

Isomeric Spiro-diketones from 1,1'-Epoxybicyclohexyl-2-one

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Re-examination of the isomerisation of 1,1'-epoxybicyclohexyl-2-one into spiro-diketones has confirmed that reaction with antimony pentachloride in sulphur dioxide affords cycloheptanespirocyclohexane-2,7-dione, whereas thermal rearrangement gives cycloheptanespirocyclohexan-2,2'-dione.

In the course of work on the synthesis and some reactions of 1,1'-epoxybicyclohexyl-2-one (I), Reese¹ found that distillation of (I) at atmospheric pressure provided a diketone for which, on very slight evidence, he suggested the structure (II). However, House and Wasson² later

stated that the diketone had the isomeric structure (III), similar to that claimed³ for the product of treatment of the epoxy-ketone (I) with antimony pentachloride in liquid sulphur dioxide.

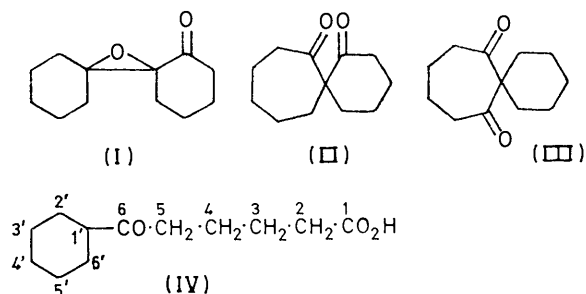
Nojima *et al.*³ found that the diketone (III), m.p. 69—70°, was converted into the expected keto-acid (IV),

¹ J. Reese, *Ber.*, 1942, **75**, 384.

² H. O. House and R. L. Wasson, *J. Amer. Chem. Soc.*, 1956, **78**, 4394.

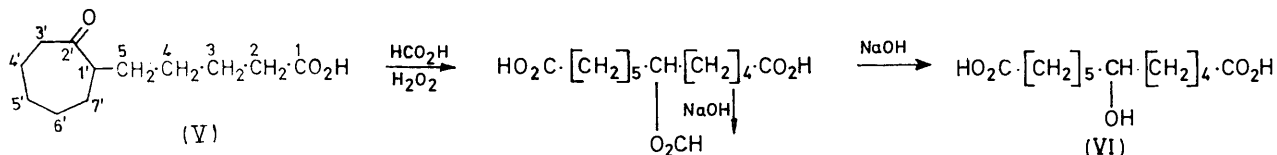
³ M. Nojima, K. Hinoue, and N. Tokura, *Bull. Chem. Soc. Japan*, 1970, **43**, 827.

m.p. 56–58°, on heating with alkali. No m.p. was reported for the diketone of House and Wasson, but its semicarbazone had a similar m.p. (223–225°) to those reported by Reese (224°) and by Nojima *et al.* (218–223°); treatment of this diketone with alkali gave a



keto-acid (m.p. 56.5–58°), forming a semicarbazone of m.p. 270–271°, whereas the semicarbazone of the synthetic keto-acid (IV)¹ is reported to have m.p. 175°.

In the present work it has been confirmed that isomerisation of the epoxy-ketone (I) with antimony pentachloride in sulphur dioxide gives the spiro-diketone (III), although the yield depends on the concentration of the antimony pentachloride used. However, reaction of (III) with semicarbazone hydrochloride and base gave a bis-semicarbazone, m.p. 257–259°; none of the mono-semicarbazone was isolated. Treatment of (III) with base provided the keto-acid (IV), m.p. 54–56°, identical



with the synthetic compound.¹ Identification of this keto-acid was based largely on mass spectral evidence [intense *m/e* 129 (α -cleavage ion), 83 (cyclohexyl cation), and 126 (McLafferty rearrangement ion)] and the ¹³C n.m.r. spectrum, in which all the peaks were assigned.

The spiro-diketone derived from thermal rearrangement of (I) was shown to have the structure (II) suggested by Reese. It was a low-melting solid (m.p. 26–28°), with semicarbazone of m.p. 226–228°, and with alkali yielded a liquid keto-acid whose semicarbazone (m.p. 162–163°) depressed the m.p. of the derivative from (IV). This keto-acid was shown to have the structure (V) by mass spectroscopic evidence [intense *m/e* 112 (McLafferty rearrangement ion)] and by synthesis, using essentially the method described by Adamson and Kenner⁴ and by Hauptmann *et al.*;⁵ it was also converted into 6-hydroxydodecanedioic acid (VI) on treatment with performic acid followed by hydrolysis. The position of the hydroxy-group in (VI) was unequivocally fixed by the intense mass spectral α -

cleavage ions *m/e* 145 and 131, which lose water to give *m/e* 127 and 113.

