NOTES.

495. *The Heat of Ionization of Some Substituted Anilines.*

By A. I. Biggs.

In a recent paper [1] the ionization constants of a number of substituted anilines and phenols at 25° were reported, the measurements being made by the spectrophotometric method. During some measurements to determine the effect of temperature on these ionization constants, it appeared that the difference in pK at 20° and at 40° was a linear function of the pK, already reported, at 25°. The pK values of phenol, aniline, and some substituted anilines have now been measured at 5° intervals between 20° and 40° and are given in the Table; we emphasize that these values are preliminary, being made in a rapid survey of the temperature effect. Over this short temperature range, and within the experimental accuracy, the pK values can be represented by: $pK = a + bt$, where the parameters can

[1] Biggs and Robinson, *J.*, 1961, 388.

be calculated by the method of least squares. Then the partial molal free energy and the enthalpy changes on ionization at 30° (the middle of our temperature range) are

$$\Delta\bar{G}^0 = 1{\cdot}387(a + bt)$$

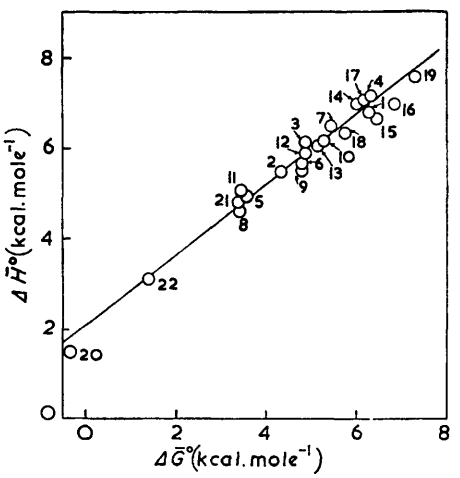
$$\text{and } \Delta\bar{H}^0 = -420{\cdot}5b$$

respectively, each in kcal. mole^{-1}.

p*K* *values of phenol, aniline, and some substituted anilines between* 20° *and* 40°.

No.	Compound *	20°	25°	30°	35°	40°
	Phenol	10·07	10·00	9·93	9·86	9·80
1	Aniline	$4{\cdot}68_6$	$4{\cdot}60_6$	$4{\cdot}52_7$	$4{\cdot}44_5$	$4{\cdot}36_6$
2	*o*-Fluoroaniline	3·25	3·20	3·12	3·05	3·00
3	*m*-Fluoroaniline	3·66	3·57	3·48	3·42	3·37
4	*p*-Fluoroaniline	4·73	4·65	4·56	4·48	4·39
5	*o*-Chloroaniline	2·70	2·64	2·58	2·53	2·46
6	*m*-Chloroaniline	3·60	3·52	3·46	3·39	3·33
7	*p*-Chloroaniline	4·07	3·98	3·92	3·83	3·76
8	*o*-Bromoaniline	2·57	2·53	2·47	2·42	2·35
9	*m*-Bromoaniline	3·60	3·53	3·46	3·39	3·34
10	*p*-Bromoaniline	3·95	3·88	3·80	3·73	3·66
11	*o*-Iodoaniline	2·61	2·55	2·49	2·43	2·37
12	*m*-Iodoaniline	3·66	3·59	3·52	3·45	3·38
13	*p*-Iodoaniline	3·87	3·79	3·71	3·65	3·58
14	*o*-Toluidine	4·52	4·44	4·36	4·27	4·18
15	*m*-Toluidine	4·80	4·72	4·64	4·56	4·48
16	*p*-Toluidine	5·16	5·07	4·99	4·90	4·83
17	*o*-Anisidine	4·61	4·52	4·45	4·35	4·28
18	*m*-Anisidine	4·30	4·23	4·15	4·08	3·99
19	*p*-Anisidine	5·44	5·34	5·24	5·16	5·08
20	*o*-Nitroaniline	−0·24	−0·26	−0·28	−0·30	−0·32
21	*m*-Nitroaniline	2·52	2·46	2·41	2·35	2·29
22	*p*-Nitroaniline	1·04	1·00	0·97	0·93	0·89

* The compounds used were the purest specimens available; they were either recrystallised from water (where possible) or distilled at low pressure in a stream of nitrogen, the middle fractions being taken.



Enthalpy change on ionization as a function of free energy change at 30°.

Plot of $\Delta\bar{H}°$ *against* $\Delta\bar{G}°$: 1, Aniline; 2—22, substituted anilines (see Table).

Enthalpy changes at 25° can also be calculated for comparison with values in the literature: for phenol we find 5·53 kcal. mole^{-1} compared with 5·60 given by Papée *et al.*[2] and 5·36 calculated from Binns's data.[3] For aniline at 25° we find $\Delta\bar{H}^0 = 6{\cdot}52$ kcal. mole^{-1} compared with 6·74 given by Zawidzki *et al.*[4]

[2] Papée, Canady, Zawidzki, and Laidler, *Trans. Faraday Soc.*, 1959, **55**, 1734.
[3] Binns, *Trans. Faraday Soc.*, 1959, **55**, 1900.
[4] Zawidzki, Papée, Canady, and Laidler, *Trans. Faraday Soc.*, 1959, **55**, 1738.

A plot (see Figure) of $\Delta\bar{H}^0$ against $\Delta\bar{G}^0$, from the 30° data, shows that, in spite of considerable scatter, there is a definite indication of a linear relation between the two quantities. This possibility is worth more detailed investigation, partly because we believe that further work would improve the accuracy of the data given in the Table and also because there is a discrepancy between the enthalpy data for the toluidines derived from the pK values in the Table and the direct calorimetric measurements by Zawidzki *et al.*[4]

Papée *et al.*[2] found a linear relation between $\Delta\bar{H}°$ and $T/\Delta\bar{S}°$ for phenol, the cresols, and the xylenols, $\Delta\bar{H}°$ *increasing* with increasing $\Delta\bar{S}°$. Fernandez and Hepler's results [5] for the nitro- and chloro-phenols do not agree with this relation: for these phenols, $\Delta\bar{H}°$ varies approximately linearly with $\Delta\bar{S}°$ but the slope is in the opposite direction, $\Delta\bar{H}°$ *decreasing* with increasing $\Delta\bar{S}°$. This difference must also appear in a graph of $\Delta\bar{H}°$ against $\Delta\bar{G}°$. It seems, therefore, that there are $\Delta\bar{H}°$–$\Delta\bar{S}°$ and $\Delta\bar{H}°$–$\Delta\bar{G}°$ relations specific to the substituent group, methyl in one case and nitro or chloro in the other. This may well be true of the anilines and we suspect that further work on their pK values, over a wider temperature range, may reveal that the linear increase of $\Delta\bar{H}°$ with $\Delta\bar{G}°$ is only an approximation; the relationship may well contain a " fine structure " sensitive to the nature of the substituent groups.

The author thanks Professor R. A. Robinson for helpful discussion and interest.

DEPARTMENT OF CHEMISTRY, PETALING JAYA, MALAYA. [*Received, September 27th,* 1960.]

[5] Fernandez and Hepler, *J. Amer. Chem. Soc.*, 1959, **81**, 1783.

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496. *Synthesis of Guanosine Diphosphate Glucose.*

By J. BADDILEY, N. A. HUGHES, and A. L. JAMES.

THE isolation of guanosine diphosphate glucose from *Eremothecium ashbyii* was reported recently from this laboratory.[1] Since the compound could not be separated from a considerable excess of guanosine diphosphate mannose and traces of guanosine diphosphate fructose, a chemical synthesis was desirable to confirm its identity. In view of the work of Khorana and his colleagues (cf. ref. 2), the most attractive route to this compound appeared to be the condensation of a guanosine-5′ phosphoramidate with a salt of α-D-glucopyranose 1-phosphate. Several guanosine-5′ phosphoramidates were synthesised and examined. The simple guanosine-5′ phosphoramidate and guanosine-5′ phosphoromorpholidate proved ineffective, probably owing to their lack of solubility in pyridine. However, guanosine-5′ *N*-cyclohexylphosphoramidate was more soluble and condensation occurred with the tri-n-octylammonium salt of α-D-glucopyranose 1-phosphate to give a product with the chromatographic properties expected for guanosine diphosphate glucose. At this time we became aware of work by Ueda and Ohtsuka [3] who synthesised guanosine diphosphate mannose by a similar route.

The synthetic product was purified by ion-exchange chromatography and isolated as its lithium salt. The nature of the product and its identity with the natural material were confirmed by chromatography in several solvent systems and by the following hydrolysis experiments. With dilute acid (pH 2) it gave D-glucose, guanosine-5′ phosphate, guanosine-5′ pyrophosphate, and inorganic phosphate; with ammonia it gave guanosine-5′ phosphate and α-D-glucopyranose 1,2-phosphate; treatment with the pyrophosphatase and 5′-nucleotidase of *Crotalus atrox* venom gave guanosine, α-D-glucopyranose 1-phosphate, and inorganic phosphate.

[1] Pontis, James, and Baddiley, *Biochem. J.*, 1960, **75**, 428.
[2] Moffatt and Khorana, *J. Amer. Chem. Soc.*, 1958, **80**, 3756,
[3] Ueda and Ohtsuka, *Chem. and Pharm. Bull. (Japan)*, 1959, **7**, 389.

By a similar method, with fructose 1-phosphate in place of glucose 1-phosphate, a small sample of guanosine diphosphate fructose was obtained. It is noteworthy that the rate of liberation of fructose from this compound by the action of dilute acid was appreciably faster than that of the natural guanosine diphosphate fructose, and it is tentatively assumed that the fructose–phosphate linkage in the natural compound is not through $C_{(1)}$ of the fructose.

Experimental

Evaporations were carried out under reduced pressure with the bath temperature of 35° or lower.

Hydrolyses of the synthetic nucleotides were performed as previously described;[1] results are quoted in the discussion.

Guanosine Diphosphate Glucose.—Cyclohexylamine (0·16 ml., 1·4 mmoles) and formamide (0·5 ml.), followed by dicyclohexylcarbodi-imide (280 mg., 1·35 mmoles) in t-butyl alcohol (2·0 ml.), were added to a solution of guanosine-5′ phosphate (75 mg., 0·21 mmole) in water (0·6 ml.). The resulting solution was heated at 80° for 10 hr. and left overnight at room temperature. Water (2 ml.) was added and the precipitated *NN′*-dicyclohexylurea was filtered off and washed with a little water. The combined filtrate and washings were extracted with ether (5 × 3 ml.) to remove any remaining carbodi-imide and the aqueous solution was evaporated to 0·5 ml. under reduced pressure. Addition of acetone (50 ml.) gave a white precipitate which, after 1 hr., was centrifuged, washed with acetone, dried, dissolved in water (1 ml.), and freeze-dried to a white powder (105 mg.). The product was shown by paper chromatography to be mainly guanosine-5′ *N*-cyclohexylphosphoramidate contaminated with a little diguanosine-5′ pyrophosphate (both as their *NN′N″*-tricyclohexylguanidinium salts); no guanosine-5′ phosphate was present. Solutions of the impure phosphoramidate (100 mg.) and tri-n-octylammonium α-D-glucopyranose 1-phosphate (400 mg., 0·65 mmole) in anhydrous pyridine (15 ml. and 10 ml. respectively) were mixed and set aside at 28° for 3 days. Pyridine was removed by evaporation; last traces were removed by the addition and subsequent evaporation of water (10 ml.). The residue was dissolved in water (10 ml.), and the pH of the solution was adjusted to 7·2 by the addition of 0·1N-lithium hydroxide solution before being passed through a column (40 cm. × 1 cm.) of Dowex-1(× 2) resin (200—400 mesh; chloride form). The column was washed with water until the washings showed no appreciable absorption at 255 mμ. The nucleotides were then removed by gradient elution, a hydrochloric acid–lithium chloride system being employed. The mixing chamber contained 0·0001N-hydrochloric acid (2 l.) and the reservoir contained 0·02N-hydrochloric acid (1 l.) and 0·4N-lithium chloride (1 l.). A linear gradient was employed at a rate of 0·5 ml./min., and fractions (10 ml.) were collected. The nucleotide content of each fraction was estimated from the absorption at 255 mμ. The nucleotides were eluted in four fractions (see below):

Fraction	Tube number	Contents	Nucleotide present (mmoles)
1	48—58	α-D-glucopyranose 1-phosphate and guanosine-5′ phosphate	0·014
2	62—67	guanosine-5′ *N*-cyclohexylphosphoramidate and guanosine-5′ phosphate	0·003
3	69—75	diguanosine-5′ pyrophosphate	0·013
4	133—146	guanosine diphosphate glucose	0·041

The pH of fraction 4 was adjusted to 6·8 with 0·5N-lithium hydroxide solution, and the solution was concentrated to 2 ml. Addition of acetone–ethanol (9 : 1; 100 ml.) gave a white precipitate which was centrifuged, washed with acetone–ethanol, and finally dried *in vacuo* to give the *lithium salt* of guanosine diphosphate glucose as a very hygroscopic grey-white powder (28 mg.). Elementary analysis indicated the compound to be heavily hydrated and efforts to obtain the anhydrous compound resulted in extensive decomposition (Found: N, 9·9; P, 8·4. $C_{16}H_{23}Li_2N_5O_{16}P_2,5H_2O$ requires N, 9·9; P, 8·7%). For ratio analysis solutions were used in which the guanosine contents were estimated spectroscopically [Found: guanosine : labile

phosphorus [4]: total phosphorus [4]: reducing hexose [5] (after hydrolysis at pH 2 for 15 min. at 100°) 1·02 : 0·86 : 2·00 : 0·95. Guanosine diphosphate glucose requires 1·00 : 1·00 : 2·00 : 1·00].

Guanosine Diphosphate Fructose.—Solutions of tri-n-octylammonium D-fructose 1-phosphate (32 mg., 0·052 mmole) and *NN'N''*-tricyclohexylguanidinium guanosine-5′ *N*-cyclohexylphosphoramidate (10 mg., 0·013 mmole) in anhydrous pyridine (5 ml. and 10 ml., respectively) were mixed and set aside at 28° for 4 days. Pyridine was removed by evaporation, water (10 ml.) was added, and the volume was reduced to 0·5 ml. by evaporation. Paper chromatography revealed the presence of D-fructose 1-phosphate, guanosine-5′ phosphate, and a compound, presumably guanosine diphosphate fructose, with the same R_F as guanosine diphosphate glucose. The reaction mixture was chromatographed as a band on Whatman No. 1 paper in the ethanol–ammonium acetate system. The band corresponding to guanosine diphosphate fructose was cut out and eluted with water. The hydrolysis experiments were carried out with this solution according to methods described previously.[1]

Paper Chromatography and Electrophoresis.—Nucleotides were examined on Whatman No. 1 paper in ethanol–1M-ammonium acetate (pH 3·8) (70 : 35 v/v) by descending development. The following $R_{adenosine}$ values were obtained: α-D-glucose 1-phosphate, 0·60; fructose 1-phosphate, 0·68; guanosine-5′ phosphate, 0·32; guanosine-5′ pyrophosphate, 0·05; diguanosine-5′ pyrophosphate, 0·27; guanosine-5′ *N*-cyclohexylphosphoramidate, 0·55; guanosine diphosphate glucose, 0·12; guanosine diphosphate fructose, 0·12; guanosine diphosphate mannose, 0·13.

