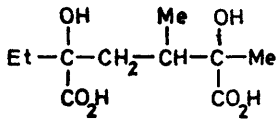
# The *Senecio* Alkaloids. The Structure and Absolute Configuration of Isoline

By E. D. Coucourakis, C. G. Gordon-Gray,* and C. G. Whiteley, Department of Chemistry and Chemical Technology, University of Natal, Pietermaritzburg, South Africa

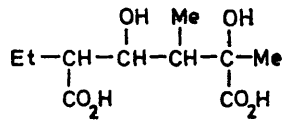
The structure and absolute configuration of the alkaloid isoline has been determined by showing that its acid portion, isolinecic acid, is (2*S*,3*R*,5*S*)-5-ethyl-2,5-dihydroxy-2,3-dimethylhexanedioic acid (1). The stereochemistry was defined by degradation of the acid to 3-methylheptane-2,5-dione (4) of known absolute configuration.



In a previous communication[1] it was shown that hydrolysis of the alkaloid isoline, obtained from *Senecio othonniformis* Fourcade, afforded a new acid, isolinecic acid,† $C_{10}H_{18}O_6$, which could be converted into its monolactone, and thence into the dilactone ($[\alpha]_D^{20}$ −50·0°) by distillation. Mainly on the basis of spectral studies, isolinecic acid was tentatively assigned structure (1) or (2). We now present evidence which not only



(1)



(2)

confirms structure (1) but also defines its absolute configuration.

Previously we mentioned that isolinecic acid dilactone differed in m.p. and i.r. and n.m.r. spectra from the dilactone obtained by Danilova *et al.*[2] from senecic acid (5-ethylidene-2-hydroxy-2,3-dimethylhexanedioic acid) by reduction of the derived bromo-dilactone. It was suggested that these differences could be due to stereochemistry. Since Danilova's work was available to us only as an abstract and since correspondence with her was not possible for us, it was decided to confirm the structure of her dilactone. Treatment of senecic acid lactone (5-ethylidene-2,3-dimethyl-6-oxotetrahydropyran-2-carboxylic acid) with bromine–water at 70° gave the bromo-dilactone, which was readily reduced to the dilactone. A comparison of n.m.r. spectra confirmed Danilova's structure for the bromo-compound. However, it seemed to us that the structure of the bromo-dilactone was unusual, in that the bromine, the positive end of the polar HOBr molecule, appeared at the β-position of an αβ-unsaturated system. We, therefore, decided to investigate this reaction.

The halogenolactonization has been used successfully for the preparation of five- and six-membered lactones from unsaturated acids.[3,4] The mechanism for ring closure, in the case of double bonds not conjugated to a carboxy-group, seems perfectly normal in that the cyclic bromonium ion, first formed by the electrophilic addition of bromine to the π-bond, is rapidly attacked by the negative carboxy-group to give the most stable lactone.

In the case of a double bond conjugated to a carboxy-group, however, the mechanism is not clear, and a study of the literature shows that the initial step in the mechanism of this reaction has not been identified.[5,6] Reeve and Israel[6] in reacting hypochlorous acid with ethyl crotonate produced kinetic evidence to show that the initial attack was that of 'positive chlorine' derived from chlorine monoxide. They proposed the unusual attack at the α-carbon to leave a carbonium ion at the β-carbon. They did not invoke the formation of the cyclic chloronium ion nor did they give the structure of the chlorohydrin.

In an attempt to get some insight into this halogenolactonization, ethyl crotonate was treated with bromine–water under the same conditions as those used for the formation of bromo-dilactone (see before). The bromohydrin was isolated, reduced with Raney nickel, and the product was purified by distillation. An n.m.r. investigation showed the presence of ethyl 3-hydroxybutyrate as the only product. Thus, identical treatment of senecic lactone and ethyl crotonate with bromine–water showed that the product from the former was the β-bromo- while that from the latter was α-bromo-compound.

