tropanyl ester. This phenomenon may be associated with some geometrical interaction of the two phenyl groups with the large tropanol ring.

Acknowledgment.—We wish to thank Dr. Monis Manning for the analysis of infrared spectra, and Dr. Franklin J. Rosenberg, Sterling-Winthrop Research Institute, for preliminary pharmacological data. The study of absorption of drugs in tumors was supported at the Massachusetts General Hospital by grants from the U. S. Atomic Energy Commission, U. S. Public Health Service, and the John A. Hartford Foundation, Inc.

Tertiary Phosphines and Phosphine Oxides Containing a 2-Haloethyl Group[1]

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Received December 16, 1965

2-Haloethylphosphines and -phosphine oxides may be considered as phosphorus analogs of nitrogen mustards. Heretofore, tertiary phosphine oxides containing a 2-haloethyl group have attracted interest as intermediates for the synthesis of the corresponding vinyl derivatives, which can function as monomers in the synthesis of organophosphorus polymers or copolymers. The existing methods for synthesis of the phosphine oxides, as well as the phosphines, are few in number. The preparation of only one monofunctional 2-haloethyl tertiary phosphine has been described,[2,3] and in that instance the compound was not obtained in pure form. Abbiss, *et al.*,[4] have described the synthesis of a bifunctional phosphorus mustard, bis(2-chloroethyl)-phenylphosphine oxide, which was obtained in analytical purity, and a related phosphine, bis(2-chloroethyl)-phenylphosphine, which was not isolated in pure form. Earlier, Hitchcock and Mann[2] obtained bis(2-bromoethyl)phenylphosphine hydrobromide as an impure gum. Three synthetic pathways have been reported[5-9] for the monofunctional 2-haloethylphosphine oxides, but only two of these have been used to obtain pure specimens. Because of our interest in obtaining the phosphines and phosphine oxides as characterizable products that could be evaluated biologically, we have investigated several routes for their preparation.

As mentioned, Hitchcock and Mann[2] reported the only 2-haloethyl tertiary phosphine heretofore appearing in the literature, 2-bromoethylethylphenylphosphine, as an uncharacterized liquid that was quaternized to a diphosphonium dibromide. We have synthesized 2-chloroethyldiphenylphosphine (I) by addition of lithium diphenylphosphide to excess 1,2-dichloroethane in tetrahydrofuran solution (eq 1). The compound was obtained as a low-melting solid of analytical purity after vacuum distillation and crystallization from petroleum ether. Addition of 1,2-dichloroethane to the phosphide gave only ethylenebis(diphenylphosphine). Earlier, we had synthesized 2-ethoxyethyldiphenylphosphine (II) by treatment of lithium diphenylphosphide with 2-chloroethyl ethyl ether and expected to prepare the 2-haloethylphosphine (I) by cleavage of the ether linkage followed by halogenation. However, we abandoned further investigation of the latter route since I was obtained by the direct method.

$$(C_6H_5)_3P \xrightarrow[THF]{Li} [(C_6H_5)_2PLi] \xrightarrow[THF]{ClCH_2CH_2X} (C_6H_5)_2PCH_2CH_2X + LiCl \quad (1)$$

I, X = Cl
II, X = OC_2H_5

We have used two synthetic pathways to obtain 2-haloethyl tertiary phosphine oxides in analytical purity. 2-Bromoethyldi-*sec*-butyl- and -diphenylphosphine oxides (III and IV, respectively) were conveniently prepared by means of the Michaelis–Arbuzov reaction between excess 1,2-dibromoethane and the appropriate ethyl disubstituted phosphinite (eq 2).

$$R_2PCl + EtOH \xrightarrow{Et_3N} R_2POEt \xrightarrow[\Delta]{BrCH_2CH_2Br} BrCH_2CH_2P(O)R_2 \quad (2)$$

