NOTES.

1042. *Molecular Weights of Mercuric Halides in Acetone.*

By (Mrs.) R. S. Satchell.

We recently suggested that acetone and nitrobenzene solutions of the mercuric halides may contain small amounts of mercuric halide dimers.[1] Experiments which superficially appear to support this suggestion have been made by Bhagwat and Tosniwal, who determined the molecular weight of mercuric chloride in acetone ebullioscopically[2] and found 336·7, 323·3, and 314·9 (calc., 271·5). However, their respective solutions contained 4·6576, 6·2784, and 8·2386 g. of mercuric chloride in 19·42 g. of acetone, and dimerisation would lead to an *increase* in the experimental molecular weight with increase in concentration. Moreover their weight fraction of solute was high for ebullioscopy, but no indication was given as to whether this was allowed for in calculation. We have remeasured the molecular weight of mercuric chloride, and also those of the bromide and the iodide, in acetone.

The molecular weights of mercuric chloride, bromide, and iodide found osmotically, and for the chloride ebullioscopically, are summarised in the Table. The solubility of mercuric iodide in acetone is too low for ebullioscopy.

For mercuric chloride both the ebullioscopic molecular weight of 272·0 $\pm$ 2·6 and the osmotic value of 270·5 $\pm$ 2·6 indicate that in the concentration range used (0·04—0·25M) its extent of dimerisation in acetone at 56 and 37° is insignificant. These results are incompatible with those of Bhagwat and Tosniwal, so we consider that their values for the molecular weight of mercuric chloride in other solvents must be treated with reserve.

[1] Satchell, *J.*, 1963, 5963.
[2] Bhagwat and Tosniwal, *J. Indian Chem. Soc.*, 1942, **19**, 492.

The results in the Table indicate that mercuric bromide and iodide are also inappreciably dimerised in acetone at 37° under our conditions.

Molecular weights of mercuric chloride, bromide, and iodide in acetone.

All the errors quoted are standard deviations.

(*a*) Osmotic measurements at 37°.

$[HgCl_2]$ (M)	0·038	0·054	0·079
M.W.	270·4 ± 2·3	270·9 ± 2·7	269·9 ± 2·0
No. of measurements	17	18	7

Mean M.W. $HgCl_2$ = 270·5 ± 2·6.

$[HgBr_2]$ (M)	0·034	0·054	0·078
M.W.	359·5 ± 3·5	358·8 ± 3·7	360·0 ± 3·1
No. of measurements	11	7	6

Mean M.W. $HgBr_2$ = 359·4 ± 3·7.

$[HgI_2]$ (M)	0·021	0·027
M.W.	454·1 ± 3·5	450·9 ± 4·0
No. of measurements	12	5

Mean M.W. HgI_2 = 453·2 ± 5·3

(*b*) Ebullioscopic measurements at 56°.

$[HgCl_2]$ (M)	0·10—0·25
M.W.	272·0 ± 2·6

Experimental.—Materials. Mercuric chloride (AnalaR; m. p. 281°) and iodide (Harrington, reagent grade; m. p. 254·5—255·0°) were used without further purification. Mercuric bromide (Hopkin and Williams, reagent grade), sublimed *in vacuo*, had m. p. 238·5—239·5°. Gravimetric analysis of the chloride and bromide for mercury (as sulphide) indicated that their respective purities were 100·1 and 99·7%. Analysis of the iodide for iodine by Medvedoskii's method [3] gave its purity as 99·9%. Azobenzene (B.D.H., chromatographic standard) was used without further purification. Naphthalene (B.D.H.) and triphenylmethane (B.D.H.) were recrystallised. They had m. p. 80 and 93°, respectively. AnalaR acetone, distilled from Drierite, had b. p. 56·4°/760 mm.

Molecular-weight determination. Osmotic measurements were made with a Mechrolab vapour pressure osmometer. Azobenzene and triphenylmethane were used as standards. The standardisation with azobenzene was carried out before, and that with triphenylmethane after, the mercuric halide measurements. Molecular weights for the mercuric halides based on the two standards agreed within ±0·5%. Instrumental readings for a particular solution were reproducible to within approximately ±1%.

Ebullioscopic measurements (five) were made over a range of concentrations (0·10—0·25M) with a Gallenkamp semimicro ebulliometer.[4] Naphthalene was used to determine the relevant ebullioscopic constant.

I thank Dr. A. G. Davies for providing an osmometer for preliminary measurements.

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[3] Medvedovskiĭ, *Aptechnoe Delo*, 1958, **7**, 17 (*Chem. Abs.*, 1959, **53**, 19670g).
[4] Heitler, *Analyst*, 1958, **83**, 223.

1043. *Oxidation of Isobutene over Copper.*

By R. S. Mann and D. Rouleau.

The vapour-phase catalytic oxidation of propene and higher olefins has received little attention, which is surprising since studies of these substances in solution have proved very rewarding. Gas-phase oxidation of isobutene has been investigated recently by Skirrow and Williams.[1] Though a qualitative study of the gas-phase oxidation of four carbon hydrocarbons has been made by Bretton, Wan, and Dodge [2] on vanadium pentoxide under conditions leading to complete oxidation, no information is available about the kinetics and activation energy of the reaction. We now describe some interesting facts observed during the kinetic investigation of the vapour phase oxidation of isobutene over a pumice supported copper catalyst.

The copper oxide catalyst containing 0·025 g.-atom of copper/gm. pumice was prepared by impregnating and evaporating solutions containing the calculated weight of AnalaR copper nitrate hexahydrate on 20—40 mesh crushed pumice stone. The impregnated material was dried overnight at 105°, and calcined at 550° for 6 hours. Isobutene and oxygen were purified by conventional methods, and stored in glass reservoirs. The kinetics were investigated in a 100 ml. cylindrical Pyrex vessel containing 0·4665 g. of catalyst sample, and attached to a standard vacuum system. Oxygen was always added first, since the addition of isobutene first reversibly poisoned the catalyst surface.

The rates of the oxidation of isobutene were calculated from pressure–time data obtained by measuring pressure changes by a mercury manometer. Below 300°, no reaction between isobutene and oxygen was observed, even after several hours, but at above 330° the rate could be conveniently measured. In the absence of the catalyst, no measurable reaction was observed up to 400°. Contrary to the observation of Skirrow and Williams [1] that during the gas-phase oxidation of isobutene a pressure decrease precedes the region of pressure increase with time, only a decrease in pressure with time was always observed for butene–oxygen ratios between 0·7 and 2·5 for catalytic oxidation.

The order of reaction was first in oxygen and zero in isobutene, as determined for the catalyst between 360 and 400°, the runs being performed in random order to nullify effects of changes in catalyst activity. The rate expression is:

$$-\mathrm{d}p/\mathrm{d}t = k(\mathrm{O_2})^1\ (iso\text{-}\mathrm{C_4H_8})^0$$

The effect of temperature is shown in the Table. The plot of $\log_{10}k$ against $1/T$°K was a good straight line, giving an activation energy of 21·65 ± 0·05 kcal./mole.

Temp.	340°	360°	380°	400°	410°
10^2k (sec.$^{-1}$)	0·343	0·557	1·04	1·59	2·10

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[*Received, January 6th*, 1964.]

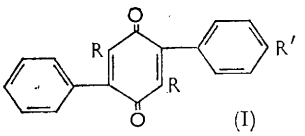
[1] Skirrow and Williams, *Proc. Roy. Soc.*, 1962, *A*, **268**, 537.
[2] Bretton, Wan, and Dodge, *Ind. Eng. Chem.*, 1952, **44**, 594.

1044. *Potential Anti-tumour Agents. Part III.*[1] *Polyporic Acid Series.*

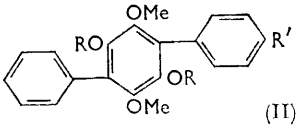
By B. F. Cain.

Because of the anti-tumour activity of certain quinones containing " alkylating " groups [2] and the decided activity of certain 4-(di-2-chloroethylamino)phenylalkanoic acids,[3] it was thought to be of interest to prepare a di-2-chloroethylamino-derivative of polyporic acid which itself shows experimental anti-tumour activity.[4]

The more direct methods of synthesis [1,5] were not used since a stable diazonium salt could not be obtained from *p-NN*-di-(2-chloroethyl)phenylenediamine—an observation originally made by Ross and Warwick.[6] Nor could any useful product be isolated from the attempted coupling of 2-phenyl-3,6-dichloro-1,4-benzoquinone and diazotized *p-NN*-di-(2-hydroxyethyl)phenylenediamine. The nitrophenylquinone (I, R′ = NO_2, R = Cl) was readily obtained by standard methods,[1] and mild alkaline hydrolysis afforded the corresponding dihydroxyquinone. Direct reduction of the latter gave an easily oxidized aminoquinol of little use for synthetic work, and reduction of the acetyl derivative of the hydroxy-quinone gave a product only slightly more stable. The most acceptable intermediates were found to be those in which the quinone hydroxyls were masked by methylation. The dimethyl ether of the nitroquinone (I; R = OCH_3, R′ = NO_2) could not be



(I)



(II)

prepared by normal alkylation procedures but was easily obtained by reaction of the corresponding dichloroquinone with the theoretical quantity of sodium methoxide. Reduction of the dimethoxyquinone with sodium borohydride gave an easily oxidizable quinol which was immediately acetylated to yield the stable diacetate (II; R = $COCH_3$, R′ = NO_2). Reduction of this compound with dithionite afforded the amine (II; R = $COCH_3$, R′ = NH_2) which, without further purification, reacted with ethylene oxide to afford the highly crystalline diethanolamine II; R = $COCH_3$, R′ = $N(CH_2CH_2OH)_2$. Alkaline hydrolysis of this intermediate in a reducing medium followed by oxidation with ferric ion yielded the dimethoxy-quinone [I; R = OCH_3, R′ = $N(CH_2CH_2OH)_2$]. Treatment of the diethanolamine derivative with phosphorus oxychloride in chloroform solution followed by acid hydrolysis gave a complex mixture from which a small quantity of a compound with the required elementary analysis and the characteristic properties of a polyporic acid derivative was isolated by chromatography. It was not obtained when thionyl chloride or phosphorus pentachloride replaced phosphorus oxychloride.

When administered to mice bearing the acute lymphocytic leukæmia, L1210, a statistically significant prolongation of life was observed but only at dose levels which markedly depressed gain in body weight and less than that observed with polyporic acid itself.

Experimental.—*3,6-Dimethoxy-5-(4-nitrophenyl)-2-phenyl-1,4-benzoquinone.*—Interaction of diazotized *p*-nitroaniline and 3,6-dichloro-2-phenyl-1,4-benzoquinone in sodium acetate buffered

[1] Part II, *J.*, 1963, 356.
[2] Domagh, *Annals N.Y. Acad. Sci.*, 1958, **68**, 1197.
[3] Ross, Davis, Roberts, and Everett, *British Empire Cancer Campaign Ann. Rep.*, 1952, **30**, 25.
[4] Burton and Cain, *Nature*, 1959, **184**, 1326.
[5] Part I, *J.*, 1961, 936.
[6] Ross and Warwick, *J.*, 1956, 1364.

solution essentially as detailed for other members of this series,[1,4] yielded **3,6-*dichloro*-5-(4-*nitrophenyl*)-2-*phenyl*-1,4-*benzoquinone***, m. p. >360° (Found: C, 57·9; H, 2·7; N, 3·4. $C_{18}H_9Cl_2NO_4$ requires C, 57·8; H, 2·4; N, 3·7%).

Treatment of the dichloro-quinone with sodium hydroxide yielded the ***dihydroxy-quinone***, m. p. 249—250° (Found: C, 64·4; H, 3·1. $C_{18}H_{11}O_6N$ requires C, 64·1; H, 3·3%). Reaction of the dichloro-quinone (0·348 g.) in benzene (15 ml.) with a solution of sodium (0·05 g.) in methanol (2·5 ml.) and working up gave the ***dimethoxy-quinone*** (0·28 g.), m. p. 182—183° (Found: C, 65·7; H, 4·4; N, 3·7. $C_{20}H_{15}NO_6$ requires C, 65·7; H, 4·1; N, 3·8%).

3,6-*Dimethoxy*-5-(4′-*nitrophenyl*)-2-*phenylquinol diacetate*.—The methoxy-quinone (1 g.) was suspended in 95% aqueous methanol (10 ml.) and sodium borohydride (0·104 g.) added; the solution was briefly boiled, cooled, and 2 ml. of a solution of acetic acid (0·82 ml.) in methanol (10 ml.) added. A further portion of sodium borohydride (0·104 g.) was added, the solution boiled briefly, and the product precipitated by the addition of excess of 2N-hydrochloric acid. This quinol could be crystallized from aqueous acetic acid but the process was wasteful and much reverted to the quinone. Accordingly the vacuum-dried quinol was acetylated by solution in acetic anhydride (10 ml.) containing 72% perchloric acid (0·02 ml.). Precipitation with water after ½ hr. gave the *acetate*, which crystallized from aqueous acetic acid in plates (0·81 g.), m. p. 221—222° (Found: C, 64·0; H, 4·4; N, 3·5. $C_{24}H_{21}NO_8$ requires C, 63·8; H, 4·7; N, 3·1%).

5-(p-*Di*-2-*hydroxyethylaminophenyl*)-3,6-*dimethoxy*-2-*phenylquinol Diacetate*.—The above quinol diacetate (0·317 g.) was suspended in 60% aqueous ethanol (10 ml.), sodium dithionite (0·750 g.) added, and the mixture heated under reflux for 15 min. Water (15 ml.) precipitated the amine in a finely divided form, best collected by centrifugation. The free amine rapidly darkened in air and was best alkylated immediately or dissolved in acid solution. A suspension of the amine in acetic acid (10 ml.) plus water (5 ml.) was cooled to 0° and ethylene oxide (2 ml.) added. During several hours at room temperature the amine dissolved to yield a homogeneous solution; a further quantity of ethylene oxide (1 ml.) was then added and the solution kept overnight. Evaporation *in vacuo* yielded a thick gum which solidified on trituration with water; crystallization from aqueous acetic acid afforded the *product* as plates (0·160 g.), m. p. 226—227° (Found: C, 66·1; H, 5·7; N, 2·6. $C_{28}H_{31}NO_8$ requires C, 65·95; H, 6·1; N, 2·7%).

