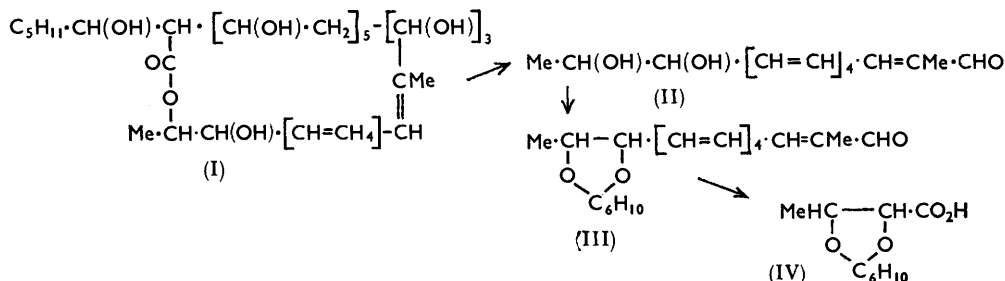


161. The Relative Configurations of Two Asymmetric Centres in Lagosin.

By M. P. BERRY and M. C. WHITING.

THE constitution of lagosin has been proved¹ to be (I), but this molecule contains twelve asymmetric carbon atoms, and the complete stereochemical problem is formidable. As a first step we have attempted the degradative sequence (I) \rightarrow (II) \rightarrow (III) \rightarrow (IV).

The preparation of the dihydroxypentaenal (II) has been described,^{1b} the details given incorporating improvements made during the present work. We chose to protect the vicinal glycol grouping as a ketal in order that after ozonolysis the fragment needed would be less hydrophilic than the oxalic and pyruvic acid, etc., formed as by-products; and wanting a fairly large protecting group of relatively good stability we chose the cyclohexylidene residue. Condensation of the polyenal (II) with cyclohexanone in the presence



of a little toluene-*p*-sulphonic acid gave the crystalline ketal (III). The two (*DL-erythro* and *DL-threo*) acids (IV) were prepared by similar condensations, no catalyst being necessary, and had m. p. 83.5–85° and 48.5–52°. The dihydroxybutyric acids required were conveniently obtained by "pertungstic acid" oxidation of crotonic² and *cis*-crotonic acid; the latter reaction is new. The two ketal acids were readily extractable from water (ether/water distribution coefficient *ca.* 2), reasonably stable at pH *ca.* 3, not readily interconverted, and easily distinguished by their characteristic infrared spectra, especially in the region of 900–950 cm.⁻¹, where the *erythro*-compound has three sharp bands. They were thus suited to our purpose.

Ozonolysis of the ketal (III) was effected in methylene chloride and the ozonide was decomposed with alkaline hydrogen peroxide. Extraction of the acid fraction and distillation gave a low yield of a syrup, the infrared spectrum of which showed all the main peaks of the *DL-erythro*-acid (IV) and none of those peculiar to the *DL-threo*-acid (IV). Unfortunately it did not crystallise, and as its optical rotation proved low and appeared to change sign, possibly because of alcoholysis, no useful conclusion can be drawn about absolute configuration from our experiments. The corresponding two hydroxyl groups in fungichromin have also been shown³ to have the *erythro*-relation, and it is virtually certain that those in lagosin have the same configuration.

Experimental.—*DL-erythro- $\alpha\beta$ -Dihydroxybutyric acid* (with J. M. A. WADE). When prepared² by treating crotonic acid (10 g.) with hydrogen peroxide (20-volume; 100 c.c.) and tungstic oxide (1 g.) at 70° for 2 hr., the crude acid was a syrup which was extracted with light petroleum to remove crotonic acid, then with ethyl acetate, leaving an appreciable uncrystallisable residue. Evaporation of the ethyl acetate extract left a product which crystallised, then separated from ethyl acetate or tetrahydrofuran-di-isopropyl ether as hygroscopic

¹ Dhar, Thaller, and Whiting, (a) *Proc. Chem. Soc.*, 1960, 310; (b) preceding paper.

² Mugdan and Young, *J.*, 1949, 2988.

³ Cope, Bly, Burrows, Ceder, Ciganek, Gillis, Porter, and Johnson, *J. Amer. Chem. Soc.*, 1962, **84**, 2170.

plates, m. p. 81.5—82.5° (Mugdan and Young² and earlier workers give values between 80.5° and 83°).

cis-Crotonic acid was prepared from but-3-yn-1-ol *via* but-3-ynoic⁴ and buta-2,3-dienoic acid⁵ and was used without purification.

DL-threo- $\alpha\beta$ -Dihydroxybutyric acid. Tungstic oxide (40 mg.), hydrogen peroxide (100-volume; 4 c.c.), and crude *cis*-crotonic acid (2.1 g.) were diluted to 30 c.c. with water and heated to 65° for 4 hr., filtered, cooled, and extracted with chloroform (3 \times 5 c.c.). Evaporation of the aqueous solution at 20° *in vacuo*, finally at 0.03 mm., left a syrup which was dissolved in tetrahydrofuran; this solution was filtered and again evaporated *in vacuo*. The residue was repeatedly extracted with warm ether, leaving a gum which was rejected; the solution was evaporated and crystallised after 4 hr. at 10⁻² mm.; the crystals, when washed with ether, had m. p. 60—71° (490 mg.). Crystallisation from tetrahydrofuran-ether gave elongated plates, m. p. 71—74° (Glattfield and Straitiff⁶ give m. p. 74—75°).

Cyclohexylidene ketals of the $\alpha\beta$ -dihydroxybutyric acids. The DL-*erythro*-dihydroxy-acid (150 mg.), cyclohexanone (5 c.c.), and anhydrous copper sulphate (600 mg.) were shaken for 20 hr. at 20°, then extracted with dry ether. The filtered extract was washed with ice-cold 10% potassium carbonate solution (2 \times 15 c.c.), which was brought to pH 4 by addition of a predetermined quantity of cooled phosphoric acid, mixed with ether. After further extraction with ether the extracts were dried and evaporated, giving a *product* (130 mg., 52%) which separated from light petroleum and had m. p. 80—85°, raised on recrystallisation to 83.5—85° (Found: C, 59.9; H, 8.05. C₁₀H₁₆O₄ requires C, 60.0; H, 8.05%).

The DL-*threo*-dihydroxy-acid (150 mg.; m. p. 60—71°), cyclohexanone (5 c.c.), and copper sulphate similarly gave the corresponding *ketal* (120 mg.), m. p. 42—50°, raised to 48.5—52° on crystallisation (Found: C, 60.35; H, 8.25%).

The infrared spectra of the two isomers were similar above 1200 cm.⁻¹, in particular having a strong band at 1780 cm.⁻¹ attributable to the internally hydrogen-bonded monomer.⁷ At 900—950 cm.⁻¹ they differed characteristically, the *erythro*-acid giving three sharp peaks at 909, 925, and 945 cm.⁻¹, while the *threo*-compound had broader peaks at 913 and 932 and an inflexion at 945 cm.⁻¹.

