42. *Eight- and Higher-membered Ring Compounds. Part II. Di-, Tri-, Tetra-, and Hexa-salicylides.*

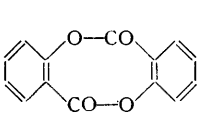
By Wilson Baker, W. D. Ollis, and T. S. Zealley.

An account is given of previous work on the anhydrosalicylic acids, and of their complete re-investigation which has been carried out. The compounds formerly described as α- and β-disalicylides have proved to be *cis*-disalicylide (I), and trisalicylide (IV) respectively. Polysalicylide is shown to be hexasalicylide (VI). The hydrolysis of these compounds and their reaction with benzylamine have been studied, and their stereochemistry is discussed.

The anhydro-derivatives of salicylic acid were chosen for early investigation in this work because, although they had been previously extensively examined there were some discrepancies in the literature, and because several such compounds had been described including two disalicylides and a tetrasalicylide (V). The two disalicylides (I) were originally supposed to be structurally different (R. Anschütz, *Ber.*, 1919, **52**, 1875; *J. pr. Chem.*, 1922,

105, 158; R. Anschütz and Riepenkröger, *Annalen*, 1924, **439**, 1), but Höhn later suggested (Richter–Anschütz, " Chemie der Kohlenstoff-Verbindungen," 1935, Vol. II, 2, 393) that they were geometrical isomers possessing " chair " and " trough " structures.

Stereoisomerism of this type has been discussed for the general case by Baker, Banks, Lyon, and Mann (*J.*, 1945, 27, where photographs of models are given), who showed that the centrosymmetrical *trans*- (or " chair ") form is rigid, whilst the *cis*- (or " trough ") form is mobile. The forms are interconvertible only by passage through a highly strained configuration or by breaking and reforming of a bond (cf. Roberts, *J. Amer. Chem. Soc.*, 1950, **72**, 3300). L. Anschütz and Neher (*J. pr. Chem.*, 1941, **159**, 264; *Ber.*, 1944, **77**, 634), in discussing the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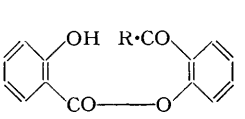
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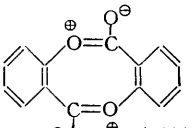
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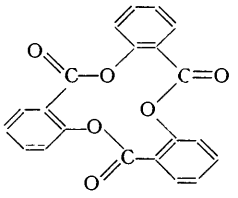
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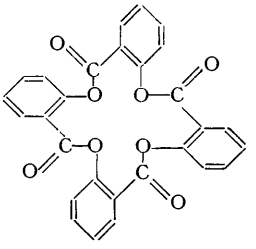
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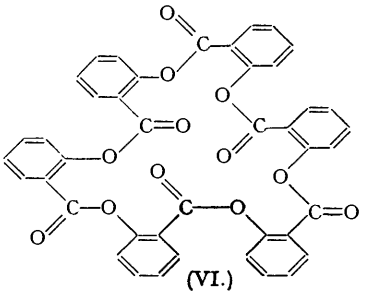

(VI.)

possible stereoisomerism of α- and β-" disalicylide " (see later) referred to the difficulty that, whereas the α-form is readily prepared from, and converted into, salicyloylsalicylic acid (" Diplosal ") (II; R = OH) and its derivatives, the β-form is not readily converted into this acid. L. Anschütz and Mayer (*J. pr. Chem.*, 1942, **159**, 343) and Meerwein (*Ber.*, 1941, **74**, 52) have commented on the absence of analogous cases of stereoisomerism, whilst Schönberg (*J.*, 1948, 891) has suggested that the two forms of disalicylide are stabilised by resonance which would give some double-bond character to the bridge carbon–oxygen bonds (see III). It appeared to the present authors that although resonance should favour the extreme *cis*-configuration, it should cause the *trans*-form, where resonance is scarcely possible in the ester groups, to be relatively less stable (*Nature*, 1949, **164**, 1049), and in view of these considerations it was felt desirable to re-investigate the anhydrosalicylic acids *de novo*. The chief result, already briefly reported (*loc. cit.*), has been to show that " β-disalicylide " is in fact trisalicylide (IV), containing a twelve-membered ring, and it has now been established that " polysalicylide " is hexasalicylide (VI) containing a twenty-four-membered ring.