5-(p-*Di*-2′-*hydroxyethylaminophenyl*)-3,6-*dimethoxy*-2-*phenyl*-1,4-*benzoquinone*.—The corresponding quinol diacetate (0·161 g.) was dissolved in boiling ethanol (5 ml.) and sodium dithionite (0·15 g.) added. To the hot solution was added a solution of potassium hydroxide (0·15 g.) and sodium dithionite (0·15 g.) in water (2·5 ml.). The flask was firmly stoppered and shaken at room temperature for 2 hr. Concentrated hydrochloric acid (0·3 ml.) was added, and the quinol was precipitated with water, collected, washed well with water, and dissolved in acetic acid (2·5 ml.). Addition of a solution of ferric alum (0·35 g.) in water (2 ml.) precipitated the *quinone*. Crystallization from aqueous ethanol then aqueous acetic acid gave the pure quinone (0·098 g.) as orange plates, m. p. 251—252° (Found: C, 67·9; H, 5·6; N, 3·1. $C_{24}H_{25}NO_6$ requires, C, 68·1; H, 5·9; N, 3·3%).

5-(p-*Di*-2-*chloroethylaminophenyl*)-3,6-*dihydroxy*-2-*phenyl*-1,4-*benzoquinone*.—The substituted diethanolamine described above (2·2 g.) was suspended in freshly distilled alcohol-free chloroform (25 ml.) and phosphorus oxychloride (4·5 g.) added. The mixture was heated under reflux for 2 hr. and evaporated *in vacuo*. The resulting brown gum was dissolved in a mixture of methanol (25 ml.) and concentrated hydrochloric acid (5 ml.) which had been saturated with anhydrous calcium chloride, and the mixture boiled for 4 hr. After cooling, water (100 ml.) was added and the mixture extracted with benzene (5 × 25 ml.), a large amount of dark solid was unextracted. The extracts were washed with water, dried ($CaCl_2$), and evaporated *in vacuo* to small volume. The concentrated extract was applied to a column of silica gel (B.D.H. chromatographic grade 2 × 20 cm.) prepared in benzene. Elution with chloroform containing 20% of acetone removed a purple band, leaving more highly coloured materials on the column. Evaporation of the eluates followed by crystallization from small volumes of toluene gave clusters of microscopic needles (0·136 g.), m. p. >360°, which had the characteristic bronze lustre of polyporic acid derivatives. The quinone was immediately soluble in aqueous sodium hydrogen carbonate to give a permanganate-coloured solution (Found: C, 60·5, 60·7; H, 4·8, 4·9; N, 2·8; Cl, 15·7, 15·8. $C_{22}H_{19}Cl_2NO_4$ requires C, 61·1; H, 4·4; Cl, 16·4; N, 3·2%).

Biological tests were performed by staff of this laboratory. Microanalyses were made by Dr. A. D. Campbell, Microanalytical Laboratory, University of Otago. This research was totally supported by the Auckland Division of the New Zealand Branch of the British Empire Cancer Campaign Society (Inc.).

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1045. *Anhydrides of Aromatic Sulphonic Acids.*

By W. FLAVELL and N. C. ROSS.

THIS Paper reports the preparation of mixed anhydrides of acetic acid with benzene- and mesitylene-sulphonic acids, and also the disproportionation of the mixed anhydrides to sulphonic anhydrides.

Few systematic investigations have been reported on the synthesis and properties of aromatic sulphonic anhydrides.[1-7] Mixed carboxylic–sulphonic anhydrides were first prepared by Baroni [8] by the reaction of a sulphonyl chloride with silver acetate at 140°. Recently, Overberger and Sarlo [9] prepared similar compounds by reaction of benzoyl and propionyl chlorides with silver benzenesulphonate in acetonitrile. Olah and Kuhn [10] obtained low yields of mixed anhydrides by reaction of sulphonic acids with keten.

The disproportionation of mixed anhydrides is accelerated by acetonitrile, so that benzene- and mesitylene-sulphonic anhydrides are the major products when silver acetate is reacted with benzene- and mesitylene-sulphonyl chloride, respectively, in acetonitrile. Thermal disproportionation of mixed anhydrides is less satisfactory as a preparative method of sulphonic anhydrides, since the latter decompose to some extent at the disproportionation temperature.

Low-molecular-weight polymers, with degrees of polymerisation up to about ten, are formed by the pyrolysis of difunctional acetic–sulphonic mixed anhydrides. The molecular weight was deduced from the amount of acetic anhydride eliminated and from the acid equivalent of the polymer. Degradative reactions become important at about 150°, insoluble, infusible products being formed.

Experimental.—Reactions involving easily hydrolysable materials were carried out under dry, oxygen-free nitrogen. Manipulation of samples was carried out in a dry-box under nitrogen. Solvents were rigorously dried and distilled before use. Benzene-*m*-disulphonyl chloride was prepared by the chlorosulphonation of benzene in the presence of trichloroethylene.[11]

Acetic benzene-m-*disulphonic dianhydride*. Silver benzene-*m*-disulphonate (36·7 g.) was added in portions to acetyl chloride (110 g.) at −10°, heated under reflux for 6 hr., and silver chloride (20·8 g.) filtered off. A white solid (7·1 g.) crystallised out slowly from the concentrated solution. A further quantity (7·7 g.) was obtained by concentration of the mother-liquor. The combined products gave small crystals of the *dianhydride* (10·5 g.), m. p. 93—95°

[1] Hubner, *Annalen*, 1884, **223**, 244.
[2] Abrahall, *J.*, 1886, **49**, 692.
[3] Billeter, *Ber.*, 1905, **38**, 2016.
[4] Meyer and Schlegl, *Monatsh.*, 1913, **34**, 569; Meyer, *ibid.*, 1915, **36**, 721.
[5] Field, *J. Amer. Chem. Soc.*, 1952, **74**, 394.
[6] Lukashevich, *Doklady Akad. Nauk S.S.S.R.*, 1957, **114**, 1025.
[7] Khorana, *Canad. J. Chem.*, 1953, **31**, 585.
[8] Baroni, *Atti. Accad. naz. Lincei. Rend. Classe Sci. fis. mat. nat.*, 1933, **17**, 1081.
[9] Overberger and Sarlo, *J. Amer. Chem. Soc.*, 1963, **85**, 2446.
[10] Olah and Kuhn, *J. Org. Chem.*, 1962, **27**, 2667.
[11] G.P. 892,750/1953.

(decomp.) (from acetyl chloride), which deliquesced rapidly in the atmosphere and darkened on heating (Found: S, 19·9%; acid equiv., 82. $C_{10}H_{10}O_8S_2$ requires S, 19·9%; acid equiv., 80·6).

Acetic benzenesulphonic anhydride. (*a*) Silver benzenesulphonate (20·0 g.) was added in portions to acetyl chloride (125 ml.) at −10°, stirred and heated at reflux temperature for 4 hr., filtered, and acetyl chloride removed from the combined filtrates by evaporation under reduced pressure. Approximately half of the residue was distilled at 0·1 mm. A small sample (0·10 g.) of acetic benzenesulphonic anhydride (Found: acid equiv., 102. Calc.: 100) was collected at 65—75°/0·1 mm. It was noted, however, that acetic anhydride (collected in a condensation trap at −78°, and identified by the formation of acetanilide) was evolved when the bath temperature reached ~100°. A second fraction was collected at 130—140°/0·02 mm., this being a clear liquid which quickly crystallised in the receiver. The crystals had m. p. 50° raised by trituration with ice–water to 85° (benzenesulphonic anhydride [6] melts at 90°) (Found: acid equiv., 145. Calc. for benzene sulphonic anhydride: 149).

The undistilled portion of the product was pumped completely free of acetyl chloride under reduced pressure at 50°. The acid equivalent of the resulting red, mobile liquid was 98·5, confirming that the remaining product was the mixed anhydride (Calc. acid equivalent: 100).

(*b*) Silver acetate (24·0 g.) was added to a solution of benzenesulphonyl chloride (25·0 g.) in acetic anhydride (100 ml.) and the suspension was heated under reflux for 6 hr. The precipitate (19·1 g.) was filtered off, and the filtrate was distilled at 0·05 mm. No fraction was obtained in the boiling range expected for acetic benzenesulphonic anhydride,[8] but acetic anhydride condensed in the cold trap as the temperature of the liquid in the distillation flask rose above 100°. A distillate (5·0 g.), quickly solidifying in the condenser, was collected at 140—145°/0·05 mm., corresponding to benzenesulphonic anhydride, m. p. 86° (after trituration with ice–water) (Found: acid equiv., 154).

Acetic mesitylenedisulphonic dianhydride. (*a*) Acetyl chloride (120 g.), cooled to 5°, was added slowly to silver mesitylenedisulphonate (15·2 g.) in a flask immersed in a cooling bath at −20°. The reactants were stirred at room temperature for 1 hr., refluxed for 2 hr., the silver chloride (8·25 g.) was filtered off, and the filtrate concentrated. Large crystals (6·85 g., 61%) of the *dianhydride* separated on cooling. Recrystallisation from acetic anhydride gave large prisms, m. p. 89—94° in air and 92—93° *in vacuo*, with discolouration at 85° (Found: S, 17·4%; acid equiv., 90·2. $C_{13}H_{16}O_8S_2$ requires S, 17·6%; acid equiv., 91·0).

(*b*) A solution of mesitylenedisulphonyl chloride (7·87 g.) in acetic anhydride (75 ml.) was added to a suspension of silver acetate (9·00 g.) in acetic anhydride (75 ml.) and heated at 80° for 18 hr. The precipitate (7·79 g.) was mostly silver chloride mixed with some silver acetate. The acetic anhyride solution was concentrated to about 50 ml. by distillation under reduced pressure, the pot-temperature being kept below 80°. The product formed crystals (2·50 g., 27%), m. p. 94° *in vacuo* (from acetic anhydride) (Found: acid equiv., 90·2).

(*c*) Mesitylenedisulphonic acid (3·01 g.) was dissolved in acetic anhydride (50 ml.), and the solution was heated at 80—85° for 5 hr. and concentrated under reduced pressure at 80°. Large red-tinged crystals separated on cooling; these were filtered off and recrystallised from acetic anhydride yielding colourless prisms of the mixed anhydride (0·96 g.), m. p. 93—94° *in vacuo* (Found: acid equivalent, 91·2).

TABLE 1.

Pyrolysis of acetic benzene-*m*-disulphonic dianhydride.

No.	Dianhydride (A) (g.)	Temp.	Time (hr.)	Acetic anhydride (B) evolved (g.)	Molar ratio B/A
1	0·469	200°	4	0·132	0·89
2	0·503	143	72	0·110	0·69
3	0·557	120	96	0·151	0·85
4	0·351	110	120	0·101	0·91

Reaction of benzenesulphonyl chloride with silver acetate in acetonitrile. A solution of benzenesulphonyl chloride (5·15 g.) in acetonitrile (50 ml.) was refluxed for 15 hr. in the presence of silver acetate (5·44 g.). Silver chloride (3·40 g.) was filtered off and the solvent removed under reduced pressure. The residual liquid was distilled at 1 mm. No distillate was obtained below a bath temperature of 150°, but at 170—180° a clear liquid distilled over, b. p. 160—162°/1 mm., which quickly solidified in the condenser to a white solid, m. p. 75°. Trituration

of this product with ice–water and subsequent drying *in vacuo* gave crystals (2·0 g.), m. p. 90·0° (Found: acid equiv., 155). Benzenesulphonic anhydride is reported [1] to melt at 90°, b. p. 240°/10 mm.

Reaction of mesitylenesulphonyl chloride with silver acetate in acetonitrile. Silver acetate (2·97 g.) was added to a solution of mesitylenesulphonyl chloride (3·55 g.) in acetonitrile (50 ml.) and the mixture was heated under reflux for 16 hr. A further quantity (25 ml.) of acetonitrile was added, the precipitate (2·07 g.) was filtered off, and the filtrate evaporated to dryness under reduced pressure. Successive recrystallisation from chloroform and from diethylene glycol dimethyl ether gave mesitylenesulphonic anhydride (1·65 g.), m. p. and mixed m. p. 222—225° (decomp.) (lit.,[6] 225°) (Found: acid equivalent, 189·5. Calc.: 191).

Pyrolysis of acetic benzene-m-*disulphonic dianhydride.* Weighed samples of the mixed anhyride were pyrolysed in Pyrex tubes connected through a condensation trap to a vacuum system. The volatile condensible product was shown to be acetic anhydride by formation of acetanilide and infrared spectroscopy. The amount of acetic anhydride evolved at several temperatures is shown in Table 1.

In experiments 1 and 2 the residue was a black solid which adhered to the walls of the tube in a thin shiny layer. The solid was insoluble in common organic solvents, and was attacked only to a small extent by aqueous alkali. The product from experiments 3 and 4 was a black, plastic solid which softened at about 60°. It reacted slowly with water, forming an acidic solution, and was completely soluble in hot, aqueous 0·1N-alkali. The acid equivalents of samples 3 and 4 were 98 and 105, respectively.

Pyrolysis of acetic mesitylenedisulphonic dianhydride. Acetic mesitylenedisulphonic dianhydride evolved acetic anhydride slowly above its melting point (93—95°) leaving a black residue. The rate of elimination of acetic anhydride at 110° is shown in Table 2.

TABLE 2.

Pyrolysis of acetic mesitylenedisulphonic dianhydride.

Temp.	Dianhydride (A) (mmole)	Time (hr.)	Acetic anhydride (B) evolved (mmole)	Molar ratio B/A
110°	0·825	1	0·384	0·47
110	0·825	4	0·440	0·53
110	0·825	22	0·551	0·67
120	2·001	24	1·025	0·51
150	3·430	6	1·510	0·44

Extensive decomposition of the products was apparent at temperatures above 110°, this being denoted by the insolubility and infusibility of the residue as well as by the incomplete elimination of acetic anhydride.

