D. G. Barnard-Smith, D. H. Desty and W. Crawford for carrying out the fractionations and also the determinations of the physical constants which are quoted in this paper.

SUNBURY-ON-THAMES
MIDDLESEX, ENGLAND

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[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, ANGLO-IRANIAN OIL CO. LTD.]

The Preparation and Physical Properties of Sulfur Compounds Related to Petroleum. II. Cyclic Sulfides[1]

BY E. V. WHITEHEAD, R. A. DEAN AND F. A. FIDLER

The preparation and physical properties of thiacyclopentane, 2- and 3-methylthiacyclopentanes, *cis*- and *trans*-2,5-dimethylthiacyclopentanes, thiacyclohexane and the 2-, 3-, and 4-methylthiacyclohexanes are given. The two forms of the 2,5-dimethylthiacyclopentane have been prepared pure for the first time. Considerable care was taken to purify the starting materials and the intermediates and in all cases the final sulfides were purified through their solid mercuric chloride derivatives before fractionation.

Introduction

The first paper of this series dealt with the syntheses and physical properties of alkane sulfides and alkane disulfides, both of which have been isolated from straight run petroleum distillates. The present paper deals with still another class of organic sulfur compounds found in these products, namely, the saturated cyclic sulfides.

The presence of this type of compound in Iranian distillates has been known for some considerable time[2] and further evidence of their presence has recently been obtained by the isolation of relatively pure specimens of thiacyclopentane, 2- and 3-methylthiacyclopentanes and thiacyclohexane from a tar oil obtained from the sulfuric acid treatment of an aromatic concentrate. It is interesting to note that the only cyclic sulfides which have been identified in or isolated from petroleum distillates have contained either 5- or 6-membered rings as is the case with the naphthene hydrocarbons.

The most interesting sulfide prepared in the present work was 2,5-dimethylthiacyclopentane. This compound can exist in *cis* and *trans* modifications and both these forms have been synthesized in a reasonably high and known degree of purity for the first time.

As in the case of the alkane sulfides, derivatives have been prepared to assist in the characterization of the compounds. The three derivatives used were the methiodides, the sulfones and the stable mercuric chloride complexes. The methiodides, as a rule, volatilize without melting and their temperatures of volatilization are given. Future work may find more satisfactory derivatives for the characterization of these compounds.

Experimental[3]

General Methods of Preparation

Preparation of Dibromides.—For the majority of the syntheses, the required dibromides have been prepared by hydrobromination of a cyclic oxide or a glycol.

Anhydrous hydrogen bromide was passed into the appropriate oxide or glycol at 100–120° until absorption was complete and the crude dibromide was purified by washing a pentane solution of it with concentrated sulfuric acid followed by fractionation under reduced pressure.

Preparation of the Sulfides

Method I. Cyclization Using Aqueous Alcoholic Solution.—An aqueous alcoholic solution of sodium sulfide was prepared by dissolving 1203 g. (5.0 moles) of sodium sulfide nonahydrate in 1100 ml. of water and 1370 ml. of ethanol. A portion (1100 ml.) of this solution was refluxed in a five-liter three-necked flask fitted with a reflux condenser and two dropping funnels. The remainder of the sodium sulfide solution was placed in one of the funnels and the dihalide (3.35 moles) in the other. The liquids in the funnels were then run into the refluxing sulfide solution at such a rate that the addition of both was completed at the same time, which was approximately 30 minutes.

Method II. Cyclization Using Aqueous Solution.—The solution of sodium sulfide nonahydrate (1410 g., 5.88 moles) in water (2820 ml.) was prepared and reacted with dihalide (3.38 moles) in a similar manner to the above, with the exception that vigorous stirring was maintained throughout the reaction.

In each of the above methods, after the addition was completed, the mixture was refluxed for a further period, the length of time depending on the compound being prepared. The desired cyclic sulfide was steam distilled[4] from the reaction product and the steam distillate was added to a boiling solution of mercuric chloride in ethanol with vigorous stirring. The mercuric chloride derivative was crystallized to constant melting point from ethanol and the cyclic sulfide regenerated from this compound by steam distillation from 15% hydrochloric acid.

