

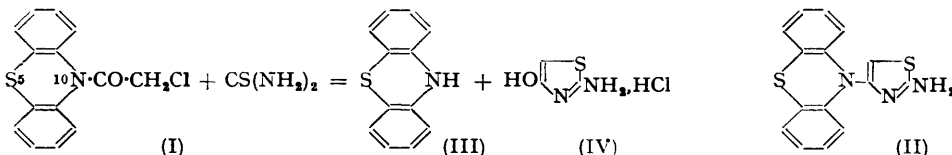
*The Preparation of Some Heterocyclic Sulphur Compounds as Possible Anthelmintics.*

By ALEXANDER MACKIE and ANAND L. MISRA.

[Reprint Order No. 5709.]

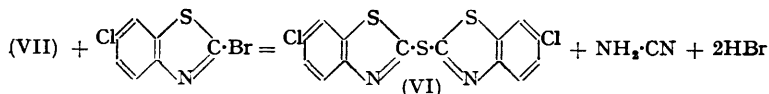
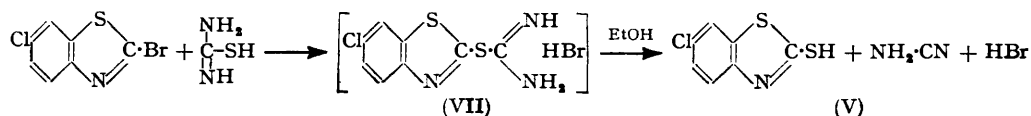
THE following observations were made during attempts to prepare a variety of heterocyclic sulphur compounds for use as anthelmintics.

10-Chloroacetylphenothiazine (I) was treated with thiourea with the view to obtain 2-amino-4-10'-phenothiazinylthiazole (II). Phenothiazine (III) and 2-amino-4-hydroxythiazole hydrochloride (IV) were isolated. It is possible that the hydrochloride of (II) was



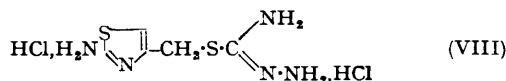
first formed, and was then immediately hydrolysed by ethanolic hydrochloric acid to (III) and (IV) (cf. Maly, *Ber.*, 1877, **10**, 1853; Davies, Maclaren, and Wilkinson, *J.*, 1950, **3493**; Ziegler, *J. Amer. Chem. Soc.*, 1941, **63**, 2946; Sprague, Land, and Ziegler, *ibid.*, 1946, **68**, 2155). When the order of addition of the reactants was reversed, a small quantity of 10-acetylphenothiazine was isolated in addition to (III) and (IV).

Next, 2-bromo-6-chlorobenzothiazole with thiourea was found to give 6-chloro-2-mercaptobenzothiazole (V) in good yield in ethanol and di-(6-chloro-2-benzothiazolyl) sulphide (VI) in very poor yield in water. This affords a good method for the preparation of 6-substituted 2-mercaptobenzothiazoles, which are otherwise obtained laboriously from



6-amino-2-mercaptobenzothiazole. These observations substantiate the previous findings by Scott and Watt (*J. Org. Chem.*, 1937, **2**, 148) and Watt (*ibid.*, 1939, **4**, 436). According to the mechanism postulated by these authors, the formation of (V) presumably depends on the formation of an unstable intermediate addition compound (VII), which decomposes into 6-chloro-2-mercaptobenzothiazole in ethanol, and reacts in water, owing to greater ionisation, with an additional molecule of 2-bromo-6-chlorobenzothiazole to form (VI), according to the annexed scheme.

Finally, 2-amino-4-chloromethylthiazole hydrochloride condensed with thiosemicarbazide to form an *S*-substituted thiosemicarbazide (VIII) (cf. Sprague, Land, and Ziegler, *loc. cit.*).



The results of the biological testing of the benzothiazoles and of the thiazolyl derivatives will be published elsewhere.

*Experimental.*—*Reaction of 10-chloroacetylphenothiazine with thiourea.* 10-Chloroacetylphenothiazine (Ekstrand, *Acta Chem. Scand.*, 1949, **3**, 302) (11.5 g.) was added to a boiling ethanolic solution (40 c.c.) of thiourea (3 g.). The mixture was refluxed for 3 hr.; plates separated, which were filtered off, washed with hot ethanol, and dried (12.5 g.). Washing with cold acetone removed the phenothiazine formed in the reaction, and the residue (5 g.), on recrystallisation

from methanol, gave colourless prisms of 2-amino-4-hydroxythiazole hydrochloride (IV) (4 g.), m. p. 206—208° (decomp.) (Found: C, 24.1; H, 3.3. Calc. for  $C_3H_6ON_2ClS$ : C, 23.6; H, 3.3%). When the order of the addition of the reactants in this reaction was reversed, phenothiazine and 10-acetylphenothiazine, m. p. 198—199°, were isolated, along with (IV).

Addition of pyridine to the hot saturated aqueous solution of the hydrochloride liberated the base, which was obtained pure on recrystallisation from water as colourless needles, becoming light brown at 220°, dark brown at 234°, m. p. 242—244° (decomp.) (Found: C, 30.9; H, 3.3. Calc. for  $C_7H_4ON_2S$ : C, 31.0; H, 3.4%); it reduced Fehling's solution. The base has been reported by King and Miller (*J. Amer. Chem. Soc.*, 1949, **71**, 367) who give m. p. 233—238° (decomp.), and by Davies, Maclaren, and Wilkinson (*J.*, 1950, 3491) who give m. p. 230—240° (decomp.). No depression of the m. p. was observed on admixture with the tautomeric  $\psi$ -thiohydantoin, m. p. 241—243° (Allen and VanAllan, *Org. Synth.*, 1947, **27**, 72). The benzylidene derivative of the base obtained above sinters at 280° and has m. p. 294° (decomp.), which was not depressed when mixed with benzylidene- $\psi$ -thiohydantoin (cf. Kucera, *Monatsh.*, 1914, **35**, 137; Stieger, *ibid.*, 1916, **37**, 653; Culvenor, Davies, Maclaren, Nelson, and Savige, *J.*, 1949, 2573).

**2-Bromo-6-chlorobenzothiazole.** This compound, prepared from 2-amino-6-chlorobenzothiazole (Kaufmann and Schulz, *Arch. Pharm.*, 1935, **273**, 22) (20 g.) by Elderfield and Short's method (*J. Org. Chem.*, 1953, **18**, 1092) for the preparation of 2-bromo-4-chlorobenzothiazole, formed dark yellow needles (16.5 g.) (from ethanol), m. p. 97—98° (Found: C, 33.8; H, 1.1.  $C_7H_3NClBrS$  requires C, 33.8; H, 1.2%).

**6-Chloro-2-mercaptobenzothiazole (V).** 2-Bromo-6-chlorobenzothiazole (2.5 g.) was added to a hot saturated ethanolic solution of thiourea (0.75 g.). The red solution was refluxed for 4 hr. on the water-bath. The separated product was collected and recrystallised from aqueous ethanol in clusters of pale yellow needles (1.5 g.), m. p. 250—252° (Found: C, 41.6; H, 2.0. Calc. for  $C_7H_4NClS_2$ : C, 41.7; H, 2.0%). Teppema and Sebrell (*J. Amer. Chem. Soc.*, 1927, **49**, 1779) give m. p. (not sharp) 245°, and Drozdov and Stavrovskaya (*J. Gen. Chem. U.S.S.R.*, 1937, **7**, 2813) m. p. 244—245°. The preparation by Sandmeyer reaction from 6-amino-2-mercaptobenzothiazole is reported in both papers.

**Di-(6-chloro-2-benzothiazolyl) sulphide (VI).** 2-Bromo-6-chlorobenzothiazole (2.5 g.) was added to a boiling aqueous solution of thiourea (0.75 g. in 15 c.c.), and the mixture refluxed on the water-bath for 4 hr. The pale yellow solid, which separated, was filtered off, shaken with cold 10% aqueous sodium hydroxide (150 c.c.), and collected. The residue was washed with water and recrystallised from chlorobenzene-light petroleum (b. p. 40—60°) as light brown needles of the sulphide (0.3 g.), m. p. 174—176° (Found: C, 45.9; H, 2.0; N, 7.4; S, 25.6.  $C_{14}H_6N_2Cl_2S_2$  requires C, 45.5; H, 1.6; N, 7.6; S, 26.0%). 2-Bromo-6-chlorobenzothiazole (1.5 g.) was recovered.

**S-(2-Amino-4-thiazolylmethyl)thiosemicarbazide dihydrochloride (VIII).** 2-Amino-4-chloromethylthiazole hydrochloride (Sprague, Land, and Ziegler, *J. Amer. Chem. Soc.*, 1946, **68**, 2155) (5 g.) was added to a boiling 70—80% ethanolic solution (30 c.c.) of thiosemicarbazide (2.5 g.), and the mixture refluxed for 2 hr. on the water-bath. A vigorous reaction set in when complete dissolution was effected and a crystalline precipitate separated, which was collected after cooling and recrystallised from aqueous methanol in colourless prisms of the pure substituted thiosemicarbazide dihydrochloride (4.5 g.), m. p. 211—212° (vigorous decomp.), becoming light brown at 195° (Found: C, 21.8; H, 3.9; N, 26.2.  $C_5H_{11}N_5Cl_2S_2$  requires C, 21.7; H, 4.0; N, 25.4%). The base, liberated from an aqueous solution of the hydrochloride on addition of slight excess of potassium acetate or pyridine, crystallised from water in colourless plates, m. p. 173—174° (decomp.).