Cyclohexylidene *ketal* of 12,13-dihydroxy-2-methyltetradeca-2,4,6,8,10-pentaenal. The dihydroxy-aldehyde (1 g.), cyclohexanone (20 c.c.), anhydrous copper sulphate (600 mg.), and toluene-*p*-sulphonic acid (5 mg.) were shaken for 48 hr. at 20° in the dark in nitrogen. The mixture was extracted with warm light petroleum (b. p. 60—80°) which was then washed with potassium hydrogen carbonate solution, dried, and evaporated *in vacuo* (finally 0.02 mm.) at 40°. Crystallisation from light petroleum gave the *ketal* (860 mg., 65%), m. p. 80.5—85.5°; the m. p. could not be improved by recrystallisation but was sharpened, without much loss, to 84—86.5° by chromatography on alumina (Found: C, 75.65; H, 8.75. C₂₁H₂₈O₃ requires C, 76.8; H, 8.6%). Other analyses gave similar results).

Ozonolysis of the *ketal* (600 mg.) was effected in methylene chloride (40 c.c.) at 0° and treatment of the ozonide solution with water (50 c.c.), sodium hydrogen carbonate (4 g.), and hydrogen peroxide (100-volume; 5 c.c.) for 48 hr. at 20°, with stirring; then the methylene chloride was evaporated. The aqueous solution was acidified with phosphoric acid (5 c.c.) and extracted with ice-cold ether (2 \times 200 c.c.). These extracts were dried and evaporated and the residue was subjected to slow distillation on to a cooled surface at 70°/0.1 mm., giving a syrup (37 mg.). Its infrared spectrum was identical (except for some general absorption which raised the absorption minima) with that of the crystalline DL-*erythro*-cyclohexylidene derivative; but it did not crystallise.

We thank Dr. V. Thaller for helpful discussions.

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[Received, July 5th, 1963.]

⁴ Heilbron, Jones, and Sondheimer, *J.*, 1949, 606.

⁵ Eglinton, Jones, Mansfield, and Whiting, *J.*, 1954, 3197.

⁶ Glattfield and Straitiff, *J. Amer. Chem. Soc.*, 1938, **60**, 1384.

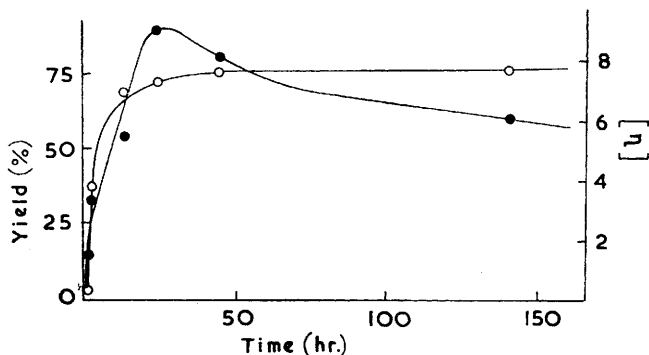
⁷ Brooks, Eglinton, and Mormon, *J.*, 1961, 106, and personal communication.

162. The Polymerisation of Tetrahydrofuran. Part I.

By D. SIMS.

POLYMERISATION of tetrahydrofuran by Friedel-Crafts catalysts to give polymers of low molecular weight was first examined by Meerwein and his co-workers.¹ Subsequently Muetterties² reported the use of phosphorus pentafluoride to give polymers of tetrahydrofuran of high molecular weight.

This catalyst has been re-examined and has been found to be capable of producing polyethers of extremely high molecular weight from pure tetrahydrofuran under strict conditions. At room temperature, there seems to be no chain-termination reaction and



Polymerisation of tetrahydrofuran with phosphorus pentafluoride, showing the change in yield (—○—) and viscosity (—●—) with time at 20° ($[PF_5] = 0.762 \text{ g. l.}^{-1}$).

when further monomer is added to the equilibrium monomer-polymer mixture it undergoes polymerisation. However, slow destruction of the catalyst by reaction with the polymer apparently occurs (see later), this reaction becoming rapid as the temperature increases.

The polymers produced below 70° are tough crystalline materials, m. p. 46° (dilatometric).

The course of the reaction at 20° is shown in the diagram. Some results giving the effect of temperature on the equilibrium degree of conversion and the intrinsic viscosity of the polymer are given in the following Table.

Polymerisation of tetrahydrofuran catalysed by phosphorus pentafluoride.

Temp.	—35°	0	20	51	70	83
Reaction time (days)	28	14	12	7	4	1
Conversion (%)	nil	95	76	53	26	2.4
Viscosity $[\eta]$ (benzene at 20°; dl. g. ⁻¹) *	—	15.0	4.6	2.3	0.6	0.16

* $[PF_5] = 0.762 \text{ g. l.}^{-1}$.

A plot of the equilibrium degree of conversion against temperature, gives a curve which on extrapolation gives a ceiling temperature of 83°, for reaction under these conditions.

The heat and entropy of polymerisation, calculated from the equilibrium monomer concentrations by the method first described by Dainton and Ivin,³ and subsequently by Bywater,⁴ is $-\Delta H_{1s} = 4.28 \pm 0.2 \text{ kcal. mole}^{-1}$ (liquid monomer \rightarrow solution of polymer), the corresponding entropy change being $-\Delta S_{1s} = 17.0 \pm 0.6 \text{ cal. mole}^{-1} \text{ deg.}^{-1}$. The heat

¹ Meerwein, Battenburg, Gold, Pfeil, and Willfang, *J. prakt. Chem.*, 1939, **154**, 83; G.P. 741,478.

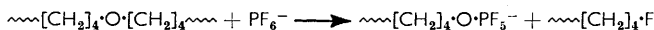
² Muetterties, U.S.P. 2,856,370.

³ Dainton and Ivin, *Nature*, 1948, **162**, 705; *Quart. Rev.*, 1958, **12**, 61.

⁴ Bywater, *Trans. Faraday Soc.*, 1955, **51**, 1267.

of fusion is in good agreement, within experimental error, with a value $-\Delta H_{1s} = 5.6$ kcal. mole⁻¹ just published.⁵ A value of $-\Delta H_{1c} = 9.1 \pm 1.0$ kcal. mole⁻¹ (liquid monomer \rightarrow crystalline polymer) has been obtained from combustion measurements on a polymer of low molecular weight "Teracol 30" (Du Pont de Nemours & Co.) using the published value for the heat of combustion of tetrahydrofuran.⁶

The rate of polymerisation, zero at -35° , increases rapidly with temperature, but the intrinsic viscosity of the polymer drops, probably partly due to a reaction similar to that suggested by Meerwein.¹



This is substantiated by the detection of fluorine in the polymer produced at 70° .

The effect of ethyl chloride and diethyl ether on the polymerisation is to reduce both the equilibrium yield and the intrinsic viscosity of the polymer, as illustrated.

Polymerisation of tetrahydrofuran at 20° in solvent.

[Monomer] (mole l. ⁻¹)	Solvent	Reaction time (days)	Conversion (%)	Viscosity $[\eta]^*$ (dl. g. ⁻¹)
6.8	EtCl	14	40	1.5
7.8	Et ₂ O	12	57	1.0

* $[\text{PF}_5] = 0.762$ g. l.⁻¹ monomer.

MINISTRY OF AVIATION,
E.R.D.E., WALTHAM ABBEY, ESSEX.

[Received, March 5th, 1963.]

⁵ Bawn, Chem. Soc. Anniversary Meeting, Cardiff, 1963.

⁶ Springall, *J.*, 1958, 1406.

163. *The Nuclear Magnetic Resonance Spectra of Some 3-Substituted Alk-2-enoic Esters.*

By J. S. PIZEY and W. E. TRUCE.