Purification of the Cyclic Sulfides.—The crude cyclic sulfides were purified by crystallization of their mercuric chloride derivatives to constant melting point. Initially, the sulfides, after regeneration from the complexes, were fractionated at atmospheric pressure in 100-plate metal-packed columns but it was found that a certain amount of decomposition occurred which reduced the purities of the final products. As a result, the fractions from the distillations were repurified through their mercuric chloride complexes and were given final distillations through 20-plate glass-packed columns under reduced pressure. With the later preparations, the 100-plate column distillation was omitted.

Thiacyclopentane

Tetrahydrofuran.—Commercial tetrahydrofuran was fractionated in a 50-plate glass helix packed column. Fractions boiling 65.9–66.2° with refractive index $n^{20}D$ 1.4077 and density d^{20} 0.8890 were bulked.

1,4-Dibromobutane.—From tetrahydrofuran in 71% theoretical yield; b.p. 88.0–89.0° (20 mm.); f.p. −16.53°; $n^{20}D$ 1.5190; d^{20} 1.8269; estimated purity 99.85 mole per cent. Thiacyclopentane was prepared from this dibromide by Method I in 91% yield.

2-Methylthiacyclopentane

2-Methyltetrahydrofuran.—Commercial 2-methylfuran was hydrogenated at 175–185° using a Raney nickel cata-

(1) Presented before the Petroleum Division of the American Chemical Society at the 117th National Meeting, Houston, Texas, March, 1950.

(2) E. H. Thierry, *J. Chem. Soc.*, **127**, 2756 (1925).

(3) Microanalyses by Weiler and Strauss, Oxford.

(4) After complete removal of the cyclic sulfide, a thick oil remained in the flask. This material would not crystallize nor would it distil under a pressure of 1 mm. but began to decompose at around 250°. It is probably a linear polymer due to intermolecular condensation.

lyst and the 2-methyltetrahydrofuran fractionated in a 50-plate column; b.p. 79.9–80.1°; $n^{20}D$ 1.4063; d^{20} 0.8604; f.p. −137.2°; estimated purity 95.0 mole per cent.

1,4-Dibromopentane.—From 2-methyltetrahydrofuran in 71% yield; b.p. 94–96° (20 mm.); $n^{20}D$ 1.5086; d^{20} 1.6861; f.p. −34.42°; estimated purity 99.0 mole per cent. 2-Methylthiacyclopentane was prepared from this dibromide by both methods I and II in approximately 90% yield.

3-Methylthiacyclopentane

Methylsuccinic Acid and Ester.—Ethyl crotonate (b.p. 137°, $n^{20}D$ 1.4249), prepared by continuous esterification of solid crotonic acid, was converted into methylsuccinic acid by the method given in reference 5. The acid was converted to the diethyl ester by continuous esterification and the crude ester fractionated in a 100-plate column: b.p. 109° (18 mm.); $n^{20}D$ 1.4185; $n^{20}C$ 1.4165; $n^{20}F$ 1.4238; d^{20} 1.0110.

2-Methylbutane-1,4-diol.—Methylsuccinic ester was reduced with hydrogen using 10% by weight of a standard copper–chromite catalyst. The yield of fractionated diol was 57%; b.p. 132.0° (15 mm.); $n^{20}D$ 1.4490; $n^{20}C$ 1.4467; $n^{20}F$ 1.4544; d^{20} 0.9909.

2-Methyl-1,4-dibromobutane.—From the diol in 71% yield after fractionation in a 20-plate column; b.p. 90–92° (18 mm.); $n^{20}D$ 1.5128; d^{20} 1.7115. 3-Methylthiacyclopentane was prepared from the dibromide by Method I in 82% yield.

cis- and *trans*-2,5-Dimethylthiacyclopentanes

2,5-Dimethyltetrahydrofuran (Mixture of *cis*- and *trans*-Isomers).—By hydrogenation of the 2,5-dimethylfuran with a Raney nickel catalyst; b.p. 90.5–91.0°; $n^{20}D$ 1.4043; d^{20} 0.8321.

***meso*- and *racemic*-2,5-Dibromohexane.**—2,5-Dimethyltetrahydrofuran was hydrobrominated by the usual method to give a 73% yield of dibromohexanes (2760 g.). This product was then fractionated under reduced pressure in a 40-plate glass-packed column. All the fractions having cloud points[6] above −20° were bulked with the residue and cooled to −30°. The solid was filtered off and crystallized three times from petroleum ether. The yield of purified solid *meso*-2,5-dibromohexane[7] was 342 g., b.p. 103–104° (24 mm.); m.p. 38.37°; estimated purity 99.85 mole per cent.

