822. *Constituents of the Leaves of* Ficus carica, *L. Part I. Isolation of Psoralen, Bergapten, ψ-Taraxasterol, and β-Sitosterol.*

By Albert Kamel Athnasios, Ibrahim El-Sayed El-Kholy, Gabea Soliman, and (in part) Mohamed Abdel Monem Shaban.

In a search for a cheap source of psoralen, noted among the furocoumarins for the treatment of leukoderma and skin depigmentation,[1] we have studied the leaves of *Ficus carica domestica*, L. (Moraceae) (var. *Sultani*), cultivated in the Agami district near Alexandria.

A light petroleum extract of the dried leaves yielded a wax from which psoralen and bergapten have been isolated. The former was identified by conversion into methoxypsoralic acid,[2] but bergapten was identified by comparison with an authentic specimen. Further, their ultraviolet absorption maxima were almost identical with those reproduced by Fowlks.[1]

The residual light petroleum extract was separated into an ethanol-insoluble fraction and a green ethanolic solution which was saponified; the unsaponifiable material afforded ψ-taraxasterol and β-sitosterol.

Experimental.—Light petroleum had b. p. 50—70°.

Extraction. The powdered air-dried leaves (4 kg.), collected in summer, were extracted (Soxhlet) with light petroleum, and the yellowish-green extract was then concentrated to about 1 l. On cooling, a yellowish wax (23 g.) separated, and when the solvent was completely removed a viscous yellowish-green oil (140 g.) was obtained.

Isolation of bergapten and psoralen. The waxy deposit was digested with warm acetone and filtered while luke-warm. The filtrate yielded the furocoumarins (12 g.) as a yellowish crystalline residue on evaporation. Bergapten was obtained from this residue on repeated crystallisation (charcoal) from ethanol, in needles, m. p. 188—189°[3] alone or mixed with an authentic specimen, kindly supplied by Dr. (Mrs.) A. Chatterjee, University College of Science and Technology, Calcutta (Found: C, 67·0; H, 3·75; OMe, 13·9. Calc. for $C_{12}H_8O_4$: C, 66·7; H, 3·8; OMe, 14·35%).

Psoralen was recovered by fractional crystallisation, from acetone, of the residue left after evaporation of the first ethanolic mother-liquor. It recrystallised from methanol in needles, m. p. 164° (Found: C, 70·7; H, 3·5. Calc. for $C_{11}H_6O_3$: C, 71·0; H, 3·2%); with dimethyl sulphate and sodium hydroxide, it gave methyl methoxypsoralate which was hydrolysed to methoxypsoralic acid, m. p. 163—164°.[2]

Fractionation of the unsaponifiable material. The oily residue (140 g.) was heated with ethanol (400 ml.) to the b. p., and, after cooling, the ethanolic solution was decanted. The residue was similarly treated with another 400 ml. of ethanol, and a sticky green residue (48 g.) then remained. The combined ethanolic solution was refluxed with potassium hydroxide (60 g.) for 3 hr., and, after removal of most of the solvent, extraction with ether gave unsaponifiable material as a yellowish-brown sticky residue (44 g.). The soap yielded greenish-solid fatty acids (28 g.).

A solution of the unsaponifiable material (11 g.) in light petroleum (200 ml.) was filtered through a column (52 × 2·5 cm.) of aluminium oxide (200 g.). Elution was with light petroleum (1 l.) and then benzene (2 l.); 200-ml. fractions were collected. The residues were recovered by evaporation of the benzene fractions collected from 4 identical columns:

Fraction	1	2	3	4	5	6	7	8	9	10
Wt. (g.)	1	5·0	2·0	2·4	1·8	1·6	1·4	1·2	1·0	0·8

Fractions 4—10 were chromatographed in light petroleum on alumina 70 g.; (27 × 2 cm.) and eluted with benzene. The terpene fraction recovered from the benzene solutions crystallised from light petroleum and recrystallised from methanol in needles, m. p. 180—190°. ψ-Taraxasteryl acetate was obtained from this product by use of pyridine–acetic anhydride and was refluxed with ethanol. The insoluble portion, m. p. 220°, crystallised from benzene–methanol and recrystallised from ethyl acetate in plates, m. p. 238°, not depressed by an

[1] Fitzpatrick and Pathak, *J. Invest. Derm.*, 1959, **32**, suppl. to No. 2, pp. 229, 255, Fowlks, *ibid.*, 249.
[2] Späth, Okahara, and Kuffner, *Ber.*, 1937, **70**, 73; Jois and Manjunath, *ibid.*, p. 434.
[3] Rodighiero and Antonello, *Farmaco, (Pavia), Ed. sci.*, 1959, **14**, 679; *Chem. Abs.*, 1960, **54**,10,070.

authentic specimen [4] (Found: C, 82·0; H, 11·1. Calc. for $C_{32}H_{52}O_2$: C, 82·0; H, 11·2%). Hydrolysis with ethanolic potassium hydroxide and benzene gave ψ-taraxasterol, needles (from methanol), m. p. and mixed m. p. 217° (Found: C, 84·5; H, 11·9. Calc. for $C_{30}H_{50}O$: C, 84·4; H, 11·8%). Its benzoate crystallised from benzene–methanol and recrystallised from ethyl acetate in plates, m. p. and mixed m. p. 276—277° (Found: C, 84·1; H, 10·2. Calc. for $C_{37}H_{54}O_2$: C, 83·7; H, 10·25%).

Each of the 4 identical columns of alumina was divided from the top into 3 sections (12, 20, and 20 cm.) which were separately eluted with boiling ethanol. The residue (4·5 g.) recovered from the four lowest sections yielded β-sitosterol (3 g.) on treatment with cold methanol. This sterol was purified by washing it with cold light petroleum and crystallised from methanol in elongated plates,[5] m. p. and mixed m. p. 137° (Found: C, 84·2; H, 12·15. Calc. for $C_{29}H_{50}O$: C, 84·0; H, 12·15%), $[\alpha]_D^{27}$ −33·3° (*c* 7·32 in $CHCl_3$). β-Sitosterol acetate crystallised from methanol in plates, m. p. and mixed m. p. 124—125° (Found: C, 81·7; H, 11·5. Calc. for $C_{31}H_{52}O_2$: C, 81·5; H, 11·5%), $[\alpha]_D^{27}$ −37·6° (*c* 1·99 in $CHCl_3$); the benzoate formed plates, m. p. and mixed m. p. 148°, from benzene–methanol (Found: C, 83·05; H, 10·4. Calc. for $C_{36}H_{54}O_2$: C, 83·3; H, 10·5%), $[\alpha]_D^{27}$ −13·8° (*c* 5·07 in $CHCl_3$); the 3,5-dinitrobenzoate formed yellowish plates, m. p. and mixed m. p. 205°, from ethyl acetate (Found: C, 71·3; H, 8·5; N, 4·8. Calc. for $C_{36}H_{52}N_2O_6$: C, 71·0; H, 8·6; N, 4·6%).

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[4] Atherinos, El-Kholy, and Soliman, *J.*, 1962, 1700.
[5] Soliman and Saleh, *J.*, 1954, 1506.

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823. *Derivatives of Naphthalene-2,7-diamine.*

By F. BELL.