The isomers (II) and (III) were also differentiated on the basis of their ¹³C n.m.r. spectra; (II) had 12 peaks, two of which were due to C=O, whereas (III) had only seven peaks, with one due to C=O, showing that, unlike (II), (III) had an axis of symmetry.

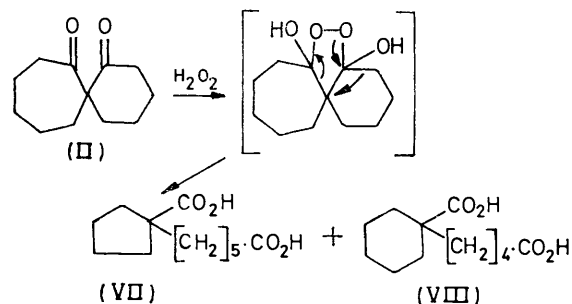
On reaction with hydrogen peroxide (neat or in *t*-butyl alcohol) the spiro-diketone (II) gave a mixture of dicarboxylic acids from which the major component, probably (VII), was isolated as a pure solid; the suggested structure was consistent with the mass spectrum, which showed intense peaks at *m/e* 210 (*M* – H₂O), 183 (*M* – CO₂H), 165 (*M* – H₂O – CO₂H), and 114 (McLafferty rearrangement ion). The presence of the isomeric dicarboxylic acid (VIII) in the crude product was indicated by an intense band at *m/e* 128 (McLafferty rearrangement ion), and both (VII) and (VIII) would be anticipated as products from (II) *via* the mechanism proposed by Payne⁶ for other 1,3-diketones (see Scheme 1).

The isomeric spiro-diketone (III) did not react with hydrogen peroxide under similar conditions.

The epoxy-ketone (I), when heated with sodium hydroxide or sodium methoxide, was largely converted into a mixture of a hydroxy-acid [probably (IX)]; intense *m/e* 99 α -cleavage ion] and its lactone (X) (γ -lactone by *i.r.* and ¹³C n.m.r.).

Thus three different rearrangements of the epoxy-ketone (I) occur, under acidic, basic, and thermal condi-

tions. The acid-catalysed reaction to give (III) presumably proceeds *via* a Wagner–Meerwein heterolytic



SCHEME 1

route,^{7,8} and the mechanism of base-catalysed decomposition of other cyclic $\alpha\beta$ -epoxy-ketones to γ -hydroxy-acids and their lactones with concurrent ring contraction has been discussed by House and Gilmore.⁹ The isomer-

⁶ G. B. Payne, *J. Org. Chem.*, 1961, **26**, 4793.

⁷ H. O. House, *J. Amer. Chem. Soc.*, 1954, **76**, 1235.

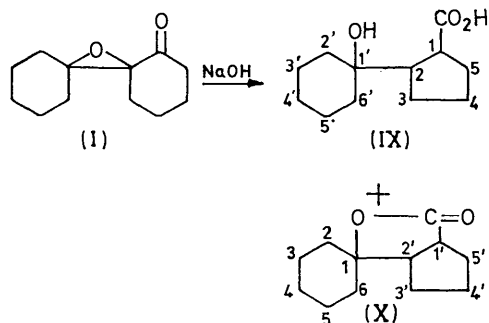
⁸ H. Gerlach and W. Müller, *Helv. Chim. Acta*, 1972, **55**, 2277.

⁹ H. O. House and W. F. Gilmore, *J. Amer. Chem. Soc.*, 1961, **83**, 3972.

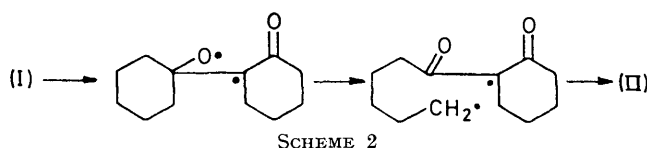
⁴ D. W. Adamson and J. Kenner, *J. Chem. Soc.*, 1939, 181.

