the united solutions, and the residue treated with water. An ethereal extract of the product was shaken with aqueous sodium thiosulphate, dried, and fractionated. 3-*Chloroallyl iodoacetate* was collected as a colourless oil (14·4 g.), b. p. 122—124°/14 mm. (Found : C, 22·8; H, 2·6. $C_5H_6O_2ClI$ requires C, 23·0; H, 2·3%).

3-*Chloroallyl Carbanilate*.—A mixture of phenyl *iso*cyanate (1 g.) and 3-chloroallyl alcohol (2 g., prepared as described by van Romburgh, *loc. cit.*) was heated for 5 minutes at 100° and then shaken with water. When the product, which solidified on standing overnight, was collected, washed with water, dried, and crystallised from light petroleum, 3-*chloroallyl carbanilate* was obtained in colourless needles, m. p. 53—54·5° (Found : C, 56·7; H, 4·6. $C_{10}H_{10}O_2NCl$ requires C, 56·7; H, 4·7%).

3-*Chloroallyl Chloroformate*.—After 3-chloroallyl alcohol (21·7 g.) had been added dropwise to carbonyl chloride (27 c.c.), cooled in a mixture of ice and salt, at such a rate that the temperature did not rise above 0°, the whole was left at room temperature overnight. The excess of carbonyl chloride was removed in a current of dry air at 20°, the residue was dried ($MgSO_4$), and distilled, and a liquid obtained over the range 90—160°. When this was fractionated through a short column, 3-*chloroallyl chloroformate* (17·5 g.) was collected at 150—160° (Found : Cl, 45·9. $C_4H_4O_2Cl_2$ requires Cl, 45·8%). After equimolecular proportions of the product and aniline had been mixed in ether, an aqueous solution containing slightly more than a molecular proportion of potassium hydroxide was gradually added with mechanical stirring at 0°. When the ethereal solution was dried and evaporated, and the residue crystallised from light petroleum, 3-chloroallyl carbanilate separated in colourless needles, m. p. 51—52°, identical (mixed m. p.) with the above substance.

3-*Chloroallyl* 2-*Chloroethylcarbamate*.—3-Chloroallyl chloroformate (10 g.) and a solution of potassium hydroxide (7·2 g.) in water (50 c.c.) were added concurrently during about ¼ hour to a solution of 2-chloroethylamine hydrochloride (15 g.) in water (20 c.c.) which was cooled in ice-water and stirred. When the product was extracted with ether, dried, and fractionated, 3-*chloroallyl* 2-*chloroethylcarbamate* was obtained as a colourless oil (6 g.), b. p. 156°/16 mm. (Found : C, 36·8; H, 4·7. $C_6H_9O_2NCl_2$ requires C, 36·4; H, 4·5%).

Di-(3-*chloroallyloxy*)*methane*.—After a mixture of 3-chloroallyl alcohol (18 g.), paraformaldehyde (3 g.), and anhydrous ferric chloride (0·5 g.) had been heated at 100° for 6 hours in a flask fitted with a reflux condenser, the lower aqueous layer was removed and the oily product washed twice with water (5 c.c.) before being dried (K_2CO_3). On distillation, *di*-(3-*chloroallyloxy*)*methane* was obtained as a colourless oil (7·1 g.), b. p. 108—123°/20 mm. (Found : C, 42·9; H, 5·3. $C_7H_{10}O_2Cl_2$ requires C, 42·6; H, 5·1%).

1 : 1-*Di*-(3-*chloroallyloxy*)*ethane*.—After powdered, anhydrous calcium chloride (3 g.) had been shaken for a few minutes with 3-chloroallyl alcohol (20 g.), the mixture was cooled to 0° and treated with acetaldehyde (5·5 g.). The whole was vigorously shaken for ¼ hour at room temperature, and then left for 30 hours with occasional shaking. Water (4 c.c.) was added to dissolve the calcium chloride, and the upper oily layer was washed with water, and dried. When distilled, it gave 1 : 1-*di*-(3-*chloroallyloxy*)*ethane* as a colourless oil (9 g.), b. p. 115—120°/16 mm. (Found : C, 45·1; H, 5·7. $C_8H_{12}O_2Cl_2$ requires C, 45·5; H, 5·7%).

1 : 1-*Di*-(3-*chloroallylthio*)*ethane*.—When a mixture of the thiol (15 g.), from 3-chloroallyl chloride, and acetaldehyde (3 g.) was cooled in ice-water and shaken for a few minutes with anhydrous zinc chloride (3 g.), an aqueous layer soon began to separate. After the whole had been left for a day, water (10 c.c.) was added, and the oily product extracted with ether. When the extract was washed with water, dried, and fractionated, 1 : 1-*di*-(3-*chloroallylthio*)*ethane* was obtained as a pale yellow oil (8·5 g.), b. p. 162—164°/13 mm. (Found : C, 38·6; H, 4·7. $C_8H_{12}Cl_2S_2$ requires C, 39·5; H, 4·9%).

3-*Chloroallyl Thiocyanate*.—Potassium thiocyanate (9·7 g.) in water (5 c.c.) was mixed with 3-chloroallyl chloride (15·7 g.) in alcohol (50 c.c.), the solution left overnight, and then refluxed for an hour. After distillation in steam, the product was extracted with ether, dried, and fractionated. 3-*Chloroallyl thiocyanate* was obtained as a colourless oil, b. p. 72—78°/0·2 mm. (Found : C, 35·2; H, 3·0. C_4H_4NClS requires C, 36·0; H, 3·0%).

3-*Chloroallyl Acetyldithiocarbamate*. After a mixture of the above thiocyanate (3·3 g.), ethanethioic acid (1·9 g.), and benzene (25 c.c.) had been refluxed for 3½ hours, the solvent was removed under reduced pressure and the residue crystallised from *sec*-butyl alcohol. 3-*Chloroallyl acetyldithiocarbamate* (4 g.)

was obtained in pale yellow plates, m. p. 105° (Found : C, 34·4; H, 3·9; S, 30·9. $C_6H_8ONClS_2$ requires C, 34·4; H, 3·8; S, 30·6%).

3-*Chloroallyldichloroarsine*.—3-Chloroallyl chloride (27·75 g.) was added to arsenious oxide (20 g.) dissolved in a solution of sodium hydroxide (24 g.) in water (200 c.c.), and contained in a flask fitted with a reflux condenser and mechanical stirrer (mercury seal). The mixture was gradually heated, with stirring, to 100°, at which it was kept for 3 hours. After all volatile material had been removed in steam, the residual aqueous solution was cooled, treated with concentrated hydrochloric acid (255 c.c.), and quickly filtered. A few crystals of potassium iodide were added, and sulphur dioxide passed through the solution for 3 hours. When the oily product was extracted with carbon tetrachloride, and the extract dried ($MgSO_4$) and fractionated, 3-*chloroallyldichloroarsine* was obtained as an almost colourless oil (11·6 g.), b. p. 104—105°/18 mm. (Found : C, 15·6; H, 2·2; Cl, 47·7. $C_3H_4Cl_3As$ requires C, 16·2; H, 1·8; Cl, 48·1%).

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DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, February* 20*th*, **1948.**]