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1046. *Electron Impact Fragmentation Patterns of Acetanilide and Benzamide.*

By J. L. Cotter.

The main features of the mass spectrum of acetanilide are shown in Table 1 which also includes for comparison the partial mass spectrum of aniline.[1] With the exception of the peak intensities at *m/e* **77**, the corresponding relative abundances below *m/e* **93** are reasonably identical. The mass spectrum of acetanilide shows a metastable peak at *m/e* 46·9:

$$46{\cdot}9\ (93^+) \longrightarrow 66^+ + 27$$

A metastable transition, giving rise to a peak at *m/e* 46·9 also occurs in the mass spectrum of aniline where it is attributed [1] to the fragmentation process:

$$C_6H_5{\cdot}NH_2^+ \longrightarrow C_5H_6^+ + HCN$$

These facts strongly suggest that the initial fragmentation of the acetanilide molecular ion involves a rearrangement, resulting in the formation of an aniline-type ion by rupture of the carbon–nitrogen bond, and concomitant transfer of a hydrogen atom to the nitrogen containing fragment:

$$CH_3{\cdot}CO{\cdot}NH{\cdot}C_6H_5^+ \longrightarrow C_6H_5{\cdot}NH_2^+ + CH_2{:}CO$$

The greater relative intensity of the peak at *m/e* **77** in the mass spectrum of acetanilide than in aniline is attributed to a contribution made to the ion intensity by the fragmentation process:

$$CH_3{\cdot}CO{\cdot}NH{\cdot}C_6H_5^+ \longrightarrow C_6H_5^+ + CH_3{\cdot}CO{\cdot}NH{\cdot}$$

The partial mass spectrum of benzamide is also shown in Table 1. Ion fragments of mass **76** could arise from the fragmentation process:

$$C_6H_5{\cdot}CONH_2^+ \longrightarrow C_6H_4^+ + H{\cdot}CONH_2$$

or from breakdown of a benzonitrile-type ion:

$$C_6H_5{\cdot}CN^+ \longrightarrow C_6H_4^+ + HCN$$

itself formed by rearrangement and fragmentation of the molecular-ion:

$$C_6H_5{\cdot}CONH_2^+ \longrightarrow C_6H_5{\cdot}CN^+ + H_2O$$

The occurrence of a metastable peak at *m/e* 56·1

$$56{\cdot}1\ (103^+) \longrightarrow 76^+ + 27$$

in the mass spectrum of benzamide supports the second process but does not discount a contribution from the first. However, Beynon *et al.*[2] report that in the mass spectrum of benzonitrile, the intensity of the $C_6H_4^+$ ion formed by loss of HCN from the benzonitrile molecular-ion, is 35% of the intensity of the base peak at *m/e* **103**, which is close to the value of 33% obtained for the relative intensity of $C_6H_4^+$ fragment ions in the mass spectrum of benzamide. This, suggesting that a benzonitrile-type ion is formed in large abundance from the benzamide molecular-ion:

$$C_6H_5{\cdot}CONH_2^+ \longrightarrow C_6H_5{\cdot}CN^+ \text{ (or } C_6H_5{\cdot}NC^+) + H_2O$$

Ionization and appearance potential results are shown in Table 2, from which the activation energies involved in the molecular-ion decomposition reactions may be estimated.

[1] Rylander, Meyerson, Eliel, and McCollum, *J. Amer. Chem. Soc.*, 1963, **85**, 2723.
[2] Beynon, Lester, and Williams, *J. Phys. Chem.*, 1959, **63**, 1861.

TABLE 1.

Partial mass spectrum of acetanilide, aniline, and benzamide (% relative intensity).

m/e	Acetanilide	Aniline	Benzamide	*m/e*	Acetanilide	Aniline	Benzamide
135	38·1			77	6·86	1·17	0·68
121			0·65	76	1·70	1·22	32·6
105			1·47	75			5·96
103			100·0	74			2·58
93	100·0	100·0		67	2·70	3·21	
92	7·94	10·8		66	29·6	32·4	
91	2·16	1·05		65	16·9	18·5	0·51
78	1·67	1·94		44			

TABLE 2.

Ionization and appearance potentials.

Molecule	*m/e*	Ion (singly charged positive ion)	I.P. or A.P. ev	No. of determinations
$CH_3{\cdot}CO{\cdot}NH{\cdot}C_6H_5$	135	$CH_3{\cdot}CO{\cdot}NH{\cdot}C_6H_5$	8·39 ± 0·10	3
$CH_3{\cdot}CO{\cdot}NH{\cdot}C_6H_5$	93	$C_6H_5{\cdot}NH_2$	8·88 ± 0·15	2
$C_6H_5{\cdot}CONH_2$	121	$C_6H_5{\cdot}CONH_2$	9·64	1
$C_6H_5{\cdot}CONH_2$	103	$C_6H_5{\cdot}CN$	10·19 ± 0·10	2

The difference between the ionization potential of the parent molecule and the appearance potential of the rearranged fragment ion gives activation energies of 0·49 ev for the formation of $C_6H_5{\cdot}NH_2^+$ from the acetanilide molecular-ion and 0·55 ev for the formation of $C_6H_5{\cdot}CN^+$ from the benzonitrile molecular ion.

Experimental.—Samples of acetanilide, m. p. 114°, and benzamide, m. p. 127°, were recrystallized from aqueous ethanol.

Ionization and appearance potentials were obtained from experimentally determined ionization efficiency curves by the method of Dibeler and Reese.[3] Argon was used to calibrate the electron energy scale in measurements on benzamide and its derived fragment ion; krypton was used in similar measurements on acetanilide. The mass spectra and ionization efficiency data were obtained with an A.E.I. mass spectrometer M.S.2-H.

ROYAL AIRCRAFT ESTABLISHMENT,
FARNBOROUGH, HANTS.

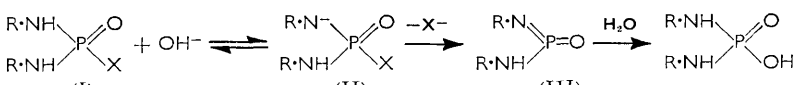
[*Received, January 29th*, 1964.]

[3] Dibeler and Reese, *J. Res. Nat. Bur. Stand.*, 1955, **54**, 127.

1047. *The Mechanism of the Alkaline Hydrolysis of* p-*Nitrophenyl* NN′-*Dimethyl- and* NN′-*Diphenyl-phosphorodiamidates.*

By D. B. COULT and M. GREEN.

WESTHEIMER suggested[1] that the high reactivity of *NN*′-dialkylphosphorodiamidic fluorides (I) (R = alkyl, X = F) in alkaline solution can be attributed to the importance of a mechanism involving preliminary removal of a proton followed by unimolecular decomposition of the conjugate base:



(I) (II) (III)

[1] Westheimer, *Chem. Soc.* "*Special Publ.*," No. 8, 1957, 181.

A similar mechanism has been suggested [2] for the 2,6-lutidine-catalysed hydrolysis of *NN'*-diethylphosphorodiamidic chloride (I) (R = Et, X = Cl). The postulated intermediate (III) is analogous to a metaphosphate which, it has been suggested,[3] is formed in various reactions of phosphonic and phosphoric acids.

The kinetics of the alkaline hydrolysis of *p*-nitrophenyl *NN'*-diphenyl- and *NN'*-dimethyl-phosphorodiamidate (II) (R = Ph or Me, X = *p*-nitrophenoxy) have now been studied and the effect of the addition of hydrogen peroxide on the rate of liberation of *p*-nitrophenoxide anion has been examined. The results are recorded in Tables 1 and 2.

Although the hydroperoxide anion HO_2^- is more reactive than the hydroxide anion in nucleophilic displacement reactions at the phosphoryl centre,[4] hydroperoxide is much less basic than hydroxide, and addition of hydrogen peroxide to a solution of sodium hydroxide converts all the hydrogen peroxide into hydroperoxide anion with a corresponding decrease in the hydroxide anion concentration. Therefore, if the alkaline hydrolysis of *p*-nitrophenyl *NN'*-dimethyl- and *NN'*-diphenyl-phosphorodiamidate proceeds exclusively by a mechanism that involves preliminary rapid formation of the conjugate base, addition of hydrogen peroxide to a reaction mixture containing either of the two esters and aqueous sodium hydroxide would decrease the rate of formation of the *p*-nitrophenoxide anion. This is because hydroxide anions would be replaced by hydroperoxide anions, which have a lower proton nucleophilicity. However, if a rate-enhancement occurs on addition of hydrogen peroxide, then reaction must take place by direct attack at the phosphoryl centre, *i.e.*, by an $S_N2(P)$ mechanism.

The addition of hydrogen peroxide to alkaline solutions of the above *p*-nitrophenyl esters enhances the rate of *p*-nitrophenoxide anion formation in both cases. At hydroxide concentrations above 10^{-3}M the rate of hydrolysis of the diphenyl compound is almost independent of hydroxide concentration, whereas that of the corresponding dimethyl derivative is linearly dependent on hydroxide concentration.

In view of the effect of the addition of hydrogen peroxide we suggest that both esters undergo alkaline hydrolysis by an $S_N2(P)$ mechanism. We further suggest that in the alkaline hydrolysis of the diphenyl compound an intermediate is rapidly and reversibly formed, and then decomposes slowly with loss of *p*-nitrophenoxide anion. This is supported by the observation that the ultraviolet spectrum of a freshly prepared alkaline solution of the diphenyl derivative contains a strong peak at 255 mμ, which is not present in the reactants or products. This peak decreased in intensity at approximately the same rate as that of the *p*-nitrophenoxide anion appeared. The presence of a strong peak in one of the products interfered with the 255 mμ peak, making accurate rate measurements impossible.

The kinetics of the hydrolysis of the diphenyl derivative can be interpreted on the basis of competing reactions, by an $S_N2(P)$ mechanism as indicated by the rate enhancement observed on addition of hydrogen peroxide, and by a mechanism involving unimolecular decomposition of the conjugate base.

Experimental.—Kinetic measurements. The rates of hydrolysis were measured in the thermostat-controlled cell of a Perkin-Elmer 137 spectrophotometer. The intensity of a peak at 410 mμ, which can be attributed to the *p*-nitrophenoxide anion, was observed. The results are recorded in Tables 1 and 2. First-order kinetics were obtained.

Preparation of materials. AnalaR propan-2-ol and distilled water were used in the preparation of the 1 : 1 v/v solvent mixture.

The following compounds were prepared by the method of Audrieth and Toy: [5] p-*Nitrophenyl*

[2] Crundon and Hudson, *J.*, 1962, 3591.
[3] Weimann and Khorana, *J. Amer. Chem. Soc.*, 1962, **84**, 4329; Todd, *Proc. Nat. Acad. Sci. U.S.A.*, 1959, **45**, 1389; Clark, Hutchinson, Kirby, and Todd, *J.*, 1961, 715; Clark and Warren, *Proc. Chem. Soc.*, 1963, 178.
[4] Green, Saville, Sainsbury, and Stansfield, *J.*, 1958, 1583.
[5] Audrieth and Toy, *J. Amer. Chem. Soc.*, 1942, **64**, 1337.

TABLE 1.

Rates of hydrolysis of *p*-nitrophenyl *NN'*-diphenylphosphorodiamidate (5×10^{-5}M) in 50/50 v/v aqueous propan-2-ol at 30·5°.

[NaOH] (M)	$[H_2O_2]$ (M)	k (min.$^{-1}$)	[NaOH] (M)	$[H_2O_2]$ (M)	k (min.$^{-1}$)	[NaOH] (M)	$[H_2O_2]$ (M)	k (min.$^{-1}$)
2×10^{-1}	—	0·066	1×10^{-1}	6×10^{-2}	0·600	5×10^{-3}	2×10^{-3}	0·058
,,	2×10^{-2}	0·177	5×10^{-2}	—	0·054	,,	4×10^{-3}	0·085
,,	4×10^{-2}	0·184	2×10^{-2}	—	0·046	$3·5 \times 10^{-3}$		0·023
,,	6×10^{-2}	0·315	1×10^{-2}	—	0·038	2×10^{-3}	—	0·0085
1×10^{-1}	—	0·060	,,	2×10^{-3}	0·076	6×10^{-4}	—	0·0039 *
,,	2×10^{-2}	0·230	,,	4×10^{-3}	0·094	2×10^{-4}	—	0·0017 *
,,	4×10^{-2}	0·418	5×10^{-3}	—	0·029			

* Calc. from observed second-order rate constants.

TABLE 2.

Rates of hydrolysis of *p*-nitrophenyl *NN'*-dimethylphosphorodiamidate (5×10^{-5}M) in 50/50 v/v aqueous propan-2-ol at 30·5°.

[NaOH] (M)	$[H_2O_2]$ (M)	k (min.$^{-1}$)	[NaOH] (M)	$[H_2O_2]$ (M)	k (min.$^{-1}$)	[NaOH] (M)	$[H_2O_2]$ (M)	k (min.$^{-1}$)
2×10^{-1}	—	1·35	2×10^{-2}	$1·5 \times 10^{-2}$	0·875	5×10^{-3}	—	0·050
1×10^{-1}	—	0·68	1×10^{-2}	—	0·083	1×10^{-3}	—	0·0086
5×10^{-2}	—	0·373	,,	2×10^{-3}	0·225	5×10^{-4}	—	0·0043
2×10^{-2}	—	0·181	,,	4×10^{-3}	0·368	1×10^{-4}	—	0·00086 *
,,	5×10^{-3}	0·460	,,	8×10^{-3}	0·590	5×10^{-5}	—	0·000435 *
,,	1×10^{-2}	0·600						

* Calc. from observed second-order rate constants.

