190. *The Reduction of Symmetrical 1,2- and 1,3-Diketones with Sodium Borohydride, and the Separation of Diastereoisomeric 1,2- and 1,3-Diols by Means of Borate Complexes.*

By JOHANNES DALE.

Acyclic, but not cyclic, 1,3-diketones can be reduced with sodium borohydride to the corresponding 1,3-diols in excellent yield if their acidic properties are ignored. In the form of their sodium salts no reduction takes place. In general, the *meso*-diol is the main product, and its formation is favoured by working at low temperature and with dilute solutions. 1,2-Diketones also give one isomer as the predominant product but, depending on the structure, it can be either the *meso-* or the racemic diol.

A method of separating acyclic diol isomers, based on the fact that *meso*-1,3-diols and racemic 1,2-diols form complexes with sodium borate, has been worked out. It is particularly well suited in connection with reduction of diketones by sodium borohydride as the complexes are formed directly.

Boric esters of some of the diols have been isolated.

A new case of resolution of a racemate by spontaneous crystallization has been observed (1,3-diphenylpropane-1,3-diol).

THE reduction of some 1,2-diketones with sodium borohydride was reported in 1949 by Chaikin and Brown,[1] but only incomplete data were presented with regard to the steric course of this reduction. The sole mention made of 1,3-diketones by these authors was a note on an unsuccessful attempt to reduce acetylacetone; only propan-2-ol was isolated, a result of hydrolysis and subsequent reduction of the acetone so formed.

We have now found that the reduction to the diol fails only when the acyclic 1,3-diketones, which are weakly acidic, are completely neutralized before reaction, presumably because of electrostatic repulsion between the enolate ion and the borohydride ion. If the acidic properties are simply ignored, the reduction proceeds rapidly and in excellent

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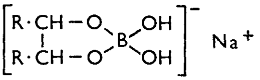
[1] Chaikin and Brown, *J. Amer. Chem. Soc.*, 1949, **71**, 122.

yield; no by-products can be isolated, and the sodium borohydride decomposes only slowly. In fact, the reduction of acyclic 1,3-diketones by sodium borohydride seems to constitute the best method available for the preparation of the corresponding 1,3-diols. Compared with catalytic hydrogenation [2] and reduction by lithium aluminium hydride,[3] it has the advantage that there is no loss of oxygen or formation of unsaturation. However, cyclic 1,3-diketones are more strongly acidic and decompose the borohydride before reduction can take place.

It seemed of interest to establish how strong an acid has to be to decompose the borohydride instead of being reduced. Since dimedone, with pK_a 5·17, was not reduced at all, but decomposed sodium borohydride violently, and acetylacetone, with pK_a 8·94,[4] was easily reduced, the limiting pK_a had to be between these values. The gap was narrowed by the finding that cyclopentane-1,2-dione (pK_a 8·75) and the triketone diacetylacetone [4] (pK_{a1} 7·42) could be smoothly reduced. [It is also interesting that monosodium maleate (pK_{a2} for maleic acid 6·5), although no ketone and although it decomposed the borohydride, apparently was partially reduced, since maleic acid could not be completely recovered but contained some strongly smelling unidentified substance, presumably γ-hydroxycrotonic acid or its lactone.]

Although the reduction of acyclic 1,2- and 1,3-diketones and cyclic 1,2-diketones thus proceeds excellently, isolation of the diols presented a problem in some cases, as a variety of boron-containing products of the general types (I—IV) were encountered, and at first made it difficult to free the diol from boron.

Of these compounds the sodium borate complexes (I and II) are formed under alkaline conditions; very often the compounds (I) can be isolated crystalline from water; they will be described in more detail in the following paper. The boric esters of the types (III) (or its anhydride) and (IV) are formed under neutral or acidic conditions. There is a notable difference in hydrolytic stability between the five-membered and the six-membered ring in these boric esters, the former being the less stable although forming the more stable complexes (see Experimental section and the two following papers). As is to be expected, the compounds (I and III) are formed when sodium borate or boric acid is in excess; (II and IV) when the diol is in excess.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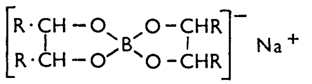
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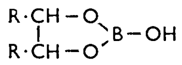
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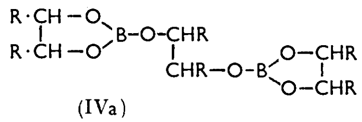
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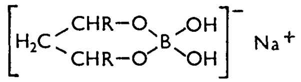
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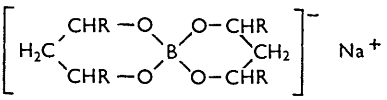
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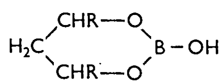
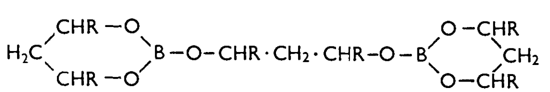

(IIIb)


(IVb)

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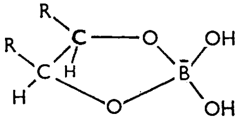
[2] Sprague and Adkins, *J. Amer. Chem. Soc.*, 1934, **56**, 2669.
[3] Dreiding and Hartman, *J. Amer. Chem. Soc.*, 1953, **75**, 3723.
[4] Schwarzenbach and Lutz, *Helv. Chim. Acta*, 1940, **23**, 1162.

Special procedures had to be developed to isolate the pure diols; these were turned to an advantage when it was observed that the formation and stability of the alkali borate complexes and the boric esters depended on the steric configuration of the diols and thus afforded a means of separating the symmetrical diols into the *meso*- and racemic forms (potentially also unsymmetrical diols into the racemic *erythro*- and *threo*-forms).