Anal. Calcd. for $C_6H_{12}Br_2$: C, 29.54; H, 4.95; Br, 65.51. Found: C, 29.6; H, 4.9; Br, 65.3.

The residual dibromohexane was fractionated through a 40-plate column. Fractions boiling at 108° at 30 mm. pressure with refractive indices of 1.5006 to 1.5009 and cloud point of −44 to −47° were bulked. The purity of this bulk, which was used for cyclization, was 96–97 mole per cent. For the determination of physical properties, a small quantity of purified racemic form was obtained by recrystallization from ether at −60 to −70° and subsequent distillation at reduced pressure. Properties of purified *racemic*-2,5-dibromohexane: b.p. 108–109° (30 mm.); $n^{20}D$ 1.5007; $n^{20}C$ 1.4975; $n^{20}F$ 1.5088; d^{20} 1.5788; f.p. −44.64°; estimated purity 99.7 mole per cent.

Anal. Calcd. for $C_6H_{12}Br_2$: C, 29.54; H, 4.95; Br, 65.51. Found: C, 29.6; H, 5.1; Br, 65.8.

***meso*- and *racemic*-2,5-Dichlorohexanes.**—A mixture of the *meso* and racemic forms of 2,5-dichlorohexane was prepared by hydrochlorination of diallyl (*vide infra*) by the procedure of crystallization and fractionation. Relatively pure *meso*-2,5-dichlorohexane was separated from this mixture; b.p. 109° (99 mm.); $n^{20}D$ 1.4491; d^{20} 1.0488; m.p. 19.88°; estimated purity, 99.90 mole per cent.

Anal. Calcd. for $C_6H_{12}Cl_2$: C, 46.46; H, 7.80; Cl, 45.74. Found: C, 46.6; H, 8.0; Cl, 45.4.

The residual dichlorohexane was refractionated in a 40-plate column. Fractions boiling at 106° at 90 mm. with refractive index $n^{20}D$ 1.4484 and cloud point between −32 and −35° were bulked to give the *racemic*-2,5-dichlorohexane which was used for cyclization (approximate purity, 96–97 mole per cent.). A small sample of this material was recrystallized from ether at −60 to −70° and had the following physical properties: b.p. 106° (91 mm.); $n^{20}D$ 1.4484; d^{20} 1.0474; f.p. −38.36°; estimated purity 99.4 mole per cent.

Anal. Calcd. for $C_6H_{12}Cl_2$: C, 46.46; H, 7.80; Cl, 45.74. Found: C, 46.7; H, 7.8; Cl, 45.9.

The *cis* and *trans* isomers of 2,5-dimethylthiacyclopentane were prepared from the *meso* and racemic dihalides, respectively, by Method I using 100% excess of sodium sulfide.

Thiacyclohexane

Tetrahydropyran.—The commercial material was purified by fractionation: b.p. 87.9–88.1°; $n^{20}D$ 1.4210; d^{20} 0.8849; f.p. −48.79; estimated purity 99.70 mole per cent.

1,5-Dibromopentane.—From tetrahydropyran in 81.5% yield; b.p. 107.8–108.0° (20 mm.); $n^{20}D$ 1.5126; d^{20} 1.7030; m.p. −39.39°; estimated purity 99.95 mole per cent. Thiacyclohexane was obtained from this dibromide by Method II in 80% yield.

2-Methylthiacyclohexane

Diallyl.—Diallyl was prepared from allyl chloride in 62% yield.[8]

5-Chlorohexene-1.—5-Chlorohexene-1 together with a mixture of the *meso* and racemic forms of 2,5-dichlorohexane, was synthesized by a modification of the method of Cortese.[9] The monochloro compound was separated from the dichlorohexanes by distillation under reduced pressure in a 20-plate column and the chlorohexene purified by refractionation at atmospheric pressure. Properties of 5-chlorohexene-1; b.p. 120.7–120.8°; $n^{20}D$ 1.4305; d^{20} 0.8934.

Anal. Calcd. for $C_6H_{11}Cl$: C, 60.76; H, 9.34; Cl, 29.90. Found: C, 60.6; H, 9.3; Cl, 29.6.