NN'-diphenylphosphorodiamidate, recrystallised from 80% aqueous methanol, had m. p. 159° (Found: C, 58·3; H, 4·2. $C_{18}H_{16}N_3O_4P$ requires C, 58·5; H, 4·4). p-*Nitrophenyl NN'-dimethylphosphorodiamidate*, recrystallised from 80% aqueous methanol, had m. p. 46—48° (Found: C, 36·6; H, 5·6. $C_8H_{12}N_3O_4P \cdot H_2O$ requires C, 36·5; H, 5·4).

We thank Mr. R. L. Rickards for the preparation of the above compounds.

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1048. *Certain Factors Relating to the Formation of Alkyl and Aryl Sulphates and Chlorosulphates.*

By J. CHARALAMBOUS, M. J. FRAZER, and W. GERRARD.

ALKYL chlorosulphates containing alkyl groups of ordinary reactivity, *e.g.*, n-butyl, react too readily with pyridine for the use of the latter in their preparation or in that of alkyl sulphates.[1-4] Thus, the tertiary base, B, and the chlorosulphate, $RO \cdot SO_2 \cdot Cl$, (R = Me, B = NMe_3;[1] R = Et, B = C_5H_5N,[2] $C_6H_5NMe_2$;[3] R = $CH_3 \cdot CH \cdot CO_2Et$, B = C_5H_5N,

[1] Delepine and Demars, *Bull. Sci. pharmacol.*, 1923, **30**, 577.
[2] Baumgarten, *Ber.*, 1926, **59**, 1166.
[3] Willcox, *Amer. Chem. J.*, 1904, **32**, 446.
[4] Gerrard, *J.*, 1940, 218.

C_9H_7N [4]) afford the alkyl chloride and the adduct BSO_3. In the light of recent revelations on the prevalence of rearrangement of the alkyl group during the formation of alkyl halides,[5] the isomeric purity of the halide product required examination.

n-Butyl chlorosulphate reacted quickly with pyridine at −80° and afforded only n-butyl chloride, seemingly indicative of a non-carbonium cation mechanism,

$$Bu^nO{\cdot}SO_2{\cdot}Cl + C_5H_5N \longrightarrow Cl^- + [Bu^nO{\cdot}SO_2{\cdot}NC_5H_5]^+ \longrightarrow Bu^nCl + C_5H_5NSO_3,$$

a postulation supported by the data in Table 1. The isobutyl ester required a higher temperature (0°) for even slower reaction, and the product comprised isobutyl chloride (67%), t-butyl chloride (30%), and butenes (3%). The chlorosulphate from (−)-ethyl lactate quickly afforded the corresponding chloride at −80°, having the preponderantly inverted configuration, but showing some loss in optical purity. In conformity with the reduced reactivity of the C–O bond when R = $\cdot CH(CH_2Cl)_2$, reaction with this chlorosulphate was negligible during 12 hours at 0°, and required 3 days at 20°. The neopentyl ester reacted even more slowly at 20° (see Table 1).

When the carbon atom attached to oxygen has low susceptibility to nucleophilic attack, a tertiary base may be used in the preparation of chlorosulphates, and examples (where R in $RO{\cdot}SO_2{\cdot}Cl$ = $CH_2{\cdot}F_3C$, $CH_2{\cdot}Cl_3C$, Ph,[6] *o*-$C_6H_4{\cdot}Me$, *p*-$C_6H_4{\cdot}Me$, *o*-$C_6H_4{\cdot}F$) have now been prepared from the alcohol or the phenol by interaction with sulphuryl chloride in the presence of pyridine and solvent ether at −80°. Aryl chlorosulphates have previously been prepared in low yield and in an impure state from sulphuryl chloride and sodium aryloxide;[7] and trifluoroethyl chlorosulphate has been similarly prepared in 24% yield from the alkoxide.[8]

Experimental.—Interaction of tertiary base and chlorosulphate. The base (*ca.* 10 g., 1 mol.), in ether, chloroform, or pentane, was added slowly to the chlorosulphate (1 mol.) in the same solvent, whereupon at the temperature stated in Table 1, a precipitate formed. This was

TABLE 1.

Alkyl chlorides from the chlorosulphates, $RO{\cdot}SO_2{\cdot}Cl$.

R	Base	Reaction rate	Temp.	Volatile products
Bu^n	C_5H_5N	Rapid	−80°	Bu^nCl (only)
Bu^n	Et_3N	,,	−80	,,
Bu^i	C_5H_5N	Slow	0	Bu^iCl (67%), Bu^tCl (30%), butenes (3%)
$\cdot CH(CH_2Cl)_2$	,,	3 Days	20	$(ClCH_2)_2CHCl$ (only)
$\cdot CH(Me){\cdot}CO_2Et$ *	,,	Rapid	−80	$CH_3{\cdot}CHCl{\cdot}CO_2Et$ *
$\cdot CH_2{\cdot}CMe_3$	,,	Very slow	20	None

* Ethyl lactate, α_D^{19} −10·23° (l = 1) gave the chlorosulphate, b. p. 84—86°/1·5 mm., n_D^{15} 1·4307, α_D^{19} −89·50° (l = 1), which gave ethyl α-chloropropionate, b. p. 46°/20 mm., n_D^{21} 1·4160, α_D^{15} + 16·00° (l = 1); previously obtained [9] with α_D^{16} −21·8° (l = 1) from ROH α_D^{16} +11·2 (l = 1), representing near approach to optical purity.

filtered off and the volatile products were characterised by analysis, physical constants, and gas chromatography.

Preparation of chlorosulphates (Table 2). A mixture of the alcohol or the phenol (10—15 g., 1 mol.) and pyridine (1 mol.) in ether was added to sulphuryl chloride (1 mol.) in ether at −80°. The pyridinium chloride was filtered off, and the chlorosulphate distilled, after treatment with boron trichloride which removed hydroxy-compound and pyridine; but did not react with the chlorosulphates.[6]

[5] Gerrard and Hudson, *J.*, 1963, 1059.
[6] Charalambous, Davies, Frazer, and Gerrard, *J.*, 1962, 1505.
[7] Battegay and Denivelle, *Compt. rend.*, 1932, **194**, 1505; Lukashevich and Kurdyumova, *J. Gen. Chem.* (*U.S.S.R.*), 1948, **18**, 1963; Bollinger, *Bull. Soc. chim. France*, 1948, 156.
[8] Cohen, *J. Org. Chem.*, 1961, **26**, 4021.
[9] Gerrard and Richmond, *J.*, 1945, 853.

TABLE 2.

Chlorosulphates, $RO{\cdot}SO_2{\cdot}Cl$.

R	Yield (%)	B. p./mm.	n_D^{20}	d_4^{20}	Found (%) Cl	Found (%) S	Formula	Required (%) Cl	Required (%) S
$\cdot CH_2{\cdot}CF_3$	85	116—118°	1·3630	1·617	17·8	—	$C_2H_2ClF_3O_3S$	17·8 *	—
$\cdot CH_2{\cdot}CCl_3$ ...	86	86/15	1·4800	1·860	56·6	12·7	$C_2H_2Cl_4O_3S$	57·2	12·9
o-C_6H_4F	82	60/0·3	1·4972	1·472	16·7	15·1	$C_6H_4ClFO_3S$	16·8	15·2 †
o-$C_6H_4{\cdot}Me$ ...	59	65/0·1	1·5155	1·329	17·4	15·9	$C_7H_7ClO_3S$	17·2	15·5
p-$C_6H_4{\cdot}Me$ ...	65	66/0·6	1·5200	1·331	17·1	15·4	$C_7H_7ClO_3S$	17·2	15·5

* Calc. † Found: F, 9·2. $C_6H_4ClFO_3S$ requires F, 9·0%.

NORTHERN POLYTECHNIC, HOLLOWAY ROAD, LONDON N.7. [*Received, March 6th,* 1964.]

1049. *The Synthesis of Alkyl* p-*Hydroxyphenyl Sulphides.*

By R. T. WRAGG.

ALKYL *p*-HYDROXYPHENYL SULPHIDES have been prepared by reduction of thiocyanatophenols (prepared by the reaction of thiocyanogen and phenols [1]) followed by alkylation of the mercapto-group. The thiocyanogen has been generated by chemical or electrochemical techniques, but the yields of thiocyanatophenols are poor. Another method is the conversion of alkyl *p*-aminophenyl sulphides into the corresponding phenol by diazotisation, but the synthesis of the starting material from *p*-chloronitrobenzene is lengthy and the overall yields are poor.[2]

Methanesulphenyl chloride,[3] MeSCl, reacts with benzene in the presence of a Lewis acid such as aluminium chloride, to give methyl phenyl sulphide in about 50% yield.[4] Chloroalkanesulphenyl halides have also been treated with benzene, toluene, and phenols; [5] reaction with the mildly activated nuclei proceeds in an easily controlled manner, but with phenols resinous products are formed. Recently,[6] sulphenyl halides have been prepared *in situ* from disulphides and sulphuryl chloride and used to obtain sulphides in good yield.

In the present investigation, several alkanesulphenyl halides, prepared according to the method of Brintzinger *et al.*[3] have been treated with phenols in the presence of Friedel–Crafts catalysts. In all cases, hydrogen chloride was evolved smoothly at room temperature, and the alkyl *p*-hydroxyphenyl sulphides were isolated in 40—60% yield.

The possibility that reaction occurs through the intermediate formation of a sulphenyl ester, R·S·OAr, followed by rearrangement, was later shown to be unlikely when anisole was found to react readily in the presence of zinc chloride to form the corresponding (alkylthio)anisole; when aluminium chloride was used as a catalyst, the ether link of the anisole was cleaved and the alkyl *p*-hydroxyphenyl sulphide was formed instead.

It has been found that a Friedel–Crafts catalyst is not necessary for reaction between an alkanesulphenyl halide and a phenol, and that the sulphenyl halide can be prepared *in situ*, by passing chlorine into a mixture of the phenol and alkanethiol or dialkyl disulphide at 0°. The yield of product was 50—60% based on the starting materials. Unchanged reactants were recovered quantitatively together with chlorophenols, to give an overall yield of 75—85%.

When di-n-butyl disulphide was used in the process, butane-1-thiol was isolated,

[1] Wood, "Organic Reactions," John Wiley and Sons, Inc., New York, 1947, Vol. III, p. 240.
[2] R. Hank, personal communication.
[3] Brintzinger, Pfansteil, Koddebusch, and Kling, *Chem. Ber.*, 1950, **83**, 87; Schneider, *ibid.*, 1951, **84**, 911.
[4] Brintzinger and Langheck, *Chem. Ber.*, 1953, **86**, 557; Brintzinger, Langheck, and Schmahl, *Angew. Chem.*, 1952, **64**, 398.
[5] Brintzinger, Schmahl, and Witte, *Chem. Ber.*, 1952, **85**, 338.
[6] G.P. 1,063,177/1959; B.P. 875,464/1961.

suggesting that the intermediates might also possess chlorinating potential. As a further indication of this, the disulphide used was shown, by gas chromatography, to contain no butanethiol as impurity.

The alkyl *p*-hydroxyphenyl sulphide formed in this reaction consisted predominantly of the *para*-isomer, together with no more than 5% of the *ortho*-compound. This was indicated by gas-phase chromatographic separation of the isomers in sufficient quantities for their ultraviolet and infrared spectra to be checked against these of authentic samples.[2]

The reaction appears to be general in the phenolic series. For example, 2-naphthol afforded butyl 2-hydroxy-1-naphthyl sulphide from n-butyl disulphide and chlorine. That the product was α-substituted was indicated by the fact that it failed to couple with benzenediazonium chloride.

Experimental.—p-*Hydroxyphenyl methyl sulphide.* Methanesulphenyl chloride (5 g.) and dry phenol (8·4 g., 1·5 equiv.) were allowed to react, under anhydrous conditions, overnight at room temperature. Hydrogen chloride was evolved. The product was distilled under diminished pressure to afford *p*-hydroxyphenyl methyl sulphide (4·5 g., 54%), b. p. 135—140°/16 mm., m. p. 84—85° (Found: C, 59·8; H, 5·7; S, 22·6. Calc. for C_7H_8OS: C, 60·0; H, 5·7; S, 22·9%).

p-(*Methylthio*)*anisole.* (*i*) Methanesulphenyl chloride (5 g.) was added to anisole (10 g., 1·5 equiv.) together with a trace of zinc chloride, and allowed to react as above. The mixture was then distilled under reduced pressure, to afford *p*-(methylthio)anisole (4·09 g., 45%), b. p. 110—120°/17 mm. (Found: C, 62·5; H, 6·6; S, 20·5. Calc. for $C_8H_{14}OS$: C, 62·3; H, 6·5; S, 20·8%). Unchanged anisole (b. p. 56°/18 mm.) was recovered.

Methyl 3-*methyl*-4-*hydroxyphenyl sulphides.* Methanesulphenyl chloride (5 g.) and dry *o*-cresol (10·2 g., 1·5 equiv.) were allowed to react at room temperature overnight. The product was distilled under reduced pressure, to afford the sulphide (2·5 g., 38%), b. p. 100—110°/2 mm. The ultraviolet and infrared spectra were identical with those of authentic samples.

Unchanged *o*-cresol (b. p. 60—65°/2 mm.) was recovered, and a considerable amount of insoluble resin remained in the distillation flask.

Butyl p-*hydroxyphenyl sulphide.*—n-butyl disulphide (100 g.) and phenol (159 g., 3 mol.) were stirred vigorously, under anhydrous conditions, at 0—5°. Chlorine (44·1 g., 5% mol. excess) was slowly bubbled through the mixture. Next morning the mixture was distilled under reduced pressure, to afford: n-butanethiol (5·1 g.), b. p. 95—98°, a mixture of phenol and *o*- and *p*-chlorophenol; di-n-butyl disulphide (60 g.); and butyl *p*-hydroxyphenyl sulphide (66 g., ~85% after allowance for recovery), b. p. 105—120°/0·1 mm. (Found: C, 65·9; H, 7·6; S, 17·5. Calc. for $C_{10}H_{14}OS$; C, 65·9; H, 7·7; S, 17·6%).