III, R = *sec*-C_4H_9
IV, R = C_6H_5

Ethylenebis(disubstituted phosphine oxides) were obtained in low yield as by-products. This method was reported by Rabinowitz and Pellon[5] who did not attempt purification of the 2-bromoethyl derivatives but dehydrohalogenated them in order to obtain the corresponding vinyl compounds for polymerization studies. Hellmann and Bader[6] prepared 2-chloroethyldiphenylphosphine oxide as a crystalline solid by the rearrangement of bis(chloromethyl)diphenylphosphonium chloride in aqueous solution, and Kabachnik and co-workers[7] and Cooper[8] prepared the same compound in the pure state by the Michaelis–Arbuzov rearrangement of 2-chloroethyl diphenylphosphinite. Miller[9] reported the preparation of $R_2P(O)CH_2CH_2X$ (R = C_2H_5, C_6H_5, and *n*-C_8H_{17}; X = halogen) by the latter method and their conversion to the corresponding vinyl derivatives but gave no indication as to whether the 2-haloethyl compounds were obtained in pure form.

Our second method, which was used to synthesize 2-bromoethyldimethylphosphine oxide (V) in low yield, is represented by eq 3. Decomposition of the phosphine oxide–magnesium salt complex under mild conditions gave difficultly purifiable mixtures, whereas isolation of 2-ethoxyethyldimethylphosphine oxide (VI) was readily accomplished when the Grignard mixture

(1) This investigation was supported by the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. PH-43-64-51, and by the C. F. Kettering Foundation.

(2) C. H. S. Hitchcock and F. G. Mann, *J. Chem. Soc.*, 2081 (1958).

(3) Many primary, secondary, and tertiary phosphines have been synthesized in which a halogen is substituted in the 2 position of alkyl groups bonded to phosphorus. The majority of these are polyhalogenated ethyl or higher alkyl derivatives, however, and only the compound reported by Hitchcock and Mann[2] can be properly categorized as a 2-haloethyl tertiary phosphine. Compound I is the only example of a phosphine of the type $R_2PCH_2CH_2$-halogen (R = alkyl or aryl) and 2-bromoethylethylphenylphosphine[2] is the only example of a phosphine of the type $RR'PCH_2CH_2$-halogen (R and R′ = alkyl or aryl but R ≠ R′).

(4) T. B. Abbiss, A. H. Soloway, and V. H. Mark, *J. Med. Chem.*, **7**, 763 (1964).

(5) R. Rabinowitz and J. Pellon, *J. Org. Chem.*, **26**, 4623 (1961).

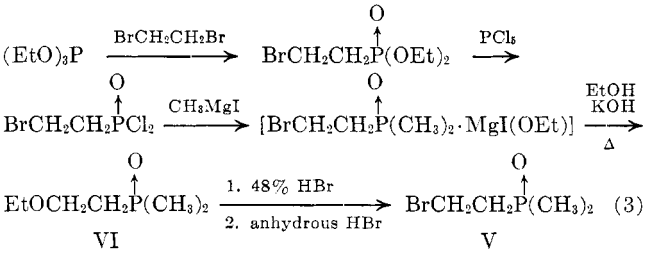
(6) H. Hellmann and J. Bader, *Tetrahedron Letters*, 724 (1961).

(7) M. I. Kabachnik, T. Ya. Medved, Yu. M. Polikarpov, and K. S. Yudina, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1584 (1962).

(8) R. S. Cooper, U. S. Patent 3,035,096 (May 15, 1962); *Chem. Abstr.*, **57**, 13805*h* (1963).

(9) R. C. Miller, Abstracts of Papers, 140th National Meeting of the American Chemical Society, Chicago, Ill., 1961, p 43Q.

was decomposed with hot, alcoholic potassium hydroxide. A low yield (20%) of dimethylvinylphosphine oxide (VII) was obtained when the Grignard mixture was decomposed at 0° instead of at reflux temperature. Presumably, the bromoethyl derivative is first dehydrohalogenated to the vinyl analog which then adds ethanol in alcoholic potassium hydroxide at the elevated temperature. Kabachnik and co-workers[7] produced the related 2-ethoxyethyldiphenylphosphine oxide by treating diphenylvinylphosphine oxide with ethanol containing potassium hydroxide.