These reactions would seem to indicate that in bromolactonization some such species as the cyclic bromonium ion must be an intermediate. What constitutes the initial attack is not clear. Is it a normal nucleophilic attack at the β-position by some such species as $Br_3^-$, which then in some way, not immediately clear, disproportionates to give the cyclic intermediate or, far more likely, is it the ready electrophilic attack of the bromine atom from hypobromous acid (or the electrophilic chlorine atom from chlorine monoxide in the case of hypochlorous acid) to give the intermediate cyclic bromonium ion as outlined in Scheme 1?

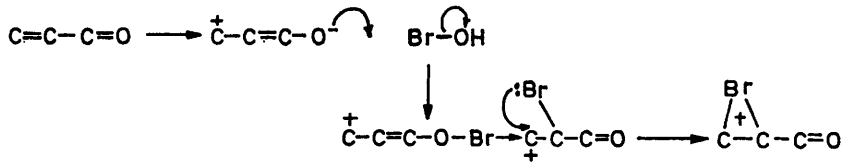
The second alternative is the more readily acceptable. In the case of ethyl crotonate, since no lactonization is possible, a water molecule or hydroxide ion attacks the bromonium intermediate at the β-position, the most positive carbon atom, whereas in the case of senecic

† This was previously referred to as 2,5-dihydroxy-3-methylheptane-2,5-dicarboxylic acid.[2]

[1] E. D. Coucourakis and C. G. Gordon-Gray, *J. Chem. Soc.* (*C*), 1970, 2312.
[2] A. V. Danilova, N. I. Koretskaya, and S. L. M. Utkin, *Zhur. obshchei Khim.*, 1962, **32**, 3823 (*Chem. Abs.*, 1963, **58**, 12,504).
[3] P. N. Craig, *J. Amer. Chem. Soc.*, 1952, **74**, 129.
[4] E. E. van Tamelen and M. Shamma, *J. Amer. Chem. Soc.*, 1954, **76**, 2315.
[5] R. P. Bell and M. Pring, *J. Chem. Soc.* (*B*), 1966, 1119.
[6] K. D. Reeve and G. C. Israel, *J. Chem. Soc.*, 1952, 2327.

lactone the intermediate is attacked by the negative carboxy-group at that carbon atom which will give the most stable lactone, namely the α-carbon atom.

Since the determination of the configuration at C-3 would automatically give the stereochemistry at C-2 and C-5, it became essential to degrade both dilactones



SCHEME 1

Having confirmed the structure of the dilactone derived from senecic acid by Danilova, it was shown by c.d. spectra (see Figure) that this dilactone, and that

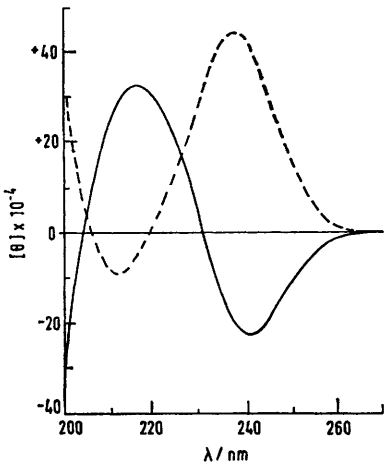


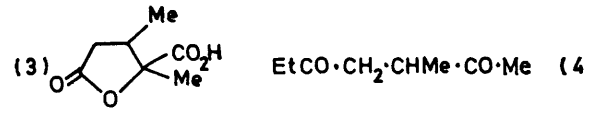

FIGURE C.d. curve of the dilactone derived from senecic acid (broken line) and isolinecic acid dilactone (solid line)

from isolinecic acid, were diastereoisomers. Furthermore the mass spectrum of each gave identical fragmentation patterns. Hence the structure of isolinecic acid must be (1).