(*ii*) Di-n-butyl disulphide (500 g.) and phenol (792 g., 3 mol. excess) were stirred with methylene chloride (5 l.) under anhydrous conditions at 0—5°. Chlorine (210 g., 5% mol. excess) was slowly bubbled through the mixture, which was then allowed to attain room temperature overnight. Distillation afforded n-butanethiol (10 g.), di-n-butyl disulphide (323 g.), and butyl *p*-hydroxyphenyl sulphide (235 g.), 73% after allowance for recovery). Unchanged phenol was recovered together with chlorophenols.

Butyl 2-*hydroxy*-1-*naphthyl sulphide.* Di-n-butyl disulphide (25 g.) and 2-naphthol (20 g.) were dissolved in methylene chloride (150 ml.) at 0—5°. Chlorine (13·0 g.) was slowly bubbled into the mixture. The product was allowed to warm to room temperature during 4 hr. and then extracted several times with 10% aqueous sodium hydroxide. The organic layer was dried ($CaSO_4$). The aqueous layer was acidified and extracted several times with ether, and the extracts were dried ($CaSO_4$). Distillation of the extracts afforded an oil which, on distillation under reduced pressure, afforded 1-chloro-2-naphthol (12·0 g.) b. p. 92—96°/0·05 mm., m. p. and mixed m. p. 70°. The original organic layer, on distillation under reduced pressure, afforded the *sulphide* (13·0 g., 45%), b. p. 64—70°/0·01 mm., n_D^{23} 1·4940 (Found: C, 72·1; H, 6·7; S, 13·4. $C_{14}H_{16}OS$ requires C, 72·4; H, 6·9; S, 13·8%).

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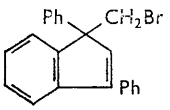
1050. *The Conversion of 1-Indenylmethyl Halides into Naphthalenes.*

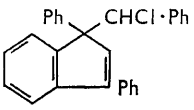
By P. M. G. Bavin.

Fluorene has been used successfully [1] in the synthesis of several complex hydrocarbons and it appeared likely that indene could serve as an intermediate for polysubstituted naphthalenes. This has now been demonstrated by synthesizing 1,4-diphenyl- and 1,2,4-triphenyl-naphthalene.

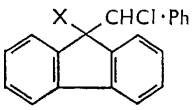
1,3-Diphenylindene [2] was readily alkylated with dibromomethane or benzylidene chloride, phenyl-lithium being used as base. The alkylations were much slower than the comparable reactions of 9-phenylfluorene [3] but proceeded at a convenient rate when benzene was used as solvent. The relative rates of alkylation of the fluorenyl and indenyl anions are as expected, being inversely related to their stabilities.[4] Both the bromide (I) and chloride (II) decomposed smoothly in boiling quinoline or by reaction with silver ion in



(I)



(II)



(IIIa; X = Me)
(IIIb; X = CO_2Me)

acetic acid to give 1,4-diphenyl- and 1,2,4-triphenyl-naphthalene, respectively, in yields of 70—90%. The chloride (II) decomposed to triphenylnaphthalene at its melting point or in boiling formic acid, resembling in these respects the chloride (IIIa), and re-emphasizing the unusual properties of the ester (IIIb).[3] The present work, together with earlier syntheses of 9,10-diphenyl [5] and 1,9,10-triphenylphenanthrene,[6] suggests that the method should have wide applicability in the synthesis of polyaryls.

The decomposition of the bromide (I) can give 1,4-diphenyl- or 1,3-diphenyl-naphthalene or 1-benzylidene-3-phenylindene. From preparative experiments, 1,4-diphenylnaphthalene was isolated in 87% yield. Gas–liquid chromatography showed that a second, higher boiling, substance was present in small amount (0·5—0·7%). Similar experiments with triphenylnaphthalene could not be carried out due to the higher boiling point.

Experimental.—Melting points were obtained by using an " Electrothermal " apparatus equipped with a thermometer calibrated for stem exposure. 1,3-Diphenylindene [2] was prepared from 3-phenyl-1-indanone supplied by Miss B. Dale; only the lower-melting form (m. p. 68—69°) has been obtained.

1,3-*Diphenylinden*-1-*ylmethyl bromide* (I). An ethereal solution of phenyl-lithium was prepared from lithium (0·5 g.) and bromobenzene (5 g.), and an ethereal solution (95 ml.) of 1,3-diphenylindene (5·4 g.) was added, followed by dibromomethane (20 g.) in benzene (150 ml.). The mixture was stirred and distilled. The colour was completely discharged when the distillate temperature reached 70°. The mixture was chilled, washed several times with water, dried ($MgSO_4$), and evaporated. The residue, in hexane, was passed through activated alumina and

[1] Suszko and Schillak, *Roczniki Chem.*, 1934, **14**, 1216; Vaillent, *Compt. rend.*, 1952, **234**, 534; Bavin, *Canad. J. Chem.*, 1960, **38**, 1099; 1959, **37**, 2023; 1962, **40**, 1399; Plieninger, Ege, and Ullah, *Chem. Ber.*, 1963, **96**, 1610; Matzner, Glazer-Tarasiejska, and Martin, *Bull. Soc. chim. belges*, 1960, **69**, 551.

[2] (*a*) Ziegler, Grabbe, and Ulrich, *Ber.*, 1924, **57**, 1983; (*b*) Dufraise and Enderlin, *Bull. Soc. chim. France*, 1934, **1**, 267.

[3] Bavin, *Canad. J. Chem.*, 1965, **42**, 1409.

[4] Conant and Wheland, *J. Amer. Chem. Soc.*, 1932, **54**, 1212; McEwen, *ibid.*, 1936, **58**, 1124.

[5] Bachmann, *J. Amer. Chem. Soc.*, 1933, **55**, 3857.

[6] Fuson and Tomboulian, *J. Amer. Chem. Soc.*, 1957, **79**, 956.

the eluted *bromide* crystallized, first from ethanol and then from hexane, to give needles (4·96 g., 69%), m. p. 127—128° (Found: C, 72·9; H, 4·9. $C_{22}H_{17}Br$ requires C, 73·1; H, 4·7%).

α-(1,3-*Diphenylinden*-1-*yl*)*benzyl chloride* (II). 1,3-Diphenylindene was alkylated with benzylidene chloride, as described above. The crude product was purified by chromatography (hexane–alumina) followed by crystallization from hexane. The *chloride* was obtained as elongated prisms (58%) which gave a vivid green solution in concentrated sulphuric acid. Most of the crystals melted at 147—149°, but a small proportion finally melted at 155°. This behaviour is probably due to the presence of a *threo-erythro*-mixture (Found: C, 85·55, 85·8; H, 5·3, 5·6. $C_{28}H_{21}Cl$ requires: C, 85·60; H, 5·4%).

1,4-*Diphenylnaphthalene*. (*a*) A solution of the bromide (I) (1 g.) in warm acetic acid was added to a similar solution of silver perchlorate (1 g.). A very rapid reaction occurred. The mixture was chilled, diluted with an equal volume of dilute hydrochloric acid, shaken with methylene chloride, and filtered. The residue was washed with methylene chloride and the combined extracts washed with sodium hydrogen carbonate solution, dried ($MgSO_4$), and evaporated. The crude product was chromatographed (hexane–alumina) and crystallized from ethanol to give, in three crops, slender needles (0·68 g., 87%), m. p. 134—135° (lit., m. p. 135—137°,[7] 136° [8]) (Found: C, 94·25; H, 5·5. Calc. for $C_{22}H_{16}$: C, 94·25; H, 5·75%).

(*b*) A solution of the bromide (1 g.) in quinoline (15 ml.) was boiled under reflux for 1 hr. The solution was chilled, poured on ice, and acidified with concentrated hydrochloric acid. The product, isolated and purified as in (*a*), separated from ethanol as needles (0·556 g., 72%), m. p. 134·5—135·5°. The crude product (0·44 g.) from bromide (I) decomposed as in (*a*), was analysed by g.l.c. [column 24 × 0·25 in. packed with 20% Silicone Gum Rubber (Methyl) SE30 supported on 60—80 mesh Diatoport P (F. and M. Scientific Corp.), programmed from 150 to 350° at 5° intervals. Helium (60 ml./min.) was the carrier]. The major component, retention temperature 261°, had a retention identical with that of pure 1,4-diphenylnaphthalene. The second component (peak area 0·7%) had a retention temperature of 265°. The starting bromide (I) gave an identical chromatogram (minor peak area 0·5%).

1,2,4-*Triphenylnaphthalene*. (*a*) The chloride (II) was decomposed as described in (*a*) above. Purification in the usual way gave 1,2,4-triphenylnaphthalene as plates (82%) (from ethanol), m. p. 162·0—162·5° (lit.,[9] m. p. 162—163°) (Found: C, 94·1; H, 5·4. Calc. for $C_{28}H_{20}$: C, 94·3; H, 5·65%). Method (*b*) gave the same hydrocarbon as plates (74%), m. p. and mixed m. p. 160—161°.

(*c*) A solution of the chloride (1 g.) in 98% formic acid (100 ml.) and acetic acid (200 ml.)was boiled under reflux for 2 hr. The hydrocarbon separated from ethanol as plates (0·79 g., 87%), m. p. 161—162°.

(*d*) The chloride (II) (0·1 g.) was kept at 175—185° for 1 hr. Crystallization of the residue from ethanol gave plates (0·064 g., 72%), m. p. and mixed m. p. 160—162°.

The author is indebted to the directors of Smith Kline and French Laboratories Ltd. for facilities and to Mr. B. J. Cross and his staff for analyses.

Smith Kline and French Laboratories Ltd.,
Welwyn Garden City, Herts.

[*Received, March 24th*, 1964.]

[7] Weiss, Abeles, and Knapp, *Monatsh.*, 1932, **61**, 162.
[8] Mustafa and Kamal, *J. Org. Chem.*, 1957, **22**, 157.
[9] Cava and Pohlke, *J. Org. Chem.*, 1962, **27**, 1564.

1051. *The Condensation of Ferrocenealdehyde with* D-*Glucitol and* D-*Mannitol.*

By A. N. de Belder, E. J. Bourne, and J. B. Pridham.

Cyclic acetal condensations of ferrocenealdehyde have not been widely investigated. Broadhead and his co-workers [1] found that the aldehyde and ethylene glycol give 2-ferrocenyl-1,3-dioxolan.

We have found that the aldehyde condenses with D-glucitol and D-mannitol to give cyclic acetals. These were prepared by refluxing the reactants in (*a*) *NN*-dimethylformamide–benzene in the presence of traces of toluene-*p*-sulphonic acid, or (*b*) *NN*-dimethylformamide in the presence of phosphoric pentoxide. 2,4-*O*-(Ferrocenylmethylene)-D-glucitol was obtained as a sharply melting product (m. p. 196—198°) provided that water was excluded during the working up of the reaction mixture. Its tetra-acetate was also crystalline. The structure of the glucitol acetal was proved by periodate oxidation. Measurement of periodate uptake was complicated by concomitant degradation of the ferrocenyl group; however, by similar techniques to those employed for the ferrocenyl glucosides,[2] the glycol groups of the glucitol acetal were found to liberate no formic acid but 1 mol. of formaldehyde with the consumption of 1 mol. of periodate. L-Xylose, identified chromatographically and as its di-*O*-benzylidene dimethyl acetal, was found to be the only major product present after periodate oxidation and hydrolysis. Thus ferrocenealdehyde resembles other aldehydes [3] in condensing with D-glucitol at positions 2 and 4 to give the favoured β*C*-ring.

From the reaction with D-mannitol, a mono- and a di-*O*-(ferrocenylmethylene)-D-mannitol were isolated. Their structures were not examined in detail. The monoacetal did not crystallise, although it formed a crystalline tetra-acetate in low yield. The diacetal gave a crystalline diacetate. Periodate oxidation and hydrolysis of the mannitol monoacetal gave erythrose and arabinose (identified by chromatography and electrophoresis), indicating that it was probably a mixture of a 1,3- and 3,4-*O*-substituted mannitol. Goldstein and his co-workers [4] reported that 3,4-di-*O*-methyl-D-mannitol consumes only 1 mol. of periodate, giving an arabinose derivative. These ring systems are also found in the mono-*O*-methylenemannitols isolated by Fletcher and Diehl.[5]

The ferrocenyl acetals were hydrolysed completely in 10 minutes by 0·01N-hydrochloric acid at 25°. Their extreme lability is to be understood if the strong electron-donating properties of the ferrocenyl group [6] assist the unimolecular decomposition of the intermediate conjugate acid.[7,8] The usefulness of such acetals as intermediates in syntheses of derivatives of polyols is reduced, however, by the fact that the acetals are formed in much lower yield from the higher polyols than from ethylene glycol,[1] because of solvent difficulties and probably also of steric factors. The mono-*O*-(ferrocenylmethylene)-hexitols are water-soluble compounds, which may be useful in the pharmaceutical field.

Experimental.—Chromatography solvents. A, Butan-1-ol–ethanol–water (4 : 1 : 5 v/v; organic layer); B, ethyl acetate–acetic acid–water (9 : 2 : 2 v/v); C, phenol saturated with water.

Electrophoresis buffers. E1, 0·1M-Borate, pH 10; E2, 0·05M-Germanate, pH 10.

Ferrocenealdehyde. This was prepared as described by Graham *et al.*[9] and had m. p. 114—118° (lit.,[9] 121°).

[1] Broadhead, Osgerby, and Pauson, *J.*, 1958, 650.
[2] de Belder, Bourne, and Pridham, *J.*, 1961, 4464.
[3] Barker and Bourne, *J.*, 1952, 905.
[4] Goldstein, Sorger-Domenigg, and Smith, *J. Amer. Chem. Soc.*, 1959, **81**, 444.
[5] Fletcher and Diehl, *J. Amer. Chem. Soc.*, 1952, **74**, 3799.
[6] Arnett and Bushick, *J. Org. Chem.*, 1962, **27**, 111.
[7] Ceder, *Arkiv Kemi*, 1954, **6**, 523.
[8] Leutner, *Monatsh.*, 1935, **66**, 222.
[9] Graham, Lindsey, Parshall, Peterson, and Whitman, *J. Amer. Chem. Soc.*, 1957, **79**, 3416.