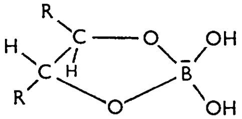
The general procedure, which had to be modified in some cases, consists in evaporating the alkaline reaction mixture, or a prepared mixture of the diols and excess of sodium metaborate, to dryness, and extracting the isomer which does not form a complex from this residue with a solvent, generally chloroform or ether. Then the extracted residue is dissolved in water, wherefrom the other isomer can then be extracted. As the hydrolysis equilibrium is continuously displaced during extraction, it is, at least for 1,3-diols, in general not necessary or advisable to acidify the alkaline solution, since then a mixture of the diol and the cyclic ester (III) may be obtained which, if distilled, forms the trisdiol diborate ester (IV). That the structure of esters of this type, which can also be formed directly from the diol and boric acid, is as shown (IV), and not of the " triple-bridge " or " cage " type suggested by Dupire,[5] could be demonstrated by the fact that tri(pentane-2,4-diol) diborate (IVb; R=H) is partially hydrolysed even by atmospheric humidity to give 1 mol. of diol and 2 mol. of the cyclic diol monoborate (IIIb), which, in contrast, is so stable against further hydrolysis that it can be extracted unchanged from aqueous solution.

In some cases when the complex is very stable, especially in the case of 1,2-diols, it is not necessary to evaporate the solution before extracting the uncomplexed isomer. In other cases care must be taken that the evaporation is not carried too far, because the anhydrous complexes may be soluble in the solvent used to extract the free diol; this happens most frequently when the groups R are large hydrocarbon groups, or when the diol is present in excess so that complexes of the type (II) are formed. The difficulty may be avoided by using benzene or hexane as extracting solvent.

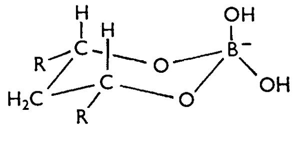
Whereas the 1,3-diol complexes (Ib) are usually sufficiently hydrolysed in water to allow the liberation of the diol by repeated extractions, the 1,2-diol complexes (Ia) are much more stable, and sometimes necessitated special procedures. Usually, the following method proved satisfactory: The alkaline solution was first extracted a few times to remove a reasonable part of the diol, then acidified, and the mixture of the remaining diol and its cyclic ester (IIIa) was next extracted completely; when this mixture was again dissolved in aqueous alkali, the net result was a reduction of the borate content, and a new crop of pure diol was extracted; this process was repeated as necessary. A very efficient method of removing most of the boric acid was to treat the extracted liquid mixture of a water-soluble diol and its boric ester with the calculated quantity of water needed to hydrolyse the boric ester; the precipitated boric acid was then filtered off, and



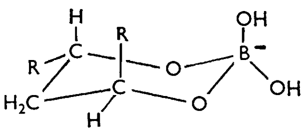
meso



Racemate



meso



Racemate

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[5] Dupire, *Compt. rend.*, 1936, **202**, 2086.

the product treated with alkali as above. If too much water was used, the boric acid dissolved, and the initial mixture was obtained on extraction. In some cases an excess of a strong complex-former, such as mannitol, can be added to liberate the diol from the alkaline solution. These methods proved much more simple and efficient than other proposed methods to eliminate boron from strong complexes, *e.g.*, its removal as methyl borate,[6,7] which is slow and tedious. However, when R represented the very bulky t-butyl group the hydrolytic stability of the complex as well as of the cyclic ester was so high that all methods failed to liberate the racemic 1,2-diol.

The question as to which isomer in a set would form the most stable complex could be predicted by considering the steric effects of the substituents R on the ring systems. Since the five-membered ring must be essentially planar, the *meso*-1,2-diol borates will have the substituents in close approach on the same side of the ring, hence must be unstable; the racemic 1,2-diol borates would be more stable, having the substituents on opposite sides.

In the six-membered ring the steric situation is probably similar to that in cyclohexane. In the *meso*-1,3-diol borates, therefore, both substituents come on the same side and can occupy the unhindered equatorial positions to form a stable ring system, whereas in the racemic 1,3-diol borates only one substituent can become equatorial, while the other one has to be axial and will come rather close to a hydrogen atom and to a hydroxyl group.

That the effect depends on the bulkiness of the substituent, is well demonstrated by the fact that when R is phenyl the separation is satisfactory under varying conditions, whereas when R is methyl both isomers form alkali-borate complexes although their stabilities differ. The stability difference is sufficient in the case of butane-2,3-diol to allow an easy separation of the isomers if complete evaporation of the complex mixture is avoided. In the case of pentane-2,4-diol only a partial separation can be achieved by using an insufficient amount of sodium borate, and in general the recently reported chromatography of borate complexes on ion-exchange columns [8,9] is preferable, although it is slow and less suitable for large quantities.

TABLE 1. *Reduction of diketones with sodium borohydride.*

Diketone reduced	Diol formed	Temp.	Solvent	Yield of diol (%)		More stable or only complex with
				meso	racemate	
Acetylacetone	Pentane-2,4-diol	15°	Aq. MeOH	90	2	*meso*
2,2,6,6-Tetramethyl-heptane-3,5-dione	2,2,6,6-Tetramethyl-heptane-3,5-diol	20	MeOH	60	16	rac. (!)
Dibenzoylmethane	1,3-Diphenylpropane-1,3-diol	20	MeOH	52	36	*meso*
		5	MeOH *	31	11	
		20	MeOH, dilution *	47	11	
		6	MeOH, dilution	59	18	
Biacetyl	Butane-2,3-diol	15—20	Aq. MeOH	40	50	rac.
Bipivaloyl	2,2,5,5-Tetramethyl-hexane-3,4-diol	30—35	MeOH	62	3	rac.
Benzil	Hydrobenzoin	40—45	MeOH	70	12	rac.
		10—15	MeOH	81	11	
				(*cis*)	(*trans*)	
Cyclohexane-1,2-dione	Cyclohexane-1,2-diol	20—25	H_2O	28	30	*meso* (*cis*)
		6—10	H_2O	11	64	
Cyclopentane-1,2-dione	Cyclopentane-1,2-diol	20—35	H_2O	26	61	*meso* (*cis*)

* The low total yield is due to the addition of too much alkali.

The relative stabilities of the borate complexes of isomeric cyclic 1,2-diols have already

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[6] Abdel-Akher, Hamilton, and Smith, *J. Amer. Chem. Soc.*, 1951, **73**, 4691.

[7] Reid and Siegel, *J.*, 1954, 520.

[8] Khym and Zill, *J. Amer. Chem. Soc.*, 1952, **74**, 2090.