The table gives the four known salicylides, previous authors (full references are given elsewhere in the text), former names, melting points, and molecular weights.

cis-*Disalicylide and Trisalicylide.*

Treatment of salicylic acid either with carbonyl chloride in pyridine (Einhorn and Pfeiffer, *Ber.*, 1901, **34**, 2952) or with phosphorus oxychloride in pyridine (Einhorn and Mettler, *Ber.*, 1902, **35**, 3646) gave a compound, m. p. 200—201°, in the latter case in 5% yield, whose molecular weight (see Table) supported a disalicylide structure. We also find that the first reaction gives a very low yield of this compound. In 1919 R. Anschütz (*loc. cit.*) followed up the earlier work of W. H. Perkin, sen., who had prepared xanthone by the distillation of salicylic acid and acetic anhydride (*Ber.*, 1883, **16**, 339; *J.*, 1883, **43**, 35), by carrying out the same distillation under diminished pressure. He isolated an " α-disalicylide," m. p. 213°, and a " β-disalicylide," considered to be identical with the substance, m. p. 200—201°, already described by Einhorn *et al.*

We find that when *O*-acetylsalicylic acid is heated under diminished pressure, acetic acid first distils in slightly less than the calculated amount, leaving a residue which is probably a polymeric anhydride, $H[O{\cdot}C_6H_4{\cdot}CO]_n{\cdot}OH$. No crystalline products can be isolated from this material, but after distillation at 300—350° two salicylides can be isolated by crystallisation,

and it appears that thermal degradation of the polymer occurs on distillation. One salicylide, m. p. 234° (24—30% yield), corresponds except for the higher melting point with "α-disalicylide," and the other, m. p. 200° (9—24% yield), was shown by direct comparison to be identical with the salicylide prepared by either of Einhorn's methods. R. Anschütz and Riepenkröger (*Annalen*, 1924, **439**, 3) have also prepared α-disalicylide, m. p. 210—212°, by reaction of salicyloyl chloride with diethylaniline, and repetition of this reaction has given us a product, m. p. 234°, identical with that prepared from *O*-acetylsalicylic acid, and in addition a smaller quantity of the salicylide, m. p. 200°. It is of interest that Schroeter (*Ber.*, 1919, **52**, 2224) obtained a disalicylide, m. p. 234°, believed to be identical with Anschütz's α-disalicylide, from salicyloylsalicyloyl chloride, $HO{\cdot}C_6H_4{\cdot}CO{\cdot}O{\cdot}C_6H_4{\cdot}COCl$, by reaction with diethylaniline.

Author(s)	Name	M. p.	Mol. wt. average
	cis-Disalicylide (*M* 240).		
R. Anschütz (1919)	α-Disalicylide	213°	231*a*
Schroeter (1919)	Salosalicylide	234	227*a*, 250*b*, 250*h*
R. Anschütz and Riepenkröger (1924)	α-Disalicylide	210—212	—
L. Anschütz and Neher (1941)	,,	213	—
L. Anschütz and Neher (1944)	,,	213—218	—
This paper	*cis*-Disalicylide	234 (decomp.)	236*c*, 248*d*, 291*e*
	Trisalicylide (*M* 360).		
Einhorn and Pfeiffer (1901)	Disalicylide	200—201°	275*a*, 279*c*
Einhorn and Mettler (1902)	,,	200—201	—
R. Anschütz (1919)	β-Disalicylide	199—200	—
L. Anschütz and Neher (1941)	,,	199—200	—
L. Anschütz and Mayer (1942)	,,	—	260*a*, 238*d*, 264*f*, 258*g*
L. Anschütz and Neher (1944)	,,	197—203	—
This paper	Trisalicylide	200	338*c*, 378*d*, 395*e*, 362*f*, 365*g*, 354±10*i*
	Tetrasalicylide (*M* 480).		
R. Anschütz (1892; 1893)	Salicylide	261—262° 260—261	—
R. Anschütz and Schroeter (1893)	Tetrasalicylide	—	472*a*
Schroeter and Eisleb (1909)	,,	—	455*a*, 483*b*, 252*h*, 240 (443)*d*
Schroeter (1919)	Chloroform salicylide	—	—
Jusa and Janovitch (1938)	Tetrasalicylide	263	501*g*
This paper	,,	298—300	497*d*
	Hexasalicylide (*M* 720).		
R. Anschütz and Schroeter (1893)	Polysalicylide	322—325°	—
This paper	Hexasalicylide	375 (decomp.)	710 ± 20*i*

a = phenol (cryoscopic); *b* = nitrobenzene (cryoscopic); *c* = benzene (ebullioscopic); *d* = chloroform (ebullioscopic); *e* = dioxan (ebullioscopic); *f* = dioxan (cryoscopic); *g* = camphor (Rast); *h* = nitrobenzene (ebullioscopic); *i* = *X*-ray crystallographical method.

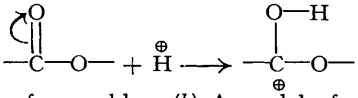
Re-determination of the molecular weights of these two salicylides by a variety of methods (see Table and Experimental section; also *Nature*, 1949, **164**, 1049) proved that the compound, m. p. 234°, is a disalicylide (I), but that the substance, m. p. 200°, is, without any possibility of doubt, trisalicylide (IV). The latter result is not in agreement with the molecular weights previously recorded (see Table), and the reason for these discrepancies is not clear. We have found, however, that consistent results are not obtained unless the solvents (particularly chloroform) are very carefully purified.

