Tetra-acetylethylene: a New Intermediate for Synthesising Heterocyclic Rings [1]

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Tetra-acetylethylene (I), prepared by oxidation with iodine of the dithallium(I) salt of tetra-acetylethane (II), reacts with hydrazine to give a mixture of 1,4,5,8-tetramethylpyridazino[4,5-*d*]pyridazine (IV) and 6-amino-1,4,5,7-tetramethylpyrrolo[3,4-*d*]pyridazine (V). Treatment of compound (I) with hydrochloric or hydrobromic acid yields furan derivatives, whose structures can be established by chemical and spectroscopic methods. Compound (I) gives a Diels–Alder adduct with 2,3-dimethylbutadiene.

THIS work arose from attempts to synthesise 1,4,5,8-tetramethylpyridazino[4,5-*d*]pyridazine (IV). Pyridazines can be obtained by the reaction of hydrazine with 2,3-unsaturated 1,4-diketones;[2-4] we therefore needed to prepare tetra-acetylethylene (3,4-diacetylhex-3-ene-2,5-dione) (I).

Attempts to prepare this compound from 3-bromoacetylacetone, in alkaline medium, failed. Oxidation, by iodine, of tetra-acetylethane (II), previously treated with sodium ethoxide (2 mol.), was equally unsuccessful. However, oxidation of the dithallium(I) salt of compound (II) afforded compound (I) as pale yellow needles, m.p. 139—140°. The i.r. evidence strongly supports a centrosymmetric structure for this compound in the solid state: only two carbonyl bands (1690 and 1680 $cm.^{-1}$) are observed in the double bond region. In solution a small distortion probably occurs, since besides the bands at 1690 and 1703 $cm.^{-1}$, the Raman modes at 1703 (C=O) and 1600 (C=C) $cm.^{-1}$ appear as weak bands at about the same frequencies.

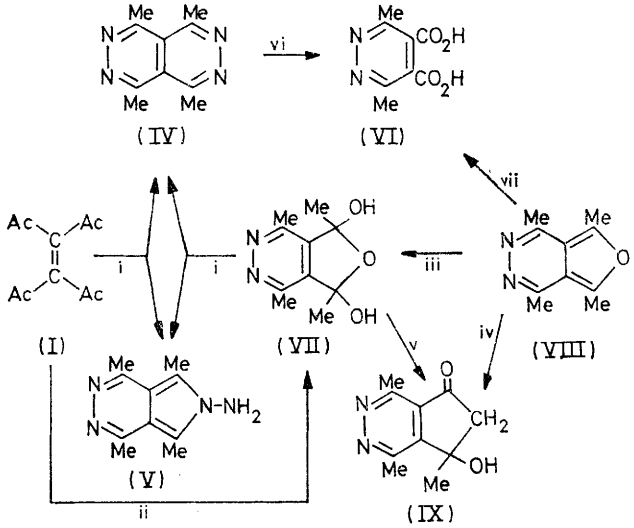
The u.v. spectrum, with a maximum at shorter wavelength (225 nm.) than that of *trans*-diacetylethylene [5] strongly supports the conclusion that all the acetyl groups are out of the plane of the double bond.

Reduction of tetra-acetylethylene with zinc and acetic acid gave some tetraketone (II) but mainly the expected cyclisation product 2,4-diacetyl-2,5-dimethylfuran.[6]

Tetra-acetylethylene (I) reacted with hydrazine hydrate yielding a mixture of 1,4,5,8-tetramethylpyridazino[4,5-*d*]pyridazine (IV) and 6-amino-1,4,5,7-tetramethylpyrrolo[3,4-*d*]pyridazine (V),[7] which was separated with benzene, in which compound (V) is almost insoluble. Compound (IV) crystallised as a colourless dihydrate, which lost water when heated. Its structure was confirmed by its chemical and spectroscopic behaviour. Oxidation with permanganate afforded 3,6-dimethylpyridazine-4,5-dicarboxylic acid (VI). The