**p-Dimethylaminobenzaldehyde S-(2-amino-4-thiazolylmethyl)thiosemicarbazone.** A hot ethanolic solution of p-dimethylaminobenzaldehyde (0.3 g. in 5 c.c.) was added to a hot aqueous-ethanolic solution (20 c.c.) of the above thiosemicarbazide hydrochloride (0.3 g.) and sodium acetate (0.35 g.). The mixture was refluxed on the water-bath for 2 hr. The separated product was cooled, collected, and recrystallised from absolute ethanol as greyish prismatic needles of the thiosemicarbazone (0.25 g.), m. p. 207—208° (decomp.) (Found: C, 50.3; H, 5.2.  $C_{14}H_{18}N_6S_2$  requires C, 50.3; H, 5.4%).

The authors thank the Agricultural Research Council for financial assistance, and the Council of Scientific and Industrial Research (India) for the award of an Assam Oil Co. Scholarship to one of them (A. L. M.).

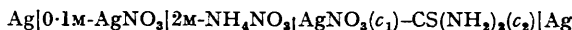
*The Stability of the Three-co-ordinated Thiourea Silver Complex.*

By W. S. FYFE.

[Reprint Order No. 4846.]

THIOUREA forms a stable complex ion with the silver ion in aqueous solution and as there are very few data on the stability of silver complexes with sulphur as the donor atom the formation constant of this complex has been measured. Morgan and Burstall (*J.*, 1928, 143) prepared a series of complexes with one, two, three, and four mols. of thiourea to one of silver.

When thiourea is added to a silver nitrate solution a precipitate which is first formed dissolves when the molar ratio of thiourea to silver is approximately 3 : 1. The formation of the complex was studied electrometrically at 25° with a simple concentration cell :



The activity coefficients used in the calculation of the formation constants were taken from McInnes (*Chem. Rev.*, 1936, 18, 341). The values used were 0.734, 0.844, 0.97 for 0.1M-, 0.01M-, and 0.001M-silver nitrate respectively. It was assumed that the activity coefficients of the complex were the same as for silver nitrate. The experimental results are summarised in the Table, *E* being the e.m.f. of the cell and  $K = [\text{AgTu}_3^+]/[\text{Ag}^+][\text{Tu}]^3$ , where Tu = thiourea. From the reasonable constancy of log *K* the three-co-ordinated

$c_1$ (M)	$c_2$ (M)	<i>E</i>	log <i>K</i>	$c_1$ (M)	$c_2$ (M)	<i>E</i>	log <i>K</i>
0.001	0.1963	0.761	13.13	0.001	0.02334	0.574	12.90
"	0.1167	0.713	13.01	0.01	0.1191	0.644	13.11
"	0.0805	0.686	13.05	"	0.0953	0.624	13.16
"	0.0744	0.680	13.05	"	0.0595	0.560	13.06
"	0.0584	0.659	13.01	"	0.0584	0.558	13.06

Mean, log *K* = 13.05.

complex appears to be stable over the limited concentration range studied. The complex is also one of the more stable silver complexes—more stable than the ammonia complexes, in agreement with expectations from overlap calculations made by the author (*J. Chem. Phys.*, 1952, 8, 1039), the stability of the sulphur-metal linkage in complexes being a function of the low electron-affinity of sulphur.

The co-ordination number of three which has been found with thiourea is unusual for silver complexes, two being usual for aqueous solution. The explanation may lie in the configuration of the sulphur atom in thiourea. The sulphur atom may be in either an *sp* or *sp*<sup>2</sup> hybrid state as it forms both a  $\sigma$ - and a  $\pi$ -bond with carbon. If the configuration is *sp*, then as the sulphur atom approaches the silver ion it may form a  $\sigma$ -bond with a *sp* hybrid orbital but it still has a *p*-orbital in a position to form a  $\pi$ -bond if silver has some suitable orbital available. If the hybridisation is *sp*<sup>2</sup>, then the silver can either form a  $\sigma$ -bond with the thiourea which will make the Ag-S-C bond angular, or it can interact and form two weak bonds with both *sp*<sup>2</sup> hybrids, the Ag-S-C bond being linear. Both these cases involve the use of *d*-orbitals from the silver atom. A further possibility which involves no *d* orbital hybridisation is that the silver atom forms a trigonal planar grouping with the three sulphur atoms with a *sp*<sup>2</sup> silver hybrid and that the remaining silver *p*-orbital will form a resonating  $\pi$ -bond with the sulphur *p*-orbitals. The structure would be analogous to that in the carbonate ion. Finally, it is possible that *d* sulphur orbitals may be involved, as suggested by the results of Craig, Maccoll, Nyholm, Orgel, and Sutton (*J.*, 1954, 332).

*The Thermal Decomposition of Ammonium Dichromate.*

By DUNCAN TAYLOR.

[Reprint Order No. 5803.]

FOR the thermal decomposition of ammonium dichromate with continuous evacuation in the temperature range 188—218°, Fischbeck and Springler (*Z. anorg. Chem.*, 1939, **241**, 209) reported that after an induction period  $t'$  the fraction decomposed at any time  $t$  is proportional to  $(t - t')^4$ , up to about 30% decomposition (approximately the maximum-rate stage), as required by a linear growth of spherical nuclei whose number increases linearly with time. From about 30 to 100% decomposition, a contracting-sphere type of mechanism applied, governed by the equation  $1 - (1 - x)^3 = \text{const.} (t - t_0)^3$ , where  $x$  is the fraction decomposed, and  $t_0$  is the time at which the maximum rate occurred. Reinvestigation of the decomposition without employing continuous evacuation has revealed new features of the kinetics, and an alternative mechanism is proposed.

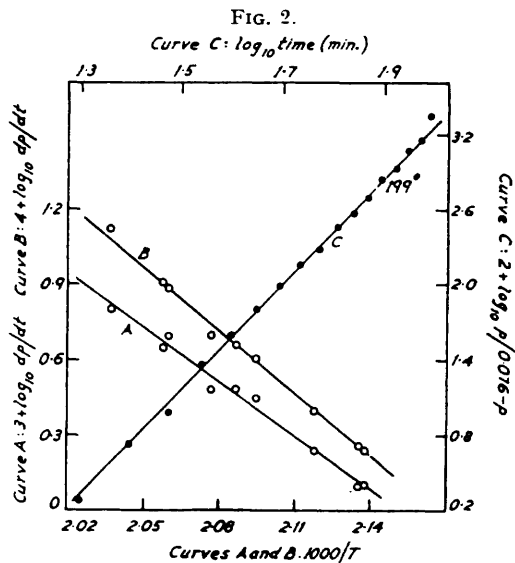
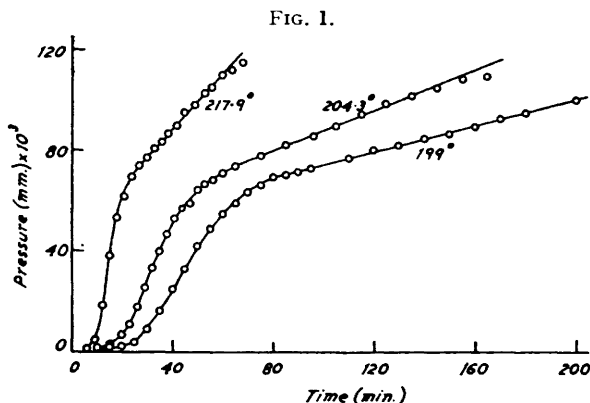
*Experimental and Results.*—Decompositions were carried out at 195—218° in an apparatus similar to that of Garner and Haycock (*Proc. Roy. Soc.*, 1952, *A*, **211**, 338) with the addition, between the reaction vessel and expansion bulbs, of a trap ( $\text{P}_2\text{O}_5$ ) to remove water vapour. The pressure of the remaining nitrogen was measured with a Macleod gauge placed after the expansion bulbs. The reaction-vessel temperature was controlled within  $\pm 0.05^\circ$  by an electric furnace and electronic relay, and was measured with a Pallador thermocouple, which was calibrated against a platinum resistance thermometer. Small crystals (0.1—0.2 mm.) of ammonium dichromate, obtained by rapid crystallisation of "AnalaR" material at 30—40°, were used in 5—14 mg. quantities in a closed vessel constructed from 2 cm.<sup>2</sup> of 0.025-mm. thick platinum foil. The thermocouple indicated a maximum heating-up period of about 5 min., and gave no evidence of self-heating of the crystals during decomposition. Before decomposition, samples were degassed for 3—4 hr. at room temperature and a pressure less than  $10^{-5}$  mm., no significant difference in rates being observed with 18 hours' evacuation. The total volume of the system was 6200 c.c.