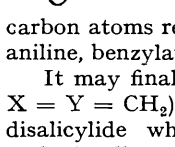
The disalicylide has been characterised as *cis*-disalicylide by determination of its dipole moment, which is 6·26 D. (Edgerley and Sutton, *Nature*, 1949, **164**, 1050; and forthcoming paper, "The stereochemistry of the salicylides and some related compounds," *J.*, in the press), and we therefore propose that the names α- and β-disalicylide be discarded and replaced by *cis*-disalicylide and trisalicylide respectively. Through the kindness of Professor L. Ansüchtz and Dr. Neher, we have been able to exchange specimens of these salicylides, and the complete identity of their α- and β-disalicylides with our *cis*-disalicylide and trisalicylide respectively has been proved by mixed-melting-point determinations, *X*-ray powder photographs (for which we are indebted to Dr. H. F. Kay and Miss B. Tucker of this University), and molecular-weight determinations. Professor L. Anschütz has accepted our identification of β-disalicylide as trisalicylide and at his request (letter dated 5th April, 1950) we quote his new molecular weights for α- and β-salicylides determined (at very high dilution owing to lack

of material) ebullioscopically in chloroform: α-compound, 217, 265; β-compound, 325, 368. It may be remarked that the melting point of *cis*-disalicylide depends to an appreciable extent on the rate of heating, and that our (corrected) melting point of 234° is obtained by rapid heating. Recent Raman spectra (Kohlrausch and Kahovec, *Monatsh.*, 1943, **74**, 333) and ultra-violet spectroscopic investigations (Wasmer, *Ber.*, 1949, **82**, 342) were interpreted in terms of *cis*- and *trans*-disalicylide forms, and now require re-interpretation in terms of *cis*-disalicylide and trisalicylide structures. Infra-red studies of the salicylides are being carried out by Mr. L. N. Short of the Physical Chemistry Laboratory, Oxford (forthcoming publication).

All the salicylides react with excess of alkali to give salicylic acid and with excess of benzylamine to give *N*-benzylsalicylamide. With methylmagnesium iodide, *cis*-disalicylide yields a mixture containing the dimeride of *o*-hydroxy*iso*propenylbenzene.

cis-Disalicylide is chemically the most reactive of the salicylides and under mild conditions gives derivatives of salicyloylsalicylic acid (II). Thus, with one equivalent of sodium hydroxide it gives salicyloylsalicylic acid (II; R = OH), with methanolic hydrogen chloride it gives methyl salicyloylsalicylate (II; R = OMe), with aniline it gives *O*-salicyloylsalicylanilide (II; R = NHPh), and with one equivalent of benzylamine it gives *N*-benzyl-*O*-salicyloylsalicylamide (II; R = $CH_2Ph{\cdot}NH$). When heated with glacial acetic acid containing about 5% of water, *cis*-disalicylide gives mainly salicyloylsalicylic acid (II; R = OH); under similar conditions phenyl benzoate is unaffected. With these reagents trisalicylide reacts much more slowly and only simple derivatives of salicylic acid can be isolated; we have utilised the greater reactivity of *cis*-disalicylide towards acetic acid to remove *cis*-disalicylide from crude trisalicylide.

In connection with the higher degree of reactivity of *cis*-disalicylide compared with trisalicylide and, in the case of acid hydrolysis, phenyl benzoate, two factors may be mentioned. (*a*) In *cis*-disalicylide the lactonic groups project so that reactions initially involving the carbonyl oxygen atoms, *e.g.*,  are facilitated, whereas in trisalicylide steric factors are less favourable. (*b*) A model of *cis*-disalicylide (see Fig. 1B, *J.*, 1945, facing p. 28) shows that in the $\cdot O{\cdot}C_6H_4{\cdot}CO{\cdot}O\cdot$ groupings the benzene rings and the ester groups are inclined at an angle of almost 90° to one another, so that there can be little resonance interaction between them of the type represented by the formula inset. In trisalicylide, however, these groups are almost coplanar. This restricted resonance in *cis*-disalicylide would cause a relative decrease in its stability compared with that of trisalicylide, and would render its carbonyl-carbon atoms relatively more cationoid and more readily attacked by anionoid reagents such as aniline, benzylamine, or alkali.



It may finally be noted that di-*o*-xylylene (*s*-dibenzo*cyclo*octadiene) (formula IV of Part I; X = Y = CH_2) possesses the *trans*-configuration (Davidson, *J.*, 1945, 30) in contrast to disalicylide which possesses the *cis*-configuration. Resonance requirements (see above) undoubtedly govern the formation of the *cis*-disalicylide. We have been unable, in the present work, to find *trans*-disalicylide and it has recently been shown that, like the salicylides, the two forms of each of the three " dicresotides " are, in fact, *cis*-dicresotides and tricresotides (Baker, Gilbert, Ollis, and Zealley, *Chem. and Ind.*, 1950, 333; following paper). The only apparent case of a substance of the general type (IV; Part I) existing in *cis*- and *trans*-stereoisomeric forms is provided by the two dithymotides derived from 2-hydroxy-6-methyl-3-*iso*propylbenzoic acid (*o*-thymotic acid) (Spallino and Provenzal, *Gazzetta*, 1909, **39**, II, 330), and a re-investigation of these compounds is in progress. *

Tetrasalicylide and Hexasalicylide.