BELL, GIBSON, and WILSON [1] made a brief study of the halogenation of naphthalene-2,7-diamine and its derivatives and this remains the only paper on direct substitution in this series. Other substitution products have been obtained indirectly. For instance, Fischer and Kern [2] converted a 2,7-dimethoxy-dinitronaphthalene into a dinitronaphthalene-2,7-diamine; as it has been recently shown [3] that the former has its nitro-groups in positions 1 and 8, the derived compound would be expected to be 1,8-dinitronaphthalene-2,7-diamine. Hey and Lawton [4] obtained 1-nitronaphthalene-2,7-diamine from 7-methoxy-8-nitro-2-naphthylamine.

It is now found that the diacetyl, dibenzoyl, and ditoluene-*p*-sulphonyl derivatives of naphthalene-2,7-diamine are all dinitrated to give products of the same orientation. From dinitro-ditoluene-*p*-sulphonamidonaphthalene there was obtained by partial deamination 1,8-dinitro-2-naphthylamine, from which it follows that all the above mentioned nitration products have the nitro-groups in positions 1 and 8. Surprisingly the descriptions of these compounds conflicted with those given by Fischer and Kern.[2] On repeating their work we found that the compounds they had prepared were impure, but that pure 1,8-dinitronaphthalene-2,7-diamine could be obtained by their method.

It was next shown that the products of monobromination of naphthalene-2,7-diamine and its ditoluene-*p*-sulphonyl derivative had the same orientation. Rather surprisingly it was found possible to dibrominate the latter smoothly, but attempts to convert the product into a dibromonaphthalene were unsucessful.

2,7-Diacetamidonaphthalene reacted with two molecular proportions of bromine in acetic acid to give an addition product, which could be decomposed to give 1-bromo-2,7-diacetamidonaphthalene. On the other hand chlorination of 2,7-diacetamidonaphthalene led directly to a uniform 1,8-dichloro-derivative.

A preliminary study of 2,3-ditoluene-*p*-sulphonamidonaphthalene showed that this on

[1] Bell, Gibson, and Wilson, *J.*, 1956, 2335.
[2] Fischer and Kern, *J. prakt. Chem.*, 1916, **94**, 34.
[3] Bell and Gorrie, *J.*, 1961, 4258.
[4] Hey and Lawton, *J.*, 1940, 384.

nitration gave a dinitro-derivative, but with bromine in acetic acid a yellow addition product. This on attempted recrystallisation decomposed to give either a monobromo-derivative, alternatively obtained by bromination of the sulphonamide in chloroform, or a dibromo-derivative, alternatively obtained by bromination in pyridine with *N*-bromosuccinimide.

Experimental.—Nitration of 2,7-*ditoluene*-p-*sulphonamidonaphthalene.* Fuming nitric acid (10 c.c.) in acetic acid (10 c.c.) was added to a warm solution of the compound (5 g.) in acetic acid (50 c.c.). The mixture became very dark and soon set to a paste of needles, m. p. *ca.* 200° (3·5 g.). Recrystallisation first from acetic acid and then from chlorobenzene gave the 1,8-*dinitro-derivative* as needles, m. p. 228° (decomp.) (Found: C, 51·8; H, 3·9. $C_{24}H_{20}N_4O_8S_2$ requires C, 51·8; H, 3·6%). This compound soon dissolved in cold concentrated sulphuric acid; pouring the solution into water precipitated the 1,8-*dinitro-diamine* which formed orange-red prisms, m. p. 302° (decomp.), from acetone (Found: C, 48·4; H, 3·2. $C_{10}H_8N_4O_4$ requires C, 48·4; H, 3·2%). If the temperature is allowed to rise too high in the nitration the product is heavily contaminated by higher nitro-compounds, and the least soluble fraction of the derived hydrolysis product is a crude trinitronaphthalene-2,7-diamine, m. p. 330° (explosive decomp.) (Found: C, 42·2; H, 2·8. $C_{10}H_7N_5O_6$ requires C, 41·0; H, 2·4%).

Nitration of 2,7-*diacetamidonaphthalene.* Fuming nitric acid (2 c.c.) in acetic acid (2 c.c.) was added to a warm solution of the compound (2 g.) in acetic acid (25 c.c.). The dark mixture soon set to a paste of needles, m. p. *ca.* 130° (2·2 g.). By repeated recrystallisation from acetic acid this product gave the 1,8-*dinitro-derivative* as stout needles, m. p. 303° (decomp.) (Found: C, 51·1; H, 3·6. $C_{14}H_{12}N_4O_6$ requires C, 50·6; H, 3·6%), identical with the product of acetylation (Ac_2O–H_2SO_4) of the 1,8-dinitro-base described above, and the 1-*nitro-derivative*, which crystallised from ethanol in prisms, m. p. 232° (the prisms obtained from acetic acid have solvent of crystallisation) (Found: C, 58·6; H, 4·4. $C_{14}H_{13}N_3O_4$ requires C, 58·5; H, 4·5%). The latter product was hydrolysed by ethanolic potassium hydroxide to 1-nitronaphthalene-2,7-diamine, which crystallised from aqueous ethanol in brown needles, m. p. 204°, in agreement with Hey and Lawton's description.[4]

Nitration of 2,7-*dibenzamidonaphthalene.* This amide (2·5 g.) was added slowly to a mixture of fuming nitric acid (15 c.c.) and acetic acid (15 c.c.). Crystals began to appear before the addition was complete and after ½ hr. they were removed (2·5 g.; m. p. 262°) and recrystallised from a large bulk of acetic acid to give the 1,8-*dinitro-derivative* as canary-yellow prisms, m. p. 265° (Found: C, 63·2; H, 3·0. $C_{24}H_{16}N_6O_4$ requires C, 63·2; H, 3·5%), identical with the compound obtained by the interaction of 1,8-dinitronaphthalene-2,7-diamine (above) with benzoyl chloride in pyridine (any unchanged base was readily removed by acetone).

2,7-Dibenzamidonaphthalene, obtained by benzoylation of the base in pyridine, crystallised from a large bulk of acetic acid in needles, m. p. 280° (lit.,[5] 267°).

Deamination of 1,8-*dinitro*-2,7-*ditoluene*-p-*sulphonamidonaphthalene.* Sodium nitrite (0·6 g.) in sulphuric acid (2·5 c.c.) was added to a cold solution of the compound (4·2 g.) in sulphuric acid (8·5 c.c.), and the mixture poured into cold acetic acid (16 c.c.). The product was introduced slowly into a stirred suspension of cuprous oxide (4 g.) in ethanol (40 c.c.). Water (300 c.c.) was then added, and the precipitate filtered off, dried, and extracted with ethylene dichloride. On concentration of the extract there was obtained material, m. p. 200—210°, which after recrystallisation from ethanolic pyridine formed needles, m. p. 218—220°. It was identified as 1,8-dinitro-2-naphthylamine by mixed m. p. and infrared spectrum, and by acetylation to give the acetyl derivative, m. p. and mixed m. p. 235°. The author is indebted to Dr. E. R. Ward for the sample of 1,8-dinitro-2-naphthylamine.

Use of twice the above amount of sodium nitrite in the above experiment, in an attempt to prepare 1,8-dinitronaphthalene, led only to tar.