Since the absolute configuration of senecic acid is known [7] to be (2*R*,3*R*), the dilactone derived from it must have the (2*R*,3*R*,5*R*)-configuration as it is impossible to form the dilactone if C-5 has the opposite configuration to C-2. The same observation was made for hygrophyllinecic acid dilactone which has the (2*R*,3*R*,4*R*)-configuration.[8] Consequently the dilactone from isolinecic acid can have the configuration (2*S*,3*R*,5*S*) or (2*R*,3*S*,5*R*); the (2*S*,3*S*,5*S*)-configuration is excluded since the two lactones are not enantiomers.

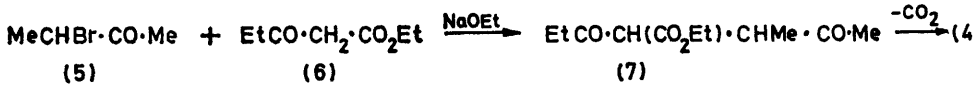
to a common intermediate in which the asymmetry at C-2 and C-5 was lost. Oxidation with potassium permanganate was successfully carried out on senecic acid-derived bromo-dilactone to give the γ-valerolactone (3), but failed when repeated on the two dilactones. Proof of structure of (3) was obtained by oxidation of senecic acid with ozone.

It was then necessary to convert both dilactones into 3-methylheptane-2,5-dione (4). Preliminary oxidations[1]




with sodium bismuthate on isolinecic acid, on a semi-micro-scale, failed to give the dione (4), and since this compound had, to our knowledge, not been reported in the literature, it was decided to synthesize it in order to ascertain its chemical and physical characteristics.

The synthesis was accomplished by two different methods. The first method is shown in Scheme 2. Preparation of the β-keto-ester (6), however, by the method of Riegel and Lilienfield,[9] was not successful; we obtained a mixture of products. This ester was obtained pure, although in lower yield than that reported, by hydrolysis of a metal halide [formed from anhydrous tin(IV) chloride, propionitrile and ethyl acetoacetate] by hydrochloric acid in chloroform.[10] Con-




SCHEME 2

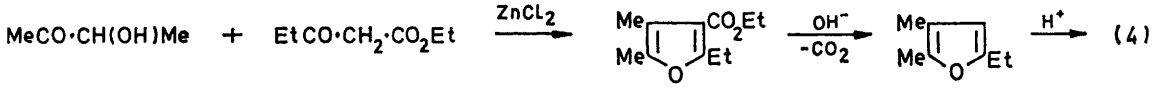
densation of the ester and the bromo-ketone (5) [11] gave the ester (7), which was decarboxylated to the dione (4) by heating with 20% aqueous potassium carbonate under reflux.[12]

The second method is shown in Scheme 3. Of the many routes to substituted furans [13-15] we chose that of

[7] J. Fridrichsons, A. McL. Mathieson, and J. D. Sutor, *Tetrahedron Letters*, 1960, 35.
[8] F. D. Schlosser and F. L. Warren, *J. Chem. Soc.*, 1965, 5707.
[9] B. Riegel and W. M. Lilienfield, *J. Amer. Chem. Soc.*, 1945, **67**, 1273.
[10] Y. Isowa, Jap.P. 17,170/1968 (*Chem. Abs.*, 1969, **70**, 57,173*h*).
[11] C. Rappe and R. Kumar, *Arkiv Kemi*, 1965, **23**, 475.
[12] V. M. Rodionov and E. F. Polunia, *Doklady Akad. Nauk S.S.S.R.*, 1949, **68**, 535 (*Chem. Abs.*, 1950, **44**, 1030*e*).
[13] C. Paarl, *Ber.*, 1884, **17**, 2756.
[14] F. Feist, *Ber.*, 1902, **35**, 1537.
[15] P. A. Yoder and B. Tollens, *Ber.*, 1901, **34**, 3446.

Gonzalez [16] modified by Hanson *et al.*[17] The furoate was hydrolysed and the acid decarboxylated by heating with copper–barium chromite catalyst in quinoline.[18] Ring fission [19] gave the dione (4).