Typical pressure-time curves are given in Fig. 1, zero time being the moment when the sample reached the hot zone of the reaction vessel. The maximum rate in the autocatalytic stage occurred in all cases at about 20% decomposition, calculated on the basis of the scheme,  $(\text{NH}_4)_2\text{Cr}_2\text{O}_7 \rightarrow \text{Cr}_2\text{O}_3, \text{H}_2\text{O} + 3\text{H}_2\text{O} + \text{N}_2$  (Fischbeck and Springler, *Z. anorg. Chem.*, 1938, **235**, 183), and had a temperature coefficient corresponding to an energy of activation of 33 kcal./mole (see Fig. 2, line *A*). Irrespective of temperature, this stage was complete after about 45% decomposition, and was followed by a constant-rate stage over the range 45—65% decomposition, with an energy of activation of 38 kcal./mole (see Fig. 2, line *B*). Both the maximum rate and the constant rate were directly proportional to the initial weight of the sample and were reproducible to within 10%. Following the constant-rate process, the pressure increased in an irregular manner and, depending on the temperature, the maximum decomposition even after several days' heating was only 75—85%. Induction periods (defined as the time required for the pressure to reach  $10^{-3}$  mm.) varied from 2 to 15 min., but in general decreased with increasing temperature. Slight grinding of the crystals did not significantly alter the rates at any stage, but prolonged grinding resulted in the disappearance of the induction period and in increased irreproducible rates, the maximum of which occurred very early.

*Discussion.*—The results differ from those of Fischbeck and Springler in the following respects: (a) the occurrence of the maximum rate earlier in the decomposition; (b) the occurrence of a constant-rate stage, indicating a linear interface reaction (cf. Jacobs and Tompkins, *Proc. Roy. Soc.*, 1952, *A*, **215**, 273); and (c) failure to attain 100% decomposition at any temperature. Furthermore, it has been found that for the initial stages of the decomposition the equation  $x = (t - t')^n$  fits the present results only approximately,  $n$  varying between 2 and 3, and that the equation of the contracting-sphere mechanism fits moderately well only from 45 to 70% decomposition, the corresponding energy of activation being about 35 kcal./mole, in contrast to 49 kcal./mole found by Fischbeck and Springler. These differences are thought not to be due to the different experimental conditions because (a) in both cases the pressure of

residual water vapour is estimated to be  $<10^{-4}$  mm., and (b) experiment showed that the decomposition of single crystals (about 8 mg.) was unaffected by the presence initially of 0.06 mm. pressure of nitrogen.

The autocatalytic stage can best be represented by the Prout-Tompkins equation,  $\log_{10} p/(p_f - p) = \text{constant} + k \log_{10} t$  (*Trans. Faraday Soc.*, 1944, **40**, 488; 1946, **42**, 468), with a single value of  $k$  instead of the usual two values, when the final pressure  $p_f$  (estimated by trial and error) corresponds to the conclusion of the stage (see Fig. 2, line C). The use of the experimental pressures in the equation involves the assumption either that the interface reaction is insignificant during the autocatalytic stage, or that the pressure due to the latter process at any time



is a constant fraction of the total. The agreement of the results with the equation is in keeping with the fact that during decomposition the ammonium dichromate lattice probably undergoes changes (as judged from the lattice dimensions of dichromate and chromic oxide) similar to those for permanganates, for whose decomposition the Prout-Tompkins mechanism was originally proposed. The need for a single value of  $k$  is unusual, but may be due to the completion of the autocatalytic stage at only about 45% decomposition. The fit of the equation was less satisfactory if allowance was made for the short induction periods, and furthermore, although the maximum rate varied regularly with temperature (see Fig. 2, line A), the variation of  $k$  with temperature was erratic. For the first 5% of the decomposition, the equation did not apply satisfactorily, and this fact taken in conjunction with the occurrence of induction periods suggests that a nucleation process may precede the autocatalytic stage.

UNIVERSITY OF EDINBURGH.

[Received, October 14th, 1954.]

*Decomposition of Mixed Diazonium Fluoroborates.*

By J. C. BRUNTON and H. SUSCHITZKY.

[Reprint Order No. 5806.]

In an unsuccessful attempt to improve the low yields attending the preparation of *o*-fluoronitrobenzene by a Balz-Schiemann reaction (Roe, "Organic Reactions," John Wiley and Sons, New York, 1949, Vol. V, p. 220), we modified the usual decomposition method: *o*-nitrobenzenediazonium fluoroborate was mixed in one series of experiments (*a*) with a diazonium fluoroborate of a negligible conversion yield, and in another (*b*) with a fluoroborate of a high conversion yield, in various proportions. We considered that this arrangement should increase the total concentration of the fluorinating agent, whatever its nature, for each of the constituents, and thereby possibly affect the yields. *p*-Carboxybenzenediazonium fluoroborate was intended for use under (*a*) because the synthesis of *p*-fluorobenzoic acid *via* this intermediate is recorded as unsuccessful (Dippy and Williams, *J.*, 1934, 1466). However, repeating the preparation, we obtained the acid in 40% yield (based on the fluoroborate), and this is, therefore, more convenient than the usual method (Schiemann and Winkelmüller, *Org. Synth.*, Vol. II, p. 299). The reported failure may have been due to the high solubility of this fluoroborate in water.

On the basis of the experimental results obtained so far (see Table) it appears that diazonium fluoroborates in admixture decompose without appreciable interaction.

The mixed decomposition method has preparative advantages. It was found convenient for the simultaneous preparation of two separable aromatic fluorine compounds. Moreover, a mildly decomposing fluoroborate proved to be an ideal diluent in the decomposition of diazonium fluoroborates containing the nitro-group, since it transforms the otherwise violent pyrolysis into a smooth reaction.

*Decomposition of o-nitrobenzenediazonium fluoroborate in admixture with similar fluoroborates, R·N<sub>2</sub>BF<sub>4</sub>.*

R·N <sub>2</sub> BF <sub>4</sub>	Molar ratio, R·N <sub>2</sub> BF <sub>4</sub> / <i>o</i> -NO <sub>2</sub> ·C <sub>6</sub> H <sub>4</sub> ·N <sub>2</sub> BF <sub>4</sub>	RF : Yield, %		<i>o</i> -C <sub>6</sub> H <sub>4</sub> F·NO <sub>2</sub> : Yield, %	
		alone	mixed	alone	mixed
<i>o</i> -Toluene .....	1·5	50—60	56	10—12	11
" .....	5·5	"	60	"	10
" .....	7·0	"	60	"	12·6
2 : 4-Dinitrobenzene .....	0·5	negl.	negl.	"	11·5
<i>p</i> -Carboxybenzene .....	0·5	40	38	"	10

*Experimental.*—No diluent was used for the decompositions, which were carried out under nitrogen (Suschitzky, *J.*, 1953, 3042). The mixtures were prepared by co-precipitating the fluoroborates from the combined solutions of the corresponding diazotised amines.

*p*-Fluorobenzoic acid. The method of Dippy and Williams (*loc. cit.*) yielded *p*-carboxybenzenediazonium fluoroborate (80%), decomp. 89°. The salt was only washed with ether. Decomposition produced the acid as a white sublimate (40%), m. p. 185° (Found: equiv., 141. Calc. for C<sub>7</sub>H<sub>5</sub>O<sub>2</sub>F: equiv., 140).

2 : 4-Dinitrobenzenediazonium fluoroborate. 2 : 4-Dinitroaniline (25 g., 0·14 mol.), dissolved in concentrated sulphuric acid (150 c.c.) and water (200 c.c.), was diazotised with 30% sodium nitrite solution. Addition of a 40% sodium fluoroborate solution (25 g.) yielded the pale yellow fluoroborate (92%, 35·7 g.), decomp. 208°. Only traces of 1-fluoro-2 : 4-dinitrobenzene, identified by mixed m. p. with an authentic sample, were obtained by pyrolysis.

We thank the Department of Scientific and Industrial Research for the award of a maintenance grant to one of us (J. C. B.).

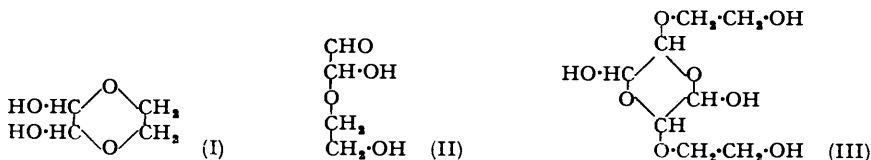
### An Addition Compound of Glyoxal and Ethylene Glycol.

By FRANK S. H. HEAD.

[Reprint Order No. 5823.]

It is well known that glyoxal and ethylene glycol in the presence of hydrochloric acid give a mixture of isomeric cyclic acetals commonly known as the naphthodioxans, but it does not seem to have been reported that a 1 : 1 compound of the semiacetal type is formed under milder conditions. This was obtained as a crystalline, water-soluble substance in 70—80% yield when an aqueous solution of glyoxal and ethylene glycol in equimolecular proportion was evaporated to dryness at room temperature *in vacuo*. When heated, it melted and decomposed, giving off a greenish-yellow vapour (presumably monomeric glyoxal). It was only slightly soluble in most organic solvents; in hot xylene it gave a yellow solution which became colourless again on cooling.

Structures such as (II), containing carbonyl groups, are excluded by absence of absorption at 1920—1520  $\text{cm}^{-1}$ . The bis-semiacetal structure (I), and polymeric structures such as (III) or its dioxolan analogue [which might be formed by way of (II)], are possible. The infra-red spectrum is not inconsistent with formula (I) since it exhibits (a) a broad, intense, absorption band at 3600—3000  $\text{cm}^{-1}$ , typical of associated hydroxyl groups, and (b) certain similarities to the spectrum of dioxan, *viz.*, bands near 1270 and 1250 and (very intense) between 1130 and 980  $\text{cm}^{-1}$ .