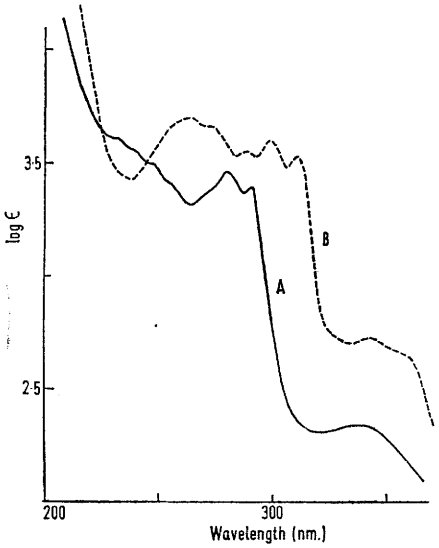
[1] G. Adembri, F. De Sio, R. Nesi, and M. Scotton, Riassunti delle Comunicazioni, Xth Congresso Nazionale della Società Chimica Italiana, Padova, June 1968, XIII–27.
[2] R. C. Elderfield, 'Heterocyclic Compounds,' vol. 6, Wiley, New York, 1957, p. 103.
[3] H. Keller and H. von Halban, *Helv. Chim. Acta*, 1944, **27**, 1253.
[4] G. Adembri, F. De Sio, and R. Nesi, *Ricerca Sci.*, 1967, **37**, 440.
[5] J. Levisalles, *Bull. Soc. chim. France*, 1957, 997.
[6] A. P. Dunlop and F. N. Peters, 'The Furans,' Reinhold, New York, 1953, p. 36.
[7] W. L. Mosby, *J. Chem. Soc.*, 1957, 3997.

n.m.r. spectrum exhibits only one signal, due to the four equivalent methyl groups. The u.v. spectrum is in good



Reagents: i, N_2H_4,H_2O; ii, N_2H_4,H_2O (1 mol.); iii, H_2O_2–AcOH; iv, $KMnO_4$ 20°; v, ^-OH; vi, $KMnO_4$; vii, $KMnO_4$ 60°

agreement with that expected on the basis of that of the parent compound [8] (see Figure).



U.v. spectra of (A) pyridazino[4,5-*d*]pyridazine [8] and (B) 1,4,5,8-tetramethylpyridazino[4,5-*d*]pyridazine (IV) in methanol

The production of compound (V) substantiates the occurrence of reduction by hydrazine, as confirmed by the evolution of nitrogen during the reaction. However, since we did not find 3,3′,5,5′-bipyrazole, we can exclude the possibility that the reduction involves compound (I) with formation of compound (II). The first step must therefore be the closure of one pyridazine ring, after which reduction occurs. This conclusion is supported by the isolation of compound (VII), which can be considered as an intermediate because with hydrazine it gave the same mixture of pyridazinopyridazine (IV) and pyrrolopyridazine (V).

The structure of compound (VII) followed from spectroscopic evidence and was confirmed by synthesis. The i.r. spectrum shows bands at 3150 (OH stretching) and 1400 cm.$^{-1}$ (pyridazine ring mode) and the u.v. spectrum is virtually identical with that of 3,6-dimethylpyridazine.[5] The compound was synthesised by 1,4-addition of hydrogen peroxide to 1,4,5,7-tetramethylfuro[3,4-*d*]pyridazine (VIII) [7] in acetic acid. It can be regarded as the hydrate of 4,5-diacetyl-3,6-dimethylpyridazine, which, like other *ortho*-dicarbonyl systems,[9] is stable only as the furan derivative. In agreement with its relationship to the diacetyl derivative, compound (VII) undergoes an intramolecular condensation to yield the hydroxy-ketone (IX). For this reason oxidation of the furopyridazine (VIII) with permanganate at room temperature gave compound (IX) rather than compound (VII). The constitution of the hydroxy-ketone (IX) was confirmed spectroscopically. The i.r. spectrum shows bands at 3170, 1730, and 1400 cm.$^{-1}$ assigned respectively to the OH and C=O groups and to the pyridazine ring. The u.v. absorption is consistent with a 3,6-dimethylpyridazine system conjugated with a carbonyl group.[7] The n.m.r. spectrum exhibits three singlets at δ 1·66, 2·7, and 2·76 p.p.m. attributable to methyl groups at the 7-, 1-, and 4-positions respectively, and an AB quartet (J_{AB} 18 Hz) near 3·08 p.p.m. that must be assigned to the non-equivalent protons of the methylene group, adjacent to an asymmetric carbon atom.