The n.m.r. spectrum of the dione (4) gave the signals $\tau$ 9·0 (d and t), 7·8 (s) and 7·6 (q) for the *Me*$CH_2$· and




SCHEME 3

*Me*CH·, MeCO·, and MeC$H_2$· groups respectively, as shown by decoupling. The other protons could not be clearly differentiated. The mass spectrum gave the accurate mass of the molecular ion of 142·098558 ($C_8H_{14}O_2$).

In order to didecarboxylate and oxidize the dilactone derived from senecic acid, it was reduced with lithium aluminium hydride to give an oil which failed to give a crystalline derivative. Oxidation of the oil with sodium bismuthate gave formaldehyde (1·8 mol) (as the dimedone derivative) together with the dione (4). Such an oxidation of isolinecic acid on a macro-scale afforded carbon dioxide (2 mol) and the dione (4).

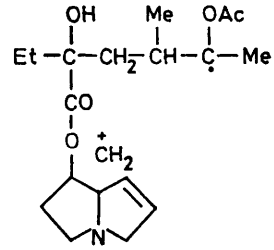
The dione from both sources were shown to have identical c.d. and o.r.d. curves, thus establishing the 3*R*-configuration in isolinecic acid (1) and hence giving the absolute configuration for this acid as [2*S*,3*R*,5*S*).

We suggested previously,[1] without any evidence, that the 5-hydroxy-group (in the acid portion) was acetylated in the parent alkaloid, isoline. We now present evidence from n.m.r. and mass spectral data to show that the acetoxy-group exists at C-2.

The n.m.r. spectrum of isoline differs from that of bisline in two respects: the acetoxy methyl signal in isoline is clearly visible at $\tau$ 8·0, and the 2-methyl group is somewhat deshielded ($\tau$ 8·6) by comparison with the same methyl group in bisline ($\tau$ 8·8). A similar deshielding effect is observed when florosenine [20] and senkirkine [21] are compared with their *O*-acetyl derivatives.

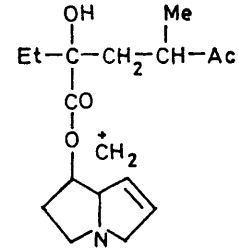
It has been shown [22-24] that in the mass spectrometer retronecine diesters undergo initial fragmentation by fission of the labile allylic ester bond, followed by systematic fragmentation of the 'necic' acid component until only the 'necine' base remains. This then undergoes fragmentation to give the well-known series of ions *m/e* 136, 120, 119, 95, 93, and 80, also found in isoline and bisline.

The empirical formulae for isoline, $C_{20}H_{29}NO_7$, and bisline, $C_{18}H_{27}NO_6$, are consistent with the molecular ion peaks at *m/e* 395 and 353, respectively. As in the case of the analogous alkaloids floridanine, floricaline, and florosenine,[20] fragmentation of isoline gives fragment (9) at *m/e* 351, which corresponds to the loss of carbon dioxide. This ion then loses an acetyl group to give an ion (10) at *m/e* 308. In bisline the peaks corresponding to this fragmentation pattern are at *m/e* 309 and 308, respectively.




*m/e* 351

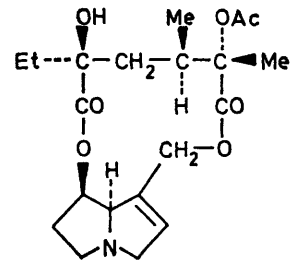
(9)



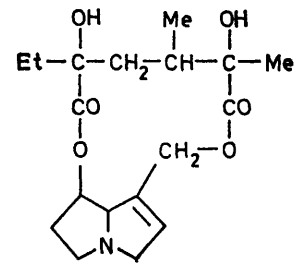

*m/e* 308

(10)

From the above discussion, and since the stereochemistry of retronecine is known,[25] the absolute structure of isoline is given as (11). Since bisline (12) was deduced from spectral data, its stereochemistry is undefined. As far as we know, the only other pyrrolizidine alkaloid with the (2*S*)-configuration in the acid portion is clivorine (13) the structure of which was determined by *X*-ray analysis.[26]




(11)