Sugars were run on Whatman No. 1 paper in butanol–pyridine–water (6 : 4 : 3 v/v) by descending development. The following R_{ribose} values were obtained: glucose, 0·70; mannose, 0·83· fructose, 0·79. Sugars were also subjected to electrophoresis on Whatman No. 1 paper in 0·05M-sodium borate buffer (pH 9·2) when the following E_{ribose} values were obtained: glucose, 1·32: mannose, 0·94; fructose 1·17.

We thank the Department of Scientific and Industrial Research for a Studentship held by one of us (A. L. J.), and the Medical Research Council and the Nuffield Foundation for financial support.

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Received, October 7th, 1960.]

[4] Fiske and Subbarow, *J. Biol. Chem.*, 1925, **66**, 375.
[5] Park and Johnson, *J. Biol. Chem.*, 1949, **181**, 149.

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497. *Arylation of 2-Furoic Acid in Meerwein's Diazo-reaction.*

By K. B. L. MATHUR and H. S. MEHRA.

p-NITRO- and *p*-CHLORO-BENZENEDIAZONIUM CHLORIDE have been reported [1] to give 5-aryl-2-furoic acids (I; R = aryl) on reaction with 2-furoic acid (I; R = H) in the presence of acetone, cupric chloride, and hydrochloric acid, but the details are lacking. We have reinvestigated this reaction at pH 3—5 (usual for arylation by the Meerwein's reaction [2]), because we thought that under the acid conditions (pH 1) stated to have been employed previously, other reactions with unsaturated acids, *e.g.*, decarboxylation, might not have been discernible.[3] But, as advocated [3a] earlier for reactions with water-soluble acids, the acetone so specifically recommended in other cases,[2] was omitted. Further the structures of the arylated acids have now been rigidly proved.

p-Chlorobenzenediazonium chloride and 2-furoic acid in the presence of cupric chloride and sodium acetate give an arylated acid in 20% yield. Using the method used by Hill *et al.*[4] for converting 5-methyl-2-furoic acid (I; R = Me) into 4-oxopent-2-enoic acid

[1] Malinowski, *Roczniki Chem.*, 1953, **27**, 54; *Chem. Abs.*, 1954, **48**, 13,678.
[2] (*a*) Meerwein, Buchner, and Emster, *J. prakt. Chem.*, 1939, **152**, 237; (*b*) Koelsch and Boekelheide, *J. Amer. Chem. Soc.*, 1944, **66**, 412.
[3] (*a*) Cf. Rai and Mathur, *J. Indian Chem. Soc.*, 1947, **24**, 383; (*b*) Denivelle and Razair, *Compt. rend.*, 1953, **237**, 570.
[4] Hill *et al.*, *Ber.*, 1890, **23**, 452; *Amer. Chem. J.*, 1893, **15**, 159; 1897, **19**, 650.

(II; R = Me), we oxidised the arylated acid by bromine water to *p*-chlorobenzoylacrylic acid (II; R = *p*-Cl·C_6H_4). The coupling product must therefore be 5-*p*-chlorophenyl-2-furoic acid (II; R = *p*-Cl·C_6H_4). There is indication that the initial product obtained by

the bromine oxidation is a mixture of *cis*- and *trans*-forms: the acid obtained by one crystallisation needs irradiation in presence of iodine in chloroform before it gives the melting point as recorded in the literature.

p-Bromo- and *m*- and *p*-nitro-benzenediazonium chlorides similarly gave monoarylfuroic acids that do not seem to be mixtures. The *m*-nitro-acid was also oxidised to *m*-nitrobenzoylacrylic acid, proving again that arylation occurred at the 5-position.

The experiments with *p*-chloro- and *p*-bromo-benzenediazonium chloride gave also, by decarboxylation, 2-*p*-chloro- and 2-*p*-bromo-phenylfuran but in yields of only a few percent. The amount of carbon dioxide evolved was, however, 10% and most of this clearly arose by decarboxylation of the unsubstituted furoic acid (cf. Bergmann *et al.*[5]).

The arylation of 2-furoic acid in the 5-position fits an aromatic character for this acid and corresponds to the homolytic arylation, mostly at the 2-position, undergone by furan itself.[6] The decarboxylation of the product, analogous to that of sorbic acid,[2b] shows the participation in the coupling reaction also of the diene form of the acid, though to a minute extent. Further, the homolytic arylation is here easier than that of benzoic acid

Experimental.—Coupling of p-*chlorobenzenediazonium chloride with* 2-*furoic acid.* *p*-Chloroaniline (6·36 g.) was dissolved in warm 25% hydrochloric acid (18 ml.). Ice (15—20 g.) was added and the precipitated hydrochloride diazotised with sodium nitrite (4 g.) in water (15 ml.). Separately, 2-furoic acid (5·6 g.) was dissolved in warm water (50 ml.) containing sodium acetate (16 g.); on cooling, the 2-furoic acid remained in solution. The diazotised solution was filtered through glass wool and added to the acid solution, followed by cupric chloride (2 g.) in water (10 ml.). There was brisk effervescence. The mixture was stirred for 3 hr. at 30° and then steam-distilled. The later part of the steam-distillate gave a small amount of 2-*p*-chlorophenylfuran,[6] m. p. 73°, dissolving in concentrated sulphuric acid with a permanganate colour. On cooling, the non-volatile material contained a red-brown solid (*ca.* 5 g.), which was filtered off, washed, and extracted with saturated sodium hydrogen carbonate solution (3 × 25 ml.). The combined extracts were acidified with hydrochloric acid, giving an acid precipitate that, after recrystallisation from 20% alcohol, had m. p. 194° (Found: C, 59·4; H, 3·7. Calc. for $C_{11}H_7O_3Cl$: C, 59·3; H, 3·15%). Recovery of this 5-*p*-chlorophenyl-2-furoic acid was easier with aqueous ammonia but then the product was slightly coloured. The yield of crude acid, m. p. 182—186°, was 2·2 g. (20%).

The acid product (0·6 g.) was dissolved in water (15—20 ml.) with the aid of alcohol. Bromine (0·9 g., 0·3 ml.) was added drop by drop with shaking to this solution. The residual bromine was also washed into the mixture with the aid of water (15 ml.). The mixture, with occasional shaking, was then kept at room temperature for 1 hr., then extracted with ether. The extract was dried (Na_2SO_4) and evaporated. The residue was semisolid and after crystallisation from benzene yielded crystals (0·2 g.), m. p. 147—148°. These were dissolved in chloroform (10 ml.) containing traces of iodine and kept in sunlight for 12 hr. The chloroform was removed and the residue again crystallised from benzene, giving crystals, m. p. 156° alone or mixed with *p*-chlorobenzoylacrylic acid[7a] (Found: C, 56·5; H, 3·8. Calc. for $C_{10}H_7O_3Cl$: C, 57·0; H, 3·3%).

Coupling of other diazonium chlorides with 2-*furoic acid.* Diazotised *p*-bromoaniline (8·6 g.)

[5] Bergmann, Dimant, and Japhe, *J. Amer. Chem. Soc.*, 1948, **70**, 1618.
[6] Johnson, *J.*, 1946, 895.
[7] (*a*) Papa, Schwenk, Villani, and Klingsberg, *J. Amer. Chem. Soc.*, 1948, **70**, 3356; (*b*) Bogert and Ritter, *ibid.*, 1925, **47**, 532; (*c*) Freund, *J.*, 1952, 3068.

was coupled with 2-furoic acid (5·6 g.) as described above. From the steam-distillate 2-*p*-bromophenylfuran, m. p. 84—86°, giving a permanganate colour in concentrated sulphuric acid,[6] was recovered. The sodium hydrogen carbonate extract of the residual solid provided the crude product (0·6 g.) which on crystallisation from 50% alcohol yielded 5-p-*bromophenyl*-2-*furoic acid*, m. p. 198° (Found: C, 49·1; H, 2 7. $C_{11}H_7BrO_3$ requires C, 49·4; H, 2·6%).

Coupling of diazotised *m*-nitroaniline (6·9 g.) in the same way gave 5-m-*nitrophenyl*-2-*furoic acid* (0·6 g., crude), m. p. 244° (from ethyl acetate) (Found: C, 56·5; H, 3·4. $C_{11}H_7NO_5$ requires C, 56·6; H, 3·0%). This acid with bromine water gave *m*-nitrobenzoylacrylic acid,[7b] m. p. and mixed m. p. 187°.

In the same way was obtained 5-*p*-nitrophenyl-2-furoic acid (from 50% alcohol), m. p. 246—247° (Found: C, 56·15; H, 2·7%). Freund [7c] obtained this acid by the oxidation of β-(5-*p*-nitrophenyl-2-furyl)acrylic acid and reported m. p. 204—205°.

Decarboxylation in the coupling reactions. The various diazotised bases (0·025 mole) were treated with 2-furoic acid (0·025 mole), and the evolved gases were swept in a current of carbon dioxide-free air into baryta water, giving barium carbonate (*ca.* 0·5 g., 10%). With the chloro-compound, the mixture was steam-distilled until 400 ml. had been collected. The distillate was extracted with ether (200 ml.) and the extract dried (Na_2SO_4). Evaporation at 30° *in vacuo* and then in a current of air gave 2-*p*-chlorophenylfuran (0·1 g., 2%). A sample of this furan (0·1 g.) when mixed with the chloro- and *p*-dichloro-benzene (0·3 g. each) was similarly recovered (0·09 g.) without much loss. This procedure was not quantitative for *p*-bromophenylfuran, but this was recovered (0·05 g.) by rejecting the first 25 ml. of the steam-distillate (supposed to contain mostly the Sandmeyer type of products) and extracting the rest of the distillate (400 ml.) with ether.

It was verified in separate experiments that the evolution of carbon dioxide was not due to spontaneous decarboxylation of the parent acid or the arylated acids, independently of the coupling process. Nor were the arylfurans the products of secondary process, *e.g.*, decomposition of the 5-arylated acids first formed.

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498. *Mixed Formals derived from Alcohols and Phenols.*

By Frank S. H. Head and (Miss) M. M. Williamson.

The reaction between phenols and formaldehyde in the presence of acid does not usually give rise to formals, since substitution in the aromatic nucleus and subsequent polymerisation occur more readily, but Breslauer and Pictet [1] obtained a mixed formal, methoxy-(phenoxy)methane, by treating phenol with aqueous formaldehyde (presumably containing methanol) and sulphuric acid at room temperature, and also from potassium phenoxide and chloromethyl methyl ether.

The following compounds have been made by the latter method: (2,4,6-tribromophenoxy)-, (2,4,5-trichlorophenoxy)-, and (2,3,4,5,6-pentachlorophenoxy)-methoxymethane, and ethoxy-(2,4,6-tribromophenoxy)methane. The two tribromophenoxy-compounds have also been obtained in about 15% yield by passing hydrogen chloride into a mixture of tribromophenol, paraformaldehyde, and the appropriate alcohol in chloroform.

Chloromethyl octadecyl ether treated with sodium methoxide gave octadecyloxymethoxymethane together with some dioctadecyloxymethane. The latter was also prepared from the chloromethyl ether and octadecanol, and directly from octadecanol and formaldehyde. An attempt to prepare di-(2,4,6-tribromophenoxy)methane by the

[1] Breslauer and Pictet, *Ber.*, 1907, **40**, 3784; see also Reychler, *Bull. Soc. chim. France*, 1907, (**4**), **1**, 1195.

direct method failed. Chloromethyl octadecyl ether (m. p. 56·5—57·5°) and dioctadecyloxymethane (m. p. 58—59°) gave only a slight depression of melting point (1—2°) on admixture with octadecanol (59°). At one stage it was thought that these substances might be unchanged octadecanol, but infrared examination confirmed the absence of hydroxyl groups from the compounds.

Experimental

Infrared absorption spectra of the octadecanol derivatives were measured on films between rock-salt plates; spectra of the other compounds were measured as Nujol mulls. The spectra showed absence of hydroxyl and carbonyl groups.

(2,4,6-*Tribromophenoxy*)*methoxymethane*.—(*a*) A warm solution of sodium ethoxide [from sodium (2·3 g.) and ethyl alcohol (30 c.c.)] was added to a solution of 2,4,6-tribromophenol (33 g.) in dry ether (100 c.c.). Chloromethyl methyl ether (7·5 c.c.) was added to the cooled mixture. After a short time the mixture was poured into an excess of dilute sodium hydroxide, and the ether layer was washed with 1% sodium hydroxide, dried (K_2CO_3), and distilled. The residue (28·7 g.) consisted of (2,4,6-*tribromophenoxy*)*methoxymethane*, m. p. 65·5—66·5° (after repeated precipitation from acetone solution with an equal volume of water) (Found: C, 25·6; H, 2·0; Br, 62·7; O, 8·6; OMe, 8·3. $C_8H_7Br_3O_2$ requires C, 25·6; H, 1·9; Br, 64·0; O, 8·5; OMe, 8·3%).

(*b*) A stream of dry hydrogen chloride was passed for about 4 hr. into a mixture of 2,4,6-tribromophenol (82·7 g.), methanol (10 c.c.), and paraformaldehyde (7·5 g.) in washed and dried chloroform (500 c.c.) at room temperature. The paraformaldehyde slowly dissolved and an upper layer of liquid formed. The whole was poured into a solution of sodium hydroxide (30 g.) in water (500 c.c.), and the mixture cooled, and worked up as above. The formal (15 g.) had m. p. and mixed m. p. 65·5—66·5° after recrystallisation from aqueous acetone; the infrared spectra of the products from preparations (*a*) and (*b*) were almost identical.