The structure (I) accords with the formation of 2 : 3-dichlorodioxan on treatment with phosphorus pentachloride, but in view of the drastic nature of the treatment this evidence may not be conclusive. Hydrolysis of the dichloro-compound with boiling water gave a solution from which the supposed dihydroxy-compound could be recovered, but it is possible that the hydrolysate contained glyoxal and glycol (cf. Böeseken, Tellegen, and Henriquez, *Rec. Trav. chim.*, 1931, 50, 909), and that these combined during the working-up.

The behaviour of the substance in aqueous solution was consistent with its formulation as a cyclic semiacetal, which might be expected to dissociate to some extent into the open-chain form (II), and then into the original components: with phenylhydrazine in acetic acid it gave an immediate precipitate of glyoxal bisphenylhydrazone, and recognised methods for the determination of glyoxal could be used to determine the amount present in the substance.

On oxidation with sodium metaperiodate, a compound (I) should reduce one mol. of periodate and give one mol. of glycol diformate. A compound (II) should also reduce one mol. of periodate, but would give one mol. of formic acid and one of glycol monoformate. A mixture of one mol. each of glyoxal and glycol should reduce two mols. of periodate very rapidly and yield two mols. each of formic acid and formaldehyde. The tabulated results (a) (given as mole/mole) show a very rapid initial reduction of about one mol. of periodate with formation of much formic acid (but  $\ll 1$  mol.) and a small amount of formaldehyde;

	(a) 0.025M-C <sub>4</sub> H <sub>8</sub> O <sub>4</sub> in 0.0734M-NaIO <sub>4</sub>			(b) 0.025M-(CH <sub>2</sub> ·O·CHO) <sub>2</sub> in 0.050M-NaIO <sub>4</sub>		
Time .....	15 mins.	1 day	22 days	1 day	5 days	21 days
Periodate reduced	1.04	1.13	1.97	0.00	0.18	0.97
Acid produced ...	0.68	0.94	2.02	0.10	0.89	1.95
CH <sub>2</sub> O produced ...	0.10	0.24	2.00	—	0.44	2.00

subsequent reduction of periodate was very slow, but after about three weeks approximated to oxidation of a 1 : 1 mixture of glyoxal and glycol. The figures for a reaction time of 15 minutes are consistent with the view that the crystalline substance is (I), but that, in

solution, it exists in equilibrium with a certain amount of (II), and of the original components. The products of oxidation would then include glycol mono- and di-formate, and the slowness of the subsequent reaction could be attributed to the slow hydrolysis of these esters [cf. Table (b)]: liberation of acid from glycol diformate preceded commencement of oxidation, but very little appeared during the first 24 hours, making it unlikely that the formic acid observed during the early stages of the oxidation of the substance arises from hydrolysis of glycol diformate.

With an excess of glycol containing hydrochloric acid, the substance gave rise to the mixture of "naphthodioxans" previously obtained by other methods, including the reaction of glycol with 2 : 3-dichlorodioxan (Böeseken *et al.*, *loc. cit.*).

*Experimental.*—*The addition compound (2 : 3-dihydroxydioxan?).* (a) A mixture of glycol (45.4 g.) and commercial 50% glyoxal (83.9 g.) was kept *in vacuo* over phosphoric oxide until it had mostly solidified (about a week). The solid substance was separated from syrup by mixing it with acetone and filtering (68 g., 77%). It formed colourless crystals from acetone (Found : C, 39.9; H, 6.3.  $C_4H_8O_4$  requires C, 40.0; H, 6.7%). The "available" glyoxal in the substance was determined by oxidation with (i) alkaline hydrogen peroxide (Friedemann, *J. Biol. Chem.*, 1927, **73**, 331) and (ii) alkaline hypiodite (cf. Head, *J. Text. Inst.*, 1947, **38**, τ 389) [Found : (i) 48.5; (ii) 48.0. Calc. for  $(CHO)_2-(CH_2\cdot OH)_2$  : 48.3%]. The glycol was determined as follows. The substance was heated for 10 min. with an excess of sodium hydroxide solution (to convert glyoxal into glycollic acid), and the solution neutralised with hydrochloric acid (cf. Friedemann, *loc. cit.*) and oxidised with an excess of sodium metaperiodate for 15 min. Formaldehyde produced was determined by the dimedone method (cf. Head and Hughes, *J.*, 1952, 2046) (Found : 52.0.  $C_4H_8O_4$  requires  $CH_2O$ , 51.7%). The substance melted indefinitely at about 100°. The infra-red absorption was measured with the dry solid, which was placed between rock-salt plates, melted, and quickly solidified to a glass-like film.

(b) 2 : 3-Dichlorodioxan (7.1 g.) was boiled under reflux with water (25 c.c.) until all the oil had dissolved (a few minutes). The cold solution was treated with sodium hydrogen carbonate until only faintly acid to Congo-red and evaporated to dryness at room temperature *in vacuo* over phosphoric oxide. Extraction of the residue with hot acetone and concentration of the extract yielded a substance (2.75 g., 51%) identical with that obtained from glyoxal and glycol.

*2 : 3-Dichlorodioxan from the addition compound.* The compound (31 g.) was added in three portions to phosphorus pentachloride (111 g.). When the vigorous reaction had abated, the mixture was heated on the steam-bath for 15 min. and then cooled. The liquor was filtered from unchanged phosphorus pentachloride, and phosphorus oxychloride was removed *in vacuo* (Widmer column). The remaining oil was dissolved in benzene, washed with water, dried ( $CaCl_2$ ), and fractionated. A fraction, b. p. 71—75°/9 mm. (21.8 g.), consisted of 2 : 3-dichlorodioxan, m. p. 29° (54%), and after recrystallisation from light petroleum (b. p. 40—60°) had m. p. and mixed m. p. 30°. A fraction, b. p. 93—94°/9 mm. (6 g.), was not identified.

*Periodate oxidation of the addition compound, and of ethylene glycol diformate.* The reaction mixtures were kept in the dark in a thermostat at 20°. For details of the analytical methods used to determine formic acid and formaldehyde, see Head and Hughes (*loc. cit.*). In view of the anomalies observed when variants of the arsenite method are used to determine periodate in the presence of partially oxidised glucose (Hughes and Nevell, *Trans. Faraday Soc.*, 1948, **44**, 941; Head and Hughes, *J.*, 1954, 603) the amount of periodate reduced by the addition compound was determined both by an arsenite method (Müller and Friedberger, *Ber.*, 1902, **35**, 2652) and by reduction with iodide in acid solution; the two methods agreed. The arsenite method was used in the experiments with glycol diformate.

*"Naphthodioxans."* A mixture of the addition compound (4 g.) and dry glycol (10 c.c.) containing about 0.5% of hydrogen chloride was heated on the steam-bath for 21 hr. Colourless needles (0.9 g.) which separated on cooling were recrystallised from methanol, and had m. p. 135° alone, or mixed with the higher-melting "naphthodioxan" (Böeseken *et al.*, *loc. cit.*). The glycol filtrate contained material of m. p. about 90°, which appeared to be the difficultly separable eutectic mixture of the higher- and lower-melting forms described by earlier workers.

The author is indebted to Dr. M. M. Davies of Aberystwyth for determining the infra-red absorption spectra.



*The Interaction of Calcium Ions with Some Citrate Buffers :  
A Correction.*

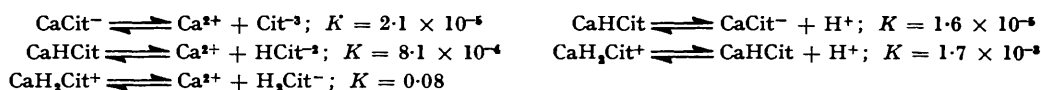
By C. W. DAVIES and B. E. HOYLE.

[Reprint Order No. 5830.]

SOME calculations of our earlier paper on this topic (*J.*, 1953, 4134) are regrettably in error. Schubert and Lindenbaum's value for the dissociation constant of the  $\text{CaCit}^-$  ion (*J. Amer. Chem. Soc.*, 1952, **74**, 3529) is  $7.0 \times 10^{-4}$  at ionic strength 0.16, and on correction to zero ionic strength this becomes  $2.1 \times 10^{-5}$  (and not  $1.27 \times 10^{-5}$  as given in our paper). This affects all our calculations of calcium-citrate interaction, and the following Table should replace Table 2 of our former paper (all concentrations are in millimoles/l.).