Interaction of 2,7-*dimethoxy*-1,8-*dinitronaphthalene with ammonia.* The compound (2 g.) was heated with an ethanolic solution (40 c.c.) of ammonia at 200° for 4 hr. After cooling, the liquid was filled with large red crystals, m. p. 296° (decomp.), best freed from a small amount of black impurity by extraction (Soxhlet) with acetone. The ammoniacal filtrate on evaporation gave a further crop of the same material. The infrared spectrum accorded with that of 1,8-dinitronaphthalene-2,7-diamine (above). On acetylation it gave the diacetyl derivative, m. p. and mixed m. p. 302°, and on benzoylation the dibenzoyl derivative, m. p. and mixed m. p. 265°.

[5] Windaus, *Ber.*, 1924, **57**, 1737.

When the above experiment was carried out at 190° the amount of crystals was smaller and evaporation of the ammoniacal solution gave material of m. p. 265° (decomp.). This gave acetyl and benzoyl derivatives of considerably lower m. p.s than those recorded above. When this product was recrystallised from *o*-dichlorobenzene it was gradually separated into the dinitro-diamine (above) and 1,8-*dinitro*-7-*methoxy*-2-*naphthylamine*, which crystallised from acetic acid in orange-red needles, m. p. 186—188° (Found: C, 50·3; H, 3·5. $C_{11}H_9N_3O_5$ requires C, 50·2; H, 3·4%) (acetyl derivative, needles, m. p. 228°). It is believed that Fischer and Kern [2] accepted this mixture of compounds as 1,8-dinitronaphthalene-2,7-diamine.

Bromination of 2,7-*ditoluene*-p-*sulphonamidonaphthalene*. (*a*) *N*-Bromosuccinimide (0·9 g.) was added to a cold solution of the compound (1 g.) in pyridine. After ¼ hr. the mixture was decomposed by dilute hydrochloric acid, and the product was purified by repeated recrystallisation from acetic acid. The *dibromo-derivative* was obtained as needles, m. p. 215° (Found: C, 46·7; H, 3·1. $C_{24}H_{20}Br_2N_2O_4S_2$ requires C, 46·1; H, 3·2%) (large depression on admixture with the 1-bromo-derivative, m. p. 213°). When this dibromo-compound was treated in pyridine with *N*-bromosuccinimide it was converted into a dark resin. Attempted hydrolysis by cold sulphuric acid led to black sparingly soluble decomposition products.

(*b*) Bromination in chloroform [1] gave only the 1-bromo-derivative, m. p. 213°, alternatively prepared by the interaction of bromonaphthalene-2,7-diamine [1] with toluene-*p*-sulphonyl chloride.

Bromination of 2,7-*diacetamidonaphthalene*. Bromine (2·8 g.) in acetic acid (2 c.c.) was added to a hot solution of the compound (2 g.) in acetic acid (25 c.c.). The liquid became filled immediately with a yellow precipitate [4·2 g.; m. p. 160—170° (decomp.)] (Found: C, 30·4; H, 2·5. $C_{14}H_{14}Br_4N_2O_2$ requires C, 29·9; H, 2·5%). When this was boiled with ethanol the yellow colour was immediately discharged to produce material of m. p. *ca.* 235° (1·4 g.), which after several recrystallisations from acetic acid gave the 1-*bromo-derivative* in needles, m. p. 250°, identical with the compound obtained by the acetylation of 1-bromonaphthalene-2,7-diamine [1] (Found: C, 51·8; H, 3·9. $C_{14}H_{13}BrN_2O_2$ requires C, 52·3; H, 4·0%). A similar result was obtained by dissolution of the addition compound in pyridine.

Chlorination of 2,7-*diacetamidonaphthalene*. An excess of sulphuryl chloride was added to a suspension of the compound in chloroform, and the mixture was evaporated. The almost pure residue crystallised from acetic acid, to give the 1,8-*dichloro-derivative* as needles, m. p. 310° (Found: C, 54·3; H, 3·9. $C_{14}H_{12}Cl_2N_2O_2$ requires C, 54·0; H, 3·9%), identical with the product of acetylation of 1,8-dichloronaphthalene-2,7-diamine.[1]

Chlorination of 2,7-*ditoluene*-p-*sulphonamidonaphthalene*. (*a*) The compound was treated with an excess of sulphuryl chloride and after the initial reaction the excess was distilled off. The residue, on recrystallisation from acetic acid, gave 1,1,8,8-tetrachloro-1,2,7,8-tetrahydro-2,7-ditoluene-*p*-sulphonamidonaphthalene [1] in almost quantitative yield.

(*b*) Addition of sulphuryl chloride (2 mol.) to a warm suspension of the compound in chloroform resulted in a high yield of 1,8-dichloro-2,7-ditoluene-*p*-sulphonamidonaphthalene, m. p. 219°.[1]

Nitration of 2,3-*ditoluene*-p-*sulphonamidonaphthalene*. Fuming nitric acid (2 c.c.) mixed with acetic acid (2 c.c.) was added to the compound [1] (1 g.) in hot acetic acid (20 c.c.). After 1 hr. the product was filtered off and recrystallised from acetic acid to yield the *dinitro-derivative* as cream needles, m. p. 233° (decomp.) (Found: C, 51·6; H, 3·3. $C_{24}H_{20}N_4O_8S_2$ requires C, 51·8; H, 3·6%). By dissolution in cold concentrated sulphuric acid this gave 1?,4?-*dinitronaphthalene*-2,3-*diamine* as orange-red needles, m. p. 222° (from *o*-dichlorobenzene) (Found: C, 49·0; H, 3·2. $C_{10}H_8N_4O_4$ requires C, 48·4; H, 3·2%).

Bromination of 2,3-*ditoluene*-p-*sulphonamidonaphthalene*. (*a*) Bromine (2·1 g.) in acetic acid (1 c.c.) was added to a warm solution of the compound (3 g.) in acetic acid (30 c.c.). No crystallisation occurred (overnight), so the liquid was poured into water; a bright yellow precipitate separated. It was not possible to recrystallise this without decomposition, which yielded either the monobromo- or the dibromo-derivative (below) and resin.

(*b*) Bromine (1·2 g.) in chloroform (3 c.c.) was added to a hot solution of the compound (3·3 g.) in chloroform (30 c.c.). The mixture was boiled for a short time and then distilled to small bulk and diluted with light petroleum. The resultant dark sticky material, on repeated recrystallisation from ethanol, gave a somewhat impure monobromo-derivative as prisms, m. p. 174—176° (Found: C, 53·8; H, 3·7. Calc. for $C_{24}H_{21}BrN_2O_4S$: C, 52·8; H, 3·8%).

(*c*) Addition of *N*-bromosuccinimide (2 mol.) to the compound in pyridine led to an almost

quantitative yield of the 1?,4?-*dibromo-derivative*, which formed needles, m. p. 244°, from acetic acid (Found: C, 46·1; H, 3·3. $C_{24}H_{20}Br_2N_2O_4S_2$ requires C, 46·1; H, 3·2%).

The author is indebted to Dr. K. R. Buck for the infrared spectra and to the Carnegie Trust for the Universities of Scotland for a grant.

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824. *A Convenient New Method of Aromatic Arylation.*

By J. I. G. CADOGAN.