[9] Nagai, Kuribayashi, Shiraki, and Ukita, *J. Polymer Sci.*, 1959, **35**, 295.

been extensively studied by Böeseken and his pupils.[10-15] In the case of the cyclohexane 1,2-diols, as expected, it is the *cis*-isomer (*meso*) which forms the most stable complex, but it is still surprisingly unstable when compared with the well-known and very stable *cis*-cyclopentane-1,2-diol complex. Derx [11] has offered an explanation in terms of the small number of molecules in " dynamic equilibrium," which have the hydroxyl groups in the right position (as in cyclopentane-1,2-diol) to form a planar five-membered ring with boric acid, but it might just as well be understood by considering the steric strain in the molecule itself; the five-membered heterocyclic ring can only become planar if the cyclohexane ring is forced into the unfavourable boat-form, and the cyclohexane ring can only assume the stable chair-form if the five-membered ring becomes skew.

Although compounds of diols with boric acid of the types (I—IV) have been isolated before,[5,11-19] and the effect of the addition of diols on the conductivity and acidity of boric acid solutions has been studied extensively and used to establish steric configurations,[10,11,15,20-23] especially of cyclic diol pairs, these compounds do not seem to have been utilized for the actual separation of isomers, except in the case of 1-methylcyclohexane-1,2-diol.[12] However, even for this diol no experimental details were given. For cyclic diols another method of separation is also available as only the *cis*-compounds form cyclic acetals with acetone,[11,12,15,21,24] but the main shortcoming is here that the hydrolysis of the acetal to liberate the diol is often accompanied by isomerization or decomposition.[12,21,24] In the acyclic series both *meso*- and racemic forms generally give isopropylidene compounds.[21]

It should be noted that many of the compounds studied by us have only slight effect on the conductivity and acidity of boric acid; and in some cases there is little difference within an isomeric pair.[10,11] Thus, Böeseken's method is actually a relatively coarse tool for structural chemical problems, compared with the sensitivity of the present separation, the reason being that hydrolysis of the complex and displacement of the hydrolysis equilibrium during extraction are prevented by removing the water.

The steric course of the sodium borohydride reduction was at first thought to be connected with the borate-complex stability, since in the first example studied, namely, acetylacetone, the resulting pentane-2,4-diol gave a stable complex and reacted with boric acid to give almost quantitatively a single crystalline stable compound of the type (IIIb), m. p. 85°. The pure isomers in this set have only recently been described,[9] but their configurations were not determined. As will be shown below, there cannot be much doubt that it is the *meso*-form which is obtained. Pentane-2,4-diol from other sources (catalytic hydrogenation) was later shown to give a smaller yield of the high-melting ester, together with lower-melting fractions which contained also the ester of the other isomer, which, when pure, melts lower (37°) than any of these mixtures.

For other diketones there is no such general correlation between steric course and complex stability, as can be seen from Table 1. First, the reduction is less stereospecific; then, 1,2-diketones give as main reduction product in general the isomer which does not form a borate complex.

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[10] Böeseken and van Giffen, *Rec. Trav. chim.*, 1920, **39**, 183.
[11] Derx, *Rec. Trav. chim.*, 1922, **41**, 312.
[12] Böeseken (and Maan), *Ber.*, 1923, **56**, 2409.
[13] Hermans, *Proc. Roy. Acad. Amsterdam*, 1923, **26**, 32.
[14] Hermans, *Z. anorg. Chem.*, 1925, **142**, 83.
[15] Maan, *Rec. Trav. chim.*, 1929, **48**, 332.
[16] Pastureau and Veiler, *Compt. rend.*, 1936, **202**, 1683.
[17] Rippere and LaMer, *J. Phys. Chem.*, 1943, **47**, 204.
[18] Morell and Lathrop, *J. Amer. Chem. Soc.*, 1945, **67**, 879.
[19] Garner and Lucas, *J. Amer. Chem. Soc.*, 1950, **72**, 5497.
[20] Böeseken, *Ber.*, 1913, **46**, 2612.
[21] Hermans, *Z. phys. Chem.*, 1924, **113**, 337.
[22] Lees, Fulmer, and Underkofler, *Iowa State Coll. J. Sci.*, 1944, **18**, 359.
[23] Knowlton, Schieltz, and Macmillan, *J. Amer. Chem. Soc.*, 1946, **68**, 208.
[24] Hermans, *Ber.*, 1924, **57**, 824.

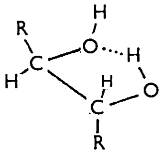
Table 1 shows also that lowering the temperature and increasing the dilution, in the cases so far studied, make the reduction more stereospecific. It is not quite clear what conclusions may be drawn with regard to the reaction mechanism, especially since they will depend on what conformation is assumed for the acyclic diketones in solution and since it is not known whether both carbonyl groups are reduced simultaneously by the same borohydride anion or in a clear two-step reaction, as indicated in the case of benzil (see p. 920).

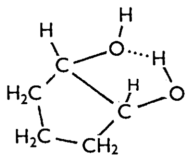
TABLE 2. *Physical properties of isomeric diols.*

	OH infrared band		Melting point	
Diol	*meso*	Racemate	*meso*	Racemate
Pentane-2,4-diol	Double [9]	Double [9]	Liquid	52—53° [9]
2,2,6,6-Tetramethylheptane-3,5-diol	Single	Double	99—100°	174
1,3-Diphenylpropane-1,3-diol	Single	Double	108—109	130
Butane-2,3-diol	Double [a,b]	Double [a,b]	34 [d]	7 [d]
2,2,5,5-Tetramethylhexane-3,4-diol	Single [b]	Double [b]	123	—
1,2-Diphenylethane-1,2-diol	Single	Double	136—137	119—120
	(*cis*)	(*trans*)	(*cis*)	(*trans*)
Cyclohexane-1,2-diol	Double [a,c]	Single [a,c]	98	104
Cyclopentane-1,2-diol	Double [a,c]	Single [a,c]	29—30 [11]	55

[a] Kuhn, *J. Amer. Chem. Soc.*, 1952, **74**, 2492. [b] *Idem, ibid.*, 1958, **80**, 5950. [c] *Idem, ibid.*, 1954, **76**, 4323. [d] Wilson and Lucas, *ibid.*, 1936, **58**, 2396.