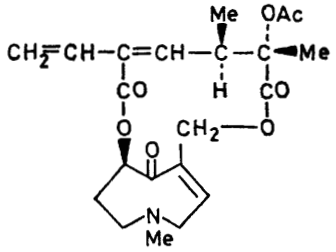



(12)

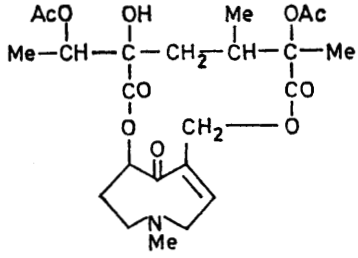
Having determined the absolute configuration of isoline, the one fact that still remains unexplained is why

[16] F. G. Gonzalez, J. L. Aparacio, and F. Sanchez-Laulke, *Anales real Soc. espaň. Fis. Quim.*, 1954, **50***B*, 407.
[17] J. C. Hanson, J. H. C. Naylor, T. Taylor, and P. H. Gore, *J. Chem. Soc.*, 1965, 5984.
[18] T. Reichstein, H. Zschokke, and W. Syz, *Helv. Chim. Acta*, 1932, **15**, 1112.
[19] H. Hunsdiecker, *Ber.*, 1942, **75***B*, 447.
[20] M. P. Cava, K. V. Rao, J. A. Weisbach, R. F. Raffauf, and B. Douglas, *J. Org. Chem.*, 1968, **33**, 3570.
[21] L. H. Briggs, R. C. Cambie, B. J. Candy, G. M. O'Donovan, R. H. Russell, and R. W. Seelye, *J. Chem. Soc.*, 1965, 2492.
[22] C. K. Atal, K. K. Kapur, C. C. J. Culvenor, and L. W. Smith, *Tetrahedron Letters*, 1966, 537.
[23] N. Neuner-Jehle, H. Nesvadba, and G. Spiteller, *Monatsh.*, 1965, **96**, 321.
[24] D. H. G. Crout, *J. Chem. Soc.* (*C*), 1969, 1379.
[25] F. L. Warren and M. E. von Klemperer, *J. Chem. Soc.*, 1958, 4574.
[26] K. B. Birnbaum, A. Klasek, P. Sedmera, G. Snatzke, L. F. Johnson, and F. Šantavy, *Tetrahedron Letters*, 1971, 3421.

isolinecic acid can be isolated as the free acid, while sceleratinic and sceleranecic acids are only isolated as the di-δ-lactones. We note that the acid present in otosenine has the (2*R*)-configuration. It would be of interest to see whether floricaline (14), which must also have the (2*R*)-configuration, would yield the free acid on hydrolysis. If not, then the stereochemistry of these acids at C-2 and C-5 must play an important part in the formation of the di-δ-lactones.




( 13 )




( 14 )

## EXPERIMENTAL

*Halogeno-dilactones from Senecic Acid* (*5-Ethylidene-2-hydroxy-2,3-dimethylhexanedioic Acid*).—Intergerrinecic acid lactone [27] (4·0 g) was treated with an excess of bromine–water at 70° to give pure 5-(1-bromoethyl)-2,3-dimethylhexane-2,5-diolide (5·1 g) as needles, m.p. 115° (from ethanol) (lit.,[2] 114°) (Found: C, 43·4; H, 4·8. Calc. for $C_{10}H_{13}BrO_4$: C, 43·3; H, 4·7%), $M^+$, 277, $\nu_{max.}$ (KBr) 1750 $cm^{-1}$ (C=O lactone), τ ($CDCl_3$; 100 MHz) 8·8 (3H, d, *Me*CH), 8·4 (3H, s, MeC), 8·3 (3H, d, *Me*CHBr), 7·7 (1H, m, MeC*H*·$CH_2$), and 5·5 (1H, q, MeC*H*Br).