Tetra-acetylethylene (I) afforded cyclic compounds not only by condensation reactions but also by addition of dienes to the double bond or of hydrogen halides to the αβ-unsaturated carbonyl system.

On heating a solution of compound (I) in chloroform with 2,3-dimethylbutadiene we obtained compound (X), which, on spectral evidence, was identified as 4,4,5,5-tetra-acetyl-1,2-dimethylcyclohexene. The i.r. spectrum shows carbonyl vibrations at 1700 cm.$^{-1}$ and a shoulder at 1650 cm.$^{-1}$ attributable to the cyclohexene double bond. The n.m.r. spectrum shows three singlets (δ 1·66, 2·23, and 2·50 p.p.m.; integral ratio 3 : 6 : 2), assigned to 2 × CH_3–C=, 4 × CH_3–C=O, and 2 × $-CH_2-$C= respectively. The presence of only three peaks is in agreement with the fact that rapid ring inversion takes place at room temperature.[10]

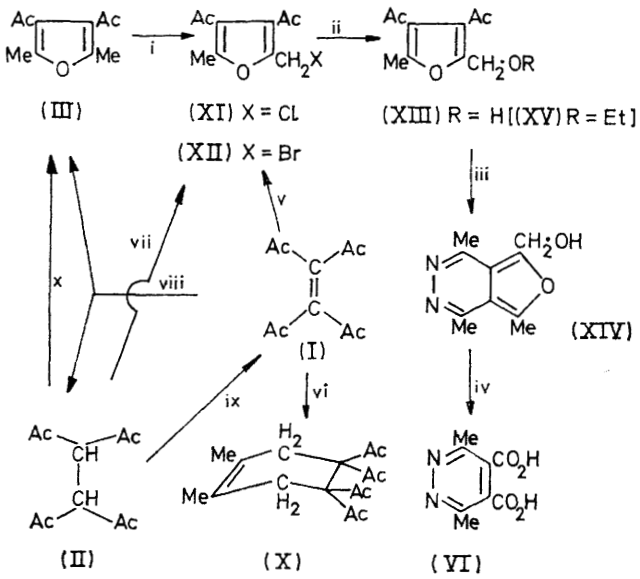
Dissolution of compound (I) in concentrated hydrochloric or hydrobromic acid followed by dilution with water gave the compounds $C_{10}H_{11}ClO_3$ (XI) and $C_{10}H_{11}BrO_3$ (XII) respectively. The latter was also obtained by treatment of compound (II) with bromine in ethanol solution. The i.r. spectra of these compounds exhibit two bands in the 1600—1500 cm.$^{-1}$ range, characteristic of an unsaturated ring system and two

[8] G. Adembri, F. De Sio, R. Nesi, and M. Scotton, *Chem. Comm.*, 1967, 1006.

[9] R. Criegee and D. Seebach, *Chem. Ber.*, 1963, **96**, 2704.