ARYLATION of atomatic compounds is generally effected by free-radical methods, of which many have been recorded in the literature.[1] In general, aryl radicals are obtained from either primary amines by way of azo- and diazo-derivatives or from carboxylic acids, through derivatives such as the corresponding peroxide or lead salt. Reagents of both classes have been widely used but there are many associated disadvantages, such as the unavailability of some carboxylic acids and the low yields of arylated products obtained in these cases. Of the former class of reactions, the Gomberg–Hey process, in which an aqueous diazotised amine is allowed to decompose at pH $\geqslant$8 in the presence of the aromatic compound to be arylated, is probably the best known. The low yields which can occur in this reaction can be attributed to the heterogeneity of the reaction as well as to the instability of the diazonium solution, which leads to side reactions and hence to the notorious tarry side products. These disadvantages have now been overcome by the use of pentyl nitrite as the diazotising reagent. It has now been shown that a selection of primary aromatic amines react with pentyl nitrite in an excess of benzene, in the *absence* of added acid to give, after a few hours at 60—80°, good yields of the corresponding biaryl, ArPh. The method is particularly satisfactory in the cases of amines, such as 3-aminopyridine, 3-aminoquinoline, and anisidine, which do not give high yields of the corresponding biaryl, *e.g.*, 3-phenylpyridine, in the Gomberg–Hey reaction.

The use of alkyl nitrites in the production of diazonium salts from protonated amines is well known [2] but little has been reported about its reactions with free amines. Griess [3] and Meyer and Ambuhl [4] found that such reactions led to the formation of diazoamino-compounds and, since it has been shown that thermal decomposition of such compounds gives aryl radicals,[5] it is tempting to invoke formation and subsequent decomposition of diazoaminobenzenes in our reactions. That this is unlikely, however, follows from the low temperature at which decomposition occurs in reactions with pentyl nitrite, compared with those necessary to induce homolysis of the corresponding diazoamino-compounds. Further, no products arising from reaction of arylamino-radicals, Ar·NH·, which are formed from diazoamino-compounds, were detected in experiments with pentyl nitrite.

Although this reaction has not been exhaustively investigated it appears to afford the simplest one-step route to biaryls yet recorded.

Experimental.—Commercial pentyl nitrite was used without purification.

The method is exemplified as follows: *p*-Chloroaniline (7 g.), benzene (200 ml.), and pentyl nitrite (9 g.) were warmed until a vigorous reaction with evolution of gas set in. This was allowed to proceed without heating until it had subsided (20 min.) and the mixture was boiled under reflux for a further 100 min. The excess of benzene and the low-boiling products were removed under reduced pressure and the residue was distilled, to give 4-chlorobiphenyl (b. p. 106°/0·1 mm.; 5·45 g.), m. p. and mixed m. p. 76° (from ethanol). A high-boiling residue was present.

The following reactions of aromatic amines with benzene and pentyl nitrite were similarly

[1] See Williams, " Homolytic Aromatic Substitution," Pergamon Press, London, 1960.
[2] See Zollinger, " Azo and Diazo Chemistry," Interscience, New York, 1961.
[3] Griess, *J.*, 1865, **18**, 298.
[4] Meyer and Ambuhl, *Ber.*, 1875, **8**, 1074.
[5] Hardie and Thompson, *J.*, 1958, 1286.

carried out: Aniline gave biphenyl (b. p. 60°/0·1 mm., m. p. and mixed m. p. 68°; 50%); 3-aminopyridine gave 3-phenylpyridine (b. p. 80°/0·1 mm.; 52%; picrate, m. p. and mixed m. p. 158—162°); *p*-anisidine gave 4-methoxybiphenyl (b. p. 118°/0·1 mm., m. p. and mixed m. p. 90°; 33%); 3-aminoquinoline gave 3-phenylquinoline (b. p. 134°/0·1 mm., m. p. and mixed m. p. 49—52°; 35%; picrate, m. p. 205° undepressed on admixture with authentic material of m. p. 209°).

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825. *A Dielectric Study of* $(PNCl_2)_3$, $(PNCl_2)_4$, *and* $(PNF_2)_4$.

By GAYNOR CORFIELD.

WITH the aims of assessing any dipole moment possessed by the compounds $(PNCl_2)_3$, $(PNCl_2)_4$, and $(PNF_2)_4$, and any intramolecular flexibility of their rings, these three compounds have been studied in benzene solution.

The dielectric parameters ε' and ε'', *i.e.*, the dielectric constant and the dielectric absorption factors, at frequencies up to $8{\cdot}5 \times 10^9$ c./sec. (3·4 cm. wavelength) have been measured at frequencies of 350, 540, 900, 3000, and 8500×10^6 c./sec. The methods were adaptations (described elsewhere [1]) of the standard Roberts–von Hippel procedures appropriate for coaxial line and wave-guide systems, with both fixed and movable short-circuit terminations.

Owing to the low polarity of the compounds concentrated solutions were desirable and the stock solutions contained the following weights of solute per 100 ml. of benzene: $(PNCl_2)_3$ 19·9 g.; $(PNCl_2)_4$ 14·8 g.; $(PNF_2)_4$ 19·0 g.

The dielectric properties of these solutions were scarcely different from that of the solvent benzene. The dielectric increment, $\Delta\varepsilon' = (\varepsilon'_{\text{solution}} - \varepsilon'_{\text{solvent}})$ varied from 0·02 to 0·06, the uncertainty in the individual ε' values at these frequencies being $\pm 0{\cdot}02$. These small increments, if real, could be due to a small dipole moment in the solute or a change in the polarizability of the medium (incorporating any change in density).

The dielectric absorption factor differentiates between these two factors: in simple instances it varies with the dipole moment (μ), the frequency ($\omega = 2\pi \times$ the frequency in c./sec.), and molar concentration (c) according to the Debye relation.

$$\varepsilon'' = \frac{(\varepsilon' + 2)^2 N\pi}{6750kT} \cdot \frac{\mu^2 C}{1} \cdot \frac{\omega\tau}{1 + \omega^2\tau^2}.$$

Usually this relation provides a means of estimating τ, the relaxation time (or reciprocal of the rate constant for the decay) of the dipole polarization when the dipole moment is known. However, in the present instances, it seems more significant to evaluate μ (effective) from an estimated τ value. Molecules of the sizes involved here have values [2] in benzene of $\tau = 15 \pm 5 \times 10^{-12}$ sec. (this range shown is generous). Using the median τ value and the maximum values of ε''/ω suggested by the results gives the following maximum values for μ (in D): $(PNCl_2)_3$ 0·14; $(PNCl_2)_4$ 0·20; $(PNF_2)_3$ 0·1; the values are almost certainly less than these, indicating the close approximation of the molecular structures to non-polarity, *i.e.*, to highly symmetrical or planar forms.

It is perhaps disappointing that no precise dipole moments and relaxation times have been evaluated, but it must be emphasized that the polarity of these compounds is so small that the most significant expression of the results is given by their maximum possible dipole moments.

Messrs. Midland Silicones Ltd. are thanked for providing the compounds.

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[1] Williams, *J. Phys. Chem.*, 1959, **63**, 534; Corfield, Horzelski, and Price, *Brit. J. Appl. Phys.*, 1961, **12**, 680.
[2] Davies, *Quart. Rev.*, 1954, **8**, 250.

826. *Orientational Control in Acid Media.*

By María L. Cortés and Gabriel Chuchani.