1-Bromo-5-chlorohexane.—From 5-chlorohexene-1 by the addition of hydrogen bromide under peroxide conditions in the presence of ultraviolet light in 80% yield. Fractionation of the product at 5 mm. pressure served to remove a small amount of the lower boiling 2-bromo-5-chlorohexane. Properties of 1-bromo-5-chlorohexane: b.p. 60° (2.5 mm.); $n^{20}D$ 1.4786; d^{20} 1.3322 and of 2-bromo-5-chlorohexane; b.p. 58° (2.5 mm.); $n^{20}D$ 1.4749; d^{20} 1.3178.

Anal. Calcd. for $C_6H_{12}Br{\cdot}Cl$: C, 36.11; H, 6.06; halogen, 57.83. Found for 1-bromo-5-cyclohexane: C, 36.0; H, 6.2; halogen 57.9.

2-Methylthiacyclohexane was prepared from 1-bromo-5-chlorohexane by Method I using 100% excess sodium sulfide in 54% yield.

3-Methylthiacyclohexane

1-Methylglutaric Acid and Ester.—By condensation of diethyl malonate (1 mole) in sodium ethoxide, prepared from sodium (1 atom) and specially dried ethanol (280 g.) with methyl methacrylate (1 mole) followed by hydrolysis and decarboxylation. The diethyl ester was prepared from the acid by continuous esterification and fractionation. Properties of 1-methylglutaric ester: b.p. 136.0° (30 mm.); $n^{20}D$ 1.4228; d^{20} 0.9999; yield of ester based on malonate and methyl methacrylate, 55%; m.p. of acid obtained by hydrolysis of fractionated ester 77–78° (cor.).

2-Methylpentane-1,5-diol.—By hydrogenation of the methylglutaric ester with copper–chromite catalyst in 84% yield; b.p. 132° (10 mm.); $n^{20}D$ 1.4527; d^{20} 0.9719.

Anal. Calcd. for $C_6H_{14}O_2$: C, 60.97; H, 11.94. Found: C, 60.9; H, 11.9.

2-Methyl-1,5-dibromopentane.—From the diol in 84% yield by hydrobromination; b.p. 117.0° (21 mm.); $n^{20}D$ 1.5082; d^{20} 1.6125. 3-Methylthiacyclohexane was prepared from this dibromide by Method II in 82% yield.

Anal. Calcd. for $C_6H_{12}Br_2$: C, 29.54; H, 4.95; Br, 65.51. Found: C, 29.9; H, 5.3; Br, 65.5.

4-Methylthiacyclohexane

5-Methylcyclohexane-1,3-dione.—This cyclic diketone was prepared by the method of Crossley and Renouf[10] in 57% yield.

(5) H. Adkins, "Organic Syntheses," Vol. 26, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 54.

(6) In this work the cloud point is the temperature at which, on melting the solid, the last crystal of solid disappears and the liquid becomes clear.

(7) J. Wislicenus, *Ber.*, **34**, 2656 (1901).

(8) R. L. Shriner, "Organic Syntheses," Vol. 27, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 7.

(9) F. Cortese, THIS JOURNAL, **52**, 1519 (1930).

(10) A. W. Crossley and N. Renouf, *J. Chem. Soc.*, **107**, 602 (1915).