⁵ S. Hauptmann, F. Brandes, E. Bauer, and W. Gabler, *J. prakt. Chem.*, 1964, **25**, 56.

isation to (II) on heating probably involves a radical reaction, similar to that suggested for the photolytic



conversion of $\alpha\beta$ -epoxy-ketones into spiro-1,3-diketones^{10,11} (Scheme 2).



EXPERIMENTAL

Low-resolution 70 eV mass spectra were obtained at an accelerating voltage of 8 kV, a trap current of 100 μ A, and a source temperature of 200°, with either an A.E.I. MS9 or MS12 instrument. Mass measurements were carried out with the MS9. Full mass spectra of compounds (I)—(VI) have been submitted to the Mass Spectrometry Data Centre, A.W.R.E. Aldermaston. ¹H N.m.r. spectra were recorded with a Perkin-Elmer R-10 spectrometer and natural abundance, proton-decoupled ¹³C n.m.r. spectra with a Bruker HFX-90 spectrometer using pulsed Fourier Transform operation (5 kHz spectral window). All chemical shifts are reported as p.p.m. downfield from tetramethylsilane. The assignment of ¹³C n.m.r. peaks is based on the results summarised by Stothers.¹² I.r. spectra were recorded with a Perkin-Elmer 457 spectrometer.

1,1'-Epoxybicyclohexyl-2-one (I), m.p. 96—98° [ν_{\max} (KBr) 1714 cm^{-1} (C=O); δ_{H} (CCl₄) 1.10—2.82br (complex); m/e 194 (C₁₂H₁₈O₂, 57.6%) and 151 (C₉H₁₁O₂, 100%)] was prepared from cyclohexylidencyclohexanone and alkaline hydrogen peroxide by the method of Reese.¹

Thermal Decomposition of the Epoxy-ketone (I).—The epoxy-ketone (174 g) was heated at 260° for 0.5 h and then distilled at 15 mmHg to give fractions (i) (6.0 g), b.p. <154°; (ii) (130.0 g), b.p. 154—170°; (iii) (3.8 g), b.p. 170—200°; and (iv) (15.0 g), b.p. 200—280°; and a residue (1.9 g). Fraction (i) contained cyclohexanone (mainly) and cyclohex-2-enone (by i.r. spectrum). Alkali extraction of fraction (iv) yielded acids (2.3 g), b.p. 218—226° at 15 mmHg [semicarbazone, m.p. 160—162°, not depressed on admixture with the derivative of (V) (see later)]. A cooled solution of fraction (ii) in petroleum (b.p. 40—60°) provided the spiro-diketone (II), m.p. 27—28° (Found: C, 74.45; H, 9.5. Calc. for C₁₂H₁₈O₂: C, 74.2; H, 9.35%); ν_{\max} (film) 1695 cm^{-1} (C=O); δ_{H} (CDCl₃) 0.90—2.87 (complex) with maxima 1.42 (CH₂ cyclic) and 2.30 (CO—CH₂); δ_{C} (CDCl₃) 21.4, 24.6, 26.2, 26.9, 29.9, 32.5, 35.4, 40.6 (C-3 or C-3'), 40.8 (C-3' or C-3), 66.1 (C-1), 210.3 (C-2' or C-2),

and 212.0 (C-2 or C-2'); m/e 194 (C₁₂H₁₈O₂, 51.2%), 166 (C₁₁H₁₆O, 55.8%), 137 (C₉H₁₀O, 55.8%), 123 (C₈H₁₁O, 69.8%), 110 (C₇H₁₀O, 32.6%), and 41 (100%) [semicarbazone, m.p. 223—225° (from ethanol) (Found: C, 62.0; H, 8.45; N, 16.85. Calc. for C₁₃H₂₁N₃O₂: C, 62.15; H, 8.4; N, 16.75%); m/e 251 (M⁺, 38.5%)].