(3)

Biological Data.—2-Chloroethyldiphenylphosphine (I) displayed cytotoxic activity at a concentration of 100 μg/ml against Eagle's KB cells, and ethylenebis(diphenylphosphine) was active down to a concentration of 0.1 μg/ml. Cell growth in these tests was less than 50% of the growth of the controls. Certain of the compounds have been tested in one or more of four tumor systems. Sarcoma 180: Compound I was toxic at 300 mg/kg/day but nontoxic and inactive at 150 mg/kg/day, and IV was toxic at 500 mg/kg/day but nontoxic and inactive at 250 mg/kg/day. Ethylenebis(diphenylphosphine) was active in the initial test at 250 mg/kg/day, but the activity was not confirmed upon further testing. Walker 256: Compound III was toxic at a dose of 250 mg/kg/day but nontoxic and inactive at 125 mg/kg/day. Compound IV showed marginal activity in one test at a dose level of 250 mg/kg/day. Adenocarcinoma 755: Compound IV was inactive at 375 mg/kg/day. Ethylenebis(diphenylphosphine) was marginally active in one test at 400 mg/kg/day. Leukemia L1210: Compound I was inactive at a dose level of 120 mg/kg/day, and ethylenebis(diphenylphosphine) was inactive at 400 mg/kg/day.

Experimental Section

Melting points were determined with a Kofler Heizbank melting point apparatus, unless otherwise noted, and are corrected. Boiling points are uncorrected. Infrared spectra were determined with a Perkin-Elmer Model 221G or 521 spectrophotometer.

2-Chloroethyldiphenylphosphine (I).—Lithium diphenylphosphide[10] (0.1 mole) in 200 ml of tetrahydrofuran was added dropwise with stirring over a period of 3 hr to 300 ml of 1,2-dichloroethane, which was cooled in an ice bath. The addition was somewhat irregular because of precipitated solids in the lithium phosphide solution. The reaction mixture was left in the ice bath and stirred overnight, allowing the temperature to rise from 0° to room temperature. Tetrahydrofuran and excess 1,2-dichloroethane were removed by evaporation *in vacuo* at room temperature. Chloroform (100 ml) was added to the residue, and 100 ml of water was rapidly added dropwise and with vigorous stirring. The organic layer was separated and evaporated to dryness *in vacuo*. Trituration of the residue with petroleum ether (bp 30–60°) while cooling on Dry Ice produced a solid (28 g, wet) that was collected on a cold filter and then distilled *in vacuo*. After removal of a forerun, the fraction boiling at 132–146° (0.2–0.5 mm) was collected and redistilled, giving a fraction with a boiling range of 110–117° (0.05 mm), which crystallized in the receiver upon cooling to room temperature. An analytical sample was obtained by crystallization from petroleum ether; mp 40–42° (uncor) (determined with Mel-Temp melting point apparatus); yield, 2.2 g (9%); $\tilde{\nu}_{max}$ (in cm^{-1}) 3075, 3050, 3030 (w), 3005 (w), 2960 (w), 1590, 1480, 1430, 1295, 750, 735, 690. All operations were performed under a nitrogen atmosphere.

Anal. Calcd for $C_{14}H_{14}ClP$: C, 67.61; H, 5.59; Cl, 14.3; P, 12.5. Found: C, 67.84; H, 5.76; Cl, 14.4; P, 12.2.

Reversing the order of addition of the reactants resulted in the formation of **ethylenebis(diphenylphosphine)**,[11] mp 143°. Issleib and co-workers reported mp 159–161°[11a] and 161–163°[11c] whereas Hewertson and Watson reported 143–144°.[11b]

Anal. Calcd for $C_{26}H_{24}P_2$: C, 78.38; H, 6.07; P, 15.55. Found: C, 78.65; H, 6.09; P, 15.1.

2-Ethoxyethyldiphenylphosphine (II).—A solution of 2-chloroethyl ethyl ether (21.7 g, 0.2 mole) in 65 ml of tetrahydrofuran was added over a period of 25 min to a tetrahydrofuran solution of lithium diphenylphosphide[10] (0.1 mole), which was cooled in an ice bath. The mixture was refluxed for 45 min and then stirred overnight at room temperature. All operations were performed under a nitrogen atmosphere. The product was isolated by treatment of the reaction mixture with 100 ml of water, separation of the upper phase, and distillation *in vacuo*. Crude II (18.7 g, 72%) was collected in the boiling range 101–150° (0.08 mm). An analytical sample was obtained after two fractional distillations using a Vigreux column; bp 131–135° (0.09 mm); $\tilde{\nu}_{max}$ (in cm^{-1}) 3075, 3060, 2980, 2935, 2870, 1590, 1480, 1440, 1100 ($-CH_2OCH_2-$), 740, 695.