<i>M</i>	<i>S</i>	pH, buffer	pH, sat. soln.	$[\text{CaH}_2\text{Cit}^+]$	$[\text{CaHCit}]$	$[\text{CaCit}^-]$	<i>I</i>	$K \times 10^5$
<i>A. Disodium hydrogen citrate solution</i>								
								(CaHCit)
5.0	9.20	5.48	4.53	0.04	1.85	1.11	0.0288	0.80
10.0	10.61	5.32	4.57	0.06	3.23	2.20	0.0372	0.81
20.0	13.30	5.20	4.64	0.08	5.03	4.22	0.0584	0.81
<i>B. Na<sub>2</sub>HCit (0.9M) + HCl (0.1M)</i>								
5.0	8.98	5.18	4.41	0.04	1.71	0.77	0.0285	0.79
10.0	10.15	5.18	4.45	0.07	3.03	1.53	0.0359	0.79
20.0	12.32	5.17	4.51	0.11	4.73	3.02	0.0543	0.84
<i>C. Na<sub>2</sub>HCit (0.8M) + HCl (0.2M)</i>								
5.0	8.77	4.90	4.27	0.05	1.51	0.48	0.0281	0.75
10.0	9.66	4.84	4.32	0.09	2.47	1.05	0.0352	0.90
20.0	11.36	4.80	4.36	0.15	4.12	1.99	0.0509	0.91
<i>D. Na<sub>2</sub>HCit (0.5M) + HCl (0.5M)</i>								
								(CaH <sub>2</sub> Cit <sup>+</sup> )
10.0	8.53	3.85	3.60	0.12	0.77	0.06	0.0326	85
20.0	9.08	3.85	3.57	0.23	1.31	0.09	0.0427	85
40.0	10.04	3.77	3.56	0.51	2.19	0.15	0.0629	68

The concordance of the results is improved, and the constants determined are now :



Heinz (*Biochem. Z.*, 1951, **321**, 314) has derived values for the dissociation constants of  $\text{CaCit}^-$  and  $\text{CaHCit}$  by electrometric titrations of citric acid in the presence of calcium chloride. His values are considerably lower than those given above. He attributed the whole anomaly in the later stages of the titration to the species  $\text{CaCit}^-$ , however, and similarly he ignored  $\text{CaCit}^-$  in calculating the dissociation constant for  $\text{CaHCit}$ . The detailed analysis of the above Table shows that this is not justifiable; the concentrations of  $\text{CaHCit}$  and  $\text{CaCit}^-$  are approximately equal in disodium hydrogen citrate solutions, and to ignore one will lead to too low a calculated dissociation constant for the other.

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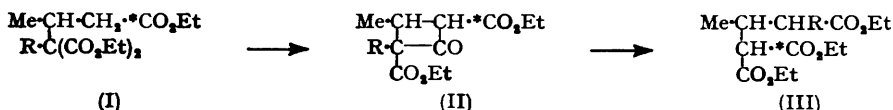
*The "Abnormal" Michael Addition.*

By G. A. SWAN.

[Reprint Order No. 5851.]

REACTION between diethyl methylmalonate and ethyl crotonate in the presence of a catalytic amount of sodium ethoxide yields the normal addition product, triethyl 2-methylbutane-1 : 3 : 3-tricarboxylate (I; R = Me), but in the presence of a molecular amount of catalyst the abnormal product, triethyl 2-methylbutane-1 : 1 : 3-tricarboxylate (III; R = Me) results. Michael and Ross (*J. Amer. Chem. Soc.*, 1930, **52**, 4598) assumed the partition of the diethyl methylmalonate into methyl and diethoxycarbonylmethyl radicals; but Holden and Lapworth (*J.*, 1931, 2368) suggested the more plausible explanation of the formation of an intermediate (II) by Dieckmann cyclisation, followed by ring-opening to give (III). More recent work has not, however, provided direct evidence of the correctness of the latter theory (Gardner and Rydon, *J.*, 1938, 48; Tsuruta, Yasuhara, and Furukawa, *J. Org. Chem.*, 1953, **18**, 1246).

If, however, one carried out the reaction with ethyl [*carboxy*-<sup>14</sup>C]crotonate, hydrolysed the ester to the tricarboxylic acid, and then decarboxylated the latter, from the normal product one should obtain inactive, and from the abnormal product radioactive carbon



dioxide, if Holden and Lapworth's theory is correct. (If Michael and Ross's theory is correct, inactive carbon dioxide should result in both cases.) A preliminary experiment along these lines (but with ethyl [*carboxy*-<sup>14</sup>C]cinnamate) had already shown the essential correctness of Holden and Lapworth's theory, when the results of similar experiments on the crotonate were published by Simamura, Inamoto, and Suehiro (*Bull. Chem. Soc. Japan*, 1954, **27**, 221). In view of that publication, further work has been abandoned.

The participation of (II) as an intermediate has been questioned, because of the four-membered ring. However, the driving force of the abnormal reaction is the greater acid strength of (III; R = Me) compared with (I; R = Me), and an experiment was carried out in support of this. In the addition of diethyl malonate to ethyl crotonate, the same product (I; R = H or III; R = H) is obtained regardless of the amount of sodium ethoxide used. If, however, [*carboxy*-<sup>14</sup>C]crotonate is used, then if the first-formed product (I; R = H: giving acid A on saponification) did in fact undergo cyclisation and ring opening as in the case where R = Me, one should obtain radioactive carbon dioxide on decarboxylation of the resulting tricarboxylic acid (B). It was demonstrated that this carbon dioxide was virtually inactive, showing that the abnormal mechanism does not operate when the above-mentioned driving force is absent.

*Radioactivity of carbon dioxide (counts/min.)*

By combustion of acid A .....	2230	By decarboxylation of acid A .....	0
" " " B .....	2230	" " " B .....	28
Calc. value for the latter if complete randomisation occurred .....		3900	

In the experimental section is recorded the preparation of three acids apparently not previously prepared by the Michael reaction.

*Experimental.*—Ethyl [*carboxy*-<sup>14</sup>C]crotonate. This was prepared (in contrast to that of the Japanese workers) as follows. Barium [<sup>14</sup>C]carbonate was converted into potassium [<sup>14</sup>C-]cyanide by McCarter's method (*J. Amer. Chem. Soc.*, 1951, **73**, 483) and thence into [*carboxy*-<sup>14</sup>C-]malonic acid (Gal and Shulgin, *ibid.*, p. 2938) and into [*carboxy*-<sup>14</sup>C]crotonic acid (Letch

and Linstead, *J.*, 1932, 454), which was esterified with ethanol in the presence of sulphuric acid.

*Reaction between ethyl [carboxy-<sup>14</sup>C]crotonate and diethyl malonate in the presence of a catalytic amount of sodium ethoxide.* Diethyl malonate (4.1 g.), and then ethyl [carboxy-<sup>14</sup>C]crotonate (2.7 g.) were added to a solution of sodium ethoxide [from sodium (0.09 g.)] in ethanol (2 ml.) and ether (30 ml.), and the solution was refluxed for 5 hr., cooled, and shaken with water (2 ml.) containing acetic acid (0.4 ml.). The ethereal layer was washed with sodium carbonate solution, dried ( $K_2CO_3$ ) and distilled twice, yielding triethyl 2-methylpropane-1:1:3-[3-carboxy-<sup>14</sup>C]tricarboxylate (5.5 g.), b. p. 145°/1.5 mm. (Found: C, 57.0; H, 8.35. Calc. for  $C_{13}H_{22}O_6$ : C, 56.95; H, 8.05%). This ester (0.35 g.) was refluxed for 10 hr. with sodium hydroxide solution (7 ml.; 10%), the mixture cooled, acidified (HCl), and extracted with ether, the extract dried ( $Na_2SO_4$ ), the ether removed, and the residue recrystallised from acetone-chloroform, affording the tricarboxylic acid *A* [0.1 g.; m. p. 136° (decomp.)] (Found: C, 44.35; H, 5.5. Calc. for  $C_7H_{10}O_6$ : C, 44.2; H, 5.25%).

*Action of sodium ethoxide (1 mole) on the ester.* The ester (2.7 g.) was added to a suspension of alcohol-free sodium ethoxide [from sodium (0.23 g.)] in ether (50 ml.), and the resulting solution was refluxed for 8 hr. When worked up as before, this yielded an ester (1.95 g.; b. p. 140°/1 mm.) (Found: C, 57.05; H, 8.35%) which on being hydrolysed yielded the tricarboxylic acid *B*, m. p. 136° (decomp.) (Found: C, 43.9; H, 5.5%).

*Radioactivity determinations.* Samples of acids *A* and *B* were decarboxylated by being heated in a vacuum, the resulting carbon dioxide being passed through a spiral trap, cooled in solid carbon dioxide, and collected in a trap cooled in liquid nitrogen, before transfer to the filling line for the gas-counting tube. Samples of acids *A* and *B* were burnt by Anderson, Delabarre, and Bothner-By's method (*Analyt. Chem.*, 1952, 24, 1298). The radioactivity determinations were carried out as described by Audric and Long (Department of Scientific and Industrial Research, Chemical Research Laboratory, Scientific Report CRL/AE 51, March, 1950) except that the counting tubes were made as described by Brownell and Lockhart (Laboratory for Nuclear Science and Engineering, M.I.T., Technical Report No. 30, Sept. 12th, 1949).

*Butane-1:3:3-tricarboxylic acid.* Diethyl methylmalonate (4.8 ml.) was added to sodium ethoxide [from sodium (0.11 g.)] in ethanol (2.2 ml.) and ether 45 ml.; ethyl acrylate (3.3 ml.) was then added cautiously, and the mixture refluxed for 2.5 hr. Worked up as above, this yielded triethyl butane-1:3:3-tricarboxylate (5.6 g.; b. p. 145°/3 mm.) (Found: C, 57.15; H, 8.05. Calc. for  $C_{13}H_{22}O_6$ : C, 56.95; H, 8.05%) (von Auwers, *Annalen*, 1896, 292, 209, gives b. p. 164.5—165°/15 mm.) which on hydrolysis yielded the acid as plates, m. p. 134° (decomp.), from acetone-chloroform (Found: C, 44.25; H, 5.3. Calc. for  $C_7H_{10}O_6$ : C, 44.2; H, 5.25%) (Wieland and Vocke, *Z. physiol. Chem.*, 1928, 177, 71, give m. p. 134°).