TABLE I

PHYSICAL CONSTANTS AND PURITIES OF THE CYCLIC SULFIDES

Sulfide	Thiacyclopentane	2-Methylthiacyclopentane	3-Methylthiacyclopentane	*cis*-2,5-Dimethylthiacyclopentane	*trans*-2,5-Dimethylthiacyclopentane	Thiacyclohexane	2-Methylthiacyclohexane	3-Methylthiacyclohexane	4-Methylthiacyclohexane
B.p., °C.	121.2	132.4	138.2	60.0 (45 mm.)	58.0 (44 mm.)	141.6	55.0 (26 mm.)	157.9	54.0 (22 mm.)
M.p., °C.	−96.06	−100.71	−81.16	−89.4	−76.35	19.07	−58.14	−60.17	−28.11
Estimated for zero impurity									
Cryoscopic const. deg.$^{-1}$	0.021	0.035	0.027	0.037	0.019	0.0054[a]	0.028	0.033	0.025
d^{20}, g./ml.	0.9998	0.9552	0.9634	0.9222	0.9188	0.9856	0.9428	0.9473	0.9471
d^{25}, g./ml.	0.9947	0.9512	0.9585	0.9177	0.9142	0.9810	0.9381	0.9430	0.9427
$n^{20}D$	1.5047	1.4909	1.4924	1.4799	1.4776	1.5067	1.4905	1.4922	1.4923
$n^{25}D$	1.5022	1.4884	1.4902	1.4774	1.4752	1.5041	1.4881	1.4899	1.4899
$n^{20}C$[b]	1.5013	1.4877	1.4892	1.4768	1.4746	1.5035	1.4874	1.4891	1.4892
$n^{25}C$[b]	1.4989	1.4853	1.4871	1.4744	1.4722	1.5009	1.4849	1.4868	1.4868
$n^{20}F$[b]	1.5128	1.4985	1.5000	1.4873	1.4850	1.5147	1.4981	1.4998	1.4999
$n^{25}F$[b]	1.5102	1.4962	1.4978	1.4848	1.4827	1.5121	1.4956	1.4975	1.4975
$n^{20}e$[b]	1.5076	1.4935	1.4951	1.4825	1.4802	1.5096	1.4932	1.4948	1.4949
$n^{25}e$[b]	1.5050	1.4911	1.4929	1.4800	1.4778	1.5070	1.4907	1.4925	1.4925
$n^{20}g$[b]	1.5193	1.5048	1.5062	1.4934	1.4910	1.5211	1.5042	1.5059	1.5060
$n^{25}g$[b]	1.5166	1.5022	1.5038	1.4907	1.4885	1.5185	1.5015	1.5037	1.5037
Est. purity, mole %	99.7	99.75	99.7	99.3	99.3	99.90	99.2	99.8	99.8

[a] This cryoscopic constant was measured by contaminating the compound with a known amount of impurity. The remainder were calculated from the heats of fusion which were determined as described in Part 1 of this series. [b] The wave lengths (Å.) of these lines were: c 6562 (hydrogen), F 4861 (hydrogen), e 5460 (mercury), g 4358 (mercury).

TABLE II

PROPERTIES OF THE SULFONES, METHIODIDES AND MERCURIC CHLORIDE DERIVATIVES OF THE CYCLIC SULFIDES

Sulfide	Sulfone[a] m.p., °C. (cor.)	Methiodide volatilization temp., °C.	Mercuric chloride derivative M.p., °C. (cor.)	Formula	Analyses, % Calculated C	H	S	Found C	H	S
Thiacyclopentane	28.86[b]	190	127–128	$C_4H_8S\cdot HgCl_2$	13.35	2.24	8.91	13.5	2.3	7.4
2-Methylthiacyclopentane	−22 (1.4810)	149–154	162	$C_5H_{10}S\cdot 2HgCl_2$	9.3	1.56	..	9.3	1.5	...
3-Methylthiacyclopentane	+0.5 (1.4770)	129.5 (m.p.)	109.5	$C_5H_{10}S\cdot HgCl_2$	16.06	2.70	8.57	15.8	2.7	8.2
cis-2,5-Dimethylthiacyclopentane	−4 (1.4761)	140–142	180	$C_6H_{12}S\cdot 2HgCl_2$	10.93	1.83	4.86	10.9	1.9	4.7
trans-2,5-Dimethylthiacyclopentane	+3 (1.4760)	141–143	110–111	$C_6H_{12}S\cdot HgCl_2$	18.11	3.04	8.06	18.8	3.1	8.3
Thiacyclohexane	97	174–176	138–139	$C_5H_{10}S\cdot HgCl_2$	16.06	2.70	8.57	16.2	2.7	8.3
2-Methylthiacyclohexane	65–66	164–169	102	$C_6H_{12}S\cdot HgCl_2$	18.58	3.11	8.27	18.4	3.1	8.4
3-Methylthiacyclohexane	83	.....[c]	136	$C_6H_{12}S\cdot HgCl_2$	18.58	3.11	8.27	18.7	3.2	7.3
4-Methylthiacyclohexane	121.5	175–180	135–136	$C_6H_{12}S\cdot HgCl_2$	18.58	3.11	8.27	18.8	3.1	8.2

[a] The figures in parentheses are the refractive indices of the liquid sulfones ($n^{20}D$). [b] Estimated melting point for zero impurity. [c] No solid derivative formed.