[10] F. A. L. Anet and M. Z. Hay, *J. Amer. Chem. Soc.*, 1965, **87**, 3147.

bands between 1690 and 1650 cm.$^{-1}$ attributable to two carbonyl stretching modes. The close similarity of these spectra to that of 3,4-diacetyl-2,5-dimethylfuran (III) suggested that the compounds were halogeno-derivatives of the furan (III). The u.v. spectra agree with this hypothesis. Furans (XI) and (XII) were prepared by treating compound (III) with *N*-chloro- or *N*-bromo-succinimide, respectively. To establish the position of the halogen atom, we sought to convert our products into the corresponding furopyridazines and to oxidise the products. In fact, we had already found that the furopyridazine (VIII) with permanganate at 60° yielded the acid (VI). Unfortunately, in our hands, the furans (XI) and (XII) gave only tarry products when treated with hydrazine. We therefore converted compound (XII) into the hydroxy-derivative (XIII), which was condensed with hydrazine to give furo-pyridazine (XIV). If the hydrolysis was carried out in ethanol we obtained the ethoxy-derivative (XV). The furopyridazine (XIV) was oxidised under the same conditions used for furopyridazine (VIII), and yielded



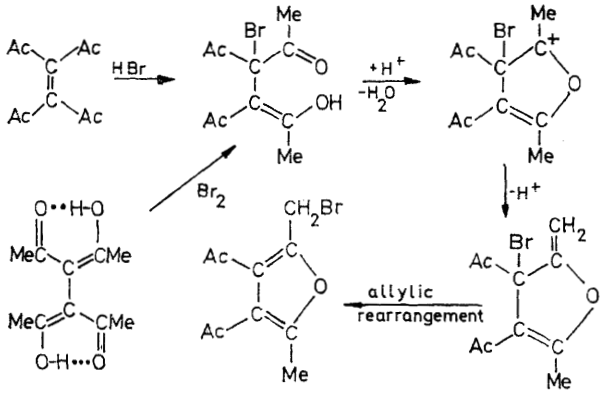
Reagents: i, *N*-chloro- or *N*-bromo-succinimide; ii, Ag_2O–H_2O (or EtOH); iii, N_2H_4,H_2O (1 mol.); iv, $KMnO_4$; v, HX; vi, $(CH_2{=}CMe)_2$; vii, Br_2; viii, Zn–$MeCO_2H$; ix, (*a*) EtOTl, (*b*) I_2; x, H^+

the same acid (VI). On the basis of these data we identified compounds (XI) and (XII) as 2-halogeno-methyl derivatives. Their formation from tetra-acetylethylene (I) can be accounted for in terms of 1,4-addition of hydrogen halide, ring closure, and aromatisation by subsequent rearrangement.

The proposed Scheme may also be assumed to apply to the formation of compound (XII) from bromine and tetra-acetylethane (II).

Recently [11] an *X*-ray analysis of compound (XII) has confirmed the reported structure.[1]

[11] L. Fanfani and P. F. Zanazzi, *Atti Accad. Naz. Lincei, Rend. Classe Sci. fis. mat. nat.*, 1968, **45**, 158.



SCHEME

EXPERIMENTAL

Tetra-acetylethylene (I).—A solution of iodine (20 g.) in dry ether (200 ml.) was added with stirring to a suspension of the dithallium(I) salt of compound (II) [12] (48 g.) in dry ether (300 ml.). The suspension was stirred for a further 30 min. The precipitate was separated and extracted with chloroform. Evaporation of the extract gave *tetra-acetylethylene* (7·5 g., 50%), m.p. 139—140° (from benzene) (Found: C, 61·0; H, 6·2. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·2%), $\lambda_{max.}$ (MeOH) 225 and 295sh nm. (log ε 3·81 and 2·21), δ ($CDCl_3$) 2·37 (s) p.p.m.

Reduction of Tetra-acetylethylene.—Zinc filings (1·6 g.) were added in portions to a warm solution of compound (I) (0·5 g.) in 50% acetic acid (50 ml.). The zinc residue was removed and the solution was extracted with chloroform; the extract was evaporated to dryness under reduced pressure. The residue was triturated with ether to give tetra-acetylethane (II) (0·05 g.); evaporation of the ethereal solution gave compound (III) (0·4 g.).