*Propane-1:1:3-tricarboxylic acid.* When prepared as above, but with diethyl malonate instead of methylmalonate, this acid had m. p. 122—123° (decomp.) (Found: C, 41.15; H, 4.8. Calc. for  $C_6H_8O_6$ : C, 40.9; H, 4.55%) (Dickens, Kon, and Thorpe, *J.*, 1922, 121, 1502, give m. p. 123°).

*2-Phenylbutane-1:3-dicarboxylic acid.* Triethyl 2-phenylbutane-1:1:3-tricarboxylate (Michael and Ross, *loc. cit.*) (0.48 g.) was refluxed for 11 hr. with a mixture of water (5 ml.) and concentrated hydrochloric acid (5 ml.). The cooled solution was extracted with ether, the extract dried ( $Na_2SO_4$ ), and the ether removed. A solution of the residue in chloroform was diluted with light petroleum (b. p. 40—60°) and stirred. The product (0.2 g.), separating from benzene-light petroleum, had m. p. 122—123° (Found: C, 64.35; H, 6.2. Calc. for  $C_{12}H_{14}O_4$ : C, 64.85; H, 6.3%) (Avery and Fossler, *Amer. Chem. J.*, 1898, 20, 516, give m. p. 125°).

Thanks are offered to King's College Research Fund for grants towards the purchase of equipment and to Professor G. R. Clemo, F.R.S., for providing other facilities.

*Steric Hindrance in Aromatic Hydrocarbon Systems.*

By H. O. PRITCHARD and F. H. SUMNER.

[Reprint Order No. 5854.]

USING a very crude molecular-orbital model we have calculated the effect of the steric repulsion between non-bonded hydrogen atoms in the diphenylmethyl and triphenylmethyl radicals. It is assumed that each ring in, say, the triphenylmethyl radical is equally twisted through an angle  $\theta$  with respect to the plane of the methyl carbon atom and that the resonance integral between two carbon atoms whose  $p_z$ -orbitals are twisted through an angle  $\theta$  with respect to each other is given by  $\beta \cos \theta$ ; thus we can calculate in terms of (the unknown)  $\beta$  the resonance energy of the triphenylmethyl radical for a series of angles by the conventional molecular-orbital treatment. We have also assumed that the repulsion between two non-bonded hydrogen atoms is closely similar to the  $^3\Sigma H_2$  molecule potential-energy curve  $V(r)$  proposed by Hirschfelder and Linnett (*J. Chem. Physics*, 1950, **18**, 130) and have used  $nV(r)$  as a trial function (where  $n < 1$ ). For the purposes of the present calculations  $\beta$  is taken to be  $-40$  kcal./mole (a value giving approximately the correct resonance energy for the benzyl radical) and  $n$  is given the value 0.5; this is a reasonable combination of parameters as it leads to angles of twist in diphenyl and in triphenylbenzene of about  $30^\circ$ , to be compared with the experimental values of  $45^\circ \pm 10^\circ$  (Bastiansen, *Acta Chem. Scand.*, 1949, **3**, 408) and  $30^\circ \pm 10^\circ$  (Lonsdale, *Z. Krist.*, 1937, **97**, 91; Farag, *Acta Cryst.*, 1954, **7**, 117) respectively. The essential qualitative conclusions are unaffected by the choice of other pairs of values for  $\beta$  and  $n$ .

Radical	(E.R.E.) $\theta=0^*$	$\theta_{\min.}$	E.R.E. at minimum (kcal.)	H-H repulsion at minimum (kcal.)	Corrected E.R.E. at minimum (kcal.)	Experimental E.R.E. (kcal.)
CH <sub>2</sub> Ph .....	$0.722\beta$ †	$0^\circ$	$0.722\beta = -28.9$	0	-28.9	-24.5
CHPh <sub>2</sub> .....	$1.301\beta$	49	$1.112\beta = -44.5$	3.3	-41.2	-30
CPh <sub>3</sub> .....	$1.800\beta$	57	$1.465\beta = -58.6$	4.7	-53.9	-27

\* E.R.E. = extra resonance energy over that of the phenyl rings.

† From Coulson, *Discuss. Faraday Soc.*, 1947, **2**, 9.

The (extra) resonance energies of the di- and the tri-phenylmethyl radical and of the benzyl radical are known (Szwarc, *Discuss. Faraday Soc.*, 1951, **10**, 336; Jaquiss, Thesis, Manchester, 1953), and these are compared with the calculated values in the Table; the calculated values are based on a C-H distance of 1.08 Å and the C-C distances given by the simple M.O. treatment (the allowance for the fact that the C-C bond lengths change slightly as the molecule is twisted only alters the calculated angle by a fraction of a degree and this effect can be ignored). It seems that  $\beta$  is a little too large, and that  $\frac{1}{2}V(r)$  rather underestimates the repulsion energy; however, no reasonable choice for the repulsion energy brings the resonance energy of the triphenylmethyl radical below that of the diphenylmethyl radical. This suggests that the latter radical has other means of relieving the hydrogen-hydrogen repulsions, and it is evident that the diphenylmethyl radical is rather flatter than our calculations show, with the phenyl-C-phenyl angle significantly greater than the normal  $120^\circ$ .

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*The Ammonolysis of Methyl 2:3-Anhydro-D-lyxofuranoside.*

By J. M. ANDERSON and ELIZABETH PERCIVAL.

[Reprint Order No. 5857.]

BAKER, SCHAUB, JOSEPH, and WILLIAMS (*J. Amer. Chem. Soc.*, 1954, **76**, 4044) in the course of a total synthesis of puromycin reported the isolation of the  $\alpha$ - and the  $\beta$ -form of methyl 3-acetamido-3-deoxy-D-arabofuranoside by ammonolysis, followed by *N*-acetylation, of the methyl 2:3-anhydro-D-lyxofuranosides. In investigations into the mode of fission of ethylene oxide rings we too carried out this series of reactions and isolated the two anomers. Baker *et al.* (*loc. cit.*) concluded that their product was the 3-amino-3-deoxy-D-arabinose derivative and not the other possible fission product, the 2-amino-2-deoxy-D-xylose derivative, inasmuch as the hydrochloride of their product had a different decomposition point and rotation from 2-amino-2-deoxy-D-xylose hydrochloride, prepared by Wolfrom and Anno (*J. Amer. Chem. Soc.*, 1953, **75**, 1038). We obtained proof that neither of the crystalline *N*-acetyl derivatives was a xylose derivative because all attempts to condense them with acetone were unsuccessful. The starting material was obtained in quantitative yield in every experiment, whereas 2-amino-2-deoxy-D-xylose would have given the 3:5-isopropylidene derivative. It is clear therefore that the main product from the fission of the oxide ring is an arabinose derivative.

Proof that no change to the pyranose form had occurred was obtained by the isolation from both anomers of the di-*O*-toluene-*p*-sulphonyl derivative followed by replacement of the primary toluene-*p*-sulphonyloxy-group by iodine. The action of sodium iodide in acetone was carried out under conditions specific for the replacement of a toluene-*p*-sulphonyloxy-group attached to a primary carbon atom (see Tipson, *Adv. Carbohydrate Chem.*, 1954, **8**, 192). Control experiments were carried out with methyl 2:3:4-tri-*O*-benzoyl-6-*O*-toluene-*p*-sulphonyl- $\alpha$ -D-mannopyranoside and toluene-*p*-sulphonamide. The former gave the same percentage yield of sodium toluene-*p*-sulphonate as did the above di-*O*-toluene-*p*-sulphonyl derivatives; the latter gave no sodium toluene-*p*-sulphonate, evidence that had the toluene-*p*-sulphonyl chloride condensed with the amino-group of the sugar it would not be removed under these conditions.

*Experimental.*—Solvents were removed under reduced pressure. Methanolic ammonia was prepared by saturating dry methanol with ammonia at 0°.

*Methyl 3-acetamido-3-deoxy- $\alpha$ -D-arabofuranoside.* Methyl 2:3-anhydro- $\alpha$ -D-lyxofuranoside (*J.*, 1953, 564) (m. p. 80°; 0.90 g.), dissolved in dry methanolic ammonia (40 ml.), was heated in a sealed tube at 120° for 48 hr. After concentration of the cooled solution, distillation gave a viscous syrup (0.85 g.), b. p. 150—170°/0.01 mm. A solution of this in water (20 ml.) and methanol (2 ml.) was stirred at 5° with anion-exchange resin (Amberlite I.R. 400; bicarbonate form) (24 ml.) and acetic anhydride (0.6 ml.) for 90 min. (Roseman and Ludowieg, *J. Amer. Chem. Soc.*, 1954, **76**, 301). Filtration and evaporation gave a syrup (0.96 g.), which formed prisms (0.52 g.) from acetone, and on recrystallisation had m. p. 120—121°,  $[\alpha]_D^{25} + 124^\circ$  (*c.* 0.7 in EtOH),  $+134^\circ$  (*c.* 1.0 in H<sub>2</sub>O) (Baker *et al.*, *loc. cit.*, record m. p. 115—116°,  $[\alpha]_D + 102^\circ$  in H<sub>2</sub>O) (Found: C, 47.2; H, 7.6; N, 6.5. Calc. for C<sub>8</sub>H<sub>17</sub>O<sub>5</sub>N: C, 46.8; H, 7.4; N, 6.8%).