2,4-O-*Ferrocenylmethylene*-D-*glucitol*. Ferrocenealdehyde (5·4 g.) in benzene (30 ml.) was added to D-glucitol (4·5 g.) in *NN*-dimethylformamide (30 ml.). After addition of toluene-*p*-sulphonic acid (50 mg.), the mixture was stirred and refluxed (*ca.* 120°) for 10 hr. in a Soxhlet apparatus containing calcium chloride. The solvents were then removed *in vacuo* and after the free acid had been neutralised with sodium methoxide, the residue was extracted with hot ethanol. The extracts were condensed and chromatographed on alumina, ethanol being used as the eluant. The top yellow band was isolated from the extruded column and extracted with ethanol. On concentration, the product crystallised. Three recrystallisations from ethanol gave yellow clusters of the *acetal* (0·5 g.), m. p. 196—198°, $[\alpha]_D^{24}$ −95° (*c* 0·1 in H_2O) (Found: C, 53·9; H, 5·9; ferrocenealdehyde, 58. $C_{17}H_{22}FeO_6$ requires C, 54·0; H, 5·9; ferrocenealdehyde, 57%). Recrystallisation of the acetal from water produced yellow needles, m. p. 168—190°. Intensive drying did not alter the m. p. With acetic anhydride in pyridine the acetal gave 1,3,5,6-*tetra*-O-*acetyl*-2,4-O-(*ferrocenylmethylene*)-D-*glucitol*, m. p. 112—113° (Found: C, 54·8; H, 5·9; Ac, 30·8. $C_{25}H_{30}FeO_{10}$ requires C, 55·0; H, 5·5; Ac, 31·5%).

Determination of the aldehyde content of the acetals. The acetal (2—5 mg.) was dissolved in ethanol in a 50-ml. volumetric flask. N-Sulphuric acid (5 ml.) was added and the solution made up to the mark with ethanol (with cooling). The absorption at 269 mμ was measured rapidly against a control made up by diluting 5 ml. of N-sulphuric acid with ethanol to 50 ml. A calibration curve of aldehyde concentration against absorption was found to be linear within the range 6—60 μg/ml.

Periodate oxidations. The acetals were oxidised in dioxan–0·02M-potassium periodate (2 : 3 v/v) adjusted by preliminary experiments to pH 6. Determination of uptake of oxidant and liberation of formic acid were carried out as described by Fleury and Lange,[10] and Anderson *et al.*,[11] respectively. For the determination of formaldehyde an initial pH 7·5 was used.[12]

Oxidation of the acetal to L-*xylose*. The monoacetal (0·2 g.) was shaken in 0·02M-potassium periodate (50 ml.; initial pH 7) until it dissolved, and the mixture was left 2 hr. The excess of periodate was destroyed with ethylene glycol (0·5 ml.) and after addition of 10N-sulphuric acid (5 ml.) the solution was heated at 90° for 1 hr. The solution was cooled, extracted with chloroform, and neutralised with barium carbonate, the precipitate being washed with hot water. After de-ionisation, the solution was freeze-dried. The presence of xylose was shown by chromatography in solvents A, B, and C. The anhydrous residue was converted into the di-*O*-benzylidene dimethyl acetal (according to the method of Breddy and Jones [13]), m. p. 210·5°, $[\alpha]_D^{22}$ +5° (*c* 0·9 in $CHCl_3$), mixed m. p. 211—212° (lit.,[14] 211—212°).

Reaction between D-*mannitol and ferrocenealdehyde*. D-Mannitol (7·2 g.) and ferrocenealdehyde (19·2 g.) in *NN*-dimethylformamide (20 ml.) were stirred at 70° in the presence of phosphoric pentoxide (0·2 g.) for 15 hr. After being cooled, the mixture was neutralised with sodium methoxide and then separated between chloroform (extract A) and water. The aqueous extract was washed four times with chloroform and then freeze-dried. The freeze-dried residue was chromatographed on a cellulose column, solvent A being used as eluant. The yellow band was eluted and the solvent evaporated. Attempts to crystallise the residue from ethanol or water failed. Finally an aqueous solution was freeze-dried to give the mono-*O*-(ferrocenylmethylene)-D-mannitol fraction as a yellow powder (1·5 g.), $[\alpha]_D^{22}$ +37° (*c* 1·0 in H_2O). The product (0·4 g.) with acetic anhydride–pyridine gave, after two recrystallisations from aqueous ethanol, yellow crystals of a *tetra*-O-*acetylmono*-O-(*ferrocenylmethylene*)-D-*mannitol* (0·1 g.), m. p. 112—113°, $[\alpha]_D^{22}$ +9° (*c* 2·0 in $CHCl_3$) (Found: C, 54·5; H, 5·6. $C_{25}H_{30}FeO_{10}$ requires C, 55·0; H, 5·5%).

Di-O-(*ferrocenylmethylene*)-D-*mannitol*. The chloroform extracts (A) from the monoacetal preparation were condensed and chromatographed on alumina, chloroform being used as the eluant. After the complete elution of the unchanged aldehyde, the column was extruded and the top yellow band was extracted with ethanol. Evaporation of the ethanol and treatment with acetic anhydride–pyridine yielded, after three recrystallisations from chloroform–ethanol, orange-yellow crystals of the *diacetate* of the diacetal (0·3 g.) m. p. 196—200°, $[\alpha]_D^{24}$ −6° (*c* 1·0

[10] Fleury and Lange, *J. Pharm. Chim.*, 1933, **17**, 107.
[11] Anderson, Greenwood, and Hirst, *J.*, 1955, 225.
[12] O'Dea and Gibbons, *Biochem. J.*, 1953, **55**, 583.
[13] Breddy and Jones, *J.*, 1945, 738.
[14] Hockett and Schaefer, *J. Amer. Chem. Soc.*, 1947, **69**, 849.

in $CHCl_3$) (Found: C, 58·7; H, 5·5; Ac, 15·5; ferrocenealdehyde, 66·3. $C_{32}H_{34}Fe_2O_8$ requires C, 58·4; H, 5·2; Ac, 13·1; ferrocenealdehyde, 65·0%). De-acetylation of this acetate gave, after two recrystallisations from chloroform–hexane, yellow-orange crystals of the *diacetal*, m. p. 195—200°, $[\alpha]_D^{20}$ +39° (*c* 2·7 in $CHCl_3$) (Found: C, 59·1; H, 5·4; Fe, 18·6. $C_{28}H_{30}Fe_2O_6$ requires C, 58·6; H, 5·3; Fe, 19·4%).

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1052. *Totally Synthetic Steroid Hormones. Part IV.*[1] (±)-9β-*Œstr*-5(10)-*en*-3-*ones and* (±)-9β,10α-*Œstr*-4-*en*-3-*ones.*

By J. M. H. GRAVES, G. A. HUGHES, T. Y. JEN, and HERCHEL SMITH.

THE therapeutic importance of various œstr-4-en-3-ones,[2] and the interesting biological properties found in several 9β,10α-androstanes and -pregnanes [3] (" retro "-steroids) suggested [4] the preparation of appropriate 9β,10α-œstr-4-en-3-ones for biological evaluation. We describe here the preparation from the (±)-9β-œstradiol (1) [5] of (±)-compounds formulated as members of this class. All are depicted here by the enantiomorph having the 13-methyl group in the β-configuration.

Reduction of the trienol (I) with lithium and ethanol in liquid ammonia gave the 3-methoxy-17β-alcohol (II; $R^1 = OH$, $R^2 = H$) which, with methanolic hydrochloric acid, was converted, presumably through the ketol (III; R = H), into a ketol assigned structure (IV; $R^1 = R^2 = H$). Oppenauer oxidation of the dienol (II; $R^1 = OH$, $R^2 = H$) gave the ketone (II; $R^1R^2 = :O$), and this, with the reagent [6] prepared by saturating a suspension of lithium aluminium hydride in tetrahydrofuran with acetylene, gave the alcohol (II; $R^1 = OH$, $R^2 = C{:}CH$). Use of the lithium acetylide–ethylenediamine complex in the last reaction (cf. ref. 6) gave lower yields and a less-pure product. Hydrolysis of the alcohol (II; $R^1 = OH$, $R^2 = C{:}CH$) with aqueous methanolic oxalic acid afforded the (±)-9β-œstrenol (III; R = C:CH). The same substrate, with methanolic hydrochloric acid, gave what is formulated as the (±)-9β,10α-œstrenone (IV; $R^1 = H$, $R^2 = C{:}CH$). The assignment of 9β,10α-configurations to the alcohols (IV; $R^1 = H^2$, $R^2 = H$, C:CH) was based initially [4] on the expectations that the acid-catalysed isomerisations of the alcohols (III; R = H, C:CH) are thermodynamically controlled [7] and that, as indicated by conformational analysis, the alcohols (IV; $R^1 = H$, $R^2 = H$, C:CH) are more stable than their respective 10β-isomers. It receives support from the formation of authentic 19-nor-9β,10α-pregn-4-en-3-ones from 3-methoxy-19-nor-9β,10α-pregna-1,3,5(10)-trienes by a similar route [8] to that described here. The 17β-hydroxyl configuration in the ketol (IV; $R^1 = R^2 = H$) [and therefore in the alcohols (I) and (II; $R^1 = OH$, $R^2 = H$)] follows from a comparison of the C-18 and C-17 proton resonances in the proton magnetic resonance spectra of the ketol (IV; $R^1 = R^2 = H$) and its acetate, with the corresponding

[1] Part III, Hartley and Smith, *J.*, 1964, 4492.
[2] *E.g.*, Fieser and Fieser, " Steroids," Reinhold, New York, 1959, p. 588 *et seq.*
[3] Westerhof and Reerink, (*a*) *Rec. Trav. chim.*, 1960, **79**, 771; (*b*) *ibid.*, p. 794; (*c*) *ibid.*, p. 1118.
[4] Graves, Ph.D. Thesis, Manchester, 1962.
[5] Douglas, Graves, Hartley, Hughes, McLoughlin, Siddall, and Smith, *J.*, 1963, 5072.
[6] Smith, H., Hughes, Douglas, Wendt, Buzby, Edgren, Fisher, Foell, Gadsby, Hartley, Herbst, Jansen, Ledig, McLoughlin, McMenamin, Pattison, Phillips, Rees, Siddall, Siuda, Smith, L. L., Tokolics, and Watson, *J.*, 1964, 4472.
[7] Birch and Smith, *J.*, 1951, 1882; Stork, Meisels, and Davies, *J. Amer. Chem. Soc.*, 1963, **85**, 3419.
[8] Edwards, Crabbé, and Bowers, *J. Amer. Chem. Soc.*, 1963, **85**, 3313.

resonances in the spectra of 19-nortestosterone, testosterone, and 17α-hydroxyandrost-4-en-3-one and their acetates (see Table). The C-18 protons resonate at closely concordant chemical shifts in the ketol (IV; $R^1 = R^2 = H$), 19-nortestosterone, and testosterone,

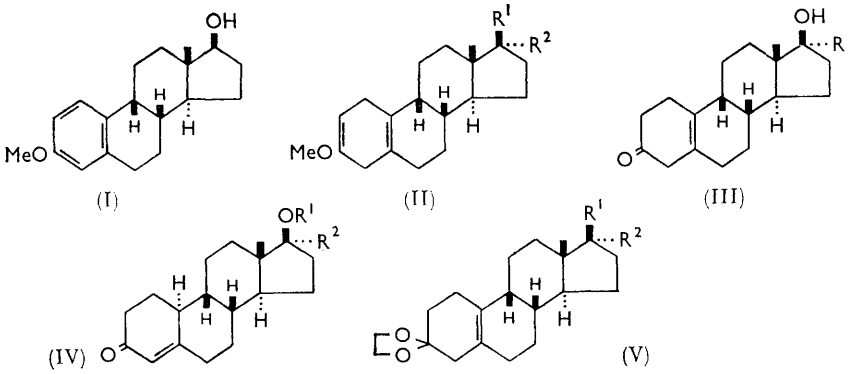
Proton magnetic reasonance data * for steroidal 17α- and 17β-ols.

Compound	C-18	C-17	Multiplicity
(IV; $R^1 = R^2 = H$)	9·20	6·21	t
17β-Hydroxy-19-norandrost-4-en-3-one	9·19	6·31	t
Testosterone	9·19	6·33	t
17α-Hydroxyandrost-4-en-3-one	9·28	6·22	d
(IV; R^1 = Ac; $R^2 = H$)	9·13	5·21	t
17β-Acetoxy-19-norandrost-4-en-3-one	9·13	5·34	t
17β-Acetoxyandrost-4-en-3-one	9·15	5·37	t
17α-Acetoxyandrost-4-en-3-one	9·19	5·12	d

* Determined for deuteriochloroform solutions on a Varian A-60 spectrometer, with tetramethylsilane as internal standard. Data are presented as τ units. d = doublet-like multiplet, t = triplet-like multiplet. All other resonances are singlets. Accuracies are of the order of ±0·025 τ.

and in their respective acetates, downfield from the corresponding resonances in 17α-hydroxyandrost-4-en-3-one and its acetate. The C-17 protons in the first three compounds and their acetates are closely similar triplet-like multiplets which are quite distinct from the doublet-like multiplets found for the β-C-17 protons in 17α-hydroxyandrost-4-en-3-one and its acetate. The alcohols (III; R = C:CH) and (IV; $R^1 = H$, R^2 = C:CH) may be formulated as 17β-ols by analogy with the stereochemical course of the reaction of 9β,10α-androst-4-ene-3,17-dione with lithium acetylide.[3b] The C-18 protons in the alcohol (IV; $R^1 = H$, R^2 = C:CH) and 17α-ethynyl-17β-hydroxyœstr-4-en-3-one resonate at chemical shifts of 9·14 and 9·15 τ, respectively, implying similar chemical environments at C-17 in both compounds.