1,4,5,8-*Tetramethylpyridazino*[4,5-d]*pyridazine* (IV).—Hydrazine hydrate (98%; 1·25 ml.) was added dropwise with stirring to a suspension of compound (I) (0·48 g.) in methanol (20 ml.). The mixture was refluxed for 90 min. and then evaporated to dryness under reduced pressure. The yellow residue (0·45 g.) was refluxed with benzene (50—70 ml.) and the pyrrolopyridazine (V) (0·25 g.), identical (mixed m.p. and u.v. and i.r. spectra) with an authentic sample,[7] was filtered off. Evaporation of the benzene solution yielded 1,4,5,8-*tetramethylpyridazino*-[4,5-d]*pyridazine* (IV) (0·2 g.), m.p. 262—263° (from water) (Found: C. 53·5; H, 7·2; N, 25·2. $C_{10}H_{12}N_4,2H_2O$ requires C, 53·6; H, 7·2; N, 25·0%), δ ($CDCl_3$) 3·14 (s) p.p.m.

Oxidation of 1,4,5,8-*Tetramethylpyridazino*[4,5-d]*pyridazine.*—Potassium permanganate in water (2·25%; 560 ml.) was added to a solution of compound (IV) (2 g.) in water (200 ml.) under reflux. Manganese dioxide was filtered off and the solution was concentrated to *ca.* 50 ml. under reduced pressure. Acidification with concentrated hydrochloric acid precipitated compound (VI) (0·85 g., 45%), identical (mixed m.p. and i.r. spectrum) with authentic material.

5,7-*Dihydro*-5,7-*dihydroxy*-1,4,5,7-*tetramethylfuro*[3,4-d]-*pyridazine* (VII).—(*a*) Hydrazine hydrate (85%; 0·34 ml.) was added dropwise at room temperature to a stirred solution of compound (I) (1 g.) in methanol (15 ml.). The

[12] R. C. Menzies and E. R. Wiltshire, *J. Chem. Soc.*, 1931, **133**, 2239.

solution was stirred for a further 2 hr. and then evaporated to dryness under reduced pressure. The residue, treated with water, gave a colourless *product* (0·25 g., 23%), m.p. 204—205° (decomp.) (from ethanol) (Found: C, 57·1; H, 6·7; N, 13·2. $C_{10}H_{14}N_2O_3$ requires C, 57·1; H, 6·7; N, 13·3%), $\lambda_{max.}$ (MeOH) 256 and 305 nm. (log ε 3·31 and 2·55).

(b) Hydrogen peroxide (30%; 14·5 ml.) was added dropwise to a stirred solution of compound (VIII) (1 g.) in glacial acetic acid (20 ml.). The mixture was refluxed for 1 hr. and left at room temperature for 3 days. The precipitate (0·54 g., 50%), m.p. 204—205° (from ethanol), was identical (mixed m.p. and i.r. spectrum) with material prepared by method (*a*).

Action of Hydrazine on Compound (VII).—Hydrazine hydrate (85%; 0·2 ml.) was added to a solution of compound (VII) (0·2 g.) in methanol (4 ml.) under reflux. Removal of the solvent under reduced pressure gave a residue. Extraction with boiling benzene left compound (V) (0·1 g.) which was identical with an authentic sample.[7] Evaporation of the benzene solution yielded compound (IV) (0·1 g.), identical (mixed m.p. and i.r. spectrum) with the product obtained before.

6,7-*Dihydro*-7-*hydroxy*-1,4,7-*trimethylcyclopenta*[d]*pyridazin*-5-*one* (IX).—(*a*) Potassium permanganate (2·75 g.) in water (125 ml.) was added dropwise at room temperature to a stirred solution of the furopyridazine (VIII) (5 g.) in water (2 l.). Manganese dioxide was removed and the brown solution, after concentration under reduced pressure to *ca.* 100 ml., was extracted with chloroform. The brown solid obtained by evaporation of the extract was dissolved in benzene (charcoal) and the solution, evaporated to dryness under reduced pressure, gave *compound* (IX) (2·5 g., 50%), m.p. 149—150° [from light petroleum (b.p. 70—120°)] (Found: C, 62·6; H, 6·4; N, 14·5. $C_{10}H_{12}N_2O_2$ requires C, 62·5; H, 6·3; N, 14·6%), $\lambda_{max.}$ (MeOH) 277 and 310sh nm. (log ε 3·37 and 2·38). The *hydrazone* was obtained as yellow needles from water, m.p. 215—216° (Found: C, 58·2; H, 6·8; N, 26·9. $C_{10}H_{14}N_4O$ requires C, 58·2; H, 6·8; N, 27·3%), $\lambda_{max.}$ (MeOH) 242 and 302 nm. (log ε 3·89 and 4·06).