*Methyl 3-acetamido-3-deoxy- $\beta$ -D-arabofuranoside.* Syrupy methyl 2:3-anhydro- $\alpha$ - $\beta$ -D-lyxoside (2.8 g.), in dry methanolic ammonia (75 ml.), was treated as described for the  $\alpha$ -form. A portion (1.01 g.) of the derived syrup in dry methanol (20 ml.) was treated with acetic anhydride (2.5 ml.), and the mixture kept at 18° for 18 hr. This, after dilution with water (10 ml.), neutralisation with solid sodium hydrogen carbonate, filtration, and evaporation to dryness, gave a residue which was extracted with chloroform. Evaporation of the dried chloroform extract gave a syrup (0.76 g.) which, on solution in methanol-acetone (50%), addition of ether to incipient turbidity and recrystallisation, yielded needles (0.16 g.), m. p. 156°,  $[\alpha]_D^{18} - 165^\circ$  (*c.* 1.0 in EtOH),  $-120^\circ$  (*c.* 1.2 in H<sub>2</sub>O) (Baker *et al.*, record m. p. 155°,  $[\alpha]_D - 119^\circ$  in H<sub>2</sub>O) (Found: C, 46.2; H, 7.3; N, 6.9%).

*Attempted isolation of an isopropylidene derivative.* Methyl 3-acetamido-3-deoxy- $\alpha$ -D-arabofuranoside (50 mg.) was shaken with dry acetone (10 ml.), anhydrous copper sulphate (1 g.), and 2 drops of acetaldehyde for 14 days. This gave a syrup (45 mg.) which crystallised

completely on trituration with acetone; the solid had m. p. and mixed m. p. with starting material 118—120°,  $[\alpha]_D^{15} +124^\circ$  (*c.* 0.7 in EtOH). Methyl 3-acetamido-3-deoxy- $\beta$ -D-arabofuranoside (50 mg.) was treated with dry acetone and anhydrous copper sulphate under the same conditions. The product (46 mg.) had m. p. and mixed m. p. with starting material 156°,  $[\alpha]_D^{15} -160^\circ$  (*c.* 0.5 in EtOH) (Found: C, 46.9; H, 7.35. Calc. for  $C_8H_{17}O_5N$ : C, 46.8; H, 7.4; for  $C_{11}H_{19}O_5N$ : C, 53.8; H, 7.8%).

*Methyl 3-acetamido-3-deoxy-2:5-di-O-toluene-p-sulphonyl- $\alpha$ -D-arabofuranoside.* Methyl 3-acetamido-3-deoxy- $\alpha$ -D-arabofuranoside (10 mg.) in dry pyridine (1 ml.) was treated with toluene-*p*-sulphonyl chloride (40 mg.) in the presence of "Drierite" for 60 hr. at room temperature. The toluene-*p*-sulphonyl derivative (11.7  $\mu$ moles) obtained after appropriate treatment, was dissolved in dry acetone and heated with sodium iodide in a sealed tube for 2 hr. at 100°. Characteristic plate-shaped crystals of sodium toluene-*p*-sulphonate (identified as the *S*-benzylthiouronium salt, m. p. 179—180°) were deposited in a yield (10.3  $\mu$ moles) comparable with that in a similar experiment carried out on methyl 2:3:4-tri-*O*-benzoyl-6-*O*-toluene-*p*-sulphonyl- $\alpha$ -D-mannopyranoside (9.3  $\mu$ moles from/11.4  $\mu$ moles). Toluene-*p*-sulphonamide failed to yield sodium toluene-*p*-sulphonate under similar treatment. Identical experiments were carried out with the  $\beta$ -anomer (10 mg.) and the derived 2:5-di-*O*-toluene-*p*-sulphonyl derivative (19.5  $\mu$ moles) on treatment with sodium iodide in acetone gave sodium toluene-*p*-sulphonate (16.5  $\mu$ moles). (Corrections for solubility of sodium toluene-*p*-sulphonate in acetone were made in all of these experiments.)

*3-Amino-3-deoxy-D-arabinose hydrochloride.* After methyl 3-acetamido-3-deoxy- $\alpha$ -D-arabofuranoside (91 mg.) had been heated at 100° with hydrochloric acid (10 ml.; 3*N*) for 60 min. and the solution had been concentrated to dryness, a syrup was obtained which crystallised from methanol; the solid had m. p. 161° (decomp.),  $[\alpha]_D^{15} -109^\circ$  (*c.* 0.3 in  $H_2O$ ) {Baker *et al.*, *loc. cit.*, record m. p. 159° (decomp.),  $[\alpha]_D -112^\circ$  in  $H_2O$ }.

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### *A New Preparation of Glycol Monoesters of Fatty Acids.*

By T. H. BEVAN, T. MALKIN, and D. B. SMITH.

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In the preparation of glycol monoesters of fatty acids, either by direct esterification or by acylation, large amounts of diesters are formed even when great excess of glycol is used (cf. Hilditch and Rigg, *J.*, 1935, 1774), and, as the diesters are the less soluble, purification of the monoesters is difficult and wasteful. Verkade, Tollenaar, and Posthumus (*Rec. Trav. chim.*, 1942, 61, 373) avoided diester formation by acylating the monotriphenylmethyl ether, and removing the triphenylmethyl group by catalytic hydrogenation. Baer, however (*J. Amer. Chem. Soc.*, 1953, 75, 5533), claims to obtain high yields of monoester by direct acylation at  $-15^\circ$ , in a mixture of dimethylformamide and chloroform. He states that the method of Verkade *et al.* is tedious, and that their products tenaciously hold traces of triphenylmethyl compounds. This van Gijzen and Verkade deny (*Rec. Trav. chim.*, 1954, 73, 496) and point out that their products melt higher than those of Baer and are presumably purer.

In view of this disagreement, the following method will be of interest, since it gives higher yields than the above methods and avoids any possibility of diester formation. Ethylene iodohydrin is acylated, and the iodine atom is then replaced by hydroxyl, by refluxing with aqueous-alcoholic silver nitrite. Both stages go smoothly in 90—95% yield.

Fischer (*Ber.*, 1920, 53, 1621) used a similar method for the preparation of 1 : 3-diglycerides, but no explanation of the use of silver nitrite is given. In several cases that we have tried, silver nitrate acts equally well.

We have not studied the behaviour of acyl bromohydrins extensively, but 2-bromoethyl palmitate is converted into 2-hydroxyethyl palmitate in 77% yield.

*Experimental.*—2-Iodoethyl palmitate. Palmitoyl chloride (4.12 g., 0.015 mole) in dry benzene (15 ml.) was slowly added to ethylene iodohydrin (2.58 g., 0.015 mole) (Wieland and Sakellarios, *Ber.*, 1920, 53, 208) in dry benzene (10 ml.) containing dry pyridine (2 ml.) and left overnight. Ether was then added, and the ethereal solution was successively washed with dilute hydrochloric acid, sodium hydrogen carbonate solution, and water, and dried ( $\text{Na}_2\text{SO}_4$ ). After filtration and removal of ether, the palmitate crystallised from alcohol-ether as colourless platelets, m. p. 55° (5.6 g., 93%) (Found: C, 53.0; H, 8.7.  $\text{C}_{18}\text{H}_{35}\text{O}_2\text{I}$  requires C, 52.7; H, 8.5%).

In the same way were made the stearate [from stearoyl chloride (7.4 g.) and iodohydrin (4.2 g.)] (10.2 g.), m. p. 62—63° (Found: C, 54.9; H, 8.9.  $\text{C}_{20}\text{H}_{39}\text{O}_2\text{I}$  requires C, 54.8; H, 8.9%), myristate [8.2 g. from the chloride (5.6 g.) and iodohydrin (4 g.)], m. p. 46—47° (Found: C, 50.3; H, 8.1.  $\text{C}_{16}\text{H}_{31}\text{O}_2\text{I}$  requires C, 50.3; H, 8.1%), and laurate [7.5 g. from the chloride (5.1 g.) and iodohydrin (4 g.)], m. p. 35—36° (Found: C, 47.5; H, 7.7.  $\text{C}_{14}\text{H}_{27}\text{O}_2\text{I}$  requires C, 47.5; H, 7.6%).

2-Hydroxyethyl palmitate. The iodoethyl palmitate (2 g.) was refluxed with a solution of silver nitrite (2.5 g.) in ethanol (20 ml.) and water (2 ml.) for  $\frac{3}{4}$  hr. The solution was then filtered hot, and the solvent was removed under reduced pressure. The residue was shaken with warm light petroleum (b. p. 60—80°), which dissolved the hydroxyethyl ester, and after filtration it was kept at 0°. The product which separated was recrystallised from light petroleum and yielded colourless plates (1.4 g.), m. p. 52—53° (Found: C, 71.6; H, 11.9. Calc. for  $\text{C}_{18}\text{H}_{35}\text{O}_3$ : C, 72.0; H, 12.0%). Similarly were made the stearate, m. p. 60—61° (95%) (Found: C, 72.9; H, 12.2. Calc. for  $\text{C}_{20}\text{H}_{40}\text{O}_3$ : C, 73.1; H, 12.3%), myristate, m. p. 43—43.5° (93%) (Found: C, 70.4; H, 11.8. Calc. for  $\text{C}_{16}\text{H}_{32}\text{O}_3$ : C, 70.5; H, 11.8%), and laurate, m. p. 31—32° (91%) (Found: C, 69.0; H, 11.5. Calc. for  $\text{C}_{14}\text{H}_{28}\text{O}_3$ : C, 68.8; H, 11.6%).