Similar treatment of the lactone (1·0 g) with chlorine–water gave the 5-(1-chloroethyl)-diolide (0·5 g), m.p. 109° (from ethanol) (lit.,[2] 107—108°) (Found: C, 51·5; H, 5·8. Calc. for $C_{10}H_{13}ClO_4$: C, 51·5; H, 5·7%).

*Preparation of the Dilactone derived from Senecic Acid.*—The bromo-dilactone from senecic acid (1·0 g) with freshly prepared Raney nickel [28] was heated under reflux in ethanol (30 $cm^3$) for 8 h. The solution was filtered, water (20 $cm^3$) was added, the alcohol was removed, and the dilactone was extracted into ether. The crude product, on sublimation (35° at 0·05 mmHg) afforded 5-ethyl-2,3-dimethylhexane-2,5-diolide, needles, m.p. 51° (lit.,[2] 51°) $[\alpha]_D^{20}$ −55·3° (Found: C, 60·5; H, 7·1. Calc. for $C_{10}H_{14}O_4$: C, 60·6; H, 7·1%).

*Oxidation of the Bromo-dilactone from Senecic Acid with Permanganate.*—To a stirred solution of the foregoing bromo-dilactone (2·5 g, 9 mmol) and potassium hydroxide (0·83 g, 18 mmol) in phosphate buffer (pH 7, 250 $cm^3$) was added dropwise 2% potassium permanganate at 60°. The apparatus was flushed with nitrogen and the carbon dioxide was collected as barium carbonate (2·8 g). When the permanganate colour of the solution persisted, it was cooled to 0°, treated with sodium sulphite, and the manganese dioxide was dissolved by adding concentrated sulphuric acid. The solution was concentrated (200 $cm^3$) and the distillate afforded acetic acid, identified as its barium salt (1·4 g). The remaining aqueous solution yielded an oily gum (800 mg), which was distilled. The fraction boiling at 90° and 0·1 mmHg, on redistillation onto a cold finger, gave the pure hygroscopic 2,3-dimethyl-5-oxotetrahydro-2-furoic acid (3), *m/e*, 158, 113, 89, and 85, τ (pyridine, 60 MHz) 9·0 (3H, d, *Me*CH) and 8·5 (3H, s, Ac).

p-*Bromophenacyl* 2,3-*Dimethyl-5-oxotetrahydro-2-furoate*.—The foregoing acid (3) (124 mg) was neutralized with 0·1N-sodium hydroxide and the solution taken to dryness *in vacuo*. *p*-Bromophenacyl bromide (200 mg) and ethanol (5 $cm^3$) were added and the solution was heated under reflux (1 h). The alcohol was removed and the residue was heated under reflux with acetone, filtered hot, and the filtrate was taken to dryness to yield the ester, plates, m.p. 74—75° (from ethanol) (lit.,[29] 82 and 109°) (Found: C, 50·7; H, 4·3. Calc. for $C_{15}H_{15}BrO_5$: C, 50·7; H, 4·3%), $\nu_{max.}$ (KBr) 1702, 1750, 1780, and 1580 $cm^{-1}$.

*Ozonolysis of Senecic Acid.*—Senecic acid (1 g) in dry ethyl acetate (20 $cm^3$) was ozonized at −76° for 4 h. Treatment with water and extraction with ether yielded a solid. Sublimation (80° at 0·1 mmHg) gave pure 2,3-dimethyl-5-oxotetrahydro-2-furoic acid (450 mg), identified by its n.m.r. and i.r. spectra and by its *p*-bromophenacyl ester.

*Ethyl 3-Oxopentanoate* (6).—Anhydrous tin(IV) chloride (74·5 g, 0·35 mol) followed by propionitrile (19·4 g, 0·35 mol) were dropped slowly onto ethyl acetoacetate (45·5 g, 0·35 mol) and the whole was heated under reflux to effect a homogeneous solution.[10] Chloroform (200 $cm^3$) and 10% hydrochloric acid (200 $cm^3$) were added at 45° and the stirring was continued at room temperature (1 h). The aqueous layer was extracted twice with chloroform (100 $cm^3$) and the combined chloroform extract, after washing with 10% hydrochloric acid and water, was dried and distilled to give an oil. Fractional distillation gave the ester (6), b.p. 54—59° at 4 mmHg.