THE use of nuclear magnetic resonance spectroscopy in determining the configuration of geometrical isomers of the type $\text{R}^1\text{CH}:\text{CH}\cdot\text{R}^2$ is well known.^{1,2} In addition, Jones *et al.*³ used the chemical shift of the vinylic proton to distinguish between geometric isomers of the type $\text{Me}\cdot\text{C}(\text{X})\text{CH}\cdot\text{CO}_2\text{Et}$. Coupling constants have been used to differentiate between geometrical isomers in which the protons are separated by four or five bonds.^{4,5} More recently, Fraser and McGreer⁶ stated that the size of the long-range coupling constants is not determined solely by the geometrical configuration about the double bond, and hence is of little value in determining the configuration.

In view of the uncertainty in the use of long-range proton-proton coupling constants, we have investigated the coupling constants in a series of 3-substituted ethyl alk-2-enoates. We have used first-order theory in analysing and assigning the spectra and have used the chemical shifts to differentiate between certain geometrical isomers. In addition, infrared measurements³ and stability considerations have previously been used to assist in assignment of configuration.

Chemical Shifts.—Jones *et al.*³ state that the chemical shifts for the vinylic methyl groups occur at higher field strengths in the *trans*- than in the *cis*-isomers, whereas the reverse is true for the vinylic proton. The ethyl β -methylthiocrotonate isomer with $\tau_{\text{H}} = 5.19$ and $\tau_{\text{CH}_3} = 7.58$ has the *cis*-configuration, and the other isomer ($\tau_{\text{H}} = 4.13$, $\tau_{\text{CH}_3} = 8.39$) has the *trans*-configuration. This assignment is supported by our infrared

¹ Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Oxford, 1959.

² Gutowsky, Karplus, and Grant, *J. Chem. Phys.*, 1959, **31**, 1278.

³ Jones, Morris, Vernon, and White, *J.*, 1960, 2349.

⁴ Fraser, *Canad. J. Chem.*, 1960, **38**, 549.

⁵ Whipple, Goldstein, and Mandell, *J. Amer. Chem. Soc.*, 1960, **82**, 3010.

⁶ Fraser and McGreer, *Canad. J. Chem.*, 1961, **39**, 505.

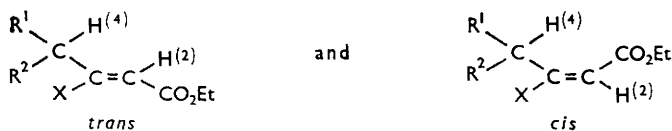
studies in the 800—1000 cm^{-1} region [ν_{max} (*cis*) 920 cm^{-1} , (*trans*) 823 and 955 cm^{-1}], and is in agreement with the stereospecific nucleophilic displacement of the chlorine in ethyl β -chlorocrotonate by the mesitylthio-ion, and with stability considerations.

It may be seen from our results that the chemical shifts for both the vinylic proton and methyl group move to higher field values as the mesomeric character ($+M$) of the 3-substituent increases (see Table). Thus the series $-\text{NR}_2 > -\text{S}\cdot\text{C}_6\text{H}_2\text{Me}_3 > -\text{S}\cdot\text{C}_6\text{H}_5 > -\text{Cl}$, forecast on the basis of mesomeric interactions with unsaturated residues,⁷ agrees with the experimentally determined chemical shifts. This effect may be used to assist in the determination of the configuration of ethyl β -piperidinocrotonate. The value quoted for the methyl protons in this ester, $\tau = 7.65$, should be higher than the values found for the methyl protons of ethyl β -mesitylthiocrotonate [τ (*cis*) = 7.58, τ (*trans*) = 8.39]. Thus the β -piperidino-compound should be the *cis*-isomer, in agreement with the vinylic-proton shift.

The further evidence in favour of the *cis*-configuration is as follows: (i) in these β -substituted crotonates, the *cis*-compounds appear to have greater thermal stability than the *trans*-compounds, possibly owing to the importance of a canonical form such as (I; X = Cl, PhS, mesitylthio, or piperidino) for the *cis*-compound, which would be more stable than the corresponding canonical form for the *trans*-compound, in which the conjugated groups are *cis* to each other; (ii) infrared studies show a strong band at 855 cm^{-1} , probably due to out-of-plane deformation of the $:\text{C}-\text{H}$ system, and such a band has been said to be characteristic of *cis*-isomers.³

The existence of two isomers of 3-chloro-4-methylpent-2-enoic acid may be seen from the two vinylic-proton peaks in the spectrum of the crude acid, in the same region as those reported by Jones *et al.*³ for *cis*- and *trans*- β -chlorocrotonic acid. Two vinylic-proton peaks (τ 3.80 and 4.06) were also observed in the spectrum of the crude ester obtained from the acid. The $\alpha\beta$ -unsaturated ester, after separation from the $\beta\gamma$ -compound by preparative gas chromatography, showed only the higher of the two peaks; no fraction was found containing the lower peak. This result indicates that the $\alpha\beta$ -unsaturated ester has the *cis*-configuration, the thermally unstable *trans*-isomer having isomerised on the column; however, this assignment is only tentative until further results can be obtained. The *cis*-assignment is supported by the strong infrared band at 857 cm^{-1} . There do not appear to be any bands in the 900—950 cm^{-1} region analogous to those obtained from the ethyl chlorocrotonates. The isomer of ethyl 4-methyl-3-phenylthio-pent-2-enoate, obtained by reaction of the 3-chloro-isomer with sodium phenyl sulphide, may possibly have the *cis*-configuration ($\tau_{\text{H}} = 4.24$, $\tau_{\text{OH}_2} = 7.45$, ν_{max} 837 cm^{-1}). This is in accordance with the theory of stereospecific reaction^{3,8} of the probable *cis*-chloropent-2-enoate with nucleophilic reagents.

Proton-proton Coupling Constants.—We have determined the coupling constants ($J_{2,4}$) for a variety of ethyl 3-substituted alkenoates of the type



where X = Cl, S·Ph, S·C₆H₂Me₃, and R¹ or R² = H or Me (see Table). In the ethyl β -chlorocrotonates and the 3-chloro-4-methylpent-2-enoic acids, $J_{2,4}(\textit{cis}) < J_{2,4}(\textit{trans})$, whilst in the ethyl β -phenylthio- and β -mesitylthio-crotonates, $J_{2,4}(\textit{trans}) < J_{2,4}(\textit{cis})$. It appears, therefore, that structural elucidations based on the relative sizes of the proton-proton coupling constants would be of little value. The relative signs of the coupling constants could not be established from the observed spectra.

⁷ Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953, pp. 75—77.

⁸ Truce and Pizey, unpublished results.

Chemical shifts and coupling constants for the compounds $R^1R^2CH\cdot C(X):CH\cdot CO_2Et$.

		Chemical shifts (τ values) ⁹ (p.p.m.)							
	R^1	R^2	X *	C:C-H(2)	<i>cis</i> - <i>trans</i>	C:C-C-H(4)	<i>cis</i> - <i>trans</i>	$J_{2,4}$ (c./sec.)	
<i>cis</i>	H	H	Cl	4.01	}	7.49	}	1.20	
<i>trans</i>	H	H	Cl	3.96		0.05		7.77	-0.26
<i>cis</i>	H	H	S·Ph	4.67	}	7.58	}	1.12	
<i>trans</i>	H	H	S·Ph	4.14		0.53		8.25	-0.67
<i>cis</i>	H	H	S·Mes	5.19	}	7.58	}	1.10	
<i>trans</i>	H	H	S·Mes	4.18		1.01		8.39	-0.81
—	H	H	piperidine	5.33		7.65		—	
—	Me	Me	Cl	4.05		7.35		0.54	
—	Me	Me	S·Ph	4.24		7.45		0.56	
<i>cis</i> †	Me	Me	Cl	3.97	}	—		0.56	
<i>trans</i> †	Me	Me	Cl	3.45		0.52	—		0.00

* S·Mes is the mesitylthio-group. † Refers to the crude acid and is a tentative assignment only.