2-Bromoethyl palmitate. Ethylene bromohydrin (1.9 g.) was acylated with palmitoyl chloride (4.2 g.) as described for palmitoyl iodohydrin, to give 2-bromoethyl palmitate (4.85 g.), m. p. 45—46° (88%) (Found: C, 59.8; H, 9.8; Br, 22.0.  $\text{C}_{18}\text{H}_{35}\text{O}_2\text{Br}$  requires C, 59.5; H, 9.7; Br, 22.0%). This ester, treated as described in the preparation of hydroxyethyl ester, except that more silver nitrite was used (3 g.), yielded monopalmitoyl glycol (1.3 g.), m. p. and mixed m. p. 52—53° (77%).

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### *The Erythrophleum Alkaloids. Cassaic Acid.*

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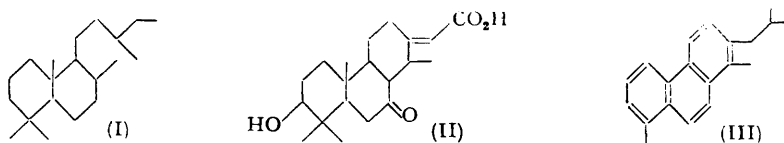
[Reprint Order No. 5895.]

THE Erythrophleum alkaloids are alkamine esters of diterpene monocarboxylic acids (see review by Dalma, "The Alkaloids," Vol. IV, edited by Manske and Holmes, Academic Press, New York, 1954, p. 265) which have remarkable cardiac activity coupled with intense local anæsthetic action. The most thoroughly investigated member is cassaine which on acid hydrolysis gave dimethylaminoethanol and cassaic acid,  $\text{C}_{20}\text{H}_{30}\text{O}_4$ , an  $\alpha\beta$ -unsaturated hydroxyketo-acid to which cassaidic, coumingic, and coumingidic acids are related. Hydrolysis of cassaine under basic conditions afforded a mixture of cassaic and allocassaic acid (Dalma, *Helv. Chim. Acta*, 1939, 22, 1947; Ruzicka and Dalma, *ibid.*, p. 1517, footnote 2). The double bond of the latter was no longer conjugated with the carboxyl group and, since both acids yielded the same dihydrocassaic acid, it was evident that no rearrangement of the carbon skeleton had occurred. This behaviour resembles the conversion of cyclohexylideneacetic acid (Kon and Linstead, *J.*, 1929, 1269), under

basic conditions, into an equilibrium mixture of *cyclohexylidene*- and *cyclohex-1-enyl*-acetic acid, the latter predominating. Thus we conclude that the carboxyl group in *cassaica* acid is in the side chain.

Ruzicka and his co-workers (Ruzicka, Engel, Ronco, and Berse, *Helv. Chim. Acta*, 1945, **28**, 1038; Engel, Ronco, Berse, Plattner, and Ruzicka, *ibid.*, 1949, **32**, 1713) oxidised dihydrocassaica acid to dioxocassaica acid, which on Wolff-Kischner reduction formed *cassanic* acid. Dehydrogenation of *cassanic* acid gave 1 : 2 : 8-trimethylphenanthrene. Methyl *cassanate* on treatment with methylmagnesium iodide followed by dehydration and dehydrogenation gave a hydrocarbon  $C_{20}H_{22}$ , which, if the carboxyl group of *cassaica* acid had been attached to the nucleus, must have been a 1 : 2 : 8-trimethyl-*x*-isopropylphenanthrene. Comparison of the ultra-violet absorption spectra of a number of synthetic alkylphenanthrenes with the  $C_{20}H_{22}$  hydrocarbon led the above authors to conclude that their hydrocarbon was trisubstituted. Consequently the carboxyl group was in a side chain, and the  $C_{20}H_{22}$  hydrocarbon must be an *isobutyldimethylphenanthrene*.

The known diterpene acids can all be derived from the hypothetical precursor (I) (the biogenetic isoprene rule of Ruzicka, *Experientia*, 1953, **9**, 366) so that if *cassaica* acid were (II) the  $C_{20}H_{22}$  hydrocarbon should be (III).



We have synthesised (III) from 1 : 8-dimethylphenanthrene taking advantage of the fact that acylation of a dihydrophenanthrene proceeds exclusively in the 2-position. The ultra-violet absorption spectrum and melting point of the resulting hydrocarbon, and the melting point of its trinitrobenzene derivative, were identical with those recorded for the  $C_{20}H_{22}$  hydrocarbon and its derivative (Ruzicka, Engel, Ronco, and Berse, *loc. cit.*); this establishes the carbon skeleton of *cassaica* acid as in (II).

The ultra-violet absorption spectrum (Ruzicka and Dalma, *loc. cit.*) of dioxocassaica acid ( $\lambda_{\max}$ , 223  $\mu\mu$ ;  $\log \epsilon$  4.2) is typical of an  $\alpha\beta$ -unsaturated acid and shows the absence of 1 : 2- and 1 : 3-dioxo-groupings, an  $\alpha\beta$ -unsaturated ketone, and the grouping  $\cdot\text{CO}\cdot\text{CH}:\text{CH}\cdot\text{CO}_2\text{H}$ ; therefore the secondary oxygen functions cannot be in the same rings. Ring c appears to be excluded as a site for one of the oxygen atoms and we favour as a working hypothesis the groupings shown in (II).

*Note Added February 9th, 1955.*—Dr. B. Engel has kindly shown that our synthetic hydrocarbon (III) does not depress the melting point of the  $C_{20}H_{22}$  compound. He has also informed us that by ozonolysis of dioxocassaica acid he has obtained oxalic acid (70%) and a trioxo-compound whose ultraviolet spectrum indicated isolated ketonic groups only, giving additional support to our deductions. The possibility that *cassaica* acid has the carbon skeleton shown in (II) has been indicated earlier by R. Tondeur (Ph.D. Thesis; E.T.H., Zurich, 1950) and we thank Dr. Engel for this information.

*Experimental.*—9 : 10-Dihydro-1 : 8-dimethylphenanthrene. Sodium (2.5 g.) was added during 30 min. to 1 : 8-dimethylphenanthrene (2.3 g.) in boiling amyl alcohol. The cooled mixture was shaken with water, and the organic layer washed until neutral and then concentrated. The oil (2.25 g.) was chromatographed on activated alumina; the light petroleum (b. p. 60—80°) eluate gave the *dihydrophenanthrene*, m. p. 144—146° (from ethanol),  $\lambda_{\max}$ , 270  $\mu\mu$  ( $\log \epsilon$  4.07) (Found, in a sublimed sample: C, 92.2; H, 7.8.  $C_{18}H_{18}$  requires C, 92.3; H, 7.7%).

2-isoButyryl-9 : 10-dihydro-1 : 8-dimethylphenanthrene. *iso*Butyryl chloride (140 mg.) and aluminium chloride (310 mg.) in nitrobenzene (5 ml.) were added successively to the dihydrophenanthrene (240 mg.) in nitrobenzene (5 ml.), and the mixture kept at 0° for 4 hr. then at room temperature for 3 hr. It was poured on cracked ice, and the nitrobenzene solution washed well with water and then concentrated to a red oil (330 mg.) which was chromatographed on activated alumina. The light petroleum eluate gave the *ketone*, m. p. 93—94° (from light



petroleum),  $\lambda_{\text{max}}$ . 290  $\text{m}\mu$  ( $\log \epsilon$  4.20) (Found in a sample dried at 50° *in vacuo*: C, 86.3; H, 7.9.  $\text{C}_{20}\text{H}_{22}\text{O}$  requires C, 86.4; H, 7.9%).

*2-isoButyl-1:8-dimethylphenanthrene*. A solution of the above dihydrophenanthrene (145 mg.) in dilute hydrochloric acid and ethanol was refluxed for 76 hr. with amalgamated zinc (1.5 g.), periodic additions of concentrated hydrochloric acid (5 ml.) being made. Exhaustive extraction with ether furnished the crude trialkyldihydrophenanthrene (140 mg.) which was heated at 350° for 15 min. with selenium (200 mg.). The solidified mass was extracted (Soxhlet) with benzene, and the product was chromatographed in light petroleum over activated alumina. The light petroleum eluate crystallised readily from methanol to give *2-isobutyl-1:8-dimethylphenanthrene* (120 mg.), m. p. 131°,  $\lambda_{\text{max}}$ . 254, 262, 284, 294, 306, 322, and 338  $\text{m}\mu$  ( $\log \epsilon$  4.58, 4.83, 4.04, 4.00, 4.07, 2.57, and 2.48) (Found, in a sublimed sample: C, 91.7; H, 8.5.  $\text{C}_{20}\text{H}_{22}$  requires C, 91.6; H, 8.5%). The yellow *trinitrobenzene derivative* had m. p. 131—132° (from ethanol) (Found, in a specimen dried at 70° for 12 hr. *in vacuo*: C, 65.7; H, 5.3.  $\text{C}_{20}\text{H}_{22}\text{C}_6\text{H}_3\text{O}_6\text{N}_3$  requires C, 65.7; N, 5.3%).

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