*3-Bromobutan-2-one* (5).—*N*-Bromosuccinimide (53 g, 0·295 mol) was added in portions to a boiling mixture of ethyl methyl ketone (85 g, 1·18 mol) in carbon tetrachloride (300 $cm^3$).[11] The solution was boiled for 1 h, cooled, and the succinimide was filtered off at 0°. Evaporation of the filtrate gave an oil, which on fractional distillation yielded 3-bromobutan-2-one, b.p. 39° at 13 mmHg.

*Ethyl 3-Methyl-4-oxo-2-propionylpentanoate* (7).—The ester (6) (24·0 g, 0·167 mol] was added dropwise, with stirring, to a solution of sodium (3·7 g, 0·161 g atom) in absolute alcohol (48 g). The mixture was heated under reflux for 30 min, cooled to below 40° and 3-bromobutan-2-one (24 g, 0·159 mol) added gradually at 30°. The solution was stirred for 1 h, first at 40° then at 50—60°, filtered, concentrated, and after water (18 $cm^3$) had been added with

[27] M. Kropman and F. L. Warren, *J. Chem. Soc.*, 1950, 700.

[28] R. Mozingo, *Org. Synth.*, 1941, **21**, 15.

[29] R. B. Bradbury and S. Masamune, *J. Amer. Chem. Soc.*, 1959, **81**, 5201.

shaking, extracted into ether. Evaporation and fractional distillation gave the ester (7), b.p. 132—137° at 0·85 mmHg.

3-*Methylheptane*-2,5-*dione* (4).—The foregoing ester (7) (14·0 g, 0·065 mol) was heated under reflux for 3 h with 25% aqueous potassium carbonate (140 g). The mixture was cooled, solid potassium carbonate (26 g) was added, and the product, an oil, was extracted into ether. Fractional distillation gave 3-*methylheptane*-2,5-*dione* (6 g), b.p. 44—45° at 0·05 mmHg, $M^+$ (mass spec.), 142·098559, *m/e* 142, 113, 85, 71, 57, and 43, $\nu_{max.}$ ($CHCl_3$) 1701 $cm^{-1}$ (C=O), $\tau$ ($CCl_4$; 60 MHz) 9·0 (6H, d and t, *Me*CH and *Me*$CH_2$), 7·8 (3H, s, Ac), and 7·6 (2H, q, MeC$H_2$); *bisthiosemicarbazone*, m.p. 159° (from ethanol) (Found: C, 42·1; H, 7·8. $C_{10}H_{20}N_6S_2$ requires C, 41·7; H, 7·0%): *bis*-2,4-*dinitrophenylhydrazone*, m.p. 199—201° (from diglyme) (Found: C, 47·5; H, 5·1. $C_{20}H_{22}N_8O_8$ requires C, 47·8; H, 4·4%).

*Ethyl* 2-*Ethyl*-4,5-*dimethyl*-3-*furoate*.—The ester (6) (28·8 g, 0·2 mol) was heated under reflux for 4 h with acetoin (16·0 g, 0·182 mol), anhydrous zinc chloride (18·2 g), and 95% ethanol (27·2 $cm^3$). The liquid was poured into water (50 $cm^3$) and extracted with benzene. The benzene solution, after washing successively with water, 5% sodium hydroxide, dilute hydrochloric acid, and water, gave an oil. Fractional distillation gave the furoate (22·4 g, 64%), b.p. 79—80° at 3 mmHg.

2-*Ethyl*-4,5-*dimethyl*-3-*furoic Acid*.—The foregoing ester was heated under reflux for 6 h with 40% sodium hydroxide (60 $cm^3$) containing alcohol (5 $cm^3$). After evaporation and acidification, the furoic acid was collected, m.p. 84° (from ethanol) (lit.,[17] 84—85°) (Found: C, 64·4; H, 6·8. Calc. for $C_9H_{12}O_3$: C, 64·3; H, 7·2%).