Some physical properties of the isomeric diols have been compiled in Table 2. The assignment of configuration to the sets for which the racemate has not been resolved are based on the behaviour towards boric acid. Additional support comes from a comparison of the melting points, which show striking regularities. Thus, among acyclic 1,3-diols it is always the racemate which is the higher melting; among acyclic 1,2-diols it is the *meso*-form. In pentane-2,4-diol the assignment is also supported by the fact that the cyclic borate of the *meso*-form, which has the higher symmetry, is the higher-melting.*


Racemate


cis

The OH stretching absorptions in the infrared region likewise reveal regularities. It has already been shown by Kuhn [25-27] that the acyclic racemic 1,2-diols and *cis*-cyclopentane-1,2-diol show a double band because of internal hydrogen bonding, leading to non-equivalent hydroxyl groups, whereas *meso*-diols (with large R groups) and *trans*-cyclopentane-1,2-diol can only form equivalent external hydrogen-bonds, or remain non-bonded in dilute solution, and therefore show a single hydroxyl band. By similar reasoning one would expect that in acyclic 1,3-diols only the *meso*-form should form an internal hydrogen bond and should give a doublet in the hydroxyl region if the ring which is formed has to be non-planar. Instead it is observed that also here it is the racemate which has a doublet and the *meso*-form which shows a single hydroxyl band. A possible explanation is that the hydrocarbon skeleton does not form the supposed planar zig-zag stretched-out

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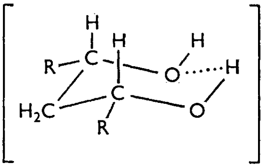
* Further support has been obtained by Dr. J. F. M. Oth (personal communication) from the nuclear magnetic resonance spectra of the two borates.

[25] Kuhn, *J. Amer. Chem. Soc.*, 1952, **74**, 2492.
[26] Kuhn, *J. Amer. Chem. Soc.*, 1954, **76**, 4323.
[27] Kuhn, *J. Amer. Chem. Soc.*, 1958, **80**, 5950.

chain, but is helically twisted, as in many polymers with 1,3-substituents along a hydrocarbon chain, thereby making the ring approximately planar: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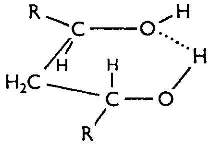
Racemate

With bulky R groups, therefore, only the racemate should be capable of forming the internally hydrogen-bonded ring-structure.

When R is t-butyl, that is in 2,2,6,6-tetramethylheptane-3,5-diol, another abnormality was noted. The separation method worked well, but surprisingly in the reversed sense, although the behaviour towards boric acid itself was normal inasmuch as only the *meso*-isomer formed an ester. The reason may be that the t-butyl groups are so bulky that none of the isomers can form a cyclic compound when there is an extra hydroxyl group on the boron atom, as is the case in the complex. On the other hand, the racemate may form more easily a polymer with sodium borate, which may be preferentially stabilized by the shielding effect of the big groups.

Finally it should be mentioned that in the case of 1,3-diphenylpropane-1,3-diol [2,3,28] only the higher-melting racemic isomer has earlier been obtained pure, and reported attempts to isolate the *meso*-form have failed (reported m. p. of isomer mixture 94—98°). This mixture could easily be separated by the borate method into the pure isomers. On the other hand, it was observed that the racemate, m. p. 130°, sometimes contained crystals which remained unmelted up to 150°, close to the melting point of each of the antipodes.[29] Obviously, one had to do with one of the rare cases when optical resolution occurs spontaneously by crystallization. By slow evaporation of methanol solutions at room temperature, crystals were obtained which separately melted at 152°. They had no typical left- or right-handed shape allowing sorting by handpicking, but the optical activity of the biggest ones could be measured separately in solution and showed either positive or negative rotation. However, the rotation was much lower than reported for the pure antipodes,[29] so evidently the big crystals are conglomerates.

We have here the strange case of an isomer set, in which the *meso*-form cannot be separated from the racemate by crystallization, although the racemate itself can be resolved spontaneously by crystallization.

EXPERIMENTAL

Reduction of Acetylacetone.—In a typical experiment acetylacetone (20 g.) in methanol (50 ml.) was dropped slowly into a stirred solution of sodium borohydride (5 g.) and sodium hydroxide (0·1 g.) in water (50 ml.). The reaction is exothermic and the temperature was kept below 20°. Then the mixture was left overnight or refluxed for 20 min. (Alternatively the sodium borohydride was added to the acetylacetone solution.) The methanol was distilled off and, on cooling, crystals were obtained. On further concentration and crystallization a total of about 30 g. may be obtained. The substance easily loses water but does not melt. Extraction of this solid sodium borate complex with chloroform yielded no material.

If the complex is dissolved in 2N-sulphuric acid and the neutral or acid solution extracted with chloroform, a liquid is obtained which on distillation gives a boron-free fraction, b. p. 201°/760 mm., 98°/10 mm., n_D^{24} 1·4335 (pentane-2,4-diol), and another fraction, b. p. 300—310°/760 mm., 190°/13 mm., n_D^{24} 1·4355. The latter compound is a very viscous oil, contains boron, can be titrated by alkali, and has no infrared OH absorption, and so must be the

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[28] Zimmerman and English, *J. Amer. Chem. Soc.*, 1954, **76**, 2285.
[29] Stühmer and Frey, *Arch. Pharm.*, 1953, **286**, 26.

*tri(pentane-*2,4-*diol) diborate* (Found: C, 54·6; H, 9·2; B, 6·6. $C_{15}H_{30}B_2O_6$ requires C, 54·9; H, 9·2; B, 6·6%). In humid air, or on addition of water, it hydrolyses, and needle-shaped crystals separate. These recrystallized from benzene–light petroleum as prisms, m. p. 82—83°, and were identified as *meso*-pentane-2,4-diol borate [9] (Found: C, 46·3; H, 8·8; B, 8·2. Calc. for $C_5H_{11}BO_3$: C, 46·2; H, 8·5; B, 8·3%); they show infrared OH absorption. The monoborate is also obtained directly by treating one mol. of diol with one mol. of boric acid. Likewise, when two mol. of the monoborate are treated with one of the diol, the high-boiling trisdiol diborate is formed.

The most efficient method of isolating the diol free from borates consisted in concentrating the initial reaction mixture or dissolving the alkali borate complex in a small quantity of water and extracting it a reasonable number of times with chloroform, that is, until about half of the diol is obtained. Then the solution is acidified and extracted to give a mixture of the diol and the monoborate. This mixture is then treated with alkali, and the alkaline solution thus obtained has a lower borate content and can be extracted again to yield a new crop of pure diol. If the procedure is repeated several times the total yield of pentanediol surpasses 90% and it can be practically completely converted into the high-melting boric ester, which is the *meso*-form (see discussion).