Experimental.—Nuclear magnetic resonance spectra were measured at 60 Mc./sec. with a Varian A60 spectrometer, tetramethylsilane being used as an internal standard. 7–10% Solutions in carbon tetrachloride were used. Infrared measurements were made on thin films, for liquid samples, and on 10% solutions in chloroform, for solid samples.

Ethyl β -chloro-cis- and -trans-crotonate were prepared from the crude acids³ by the method of Scheibler and Voss¹⁰ and were separated by use of a Todd column; they were chromatographically pure.

Ethyl β -phenylthio-cis- and -trans-crotonate were prepared by use of the stereospecific reaction^{3,8} between sodium phenyl sulphide and the appropriate ethyl chlorocrotonate (78 and 87% yield, respectively). The isomers were purified by use of a Todd column and were chromatographically pure.

Ethyl β -mesitylthio-cis- and -trans-crotonate were prepared from sodium mesityl sulphide (1 mol.) and the appropriate ethyl chlorocrotonate (1 mol.), in ethanol as solvent. The *cis-ester*, recrystallised from aqueous ethanol, had m. p. 52.5–53.5° (94.5%) (Found: C, 68.4; H, 7.75; S, 12.0. $C_{15}H_{20}O_2S$ requires C, 68.15; H, 7.65; S, 12.1%), ν_{max} . 850 and 920 cm^{-1} . The band at 850 cm^{-1} appears in mesitylenethiol and probably covers the normal band due to C-H deformation. The *trans-ester* was recrystallised from aqueous ethanol (55% yield), m. p. 64° (Found: C, 68.5; H, 7.8; S, 12.45%), ν_{max} . 823, 850, and 955 cm^{-1} .

Ethyl 3-chloro-4-methylpent-2-enoate was prepared by esterification¹⁰ of the crude acid obtained from the reaction of phosphorus pentachloride with ethyl isobutyrylacetate. The *pent-2-enoate* was separated from the accompanying *pent-3-enoate* chromatographically, by use of an Aerograph "Autoprep" unit with a 20' \times 3/8" poly-(*m*-phenyl ether) 6-ring column at 180°, and had b. p. 58–60°/3.2 mm., n_D^{27} 1.4578 (Found: C, 54.5; H, 7.5; Cl, 20.25. $C_8H_{13}ClO_2$ requires C, 54.4; H, 7.4; Cl, 20.1%), λ_{max} . 225 $m\mu$ (ϵ 49,000), ν_{max} . 1640 and 857 cm^{-1} .

Ethyl 4-methyl-3-phenylthiopent-2-enoate was prepared by the reaction of sodium phenyl sulphide (1 mol.) with the 3-chloro-compound (1 mol.), in ethanol as solvent, and had b. p. 115°/2 mm. (Found: C, 67.4; H, 7.3; S, 12.6. $C_{17}H_{24}O_2S$ requires C, 67.2; H, 7.25; S, 12.8%), ν_{max} . 837 cm^{-1} .

Ethyl β -piperidinocrotonate was prepared by the reaction of ethyl β -chloro-*cis*-crotonate with piperidine in dry ether at room temperature for seven days (92% yield). The reaction of piperidine with ethyl β -chloro-*trans*-crotonate under similar conditions gave a compound with similar physical constants.

The authors thank the National Institutes of Health and the U.S. Army Research Office for financial support.

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[Received, June 19th, 1963.]

⁹ Tiers, *J. Phys. Chem.*, 1958, **62**, 1151.

¹⁰ Scheibler and Voss, *Ber.*, 1920, **53**, 382.

164. ω -(3,5-Dioxo-1,2,4-triazin-6-yl)-alkanoic Acids (Azauracyl-alkanoic Acids).

By G. B. BARLOW.

1,2,4-TRIAZINE-3,5-DIONE (azauracil) and many of its derivatives show pronounced biological activity. The 6-alkyl derivatives display narcotic activity,¹ and in particular the *N*²-riboside² has marked antimitotic properties and can terminate pregnancy in mice.³

Azauracils substituted in the 6-position are readily prepared by the ring-closure of α -oxo-carboxylic acid semicarbazones in the presence of sodium ethoxide.¹ The use of α -oxo-dicarboxylic acid semicarbazones leads directly to the azauracyl-alkanoic acids, some of which, with their esters, have been prepared and examined for biological properties, with particular emphasis on narcosis and abortifacient action. Details of the acids and esters are included in Tables 1 and 2, and Table 3 lists the acid dissociation constants and ultraviolet spectra.

TABLE 1.
Azauracyl-alkanoic acids, $R \cdot [CH_2]_n \cdot CO_2H$ ($R =$ azauracyl).

<i>n</i>	Yield (%)	M. p.	Found (%)				Equiv.	Formula	Required (%)			
			C	H	N	C			H	N	Equiv.	
2	—	196—198°	39.5	4.1	22.6	183	C ₆ H ₇ N ₃ O ₄	38.9	3.8	22.7	185	
3	63	204	42.2	4.5	21.6	192	C ₇ H ₉ N ₃ O ₄	42.2	4.6	21.1	199	
4	70	187—188	44.9	5.1	20.1	216	C ₈ H ₁₁ N ₃ O ₄	45.0	5.3	19.7	213	
5	43	187—188	46.9	5.7	18.6	236	C ₉ H ₁₃ N ₃ O ₄	47.6	5.8	18.5	227	

TABLE 2.
Ethyl azauracyl-alkanoates, $R \cdot [CH_2]_n \cdot CO_2Et$ ($R =$ azauracyl).

<i>n</i>	Yield (%)	M. p.	Found (%)				Equiv.	Formula	Required (%)			
			C	H	N	C			H	N	Equiv.	
1	—	187—188° (decomp.)	42.2	5.4	21.2	202	C ₇ H ₉ N ₃ O ₄	42.2	4.6	21.1	199	
2	—	113—114	45.3	5.3	20.55	209	C ₈ H ₁₁ N ₃ O ₄	45.0	5.3	19.7	213	
3*	61	93—94	—	—	18.8	229	C ₉ H ₁₃ N ₃ O ₄	—	—	18.5	227	
4†	66	108—109	50.2	6.3	16.9	245	C ₁₀ H ₁₅ N ₃ O ₄	49.9	6.3	17.4	241	
5	93	108—109	51.9	6.6	16.3	251	C ₁₁ H ₁₇ N ₃ O ₄	51.8	6.7	16.5	255	

* Gave amide m. p. 94—95° [Found: N (amide), 7.1%; Equiv., 199; pK_a 7.25. C₇H₁₀N₄O₃ requires N (amide), 7.1%; Equiv., 198]. † Gave amide m. p. 109—111° [Found: N (amide), 6.6%; Equiv., 215; pK_a 7.51. C₈H₁₂N₄O₃ requires N (amide), 6.6%; Equiv., 212].

TABLE 3.

Ultraviolet spectra (in methanol) and acid dissociation constants of azauracyl-alkanoic acids and their esters.