Decomposition of the Epoxy-ketone (I) with Antimony Pentachloride.³—A solution of the epoxy-ketone (18 g) in liquid sulphur dioxide (ca. 100 cm³) at -55° was treated with antimony pentachloride (5 cm³). The temperature was allowed to rise to 0°, then the solution was stored for 1 h, treated with cold water, and extracted with ether. Solid antimony derivatives were filtered off, the dried filtrate was flash-distilled and the distillate was redistilled to provide a product (12.6 g), b.p. 145—155° at 15 mmHg, which, crystallised from petroleum (b.p. 40—60°), gave the spiro-diketone (III) (10.6 g), m.p. 73—75° (Found: C, 74.3; H, 9.4%; ν_{\max} (KBr) 1685 cm^{-1} (C=O); δ_{H} (CDCl₃) 0.83—2.71br, with maxima 1.70 (CH₂ cyclic) and 2.37 (CO—CH₂); δ_{C} (CDCl₃) 21.6, 25.0 (C-4'), 27.7, 29.1, 40.4 (C-3 and C-6), 64.7 (C-1), and 212.6 (C-2 and C-7); m/e 194 (C₁₂H₁₈O₂, 95.1%), 166 (C₁₁H₁₆O, 61.0%), 137 (C₉H₁₀O, 26.8%), 123 (C₈H₁₁O, 53.7%), 110 (C₇H₁₀O, 58.5%), and 55 (100%) [bis-semicarbazone, m.p. 257—259° (from aqueous acetic acid) (Found: C, 54.5; H, 7.85; N, 27.4. Calc. for C₁₄H₂₄N₆O₂: C, 54.55; H, 7.8; N, 27.25%); m/e 308 (M⁺, 14.3%)].

When a solution of the epoxy-ketone (5 g) in liquid sulphur dioxide (ca. 25 cm³) was treated with less antimony pentachloride (0.1 cm³) and worked up as before, the product (4.1 g), b.p. 145—152° at 15 mmHg, afforded the crystalline spiro-diketone (III) (0.2 g) (from cooled petroleum) and the filtrate, analysed by g.l.c.—mass spectroscopy, was shown to contain further spiro-diketone (18.5%), together with octahydrodibenzofuran (18.1%) and isomers (55.4 and 5.6%) of 2-(cyclohex-1-enyl)-2-hydroxycyclohexanone.³ Catalytic hydrogenation afforded crystalline 1-cyclohexylcyclohexane-1,2-diol, m.p. 142—144°, as obtained by Nojima *et al.* from this unsaturated keto-alcohol.

Decomposition of the Epoxy-ketone (I) with Sodium Methoxide.—The epoxy-ketone (5 g) was heated under reflux for 5 h with a solution of sodium (1 g) in methanol (20 cm³). The solution was cooled, diluted with water, and extracted with ether, and the aqueous phase was acidified and re-extracted with ether. Distillation of the neutral product gave a main fraction (2.6 g), b.p. 170—180° at 15 mmHg, presumably the lactone (X) [ν_{\max} (film) 1763 cm^{-1} (C=O of γ -lactone); δ_{H} (CDCl₃) 0.85—2.10 (CH₂) and 2.10—3.32 (CH); δ_{C} (CCl₄) 23.0, 23.2, 25.5, 26.7, 27.5, 29.1, 33.0, 38.7, 45.7 (C-2'), 48.6 (C-1'), 84.6 (C-1), and 178.6 (C-6'); m/e 194 (C₁₂H₁₈O₂, 25.5%) and 151 (C₉H₁₁O₂, 100.0%)].

The acid product (0.8 g), b.p. 160—210° at 15 mmHg, crystallised from ethyl acetate, gave 2-(1-hydroxycyclohexyl)cyclopentanecarboxylic acid (IX), m.p. 132—133° (Found: C, 67.9; H, 9.5%; acid equiv., 215.4. C₁₂H₂₀O₃ requires C, 67.9; H, 9.45%; acid equiv., 212); ν_{\max} (KBr) 1700 (C=O) and 945 cm^{-1} (OH); δ_{H} [(CD₃)₂SO] 0.87—2.10 (CH₂) and 2.10—3.04 (CH); δ_{C} [(CD₃)₂SO] 22.2 (C-3' and C-5'), 26.1, 26.5, 27.4, 32.6, 36.5 (C-2' or C-6'), 36.7 (C-6' or C-2'), 44.2 (C-2), 52.8 (C-1), 71.3 (C-1'), and 179.2 (C-6); m/e 212 (C₁₂H₂₀O₃, 1.8%) and 99 (C₆H₁₁O, 100.0%).

¹¹ H. J. Wüthrich, A. Siewinski, H. Schaffner, and O. Jeger, *Helv. Chim. Acta*, 1973, **56**, 239.