Tetraphenylmethane undergoes fission by strong acid,[1] producing appreciable amounts of triphenylmethanol, in some cases with triphenylmethane. This raises a possible objection to the conclusion, based on competition of aniline and phenol in similar acid media,[2] that an amino- is more efficient than a hydroxyl group in orientational control, since, under the conditions used, the trityl group may be thought to be transferred to the other competing compound. Accordingly, aniline was refluxed in an acid medium with *p*-tritylphenol for a week, and phenol with *p*-tritylaniline. No reaction occurred, except in one case where a small amount of 9-phenylfluorene was isolated. Competition experiments of amine and phenol gave the results tabulated. This work shows that the use of acid media for tritylation does not affect our recent conclusions [3] and supports the view [2] that the amino-group of the anilines is probably free at the moment of condensation.

Experimental.—p-*Tritylaniline and phenol.* A mixture of *p*-tritylaniline [4] (0·01 mole), phenol (0·05 mole), glacial acetic acid (50 ml.), and concentrated sulphuric acid (4 ml.) was refluxed for a week, then diluted with water (400 ml.) and treated with 50% sodium hydroxide solution until no more precipitate was formed. The solid was dried and dissolved in benzene and separated chromatographically (75 g. of Woelm alumina, grade 1). Elution with benzene gave 9-phenylfluorene (0·0015 mole), m. p. 144—145° alone or mixed with an authentic sample.[5] 81% of the *p*-tritylated aniline was recovered by elution with chloroform.

The above reaction with concentrated hydrochloric acid (8 ml.), and reaction between aniline and *p*-tritylphenol in either acid, showed no change (chromatographic separation).

Competition of amines *o*-R·C_6H_4·NH_2 and phenols *o*-R·C_6H_4·OH for triphenylmethanol.

	4-Trityl-amine isolated (%) by			4-Trityl-amine isolated (%) by	
R	Acid	KOH–EtOH *	Chromatography	Acid	KOH–EtOH *	Chromatography
MeO	HCl	63 †	83	H_2SO_4	70 †	83
Me	,,	74 †	86	,,	77	83
Cl	,,	93	85	,,	87	77
H	,,	82 ‡	80	,,	75 ‡	82

Products were identified by mixed m. p.s (cf. ref. 3). * Average of 3 runs each. † Traces of $CHPh_3$ also obtained. ‡ From Chuchani; [2] in these cases 0·5% (H_2SO_4) and 2% (HCl) of tritylated phenol was isolated, but none was obtained in the other cases.

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[*Received, April 16th*, 1962.]

[1] Boyd and Hardy, *J.*, 1928, 630; Hardy, *J.*, 1929, 1000.
[2] Chuchani, *J.*, 1961, 575.
[3] Cortés and Chuchani, *J. Org. Chem.*, 1962, **27**, 125.
[4] MacKenzie and Chuchani, *J. Org. Chem.*, 1955, **20**, 336.
[5] Kliegl, *Ber.*, 1905, **38**, 284.

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827. *The Use of Chloromercurates to Facilitate the Infrared Examination of Bases (Exemplified by Tetrahydropyrimidines).*

By R. F. Evans.

Recent work has illustrated the advantages of using complex metal halide salts instead of hydrohalides in the measurement of the infrared spectra of amine salts. In such salts as the tetrachloroborates,[1] tetrafluoroborates,[2] hexafluorophosphates,[2] hexachloroantimonates,[3] -stannates,[3] -platinates,[3,4] and -plumbates,[2] and tetrachloro-[4,5] and tetrabromo-aurates,[5] the effects of hydrogen bonding are minimised, so that the spectrum observed in the 700—4000 cm.$^{-1}$ region is that of the amine cation undistorted by hydrogen

[1] Kynaston, Larcombe, and Turner, *J.*, 1960, 1772.
[2] Nuttall, Sharp, and Waddington, *J.*, 1960, 4965.
[3] Mecke and Kutzelnigg, *Spectrochim. Acta*, 1960, **16**, 1216, 1225; 1961, **17**, 530; *Chem. Ber.*, 1961, **94**, 1706.
[4] Brown and Evans, *J.*, 1962, 527.
[5] Schöpf, Koop, and Werner, *Chem. Ber.*, 1960, **93**, 2457.

bonding. An additional advantage is that these complex anions rarely absorb in this region. In order to observe the infrared spectra of the cations of compounds with very weakly basic centres, the latter must be protonated with strong acids; the salts with complex metal halogen acids will be more stable [6] and readily isolable than those with the simple hydrohalogen acids, since the latter have a greater tendency to lose hydrogen halide by hydrolysis and volatilisation. Certain unsaturated cations [5] retain their identity in salts with metal halide anions only; with the hydrohalides, the chemical nature of the cation has been altered by addition of water or alcohol across the double bond.

Since chloromercurates were found to give satisfactory results in the pyridine series,[7] infrared studies with these complex salts were continued in the 1,4,5,6-tetrahydropyrimidine field. Admixture of equivalent quantities of the (usually deliquescent) hydropyrimidine hydrochloride and mercuric chloride in methanol usually precipitated the non-hygroscopic trichloromercurate. Occasionally tetrachloromercurates and higher complexes were also formed but these gave closely similar values for the frequencies of vibration of the cation. The chloromercurates were readily decomposed in aqueous-methanolic solution by hydrogen sulphide, to give the hydrochlorides which were easily converted into other salts, such as the picrates, by double decomposition.

For comparative purposes, salts of 1,4,5,6-tetrahydropyrimidine derivatives with other complex chloro-acids were prepared. The preparation of the hexachloroantimonate involved the use of a fuming liquid, antimony pentachloride, and the resulting salt lost hydrogen chloride. A suitable specimen for analysis could be obtained only by drying it in an atmosphere of hydrogen chloride.[8] Unlike the chloromercurates, the hexachloroplatinates, *e.g.*, that of 2-amino-1,4,5,6-tetrahydropyrimidine, could not be recrystallised from methanol, since the solvent reduced the anion of the salt to the tetrachloroplatinate: the cation was not affected during this process. The infrared spectra of the chloroplatinates were preferably measured in potassium or silver chloride discs because, in potassium bromide discs, double decomposition giving potassium chloroplatinate and amine hydrobromide sometimes occurred. Similar double decompositions had been observed with amine perchlorates,[9] but no such effect was observed with the chloromercurates.

Infrared data from a representative collection of salts are given in the Table. All the complex anions used brought about a general sharpening of the bands in the spectrum. The most striking change occurred in the N–H stretching region, where the two broad intense bands of the hydrochloride, spread over several hundred cm.$^{-1}$, were replaced by one sharp intense peak. In a large complex anion MCl_n^-, the negative charge is shared by several chlorine atoms so that the contribution of the electrostatic component $^+N–H \cdots Cl^-$, which is the major contributing structure to the hydrogen bond in ammonium salts,[10] would be greatly diminished. Hence there should be a correlation between the fractional negative charge on the chlorine in the complex anion and the strength of the hydrogen bond. The greater the fractional negative charge, the stronger should be the hydrogen bond which would lead to a lower value for the ν(N–H) frequency. From the Table, it will be seen that the value of ν(N–H) did have a tendency to decrease on proceeding from 1,4,5,6-tetrahydropyrimidine hexachloroantimonate (in which each chlorine atom bears a fractional negative charge of 1/6) *via* the chloroaurate (1/4) to the hexachloroplatinate and the trichloromercurate (charge 1/3 in each case). In examples where a tetrachloromercurate was also formed (charge 1/2), a further drop in ν(N–H) was observed. A similar drop occurred in going from the hexa- to the tetra-chloroplatinate of 2-amino-1,4,5,6-tetrahydropyrimidine.