<i>n</i>	Acids				Esters		
	pK_{a1}	pK_{a2}	$\epsilon_{max. at}$		pK_a	$\epsilon_{max. at}$	
			211 m μ	254 m μ		210 m μ	252 m μ
1	—	—	—	—	6.13	9730*	5280†
2	4.14	7.77	6380	5180	7.22	6310	5500
3	4.77	7.92	6460	5770	7.17	6770	5830
4	4.97	7.95	6640	5910	7.52	7050	5900
5	4.77	7.58	6430	6000	7.57	6440	5850

* $\lambda_{max.}$ 224 m μ . † $\lambda_{max.}$ 261 m μ .

Azauracyl-butyric, -valeric, and -caproic acid were readily soluble in dioxan, and, on the addition of 1—2 volumes of light petroleum, crystalline deposits were formed. Examination of the compounds by titration and infrared absorption showed the presence of dioxan; in the cases of the butyric acid and the caproic acid the molecular ratio was 1 : 1, but the valeric acid adduct decomposed too rapidly to allow a quantitative examination. Dioxan is known to form complexes with a variety of molecules.⁴ Hydrogen bonding

¹ Chang, *J. Org. Chem.*, 1958, **23**, 1951.

² Skoda, Hess, and Sorm, *Experientia*, 1957, **13**, 150.

³ Sanders, Wiesner, and Yudkin, *Nature*, 1961, **189**, 1015.

⁴ Hassel and Romming, *Quart. Rev.*, 1962, **16**, 1.

could occur between the dioxan and either the carboxylic acid group or N-4 of the triazine ring; the fact that complex formation did not occur with the esters may indicate the necessity for both requirements.

None of these compounds had any narcotic or tranquillising effects, and there was no sign of interference in pregnancy in mice.

Experimental.— α -Oxo-succinic and -glutaric acid were available commercially. α -Oxo-adipic, -pimelic, and -suberic acid were synthesised from diethyl oxalate and the appropriate diester.⁵

Ring-closure. A solution of the α -oxo-dicarboxylic acid semicarbazone (0.1 mole) in ethanol (150 ml.) and ethylene glycol (125 ml.) was heated under reflux for 24 hr. in the presence of sodium ethoxide (0.4 mole). The solvents were evaporated *in vacuo* and the residue acidified with hydrochloric acid. The solid which appeared overnight was purified by precipitation from ethyl acetate by the addition of light petroleum (b. p. 40–60°).

The azauracyl-acids could be esterified by refluxing in ethanol with 5% of concentrated sulphuric acid; they were recrystallised from water. The esters were also formed slowly by refluxing the α -oxo-dicarboxylic acid semicarbazones in ethanol with a trace of sulphuric acid.

Amides were formed by the action of concentrated aqueous ammonia on ethereal solutions of the esters, and were purified by precipitation from ethanol with light petroleum (b. p. 40–60°).

Dioxan complexes. The adducts were precipitated from dioxan solutions of the acids by addition of light petroleum (b. p. 40–60°): azauracylbutyric acid *adduct* (Found: Equiv., 283. 1:1 Adduct requires Equiv., 287); azauracylcaproic acid *adduct* (Found: Equiv., 304. 1:1 Adduct requires Equiv., 315). Both adducts showed ν_{\max} . at 1118, 1075, 1043, 891, and 875 cm^{-1} .

The biological testing was carried out by Mrs. S. Keene, and the project was financed by the London Research Foundation.

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QUEEN ELIZABETH COLLEGE, LONDON W.8.

[Received, June 24th, 1963.]

⁵ Friedman and Kosower, *Org. Synth.*, Coll. Vol. III, 1955, p. 510.

165. A Convenient Preparation of L-Homocystine from L-Methionine.

By D. B. HOPE and J. F. HUMPHRIES.

UNTIL now the most convenient preparation of L-homocystine had been that of du Vigneaud and Patterson¹ who, following the method used earlier² for DL-homocystine, boiled L-methionine with 18N-sulphuric acid. From the partly racemic product low yields (~20%) of pure L-homocystine could be obtained by recrystallisation from water. Stekol³ prepared DL-homocystine by demethylation of DL-methionine with sodium in liquid ammonia; this method has been used⁴ to synthesise sulphides derived from DL-homocystine, and by a modification of it we have prepared L-homocystine from L-methionine in yields of more than 90%.

We reduced L-methionine with sodium in liquid ammonia and, after oxidation of the homocysteine with potassium ferricyanide, obtained homocystine whose optical rotation (+10–30°) showed that considerable racemisation had occurred. This was unexpected since S-benzyl-L-homocysteine can be debenzylated by the same reagent to give optically pure L-homocystine.¹ Reduction in the presence of one molar equivalent of methanol almost completely suppressed the racemisation, the homocystine obtained having $[\alpha]_D =$

¹ du Vigneaud and Patterson, *J. Biol. Chem.*, 1935, **109**, 97.

² Butz and du Vigneaud, *J. Biol. Chem.*, 1932, **99**, 135.

³ Stekol, *J. Biol. Chem.*, 1941, **140**, 827.

⁴ Stevens, Johnson, and Watanabe, *J. Biol. Chem.*, 1955, **212**, 49; McHale, Mamalis, and Green, *J.*, 1960, 2847; Frankel and Gertner, *J.*, 1961, 463.

+74—75°. D-Methionine has been similarly demethylated to give D-homocystine with $[\alpha]_D = -74.5^\circ$. Other substances which behave as weak acids in liquid ammonia, *e.g.*, water and ethanol, also suppressed racemisation. We concluded that a base was responsible for racemisation, which was found to occur during the work-up of the product and can be avoided completely by adding to the reaction mixture, immediately after the reduction, ammonium chloride in an amount equimolar with the methionine used. Ammonium chloride is preferable to methanol because the optical purity of the product is higher, and also because methanol causes frothing of the liquid ammonia owing to the formation of the sparingly soluble sodium methoxide.

Experimental.—L-Methionine (10 g.) was dissolved in anhydrous liquid ammonia (400 ml.) and the solution was stirred mechanically. Small pieces of sodium were added until the initial vigorous reaction ceased (1.6 g. of sodium were consumed rapidly, presumably reducing the proton derived from the carboxyl group), and addition was continued until a blue colour persisted for 20 min. (total sodium added was 4.88 g., 3.1 atom-equiv.). Ammonium chloride (3.6 g., 1 molar equiv.) was then added slowly; a vigorous reaction occurred and the deposit of sodamide disappeared. The remaining ammonia (approx. 200 ml.) was allowed to evaporate, the residue was dissolved in water (150 ml.), the solution was filtered, the pH of the filtrate was adjusted to 7 with glacial acetic acid, and a saturated solution of potassium ferricyanide was added until a yellow colour persisted. During the oxidation the pH was kept at 6—8 by addition of N-sodium hydroxide. The mixture was set aside at 4° overnight, and the crystalline product was filtered off, washed with water until free from ferrocyanide ions, and then with ethanol and with ether. The material, dried at 80° (8.28 g., 92%), showed $[\alpha]_D^{20} + 77.0^\circ$ (*c* 1 in N-HCl) both before and after recrystallisation from water (4.5 g. in 1200 ml.) (79% recovery) (Found: C, 35.9; H, 5.9; N, 10.2; S, 23.6. Calc. for $C_8H_{16}N_2O_4S_2$: C, 35.8; H, 6.0; N, 10.4; S, 23.9%).