Anal. Calcd for $C_{16}H_{19}OP$: C, 74.40; H, 7.41; P, 11.99. Found: C, 74.40; H, 7.41; P, 12.22.

2-Bromoethyldi-*sec*-butylphosphine Oxide (III).—A solution of di-*sec*-butylphosphinous chloride[12] (26.3 g, 0.146 mole) in 25 ml of ether was added dropwise and with stirring over a period of 1 hr to a solution of 6.7 g of ethanol (0.146 mole) and 11.5 g of pyridine (0.146 mole) in 150 ml of ether, which was cooled in an ice bath and maintained under a nitrogen atmosphere. The mixture was left in the ice bath and stirred overnight allowing the temperature to rise from 0° to room temperature. The precipitated amine salt was removed by filtration, and the filtrate was concentrated by evaporation using a water aspirator. The residue was filtered again to remove a trace of solid and distilled to afford 22.2 g (80%) of ethy di-*sec*-butylphosphinite, bp 67–72° (4 mm). The phosphinite (21 g, 0.11 mole), which was used without further purification, was added, with vigorous stirring, over a period of 30 min to 340 ml of refluxing 1,2-dibromoethane (4.4 moles) under a nitrogen atmosphere. The solution was refluxed for 30 min after the phosphinite addition during which time 4 ml of ethyl bromide was collected in a Dean–Stark trap (theory, 8.2 ml). Excess 1,2-dibromoethane was removed by evaporation *in vacuo* with mild heating leaving a syrupy residue; yield 24 g (81%); Br, 29.1. An analytical sample was obtained by vaporization under high vacuum at 86–124° (0.15 μ); $\tilde{\nu}_{max}$ (cm^{-1}) 2970, 2940, 2880 (CH); 1460 (s), 1375 (m), 1230 (m), 1200 (s) (P=O), 1105 (m), 1045 (m), 980 (s), 850 (m).

Anal. Calcd for $C_{10}H_{22}BrOP$: C, 44.62; H, 8.24; Br, 29.7; P, 11.51. Found: C, 44.54; H, 8.26; Br, 29.7; P, 11.76.

2-Bromoethyldiphenylphosphine oxide[5] **(IV)** was prepared following the procedure described above for III. During removal of excess 1,2-dibromoethane, the product IV (61%, mp 119–122°) crystallized and was collected. Further concentration to dryness and crystallization of the residue from benzene afforded a second crop of IV, thereby making the crude yield almost quantitative. An analytical sample was obtained following three recrystallizations from benzene; mp 128–129°.

Anal. Calcd for $C_{14}H_{14}BrOP$: C, 54.42; H, 4.57; Br, 25.87; P, 10.00. Found: C, 54.66; H, 4.59; Br, 25.7; P, 10.2.

A small amount of **ethylenebis(diphenylphosphine oxide)**[13] was isolated from the reaction residue and was identified by its

(10) A. M. Aguiar, J. Beisler, and A. Mills, *J. Org. Chem.*, **27**, 1001 (1962).

(11) (a) K. Issleib and D. W. Müller, *Ber.*, **92**, 3175 (1959); (b) W. Hewertson and H. R. Watson, *J. Chem. Soc.*, 1490 (1962); (c) K. Issleib, K. Krech, and K. Gruber, *Ber.*, **96**, 2186 (1963).

(12) W. Voskuil and J. F. Arens, *Rec. Trav. Chim.*, **82**, 302 (1963).

(13) (a) K. Issleib and D. W. Müller, *Ber.*, **92**, 3175 (1959); (b) G. M. Kosolapoff and R. F. Struck, *J. Chem. Soc.*, 2423 (1961); (c) M. I. Kabachnik, T. Ya. Medved, Yu. M. Polikarpov, and K. S. Yudina, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 2029 (1961); (d) P. T. Keough and M. Grayson, *J. Org. Chem.*, **27**, 1817 (1962); (e) A. M. Aguiar and J. Beisler, *ibid.*, **29**, 1660 (1964); (f) L. D. Quin and H. G. Anderson, *ibid.*, **29**, 1859 (1964).