2-Methylglutaric Acid and Ester.—From the diketone by oxidation with alkaline sodium hypochlorite in 95% yield[11]; m.p. of 2-methylglutaric acid obtained by hydrolysis of the fractionated ester 84–85° (cor.). Continuous esterification of the acid gave the diethyl ester which was fractionated in a 100-plate column at 30 mm. pressure; b.p. 136° (30 mm.); $n^{20}D$ 1.4239; d^{20} 0.9999.

3-Methylpentane-1,5-diol.—By hydrogenation of the ester with a copper–chromite catalyst in 70% yield; b.p. 134° (9 mm.); $n^{20}D$ 1.4534; d^{20} 0.9738.

Anal. Calcd. for $C_6H_{14}O_2$: C, 60.97; H, 11.94. Found: C, 61.0; H, 12.1.

3-Methyl-1,5-dibromopentane.—From the diol in 84% yield by hydrobromination; b.p. 116–117° (20 mm.); $n^{20}D$ 1.5084; d^{20} 1.6135. 4-Methylthiacyclohexane was obtained from this dibromide by Method I in 80% yield.

Anal. Calcd. for $C_6H_{12}Br_2$: C, 29.54; H, 4.95; Br, 65.51. Found: C, 29.7; H, 5.1; Br, 65.3.

Physical Constants of the Cyclic Sulfides.—As in the case of the alkane sulfides and disulfides, considerable difficulty has been experienced in determining the freezing points and purities of these compounds. In the majority of cases too, a considerable number of determinations were necessary before liquid–solid equilibria were established to enable satisfactory curves to be drawn. The physical constants and purities of the cyclic sulfides are given in Table I.

(11) G. Komppa, *Ber.*, **32**, 1421 (1899).

Preparation of Derivatives

(a) **Mercuric Chloride Complexes.**—These derivatives were prepared by adding the cyclic sulfides (0.025 mole) to mercuric chloride (0.125 mole) dissolved in ethanol (100 ml.) refluxing the solution for 30 minutes, cooling and filtering. The solid derivatives were crystallized to a constant melting point from ethanol. It was found necessary to dry these complexes simply by exposure of small portions to the atmosphere for a short time since it was observed that drying the samples *in vacuo* in many cases tended to remove a certain amount of the sulfide. By this method it was possible to obtain derivatives of constant melting point and composition from each individual sulfide. The melting points and analyses of the mercuric chloride derivatives are given in Table II.

(b) **Methiodides.**—Solutions of the cyclic sulfides (0.057 mole) and methyl iodide (0.063 mole) in ethanol (25 ml.) were refluxed for a period of 90 minutes. The methiodides which were crystallized twice from ethanol were all solids except that from 3-methylthiacyclohexane.

Only one of these derivatives, that from 3-methylthiacyclopentane was found to melt normally, the remainder all volatilized over a distinct range. These volatilization temperatures are recorded in Table II.

(c) **Sulfones.**—The cyclic sulfides (0.06 mole) were dissolved in glacial acetic acid (110 ml.) and hydrogen peroxide (57 ml. of 30% w/w, 0.53 mole) was added with shaking and cooling. After allowing to stand for 24 hours the sul-

fones were isolated in the usual manner and, where solid, were crystallized to constant melting point from ethanol. The properties of the sulfones are given in Table II.

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Nitrogen Mustards

BY EVELYN WILSON AND MAX TISHLER

A number of new compounds belonging to the general class of nitrogen mustards have been synthesized for testing as chemotherapeutic agents against neoplastic diseases.

The discovery of nitrogen mustards (I) as chemotherapeutic agents in the treatment of certain neoplastic diseases[1-7] prompted a coöperative reasearch program with the Sloan–Kettering Institute for Cancer Research in order to explore further the potentialities of nitrogen mustards.

We have prepared a large number of nitrogen mustards and related compounds, which have been screened at the Sloan–Kettering Institute. Since the biological data of many of these compounds have been and are being reported,[8] the chemical data are now presented.