Larger amounts (up to 30 g.) of L-methionine have been reduced in 1 litre of liquid ammonia by adding the methionine in four or five portions, to avoid the accumulation of sodamide and the consequent difficulty in stirring the reaction mixture. Sufficient ammonium chloride to produce a clear solution was added at the end of the reaction.

This research was supported by a grant from the U.S. Air Force, Office of Aerospace Research, through its European Office.

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[Received, June 29th, 1963.]

166. *Aquation of the Trisoxalatorhodate(III) Ion.*

By R. D. GILLARD and G. WILKINSON.

THE various hydrates of the compound usually called potassium trisoxalatorhodate(III) have been shown¹ to contain monodentate oxalato-groups; in this work we refer to the complex ion containing rhodium and three oxalate groups as "trisoxalatorhodate(III)." A kinetic study² of the aquation of the "trisoxalate" species has shown that the bisaquobisoxalatorhodate(III) anion is a stable intermediate, though no conclusion as to the stereochemistry of the bisquo-species was possible. We have now succeeded in separating the *cis*- and the *trans*-isomer of the bisaquobisoxalatorhodate(III) anion from the "trisoxalato"-species, and from each other, by means of anion exchange. The *trans*-isomer, having less affinity for Deacidite FF than either of the other species, can be eluted with water; the *cis*-isomer is eluted by a dilute solution of potassium chloride, and the "trisoxalatorhodate(III) anion" only by saturated potassium chloride solution.

The electronic spectra (see Table) of "trisoxalatorhodate(III)" and both *cis*- and *trans*-bisaquobisoxalatorhodate(III) anions are very similar. The transition ${}^1T_{1g} \leftarrow {}^1A_{1g}$ ("band I") in d^6 complexes with O_h symmetry is expected to split when the symmetry is lowered to D_4 or C_2 . However, the size of the splitting is a function of the ligands, and replacement of the oxalate group by water molecules, with similar ligand-field strength,

¹ Porte, Gutowsky, and Harris, *J. Chem. Phys.*, 1961, **34**, 66.

² Barton and Harris, *Inorg. Chem.*, 1962, **1**, 251.

Electronic spectra of oxalato-complexes of rhodium(III).

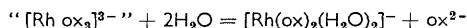
(Frequencies are in cm^{-1} .)

Complex	ν_1	ϵ_1	ν_2	ϵ_2	Notes
" $[\text{Rh ox}_3]^{3-}$ "	25,000	230	33,000	—	<i>a, b</i>
<i>cis</i> - $[\text{Rh ox}_2(\text{H}_2\text{O})_2]^-$	24,880	120	40,000	10^3	
<i>trans</i> - $[\text{Rh ox}_2(\text{H}_2\text{O})_2]^-$	24,810	92	39,500	10^3	
<i>cis</i> - $[\text{Rh ox}_2\text{Cl}_2]^{3-}$	22,900	170	28,400	262	<i>c</i>
<i>trans</i> - $[\text{Rh ox}_2\text{Cl}_2]^{3-}$	21,500	58	25,000	40	

a, All spectra were measured in water. *b*, Jørgensen³ recorded ν , 25,130, ϵ , 290; ν_2 33,000 cm^{-1} . *c*, Jørgensen⁴ recorded ν , 22,900, ϵ , 190; ν_2 28,400, ϵ 275.

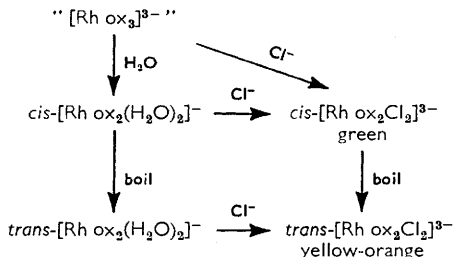
does not lead to observable splitting of band I. The second (${}^1T_{2g} \leftarrow {}^1A_{1g}$ in O_h) ligand-field band was hidden by the intense allowed transitions around 250 μ . Because of the similarity in spectra, analysis by spectrophotometry of mixtures produced by aquating "*trisoxalatorhodate*(III)" is probably unreliable and the validity of using absorption at 400 μ for kinetic measurements of the aquation process is dubious.

Infrared spectra of all three anions are also similar; our characterisation as *bis*aquobisoxalatorhodates(III) is based on analysis, reactions with chloride ion to form the known dichlorobisoxalatorhodate(III) anions, and the knowledge from kinetics that, apart from starting material, only bisoxalato-species are present in our reaction mixture. The stereochemistry of the isomers is indicated by several facts. *cis*-Isomers are usually more firmly held on ion-exchange resins than the corresponding *trans*-isomers. That rearrangement does not occur at all readily for complexes of rhodium(III) supports our conclusion that the major product of the reaction



is the *cis*-*bis*aquobisoxalatorhodate(III) anion. We find that this *cis*-isomer reacts readily with chloride ions to give the known complex *cis*-dichlorobisoxalatorhodate(III), which was isomerised to *trans*-dichlorobisoxalatorhodate(III) when boiled, as noted by Delépine.⁵

We have now obtained potassium *cis*-dichlorobisoxalatorhodate(III) by heating the double salt of potassium chloride and potassium "*trisoxalatorhodate*(III)"; the *cis*-dichloro-compound is also formed when an intimate mixture of potassium chloride and "*potassium trisoxalatorhodate*(III)" is heated. The reactions we have observed are summarised below:



In our 90% aquated product, the concentrations of *cis*- and *trans*-*bis*aquobisoxalatorhodate(III) anions are in the ratio 7 : 1.

Experimental.—Microanalyses were by the Microanalytical Laboratory, Imperial College. Electronic spectra were measured with Unicam S.P. 500 and Perkin-Elmer "*Spectracord*" instruments, and infrared spectra with a Perkin-Elmer model 21 spectrometer having calcium fluoride and sodium chloride optics.

Preparation of partially aquated salt mixture. Hexapotassium trisoxalatorhodate hydroxo-(hydrogen oxalato)bisoxalatorhodate(III) octahydrate (orange) was prepared by Werner and Poupardin's method⁶ and converted into the yellow so-called monohydrate by pumping at 45°. The monohydrate (1.25 g.; 2.5×10^{-3} mole) in water (5 ml.) was treated with concentrated

³ Jørgensen, *Acta Chem. Scand.*, 1956, **10**, 500.

⁴ Jørgensen, *Acta Chem. Scand.*, 1957, **11**, 151.

⁵ Delépine, *Anales Soc. espñ. Fis. Quim.*, 1929, **27**, 485.

⁶ Werner and Poupardin, *Ber.*, 1914, **47**, 1955.

perchloric acid (72%) till the solution was 3M. After 1 hr. boiling, the solution was cooled and solid potassium carbonate was added until no more carbon dioxide was evolved. The mixture was then cooled (ice-bath) and the potassium perchlorate removed by filtration. The yellow filtrate was slowly treated with ethanol (10 ml.), and again filtered to remove the further amount of potassium perchlorate formed. The filtrate was poured into ethanol (100 ml.) and the yellow precipitate was collected, washed with alcohol, and dried in a vacuum desiccator. The dry product (A) was fairly deliquescent in moist air; this was due to the potassium *cis*-bisaquobisoxalatorhodate(III) content; neither "potassium trisoxalatorhodate(III) hydrate" nor potassium *trans*-bisaquobisoxalatorhodate(III) is deliquescent. The product A showed absorptions in the infrared spectrum (in cm^{-1}) at 3500—2700bd s, 1850—1550bd s, 1403m, 1340w, 1260bd s, 970w, 984m, 822s, 814sh, and 776m.