When acetylacetone in the form of its sodium salt is treated with sodium borohydride, no reaction takes place: the temperature remains constant even if the whole portion is added at once. However, the diketone is slowly hydrolyzed to acetone and acetate, and after storage overnight a nearly quantitative yield of propan-2-ol can be obtained.

*Attempts to separate the Pentane-*2,4-*diol Isomers.*—An isomeric mixture, b. p. 86—88°/5 mm., of pentane-2,4-diols was obtained by catalytic hydrogenation of acetylacetone over Raney nickel at 100°/(initial)136 atm. in 83% yield. The crude boric ester was prepared and melted in the range 60—70°. Partial separation of this borate mixture was achieved by fractional crystallization from hexane, but was very slow and tedious. The diol mixture was also treated with an excess of sodium metaborate in water, and the water evaporated, but nothing could be extracted from this solid with chloroform. Apparently, in this system both isomers form a complex.

If an insufficient amount of sodium borate is used, the excess of diol can be extracted if the evaporation is not complete, but if the water is removed completely, the chloroform-soluble "spiro"-complex (IIb) is extracted. It can be prepared by mixing calculated quantities of the components, and is precipitated slowly from a concentrated chloroform solution. It is an amorphous solid and does not melt below 350°. It burns in a flame to leave a white residue. The expected amount of sodium chloride was precipitated when dry hydrogen chloride was bubbled into a chloroform solution of this complex.

When the original diol mixture was left for a week at room temperature, it crystallized partly. After another week at 0° about 8% had crystallized and was filtered off. This crude racemic diol had m. p. 40—47° (reported [9] m. p. 52—53°) which could not be raised further by recrystallization from benzene–carbon disulphide. As with the *meso*-diol, the cyclic borate of the racemic diol can be prepared simply by mixing the diol with an excess of boric acid in a little water and extracting the product with chloroform. After recrystallization from very little hexane at 0° the racemic pentane-2,4-diol borate melted at 40° (reported [9] m. p. 37°) (Found: C, 45·9; H, 8·6; B, 8·3. Calc. for $C_5H_{11}BO_3$: C, 46·2; H, 8·5; B, 8·3%). When the diol was esterified with boric acid by azeotropic distillation of the formed water with chloroform a liquid was obtained having b. p. 102—104°, n_D^{21} 1·4336. It contained no hydroxyl group, but all CH proton signals in the nuclear magnetic resonance spectrum were identical with those of the above ester; hence it must be racemic *pentane-*2,4-*diol borate anhydride* (Found: C, 49·45; H, 8·6; B, 8·7. $C_{10}H_{20}B_2O_5$ requires C, 49·65; H, 8·35; B, 8·95%). Addition of the calculated quantity of water to the liquid caused complete solidification, and recrystallization of the solid gave the same ester as was obtained by the first method.

Pentane-2,4-diol was also prepared from aldol in a Grignard reaction with methylmagnesium iodide in 20% yield. The m. p. of the boric ester from this product could not be raised above 69—73° by fractional crystallization.

Reduction of 2,2,6,6-*Tetramethylheptane*-3,5-*dione.*—The 1,3-diketone (furnished by Miss J. Golaire, University of Liège) was prepared in a Claisen condensation between phenyl pivalate and pinacolone.[30] Then a methanolic solution of sodium borohydride (200 mg.) and a little

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[30] Man, Swamer, and Hauser, *J. Amer. Chem. Soc.*, 1951, **73**, 901.

sodium hydroxide (15 mg.) was dropped slowly into a stirred solution of this diketone (210 mg.) in methanol. After refluxing for 1 hr. the solution was evaporated and the residue extracted with ether. A solid (120 mg.) was obtained which recrystallized from pentane. It sublimed at 70°/0·2 mm. as needles, m. p. 99—100°, and must be one isomeric 2,2,6,6-*tetramethylheptane*-3,5-*diol* (Found: C, 69·9; H, 12·6. $C_{11}H_{24}O_2$ requires C, 70·15; H, 12·8%). The solid complex was treated with water and extracted with ether. Crystallization from hexane yielded the isomeric diol (33 mg.) as fibre-like crystals, m. p. 174° (determined in a sealed capillary owing to sublimation) (Found: C, 70·0; H, 12·7%).

The higher-melting isomer was recovered unchanged when it was evaporated with boric acid in methanol and the residue extracted with benzene, whereas the lower-melting isomer gave its borate anhydride, m. p. 130—131° after crystallization from pentane and sublimation at 100°/0·3 mm. (Found: C, 64·15; H, 10·9. $C_{22}H_{44}B_2O_5$ requires C, 64·4; H, 10·8%). Further, since the higher-melting isomer has a double infrared OH band, and the lower-melting a single band, there is no doubt that they represent the racemate and the *meso*-form respectively; that is, the separation method works in the opposite sense.

A mixture of the two isomers shows no depressed m. p., but melts at an intermediate temperature. The *meso*-form could not be obtained pure by crystallization of such mixtures.

When the diketone is hydrogenated over Raney nickel the racemate is obtained in a yield of 63% and the *meso*-form only in 4% (personal communication from Miss J. Golaire).

Reduction of Dibenzoylmethane.—A methanolic solution of sodium borohydride (1 g.) and sodium hydroxide (0·07 g.) was dropped into a stirred solution of dibenzoylmethane (9 g.) in methanol. There was little evolution of heat and the mixture was refluxed for 2 hr.

If the solution is neutralized or acidified, the methanol removed, and the aqueous solution then extracted with ether, a semisolid is obtained which by crystallization from benzene gives racemic 1,3-diphenylpropane-1,3-diol (2·2 g.), m. p. 128—129°. The benzene mother-liquor contains boron; it can be washed free from boron with alkali, and then on evaporation provides material which by crystallization from benzene–light petroleum furnishes an inhomogeneous substance (5·7 g.), m. p. 92—97°; this cannot be further resolved by crystallization. However, when this mixture is treated with an excess of sodium metaborate in water–methanol and evaporated, and the dry residue extracted with ether, another crop of the racemic diol (1·0 g.) is obtained. The residue is then dissolved in water, and the solution extracted with ether. Crystallization from benzene gives needles (4·7 g.), m. p. 108—109°. A comparison of the infrared spectra shows that the product does not contain the racemate; hence it must be the pure meso-1,3-*diphenylpropane*-1,3-*diol* (Found: C, 79·1; H, 6·9. $C_{15}H_{16}O_2$ requires C, 78·9; H, 7·05%).