Ethoxy-(2,4,6-*tribromophenoxy*)*methane*.—(*a*) By using method (*a*), but with chloromethyl ethyl ether (9·0 c.c.), *ethoxy*-(2,4,6-*tribromophenoxy*)*methane* was obtained as needles (25·5 g.), m. p. 57—58° raised to 59—60° by recrystallisation from a small amount of ethyl alcohol (Found: C, 27·7; H, 2·6; O, 8·3; OEt, 11·6. $C_9H_9Br_3O_2$ requires C, 27·8; H, 2·3; O, 8·2; OEt, 11·6%).

(*b*) Use of ethyl alcohol (14·4 c.c.) instead of methanol in method (*b*), above gave the formal (14 g.), m. p. and mixed m. p. 58·5—59·5° after recrystallisation from 67% aqueous acetone. The infrared spectra of the two samples were almost identical.

(2,4,5-*Trichlorophenoxy*)*methoxymethane*.—By method (*a*), 2,4,5-trichlorophenol (20 g.) gave a crude liquid (19·9 g.) which solidified at 0°. Recrystallisation from light petroleum (b. p. 60—80°) gave (2,4,5-*trichlorophenoxy*)*methoxymethane* (crystals), m. p. 53—55° (Found: C, 39·6; H, 2·9; OMe, 12·6. $C_8H_7Cl_3O_2$ requires C, 39·8; H, 2·9; OMe, 12·8%).

(2,3,4,5,6-*Pentachlorophenoxy*)*methoxymethane*.—Chloromethyl methyl ether (8·5 c.c.) was added to a suspension of technical sodium pentachlorophenoxide (32 g.) in dry ether (100 c.c.). The crude product (21·7 g.), worked up as above, was dissolved in acetone (150 c.c.), and the solution filtered and water (30 c.c.) added. (2,3,4,5,6-*Pentachlorophenoxy*)*methoxymethane* separated as needles (11·7 g.; m. p. 78—79°), which after further purification had m. p. 79—80° (Found: C, 31·1; H, 1·7; Cl, 56·8; O, 10·1; OMe, 9·8. $C_8H_5Cl_5O_2$ requires C, 31·0; H, 1·6; Cl, 57·1; O, 10·3; OMe, 10·0%).

Dioctadecyloxymethane.—(*a*) Chloromethyl octadecyl ether [2] (6·4 g.; m. p. 56·5—57·5° after crystallisation from ether) and a solution of octadecanol (5·4 g.) in pyridine (20 c.c.) were heated at 100° for 6 hr. The mixture was dissolved in chloroform, and the solution washed with dilute sodium carbonate and with water, dried (K_2CO_3), and evaporated, finally under reduced pressure. The residue (10·8 g.; m. p. 50—52°) was crystallised from ether and then from light petroleum (b. p. 60—80°), giving *dioctadecyloxymethane*, m. p. 58—59° [Found: C, 80·8; H, 14·0%; *M* (in camphor), 429. $C_{37}H_{36}O_2$ requires C, 80·4; H, 13·8%; *M*, 552].

(*b*) A mixture of octadecanol (27 g.), paraformaldehyde (3 g.), and concentrated sulphuric acid (1 c.c.) was heated at 100° for 6 hr. The product, worked up as above, had m. p. and mixed m. p. 58—59° (Found: C, 80·8; H, 13·7%; *M*, 408). The infrared spectra of materials prepared by methods (*a*) and (*b*) were almost identical.

[2] Kursanov and Setkina, *Zhur. priklad. Khim.*, 1943, **16**, 36.

(Octadecyloxy)methoxymethane.—Chloromethyl octadecyl ether (85·6 g.) was added to the solution from sodium (9·2 g.) and methanol (200 c.c.), and the whole was refluxed for 2 hr., after which the methanol was distilled off. The residue was treated with water and extracted with chloroform; the extract was washed, dried (K_2CO_3), and evaporated. The crude product (70·5 g.) was crystallised from light petroleum (120 c.c.; b. p. 60—80°) and the crystals were discarded. The residue, recovered from the solvent, was crystallised from ethyl alcohol (35 c.c.), the crystals again being rejected and the solute (26 g.) recovered and dissolved in light petroleum (80 c.c.). The solution was left overnight in the refrigerator, freed from crystals, concentrated to half volume, and cooled to well below 0°. *(Octadecyloxy)methoxymethane* separated as waxy crystals (13 g.), m. p. 28—29°, very soluble in organic solvents, but insoluble in water (Found: C, 76·5; H, 13·5; OMe, 9·4. $C_{20}H_{42}O_2$ requires C, 76·4; H, 13·4; OMe, 9·9%).

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SHIRLEY INSTITUTE, DIDSBURY, MANCHESTER. [*Received, November 28th*, 1960.]

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499. *The Pyrolysis of Divinylmercury and the Strength of the C–H Bond in Ethylene.*

By A. F. TROTMAN-DICKENSON and G. J. O. VERBEKE.

VALUES of 91·5 (ref. 1) and 122 (ref. 2) kcal. mole^{-1} for the strength of the C–H bond in ethylene, determined by electron impact, were reported several years ago. The present pyrolysis study was intended to narrow the range of choice. After the investigation began, Harrison and Lossing [3] determined the ionization potential of the vinyl radical directly and found $D(C_2H_3\text{–}H) = 105 \pm 3$ kcal. mole^{-1}, a value in better accord with the reactivity of methyl radicals with ethylene.[4]

Twenty-nine pyrolyses of divinylmercury were carried out by us in a typical toluene carrier flow system [5] between 502° and 642°. Most runs occupied 20 min., a few 10 or 30 min. First-order rate constants were calculated from the amount of mercury released. In eight runs below 590° concordant results were obtained from measurements of the ethylene, acetylene, and buta-1,3-diene formed. The range of conditions investigated was limited by the time available. In one run the pressure was 24 mm., for another 17 mm., and for the rest 16·1 mm. The contact times lay between 0·90 and 1·54 sec., except that in four runs where the reaction vessel was packed with fire-polished silica tubes the time rose to about 2·5 sec. In four runs near 601° the amount of divinylmercury passed in 20 min. varied between 346 and 3860 μmole without effect on the first-order rate constant; a fifth run with 423 μmole gave a 50% higher constant. Packing the reaction vessel did not alter the rate constants; hence if the rate is assumed to be independent of contact time, the initial decomposition of the alkylmercury is homogeneous.

The simplest reaction scheme that could be expected to account for the products is:

$$(C_2H_3)_2Hg \longrightarrow C_2H_3Hg\cdot + C_2H_3\cdot \quad (1)$$

$$C_2H_3Hg\cdot \longrightarrow Hg + C_2H_3\cdot \quad (2)$$

$$C_2H_3\cdot + C_6H_5{\cdot}CH_3 \longrightarrow C_6H_5{\cdot}CH_2\cdot + C_2H_4 \quad (3)$$

$$2C_2H_3\cdot \longrightarrow C_4H_6 \quad (4)$$

$$2C_2H_3\cdot \longrightarrow C_2H_4 + C_2H_2 \quad (5)$$

$$2C_6H_5{\cdot}CH_2\cdot \longrightarrow (C_6H_5{\cdot}CH_2\cdot)_2 \quad (6)$$

At the lower temperatures the rate constants, calculated from the gaseous products on the basis of this reaction mechanism, were essentially the same as those obtained, on

[1] Stevenson, *J. Amer. Chem. Soc.*, 1943, **65**, 209.
[2] Field, *J. Chem. Phys.*, 1953, **21**, 1506.
[3] Harrison and Lossing, *J. Amer. Chem. Soc.*, 1960, **82**, 519.
[4] Trotman-Dickenson and Steacie, *J. Chem. Phys.*, 1951, **19**, 169.
[5] Price and Trotman-Dickenson, *Trans. Faraday Soc.*, 1957, **53**, 939.

the assumption of first-order decomposition, from the amount of mercury set free. At higher temperatures the rate constants obtained from the gas analysis were lower than those based on the mercury determination. In one of the experiments at 696°, where complete decomposition of the alkylmercury was attempted, the gaseous products were collected. They corresponded to only 71% decomposition, whereas the mercury determination indicated 93·2%. Evidently an additional reaction becomes important at the higher temperatures. This is probably the condensation of vinyl radicals, or of acetylene, to less volatile material. The difference between k_{gas} and $k_{mercury}$ increases more rapidly with temperature in the packed reaction vessel, so the condensation is probably heterogeneous. An attempt was made to fit the relative reaction rates of vinyl radicals with one another and with toluene to an Arrhenius plot. Allowance was also made here for the occurrence of the reactions (7) and (8), which were presumed to be the source of small

$$C_2H_3\cdot \longrightarrow C_2H_2 + H \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

$$H + C_6H_5\cdot CH_3 \longrightarrow C_6H_5\cdot CH_2\cdot + H_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

quantities of hydrogen found in the products, and the possible non-occurrence of reaction (5). None of these attempts fitted the results. The effect of an altered surface–volume ratio on the relative rates of production of C_2 and C_4 products showed that the combination of vinyl radicals is also partly heterogeneous.

An Arrhenius plot of the rate constants from the mercury determination, fitted by the method of least squares, yields

$$\log_{10} k\ (\text{sec.}^{-1}) = (11{\cdot}94 \pm 0{\cdot}2) - (48{,}300 \pm 900)/2{\cdot}303RT.$$

The errors, determined by the normal statistical method, may well be smaller than the systematic errors. The latter cannot be estimated with certainty. The rate constants, calculated from the mercury analysis, may reasonably be assumed to be the rate of dissociation of the first mercury–carbon bond in divinylmercury. If the activation energy for the back-reaction is zero, the measured activation energy corresponds to the strength of this bond. The heat of formation of divinylmercury is not known. However, if there is no interaction between the two double bonds and the value of D_2 in divinylmercury is the same as in dimethyl- and diethyl-mercury,[6] it can be said that:

$$D(CH_3\cdot Hg{-}CH_3) - D(C_2H_3\cdot Hg{-}C_2H_3) = 2D(CH_3{-}H) - 2D(C_2H_3{-}H).$$

Then $D(CH_3{-}H)$ may be taken as 103·9 kcal./mole (ref. 7) and $D(CH_3\cdot Hg{-}CH_3)$ as 51·3 kcal./mole (refs. 5 and 8). These values, together with the result of this study, give a value of 102·4 kcal./mole for the first hydrogen in ethylene and 63 kcal./mole for the heat of formation of the vinyl radical. Purely on a numerical basis, an uncertainty of 3 kcal./mole must be assigned to these values.

Experimental.—Divinylmercury was prepared from vinylmagnesium bromide and mercuric chloride in tetrahydrofuran.[9] The excess of Grignard reagent was destroyed with ammonium chloride solution, and the organic fraction dried (Na_2SO_4). After removal of the tetrahydrofuran, divinylmercury was distilled three times at *ca.* 20 mm. and stored under a vacuum at −183°.

Toluene was purified by partial pyrolysis and fractional distillation, and thoroughly degassed.

The pyrolysis apparatus [5] was modified to ensure that no extraneous mercury reached the reaction system. Mercury from the decomposition of the alkylmercury was removed from the gas stream by a U-trap immersed in an ice–salt bath. Bibenzyl was removed by carefully rinsing the trap with ether. The mercury was dissolved in nitric acid and converted into

[6] Gowenlock, Polanyi, and Warhurst, *Proc. Roy. Soc.*, 1953, *A*, **219**, 270.
[7] Fettis and Trotman-Dickenson, unpublished results.
[8] Gowenlock, Polanyi, and Warhurst, *Proc. Roy. Soc.*, 1953, *A*, **218**, 269.
[9] Bartocha, Brinkman, Kaesz, and Stone, *Proc. Chem. Soc.*, 1958, 116.

mercuric nitrate with potassium thiocyanate.[10] The gaseous products of several experiments were collected. Ethylene, acetylene, and buta-1,3-diene were distilled from a LeRoy low-temperature still and measured in a gas-burette. The completeness of separation was checked by infrared analysis (Mr. J. L. Duncan is thanked for these analyses).

We are grateful for the award of an I.C.I. Fellowship to G. J. O. V. and to Dr. S. J. W. Price for preliminary experiments.

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[10] Kolthoff and Sandell, " Textbook of Quantitative Analysis," Macmillan, London, 1943, p. 116.

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500. *Solvent Shifts in the Infrared Spectra of Metal Carbonyls and Their Derivatives.*

By C. C. BARRACLOUGH, J. LEWIS, and R. S. NYHOLM.

RECENT work has shown that useful information can be obtained from the infrared spectrum of a compound in a variety of solvents.[1] The shifts are frequently much larger than previous theories, based on the variation in dielectric constant of the solvent, would suggest. This effect is most pronounced for compounds containing a group with a large dipole moment, *e.g.*, groups such as C=O, N=O, S=O. In the present work the infrared spectra of a variety of metal carbonyls and substituted metal carbonyls have been measured. The large solvent shifts observed in some cases suggest that appreciable solute-solvent interaction must be occurring in these cases, and the implications of these interactions are considered.

RESULTS

The spectra have been measured mostly in cyclohexane and chloroform, because of solubility limitations, and also because the bands become very broad and frequently overlap in the more polar solvents. The carbonyl stretching frequencies given in Tables 1—4 are grouped according to the nature of the compounds, and the frequencies are believed to be accurate to ± 2 cm.$^{-1}$.

TABLE 1. *Metal carbonyls; carbonyl frequencies in cm.*$^{-1}$.

$Fe(CO)_5$		$Mn_2(CO)_{10}$		$Co_2(CO)_8$		$Co_2(CO)_8$	
C_6H_{12}	$CHCl_3$	C_6H_{12}	$CHCl_3$	C_6H_{12}	$CHCl_3$	C_6H_{12}	$CHCl_3$
2021	2019	2043	2043	2068	2071	2029	1845
2000	1998	2013	2010	2058	2042	2022	
		1982	1980	2042	2005	1867	
						1857	

TABLE 2. *Substituted metal carbonyls; frequencies in cm.*$^{-1}$.

(D = *o*-phenylenebisdimethylarsine)

	Cr		Mo		W			
	C_6H_{12}	$CHCl_3$	C_6H_{12}	$CHCl_3$	C_6H_{12}	$CHCl_3$		
$MD(CO)_4$ ...	2018	2012	2026	2024	2020	2016		
	1931	1922	1938	1934	1934	1923		
	1908	1898	1923	1918	1912	1905	$NiD(CO)_2$	
			1914	1894			C_6H_{12}	$CHCl_3$
$MD_2(CO)_2$	1866	1845	1887	1859		1850	2011	2001
	1815	1770	1828	1786		1774	1952	1934

TABLE 3. *Carbonyl halides; frequencies in cm.*$^{-1}$.