¹² J. B. Stothers, 'Carbon-13 N.M.R. Spectroscopy,' Academic Press, New York, 1972.

¹⁰ J. R. Williams and G. M. Sarkisian, *J. Org. Chem.*, 1972, **37**, 4463.

Replacement of sodium methoxide by sodium hydroxide in aqueous ethanol gave rise to the same products but with a much higher proportion of hydroxy-acid. A portion of the lactone was converted into the hydroxy-acid on prolonged refluxing with a solution of potassium hydroxide in ethylene glycol.

Reaction of the Spiro-diketone (II) with Alkali.—The diketone (90 g) was heated on a water-bath for 2 h with a solution of sodium hydroxide (40 g) in aqueous ethanol. The mixture was cooled and extracted with ether, and the aqueous phase was acidified and re-extracted with ether. The neutral product (2.4 g), b.p. 130–155° at 15 mmHg, was found (i.r.) to consist largely of octahydrodibenzofuran, and the acid product (92.4 g), b.p. 219–225° at 15 mmHg, was the keto-acid (V) (Found: C, 68.0; H, 10.15. Calc. for $C_{12}H_{20}O_3$: C, 67.9; H, 9.45%); ν_{\max} (film), 1700 (C=O, acid), 1725 (C=O, ketone), and 930 cm^{-1} (OH); δ_H (CCl_4) 0.80–3.00 (complex) [maxima at 1.38 (CH_2 , chain and ring) and 2.28 ($CO\cdot CH_2$ and $CO\cdot CH$)] and 9.69 (CO_2H); δ_C (CCl_4) 24.2, 24.5, 26.4, 28.3, 29.2, 31.1, 31.6, 33.4 (C-2), 42.2 (C-3'), 51.5 (C-1'), 177.6 (C-1), and 214.9 (C-2'); m/e 212 ($C_{12}H_{20}O_3$, 2.8%), 113 ($C_7H_{12}O$, 100.0%), and 60 (7.5%) [semicarbazone, m.p. 162–163° (from acetone) (Found: C, 58.05; H, 8.75. Calc. for $C_{13}H_{23}N_3O_3$: C, 57.95; H, 8.6%), not depressed on admixture with the derivative of the synthetic keto-acid (V) (see later); 2,4-dinitrophenylhydrazone, m.p. 156–157° (from benzene) (Found: C, 54.95; H, 6.1; N, 14.4. $C_{18}H_{24}N_4O_6$ requires C, 55.25; H, 5.9; N, 14.3%)].

Treatment of the spiro-diketone with sodium methoxide gave similar products.

Reaction of the Spiro-diketone (III) with Alkali.—The diketone (4.2 g), refluxed with a solution of sodium hydroxide (2.5 g) in water (15 cm^3) and ethanol (15 cm^3) for 2 h, provided a solid acid (3.9 g), m.p. 54–56° (from benzene-petroleum), not depressed on admixture with the synthetic keto-acid (IV) (see later).

Reaction of the Spiro-diketones with Hydrogen Peroxide.—The diketone (II) (5.7 g) was mixed with 30% hydrogen peroxide (3.5 cm^3) and the mixture was evaporated at ca. 20° and 15 mmHg during 3 h. The residue was warmed to decompose unchanged peroxide and, from a cooled ether-petroleum solution, gave a slightly sticky solid (4.0 g). Evaporation of the filtrate, followed by treatment of the residue with fresh hydrogen peroxide (3.0 cm^3) afforded more (1.2 g) of the same solid. Recrystallisation gave 6-(1-carboxycyclopentyl)hexanoic acid (VII), m.p. 95–97° (from water) (Found: C, 62.9; H, 9.2%; acid equiv., 113.2. $C_{12}H_{20}O_4$ requires C, 63.2; H, 8.8%; acid equiv., 114); ν_{\max} (KBr) 1690 (C=O) and 940 cm^{-1} (OH); δ_H ($CDCl_3$) 1.05–1.85 (CH_2), 1.85–2.63 ($CO\cdot CH_2$), and 10.30 (CO_2H); m/e 210 ($C_{12}H_{18}O_3$, 2.4%), 183 ($C_{11}H_{18}O_2$, 12.9%), 165 ($C_{11}H_{17}O$, 29.2%), and 114 ($C_6H_{10}O_2$, 100%). The crude product also had a strong band at m/e 128 (McLafferty rearrangement ion) derived from the isomer (VIII).