The preferred method is to evaporate the alkaline reaction mixture directly, and extract the residue to yield the racemate, whereafter the residue is dissolved in water and this solution extracted to yield the *meso*-form.

When the amount of alkali, which is added to stabilize the sodium borohydride solution, is substantially higher, the yield becomes lower and complications arise during the working-up. Thus, the sodium salt of dibenzoylmethane (yellowish needles, m. p. > 330°) and a reduced hydrolysis product, α-methylbenzyl alcohol, enter the ether together with the racemic diol. If sufficient alkali is added to neutralize the dibenzoylmethane completely, no reduction takes place, but after 2 hours' refluxing the substance is partly hydrolysed into acetophenone and benzoate, as α-methylbenzyl alcohol and benzoic acid were isolated, and only 40% of the starting material was recovered.

Whereas the total yield of diols thus seems to be determined chiefly by the amount of alkali added, a decrease of the reaction temperature, and of the concentration of both reactants, had a marked effect on the relative yields of the two isomers (cf. Table 1). A typical "high-dilution" experiment was performed as follows: A solution of dibenzoylmethane (3 g.) in methanol (200 ml.) and another solution of sodium borohydride (1 g.) and sodium hydroxide (0·1 g.) in methanol (100 ml.) were dropped slowly at the same time into 250 ml. of methanol with stirring. The products were isolated as described above.

Spontaneous Resolution of Racemic 1,3-*Diphenylpropane*-1,3-*diol.*—Crystallization from benzene or ethyl acetate or mixtures thereof yielded in general only the racemate, m. p. 130°. Occasionally, some needles melted at 150°. When a concentrated methanol solution was left overnight at room temperature in an open vessel, big crystals of the antipodes were obtained, m. p. 151·5° (lit.,[29] 152·5°). Some of them were as long as 2 cm. and weighed 800 mg. Single crystals were dissolved separately in methanol and the specific rotation measured. For crystals weighing from 50 to 100 mg. $[\alpha]_D^{20}$ varied between 20° and 40°, positive or negative. Stühmer and Frey [29] report $\pm 106{\cdot}5°$. With bigger crystals even lower values were obtained. Evidently, the bigger the crystal, the higher the probability of formation of a conglomerate.

Reduction of Biacetyl.—A solution of biacetyl (34·4 g.) in water (50 ml.) and methanol (25 ml.) was dropped slowly into a solution of sodium borohydride (10 g.) and sodium hydroxide (0·6 g.) in water (100 ml.). The temperature was kept at 15—20°. The mixture became colourless. After a short period of heating, the solution was concentrated until crystallization of the complex began, and the *meso*-butane-2,3-diol was then extracted with chloroform. The quantity corresponding to the excess of diol over sodium borate in the solution was easily extracted, but repeated extractions were necessary to remove the rest of the *meso*-diol. The product (13·8 g.) distilled at 58—60°/0·4 mm. as a viscous oil,[23] n_D^{24} 1·4372. It was identified as its di-*p*-nitrobenzoate,[31] m. p. 188—189°, obtained in 95% yield. The borate solution was then acidified and extracted with ether. A ~1 : 3 mixture (20·4 g.) of the racemic butane-2,3-diol and its borate was obtained. The free diol was isolated by treatment of the mixture with excess of concentrated sodium hydroxide solution and extraction with chloroform, whereupon the solution was again acidified and the whole process repeated to yield another crop of borate-free diol. However, the method became much more efficient if the mixture was treated with the exactly calculated quantity of water to hydrolyse the borate, and the precipitated boric acid filtered off, before the alkali treatment. (N.B. Excess of water redissolves the boric acid.) The racemic diol distilled at 176°/760 mm., had n_D^{24} 1·4318, and was identified as its di-*p*-nitrobenzoate,[31] m. p. 128°, obtained in 90% yield.

If each of the butane-2,3-diol isomers is treated with an excess of sodium borate in water, a precipitate is formed. After evaporation nothing can be extracted from the residue with chloroform.

*Butane-*2,3-*diol Borates.*—Each of the diols was treated with an excess of boric acid and the water removed by azeotropic distillation with chloroform. The *meso*-butane-2,3-diol borate anhydride distilled at 160—180°/11 mm. as an extremely viscous oil, n_D^{22} 1·4360 (cf. Morell and Lathrop [18]), indicating that the ring structure is somewhat unstable so that partial rearrangement into polymeric structures takes place in the condensed state (Found: C, 45·3; H, 8·1; B, 9·2. Calc. for $C_8H_{16}B_2O_5$: C, 44·9; H, 7·55; B, 10·1%). The racemic *butane-*2,3-*diol borate anhydride* distilled at 82—89°/0·7 mm. as a moderately viscous liquid, n_D^{27} 1·4233 (Found: C, 44·2; H, 7·55; B, 9·8%). Each of the borates was treated with the calculated quantity of water (one mol.) necessary to produce the simple cyclic borate, but instead the corresponding quantity of boric acid was precipitated.

Preparation of Pivaloin and Bipivaloyl.—Ethyl pivalate was prepared by heating pivalic acid (50 g.) and absolute ethanol (125 ml.) in an autoclave at 200°/25 atm. for 64 hr. in the absence of a catalyst. As the ester is very volatile with ethanol, the ethanol was not distilled, but the reaction mixture diluted with a four-fold volume of water and extracted with ether, then dried and distilled. 50·6 g. (80%) of the ester, n_D^{20} 1·3920, passed over at 118°/760 mm.

The ester was condensed with sodium [32] and gave a 60% yield of pivaloin, b. p. 85—95°/12 mm., together with a 12% yield of the yellow bipivaloyl, b. p. 55—60°/12 mm.

Bipivaloyl was also obtained by oxidation of pivaloin with chromic acid [33] in a yield of 57% (b. p. 161—170°/760 mm.).