$Fe(CO)_4I_2$		$Fe(CO)_4Br_2$		$Mn(CO)_5I$	
C_6H_{12}	$CHCl_3$	C_6H_{12}	$CHCl_3$	C_6H_{12}	$CHCl_3$
2132	2136	2151	2156	2123	2123
2086	2091	2109	2114	2045	2043
2081	2071	2099	2109	2004	2006
2063		2075	2083		

[1] *Proc. Roy. Soc.*, 1960, **255**, 1—81.

TABLE 4. *Carbonyl frequencies (in cm.$^{-1}$) for* $Ni(CO)_2(PPh_3)_2$.

Cyclohexane 2010, 1954; chloroform 2004, 1939; bromoform 1999, 1938; methylene iodide 1997, 1935

DISCUSSION

The unsubstituted metal carbonyls being considered first, one finds that there are no shifts for the frequencies corresponding to the terminal carbonyl groups except for cobalt carbonyl, although the bands become broader. It is noteworthy that the frequency corresponding to the bridging carbonyl groups in cobalt carbonyl undergoes a significant shift. The infrared spectrum for cobalt carbonyl in cyclohexane shows two bands for the bridging carbonyl groups but in chloroform all the bands are much broader and several overlap.

The shifts are most striking for the diarsine-substituted carbonyls and increase with the degree of substitution. For comparison the shifts for some organic carbonyl compounds are shown in Table 5 (taken from ref. 2), and it can be seen that the bisdiarsine-substituted carbonyls show even larger solvent shifts than these.

Dipole-moment measurements have been made on a number of substituted metal carbonyls,[3] including the two nickel compounds used in the present work, and values of the order of 3—5 Debyes were obtained. It was suggested that nearly all the dipole moment arose from the metal–substituent bond, and practically none from the carbonyl groups. The most obvious interpretation of the present results, however, is that a strong dipole must exist on the carbonyl group of the diarsine-substituted metal carbonyls and that the solvent shift is due to some form of interaction of this dipole with the solvent molecules. The nature of the interaction is uncertain; it is probably a dipole–dipole interaction of which several kinds are possible. In cobalt carbonyl the shift associated with the bridging carbonyl groups is in accord with the qualitative idea that these bridging groups are analogous to the carbonyl group in a cyclic ketone.

TABLE 5. *Carbonyl frequencies in cm.$^{-1}$.*

Solvent	Benzophenone	Cyclohexanone	Acetone
C_6H_{12}	1670	1724	1723
$CHCl_3$	1658	1705	1712

It is possible to interpret the increase in solvent shift from the mono- to the bis-diarsine derivatives of the Group VI metals in terms of the relative π bonding properties of arsenic ligands and carbon monoxide molecules. Present ideas on the structure of metal carbonyls[4] suggest there is appreciable double-bond character in the metal–carbon bonds due to back donation of electrons from the metal atom to the carbon monoxide groups through π bonds. It is believed that the arsenic and phosphorus atoms of the common ligands in substituted metal carbonyls do not possess such good electron-acceptor properties for this back donation.[5] The negative charge accumulated on the central metal atom still has to be dispersed in accordance with the Pauling electroneutrality principle, and it is assumed that the amount of back donation to the remaining carbonyl groups must be increased, leading to an increase in the metal–carbon bond order and a lowering in the carbon–oxygen bond order.

FIG. 1.

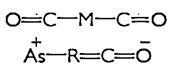
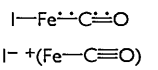


FIG. 2.



If this process is drawn up as shown in Fig. 1 it can be seen there is a build up of formal

[2] Bellamy and Williams, *Trans. Faraday Soc.*, 1959, **55**, 14.
[3] Chatt and Hart, *J.*, 1960, 1378.
[4] Sheline and Cable, *Chem. Rev.*, 1956, **56**, 1.
[5] Meriwether and Fiene, *J. Amer. Chem. Soc.*, 1959, **81**, 4200.

negative charge on the oxygen atom of the carbonyl group, and this charge will increase as the metal–carbon bond order increases, *i.e.*, as more carbonyl groups are replaced.

The lowering of the carbonyl frequencies on substitution by phosphines and arsines has been observed previously but the present results on solvent shifts give additional support to current hypotheses concerning the relative π-bonding properties of carbon monoxide and tertiary phosphine and arsine ligands. The magnitude of the shift is greater the lower the original carbonyl frequency.

The iron carbonyl halides show quite different behaviour, the direction of the shifts being in the opposite direction to those already considered. Although the shifts are small, they are well outside the range of experimental error and again some form of solute–solvent interaction must be postulated. It is difficult to find an explanation in terms of a direct interaction of solvent molecules with the carbonyl groups since this type of mechanism will always produce a lowering in frequency towards more polar solvents.

A tentative explanation has been based on Bellamy's suggestion for a similar phenomenon with nitrosyl chloride [6] and is as follows. The iron–halogen bond is considered to have appreciable ionic character, *i.e.*, the wave function is regarded as involving a linear combination of the wave functions for the two structures shown in Fig. 2. In the ionic form the amount of back donation of negative charge from the metal to the carbonyl groups will be less than in the covalent structure because of the positive charge on the metal atom. This will mean that the carbon–oxygen bond order and hence the frequency will be higher in the ionic structure than in the covalent structure. When the iron carbonyl halide molecule is put in a polar solvent the ionic structure will be favoured, the ionic character of the metal halogen bond will increase and the carbonyl stretching frequencies will rise. An alternate way of looking at this problem is in terms of preferential solvation of the halide ion by the solvent.

The present results are relatively few in number, and the interpretations put forward are only tentative, but they do suggest another method of obtaining information about the structures of metal–carbonyl derivatives. From the purely practical viewpoint it appears that polar solvents such as chloroform are not satisfactory solvents for the measurement of solution spectra of metal carbonyl derivatives since the frequencies may be shifted by solute–solvent interaction. It is possible that the values of the frequencies observed for the solid state may be affected in a similar manner since inter- or intramolecular interactions may be taking place.

Experimental.—The spectra have been measured in a dilute solution of the various solvents, a Grubb-Parsons GS 2A double-beam grating spectrometer being used. Most of the compounds were prepared by published methods, but the authors are also grateful to Dr. M. Stiddard and Dr. D. V. R. Rao for supplies of some of these.

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[6] Bellamy, " The Infra-red Spectra of Complex Molecules," 2nd Edn., p. 382, Methuen & Co., Ltd., London, 1958.

501. *The Occurrence of Organotin Cations.*

By I. R. Beattie and T. Gilson.

Lower alkyltin chlorides, R_3SnCl and R_2SnCl_2, usually melt about 200° lower than the corresponding fluorides.[1] Furthermore, the chlorides are normally soluble in organic solvents whilst the fluorides are much less soluble and tend to dissolve only in hydroxylic solvents. This behaviour has led to the assumption [2] that organotin fluorides contain ions of the type R_2Sn^{2+} and R_3Sn^+. The trifluorides (like the triacetates) are unknown. The evidence for the discrete organotin cation in the solid is fragmentary. By analogy with the dimethylthallium ion,[3] isosteric with the mercury dialkyls, we might expect to find a linear dimethyltin ion. However, this entity would bear a double positive charge, making its free existence less likely.

On the basis of solubility data, Rochow *et al.*,[4] have stated: " We believe in anhydrous salts the Me_2Sn^{2+} ion resembles Sn^{2+}." Although Me_2Tl^+ salts resemble Tl^+ salts in solubility, it is difficult to accept solubility data *alone* as evidence of a particular formulation. The only other relevant data for the solid concerns the infrared spectra of certain organotin carboxylates. From the position of the C–O stretching frequencies, Okawara *et al.*[5] have suggested that these compounds contain carboxylate anions. However, the main problem here is a stereochemical one, not one of " degree of ionic character." For example, with the acetate group the symmetry is low, so that co-ordination would not be expected to alter the selection rules. Thus we should not expect to find great differences between the spectra of ionic acetates and chelate or bridging acetate groups. Alternatively, there would be considerable difference between the free carbonyl group in an ester and $\cdot CO_2$ acting as a chelate or bridging group. This is supported by some results by Duncanson *et al.*,[6] who have shown that carbonyl frequencies in tetra-acetyl diborate occur at 1718 and 1605 cm.$^{-1}$. These are interpreted in terms of two free carbonyl groups and two bridging or chelate carbonyl groups, respectively (since boron has a maximum covalency of four). The value of 1605 cm.$^{-1}$ for the bridging or chelate group is close to that found in ionic acetates, where the C–O stretching frequency of representation B_1 ν_8 has a value of about 1580 cm.$^{-1}$.

In order that the effect of bridging on the infrared spectra of acetates could be examined

C–O *stretching frequencies (in cm.*$^{-1}$*) of certain acetates.*

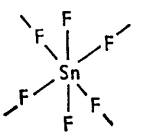
Representation * C_{2v}	NaOAc	Me_3SnOAc	$[Cu(OAc)_2,H_2O]_2$	$Be_4O(OAc)_6$	$Zn_4O(OAc)_6$	$(OAcMe_2Sn)_2O$
A_1 ν_3	1408	1428	1418	1481	1443	1410
B_1 ν_8	1578	1576	1603	1623	1598	1580

* Refers to NaOAc.

for compounds which would conventionally be regarded as covalent and where the crystal structures are known, we have observed the spectra of the basic acetates of zinc and beryllium [7] in solution in bromoform (to avoid crystal field effects). The Table shows

[1] For a recent review of organotin compounds see Ingham, Rosenberg, and Gilman, *Chem. Rev.*, 1960, **60**, 459.
[2] See, for example, Sidgwick, " Chemical Elements and Their Compounds," Oxford, 1950.
[3] Powell and Crowfoot, *Z. Krist.*, 1934, **87**, 370.
[4] Rochow, Seyferth, and Smith, *J. Amer. Chem. Soc.*, 1953, **75**, 3099.
[5] Okawara and Rochow, *J. Amer. Chem. Soc.*, 1960, **82**, 3285.
[6] Duncanson, Gerrard, Lappert, Pyszora, and Shafferman, *J.*, 1958, 3652.
[7] For the structures of basic zinc acetate and basic beryllium acetate, see Koyama and Saito, *Bull. Chem. Soc. Japan*, 1954, **27**, 112 (in English), and Wells, " Structural Inorganic Chemistry," Oxford, 1945.

the C–O stretching vibrations for these compounds, together with those of certain organotin acetates,[8] sodium acetate,[9] and $[Cu(OAc)_2,H_2O]_2$.[10] Although the range of frequencies is quite large these spectra were taken under a variety of conditions. We found shifts of up to 50 cm.$^{-1}$ for $[Cu(OAc)_2,H_2O]_2$ depending on whether we studied a dilute potassium chloride disc or a mull in Nujol or hexachlorobutadiene. Further, the reported values of the frequency for sodium acetate cover a range of about 20 cm.$^{-1}$. Although the spectra of the organotin acetates do not show any similarity to that of acetoxytrimethylsilane,[8] with a carbonyl stretch at 1725 cm.$^{-1}$ and a C–O–(Si) stretch at 1267 cm.$^{-1}$, there is clearly no *simple* way of distinguishing between a discrete acetate ion and a bridging acetate group. Therefore the infrared spectra of organotin diacetates could be interpreted in terms of an octahedral distribution about the tin involving bridging or chelate acetate groups. In the case of trialkyltin acetates a co-ordination number of five appears to be necessary. This may at first appear to be unlikely. However, by analogy with iodine, which is in the same period as tin, and replacing the three equatorial lone pairs by alkyl groups, a formulation with two bridging acetate groups is acceptable. In a similar way we can rationalise the chemistry of the fluorides. Tin tetrafluoride is a solid which sublimes at 705° and is insoluble in most organic solvents, in sharp contrast to the other halides. This is not due to a sudden change in bond character between the fluoride and the chloride, but to a different crystal structure. The tin tetrahalides, other than the fluoride, almost certainly have molecular crystal structures.[11] Each tin in tin tetrafluoride appears from *X*-ray powder data to be surrounded by six fluorines (I), four bridging and two non-bridging.[12]



(I)

If the two non-bridging axial fluorines are replaced by alkyl groups we have a possible formulation for dialkyltin difluorides which would explain their anomalous properties.

The purpose of this Note is to draw attention to certain ambiguities in the interpretation of the infrared spectra of organotin carboxylates, and to indicate that an alternative interpretation is in agreement with the available data.

Experimental.—Basic beryllium acetate was prepared from beryllium carbonate and acetic acid.[13] Basic zinc acetate was prepared by *slow* sublimation from anhydrous zinc acetate at 200° in a high vacuum. The spectra were taken in bromoform (dried under calcium hydride), rock-salt optics being used.

We thank Messrs. Albright and Wilson, Ltd., for a grant (to T. G.).

Department of Chemistry,
King's College, London, W.C.2. [*Received, December 14th*, 1960.]

[8] Okawara, Webster, and Rochow, *J. Amer. Chem. Soc.*, 1960, **82**, 3287.
[9] Jones and McLaren, *J. Chem. Phys.*, 1954, **22**, 1796; Nakamura, *J. Chem. Soc. Japan*, 1958, **79**, 1411; Ito and Bernstein, *Canad. J. Chem.*, 1956, **34**, 170.
[10] Nakamoto, Fujita, Tanaka, and Kobayashi, *J. Amer. Chem. Soc.*, 1957, **79**, 4904; for the structure of $[Cu(OAc)_2,H_2O]_2$ see van Niekerk and Schoening, *Acta Cryst.*, 1953, **6**, 227.
[11] See, for example, tin tetraiodide, Mellor and Fankuchen, *Acta Cryst.*, 1955, **8**, 343.
[12] Hoppe, *Angew. Chem.*, 1957, **69**, 399.
[13] T. Moeller, *Inorg. Synth.*, 1950, **3**, 4.

502. *An Alkaloid from* Callichilia *Species.*

By M. D. Patel, J. M. Rowson, and D. A. H. Taylor.

Callichilia barteri (Apocyanaceae) is a small shrub, common in southern Nigeria. Extraction of the roots gave an alkaloid $C_{42}H_{48}N_4O_6$, having two basic centres, pK_B 9·5 and 7·4. Extraction of the less common *Callichilia stenosepala* gave the same alkaloid.

The properties of the alkaloid and its colour reactions are identical with those described for vobtusine, an alkaloid obtained by Goutarel, Rassat, Plat, and Poisson [1] from *Callichilia subsessilis* and from other plants.