(*b*) A suspension of the dihydroxy-derivative (VII) (0·2 g.) and sodium carbonate decahydrate (0·27 g.) in water (8 ml.) was stirred for 2—3 hr. at 60° and then overnight at room temperature. The red-brown solution was extracted with chloroform. Evaporation of the extract yielded a residue which, treated as described in (*a*), gave a product identical (m.p., mixed m.p., and i.r. spectrum) with the product just described.

4,4,5,5-*Tetra-acetyl*-1,2-*dimethylcyclohexene* (X).—A solution of compound (I) (1 g.) and 2,3-dimethylbutadiene (1·2 ml.) in chloroform (10 ml.) was refluxed for 16 hr. Removal of the solvent left *compound* (X) (0·56 g., 40%), m.p. 106—108° [from light petroleum (b.p. 70—120°)], as colourless needles (Found: C, 69·0; H, 8·2. $C_{16}H_{22}O_4$ requires C, 69·0; H, 8·0%).

3,4-*Diacetyl*-2-*bromomethyl*-5-*methylfuran* (XII).—(*a*) Compound (I) (0·2 g.) was dissolved in concentrated hydrobromic acid (2 ml.). By adding water (5—6 ml.) to the yellow solution a colourless *compound* was obtained (0·26 g., 86%), m.p. 84—86° (from ethanol and by sublimation at 60°/0·05 mm. Hg) (Found: C, 46·5; H, 4·3; Br, 31·1. $C_{10}H_{11}BrO_3$ requires C, 46·4; H, 4·3; Br, 30·8%), $\nu_{max.}$ (KBr) 1680 and 1650 (C=O) cm.$^{-1}$, $\lambda_{max.}$ (MeOH) 271 nm. (log ε 3·86).

(*b*) A mixture of *N*-bromosuccinimide (0·8 g.) and furan (III) (0·8 g.) in carbon tetrachloride (40 ml.) was refluxed for 1 hr. Succinimide was then filtered off and the solution was evaporated to dryness under reduced pressure. The residue (1·1 g., 96%) was identical (mixed m.p. and i.r. spectrum) with the sample obtained by method (*a*).

(*c*) Bromine (2·5 ml.) in chloroform (3 ml.) was added dropwise to a stirred and cooled (0°) solution of compound (II) (10 g.) in ethanol (600 ml.). Evaporation of the colourless solution gave a brown-yellow residue (6·5 g., 50%), m.p. 84—86° (from ethanol), mixed m.p. and i.r. spectrum identical with those of the product prepared by method (*a*).

3,4-*Diacetyl*-2-*chloromethyl*-5-*methylfuran* (XI).—(*a*) By adding water to compound (I) (1 g.) dissolved in concentrated hydrochloric acid (10 ml.), a colourless *precipitate* (0·85 g., 78%) was obtained, m.p. 77—80° [from light petroleum (b.p. 60—80°)] (Found: C, 56·1; H, 5·2; Cl, 16·4. $C_{10}H_{11}ClO_3$ requires C, 56·0; H, 5·1; Cl, 16·5%), $\nu_{max.}$ (KBr) 1690 and 1650 (C=O) cm.$^{-1}$, $\lambda_{max.}$ (MeOH) 268 nm. (log ε 3·81).

(*b*) As in procedure (*b*) for compound (XII), the furan (III) (1 g.) was treated with *N*-chlorosuccinimide (0·75 g.) The suspension, refluxed for 1 week gave, in a very low yield, compound (XI), identical (mixed m.p. and i.r. spectrum) with material prepared by method (*a*).