Reduction of Bipivaloyl.—A solution of sodium borohydride (0·8 g.) in methanol containing sodium hydroxide (0·1 g.) and a little water was added dropwise to a stirred solution of bipivaloyl (3·60 g.) in methanol at 30—35°. After refluxing for 1 hr., the colourless solution was evaporated, and the solid mass extracted with benzene (ether dissolves also the complex). The benzene was evaporated and yielded the known [27] *meso*-2,2,5,5-tetramethylhexane-3,4-diol (2·13 g.), m. p. 120°, which, recrystallized from hexane, had m. p. 125°.

The residue from the benzene treatment was dissolved in 2N-sulphuric acid and extracted with ether. The ether solution slowly precipitated a solid. The ether was evaporated and the residue treated with hexane, whereby some boric acid remained undissolved. The hexane solution contained a solid (200 mg.) which, when heated first melted at 90—110°, then resolidified,

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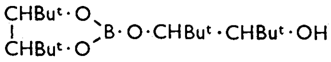
[31] Robertson and Neish, *Canad. J. Res.*, 1948, **26**, *B*, 737.

[32] *Org. Synth.*, Coll. Vol. II, p. 114.

[33] Leonard and Mader, *J. Amer. Chem. Soc.*, 1950, **72**, 5388.

and melted again at 150—151°. This substance was recrystallized from benzene–light petroleum, then having m. p. 152°. It contained boron and must be the mixed ester, 1,2-*di-t-butylethylene* 2-*hydroxy*-3,3-*dimethyl*-1-*t-butylbutyl monoborate,*



$$\begin{array}{l}\mathrm{CHBu^t\cdot O}\\ \quad|\\ \mathrm{CHBu^t\cdot O}\end{array}\!\!>\mathrm{B\cdot O\cdot CHBu^t\cdot CHBu^t\cdot OH}$$

(Found: C, 67·2; H, 11·4. $C_{20}H_{41}BO_4$ requires C, 67·4; H, 11·6%), with the racemic diol in the ring and the *meso*-diol in the side chain for the following reasons: The infrared spectrum of the solid shows a sharp band at 2·83 μ, indicating a sterically shielded, non-bonded hydroxyl group, which explains why the usual trisdiol diborate (IVb) is not formed and also the hydrolytic stability of the compound. Further, by treatment with aqueous-methanolic alkali, evaporation, and re-extraction of the residue, a crop of the *meso*-diol was obtained, while the residue after acidification yielded the cyclic racemic 2,2,5,5-*tetramethylhexane*-3,4-*diol monoborate,* which crystallizes from hexane as needles, m. p. 98—100° (Found: C, 59·9; H, 10·6; B, 5·4. $C_{10}H_{21}BO_3$ requires C, 60·05; H, 10·6; B, 5·4%). The infrared spectrum of this ester shows a hydroxyl band at 2·98 μ.

The free racemic diol could not be extracted from an alkaline aqueous solution of its borate even in the presence of mannitol, nor could the boron be removed as methyl borate or by refluxing in humid ether (to precipitate boric acid). In some cases the m. p. of the recovered material tended to rise as much as to 120°, and estimation of the boron by titration then showed that the *anhydride* had been formed (Found: B, 5·65. $C_{20}H_{40}B_2O_5$ requires B, 5·7%).

Reduction of Pivaloin.—2,2,5,5-Tetramethylhexane-3,4-diol was also obtained in a similar reduction of pivaloin with sodium borohydride. At room temperature the yield of the *meso*-diol was 81%, of the racemic diol only 0·2%. In refluxing methanol the yield of the *meso*-form was 84%; no racemate was then isolated. As a comparison, pivaloin was reduced with lithium aluminium hydride in ether at −60° (cf. Kuhn [27]). The *meso*-diol was obtained in 80% and the racemic diol borate in 10% yield.

Attempts to isomerize meso-2,2,5,5-*Tetramethylhexane*-3,4-*diol to the Racemate.*—To obtain larger quantities of the racemic diol, the *meso*-diol was heated in a sealed tube with excess of boric acid in the hope that the formation of the stable borate of the racemate would favour conversion into this isomer. At 130° no change took place during 60 hr. Also after heating at 180°, the *meso*-form was recovered almost completely, together with very little (0·1%) of the mixed bisdiol monoborate (see above), m. p. 150—151°, and a volatile liquid. At 200° during 16 hr. the diol was completely converted into this liquid. The liquid had a ketonic smell and distilled at 148—150°/760 mm. The infrared spectrum showed the absence of hydroxyl groups and a strong band at 5·82 μ (ketone), hence it must be 2,2,5,5-tetramethylhexan-3-one, possibly containing some hydrocarbon (Found: C, 78·8; H, 12·7. Calc. for $C_{10}H_{20}O$: C, 76·9; H, 12·9%). When the boric acid was replaced by boron oxide, the ketone was formed already at 150°.

Reduction of Benzil.—A solution of sodium borohydride (1·5 g.) and sodium hydroxide (0·2 g.) in methanol (50 ml.) was dropped slowly into a cooled suspension of benzil (10·5 g.) in methanol (100 ml.) at 10—15°. No colour phenomena reported by Chaikin and Brown [1] were observed, only a gradual bleaching of the yellow colour of benzil. When approximately one keto-group had been reduced, the mixture consisted of a suspension of colourless crystals in a colourless liquid. On further reduction the crystals gradually dissolved. Finally, the solution was refluxed for 10 min. and left overnight.

If the reaction mixture is neutralized and worked up without utilizing the borate complex for separation, most of the hydrobenzoin (*meso*-1,2-diphenylethane-1,2-diol) crystallizes since it is the main product, but the next crystal crop melts at about 110° and is a mixture of hydrobenzoin and isohydrobenzoin (racemic 1,2-diphenylethane-1,2-diol) which is difficult to separate further by crystallization.

A quantitative separation was possible by evaporating directly the alkaline reaction mixture. In this case, however, the residue was almost completely soluble in chloroform and the extract consisted of a mixture of hydrobenzoin and the isohydrobenzoin–borate complex. When the mixture was boiled with benzene the hydrobenzoin passed into solution, from which it crystallized on cooling (8·45 g.; m. p. 136—137°). The complex was insoluble in benzene and melted with decomposition at about 220°. It was dissolved in 2N-sulphuric acid and the solution extracted with chloroform. 1·10 g. of isohydrobenzoin were obtained, having m. p. 119—120° after recrystallization from benzene or water.