infrared spectrum and melting point (270–272°). Reported melting points for the compound are 252–254,[13a] 276–278,[13b] 269–270,[13c] 273–275,[13d] 267–268.5,[13e] and 273°.[13f]

2-Ethoxyethyldimethylphosphine Oxide (VI).—Methylmagnesium iodide was prepared from 10.2 g of Mg and 60 g of methyl iodide in 250 ml of ether. 2-Bromoethylphosphonic dichloride[14] (43 g) in 50 ml of ether was added dropwise with stirring at room temperature over a period of 1.5 hr, and the mixture was stirred overnight at room temperature. Ethanolic KOH (60 g in 2000 ml of ethanol) was added with vigorous stirring, and $Mg(OH)_2$ was removed by filtration. The basic filtrate was refluxed 1 hr, neutralized with concentrated HCl, and filtered, and the filtrate was concentrated *in vacuo*. Distillation *in vacuo* gave 2-ethoxyethyldimethylphosphine oxide (VI), yield 15.3 g (54%), bp 98–101° (0.5 mm). An analytical sample was obtained by redistillation *in vacuo* through a Vigreux column; yield 9.6 g, bp 104–105° (1.5 mm).

Anal. Calcd for $C_6H_{15}O_2P$: C, 47.99; H, 10.07; P, 20.63. Found: C, 47.99; H, 10.05; P, 20.74.

2-Bromoethyldimethylphosphine Oxide (V).—2-Ethoxyethyldimethylphosphine oxide (VI) (5.1 g) was refluxed with stirring for 4 hr with 20 ml of 48% HBr. The solution was concentrated by distillation at atmospheric pressure, and the last traces of water were removed by evaporation *in vacuo*. The residue in chloroform solution was treated with anhydrous HBr (passed rapidly into the solution) for 4 hr at reflux. After cooling, the lower layer was separated and distilled *in vacuo;* the fraction that boiled in the range 101–122° (0.07–0.5 mm) was collected. The distillate (crystallized in the receiver) was sublimed *in vacuo*, and the sublimate was crystallized three times from $CHCl_3$ (3, 1, and 1 ml); yield 450 mg (7%), mp 89–90°.

Anal. Calcd for $C_4H_{10}BrOP$: C, 25.96; H, 5.41; Br, 43.20; P, 16.73. Found: C, 25.76; H, 5.58; Br, 43.37; P, 16.53.

Dimethylvinylphosphine Oxide (VII).—Treatment of methylmagnesium iodide (0.18 mole) with 2-bromoethylphosphonic dichloride[14] (0.09 mole) as described for VI followed by decomposition of the cold (0°) reaction mixture with alcoholic KOH, filtration, neutralization of the filtrate with concentrated HCl, filtration, and concentration of the filtrate *in vacuo* gave a syrupy residue that was distilled *in vacuo*. A fraction was collected with bp 68–69° (1.6 mm); yield 1.83 g (20%); $\bar{\nu}_{max}$ (in cm^{-1}) 3080, 3030, 2990, 2970, 2905 (CH including $CH{=}CH_2$), 1615, 1400 ($-CH{=}CH_2$), 1295 (PCH_3), 1165 ($P{=}O$); positive test for unsaturation with $KMnO_4$.

Anal. Calcd for C_4H_9OP: P, 29.74. Found: P, 29.99.

Acknowledgment.—The authors express their appreciation to Dr. J. A. Montgomery for encouragement in this work and to Drs. W. J. Barrett, W. C. Coburn, Jr., P. D. Sternglanz, and members of the Analytical Section of Southern Research Institute who performed the spectral and microanalytical determinations reported. Some of the microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. Tumor and tissue culture test data were obtained by the Chemotherapy Division of Southern Research Institute under the direction of Drs. F. M. Schabel, Jr., W. R. Laster, Jr., and G. J. Dixon.

(14) G. M. Kosolapoff, *J. Am. Chem. Soc.*, **70**, 1971 (1948); P. A. Rossiiskaya and M. I. Kabachnik, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 389 (1947).