To see whether the size of the anion in these complex halide salts had an effect on the hydrogen bonding, the bromine and iodine analogues of 1,4,5,6-tetrahydropyrimidine

[6] Klages and Wolf, *Chem. Ber.*, 1959, **92**, 1842.
[7] Evans and Kynaston, *J.*, 1962, 1005.
[8] White, personal communication.
[9] Werner and Keller, *Chem. Ber.*, 1960, **93**, 1274.
[10] Chenon and Sandorfy, *Canad. J. Chem.*, 1958, **36**, 1181.

Infrared spectra (cm.$^{-1}$) of 1,4,5,6-tetrahydropyrimidine derivatives.

1,4,5,6-Tetrahydropyrimidine derivative	Fractional negative charge per halogen atom	ν(as N–C–N)	ν(NH)	δNH
Parent				
Hydrochloride	1	1675	3170, 2970	1587
Hexachloroantimonate	1/6	1690	3390	1572
Tetrachloroaurate	1/4	1690	3340	1575
Hexachloroplatinate	1/3	1693	3310	1575
Trichloromercurate	1/3	1684	3300	1569
Hydrobromide	1	1675	3120, 2980	1587
Tribromomercurate	1/3	1690	3325	1573
Hydriodide	1	1685	3200, 2990	1573
Tetraiodomercurate	1/2	1687	3300	1564
2-t-Butyl				
Hydrochloride	1	1631	3170	1600
Trichloromercurate	1/3	1635	3300	1597
Tetrachloromercurate	1/2	1637	3280	1597
2-Amino				
Hydrochloride	1		3240	
Hexachloroantimonate	1/6		3400	
Pentachlorodimercurate	1/5		3330	
Hexachloroplatinate	1/3		3310	
Tetrachloroplatinate	1/2		3300	

chloromercurate were examined. Compared with the trichloromercurate, there had been a decrease in the strength of the hydrogen bonding in the bromomercurate, which has the larger anion. The tri-iodomercurate, which would have the largest anion, could not be obtained; the iodo-derivative formed under a variety of conditions was the tetraiodomercurate.

For all substances examined, the most intense band of the spectrum was the asymmetric N–C–N stretching band; its frequency was slightly raised when the anion was only weakly hydrogen-bonding. The NH deformation frequency around 1580 cm.$^{-1}$ was lowered slightly as the hydrogen bonding in the salt became weaker. With the 2-amino-compounds, band overlap in the 1600—1700 cm.$^{-1}$ region made assignment uncertain.

Experimental.—Analyses are by Dr. J. E. Fildes and her staff. The preparation of most of the tetrahydropyrimidine salts has been described elsewhere.[4,11]

1,4,5,6-*Tetrahydropyrimidine hexachloroantimonate* was obtained by mixing a solution of the hydrochloride (0·3 g.) in water (1 ml.) with a 10% solution of antimony pentachloride in concentrated hydrochloric acid (5 ml.). Crystallisation from concentrated hydrochloric acid at −15° afforded a specimen of m. p. 244—252° (decomp.) (Found: C, 11·5; H, 2·25; N, 6·5. $C_4H_9Cl_6N_2Sb$ requires C, 11·4; H, 2·2; N, 6·7%). The *tribromomercurate* (from equivalent quantities of the hydrobromide and mercuric bromide in methanol–ethanol) formed needles, m. p. 162—164° (Found: C, 9·2; H, 1·8; Br, 45·5; N, 5·3. $C_4H_9Br_3HgN_2$ requires C, 9·1; H, 1·7; Br, 45·6; N, 5·3%). The *tetraiodomercurate*, from the hydriodide and mercuric iodide in ethanol, formed yellow-green crystals, m. p. 269—270° (Found: C, 11·0; H, 2·1; I, 58·1; N, 6·3. $C_8H_{18}HgI_4N_4$ requires C, 10·9; H, 2·1; I, 57·8; N, 6·4%).

2-*Amino*-1,4,5,6-*tetrahydropyrimidine hexachloroantimonate*, obtained from the hydrochloride and antimony pentachloride in concentrated hydrochloric acid, had m. p. 226—229° (decomp.) (Found: C, 11·05; H, 2·3; Cl, 48·9; N, 9·7. $C_4H_{10}Cl_6N_3Sb$ requires C, 11·1; H, 2·6; Cl, 48·4; N, 9·7%). The *hexachloroplatinate*, precipitated when cold methanolic solutions of the hydrochloride and chloroplatinic acid were mixed, was a buff-coloured solid, m. p. 186—191° (decomp.) (Found: C, 15·9; H, 3·3; Cl, 35·1; Pt, 32·05. $C_8H_{20}Cl_6N_6Pt$ requires C, 15·8; H, 3·3; Cl, 35·0; Pt, 32·1%). On recrystallisation from methanol–ethyl acetate, the red *tetrachloroplatinate*, m. p. 186° (decomp.), was formed and this depressed the m. p. of the hexachloroplatinate (Found: C, 18·1; H, 4·0; Cl, 26·9; Pt, 36·25. $C_8H_{20}Cl_4N_6Pt$ requires C, 17·9; H, 3·8; Cl, 26·4; Pt, 36·3%). The *pentachlorodimercurate*, m. p. 117—118·5°, crystallised from methanol containing the hydrochloride and mercuric chloride in 1 : 3 molecular proportions (Found: C, 7·3; H, 1·5; Cl, 26·1; Hg, 58·7; N, 5·9. $C_4H_{10}Cl_5Hg_2N_3$ requires C, 7·1; H, 1·5; Cl, 26·1; Hg, 59·1; N, 6·2%). Hydrogen sulphide was passed into a solution of the chloromercurate (0·05 g.) in water (1 ml.) and methanol (5 ml.), and the mercuric

[11] Brown and Evans, *J.*, 1962, in the press.

sulphide was filtered off. The filtrate with picric acid yielded 2-amino-1,4,5,6-tetrahydropyrimidine picrate, m. p. and mixed m. p. 185—186°.[12]

The infrared spectra were determined with a Perkin–Elmer 21 double-beam spectrophotometer fitted with a sodium chloride prism. The hydropyrimidine salts were examined in potassium bromide discs, except for the chloroplatinates which were examined in potassium chloride discs.

I thank Professor A. N. Hambly, Dr. E. Spinner, and Mr. J. C. B. White for helpful discussion.

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Canberra, Australia. [*Received, May 7th*, 1962.]

[12] Hafner and Evans, *J. Org. Chem.*, 1959, **24**, 1157.

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828. *Constituents of the Lipids of Tubercle Bacilli. Part IX.**

By N. Polgar and W. Smith.

In previous studies[1] of the lipids of tubercle bacilli (human strains) the methanol-soluble acids, resulting from partial hydrolysis of the lipid extracts, gave on ester fractionation followed by chromatography (over silica) of the higher-boiling methyl ester fraction (i) a fraction which was dextrorotatory and has been subjected to the studies on mycolipenic acid already described,[1-3] and (ii) a more strongly adsorbed fraction showing no measurable optical rotation. A preliminary study of fraction (ii) is now reported.