R. Anschütz (*Ber.*, 1892, **25**, 3506, 3512; *Annalen*, 1893, **273**, 73; D.R.-P. 68,960, 69,708, 70,614; " Friedländer," 1893, **3**, 822, 824, 825) and R. Anschütz and Schroeter (*Annalen*, 1893, **273**, 97) have reviewed the early work on anhydrosalicylic acids (Gerhardt, *Annalen*, 1853, **87**, 159; Kraut, *ibid.*, 1869, **150**, 13; Schiff, *ibid.*, 1872, **163**, 218) which they regarded as inconclusive, and themselves prepared two compounds by dehydration of salicylic acid with phosphorus oxychloride in toluene or xylene. These compounds were described as tetrasalicylide (V), m. p. 260—261°, and " polysalicylide," $[O{\cdot}C_6H_4{\cdot}CO]_n$, m. p. 322—325°, both of which could be hydrolysed to salicylic acid and gave phenyl salicylate with phenol. The tetrasalicylide was

* *Added in Proof.*—It has now been found by Mr. B. Gilbert in this laboratory that these two supposed dithymotides are, in fact, di- and tri-thymotides.

characterised as a well-crystalline adduct with two molecules of chloroform (see *Ber.*, 1892, **25**, 3512). The molecular-weight determinations carried out in phenol could not be regarded as satisfactory, and Schroeter and Eisleb (*Annalen*, 1909, **367**, 164) made further determinations with very varying results (see Table). Tetrasalicylide was later prepared by Jusa and Janovitch (*Monatsh.*, 1938, **71**, 202) and a determination of the molecular weight was made in camphor (Rast), but in view of our observations that Rast determinations are unsatisfactory with the salicylides we have re-investigated this compound.

By interaction of salicylic acid and phosphorus oxychloride in toluene we obtained a mixture of products from which were isolated trisalicylide (1%), tetrasalicylide (m. p. 298—300°; 35%) and hexasalicylide [m. p. 375° (decomp.); 35%]. Determination of the molecular weight of tetrasalicylide ebullioscopically in chloroform (Table) confirmed its structure, and in spite of its melting point being higher than previously recorded, the formation of the chloroform complex showed that it was identical with the substance already described. The salicylide, m. p. 375°, is apparently identical with R. Anschütz and Schroeter's " polysalicylide " in spite of its much higher melting point; it crystallises well from boiling nitrobenzene, but has too low a solubility in organic solvents for the molecular weight to be determined in the usual way. *X*-Ray crystallographical studies kindly undertaken by Dr. Kay and Miss Tucker have proved that it is a hexasalicylide (VI) and they have reported as follows :

" The specimens consisted of small, colourless, monoclinic crystals with external faces (001) (1$\bar{1}$0) (110). *X*-Ray and direct measurement give $\beta = 75° \pm 2°$. The unit-cell dimensions were determined by single-crystal methods as $a = 15{\cdot}0 \pm 0{\cdot}1$, $b = 14{\cdot}3 \pm 0{\cdot}1$, $c = 8{\cdot}1 \pm 0{\cdot}1$ A.; calculated volume of unit cell = $(1684 \pm 40) \times 10^{-24}$ c.c.

" The density was determined by the flotation method in three different solvent mixtures, giving the mean value $1{\cdot}407 \pm 0{\cdot}005$ g./c.c. Hence the number of $O{\cdot}C_6H_4{\cdot}CO$ groups per unit cell is 12. This permits either 2, 4, or 6 molecules per unit cell, and as it is not di- or tri-salicylide, it must be hexasalicylide.

" From these measurements the molecular weight observed is 710 ± 20."

Mr. I. S. Loupekine of the Department of Geology has measured the three principal refractive indices of hexasalicylide; he reports as follows :

" The optic axial plane is (010); $Z \wedge c$ (in acute β) $= 15° \pm 3°$ (+) $2V = 30°$ approx. Refractive indices ($\pm 0{\cdot}003$) are $\alpha = 1{\cdot}602$, $\beta = 1{\cdot}611$, $\gamma = 1{\cdot}760$. These optical data do not give any conclusive evidence of a planar structure."