Experimental.—Callichilia barteri. The ground roots (5 kg.) were percolated exhaustively with hot methylated spirit, and the extract concentrated to small volume. The residue was dissolved in chloroform and extracted with dilute sulphuric acid, the acid layer basified with ammonia, and the precipitate taken up in chloroform. Evaporation of the solvent gave a brown resin (30 g.) which was chromatographed on alumina. The material eluted with chloroform rapidly crystallised; recrystallisation from chloroform–methanol gave the alkaloid (4·3 g.) as brownish plates, m. p. 312° (decomp.), $[\alpha]_D^{20} = -320°$ ($CHCl_3$), readily soluble in chloroform and very sparingly in other solvents (Found: C, 71·8, 71·6; H, 6·9, 6·9; O, 13·4; N, 7·8; OMe, 9·3, 9·5%; equiv., 360. $C_{42}H_{48}N_4O_6$ requires C, 71·6; H, 6·9; O, 13·6; N, 7·95; 5OMe, 9·8%; equiv., 356). The alkaloid gave a blue colour with sulphuric acid containing ferric chloride, with nitric acid, and with nitrous acid. The *methiodide* formed yellowish crystals decomposing at 250° (Found: C, 50·1; H, 5·5; I, 24·1; N, 5·3. $C_{44}H_{54}I_2N_4O_6,4H_2O$ requires C, 49·8; H, 6·0; I, 24·0; N, 5·3%). Potentiometric titration of the base in hydrochloric acid indicated two basic centres, pK_B 9·5 and 7·4.

Callichilia stenosepala. The ground whole plant (2·7 kg.), collected in the forest near Benin, was extracted as above and gave the same alkaloid (0·7 g.), identical in spectra, m. p., and colour reactions.

Herbarium specimens are preserved in the Department of Pharmacy, Nigerian College, Ibadan.

Department of Pharmacy, Nigerian College, Ibadan.
Department of Chemistry, University College, Ibadan. [*Received, December 28th,* 1960.]

[1] Goutarel, Rassat, Plat, and Poisson, *Bull. Soc. chim. France,* 1959, 893.

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503. *The Synthesis and Reactions of Branched-chain Hydrocarbons. Part XIV.* The Free-radical Halogenation of t-Butylbenzene.*

By J. R. B. Boocock and W. J. Hickinbottom.

The free-radical halogenation of alkylbenzenes in the side chain is sufficiently well established to be a recognised test for a free-radical mechanism. In t-butylbenzene there is no α-CH group for this type of chlorination and it was of special interest to determine the products of free-radical halogenation.

Chlorination in the liquid phase by sulphuryl chloride promoted by benzoyl peroxide is reported by Kharasch and Brown [1] to give a 70% yield of ββ-dimethylphenethyl chloride. On the other hand, Backhurst, Hughes, and Ingold [2] reported, while our work was in

* Part XIII, Foster and Hickinbottom, *J.*, 1960, 680.

[1] Kharasch and Brown, *J. Amer. Chem. Soc.*, 1939, **61**, 2147.
[2] Backhurst, Hughes, and Ingold, *J.*, 1959, 2742.

progress, that t-butylbenzene undergoes rearrangement during chlorination in the gas phase under irradiation, giving αα-dimethylphenethyl chloride as the main product.

It is here shown that the free-radical chlorination of t-butylbenzene, in the liquid phase by *N*,2,4,6-tetrachloroacetanilide, gives a product containing about 75% of ββ-dimethylphenethyl chloride; also formed are 2-methyl-1-phenylpropene (~5%) and t-butylchlorobenzenes (~20%). In spite of a careful search, αα-dimethylphenethyl chloride was not identified among the products. The only possible evidence of rearrangement is the 2-methyl-phenylpropene which might conceivably arise by elimination of hydrogen chloride from the chlorinated product. If this is so the rearrangement does not amount to more than ~6%.

In the free-radical bromination of t-butylbenzene in the liquid phase by *N*-bromosuccinimide, nuclear bromination to give *p*-bromo-t-butylbenzene is the principal reaction; an unsaturated fraction boiling in the same range as 2-methyl-1-phenylpropene was obtained, but only as a minor constituent.

A significant feature of these halogenations is the occurrence of nuclear chlorination and bromination. There appears to be no previous record of substitution of this type in free-radical halogenation, although since this work was completed, Backhurst [3] has reported that vapour-phase bromination gives some nuclear-brominated product.

It is known, from other evidence, that the t-butyl group is chlorinated relatively slowly, and it is a reasonable assumption that there is a competing nuclear attack. Support for this is provided by free-radical bromination, which is known to be much slower [4] at a saturated system than chlorination, and consequently the main reaction is nuclear bromination.

Experimental.—Free-radical halogenation of t-butylbenzene. (*a*) Commercial t-butylbenzene, purified by distillation from sodium, had b. p. 167—168°, n_D^{20} 1·4927. The hydrocarbon (118 g.), *N*,2,4,6-tetrachloroacetanilide (55 g.), and benzoyl peroxide (2·2 g.) were stirred together at 90°. After 30 hr. there was no longer a positive reaction for the *N*-chloro-compound; 2,4,6-trichloroacetanilide separated on cooling, and more was precipitated by light petroleum (b. p. <40°). Distillation of the light petroleum solutions gave unchanged t-butylbenzene, b. p. 52—56°/14 mm., n_D^{20} 1·4919—1·4945, and a chlorinated product which was separated by distillation through a spinning-band column into the well-defined fractions: (*a*) b. p. 62—68°/10 mm., n_D^{20} 1·5308 (1·2 g.); (*b*) 86—87°/10 mm., n_D^{20} 1·5130 (4·6 g.); (*c*) b. p. 96—98°/11 mm., n_D^{20} 1·5245 (20 g.). Fraction (*a*) consisted mainly of 2-methyl-1-phenylpropene; it was unsaturated and was identified by its infrared spectrum. Fraction (*c*) was ββ-dimethylphenethyl chloride (Found: C, 71·0; H, 7·8; Cl, 20·9. Calc. for $C_{10}H_{13}Cl$: C, 71·2; H, 7·8; Cl, 21·0%). It gave a precipitate of silver chloride only slowly with boiling alcoholic silver nitrate. It was identified by comparison of its infrared spectrum with that of an authentic specimen prepared by Smith and Sellas's method [5] (b. p. 97·5/11 mm., n_D^{20} 1·5245). Both samples on nitration with fuming nitric acid gave the *p*-nitro-compound, m. p. 62—64°. Fraction (*b*) was essentially t-butylchlorobenzene (Found: C, 71·5; H, 7·9; Cl, 21·1. Calc. for $C_{10}H_{13}Cl$: C, 71·2; H, 7·8; Cl, 21·0%). Its infrared spectrum is identical with that of t-butylchlorobenzene obtained by chlorination of t-butylbenzene with chlorine and iron powder, and both samples gave 4-chloro-2-nitro-1-t-butylbenzene, m. p. 114·5—116°, on nitration.

(*b*) t-Butylbenzene (50 g.), *N*-bromosuccinimide (31 g.), and benzoyl peroxide were heated together at 90°. The reaction was stopped after 87 hr. although it had not finished. Distillation gave unchanged t-butylbenzene and fractions (*a*) (0·8 g.), b. p. 59—60°/10 mm., n_D^{20} 1·5038, olefinic and containing some labile bromine, (*b*) b. p. 92—94°/10 mm., n_D^{20} 1·5292 (0·8 g.), and (*c*) (8·7 g.) b. p. 100—103·5°/11 mm., $n_D^{17·7}$ 1·5345—1·5343 (Found: C, 56·7; H, 6·0; Br, 37·2. Calc. for $C_{10}H_{13}Br$: C, 56·4; H, 6·15; Br, 37·5%). Fraction (*c*) was identified at *p*-bromo-t-butylbenzene by comparison of its infrared spectrum with that of an authentic

[3] Backhurst, *J.*, 1960, 1958.
[4] Walling, "Free Radicals in Solution," J. Wiley and Sons, Inc., New York, pp. 369—375.
[5] Smith and Sellas, *Org. Synth.*, 1952, **32**, 90.

specimen, by the preparation from it (Grignard) of *p*-t-butylbenzoic acid, m. p. and mixed m. p. 163·5—165·5°, and by nitration to give 4-bromo-2-nitro-1-t-butylbenzene, m. p. and mixed m. p. 133·5—134·5°.

For comparison, ββ-dimethylphenethyl bromide was prepared from the corresponding alcohol by the action of hydrogen bromide; it had b. p. 41°/0·1 mm., n_D^{20} 1·5401 (lit.,[6] b. p. 88—89°/5·3 mm., n_D^{25} 1·5382). This readily gave a precipitate of silver bromide with cold alcoholic silver nitrate; the product obtained from t-butylbenzene did not.

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QUEEN MARY COLLEGE (UNIVERSITY OF LONDON),
MILE END ROAD, LONDON, E.1. [*Received, December 16th*, 1960.]

[6] Duffin, Hughes, and Ingold, *J.*, 1959, 2740.

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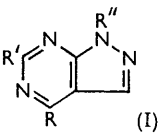
504. *The Preparation of Some* 1- *and* 2-β-D-*Ribofuranosylpyrazolo*[3,4-d]*pyrimidines.*

By J. DAVOLL and K. A. KERRIDGE.

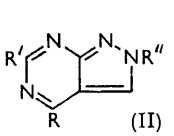
A NUMBER of pyrazolo[3,4-*d*]pyrimidines, particularly the 4-amino- and 4-butylamino-compounds and their 1-methyl derivatives, have shown activity [1] *in vivo* against experimental neoplasms. The possibility that these compounds antagonise naturally occurring purines has been demonstrated by the partial reversal by adenine of the inhibition of *Neurospora crassa* by 4-aminopyrazolo[3,4-*d*]pyrimidine.[2] The ribosyl derivatives of some pyrazolo[3,4-*d*]pyrimidines were prepared because of the known greater effectiveness of some nucleosides than the corresponding free bases as antimetabolites.[3]

The pyrazolo[3,4-*d*]pyrimidines were prepared by Robins' methods,[4] except that 4,6-diaminopyrazolo[3,4-*d*]pyrimidine was more conveniently prepared by fusing guanidine carbonate with 3-amino-4-cyanopyrazole. Benzamido-derivatives were prepared by fusing the appropriate amino- or diamino-derivative with benzoic anhydride.

β-D-Ribofuranosylpyrazolo[3,4-*d*]pyrimidines were prepared by condensing the chloromercuri-derivatives of the appropriate pyrazolo[3,4-*d*]pyrimidines in toluene with tri-*O*-benzoyl-D-ribofuranosyl chloride. The resulting nucleoside benzoates were debenzoylated with either methanolic ammonia or sodium methoxide. The chloromercuri-derivatives of 4-benzamido- and 4,6-dibenzamido-pyrazolo[3,4-*d*]pyrimidine gave mixtures of



(I)



(II)

positional isomers of types (I) and (II), but only one isomer, of type (I), could be obtained from the condensation of the chloromercuri-derivative of the parent ring system with the ribosyl chloride.

Assignment of structure was made from a comparison of the ultraviolet absorption

[1] Skipper, Robins, Thomson, Cheng, Brockman, and Schabel, jun., *Cancer Research*, 1957, **17**, 579.
[2] Fuerst, Somers, and Hsu, *J. Bact.*, 1956, **72**, 387.
[3] Hall, *J. Amer. Chem. Soc.*, 1958, **80**, 1145, ref. 2.
[4] Robins, *J. Amer. Chem. Soc.*, 1956, **78**, 784.

spectra of the compounds obtained with the corresponding spectra of 4-amino-1- and -2-methylpyrazolo[3,4-*d*]pyrimidine [5,6] and 4,6-diamino-1-methylpyrazolo[3,4-*d*]pyrimidine.[7] The absorption maxima of all these compounds are shown in the Table.

The guanosine analogue (I; R = OH, R′ = NH_2, R″ = $C_5H_9O_4$) was prepared by standard methods [8] from the corresponding diamino-derivative, but attempts to prepare the isomeric compound (II) were unsuccessful.

Ultraviolet absorption spectra, $\lambda_{max.}$(mμ) ($10^{-3}\varepsilon$ *in parentheses*).

	In 0·1N-HCl	At pH 6·8	In 0·1N-NaOH
(I; R = R′ = H, R″ = Me) [5]	261	—	262
(I; R = R′ = H, R″ = $C_5H_9O_4$ [a])	—	261 (3·9)	—
(I; R = NH_2, R′ = H, R″ = Me) [5]	259 (9·4)	261 (9·0), 277 (9·25)	262 (9·7), 275 (9·7)
(I; R = NH_2, R′ = H, R″ = $C_5H_9O_4$ [a]) ...	—	268 (11·4)	—
(I; R = R′ = NH_2, R″ = Me) [7]	—	—	276 (10·2)
(I; R = R′ = NH_2, R″ = $C_5H_9O_4$ [a])	—	258 (9·5), 276 (10·11)	—
(I; R = OH, R′ = NH_2, R″ = Me) [7]	—	—	267 (19·3)
(I; R = OH, R′ = NH_2, R″ = $C_5H_7O_4$ [a])	252 (14·45)	253 (14·55)	264 (11·0)
(II; R = NH_2, R′ = H, R″ = Me) [6]	268 (9·9)	270 [b] (8·7), 287 (11·0)	287 (10·9)
(II; R = NH_2, R′ = H, R″ = $C_5H_9O_4$ [a]) ...	—	275 [b] (7·65), 284 (8·0)	—
(II; R = R′ = NH_2,, R″ = $C_5H_9O_4$ [a]) ...	—	263 (4·2), 290 (3·7)	—

[a] β-D-Ribofuranosyl. [b] Inflexion.

Experimental.—*4,6-Diaminopyrazolo*[3,4-*d*]*pyrimidine.* 3-Amino-4-cyanopyrazole [4] (10·8 g., 0·1 mole) was finely ground with guanidine carbonate (27·3 g., 0·3 equiv.), and the mixture heated at 150—160° for 40 min., then cooled and dissolved in boiling water (250 ml.), and the solution treated with charcoal. The material which separated was recrystallised from water (190 ml.) to give crystals (9·4 g.), m. p. 280—284°. A further recrystallisation from water gave pure 4,6-diaminopyrazolo[3,4-*d*]pyrimidine, m. p. 291°; $\lambda_{max.}$ at pH 11 254 (ε 7000), 274 (ε 8500); lit.,[9] $\lambda_{max.}$ at pH 11 255 (8100), 274 (ε 9400).