We have mainly been interested in synthesizing compounds that are structural variants of the effective nitrogen mustard N-methyl-β,β'-dichlorodiethylamine (I, R = CH_3).[1-6] Formula II represents the generalized structure of a nitrogen

$$\underset{\text{I}}{R{-}N{-}(CH_2CH_2Cl)_2} \qquad \underset{\text{II}}{R{-}N(CH_2CH(X)Y)_2}$$

mustard when X = Cl, Y = H. Table I lists the compounds that have a variation of this basic structure. The variations in general were limited to: (1) a change in the nature of the R– group; (2) the introduction into the molecule of an additional β,β'-dichlorodiethylamino group; (3) substitution of the β-chloro-*n*-propyl group (X = Cl, Y = CH_3) for the usual β-chloroethyl group (X = Cl, Y = H); (4) introduction of an additional β,β'-dichlorodipropylamino group into the molecule; (5) substitution of bromine for chlorine; (6) substitution of fluorine for chlorine; and some of the compounds of course show a combination of these structural variations.

A number of other compounds (Table II) were also synthesized. These compounds, although they are not represented by the nitrogen mustard formula II, are related to that class of compounds.

The compounds listed in Table I, except N-*n*-butyl-β,β'-difluorodiethylamine hydrochloride, were prepared by the action of a thionyl halide on the corresponding aminoalcohol or on its halogen acid salt (Table Ia).

N-*n*-Butyl-β,β'-difluorodiethylamine hydrochloride (XXXI) was prepared from the condensation of β-fluoroethyl bromide with *n*-butylamine. Both the mono- (XLV) and disubstituted (XXXI) product form. The two compounds can

$$n\text{-}C_4H_9NH_2 + 2BrCH_2CH_2F \xrightarrow[2.\ HCl]{1.\ K_2CO_3\text{–}C_6H_6} \begin{cases} \longrightarrow n\text{-}C_4H_9NHCH_2CH_2F\cdot HCl \quad \text{(XLV)} \\ \longrightarrow + n\text{-}C_4H_9N(CH_2CH_2F)_2\cdot HCl \quad \text{(XXXI)} \end{cases}$$

be effectively separated however by fractional crystallization of their hydrochlorides from benzene.

The intermediate aminoalcohols that were not commercially available were generally obtained by the condensation of the appropriate alkyl halide and dialkanolamine. The intermediate aminoalcohol whenever possible was purified either by distillation or by conversion into its halogen acid

$$RX + NH(CH_2CHOHY)_2 \xrightarrow[K_2CO_3]{EtOH}$$

$$R{-}N(CH_2CHOHY)_2 \xrightarrow{SOX_2} RN(CH_2CHY)_2\cdot HX \quad (X\ \text{below}\ CHY)$$

X = Cl, Br Y = H, CH_3

salt. Whenever either method of purification was not practicable, the crude condensation product was used for the halogenation reaction.

Experimental

The nitrogen mustard-free bases are strong vesicants and are therefore preferably isolated as salts. The salts, although their vesicant action is considerably less than that of the free bases, are sufficiently vesicant to make their handling somewhat hazardous. Handling of these compounds should always be done in a well-ventilated hood; and use of rubber gloves is also recommended. A 3% solution of sodium thiosulfate or potassium permanganate should be used immediately if any spilling or splashing does occur. Precautions should also always be taken to prevent any solid particles of the compound from coming in contact with the eyes.

Procedures for the preparation of specific compounds are described. These procedures however also illustrate the general methods used for the synthesis of the other compounds. The reagents needed, the amount of halogenating reagent required, and the solvent used for crystallization will of course vary for the particular compound being prepared. The tables provide this information. The precursors of the compounds shown in Tables I and II, and their mode of synthesis, are listed in Tables Ia and IIa,

(1) Gilman and Philips, *Science*, **103**, 409 (1946).
(2) Goodman, *et al.*, *J. Am. Med. Assoc.*, **132**, 126 (1946).
(3) Jacobson, *et al.*, *ibid.*, **132**, 263 (1946).
(4) Rhoads, *ibid.*, **131**, 656 (1946).
(5) Tafel, *Yale J. Biol. Med.*, **19**, 971 (1947).
(6) Ap Thomas and Cullumbine, *Lancet*, **1**, 899 (1947).
(7) *J. Am. Med. Assoc.*, **135**, 98 (1947).
(8) Burchenal, *et al.*, *Cancer Res.*, **8**, 385, 387 (1948); **9**, 553 (1949); *Cancer*, **1**, 399 (1948); **2**, 1 (1949); Burchenal, *Radiology*, **50**, 494 (1948); Stock, *Am. J. Med.*, **8**, 658 (1950).