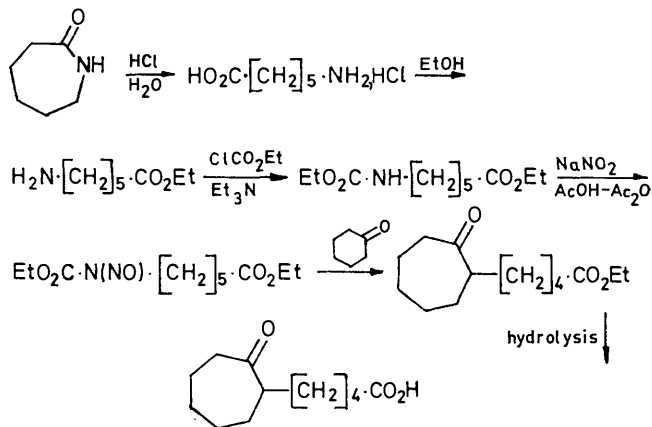
The isomeric spiro-diketone (III), similarly treated, was recovered unchanged.

Reaction of the Keto-acid (V) with Performic Acid.—The keto-acid (0.4 g) was heated with 30% hydrogen peroxide (3 cm^3) and formic acid (in excess) on a water-bath for 1.5 h.

Unchanged formic acid was evaporated off and the residue was crystallised from water, then from benzene-petroleum, to give 6-formyloxylododecanedioic acid, m.p. 62–66° (Found: C, 56.8; H, 7.9. $C_{13}H_{22}O_6$ requires C, 56.9; H, 8.0%). Hydrolysis of the formate with hot sodium hydroxide solution yielded the 6-hydroxy-acid (VI), m.p. 93–94° (from ethyl acetate) (Found: C, 58.05; H, 8.8%; acid equiv., 123.9. $C_{12}H_{22}O_5$ requires C, 58.5; H, 8.9%; acid equiv., 123); ν_{\max} (KBr) 1700 (C=O), 940, and 3500 cm^{-1} (OH); δ_H [$(CD_3)_2SO$] 1.17–2.00 (CH_2), 2.10–2.60 ($CO\cdot CH_2$), and 3.45 ($CH\cdot O$); m/e 247 ($M + 1$, 0.3%), 145 ($C_7H_{13}O_3$, 25.0%), 131 ($C_6H_{11}O_3$, 35.0%), 127 ($C_7H_{11}O_2$, 100%), and 113 ($C_6H_9O_2$, 85.4%).

Synthesis of the Keto-acid (IV).—The method of Reese,¹ involving chromic acid oxidation of cyclohexylcyclohexan-2-one, gave the acid, m.p. 54–56° [ν_{\max} (KBr) 1690 (C=O) and 916 cm^{-1} (OH); δ_H ($CDCl_3$) 0.74–2.73 (complex) [maxima at 1.59 (CH_2 , cyclic and acyclic) and 2.33 ($\alpha\text{-}CH_2$)] and 11.35 (CO_2H); δ_C ($CDCl_3$), 23.1 (C-3' and C-5'), 24.4 (C-4'), 25.7 (C-3 and C-4), 28.6 (C-2' and C-6'), 33.9 (C-2), 40.0 (C-5), 50.9 (C-1'), 179.5 (C-1), and 213.7 (C-6); m/e 212 ($C_{12}H_{20}O_3$, 7.4%), 129 ($C_6H_9O_3$, 19.0%), 126 ($C_8H_{14}O$, 12.0%), and 83 (C_6H_{11} , 100.0%)] [semicarbazone, m.p. 176–178° (from acetone) (Found: C, 58.05; H, 8.3; N, 15.5. Calc. for $C_{13}H_{23}N_3O_3$: C, 57.95; H, 8.6; N, 15.6%)].

Synthesis of the Keto-acid (V).—The method used, starting with ϵ -caprolactam, was essentially that described in refs. 4 and 5 (Scheme 3). The final product, b.p. 228–229° at



15 mmHg, acid equiv. 211.5, had i.r., n.m.r., and mass spectra identical with those of the product from reaction of the spiro-diketone (II) with alkali (see before), and the m.p. of its semicarbazone was not depressed on admixture with the corresponding derivative of that reaction product.

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