The mixed product was very soluble in water, and addition of solutions of either hexamminecobalt(III) chloride or the analogous compound of ethylenediamine gave yellow precipitates containing the "trisoxalatorhodate(III)" anion. In one experiment, the precipitated trisethylenediaminecobalt(III) trisoxalatorhodate(III) hydrate, which presumably contains rhodium(III) in complex ions of both C_2 and D_3 symmetry, was collected and washed with ice-water (Found: C, 22.7; H, 4.6; N, 11.7. $C_{12}H_{26}CoN_{13}Rh$ requires C, 23.1; H, 4.2; N, 11.9%). The infrared spectrum (of mulls) was identical with that of an authentic sample, prepared from pure hexapotassium trisoxalatorhodate(III) hydroxo(hydrogen oxalato)bisoxalatorhodate(III). Both specimens showed bands (in cm^{-1}) at 3500s, 3241s, 3193sh, 1725m, 1697s, 1676s, 1660s, 1600sh, 1300m, 1259w, 1237s, 1169sh, 1159s, 1118m, 1060s, 1030w, 1016m, 898m, 849m, 819sh, and 808s. However, this procedure failed to remove all the unchanged "trisoxalatorhodate(III)" anion. The following ion-exchange procedure allowed the separation of all three components of the solution and isolation of the pure salts.

Anion exchange separation. 1. *Potassium trans-bisaquo-oxalatorhodate(III) dihydrate.* The yellow mixture (A) (0.97 g.) was dissolved in the minimum of water (1.8 ml.), and the solution run on to a column (25 g.) of anion-exchange resin (Deacidite FF, chloride form; mesh). A bright yellow solution of potassium *trans*-bisaquobisoxalatorhodate(III) was obtained, when the column was eluted with water (4 ml.). This fraction was poured into well-stirred ethanol (20 ml.), and the yellow precipitate collected (yield 0.12 g., 12.3% based on original rhodium). It was recrystallised [water (0.5 ml.) and ethanol (4 ml.)] to give yellow crystals of *potassium trans-bisaquobisoxalatorhodate(III) dihydrate* (Found: C, 12.1; H, 2.5; Rh, 27.0. $C_4H_8KO_{12}Rh$ requires C, 12.3; H, 2.1; Rh, 26.4%). The infrared spectrum of mulls showed bands (in cm^{-1}) at 3410s bd, 1681sh, 1659s, 1400m, 1245m, 893w, 815s, and 755w.

2. *Potassium cis-bisaquobisoxalatorhodate(III) hydrate.* After the removal of the *trans*-isomer from the column, the resin was washed with water (50 ml.), and then with a 10% solution of potassium chloride as eluant. The bright yellow eluate (ca. 10 ml.) was treated slowly with an equal volume of ethanol, cooled to 0°, and left for 2 hr. The precipitated potassium chloride was removed by filtration, and slow concentration of the filtrate *in vacuo* gave yellow crystals of *potassium cis-bisaquobisoxalatorhodate(III) hydrate* (yield 0.72 g., 77.4% based on original rhodium) recrystallised twice by dissolving in water and concentrating *in vacuo* (Found: C, 12.7; H, 2.0; Rh, 28.1. $C_4H_8KO_{11}Rh$ requires C, 12.9; H, 1.6; Rh, 27.7%). The infrared spectrum showed bands (in cm^{-1}) at 3381s bd, 1701m, 1677s, 1600m, 1400m, 1306m, 1258w, and 814m bd.

3. *Recovery of the unchanged "trisoxalatorhodate(III)" from the column.* After the removal of the *cis*-isomer from the column, the resin was washed with a 10% solution of potassium chloride (8 ml.), and then with a saturated solution of potassium chloride. The yellow eluate (8 ml.) was treated with an equal volume of ethanol and the precipitated potassium chloride removed. The electronic spectrum of a portion of the filtrate, suitably diluted, was identical with that of the authentic "trisoxalatorhodate(III)." When a solution of trisethylenediaminecobalt(III) chloride was added to the undiluted filtrate, a yellow precipitate of trisethylenediaminecobalt(III) trisoxalatorhodate(III) hydrate (0.12 g., 7.7%, based on original rhodium content), was obtained, whose infrared spectrum was identical with that of an authentic sample.

Within the limits of the experiment, the composition of A, the original reaction product, was: $K_3Rh\text{ ox}_3\cdot H_2O$, 7.7%; *trans*- $K[Rh\text{ ox}_2(H_2O)_2]\cdot 2H_2O$, 12.3%; *cis*- $K[Rh\text{ ox}_2(H_2O)_2]\cdot H_2O$, 77.4%. Losses during working up accounted for the remaining 3%, mostly due to the *cis*-isomer.

Conversion of bisquo- into dichloro-bisoxalatorhodate(III) complexes. Potassium *cis*-bisaquobisoxalatorhodate(III) hydrate (0.37 g.; 10^{-3} mole) and potassium chloride (0.22 g.; 3×10^{-3}

mole) were dissolved in water (5 ml.), and the solution kept at 90° for 30 min.; it was first green (due to *cis*-dichlorobisoxalatorhodate(III)) then red-brown. It was cooled and kept *in vacuo* overnight; yellow-orange crystals of potassium *trans*-dichlorobisoxalatorhodate(III) hydrate were then obtained. The infrared spectrum showed bands within 2 cm.⁻¹ of those reported by Holtzclaw and Collman,⁷ who wrongly describe the compound as the *cis*-isomer. The electronic spectrum of our product agreed with that reported for the *trans*-isomer.⁴ The green potassium *cis*-dichlorobisoxalatorhodate was obtained when a finely ground moist mixture of the *cis*-bisaquo-complex and potassium chloride in the requisite proportions was heated to 125°. Boiling a solution of *cis*-dichlorobisoxalatorhodate(III) causes isomerisation to the *trans*-dichloro-species; this is where the error in ref. 5 arose, since their preparative method involved refluxing the solution.

The *trans*-bisaquobisoxalatorhodate(III) anion reacted with chloride ion under similar conditions to those described above, giving *trans*-dichlorobisoxalatorhodate(III), identified by its electronic spectrum.⁴ Both *cis*- and *trans*-bisaquobisoxalatorhodates(III), and "trisoxalatorhodate(III)," when boiled with concentrated hydrochloric acid, gave only the hexachlororhodate(III) anion, identified by its electronic spectrum.³

We thank Johnson, Matthey and Co., Ltd., for the loan of rhodium salts.

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[Received, June 14th, 1963.]

⁷ Holtzclaw and Collman, *J. Amer. Chem. Soc.*, 1958, **80**, 2054.

167. Oxidation of Phenols to *p*-Benzoquinones by Peracetic Acid.

By D. BRYCE-SMITH and A. GILBERT.

CHAMBERS, GOGGIN, and MUSGRAVE obtained 0—80% yields of *p*-benzoquinones by oxidation of various phenols with trifluoroperacetic acid.¹ Although peracetic acid is reported to attack the *ortho*-positions of phenols,² we have found it to oxidise 2,6- and (more significantly) 2,5-dimethylphenol to good yields of the corresponding *p*-benzoquinones in a mixture of sulphuric acid and acetic acid. The method may well be more generally useful and seems to be simpler and cheaper than those now available;^{1,3,4} but phenol itself is oxidised mainly to *cis,cis*-muconic acid by peracetic acid,⁵ and gives only 15% of *p*-benzoquinone under the present conditions.