The formation of tetra- and hexa- rather than di- and tri-salicylides under the above reaction conditions has led us to investigate the action of phosphorus oxychloride on the various salicylides themselves. Under the normal conditions of reaction, *cis*-disalicylide was converted into a mixture of tetra- and hexa-salicylides, no trisalicylide being detected; trisalicylide was partly unchanged and partly converted into tetrasalicylide and hexasalicylide; tetrasalicylide was partly unchanged and partly converted into hexasalicylide and a small amount of tri-salicylide; hexasalicylide was unchanged. These results show that, in the presence of phosphorus oxychloride, the order of stability of the salicylides is *cis*-di- $\ll$ tri- $<$ tetra- $<$ hexa-salicylide; this may be partly due to the fact that the more insoluble products of higher molecular weight separate from the mixture during the reaction. The stabilities of the four salicylides towards hydrolysis with 2N-aqueous sodium hydroxide are also in the same order, but here again solubility may be a factor of importance (see Experimental). It may be recalled that L. Anschütz and Neher (*Ber.*, 1944, **77**, 638) found that treatment of salicyloylsalicylic acid with phosphorus oxychloride in xylene gave tri- (17·2%), tetra- (15·1%), and hexa-salicylide (53·8%).

Constellations of the Salicylides.

That disalicylide exists in the *cis*- rather than the *trans*-configuration appears to be caused by resonance requirements in the ester bridges; in the extreme folded form of the molecule there can be maximum contributions from the polarised ester groupings $-\overset{\ominus O}{\underset{|}{C}}=\overset{\oplus}{O}-$. Two enantiomorphs of *cis*-disalicylide are possible (see Beilstein, " Handbuch der Organischen Chemie," 4th Edn., 1934, **19**, 172, 500), but an attempt to effect its resolution (L. Anschütz and Neher, *Ber.*, 1944, **77**, 637) was unsuccessful. In a model these antipodes are interconvertible by manipulation without distortion of the normal bond angles or bond lengths, but in the intermediate twisted phase (see illustration of the model of the structurally similar molecule of *s*-dibenz*cyclo*octadiene, Fig. 1A in *J.*, 1945, facing p. 28) there can be little or no resonance in the ester groups, and the oxygen atoms of the two carbonyl groups are

brought close together so that steric interaction might occur. There is thus a considerable energy barrier to be surmounted before the optically active forms can be interconverted, and it seems likely that resolution into stable enantiomorphs may be possible.

In approaching the question of the constellation of the salicylides the following requirements must be borne in mind : (*a*) resonance will be at a maximum within the ester groups, —O—CO—, and between these groups and the benzene rings only when the whole molecule is flat; (*b*) steric interaction of atoms or groups must be absent or only slight; (*c*) normal bond lengths and intervalency angles must be maintained as far as possible; (*d*) the *trans*-ester configuration is likely to be favoured rather than the *cis*- (Marsden and Sutton, *J.*, 1936, 1383).

These points have been considered in discussing the structures of disalicylide and trisalicylide (this and the forthcoming paper by Edgerley and Sutton). The latter most probably possesses three *trans*-ester groups (IV), and, to meet the requirements (*b*) and (*c*) above and to give a dipole moment in agreement with that found (2·95 D.), it is necessary to assume that the three $\cdot C_6H_4\cdot CO\cdot O\cdot$ groups are arranged on the faces of a low triangular-based pyramid.

With regard to tetrasalicylide (V), a structure in which the four planar $O\cdot C_6H_4\cdot CO\cdot$ units are arranged alternately up and down round the central square of four oxygen atoms, satisfies the requirements (*b*) and (*c*) and is compatible with its dipole moment of 2·07 D.

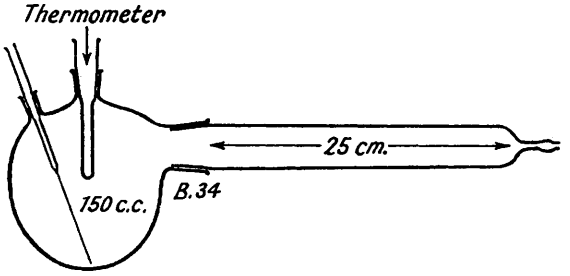
Pentasalicylide has not been found, and it seems most unlikely that it is formed in any of the reactions which have been investigated. It could not possess an alternating arrangement of the salicylide units, and its non-formation suggests that both tetra- and hexa-salicylide have some such arrangement of these groups. Hexasalicylide has a very low solubility in all solvents, and it has not been possible to determine its dipole moment. If we accept some alternating feature in its constellation, and as six *cis*-ester linkages are ruled out [see (*b*) and (*c*) above], it most probably has either six *trans*- or alternate *cis*- and *trans*-ester linkages. The latter is shown in formula (VI).

The complete solutions of these problems of constellation are only likely to be reached as the result of *X*-ray crystallographical studies.

Experimental.

All m. p.s are corrected. In cases where any decomposition occurred and the m. p. varied with the rate of heating, the m. p.s given were obtained by rapid heating, *i.e.*, the m. p. tube was placed in the bath, the temperature of which was steadily rising, some 5° below the final m. p. This procedure ensures the minimum accumulation of decomposition products before liquefaction, and gives a reproducible value. The discrepancies between some of our m. p.s and those previously recorded are almost certainly due to the difference between our method of m. p. determination with rapid heating and the more normal method of slower heating.