Another synthesis of the ketol (IV; $R^1 = H$, R^2 = C:CH) depends on the acid-catalysed conversion of the alcohol (II; R^1 = OH, $R^2 = H$), with ethylene glycol in refluxing benzene, into the ketal (V; R^1 = OH, R = H). The 5(10)-position of the double bond is confirmed by the absence of nuclear magnetic resonance due to a vinylic proton. The result is to be



contrasted to the formation [9] under similar conditions of a mixture œstr-5(10)- and œstr-5-enes from the 9α-epimer of the alcohol (II; R^1 = OH, $R^2 = H$). Oxidation of the ketal (V; R^1 = OH, $R^2 = H$) with chromium trioxide in pyridine gave the ketone (V; R^1R^2 = :O) which was converted with lithium aluminium hydride–acetylene [6] into the alcohol

[9] Ringold, Rosenkranz, and Sondheimer, *J. Amer. Chem. Soc.*, 1956, **78**, 2477.

(V; R^1 = OH, R^2 = C:CH), and thence, by methanolic hydrochloric acid, into the alcohol (IV; R^1 = H, R^2 = C:CH), identical to that prepared by the first method. Velluz *et al.*[10] independently prepared what are probably the (−)-enantiomorphs of the alcohols (IV; R^1 = H, R^2 = H and C:CH).

Biological Activities.—The ketol (IV; R^1 = R^2 = H) showed 1% of the androgenic and myotrophic activities of testosterone propionate in the Hershberger test,[11] and was devoid of activity in the Clauberg test.[12] The acetate (IV; R^1 = Ac, R^2 = H) had no activity in an anti-androgenic test (cf. ref. 13). The alcohol (III; R = C:CH), the 9β-epimer of the clinically important œstrogenic-progestational agent,[14] had no activity in the Clauberg test.[12] The alcohol (IV; R^1 = H, R^2 = C:CH) was inactive in the same test. These are the first published reports on the biological testing of 19-nor-9β,10α-steroids.

Experimental.—General instructions are as for Part I.[5]

(±)-17β-*Hydroxy*-9β-*œstr*-5(10)-*en*-3-*one* (III; R = H). (±)-3-Methoxy-9β-œstra-1,3,5(10)-trien-17β-ol (0·4 g.) in tetrahydrofuran (15 c.c.)–ether (5 c.c.) was added with stirring to lithium (0·5 g.) in liquid ammonia (100 c.c.). After 15 min., ethanol (15 c.c.) was added dropwise, followed by water. The crystalline (±)-3-methoxy-9β-œstra-2,5(10)-dien-17β-ol (0·377 g.), m. p. 97—100°, $\nu_{max.}$ (d) 3350, 1695, and 1665 cm.$^{-1}$, was hydrolysed by methanolic oxalic acid [6] to give the *ketone* (0·15 g.), m. p. 136—138°, $\nu_{max.}$ (e) 3195 and 1721 cm.$^{-1}$ (Found: C, 79·0; H, 9·3. $C_{18}H_{26}O_2$ requires C, 78·8; H, 9·55%).

(±)-17β-*Hydroxy*-9β,10α-*œstr*-4-*en*-3-*one* (IV; R^1 = R^2 = H), prepared from (±)-3-methoxy-9β-œstra-2,5(10)-dien-17β-ol by hydrolysis with methanolic hydrochloric acid,[6] formed crystals, m. p. 188—190° (from ethyl acetate–light petroleum), $\lambda_{max.}$ 243 mμ (ε 16,300), $\nu_{max.}$ (d) 3400, 1656, and 1613 cm.$^{-1}$ (Found: C, 78·9; H, 9·5. $C_{18}H_{26}O_2$ requires C, 78·8; H, 9·5%). The *acetate* (IV; R^1 = Ac, R^2 = H) had m. p. 130—131° (from acetone–hexane), $\lambda_{max.}$ 242 mμ (ε 17,200), $\nu_{max.}$ (d) 1739, 1658, 1608, and 1235 cm.$^{-1}$ (Found: C, 75·95; H, 8·85. $C_{20}H_{28}O_3$ requires C, 75·9; H, 8·85%).

(±)-17α-*Ethynyl*-17β-*hydroxy*-9β-*œstr*-5(10)-*en*-3-*one* (III; R = C:CH). (±)-3-Methoxy-9β-œstra-2,5(10)-dien-17β-ol (0·45 g.) was refluxed for 2 hr. under nitrogen in cyclohexanone (5 c.c.)–toluene (15 c.c.) containing aluminium isopropoxide (0·25 g.). The product was kept for 16 hr. in a solution prepared by saturating a suspension of lithium aluminium hydride (2 g.) in ether (25 c.c.) with gaseous acetylene. The crude (±)-17α-ethynyl-3-methoxy-9β-œstra-2,5(10)-dien-17β-ol (0·38 g.), with methanolic oxalic acid,[6] gave the *ketone* (0·092 g.), m. p. 140—143° (after chromatography on Florex and recrytallisation from light petroleum–ether), $\nu_{max.}$ (e) 3547, 3266, and 1720 cm.$^{-1}$ (Found: C, 80·2; H, 8·4. $C_{20}H_{22}O_2$ requires C, 80·5; H, 8·7%).

(±)-3,3-*Ethylenedioxy*-17α-*ethynyl*-9β-*œstr*-5(10)-*en*-17β-*ol* (V; R^1 = OH, R^2 = C:CH). (±)-3-Methoxy-9β-œstra-2,5(10)-dien-17β-ol (8·4 g.) was refluxed for 20 hr. in benzene (180 c.c.) containing ethylene glycol (28 c.c.) and toluene-*p*-sulphonic acid monohydrate (1·8 g.), with continuous removal of water (Dean–Stark trap). The gummy product was stirred in pyridine (100 c.c.) containing chromic anhydride (10 g.) under nitrogen for 30 min. at 0° and 20 hr. at 25°. After dilution with ethyl acetate, the mixture was filtered through a Celite–alumina mixture. The solid product (4·2 g.) was recrystallised from di-isopropyl ether to give (±)-3,3-*ethylenedioxy*-9β-*œstr*-5(10)-*en*-17-*one* (V; R^1R^2 = :O) *hemihydrate*, m. p. 120—124°; $\nu_{max.}$ (d) 3413 and 1736 cm.$^{-1}$ (Found: C, 74·3; H, 8·7. $C_{20}H_{28}O_3,\frac{1}{2}H_2O$ requires C, 73·8; H, 8·9%). The foregoing ketal (0·75 g.) was stirred for 72 hr. at 25° in a solution prepared by saturating a suspension of lithum aluminium hydride (2·33 g.) in tetrahydrofuran (50 c.c.) with gaseous acetylene. The product was chromatographed on neutral alumina and recrystallised from di-isopropyl ether–hexane to give the *alcohol* (0·18 g.), m. p. 124—126°, $\nu_{max.}$ (d) 3401 and 3257 cm.$^{-1}$ (Found: C, 76·9; H, 8·7. $C_{22}H_{30}O_3$ requires C, 77·15; H, 8·85%).

(±)-17α-*Ethynyl*-17β-*hydroxy*-9β,10α-*œstr*-4-*en*-3-*one* (IV; R^1 = H, R^2 = C:CH). (*a*) (±)-17α-Ethynyl-3-methoxy-9β-œstr-2,5(10)-dien-17β-ol, with methanolic hydrochloric acid,[6] gave

[10] Velluz, Nominé, Bucourt, Pierdet, and Tessier, *Compt. rend.*, 1961, 3903.
[11] Hershberger, Shipley, and Meyer, *Proc. Soc. Exp. Biol. Med.*, 1953, **83**, 175.
[12] Elton and Edgren, *Endocrinology*, 1958, **63**, 464.
[13] Dorfman and Dorfman, *Acta Endocrinologica*, 1960, **33**, 308.
[14] Pincus, Chang, Hafez, Zarrow, and Merrill, *Science*, 1956, **124**, 890; *Endocrinology*, 1956, **59**, 695.

the *ketone*, m. p. 222—224° (after chromatography on alumina and recrystallisation from ethyl acetate–light petroleum), $\lambda_{max.}$ 239 mμ (ε 16,200), $\nu_{max.}$ (e) 3480, 3300, and 1665 cm.$^{-1}$ (Found: C, 80·3; H, 8·5. $C_{20}H_{26}O_2$ requires C, 80·5; H, 8·7%).

(*b*) (±)-3,3-Ethylenedioxy-17α-ethynyl-9β-œstr-5(10)-en-17β-ol (0·3 g.) in methanol (10 c.c.)–10% hydrochloric acid (2 c.c.) was kept for 30 min. on a steam-bath. Recrystallisation of the product from acetone–hexane gave the ketone (0·15 g.), m. p. 226—228°, undepressed by the sample prepared in (*a*).

We thank the D.S.I.R. for a maintenance grant (to J. M. H. G.) and Manchester University for an Imperial Chemical Industries Limited Research Fellowship (to G. A. H.). Microanalyses are by Mr. E. S. Morton (Manchester) and Dr. G. Ellis and his staff (Wyeth). Spectra were determined by Drs. J. G. Watkinson (Manchester) and G. Ellis (Wyeth), and their respective staffs. Biological data were obtained by Dr. R. A. Edgren (Wyeth) and his associates, and The Endocrine Laboratories, Madison 1, Wisconsin.

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1053. *Electron-impact Fragmentation Patterns of* 3,5-*Diphenyl*-1,2,4-*oxadiazole and* 2,5-*Diphenyl*-1,3,4-*oxadiazole.*

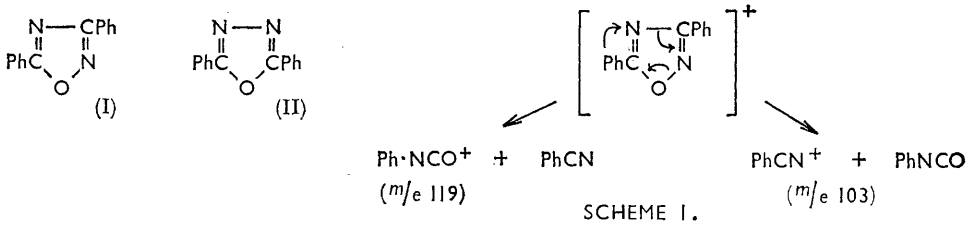
By J. L. Cotter.

The main features of the mass spectra of 3,5-diphenyl-1,2,4-oxadiazole (I) and of 2,5-diphenyl-1,3,4-oxadiazole (II) are shown in the Table; also included are the ionization potentials of these compounds and the appearance potentials of selected fragment ions.

Intensities and ionization or appearance potentials of the principal ions in the mass spectra of 3,5-diphenyl-1,2,4-oxadiazole, and 2,5-diphenyl-1,3,4-oxadiazole.

	m/e	Relative intensity (%)	Ionization * or appearance † potential (ev)
3,5-Diphenyl-1,2,4-oxadiazole	222	48·4	9·2 ± 0·1 *
	119	100·0	10·8 ± 0·1 †
	103	61·0	10·2 ± 0·1 †
	89	12·9	
	77	18·1	
	76	22·5	
2,5-Diphenyl-1,3,4-oxadiazole	222	89·0	8·9 ± 0·3 *
	166	22·4	
	165	52·8	
	105	100·0	12·1 ± 0·2 †
	77	72·6	

3,5-*Diphenyl*-1,2,4-*oxadiazole*.—The principal peaks in the mass spectrum of this compound are at *m/e* 119 and 103. It is suggested that the ions giving rise to these peaks result from a direct fragmentation and rearrangement of the molecular ion, formulated as in Scheme 1.



SCHEME 1.

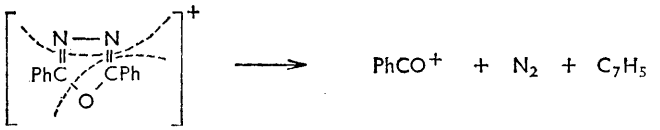
The assignment of the ions $PhNCO^+$ and $PhCN^+$ to the peaks at *m/e* 119 and 103, respectively, is supported by the occurrence of two metastable peaks, one at *m/e* 69·6, $119^+ \longrightarrow 91^+ + 28$, which indicates the fragmentation process

$$PhNCO^+ \longrightarrow PhN^+ + CO$$

and the other at *m/e* 56·1, $103^+ \longrightarrow 76^+ + 27$, which indicates the fragmentation process:

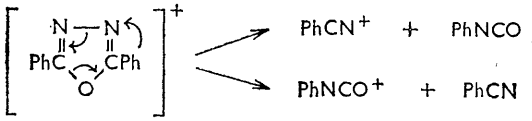
$$PhCN^+ \longrightarrow C_6H_4^+ + HCN$$

2,5-*Diphenyl*-1,3,4-*oxadiazole*.—The principal peak in the mass spectrum of this compound is at *m/e* 105. The experimentally determined ratios of the isotope ion-intensities at *m/e* 106 and 107 to the ion-intensity at *m/e* 105 were 0·0806 and 0·0044, respectively. These ratios are reasonably consistent with the assignment of the ion at *m/e* 105 to $C_7H_5O^+$. This ion might arise by the fragmentation processes:



the main driving force being the formation of molecular nitrogen.

The relatively low intensities of the peaks at *m/e* 119 (0·36%) and 103 (5·12%) in the mass spectrum of 2,5-diphenyl-1,3,4-oxadiazole are surprising, and show that the alternative fragmentation processes:



do not occur to any appreciable extent.

The relatively intense peak at *m/e* 77 is attributed to Ph^+, and the presence of a metastable peak at *m/e* 56·5, $105^+ \longrightarrow 77^+ + 28$, implies that the phenyl cation is formed in a one-step fragmentation process:

$$PhCO^+ \longrightarrow Ph^+ + CO$$

Ions of *m/e* 194, formed by the loss of nitrogen or carbon monoxide from the molecular ion, are of relatively low intensity (0·45%).