The methyl esters, b. p. >150°/0·1 mm., obtained essentially by the procedure described earlier,[1] were passed over silica; the infrared spectra of the more strongly adsorbed fractions showed the presence of ketone and hydroxyl groups in addition to the ester grouping. These fractions, when distilled, chromatographed on alumina, and subsequently crystallised at low temperature, produced from certain eluates (see Experimental) crystals *A*, m. p. 45—46°, and *B*, m. p. 52—54°, and a wax *C*, m. p. 40—44°. Product *A* was identified as methyl 10-oxostearate by oxidative degradation and by comparison with an authentic specimen; *B*, showing $[\alpha]_D$ −0·25°, was found, by oxidative degradation, to be methyl (—)-10-hydroxystearate. Examination of *C* by vapour-phase chromatography showed the presence of *A* and *B* (as minor components) together with five other components with greater retention times. More detailed study of the ester fraction is desirable in view of the possible significance of the parent acids as metabolic intermediates.

Experimental.—Petrol refers to light petroleum, b. p. 40—60°. The alumina used for chromatography was acid-washed and standardised according to Brockmann and Schodder.[4] Vapour-phase chromatography was carried out on a Pve Argon Chromatograph with a 4-ft. column containing 10% " Apiezon L " on " Embacel."

Isolation of esters A, B, *and* C. The methanol-soluble acids, obtained on partial hydrolysis of the acetone and isopropyl ether extracts of tubercle bacilli,[1] were converted by the action of 5% methanolic sulphuric acid into their methyl esters. The esters having b. p. <150°/0·1 mm. were removed by distillation through a 15-cm. column packed with wire-gauze rings, and the residue worked up as follows.

A 46-g. portion was chromatographed in petrol on silica (400 g.). The following fractions were taken: (1) petrol (550 ml.) (22·34 g.); (2) petrol (600 ml.) (5·48 g.); (3) ether (800 ml.) (17·87 g.) (99% recovery). Fraction 1 corresponds to the crude mixture of dextrorotatory αβ-unsaturated methyl esters.[1] Fraction (2) showed bands at 3333w (hydroxyl), 1739s (ester), 1709s (ketone), and 1639w cm.$^{-1}$ (conjugated C=C), whilst fraction (3) showed bands at 3333s, 1739s, 1709w, and 1639s cm.$^{-1}$. Fractions (2) and (3) were combined and distilled: material having b. p. <127°/0·01 mm. (4·28 g.) showed in its infrared spectrum the band at 1739 cm.$^{-1}$ (s) (ester) and a weak band at 3333 cm.$^{-1}$ (OH); the material boiling >127°/0·01 mm. (11·97 g.) showed strong bands at 3333 cm.$^{-1}$ (OH) and 1709 cm.$^{-1}$ (ketone).

* Part VIII, Morgan and Polgar, *J.*, 1957, 3779.

[1] Chanley and Polgar, *J.*, 1954, 1003.
[2] Polgar, *J.*, 1954, 1008.
[3] Millin and Polgar, *J.*, 1958, 1902.
[4] Brockmann and Schodder, *Ber.*, 1941, **74**, 73.

The higher-boiling material was chromatographed in petrol on alumina (activity III; 400 g.) and the following fractions were collected: (a) petrol (800 ml.) (7·2 g.); (b) petrol (600 ml.) (0·55 g.); (c) petrol–ether (9 : 1; 200 ml.) (0·41 g.); (d) petrol–ether (5 : 1; 400 ml.) (1·3 g.); (e) ether (600 ml.) (2·03 g.) (95·5% recovery). A solution of fraction (d) in petrol at −6° slowly deposited crystals *A*, m. p. 45—46°; their infrared spectrum showed carbonyl bands (of equal intensity) at 1739 (ester) and 1709 cm.$^{-1}$ (ketone). From a solution of fraction (e) in petrol at −6° crystals *B*, m. p. 49—50°, were obtained, showing in their infrared spectrum a very strong band at 3333 cm.$^{-1}$ (OH) and only a single carbonyl band at 1739 cm.$^{-1}$. The mother liquors of *A* and *B* were combined with fractions (b) and (c), and the whole (4·03 g.) chromatographed in petrol on alumina (activity III/IV; 200 g.). On elution with benzene–petrol (1 : 1) the first eluates yielded more *A*; the later eluates deposited from petrol at −6° a pale yellow wax *C*, m. p. 40—44°, which showed in its infrared spectrum a band at 3571 cm.$^{-1}$ (OH). Further elution with benzene–ether (10 : 1) gave material containing *B*.

Ester A. This ester (Found: C, 73·0; H, 11·6. Calc. for $C_{19}H_{36}O_3$: C, 73·0; H, 11·6%) showed no depression of m. p. on admixture with authentic methyl 10-oxostearate (m. p. 45—46°) (Bergström *et al.*[5] give m. p. 45·8—46·1°). Vapour-phase chromatography showed that it was homogeneous. Its structure was confirmed by oxidation with chromic oxide in glacial acetic acid at 40° for 16 hr.; the methyl esters of the acidic products (prepared with ethereal diazomethane) showed on vapour-phase chromatography (199°) the presence of two major components having retention times identical with those of dimethyl azelate and sebacate (there were no components with longer retention times). In a comparative experiment, similar oxidation of methyl 12-oxostearate gave dimethyl undecanedioate and dodecanedioate.

Ester B. After recrystallisation from petrol this had m. p. 52—54°, $[\alpha]_D^{22}$ −0·25° ± 0·05° (*c* 6·45 in chloroform; *l*, 0·2) (photoelectric polarimeter) (Found: C, 72·5; H, 12·1. Calc. for $C_{19}H_{38}O_3$: C, 72·6; H, 12·2%). Vapour-phase chromatography (250°; flow-rate, 30 ml./min.) indicated that the product was a single compound (retention time, 7·6 min.; retention time of a sample of methyl 12-hydroxystearate, 7·7 min.). Oxidation with chromic oxide in glacial acetic acid at 40° for 16 hr., followed by conversion of the resulting acids into their methyl esters, gave a mixture of two major components whose retention times (vapour-phase chromatography at 197°; flow-rate, 35 ml./min.) were 7·4 and 11·0 min. (there were no components with longer retention times). Under the same conditions the retention times of dimethyl azelate and sebacate were 7·4 and 11·0 min., respectively. These results indicated that *B* was methyl (−)-10-hydroxystearate.

Ester C. This product (Found: C, 75·6; H, 12·4%) showed a sharp hydroxyl band at 3571 cm.$^{-1}$ which was different from that of the ester *B*. Vapour-phase chromatography (258°; flow-rate, 30 ml./min.) showed the presence of seven compounds, with retention times of 7·1, 8·15, 9·4, 11·2, 12·4, 14·6, and 16·0 min. (14·6 min., retention time of the main component). Under the same conditions the retention times of methyl 10-hydroxystearate, 10-oxostearate, and ricinoleate were 8·15, 7·1, and 7·4 min., respectively.

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[5] Bergström, Aulin-Erdtman, Rolander, Stenhagen, and Östling, *Acta Chem. Scand.*, 1952, **6**, 1157.