Action of Heat on O-*Acetylsalicylic Acid* (cis-*Disalicylide and Trisalicylide*).—(See R. Anschütz, *Ber.*, 1919, **52**, 1883.) The yields in this reaction are markedly dependent on the conditions of the experiment. The apparatus illustrated below was found to be the most satisfactory, the entire bulb being heated in an air-bath.



O-Acetylsalicylic acid (50 g.) was heated just above its m. p. (*ca.* 160°) at 15 mm. pressure and the temperature was increased slowly to *ca.* 200° during 0·5 hour, whereafter no more acetic acid (yield *ca.* 15 g.) was formed. The temperature was then increased to 300—350°/15 mm. and after 2—3 hours a semi-crystalline sublimate was obtained. This was triturated with 2N-sodium hydroxide, then with water, and dried (yield, 20—25 g.). Fractional crystallisation from chloroform gave *cis*-disalicylide (8—10 g., 24—30%) as colourless, twinned rhombs, m. p. 234° (decomp.) (Found : C, 69·8; H, 3·4. Calc. for $C_{14}H_8O_4$: C, 70·0; H, 3·4%). *cis*-Disalicylide crystallised unchanged from nitrobenzene or benzene (cf. Schroeter, *Ber.*, 1919, **52**, 2227).

The residue obtained from the chloroform mother-liquors was boiled with glacial acetic acid and a little water (5%) for 0·5 hour to hydrolyse remaining *cis*-disalicylide, and after removal of the acetic acid under reduced pressure, the residue was washed with 2N-sodium hydroxide, then water, dried, and

recrystallised several times from benzene, giving *trisalicylide* (3—8 g., 9—24%) as colourless needles, m. p. 200° (Found : C, 69·8; H, 3·2. $C_{21}H_{12}O_6$ requires C, 70·0; H, 3·4%).

In one experiment in which the temperature was maintained at 240—250°/0·5 mm., the sublimation required 6—7 hours for completion. The product (14 g.) from acetylsalicylic acid (50 g.), when worked up as before, gave *cis*-disalicylide (1·2 g.) and trisalicylide (0·4 g.), but the main product was xanthone (3·2 g.), m. p. 175°.

Action of Diethylaniline on Salicyloyl Chloride (cis-*Disalicylide and Trisalicylide*).—Salicyloyl chloride, prepared from salicylic acid (50 g.) (Kirpal, *Ber.*, 1930, **63**, 3190), was treated with diethylaniline as described by R. Anschütz and Riepenkröger (*Annalen*, 1924, **439**, 3). Repeated crystallisation of the final product from chloroform gave pure *cis*-disalicylide (10 g., 23%), m. p. and mixed m. p. 234° (decomp.).

Concentration of the original benzene–diethylaniline mother-liquors left a crystalline residue which, after several recrystallisations from benzene, was found to be trisalicylide (0·6 g., 1·4%), m. p. and mixed m. p. 200°.

Action of Phosphorus Oxychloride on Salicylic Acid (*Trisalicylide, Tetrasalicylide, and Hexasalicylide*).—Reaction of salicylic acid (50 g.) with redistilled phosphorus oxychloride (50 g.) in dry toluene (100 c.c.) at 100° was carried out as described by R. Anschütz and Schroeter (*Ber.*, 1892, **25**, 3506; *Annalen*, 1893, **273**, 76). The solid was collected and extracted with hot chloroform (500 c.c.), and the extract concentrated. The tetrasalicylide–chloroform complex separated as large, colourless rhombs which were heated at 100°/1 mm., giving tetrasalicylide (15 g., 35%) as opaque pseudomorphs, m. p. 298—300° (rapid heating) (Found : C, 69·6; H, 3·3. Calc. for $C_{28}H_{16}O_8$: C, 70·0; H, 3·4%). Recrystallisation from benzene gave colourless plates, m. p. 298—300°. The loss in weight when a freshly prepared specimen of the tetrasalicylide–chloroform *complex* (4·358 g.) was heated at 100°/1 mm. was 33·5%; $C_{28}H_{16}O_8,2CHCl_3$ requires $CHCl_3$, 33·2%.

The chloroform-insoluble material (15·3 g., 35%) was recrystallised form boiling nitrobenzene (1·5 l.), giving *hexasalicylide* as colourless, microcrystalline needles, m. p. 375° (rapid heating, decomp.; this m. p. was markedly dependent on the rate of heating) (Found : C, 69·8; H, 3·4. $C_{42}H_{24}O_{12}$ requires C, 70·0; H, 3·4%). Hexasalicylide very slowly sublimes unchanged at 200—250°/0·1 mm.

The original toluene solution obtained by filtration of the reaction mixture was washed with 2N-sodium hydroxide (acidification gave salicylic acid, 2·6 g., 5%), and a small amount of a sparingly soluble sodium salt separated at the interface. The toluene layer yielded a residue which, when recrystallised from benzene, gave trisalicylide (0·3 g., 1%), m. p. and mixed m. p. 200°.