3,4-*Diacetyl*-2-*hydroxymethyl*-5-*methylfuran* (XIII).—(*a*) Sodium carbonate decahydrate (0·86 g.) was added in small portions during 2 hr. to a stirred solution of furan (XII) (0·2 g.) in acetone (1·5 ml.) and water (2 ml.). The solution was evaporated and the residue was extracted with carbon tetrachloride. Evaporation of the extract yielded *compound* (XIII) (0·07 g., 46%), m.p. 68—69° [from light petroleum (b.p. 40—70°)] (Found: C, 61·0; H, 6·1. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·1%), $\lambda_{max.}$ (MeOH) 267 nm. (log ε 3·76), $\nu_{max.}$ (Nujol) 3400 (OH), 1685 (C=O), and 1660 (C=O) cm.$^{-1}$.

(*b*) Silver oxide (*ca.* 2 mol.) was added to a solution of the bromo-derivative (XII) (0·5 g.) in tetrahydrofuran (20 ml.) and water (15 ml.). The mixture, protected from light, was stirred for 4 hr., and set aside overnight. The silver was then filtered off and the solvent was evaporated to yield a product (0·2 g., 53%) with m.p., mixed m.p., and i.r. spectrum identical with those of the product prepared by method (*a*).

3,4-*Diacetyl*-2-*ethoxymethyl*-5-*methylfuran* (XV).—Silver oxide (*ca.* 2 mol.) was added to a solution of the bromo-derivative (XII) (0·5 g.) in ethanol (50 ml.) and the mixture was stirred for 6 hr. at room temperature in the dark. The solid was then filtered off and the solution was evaporated to dryness under reduced pressure. The residue, sublimed at 30°/0·05 mm. Hg, gave *compound* (XV) (0·26 g., 60%), m.p. 40—42° (Found: C, 64·3; H, 7·2. $C_{12}H_{16}O_4$ requires C, 64·3; H, 7·2%), $\lambda_{max.}$ (MeOH) 266 nm. (log ε 3·75), $\nu_{max.}$ (Nujol) 1685 (C=O), 1650 (C=O), and 1100 (C–O–C) cm.$^{-1}$.

5-*Hydroxymethyl*-1,4,7-*trimethylfuro*[3,4-d]*pyridazine* (XIV).—Hydrazine hydrate (85%; 0·06 ml.) was added to a solution of the hydroxy-compound (XIII) (0·2 g.) in ethanol (2 ml.) and the mixture was refluxed for 10 min., then cooled and filtered. *Compound* (XIV) crystallised from water as pale yellow needles (0·12 g., 56%), m.p. 164—166° (decomp.) (Found: C, 56·9; H, 6·5; N, 13·3. $C_{10}H_{12}N_2O_2,H_2O$ requires C, 57·1; H, 6·7; N, 13·3%), $\lambda_{max.}$ (MeOH) 272 and 330 nm. (log ε 3·54 and 3·71).

Oxidation of 1,4,5,7-*Tetramethylfuro*[3,4-d]*pyridazine*.—

Potassium permanganate (19 g.) in water (760 ml.) was added dropwise to a stirred solution of compound (VIII) (3·9 g.) in water (1·5 l.) kept at 60°. Manganese dioxide was filtered off and the solution was concentrated under reduced pressure to *ca.* 100 ml. By acidification with concentrated hydrochloric acid 3,6-dimethylpyridazine-4,5-dicarboxylic acid (2·6 g., 65%) was obtained, m.p. 226—228° (from water), identical with authentic material (mixed m.p. and i.r. spectrum).

Oxidation of 5-Hydroxymethyl-1,4,7-trimethylfuro[3,4-d]-*pyridazine.*—Oxidation of compound (XIV) (1 g.) with potassium permanganate (4 g.) was carried out as for compound (VIII). The product (0·59 g., 60%) was identical with authentic 3,6-dimethylpyridazine-4,5-dicarboxylic acid.

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