4-Benzamidopyrazolo[3,4-d]*pyrimidine.* 4-Aminopyrazolo[3,4-*d*]pyrimidine [4] (22 g., 0·2 mole) was heated with benzoic anhydride (68 g., 0·3 mole) at 180° for 45 min. The cooled, solidified product was ground with ether leaving a solid (36 g.) of indefinite m. p. This material was dissolved in 60% aqueous ethanol (1500 ml.), and the solution filtered and concentrated to 500 ml. by distillation at atmospheric pressure. The cooled slurry was centrifuged to give *4-benzamidopyrazolo*[3,4-d]*pyrimidine* (22 g.), m. p. 223—224° (Found: C, 59·4; H, 4·0; N, 28·5. $C_{12}H_9N_5O,\frac{1}{4}H_2O$ requires C, 59·1; H, 3·9; N, 28·7%).

4,6-Dibenzamidopyrazolo[3,4-d]*pyrimidine.* 4,6-Diaminopyrazolo[3,4-*d*]pyrimidine (30 g., 0·2 mole) was heated with benzoic anhydride (135·6 g., 0·6 mole) at 200° for 45 min. The cooled residue was recrystallised twice from butanol to give white needles of *4,6-dibenzamidopyrazolo*[3,4-d]*pyrimidine* (33 g.), m. p. 286° (Found: C, 63·5; H, 4·2; N, 23·1. $C_{19}H_{14}N_6O_2$ requires C, 63·7; H, 3·9; N, 23·5%).

Chloromercuri-derivatives. The pyrazolo[3,4-*d*]pyrimidine (0·1 mole) was added as a suspension in 50% aqueous ethanol (500 ml.) to a solution of mercuric chloride (0·1 mole) in the same solvent (150 ml.). To the stirred suspension was added N-sodium hydroxide (1 equiv.) at such a rate that the yellow colour of mercuric oxide disappeared before the next drop was added. Celite 545 (1 g. for 1 g. of base used) was then added to the white suspension which was stirred for an additional 30 min. The chloromercuri-derivatives were collected by filtration, washed with water, and dried. Yields were 80—90%.

*Reaction of chloromercuri-derivatives with tri-*O*-benzoyl-*D*-ribofuranosyl chloride.* The condensations and debenzoylations were carried out in the manner described by Kissman

[5] Cheng and Robins, *J. Org. Chem.*, 1956, **21**, 1240.
[6] Schmidt, Eichenberger, Wilhelm, and Druey, *Helv. Chim. Acta*, 1959, **42**, 763.
[7] Cheng and Robins, *J. Org. Chem.*, 1958, **23**, 852.
[8] Davoll and Lowy, *J. Amer. Chem. Soc.*, 1951, **73**, 1650.
[9] Robins, *J. Amer. Chem. Soc.*, 1957, **79**, 6407.

et al.[10] except that the ribosyl chloride was prepared with the addition of acetyl chloride,[11] and toluene instead of xylene was used as the solvent. The isomers were separated by crystallisation, the isomer of structure (I) being less soluble. Seed crystals were obtained by partition chromatography on Celite 545, water-saturated n-butanol being used as the mobile phase. Yields of mixed isomers were 10—20%. The following compounds were obtained by these methods:

1-β-D-*Ribofuranosyl*-1H-*pyrazolo*[3,4-d]*pyrimidine* (I; R = R′ = H, R″ = $C_5H_9O_4$), needles (from water), m. p. 216°, $[\alpha]_D^{23}$ −65·5° (*c* 0·98 in H_2O) (Found: C, 47·7; H, 4·9; N, 22·1. $C_{10}H_{12}N_4O_4$ requires C, 47·6; H, 4·8; N, 22·3%). 4-*Amino*-1-β-D-*ribofuranosyl*-1H-*pyrazolo*-[3,4-d]*pyrimidine* (I; R = NH_2; R′ = H, R″ = $C_5H_9O_4$), needles (from water), m. p. 246°, $[\alpha]_D^{23}$ −23·1° (*c* 0·98 in H_2O) (Found: C, 45·1; H, 5·1; N, 26·2. $C_{10}H_{13}N_5O_4$ requires C, 44·9; H, 4·9; N, 26·2%). 4,6-*Diamino*-1-β-D-*ribofuranosyl*-1H-*pyrazolo*[3,4-d]*pyrimidine* (I; R = R′ = NH_2, R″ = $C_5H_9O_4$), needles (from water), m. p. 253°, $[\alpha]_D^{23}$ −84·5° (*c* 0·49 in H_2O) (Found: C, 42·8; H, 5·4; N, 30·2. $C_{10}H_{14}N_6O_4$ requires C, 42·6; H, 5·0; N, 29·8%). 4-*Amino*-2-β-D-*ribofuranosyl*-2H-*pyrazolo*[3,4-d]*pyrimidine* (II; R = NH_2, R′ = H, R″ = $C_5H_9O_4$), needles (from water) m. p. 137° (decomp.), $[\alpha]_D^{21}$ −76·6° (*c* 0·39 in H_2O) (Found: C, 44·5; H, 5·2; N, 26·0. $C_{10}H_{13}N_5O_4$ requires C, 44·9; H, 4·9; N, 26·2%). 4,6-*Diamino*-2-β-D-*ribofuranosyl*-2H-*pyrazolo*[3,4-d]*pyrimidine* (II; R = R′ = NH_2, R″ = $C_5H_9O_4$), white microcrystals (from water), m. p. 230° (decomp.), $[\alpha]_D^{23}$ −55·5° (*c* 0·38 in H_2O) (Found: C, 40·1; H, 5·4; N, 27·5. $C_{10}H_{14}N_6O_4,H_2O$ requires C, 40·0; H, 5·3; N, 28·0%).

4,6-*Diacetamido*-1-*tri*-O-*acetyl*-β-D-*ribofuranosyl*-1H-*pyrazolo*[3,4-d]*pyrimidine* (I; R = R′ = AcNH, R″ = $C_{11}H_{15}O_7$). The 4,6-diamino-compound (0·56 g., 0·002 mole) was refluxed with acetic anhydride (5 ml.) for 45 min. A white crystalline solid (1·05 g., m. p. 110—128°) was obtained by distilling off the excess of acetic anhydride *in vacuo*. Recrystallisation of this material from alcohol (9 ml.) gave the *product* as needles (0·6 g.), m. p. 138—143° (decomp.) (Found: C, 48·4; H, 5·2; N, 17·3. $C_{20}H_{24}N_6O_9$ requires C, 48·8; H, 4·9; N, 17·1%). An identical product was obtained when the 4,6-diamino-compound (2·52 g.) was heated with acetic anhydride (27 ml.) and pyridine (50 ml.) on a steam-bath for 2 hr.

6-*Acetamido*-4-*amino*-1-β-D-*ribofuranosyl*-1H-*pyrazolo*[3,4-d]*pyrimidine* (I; R = NH_2, R′ = AcNH, R″ = $C_5H_9O_4$). To the above penta-acetyl compound (0·5 g.) dissolved in methanol (8 ml.) was added a saturated solution of methanolic ammonia (16 ml.), and the mixture was kept for 24 hr. at 3°. Removal of solvent *in vacuo* and crystallisation of the residue from water (4 ml.) gave the *acetamido-compound* as white needles (0·27 g.), m. p. 122—126° (decomp.) (Found: C, 42·1; H, 5·8; N, 24·8. $C_{12}H_{16}N_6O_5,H_2O$ requires C, 42·1; H, 5·3; N, 24·6%).

6-*Acetamido*-4-*hydroxy*-1-β-D-*ribofuranosyl*-1H-*pyrazolo*[3,4-d]*pyrimidine* (I; R = OH; R′ = AcNH; R″ = $C_5H_9O_4$). The above acetamido-compound (0·42 g.) suspended in a solution of sodium nitrite (1 g.) in water (5 ml.) was treated with 10% acetic acid (10 ml.), and the mixture kept for 24 hr. at room temperature. The nucleoside slowly dissolved. This solution was evaporated *in vacuo*, treated with ethanol (10 ml.), and concentrated to 4 ml., slowly giving a white solid (0·25 g.). Crystallisation from water gave the *hydroxy-compound* (0·2 g.) as needles, m. p. 235° (Found: C, 44·5; H, 5·0; N, 21·1. $C_{12}H_{15}N_5O_6$ requires C, 44·3; H, 4·7; N, 21·5%).

6-*Amino*-4-*hydroxy*-1-β-D-*ribofuranosyl*-1H-*pyrazolo*[3,4-d]*pyrimidine* (I; R = OH; R′ = NH_2; R″ = $C_5H_9O_4$). The above compound (0·4 g.) was refluxed with 0·3N-sodium methoxide (8 ml.) for 0·5 hr. The solution was neutralised with 10% aqueous acetic acid and evaporated to dryness *in vacuo*. Crystallisation of the residue from water (9·5 ml.) gave needles (0·3 g.), m. p. 263° (Found: C, 42·2; N, 4·9; N, 24·4. $C_{10}H_{13}N_5O_5$ requires C, 42·4; H, 4·6; N, 24·7%).

The authors thank Dr. R. E. Bowman for many helpful discussions, Miss E. M. Tanner for determination of the spectra, and Mr. F. Oliver for the microanalyses.

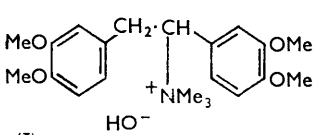
PARKE, DAVIS & COMPANY, RESEARCH DEPARTMENT,
STAINES ROAD, HOUNSLOW, MIDDLESEX. [*Received, January* 18*th*, 1961.]

[10] Kissman, Pidacks, and Baker, *J. Amer. Chem. Soc.*, 1955, **77**, 18.
[11] Baker and Schaub, *J. Amer. Chem. Soc.*, 1955, **77**, 5900.

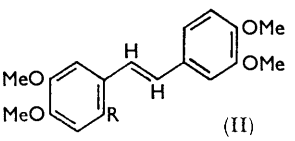
505. cis- *and* trans-3,3′,4,4′-*Tetramethoxystilbenes.*

By A. R. Battersby and I. A. Greenock.

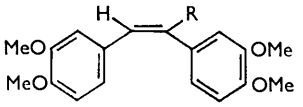
The Hofmann elimination reaction is known to be concerted and bimolecular.[1,2] Of the two transition states which allow *trans*-coplanar elimination [1,3] from the methohydroxide (I), that which leads to the *trans*-3,3′,4,4′-tetramethoxystilbene (II; R = H) should be greatly favoured by non-bonded interactions.[4] It was therefore surprising when the stilbene prepared [5] by this reaction showed an ultraviolet absorption curve closely corresponding with those of known *cis*-stilbenes.[6] Our interest in this anomaly was increased by the report of another stilbene, apparently *cis*, prepared by an elimination reaction.[7] The tetramethoxystilbene had the m. p. reported [8] for 3,3′,4,4′-tetramethoxystilbene, but in none of these studies was the stereochemistry established. Accordingly, *cis*- and *trans*-3,3′,4,4′-tetramethoxystilbenes (II and III; R = H) were prepared.



(I)



(II)



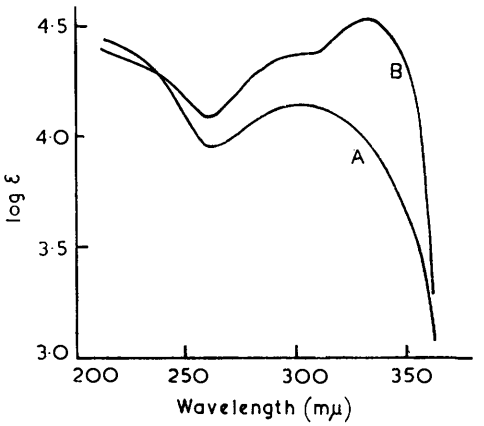
(III)

It is firmly established [9] that *trans*-cinnamic acids are formed in the Perkin reaction so that the acid obtained [10] by condensation of veratraldehyde with 3,4-dimethoxyphenylacetic acid has the structure (III; R = CO_2H). Stereospecific decarboxylation [11] of this acid over copper chromite in quinoline yielded *cis*-3,3′,4,4′-tetramethoxystilbene (III; R = H), m. p. 117—118° (ultraviolet absorption, curve A), which differed from the product of the Hofmann elimination. Catalytic hydrogenation of the *cis*-stilbene (III; R = H) yielded the known 3,3′,4,4′-tetramethoxybibenzyl.

Isomerisation of the *cis*-stilbene by iodine in boiling nitrobenzene [11] gave the *trans*-stilbene (II; R = H), m. p. 153—154°, which was identical with the Hofmann product. When the ultraviolet absorption of samples of stilbene from the isomerisation route and from the Hofmann elimination were measured without delay they showed the same curve which is typical of *trans*-stilbenes (curve B). The same result was obtained when a freshly prepared solution was kept in the dark for 38 days before measurement of the absorption. However, when the solution was kept on the bench (no direct sunlight), the absorption spectrum changed; after 10 days the curve was that of the *cis*-stilbene.

[1] Dhar, Hughes, Ingold, Mandour, Maw, and Woolf, *J.*, 1948, 2093, and refs. therein.
[2] *Inter al.*, Hückel, Tappe, and Legutke, *Annalen*, 1940, **543**, 191; von Doering and Meislich, *J. Amer. Chem. Soc.*, 1952, **74**, 2099; Shiner and Smith, *J. Amer. Chem. Soc.*, 1958, **80**, 4995.
[3] Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 1066; Booth and King, *J.*, 1958, 2688, and earlier papers; Jewers and McKenna, *J.*, 1960, 1575, and earlier papers.
[4] Cram, Greene, and DePuy, *J. Amer. Chem. Soc.*, 1956, **78**, 790; Barton and Cookson, *Quart. Rev.*, 1956, **10**, 48, and refs. therein.
[5] Battersby and Binks, *J.*, 1958, 4333.
[6] Calvin and Alter, *J. Chem. Phys.*, 1951, **19**, 765.
[7] Bergmann and Pelchowicz, *J. Amer. Chem. Soc.*, 1953, **75**, 4281.
[8] Feuerstein, *Ber.*, 1901, **34**, 415; Richtzenhain and von Hofe, *Ber.*, 1939, **72**, 1890; Wood, Bacon, Meibohm, Throckmorton, and Turner, *J. Amer. Chem. Soc.*, 1941, **63**, 1334; Quelet, Hoch, Borgel, Mansouri, Pineau, Tchiroukine, and Vinot, *Bull. Soc. chim. France*, 1956, 26.
[9] Collected refs. given by Zimmerman and Ahramjian, *J. Amer. Chem. Soc.*, 1959, **81**, 2086.
[10] Walker, *J. Amer. Chem. Soc.*, 1954, **76**, 3999.
[11] Taylor and Crawford, *J.*, 1934, 1130; Ruggli and Staub, *Helv. Chim. Acta*, 1937, **20**, 37.