Alkaline Hydrolysis of the Salicylides.—The finely powdered salicylides were heated at 100° with excess of 2N-sodium hydroxide till dissolution was complete; acidification then gave salicylic acid, m. p. and mixed m. p. 156° in each case. The times required for complete dissolution were : *cis*-disalicylide, 20 minutes; trisalicylide, 2 hours; tetrasalicylide, 12 hours; hexasalicylide, 48 hours. The yields of salicylic acid were 93, 87, 85, and 86% respectively.

Similarly, phenyl benzoate required 50 minutes at 100° for complete dissolution and gave benzoic acid (83%).

Reaction of the Four Salicylides with Excess of Benzylamine.—The salicylides were each refluxed for 3 hours with excess of benzylamine and a trace of ammonium chloride, and the cooled products poured into dilute hydrochloric acid. The solids were collected and dissolved in 2N-sodium hydroxide, and the solutions filtered and acidified with dilute hydrochloric acid. The precipitates were recrystallised from aqueous ethanol, giving in each case *N*-benzylsalicylamide, m. p. and mixed m. p. with an authentic specimen 136° (Dermer and King, *J. Org. Chem.*, 1943, **8**, 168, give m. p. 136·5—137°). The yields were : *cis*-di- 95, tri- 89, tetra- 85, and hexa-salicylide 85%.

N-*Benzyl*-O-*salicyloylsalicylamide.*—*cis*-Disalicylide (1 g.) was refluxed with benzylamine (0·45 c.c.) in benzene (80 c.c.) for 7 hours. Removal of the solvent gave a solid (m. p. 106°) which, after crystallisation from aqueous ethanol and then from benzene–light petroleum (b. p. 60—80°), gave N-*benzyl*-O-*salicyloylsalicylamide* (0·9 g., 62%) as colourless needles, m. p. 112° (Found : C, 72·8; H, 5·0; N, 4·8. $C_{21}H_{17}O_4N$ requires C, 72·6; H, 5·0; N, 4·0%).

Formation of Salicyloylsalicylic Acid (" *Diplosal* ") *from* cis-*Disalicylide.*—(a) *Alkaline hydrolysis.* *cis*-Disalicylide (1 g.) in dioxan (50 c.c.) and sodium hydroxide (0·16 g.) in water (20 c.c.) were heated at 100° for 15 minutes and then concentrated under reduced pressure, water was added, and the mixture filtered and acidified. The precipitate (0·47 g., m. p. 110—120°) was collected, washed, and dried, and salicylic acid removed by 3 hours' heating at 100°/1 mm. The residue (0·2 g.) was recrystallised from benzene (1 c.c.), giving salicyloylsalicylic acid, m. p. 148—149° (cf. L. Anschütz and Neher, *loc. cit.*, who give m. p. 148°).

(b) *Acid hydrolysis.* *cis*-Disalicylide (1 g.) and 95% acetic acid (50 c.c.) were boiled under reflux for 0·5 hour, the solvents were removed under reduced pressure, and the residue was triturated with cold 2N-sodium hydroxide. The insoluble material (200 mg.) was collected and identified as unchanged *cis*-disalicylide, m. p. and mixed m. p. 232—234°. Acidification of the filtrate gave a precipitate (670 mg.; m. p. 138—141°) which gave salicylic acid (120 mg., 11%; m. p. 156°) on sublimation at 100°/0·5 mm. for 3 hours, and the residue (550 mg., 51%) was salicyloylsalicylic acid, m. p. and mixed m. p. 148—149°.

In similar experiments with phenyl benzoate, the recovery of starting material was 94% after boiling under reflux for 0·5 hour and 87% after 3 hours; no benzoic acid was detected.

Reaction of cis-*Disalicylide with Methylmagnesium Iodide.*—To a solution of methylmagnesium iodide, prepared from magnesium (7·2 g.) and methyl iodide (4·2 g.) in ether (100 c.c.), was added a

suspension of *cis*-disalicylide (3 g.) in benzene (100 c.c.). After boiling under reflux for 4 hours the mixture was poured on ice, acidified with dilute hydrochloric acid, and extracted with ether. The extract was washed with 2N-sodium hydroxide and water and dried ($MgSO_4$), and the ether removed. The residue was distilled, giving a yellow resinous material (1·2 g.; b. p. 140—150°/0·4 mm.) which separated from light petroleum (b. p. 40—60°) as colourless tablets, m. p. 95°; this compound gave an acetyl derivative, m. p. 95°. Mixed m. p.s of these substances with the dimeride of *o-iso*propenylphenol and its acetyl derivative (Fries, Gross-Selbeck, and Wicke, *Annalen*, 1914, **402**, 306) showed no depression. This dimeride is probably 2′-hydroxy-2 : 4 : 4-trimethylflavan (Baker and Besly, *J.*, 1940, 1103).

Phenyl benzoate and methylmagnesium iodide gave phenol (95%) and dimethylphenylcarbinol (98%) under the same conditions.