The yield of each isomer is very close to the yield obtained with lithium aluminium hydride.[34] At higher temperatures the reduction was less stereospecific (Table 1).

Reduction of Cyclohexane-1,2-*dione*.—A solution of sodium borohydride (2 g.) and sodium hydroxide (0·1 g.) in water (100 ml.) was dropped slowly into a stirred solution of cyclohexane-1,2-dione (6·40 g.) in methanol (100 ml.). The temperature was kept between 6° and 10°. After evaporation (the last traces of water must be carefully removed) a solid remained from which *trans*-cyclohexane-1,2-diol (4·09 g.) was extracted with chloroform (m. p. 103—104° after crystallization from benzene). The residue was dissolved in water and the solution extracted with chloroform, yielding 0·70 g. of *cis*-cyclohexane-1,2-diol, m. p. 95—97°. The mixture of these two diols was inseparable by crystallization and started to melt at 60—70°.[35]

When the reduction was conducted at room temperature, there was practically no stereospecificity (cf. Table 1).

With lithium aluminium hydride only one keto-group is reduced.[34]

The cis-*cyclohexane*-1,2-*diol borate* was prepared separately from 4 g. of *cis*-diol and an excess of boric acid by azeotropic distillation of the water with chloroform. On distillation the main fraction passed over at 190°/10^{-3} mm. and solidified to a glass which analysis showed to be the *anhydride* (Found: C, 54·15; H, 7·95; B, 7·9. $C_{12}H_{20}B_2O_5$ requires C, 54·2; H, 7·6; B, 8·15%). It is insoluble in carbon tetrachloride and hydrolyzed completely in water.

Reduction of Cyclopentane-1,2-*dione*.—Cyclopentane-1,2-dione, m. p. 52—53°, was prepared according to Dieckmann's directions.[36] A solution of the diketone (630 mg.) in water was dropped into a stirred solution of sodium borohydride (250 mg.) in water containing a little alkali. The temperature increased slowly from 20° to 35°. Finally the mixture was heated, then concentrated until crystallization began. Several extractions with chloroform yielded a total of about 390 mg. of boron-free oil which was distilled *in vacuo*; it then had m. p. 55°, hence it must be pure *trans*-cyclopentane-1,2-diol.[11] It is very hygroscopic; sublimed crystals liquefy at once when exposed to air. The remaining solid borate complex of the *cis*-diol was acidified with sulphuric acid and extracted with chloroform. About 240 mg. of a viscous oil were obtained, which is practically pure *cis*-cyclopentane-1,2-diol borate. When treated with a concentrated solution of alkali no free diol could be extracted, but after addition of a large excess of mannitol the *cis*-diol was liberated and could be slowly extracted. It distilled at 98°/9 mm. and had $n_D^{24\cdot5}$ 1·4736.

cis-Cyclopentane-1,2-diol borate was also prepared separately from 16 g. of *cis*-diol and excess of boric acid by azeotropic distillation of the water. It distilled at 117—119°/0·5 mm., as a liquid, n_D^{15} 1·4710, which later crystallized. The m. p. 32—43°, could not be improved by recrystallization. The substance is extremely hygroscopic, and analysis shows it to be present mainly in the form of its *anhydride* (Found: C, 49·5; H, 7·1; B, 9·05. $C_{10}H_{16}B_2O_5$ requires C, 50·5; H, 6·8; B, 9·1%).

Attempts to reduce Cyclohexane-1,3-*diones*.—Cyclohexane-1,3-dione and 5,5-dimethylcyclohexane-1,3-dione (dimedone) rapidly decomposed the sodium borohydride and were recovered practically completely after the reaction. If the diones were used in the form of their sodium salts, no temperature rise was observed when the borohydride was added. Even after 4 hours' refluxing, the starting material could be recovered almost completely.

Preparation of Diacetylacetone.—2,6-Dimethyl-4-pyrone was prepared by treating dehydroacetic acid (70 g.) with concentrated hydrochloric acid.[37] The dimethylpyrone was then treated with barium hydroxide, and the barium salt isolated.[38] Cautious acidification of a suspension of the salt in cold water and extraction with ether yielded the triketone (28 g.) which, recrystallized from light petroleum below 40°, had m. p. 49°.

Reduction of Diacetylacetone.—A solution of sodium borohydride (8·1 g.) and sodium hydroxide (0·2 g.) in water (100 ml.) was dropped into a stirred and cooled solution of diacetylacetone (19 g.) in methanol (100 ml.). The reaction was strongly exothermic, and the solution was maintained at 20°. When about two-thirds of the borohydride had been added, further addition

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[34] Trevoy and Brown, *J. Amer. Chem. Soc.*, 1949, **71**, 1675.

[35] Svirbely and Goldhagen, *J. Phys. Chem.*, 1953, **57**, 597.

[36] Dieckmann, *Ber.*, 1894, **27**, 102, 965; 1897, **30**, 1470; 1902, **35**, 3208.

[37] King, Ozog, and Moffat, *J. Amer. Chem. Soc.*, 1951, **73**, 301.

[38] Feist, *Annalen*, 1890, **257**, 276.

did not produce a heat effect even when the rest was added all at once. After neutralization with 4N-sulphuric acid the mixture was evaporated and the residue extracted with chloroform to yield 15 g. of a very viscous boron-containing oil. The infrared spectrum showed the presence of hydroxyl groups and the absence of carbonyl and olefin absorption. Treatment with concentrated alkali gave an insoluble amorphous, ill-defined complex. For this reason and in view of the larger number of possible isomers, no serious attempt was made to effect separation or quantitative isolation of the isomers, but the solid was extracted with ether to give a viscous boron-free *heptane*-2,4,6-*triol*, b. p. 128—132°/0·02 mm., n_D^{23} 1·4642 (2·3 g.) (Found: C, 56·65; H, 11·0. $C_7H_{16}O_3$ requires C, 56·7; H, 10·9%). After long standing a part of the oil crystallized. The crystals (0·55 g.) were pressed dry on a porous plate. They were insoluble in ether; but soluble in acetone, and had m. p. 91·5° after recrystallization from dioxan.

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