The Hofmann product is thus the expected *trans*-stilbene (II; R = H) and the ultraviolet absorption recorded [5] is that of a *cis*-stilbene as a result of very ready photochemical isomerisation,[12] no doubt due to direct sunlight. The stilbene (II; R = CH_2·NMe_2), also



prepared [5] by Hofmann elimination, shows a typical *trans*-stilbene absorption spectrum which changes under the influence of light to that of a *cis*-stilbene.

Experimental.—cis-3,3′,4,4′-*Tetramethoxystilbene* (III; R = H). α-(3,4-Dimethoxyphenyl)-3,4-dimethoxycinnamic acid [10] (3·03 g.) was added during 5 min. to a suspension of copper chromite (0·38 g.) in quinoline (12 ml.) at 210°. The temperature was then raised to 220° for 25 min. and the cooled mixture was treated with an excess of 4N-hydrochloric acid (100 ml.). An oil separated which was extracted into ether, and the extracts were washed with dilute acid, aqueous sodium carbonate, and water. Evaporation of the dried ethereal solution and recrystallisation of the residue from ethanol yielded cis-3,3′,4,4′-*tetramethoxystilbene* (III; R = H) (2·0 g.), m. p. 117—118° (Found: C, 71·6; H, 6·7; OMe, 41·7. $C_{18}H_{20}O_4$ requires C, 72·05; H, 6·7; OMe, 41·3%); $\lambda_{min.}$ 263, $\lambda_{max.}$ 302 mμ (log ε 3·93 and 4·13, respectively) in ethanol. There were only very weak bands at 930 and 975 $cm.^{-1}$.

Hydrogenation of the foregoing product in ethanol at 23°/755 mm. over platinum (uptake 1·04 mol.) yielded 3,3′,4,4′-tetramethoxybibenzyl, m. p. and mixed m. p. 108—109°, having an infrared spectrum identical with that of an authentic sample.

trans-3,3′,4,4′-*Tetramethoxystilbene* (II; R = H). A solution of the above stilbene (5 g.) and iodine (0·1 g.) in anhydrous nitrobenzene (5 ml.) was heated under reflux for 15 min. The crystals which separated from the cooled solution were collected and recrystallised from ethanol to give the *trans*-stilbene (II; R = H) (3·72 g.), m. p. and mixed m. p. with sample from Hofmann elimination,[5] 153—154° (Found: C, 72·2; H, 6·5. Calc. for $C_{18}H_{20}O_4$: C, 72·05; H, 6·7%); $\lambda_{min.}$ 261, $\lambda_{max.}$ 330 mμ (log ε 4·09 and 4·54, respectively) in ethanol. The infrared spectra of the two samples of *trans*-stilbene were identical (strong band at 960 $cm.^{-1}$, CH out-of-plane deformation).

THE UNIVERSITY, BRISTOL. [*Received, January 18th,* 1961.]

[12] Stoermer, *Ber.*, 1909, **42**, 4871.

506. *The Structure of Disalicylaldehydenickel.*

By J. R. Miller and A. G. Sharpe.

Curtiss, Lyle, and Lingafelter [1] found disalicylaldehydenickel to be isomorphous with its zinc analogue; they suggested that the co-ordination was tetrahedral on the grounds that all tetraco-ordinated zinc compounds of known structure were tetrahedral, and for several years the compound occupied a key position in the stereochemistry of nickel. However, Lyle, Morosin, and Lingafelter [2] have since found that the unit cell of the nickel compound is large and unsymmetrical, and, by comparison with bisacetylacetonenickel,[3] have suggested that it is polymeric, containing four trimers in the unit cell. We here report evidence which confirms this suggestion.

The compound was prepared by heating the dihydrate *in vacuo* at 100° for 80 hr. (Found: C, 54·0; Ni, 19·6. Calc. for $C_{14}H_{10}NiO_4$: C, 55·9; Ni, 19·5%); it was amorphous and could not be recrystallised.

The magnetic moment is 3·28 B.M. (Basolo and Matoush [4] found 3·0 B.M.). This almost certainly rules out a square-planar configuration, and indicates distorted tetrahedral, octahedral, or tetragonal symmetry.

In the visible region, the reflectance spectrum is almost identical with that of bisacetylacetonenickel, but rather different from that of a solution of nickel chloride and salicylaldehyde in dimethylformamide, which was taken by Maki [5] as a spectrum of the anhydrous compound. The important spectra are shown in the Table. Absorption maxima are in wavenumbers.

$Ni(SA)_2$	8850	*ca.* 13,700 (40%)	15,270	25,000 (100%)
Reflectance	(54% abs.)	infl.	(47%)	charge-transfer
$Ni(acac)_2$ [6]	8800	12,900	15,250	—
In benzene	($\varepsilon = 12$)	infl. ($\varepsilon = 5$)	($\varepsilon = 12$)	—
$NiCl_2$ + SAH [5]	7810	12,990 (0·12)	16,000 (0·16)	—
In DMF	(o.d. 0·14)	14,290 (0·16)	17,240 (0·14)	
$Ni(SA)_2,2H_2O$ [5]	9350 (0·26)	12,990 (0·07)	15,870 (0·36)	23,810 (0·80)
Reflectance	10,530 (0·15)			

SAH = Salicylaldehyde; acacH = acetylacetone; DMF = dimethylformamide.

These spectra are quite different from those of known tetrahedral nickel(II) complexes,[7] and this configuration is therefore not further discussed. Jørgensen [6] interpreted the acetylacetonate spectrum on the basis of an octahedral configuration with tetragonal splitting, whilst Maki [5] preferred a planar configuration with axial perturbation; the difference is only one of degree.

There are two possible ways by which the nickel atom could have an approximately octahedral environment: the benzene rings of one molecule could co-ordinate to the nickel atoms of adjacent molecules, or the oxygen atoms of adjacent molecules could be shared between nickel atoms. The first possibility is considered unlikely because the infrared spectrum of the anhydrous compound is very similar to that of the dihydrate, the

[1] Curtiss, Lyle, and Lingafelter, *Acta Cryst.*, 1952, **5**, 388.
[2] Lyle, Morosin, and Lingafelter, *Acta Cryst.*, 1959, **12**, 938.
[3] Bullen, *Nature*, 1956, **177**, 537.
[4] Basolo and Matoush, *J. Amer. Chem. Soc.*, 1953, **75**, 5663.
[5] Maki, *J. Chem. Phys.*, 1958, **29**, 162.
[6] Jørgensen, *Acta Chem. Scand.*, 1955, **9**, 1362.
[7] See, for example, Gruen and McBeth, *J. Phys. Chem.*, 1959, **63**, 393.

crystal structure of which precludes interaction between the nickel atoms and the benzene rings.[8] The conclusion is that the substance has a polymerised structure, individual formula units being linked through oxygen atoms.

Fackler and Cotton [9] have recently found that complexes of nickel(II) with certain β-diketones are associated in solution, and that their anomalous magnetic moments may be explained in terms of equilibria: monomer (red, diamagnetic) $\rightleftharpoons$ associated species (green, paramagnetic). We suggest that the similarity of the spectra of anhydrous bisacetylacetonenickel in benzene solution and of the solid dihydrate [5,6] must be due to a similar phenomenon, and that such association may be of general occurrence.

We thank Dr. A. R. Caverhill, of Imperial Chemical Industries Limited, Fibres Division, Harrogate, for the reflectance spectrum of disalicylaldehydenickel, and the D.S.I.R. for a maintenance grant (to J. R. M.).

UNIVERSITY CHEMICAL LABORATORY,
CAMBRIDGE. [*Received, December 21st*, 1960.]

[8] Lingafelter, Breazeale, and Stewart, *Acta Cryst.*, 1957, **10**, 785.
[9] Fackler and Cotton, *J. Amer. Chem. Soc.*, 1960, **82**, 5005.

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507. 6-*Methylthiamine Chloride Hydrochloride.*

By J. BIGGS and P. SYKES.

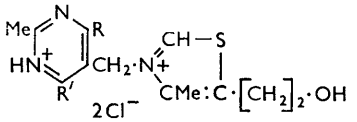
IT has been suggested [1] that thiamine chloride hydrochloride, when acting as a catalyst in the non-enzymic decarboxylation of pyruvate in the presence of acetaldehyde to yield acetoin + carbon dioxide,[2] first assumes a conformation in which the unsubstituted 6-position of the pyrimidine nucleus is spatially adjacent to the 2'-position of the thiazole nucleus (I; R = H, R' = NH_2). The attack by pyruvate on this position in the thiazole (the vital stage in the above decarboxylation) [3] would then be sterically facilitated, whereas the pyrimidine 4-amino-group which is in close proximity in the conformation usually written for thiamine (I; R = NH_2, R' = H) could well inhibit the pyruvate's close approach. We have, therefore, as a test of the hypothesis, synthesised 6-methylthiamine chloride hydrochloride (I; R = Me, R' = NH_2) in which the steric advantage of the former conformation has been extinguished and which would thus be expected on the above hypothesis to exhibit little or no catalytic activity.

4-Amino-5-cyano-2,6-dimethylpyrimidine (II; R = CN), prepared by a slight modification of the method of Todd and his co-workers,[4] was reduced catalytically to yield 4-amino-5-aminomethyl-2,6-dimethylpyrimidine (II; R = $CH_2 \cdot NH_2$). Treatment of this diamine with carbon disulphide, alkali, and 5-acetoxy-3-chloropentan-2-one yielded the thiazoline-2-thione (III), which on oxidation with hydrogen peroxide followed by exchange of SO_4^{2-} by $2Cl^-$ yielded the vitamin analogue (I; R = Me, R' = NH_2) in the usual way.[5]

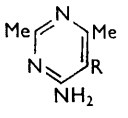
The addition of alkali to its aqueous solution produced a yellow colour which was changed into a thiochrome-like fluorescence on oxidation with ferricyanide—observations in accord with our views on the action of oxidising agents on thiamine itself.[6] 6-Methylthiamine (I; R = Me, R' = NH_2) was found, like thiamine, to undergo ready exchange

[1] Private communication from Professor Eberhardt.
[2] Mizuhara, Tamura, and Arata, *Proc. Japan Acad.*, 1951, **27**, 302; Downes and Sykes, *Chem. and Ind.*, 1957, 1095.
[3] Breslow, *J. Amer. Chem. Soc.*, 1958, **80**, 3719.
[4] Kenner, Lythgoe, Todd, and Topham, *J.*, 1943, 388.
[5] Biggs and Sykes, *J.*, 1959, 1849.
[6] Sykes and Todd, *J.*, 1951, 534; Nesbitt and Sykes, *J.*, 1954, 4585.

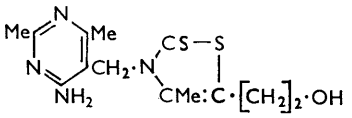
in deuterium oxide of the hydrogen atom in the 2′-position of the thiazole nucleus [7] and on being tested as a catalyst in the non-enzymic conversion of pyruvate + acetaldehyde ⟶ acetoin + carbon dioxide it showed 18% of the activity exhibited by thiamine under similar conditions. The magnitude of this catalytic activity, compared with that (5%)



(I)



(II)



(III)

of the isomer in which a methyl group has been introduced on the nearby internuclear methylene group but which still contains an unsubstituted pyrimidine 6-position,[5] suggests that the above hypothesis is untenable.

Experimental.—*4-Amino-5-cyano-2,6-dimethylpyrimidine* (II; R = CN). The method of Todd and his co-workers [4] was essentially followed but use of two mol. of acetamidine per mol. of malononitrile, instead of one, raised the yield from 50 to 90%. The product had m. p. 227° (decomp.) [lit.[4] m. p. 218°, and Huber and Hölscher [8] (using a different method), m. p. 220·5°] (Found: C, 57·1; H, 5·5; N, 38·2. Calc. for $C_7H_8N_4$: C, 56·9; H, 5·4; N, 37·8%).

4-Amino-5-aminomethyl-2,6-dimethylpyrimidine (II; R = $CH_2{\cdot}NH_2$). Catalytic reduction of the above cyanopyrimidine in glacial acetic acid–3N-hydrochloric acid with palladium–charcoal (10%) as catalyst yielded the dihydrochloride (cf. Huber and Hölscher [8]), m. p. 297—298° (decomp.) [lit.[8] m. p. 192—193° (decomp.) (? misprint)]. When an aqueous solution of the dihydrochloride was made alkaline with sodium hydrogen carbonate, solid separated which on recrystallisation from water yielded the *diamine* as needles, m. p. 200° (Found: C, 55·0; H, 8·2; N, 37·1. $C_7H_{12}N_4$ requires C, 55·2; H, 8·0; N, 36·8%).

3-(4-Amino-2,6-dimethyl-5-pyrimidylmethyl)-5-2′-hydroxyethyl-4-methylthiazoline-2-thione (III). The above diamine dihydrochloride (2·1 g.) was dissolved in water (8 ml.) and sodium hydroxide (0·75 g., 2 mol.) added, followed by ethanol (6 ml.), ammonia (*d* 0·88; 0·78 g.) and carbon disulphide (0·88 g.). The mixture, which became warm, was shaken until all the carbon disulphide had dissolved. 5-Acetoxy-3-chloropentan-2-one (1·65 g.) was added, the mixture was shaken vigorously for 30 min. and set aside overnight. The residue obtained on evaporating the mixture to dryness under reduced pressure was dissolved in 3N-hydrochloric acid (10 ml.), and the resulting solution warmed at 60° for 15 min. and then made just alkaline with sodium hydrogen carbonate. Solid separated which on recrystallisation from methanol (charcoal) yielded the *thiazoline-2-thione* (2·07 g., 71%) as needles, m. p. 246° (Found: C, 50·5; H, 6·0; N, 18·2. $C_{13}H_{18}N_4OS_2$ requires C, 50·3; H, 5·8; N, 18·1%).

3-(4-Amino-2,6-dimethyl-5-pyrimidylmethyl)-5-2′-hydroxyethyl-4-methylthiazolium chloride hydrochloride (*6-methylthiamine chloride hydrochloride*) (I; R = Me, R′ = NH_2). The thiazoline-2-thione (1·0 g.), water (30 ml.), and 24% hydrogen peroxide solution (1·33 g., 3 mol.) were stirred until the solid had dissolved (4 hr.), then treated with barium chloride solution until solid was no longer precipitated. The barium sulphate was removed on a centrifuge, and the solution evaporated to dryness. The residue was dissolved in methanol (20 ml.), decolorised with charcoal, and ether (30 ml.) then added slowly during 2 hr. The quaternary *chloride hydrochloride* (0·61 g., 54%) separated as needles, m. p. 233° (decomp.) (Found: C, 40·4; H, 6·4; N, 14·5. $C_{13}H_{20}Cl_2N_4OS,2H_2O$ requires C, 40·4; H, 6·2; N, 14·5%).