The fragment ion at *m/e* 166 corresponds to the loss of both nitrogen and carbon monoxide from the molecular ion. The fragment ion at *m/e* 165 is more difficult to assign; it might correspond to the loss of a hydrogen atom from the ion at *m/e* 166. This is supported

by the occurrence of ions at *m/e* 166 and 165 in the mass spectrum of diphenylmethane.[1]* Other possibilities are that it arises by the loss of both a nitrogen molecule and the atoms carbon, hydrogen, and oxygen from the molecular ion, or by loss of the atoms carbon, hydrogen, and oxygen from the fragment ion at *m/e* 194.

Experimental.—Samples of 3,5-diphenyl-1,2,4-oxadiazole, m. p. 109°, and 2,5-diphenyl-1,3,4-oxadiazole, m. p. 140·5°, were kindly made available by Dr. J. P. Critchley.

Mass spectra were obtained with 75-v electrons and an accelerating voltage of 1975 v using an Associated Electrical Industries Ltd. mass spectrometer M.S.2-H. The temperature of the heated inlet system was 185°. Ionization and appearance potentials were obtained from the experimentally determined ionization-efficiency curves by the method of Dibeler and Reese.[2]

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ROYAL AIRCRAFT ESTABLISHMENT, FARNBOROUGH, HANTS. [*Received, April 13th*, 1964.]

* The author thanks a Referee for bringing this supporting evidence to his attention.

[1] A.P.I. Research Project 614.
[2] Dibeler and Reese, *J. Res. Nat. Bur. Stand., Sect.* A, 1955, **54**, 127.

1054. *The Reaction of 1-Naphthaldehyde with Aqueous Dimethylformamide and Potassium Cyanide.*

By T. VAN ES and W. PRINZ.

WHEN 1-naphthaldehyde was refluxed with potassium cyanide in aqueous dimethylformamide α-dimethylamino-1-naphthylacetonitrile, 1-$C_{10}H_7$·CH(NMe_2)·CN, was obtained. The compound is soluble in dilute acid and is recovered unchanged when the solution is made alkaline; hot dilute acid, however, decomposes it to hydrogen cyanide and 1-naphthaldehyde. Ammonia is evolved when it is heated with alkali. The hydrolysis of dimethylformamide to dimethylamine during the refluxing accounts for the formation of the compound, as is evidenced by the fact that it is also formed when 1-naphthaldehyde is refluxed with potassium cyanide and aqueous dimethylamine. Treatment with nitric acid gives 5-nitro-1-naphthaldehyde.[1]

Compounds of this type are well known,[2,3] and the present example was synthesised by one of the available methods. The reaction was also applied to benzaldehyde, when benzoin as well as α-dimethylamino-phenylacetonitrile [3] were obtained.

Experimental.—*α-Dimethylamino-1-naphthylacetonitrile.* 1-Naphthaldehyde (5·2 g.), potassium cyanide (2·2 g.), water (25 ml.), and dimethylformamide (35 ml.) were refluxed for 2·5 hr., and the mixture was poured into water. The solid (5·6 g., 78%) which separated gave *needles*, m. p. 91° (from aqueous ethanol) (Found: C, 80·0; H, 6·9; N, 13·5%; *M*, 215. $C_{14}H_{14}N_2$ requires C, 79·9; H, 6·7; N, 13·3%; *M*, 210). The same product was also formed (20%) when 25% aqueous dimethylamine was used instead of dimethylformamide.

The bisulphite addition compound of 1-naphthaldehyde (5·2 g., 0·02 mole) and dimethylamine (excess) were set aside overnight. The resulting solid was warmed with a concentrated aqueous solution of potassium cyanide (1·3 g., 0·02 mole); the oil which formed solidified. Crystallisation gave the above nitrile (3·3 g., 78%).

α-Dimethylamino-1-naphthylacetamide. The above nitrile (1 g.) and polyphosphoric acid

[1] Ruggli and Burckhardt, *Helv. Chim. Acta*, 1940, **23**, 441.
[2] Knoevenagel and Mercklin, *Ber.*, 1904, **37**, 4087; Stewart and Cook, *J. Amer. Chem. Soc.*, 1928, **50**, 1973.
[3] Stevens, Cowan, and McKinnon, *J.*, 1931, 2568; Luten, *J. Org. Chem.*, 1938, **3**, 588.

(10 g). were heated at 110° for 1·5 hr.[4] The mixture was poured into water and the solution neutralised. The solid which separated gave needles (0·9 g., 83%), m. p. 125° (from aqueous ethanol) (Found: N, 12·0. $C_{14}H_{16}N_2O$ requires N, 12·3%).

5-*Nitro*-1-*naphthaldehyde*. The above nitrile (1 g.) was added to ice-cold fuming nitric acid (*d* 1·5; 10 ml.). The mixture was kept for 1 hr. in an ice-bath and then poured into water, to give yellow needles (0·8 g., 83%), m. p. 137° (lit.,[1] 136—137°) (from propan-2-ol). Oxidation of this material with hydrogen peroxide in acetic acid gave 5-nitro-1-naphthoic acid, m. p. 236—238° (lit.,[1] 236—237°).

α-*Dimethylamino-phenylacetonitrile*.[3] Benzaldehyde, under the reaction conditions described, gave benzoin (0·76 g., 22%). The filtrate was repeatedly extracted with ether, and the dried extract with hydrogen chloride gave the dimethylamino-hydrochloride (13·0 g., 71%), m. p. 171—172° (from ethanol).

The amine-nitrile (1 g.) was hydrolysed to the amide with polyphosphoric acid as described above. The amide had m. p. 151° (from water) (0·75 g., 69%) (Found: N, 15·6. $C_{10}H_{14}N_2O$ requires N, 15·7%).

DEPARTMENT OF CHEMISTRY, UNIVERSITY OF THE WITWATERSRAND,
JOHANNESBURG, SOUTH AFRICA. [*Received, April 13th*, 1964.]

[4] Snyder and Elston, *J. Amer. Chem. Soc.*, 1954, **76**, 3039.

1055. *The Reaction of α-Pinene Oxide with Boron Trifluoride.*

By M. P. HARTSHORN, D. N. KIRK, and A. F. A. WALLIS.

IN the course of other investigations we required considerable quantities of pinocamphone (Ia). By analogy with boron trifluoride-catalysed rearrangements of epoxides of steroidal trisubstituted olefins, which can give ketonic products [1] in good yield, it was hoped that α-pinene oxide (2,3-epoxypinane) might be converted largely into pinocamphone (Ia) on treatment with boron trifluoride etherate.

Various rearrangements of α-pinene oxide have been described. Whilst pyrolysis of α-pinene oxide either in the presence of an iron catalyst [2] or in a sealed tube [3] yields pinocamphone (Ia), no ketonic material has hitherto been obtained from isomerisations carried out in solution. Reaction with zinc bromide in benzene solution was reported [4] to yield the aldehyde (II), which could also be obtained, together with an ester fraction, by treatment of α-pinene oxide with acetic acid.[5] However, the reaction of α-pinene oxide with quinaldine–toluene-*p*-sulphonic acid [6] gave a mixture of five hydrocarbons (one of which was *p*-cymene) and a fraction containing the aldehyde (II) and its isomer (III). More recently, reaction of α-pinene oxide with anhydrous hydrogen fluoride was reported [7] to give the fluoro-alcohol (IV).

Reaction of α-pinene oxide with boron trifluoride in ether gives a complex mixture of *p*-cymene, aldehydes (II) and (III), pinocamphone (Ia), *trans*-carveol (V), the fluoro-alcohol (IV), and a further minor component which was not examined. The compounds were identified by comparison of retention times on gas–liquid chromatography (g.l.c.) with those of authentic samples. The relative proportions of each component are given in the Table as are those from reactions with zinc bromide and with anhydrous hydrogen

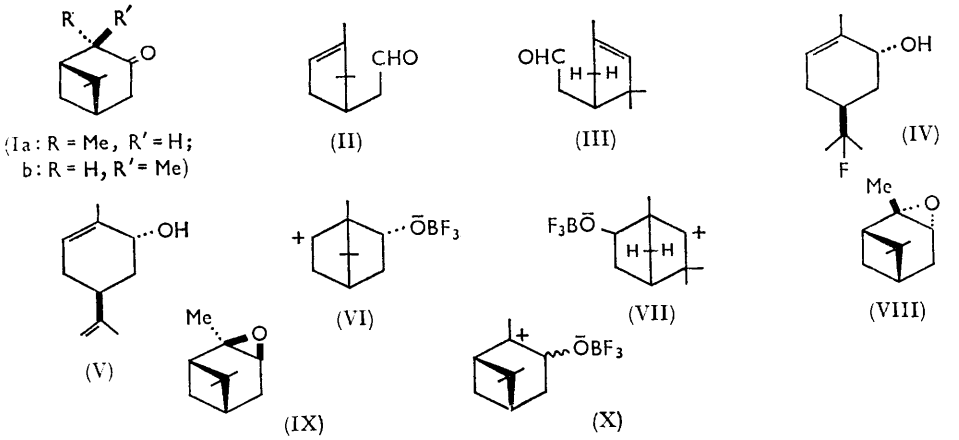
[1] Henbest and Wrigley, *J.*, 1957, 4596, 4765.
[2] Booth and Klein, U.S. Patent, 2,803,695/1957.
[3] Isaeva and Arbuzov, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1959, 1049.
[4] Arbuzov, *Ber.*, 1935, **68**, 1430.
[5] Royals and Harrell, *J. Amer. Chem. Soc.*, 1955, **77**, 3405.
[6] King and Farber, *J. Org. Chem.*, 1961, **26**, 326.
[7] (*a*) Farges, *Bull. Soc. chim. France*, 1962, 1266; (*b*) Farges and Kergomard, *ibid.*, 1963, 55.

fluoride. Of particular significance is the presence of *ca.* 20% of pinocamphone (Ia) in the products from the zinc bromide reaction.

Relative proportions of products from the reaction of α-pinene oxide.

	BF_3	$ZnBr_2$	HF
p-Cymene	2	4	2
2,2,3-Trimethylcyclopent-3-enylacetaldehyde (II)	6	6	3
2,2,4-Trimethylcyclopent-3-enylacetaldehyde (III)	55	70	30
Pinocamphone (Ia)	15	20	—
trans-Pinocarveol	—	—	4
trans-Carveol (V)	2	—	11
Fluoro-alcohol (IV)	18	—	50
Unknown	2	—	—

The presence of both aldehydes (II) and (III) among the products of the boron trifluoride-catalysed reaction may be interpreted on one of two bases. Co-ordination of boron trifluoride with the epoxide, followed by cleavage of the C(2)–O bond and attack by C-6 or C-7 on C-2 would give carbonium ions (VI) and (VII), respectively. These could then



collapse to give the aldehydes (II) and (III). If it is assumed that attack by C-6 on C-2, for example, must be concerted with C(2)–O bond cleavage, then the intermediate from which aldehyde (II) is derived must have the 2α,3α-epoxide [8] structure (VIII). Similarly, C(2)–O bond cleavage concerted with attack by C-7 on C-2 would require that aldehyde (III) be derived from the β-epoxide (IX). By this argument, the α-pinene oxide must be a mixture of α- and β-isomers, with a β-isomer content of at least 6%.

However, if ionisation of the C(2)–O bond were complete, to give the discrete carbonium ion (X), subsequent nonconcerted attack either by C-6 or C-7 on C-2 would give rise ultimately to the aldehydes (II) and (III), even if the original α-pinene oxide were the pure α-isomer (VIII). Assuming the homogeneity of the *trans*-fluoro-alcohol (IV), the remaining products of boron trifluoride-catalysed rearrangement of α-pinene oxide could have arisen from the α-epoxide (VIII) by either a concerted or a nonconcerted mechanism.

Isopinocamphone (Ib), which might have been expected to arise from the β-epoxide (IX) by a similar mechanism to that for formation of pinocamphone (Ia) from the α-epoxide (VIII), could not be identified among the products. As a control it was shown that treatment of isopinocamphone (Ib) with boron trifluoride did not result in significant epimerisation to pinocamphone (Ia).

Reactions of α-pinene should occur preferentially by attack on the " α " face [8] of the double bond due to the steric hindrance to approach from the " β " face. However, it is

[8] Hartshorn and Wallis, *J.*, 1964, 5254.

not possible on these steric grounds to exclude the possibility of the formation of *ca.* 5—6% of products derived from the less-favourable " β " face attack. As the presence of this level of β-epoxide impurity in the α-pinene oxide could not be demonstrated by g.l.c. it is not possible to define the mode of formation of the aldehyde (III). From the Table it is clear that, whereas the proportion of this aldehyde (III) formed is relatively independent of the reaction conditions, formation of pinocamphone (Ia) in solution occurs only on reaction with Lewis acids.

Experimental.—G.l.c. was carried out using columns of 10% Apiezon M and poly(ethylene glycol adipate) on Celite in a Pye Argon gas chromatograph.

Rearrangement of α-pinene oxide with boron trifluoride etherate. Redistilled boron trifluoride etherate (0·9 c.c.) was added dropwise to a stirred ice-cold solution of α-pinene oxide {1 g.; $[\alpha]$ +43° (*c* 1·12, in $CHCl_3$)} in ether (10 c.c.). After 5 min. the product was isolated with ether to give an oil (1·01 g.). Analysis by g.l.c. gave the product composition shown in the Table.

Reaction of α-pinene oxide with anhydrous hydrogen fluoride.[7] A solution of α-pinene oxide (4·5 g.) in ether (10 c.c.) was added dropwise over 10 min. to a stirred ice-cold solution of hydrogen fluoride (2 g.) in ether (100 c.c.). After a further 10 min. the product was isolated with ether to give an oil (4·7 g.). Analysis by g.l.c. gave the product composition shown in the Table.

Reaction of α-pinene oxide with zinc bromide. The reaction was carried out by the method of Arbuzov.[4] Product composition figures are given in the Table.

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