Reaction of Tetrasalicylide with Acetic Anhydride and Concentrated Sulphuric Acid.—This reaction is claimed by Schroeter (*Ber.*, 1919, **52**, 2230) to yield "acetyl-tetrasalicylic acid," $CH_3{\cdot}CO{\cdot}(O{\cdot}C_6H_4{\cdot}CO)_4{\cdot}OH$, as an amorphous material, m. p. *ca.* 120°, but we have been unable to confirm this and have isolated only salicyloylsalicylic acid. A mixture of acetic anhydride (10 c.c.), concentrated sulphuric acid (6·5 c.c.), and glacial acetic acid (0·12 c.c.) was added to a solution of tetrasalicylide (1 g.) in acetic anhydride (10 c.c.). After 5 minutes' heating at 100°, the mixture was cooled rapidly and poured on ice, and the solid (0·9 g.; m. p. 70—80°) collected, washed, dried, and then shaken with cold ether (70 c.c.). The insoluble residue (0·15 g.) was recrystallised from benzene, giving tetrasalicylide, m. p. and mixed m. p. 295—297°. The ethereal solution was extracted with dilute sodium hydroxide solution; acidification gave a solid (0·36 g., m. p. 128—130°) which was recrystallised from benzene–light petroleum (b. p. 60—80°), giving salicyloylsalicylic acid (diplosal) as fibrous needles, m. p. 131—132°. When the specimen was kept the m. p. rose to 148—149° and gave no depression with an authentic specimen (see above) (Found : C, 64·9; H, 4·0. Calc. for $C_{14}H_{10}O_5$: C, 65·1; H, 3·9%).

Action of Phosphorus Oxychloride on the Four Salicylides.—Each salicylide (2 g.), phosphorus oxychloride (2·4 g.), and toluene (5 c.c.) were heated at 100° for 6 hours, water (0·15 g.) added, and the heating continued for 15 hours. More water was then added and the mixture worked up as described above for the reaction of salicylic acid with phosphorus oxychloride. *cis*-Disalicylide gave tetrasalicylide (25%) and hexasalicylide (55%); trisalicylide gave tetrasalicylide (19·5%), hexasalicylide (55%), and recovered trisalicylide (7·5%); tetrasalicylide gave trisalicylide (2%), recovered tetrasalicylide (49%), and hexasalicylide (27%); hexasalicylide was recovered quantitatively.

Determination of the Molecular Weights of the Salicylides.—The solvents were purified as follows. AnalaR benzene was dried over sodium wire and fractionally distilled. The chloroform was washed with concentrated sulphuric acid, then water, dried over calcium chloride, and fractionally distilled. The chloroform was used within a few hours of purification. The dioxan was purified as recommended by Vogel ("Practical Organic Chemistry," 1948, p. 175). All solutes were heated under reduced pressure in a drying "pistol" before use, and were analytically pure. After the determinations the solutes were recovered quantitatively and with unchanged m. p.s by removal of the solvent under diminished pressure.

The ebullioscopic determinations were carried out in the Menzies–Wright apparatus (*J. Amer. Chem. Soc.*, 1921, **43**, 2314). In this method the molecular weight is usually determined after the addition of each solute pellet using equation (1), and the means of these values then calculated:

$$M = 100K'w/VF(x - x_0) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where M = the molecular weight of solute, K' = the ebullioscopic constant for 100 c.c. of solvent, the volume being measured at its boiling point, w = the weight of solute, V = the volume of solvent available for solution at the boiling point, F = the differential thermometer-conversion factor at the b. p., x = the difference between liquid heights in the differential thermometer for the solution at its b. p., and x_0 = the difference between liquid heights in the differential thermometer for the pure solvent at its b. p.

In the original method the accuracy of the results is controlled by x_0. This is undesirable for the reason given below, and the following modification was used. In our determinations the solute was added in the form of four pellets, and the five readings of the differential thermometer were plotted against the weight of solute (the maximum concentration of solute was <2%). In drawing a straight line through these points, most attention was paid to the last four, which were usually collinear, as the first point frequently did not lie exactly on the same straight line.

From equation (1),

$$x = Sw + x_0, \text{ where } S = 100K'/VFM \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

and the slope S of the line can be determined after plotting x against w, from which the molecular weight was calculated.

The ebullioscopic constants K' used in these Menzies–Wright determinations were: benzene 32·0, chloroform 27·7 (Menzies and Wright, *loc. cit.*), and dioxan 34·6 (calculated from data given by Herz and Lorentz, *Z. physikal. Chem.*, 1929, **140**, 414). For the cryoscopic determination of molecular weight in dioxan we have used $K = 50{\cdot}1$ (previous reference).

Rast determination of the molecular weight of *cis*-disalicylide gave values of 312, 600, 707, and 272, which are clearly unreliable; the varying results are probably explained by the low solubility and instability of *cis*-disalicylide in molten camphor.

Microanalyses are by Drs. Weiler and Strauss, Oxford, and Mr. W. M. Eno, Bristol. Determinations of molecular weights by Rast's method are by Drs. Weiler and Strauss.

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