Exchange in deuterium oxide solution; nuclear magnetic resonance spectra. The above chloride hydrochloride (0·25 g.) was dissolved in water (0·25 ml.) and treated with N-sodium hydroxide (0·70 ml., 1 mol.); the solution exhibited a sharp peak on the hydrogen nuclear magnetic resonance spectrum at 181 cycles/sec. to the lower field side of the resonance of the hydrogen nuclei in the solvent water, corresponding to the 2-hydrogen atom in the thiazole nucleus.[5,7] A second portion of the chloride hydrochloride was then similarly converted into

[7] Breslow, *J. Amer. Chem. Soc.*, 1957, **79**, 1762.
[8] Huber and Hölscher, *Ber.*, 1938, **71***B*, 87.

the quaternary chloride, the solution freeze-dried, the residue dissolved rapidly in deuterium oxide, and the spectrum immediately examined: the peak at 181 cycles/sec. was no longer detectable.

Catalytic activity in the acetoin test. The test [2] was run in triplicate and the acetoin produced was estimated.[9] The above analogue exhibited 18% of the catalytic activity of the thiamine chloride hydrochloride, used as a control.

One of us (J. B.) is indebted to the Department of Scientific and Industrial Research for a Senior Award; we also make grateful acknowledgment to Roche Products Ltd. for gifts of material.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, January 24th*, 1961.]

[9] Westerfeld, *J. biol. Chem.*, 1945, **161**, 495.

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508. *Preparation and Properties of Trifluoromethylthiosilver.*

By H. J. EMELÉUS and D. E. MACDUFFIE.

TRIFLUOROMETHYLTHIOSILVER was prepared by Man, Coffman, and Muetterties [1] by reaction of aqueous silver nitrate with bistrifluoromethylthiomercury; the latter being prepared by heating mercuric fluoride with carbon disulphide. This Note describes the direct preparation of the silver compound in 70—80% yield from silver fluoride and carbon disulphide in an autoclave at 140°:

$$3AgF + CS_2 = AgS{\cdot}CF_3 + Ag_2S$$

The compound, isolated by extraction with acetone, was a white solid which was stable in air but decomposed when heated above 80° in a glass vessel *in vacuo*. Its infrared spectrum showed strong absorption bands at 1138, 1103, and 1083 cm.$^{-1}$ (C–F stretching), a sharp band of medium intensity at 755 cm.$^{-1}$ (C–S stretching, CF_3 deformation), and a number of weaker bands at 1200—1500 and 400—800 cm.$^{-1}$. The chief frequencies are also found in the spectrum of the mercurial.[2]

The compound was insoluble in water, dilute or concentrated hydrochloric acid, and dilute nitric acid but dissolved in hot 1 : 1 nitric acid. It dissolved readily in acetone, acetonitrile, dimethyl sulphoxide, and *NN*-dimethylformamide. The solubility in other solvents (in mg. per 100 g. of solvent at 24°) was: ether, 15·0; toluene, 13·5; hexane, 6·7; benzene, 5·1; carbon disulphide, 4·8; carbon tetrachloride, 0·2. It also dissolved in pyridine but a 10^{-2}M solution deposited a black precipitate after a few days at 20°. When the solvent was removed at 0° from a fresh pyridine solution, the adduct $2AgS{\cdot}CF_3,C_5H_5N$ remained. Dimethylamine gave the adduct $2AgS{\cdot}CF_3,Me_2NH$.

Reactions with halogens [2] and methyl iodide [3] paralleled those of the mercury analogue and showed that the $\cdot SCF_3$ group can be transferred intact. Thus, with excess of chlorine, trifluoromethylsulphenyl chloride and silver chloride resulted. With excess of the silver compound bistrifluoromethyl disulphide was also formed. The latter compound was the only volatile product of reaction with excess of bromine or an equivalent quantity of iodine. Excess of methyl iodide gave methyl trifluoromethyl sulphide at 20°. With excess of trimethylsilyl chloride, conversion into silver chloride was lower (64%) and trimethylsilyl fluoride was isolated. Trifluoromethyl trimethylsilyl sulphide was probably first formed; its decomposition to trimethylsilyl fluoride would parallel that of silyl

[1] Man, Coffman, and Muetterties, *J. Amer. Chem. Soc.*, 1959, **81**, 3575.
[2] Haszeldine and Kidd, *J.*, 1953, 3225; Emeléus and Pugh, *J.*, 1960, 1108.
[3] Downs and Emeléus, unpublished work.

trifluoromethyl sulphide to silyl fluoride.[4] The reaction of trifluoromethylthiosilver with inorganic and organic halogen-containing compounds offers the advantage of the quantitative formation of silver halide. This simplifies the interpretation of the results of conductimetric titrations, a number of which will be reported in a later communication.

Experimental

Preparation of Trifluoromethylthiosilver.—In a typical experiment, dry silver fluoride (14·88 g.) and dry " AnalaR " carbon disulphide (15 ml.) were heated for 12 hr. in a steel autoclave (300 ml.) at 140°. The infrared spectrum of the volatile products showed the presence of carbonyl oxysulphide and silicon tetrafluoride, formed by reaction of primary products with glass, and of carbon disulphide. The black involatile residue (10·50 g.) was extracted with dry acetone, which was removed *in vacuo* at 20°. The last traces of solvent were removed at 70° during 5 hr. The product was trifluoromethylthiosilver (6·50 g., 79%) (Found: C, 5·9; Ag, 51·0; S, 15·0. Calc. for $CAgF_3S$: C, 5·7; Ag, 51·6; S, 15·3%). Silver was estimated as chloride after decomposition of the compound with 1 : 1 nitric acid, and sulphur as sulphate after fusion in a Parr bomb with sodium peroxide, potassium nitrate, and sucrose.[5]

Reactions of Trifluoromethylthiosilver.—(*i*) *With pyridine.* The compound (0·082 g.) was dissolved in dry " AnalaR " pyridine (*ca.* 2 ml.). The solvent was removed *in vacuo* at 0° and the crystalline residue dried to constant weight at 25°. The *adduct* $2AgS{\cdot}CF_3{,}C_5H_5N$ remained (Found: C, 16·5; H, 1·6; Ag, 43·7; N, 2·6; S, 12·7. $C_7H_5Ag_2F_6NS_2$ requires C, 16·9; H, 1·0; Ag, 43·4; N, 2·8; S, 12·9%).

(*ii*) *With dimethylamine.* No apparent reaction occurred on shaking the silver compound (0·186 g.) with dimethylamine (29 g.) in a sealed tube at 20° (24 hr.). Removal of the solvent at 20° *in vacuo* to constant weight gave a dark brown residue of $2AgS{\cdot}CF_3{,}Me_2NH$ (Found: C, 10·2; H, 1·6; Ag, 46·3; N, 3·1; S, 14·3. $C_4H_7Ag_2F_6NH_2$ requires C, 10·4; H, 1·5; Ag, 46·6; N, 3·0; S, 13·9%).

(*iii*) *With chlorine.* The silver compound (0·286 g.) reacted immediately with excess of chlorine at 20°. Chlorine was removed from the volatile products by shaking them several times with dry iodine (0·65 g.) and removing residual volatile material at −95° to minimise evaporation of iodine chlorides. Repeated trap-to-trap distillation gave *trifluoromethanesulphenyl chloride*, which was involatile at −131° (0·134 g., 72%) (Found: *M*, 131. $CClF_3S$ requires *M*, 137). The infrared spectrum confirmed this identification. The involatile residue on extraction with acetone gave unchanged trifluoromethylthiosilver (0·018 g.), identified by its infrared spectrum. Extraction with 1 : 1 nitric acid then left silver chloride (0·181 g., 92·5%). With 0·448 g. of the silver compound and 0·145 g. of chlorine the products were bistrifluoromethyl disulphide (0·066 g., 16%) (*M*, 201), trifluoromethanesulphenyl chloride (0·134 g., 80%) (*M*, 138), and silver chloride (0·261 g., 89%).

(*iv*) *With bromine.* Trifluoromethylthiosilver (0·226 g.) was left in contact with bromine (0·317 g.) for several days at 20°. The products identified were *bistrifluoromethyl disulphide* (0·074 g., 68%) (Found: *M*, 203. Calc. for $C_2F_6S_2$: *M*, 202) (the infrared spectrum confirmed this identification), silver bromide (0·113 g., 56%), and unchanged silver compound (0·010 g.).

(*v*) *With iodine.* The compound (0·263 g.) and an equivalent quantity of dry iodine (0·160 g.) were placed in opposite limbs of a tube, which was evacuated and sealed. Reaction occurred at once when the solids were mixed at 20°. The products, after several weeks, were bistrifluoromethyl disulphide (0·097 g., 77%) (*M*, 202) (the infrared spectrum confirmed this identification), silver iodide (0·222 g., 75%), and an unidentified mixture of orange and brown solids (0·058 g.).

(*vi*) *With methyl iodide.* The compound (0·205 g.) reacted with methyl iodide (0·295 g.) during several days at 20°. The products were methyl trifluoromethyl sulphide (0·093 g., 82%) (Found: *M*, 116. Calc. for $C_2H_3F_3S$: *M*, 116) (the infrared spectrum confirmed this identification) and silver iodide (0·216 g., 94%).

(*vii*) *With trimethylsilyl chloride.* Trifluoromethylthiosilver (0·184 g.) and trimethylsilyl chloride (0·123 g.) reacted slowly at 20°. The products identified after several days were trimethylsilyl fluoride (0·030 g., 37%) (Found: *M*, 92. Calc. for C_3H_9FSi: *M*, 92) (the infrared

[4] Downs and Ebsworth, *J.*, 1960, 3516.
[5] Wurzschmitt and Zummermann, *Fortschr. chem. Forsch.*, 1950, **1**, 485.

spectrum confirmed this identification), silver chloride (0·081 g., 64%), and unchanged silver compound (0·051 g.).

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509. *Tumour Inhibitors from Plant Sources. Part I.*

By B. F. CAIN.

THE continuation of our programme [1] to screen the New Zealand native and naturalized flora for tumour-inhibiting substances has drawn attention to several plants. Acetone extracts of one of the naturalized species *Anthriscus neglecta* Boiss and Rent * (family, Umbelliferae) [Syn. *A. scandicina* (Web) Mansf.] gave materials capable of producing a statistically significant life-extension in mice bearing the acute lymphocytic leukemia L1210 in mice.†

A lignan, " anthricin," had been isolated from the related *A. sylvestris* Hoffm.,[2] and Hartwell and Schrecker [3] have shown the identity of this material with deoxypodophyllotoxin. *A. neglecta* has also given deoxypodophyllotoxin (0·006% of total plant) and this compound accounts for over 60% of the toxicity of the original extracts.

As a guide in designing fractionation procedures reversed-phase paper-chromatography was used. Tetracyanoethylene [4] gave a range of colours with non-phenolic lignans and as a detecting agent on paper strips is more convenient and sensitive than the reagent described by Jorgenson and Kofod.[5]

Experimental.—Finely ground whole plant (4·4 kg.) was extracted with successive quantities of cold acetone (40 l. total), the extracts being evaporated *in vacuo* to yield a green tar (280 g.). This was shaken with water (2 l.) and chloroform (6 × 1 l.), and the extracts were dried (Na_2SO_4) and evaporated (62·4 g.). The solid was dissolved in aqueous methanol (85% v/v; 1 l.) and extracted with light petroleum (b. p. 60—80°; 3 × 400 ml.). The petrol extracts on evaporation gave non-toxic waxes (43·2 g.) which were discarded. To the aqueous methanol solution, neutral lead acetate (20 g.) in 85% aqueous methanol plus acetic acid (2 ml.) was added, the precipitate removed, and the aqueous solution evaporated to half volume. After addition of an equal volume of water toxic material (12·9 g.) was removed by extraction with ethyl acetate (4 × 500 ml.).

A column of Celite (dried at 110°; 100 g.) containing propylene glycol (55 ml.) was prepared in light petroleum. The active fraction was applied to the column in benzene–light petroleum (1 : 1), elution with this mixture being continued for 2 l. followed by benzene. The eluted fractions (50 ml.) were grouped according to paper-chromatographic evidence, and those containing material of R_f 0·93 (see below) were combined and evaporated after being washed free from propylene glycol with water. Crystallization was effected first from toluene then aqueous ethanol, deoxypodophyllotoxin (0·246 g.) being obtained as prisms, m. p. and mixed m. p. 167·5—168°, $[\alpha]_D^{18}$ −114° (c = 1, in $CHCl_3$) (Found: C, 66·5; H, 5·4. Calc. for $C_{22}H_{22}O_7$: C, 66·3; H, 5·6%). Paper chromatograms also failed to distinguish this and authentic material.[3] Isomerization [3] gave deoxypicropodophyllotoxin, m. p. 171—172°, $[\alpha]_D$ +31° (in $CHCl_3$) (Found:

* Samples were identified by Dr. R. Cooper of the Auckland Institute and Museum, Herbarium number 46,543.

† The author is indebted to Dr. J. F. Burton of these laboratories for details of the biological tests.

[1] Cain, *J.*, 1961, 936.
[2] Noguchi and Kawanami, *J. Pharm. Soc. Japan*, 1940, **60**, 629.
[3] Hartwell and Schrecker, *J. Amer. Chem. Soc.*, 1954, **176**, 4034.
[4] Tarbell and Huang, *J. Org. Chem.*, 1959, **24**, 887.
[5] Jorgenson and Kofod, *Acta Chem. Scand.*, 1954, **8**, 941.

C, 66·0; H, 5·5. Calc. for $C_{22}H_{22}O_7$: C, 66·3; H, 5·6%). The m. p. was not depressed by a sample prepared from authentic deoxypodophyllotoxin.

Paper chromatography. Whatman's No. 1 discs (27 cm. diam.) were dipped in a solution of propylene glycol in acetone (40% v/v) excess of solvent was blotted off, and the papers were dried in air for 10 min. Spots were applied and the papers were developed radially with benzene saturated with propylene glycol. When developed, papers were oven-dried and sprayed with a 1% solution of tetracyanoethylene in freshly distilled acetone. Typical R_f values were: podophyllotoxin, 0·01 (purple); deoxypodophyllotoxin, 0·93 (purple); α-peltatin, 0·09 (blue); β-peltatin, 0·54 (purple); matairesinol, 0·44 (blue).

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