Glycerol 1,3- and 1,2,4-Butanetriol 1,4-Bismethanesulfonates

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Received December 15, 1965

The title compounds were prepared for antitumor screening. Especially 1,2,4-butanetriol 1,4-bismethanesulfonate is closely related to both busulfan and L-threitol 1,4-bismethanesulfonate;[1] the latter compound possesses antineoplastic activity[2] and has recently been clinically compared[3] with busulfan. The (*S*)-1,2,4-butanetriol derivative was prepared from diethyl L-maleate. After protection of the hydroxy group the synthesis was based on the principle described[1b] for L-threitol 1,4-bismethanesulfonate from diethyl 2,3-*O*-isopropylidene-L-tartrate.

Screening of these bismethanesulfonates by the Cancer Chemotherapy National Service Center, National Institutes of Health, has revealed no significant inhibition of cell growth in the KB cell culture system. For DL- and (*S*)-butanetriol bismethanesulfonate a summary of the test data in the Walker carcinoma system is presented in Table I. The glycerol derivative was completely inactive in this system.

TABLE I

SCREENING DATA IN THE WALKER CARCINOSARCOMA 256 (SUBCUTANEOUS) SYSTEM FOR DL- AND (*S*)-1,2,4-BUTANETRIOL 1,4-BISMETHANESULFONATE

Config	Daily dose, mg/kg[a]	Survivors	Mean tumor weight (test/control), %[b]	ED_{90},[c] mg/kg/day
DL	200	6/6	0	
	100	6/6	0	
	50	5/6	14	57
	25	6/6	93	
(*S*)	200	6/6	0	
	100	5/6	8	
	50	4/6	78	96
	25	2/6	---	

[a] Administered intraperitoneally once daily, days 1 through 5 postinoculation. [b] Sacrificed and evaluated 10 days postinoculation. [c] The dose that inhibits growth to 10% of control growth.

Experimental Section[4]

Glycerol 1,3-Bismethanesulfonate.—A mixture of 1,3-dibromo-2-propanol (21.6 g), silver methanesulfonate (42 g), and acetonitrile (100 ml) was refluxed for 18 hr. After filtration from silver bromide (33 g) and evaporation *in vacuo*, the residue was extracted with acetone leaving unreacted silver methanesulfonate. Addition of 10 *N* ethanolic HCl (0.1 ml), filtration (decolorizing carbon), evaporation, and recrystallization from ethanol (120 ml, 99.9%) yielded the crude material (7 g), mp 66–67°. Several recrystallizations from ethanol (99.9%) gave the colorless analytically pure compound, mp 66–67°.

Anal. Calcd for $C_5H_{12}O_7S_2$: C, 24.19; H, 4.87; S, 25.83. Found: C, 24.29; H, 4.95; S, 25.85.

DL-1,2,4-Butanetriol 1,4-Bismethanesulfonate.—To a solution of 1,4-dibromo-2-butanone[5] (40 g) in diethyl ether (250 ml), a solution of $NaBH_4$ (2.2 g) in cold water (40 ml) was added dropwise while stirring at 5–8°. The reaction mixture was stirred for an additional 2 hr to attain room temperature. The organic layer was washed with water, dried ($MgSO_4$), and fractionated *in vacuo*, resulting in slightly impure 1,4-dibromo-2-butanol (24.5 g), bp 110–116° (10 mm). This product (23 g) was treated with silver methanesulfonate for 4 hr as described for 1,3-dibromo-2-propanol. After evaporation of the acetone solution crystallization was effected by treatment with a mixture of diethyl ether–acetone (9:1); yield 7.2 g, mp 72.5–73.5° (ethanol, 99.9%).

(1) (a) P. W. Feit, *Tetrahedron Letters*, 716 (1961); (b) *J. Med. Chem.*, **7**, 14 (1964).

(2) (a) R. Jones, W. B. Kessler, H. E. Lessner, and L. Rane, *Cancer Chemotherapy Rept.*, **10**, 99 (1960); (b) F. R. White, *ibid.*, **24**, 95 (1962).

(3) V. Loeb, Jr., *ibid.*, **42**, 39 (1964).

(4) Analyses by G. Cornali and W. Egger of these laboratories. Melting points were rounded off to half degrees, using a Hershberg apparatus with thermometers subdivided in 0.1°.

(5) J. R. Catch, D. F. Elliot, D. H. Hey, and E. R. H. Jones, *J. Chem. Soc.*, 278 (1948).