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829. *A Synthesis of* (±)-α-*Lipoic Acid from Anisole.*

By B. A. LEWIS and R. A. RAPHAEL.

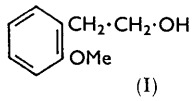
ALTHOUGH many syntheses of α-lipoic acid are now extant,[1] the following route from anisole possesses advantages in simplicity and availability of starting material. Metallation of anisole[2] with butyl-lithium followed by reaction with ethylene oxide gave *o*-2-hydroxyethylanisole (I). Reduction (Birch's method) then yielded the dihydro-compound (II; R = H), which was benzoylated to the corresponding ester (II; R = Bz). Mild acid hydrolysis of this ester produced the conjugated ketone (III), readily reducible to the saturated ketone by catalytic hydrogenation. Baeyer–Villiger oxidation[3] converted the ketone into a mixture of 8-benzoyloxy-6-hydroxyoctanoic acid (IV) and the corresponding ε-lactone (the former predominating). This mixture was then treated directly with

[1] Reed, "Organic Sulfur Compounds," Vol. I, p. 443, Ed. Kharasch, Pergamon Press, London, 1961.

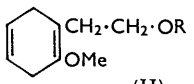
[2] Gilman and Webb, *J. Amer. Chem. Soc.*, 1940, **62**, 987.

[3] Segre, Viterbo, and Parisi, *J. Amer. Chem. Soc.*, 1957, **79**, 3503.

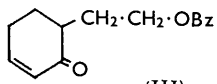
thiourea and hydriodic acid, followed by base, and the resulting crude 6,8-dimercapto-octanoic acid oxidised by ferric chloride to the cyclic disulphide, α-lipoic acid.



(I)



(II)



(III)

$HO_2C\cdot[CH_2]_4\cdot CH(OH)\cdot[CH_2]_2\cdot OBz$ (IV)

Experimental.—Light absorption properties of all compounds were fully compatible with the structures assigned.

o-2-*Hydroxyethylanisole* (I). Anisole (54 g.) in dry ether (100 ml.) was added slowly to a stirred solution of butyl-lithium [from n-butyl bromide (68·5 g.)], the mixture heated under reflux for 15 hr. and cooled. Ethylene oxide (26·4 g.) was allowed to vapourise overnight into the reaction mixture which was then poured into ice–water. Isolation by means of ether followed by drying ($MgSO_4$) and distillation gave the *alcohol* (55 g.; 72%), b. p. 140—148°/18 mm., n_D^{25} 1·5361 (Found: C, 70·5; H, 7·5; OMe, 19·8. $C_9H_{12}O_2$ requires C, 71·0; H, 7·9; OMe, 20·4%). The *α-naphthylurethane* crystallised from light petroleum (b. p. 60—80°) in needles, m. p. 134—135° (Found: C, 75·1; H, 6·4; N, 4·4. $C_{20}H_{19}O_3N$ requires C, 74·7; H, 6·0; N, 4·4%).

3,5-*Dihydro*-2-2′-*hydroxyethylanisole* (II; R = H). To a stirred solution of the above alcohol (45·6 g.) in dry ether (100 ml.) and liquid ammonia (300 ml.) thin strips of lithium metal (9·6 g.) were added during 30 min. After a further 30 min. the blue colour was discharged by dropwise addition of ethanol. Evaporation of the ammonia, isolation with ether, and distillation gave the *dihydro-alcohol* (II) (37·8 g.; 82%), b. p. 126—130°/12 mm., n_D^{29} 1·5070 (Found: C, 69·3; H, 9·0; OMe, 19·6. $C_9H_{14}O_2$ requires C, 70·1; H, 9·1; OMe, 20·1%). The *α-naphthylurethane* crystallised from light petroleum in needles, m. p. 130° (Found: C, 74·5; H, 6·6; N, 4·25. $C_{20}H_{21}O_3N$ requires C, 74·3; H, 6·55; N, 4·3%). Treatment with benzoyl chloride in ether–pyridine furnished an essentially quantitative yield of the *benzoate*, b. p. 170—176°/0·35 mm., n_D^{22} 1·5462 (Found: C, 74·1; H, 7·1; OMe, 12·4. $C_{16}H_{18}O_3$ requires C, 74·4; H, 7·0; OMe, 12·0%).

2-2′-*Benzoyloxyethylcyclohexanone*. The above benzoate (12·9 g.) in ether (100 ml.) was shaken with sulphuric acid (6N; 50 ml.) overnight. Isolation with ether and distillation gave 6-2′-*benzoyloxyethylcyclohex-2-enone* (III) (11·9 g.), b. p. 144—148°/0·04 mm., n_D^{24} 1·5390 (Found: C, 73·5; H, 6·7. $C_{15}H_{16}O_3$ requires C, 73·7; H, 6·6%) [2,4-*dinitrophenylhydrazone*, red needles, m. p. 146—147°, from chloroform (Found: C, 59·0; H, 4·85; N, 13·1. $C_{21}H_{20}O_6N_4$ requires C, 59·4; H, 4·75; N, 13·2%)]. Catalytic hydrogenation of the unsaturated ketone (10 g.) in ethanol over 10% palladium–charcoal gave the saturated *oxo-benzoate* (8·9 g.), b. p. 151—156°/0·1 mm., n_D^{25} 1·5261 (Found: C, 73·2; H, 6·9. $C_{15}H_{18}O_3$ requires C, 73·1; H, 7·3%) [2,4-*dinitrophenylhydrazone*, orange needles, m. p. 134°, from chloroform (Found: C, 58·7; H, 4·8; N, 13·6. $C_{21}H_{22}O_6N_4$ requires C, 59·1; H, 5·2; N, 13·2%)].

α-*Lipoic Acid*. A solution of the saturated oxo-benzoate (2·5 g.) in peracetic acid (40%; 25 ml.) was set aside for 36 hr. and poured into water. Isolation by chloroform and distillation gave a viscous oil (1·78 g.), b. p. 158—168°/10^{-2} mm., whose spectroscopic properties and elementary analysis showed it to be a mixture of the hydroxy-acid (IV) and the corresponding ε-lactone. This product was heated under reflux for 36 hr. with hydriodic acid (55%; 5 g.) and thiourea (3 g.). Aqueous potassium hydroxide (15 ml.; 30%) was then added and the solution heated under reflux for 12 hr. under nitrogen. The cooled solution was extracted with ether and the aqueous layer acidified with dilute sulphuric acid. Isolation by means of chloroform and removal of benzoic acid by sublimation at 60°/10^{-2} mm. gave a yellow residual oil consisting of crude 6,8-dimercapto-octanoic acid (1·4 g.). To a solution of this product in sodium hydroxide (2N; 3 ml.) was added ferric chloride (6 mg.) in water (20 ml.), and oxygen was bubbled through for 12 hr. The solution was shaken with chloroform, the aqueous layer acidified with dilute hydrochloric acid, and the product isolated by extraction with chloroform. Evaporation gave an oil which solidified on trituration with light petroleum. Crystallisation from hexane gave α-lipoic acid (1·1 g.) as yellow needles, m. p. 60—60·5° (Found: C, 46·3; H, 6·5; S, 31·2. Calc. for $C_8H_{14}O_2S_2$: C, 46·6; H, 6·7; S, 31·3%).

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