2-*Ethyl*-4,5-*dimethylfuran*.—The furoic acid (8·7 g, 51·9 mmol) was boiled with barium–copper chromite catalyst (1·5 g) and quinoline (15·0 g).[18] The temperature was raised and the fraction b.p. 140—200° was collected. Fractional distillation gave 2-ethyl-4,5-dimethylfuran, b.p. 50° at 18 mmHg.

3-*Methylheptane*-2,5-*dione from* 2-*Ethyl*-4,5-*dimethylfuran*.—2-Ethyl-4,5-dimethylfuran (10 g, 81 mmol) was heated under reflux at 120° for 4 h with a mixture of glacial acetic acid (15 g), water (5 g), and 20% sulphuric acid (10 drops). The solution was made basic with 1% sodium carbonate and extracted into ether. Evaporation gave an oil, fractional distillation of which afforded 3-methylheptane-2,5-dione (4·4 g, 50%), b.p. 44—45° at 0·05 mmHg, identified by its n.m.r. and i.r. spectra.

*Reduction of the Dilactone derived from Senecic Acid with Lithium Aluminium Hydride*.—The dilactone (see before) (1 g) was dissolved in anhydrous tetrahydrofuran (100 $cm^3$) and was heated under reflux with an excess of lithium aluminium hydride for 96 h. Water (50 $cm^3$) was added at 0°, and the resulting aluminium hydroxide filtered off, dissolved in hydrochloric acid (2N), and reprecipitated with sodium hydroxide. The combined filtrates were taken to dryness under reduced pressure. Water (100 $cm^3$) was added and the solution was continuously extracted with ether (24 h) to yield a polyol after distillation (150° at 0·2 mmHg) as a viscous oil (1·01 g).

*Oxidation of the Foregoing Polyol with Sodium Bismuthate*.—Sodium bismuthate (840 mg) was added to a solution of the preceding polyol (240 mg) and 3·3M-phosphoric acid (6 $cm^3$) in water (10 $cm^3$). The mixture, after standing for 48 h, was filtered and the filtrate was treated with dimedone (1·34 g) to give formaldehyde dimedone (563 mg), m.p. 193°. In a similar experiment the polyol (550 mg) was oxidized with an excess of bismuthate (3 g). The aqueous solution, after removal of the bismuth phosphate, was continuously extracted with ether (24 h). After evaporation, making basic with 1% sodium carbonate, and re-extraction with ether, the resulting mobile oil (300 mg) was distilled. The middle fraction, b.p. 42—44° at 0·05 mmHg, gave pure 3-methylheptane-2,5-dione (180 mg), $[\alpha]_D^{20}$ +47·8° (*c* 30·74 g $dm^{-3}$ in EtOH).

*Oxidation of Isolinecic Acid* (5-*Ethyl*-2,5-*dihydroxy*-2,3-*dimethylhexanedioic Acid*) (1).—Sodium bismuthate (5 g) was added to a solution of the acid (1) (1·2 g) and 3·3M-phosphoric acid (16 $cm^3$) in water (50 $cm^3$) and the mixture was kept under a stream of nitrogen until evolution of carbon dioxide ceased. Filtration and extraction of the filtrate with ether afforded an oil. The oil, in water, was made basic with 1% sodium carbonate and re-extracted into ether to give pure 3-methylheptane-2,5-dione (390 mg) after distillation (at 43° and 0·05 mmHg), $[\alpha]_D^{20}$ +48·7° (*c* 30·82 g $dm^{-3}$).

We thank Dr. K. Pachler for n.m.r. spectra, Dr. S. Eggers and Dr. M. Toube for the mass spectra, Dr. L. Visser for c.d. and o.r.d. spectra, and the South African Council for Scientific and Industrial Research for grants (to E. D. C. and C. G. G.).

[2/545 *Received*, 8*th March*, 1972]