Experimental.—2,5-Dimethyl-*p*-benzoquinone. To a stirred solution of 2,5-dimethylphenol (15 g.) in glacial acetic acid (100 ml.) containing sulphuric acid (1.0 ml.) was added 80% hydrogen peroxide (12 ml.) during 45 min.; the temperature was kept below 20°. After a further 60 min., the temperature was allowed to rise to 60° (but not higher); the exothermic reaction ceased after 10 min. at 60°. Cooling and the addition of water gave yellow crystals of the quinone (12.5 g., 74.8%), m. p. 124—124.5° (lit.,⁶ 125°). The m. p. was not raised by recrystallisation from 1 : 1 benzene—light petroleum (b. p. 60—80°).

Under similar conditions, 2,6-dimethylphenol gave 2,6-dimethyl-*p*-benzoquinone, m. p. 72—73° (lit.,⁷ 73°), in 68% yield.

An attempt to shorten the time for addition of the hydrogen peroxide led to an over-vigorous reaction. The time given should probably be extended for larger scale preparations.

One of us (A. G.) thanks the D.S.I.R. for a maintenance grant and Esso Research Limited for laboratory facilities.

CHEMISTRY DEPARTMENT, THE UNIVERSITY, READING.

[Received, July 25th, 1963.]

¹ Chambers, Goggin, and Musgrave, *J.*, 1959, 1804.

² Böeseken and Metz, *Rec. Trav. chim.*, 1935, **54**, 345.

³ Ansell, Nash, and Wilson, *J.*, 1963, 3028.

⁴ Teuber and Rau, *Chem. Ber.*, 1953, **86**, 1036; Teuber, U.S. Pat. 2,182,210/1957.

⁵ Böeseken, *Proc. Acad. Sci. Amsterdam*, 1932, **35**, 750.

⁶ Auwers and Michealis, *Ber.*, 1914, **47**, 1289.

⁷ Noeltling and Torel, *Ber.*, 1885, **18**, 2679.

168. *Lithium Aluminium Hydride Reduction of Poly(fluoro-cyclic imides).*

By M. T. CHAUDHRY, G. A. POWERS, R. STEPHENS, and J. C. TATLOW.

POLYFLUORO-AMIDES are readily reduced¹⁻⁴ to amines by lithium aluminium hydride in ether. This method of reduction has now been used for the preparation of 3,3,4,4-tetrafluoropyrrolidine and 3,3,4,4,5,5-hexafluoropiperidine from tetrafluorosuccinimide⁵ and hexafluoroglutarimide,⁵ respectively. As with the analogous reduction of *NN'*-substituted perfluoroglutarimides,³ the reaction was sluggish, giving only moderate yields, but did not appear to produce detonable complexes.¹

In the reduction of hexafluoroglutarimide small amounts of two other compounds were isolated and tentatively identified as intermediates⁶ in the reduction process, *viz.*, 3,3,4,4,5,5-hexafluoro-piperidine and -piperidone. An attempted partial reduction of tetrafluorosuccinimide gave only the pyrrolidine and starting material.

As expected, the tetrafluoropyrrolidine and hexafluoropiperidine were basic,³ giving crystalline hydrochlorides; both were fully characterised. Mass spectrometry⁷ and magnetic resonance spectroscopy⁸ confirmed the structures allocated.

The possibility of pyrolytic dehydrofluorination of the tetrafluoropyrrolidine and hexafluoropiperidine, to the unknown 3,4-difluoropyrrole and 3,4,5-trifluoropyridine, was of particular interest. Thus, it is known that sodium fluoride at 300–400° dehydrofluorinates polyfluorocyclohexanes with negligible degradation.⁹ However, when tetrafluoropyrrolidine was treated in this way it gave at least nine compounds and a separation was not attempted. Under the same conditions hexafluoropiperidine gave essentially starting material and a polyfluoropyridine. The latter gave a single peak on gas-chromatographic analysis (dinonyl phthalate being used as stationary phase), but was shown by mass spectrometry⁷ to be 3,4,5-trifluoropyridine containing 2% of 2,3,4,5-tetrafluoropyridine. The infrared and ultraviolet spectra had features consistent with such a system. Sufficient material for accurate chemical study was not available. However, the basicity of the nitrogen atom and the nucleophilic susceptibility of the 4-fluorine atom was probably reflected in what appeared to be an initial self-condensation reaction of the type observed with 4-halogenopyridines.¹⁰ Thus, when kept at room temperature for 2 weeks a crystalline solid was formed which displayed the infrared and ultraviolet spectra expected for a system containing polyfluoropyridine nuclei. Support for this was provided by the reaction of the trifluoropyridine fraction with hydrazine hydrate to give a difluorohydrazinopyridine. With Fehling's solution the latter gave an unknown difluoropyridine¹¹ (presumably 3,5-difluoropyridine), but only infrared and mass-spectroscopic characterisation was possible.

The unexpected formation of 2,3,4,5-tetrafluoropyridine may occur in two ways. Firstly, from isomerisations of the S_N2' type observed between acyclic¹² and cyclic⁹ fluoro-olefins and fluoride ions, *viz.*, $F^- + \cdot CF=CF \cdot CF_2 \longrightarrow \cdot CF_2 \cdot CF=CF + F^-$, followed by a final dehydrogenation of a diene to the pyridine. Alternatively, direct nucleophilic

¹ Reid and Smith, *Chem. Eng. News*, 1951, **29**, 3042.

² Bourne, Henry, Tatlow, and Tatlow, *J.*, 1952, 4014.

³ Marks and Schweiker, *J. Amer. Chem. Soc.*, 1958, **80**, 5789.

⁴ Bissell and Finger, *J. Org. Chem.*, 1959, **24**, 1256.

⁵ Henne and Zimmer, *J. Amer. Chem. Soc.*, 1951, **73**, 1103.

⁶ Newman and Fukunaga, *J. Amer. Chem. Soc.*, 1960, **82**, 693.

⁷ J. Majer, personal communication.

⁸ L. F. Thomas, personal communication.

⁹ Rimmington, Stephens, and Tatlow, forthcoming publication.

¹⁰ Roe and Hawkins, *J. Amer. Chem. Soc.*, 1947, **69**, 2443; Den Hertog, *Rec. Trav. chem.*, 1945, **64**, 85.

¹¹ Finger, Starr, Roe, and Link, *J. Org. Chem.*, 1962, 3965.

¹² Fried and Miller, *J. Amer. Chem. Soc.*, 1959, **81**, 2078; Miller, Fried, and Goldwhite, *ibid.*, 1960, **82**, 3091.

substitution by fluoride ion at C-2 of 3,4,5-trifluoropyridine is a remote possibility (of 2,4,5-trifluoropyrimidine and argentic fluoride¹³).

Experimental.—*Gas chromatography.* Analytical work was carried out by using columns (2 m. long by 4 mm. diam.) packed with dinonyl phthalate–kieselguhr (1 : 2) (unit A) or silicone gum–kieselguhr (1 : 2) (unit B). Preparative-scale work used a column (488 cm. × 75 mm. diam.) packed with dinonyl phthalate–kieselguhr (1 : 2) (column A) and silicone gum–kieselguhr (1 : 2) (column B).

3,3,4,4-Tetrafluoropyrrolidine. Tetrafluorosuccinimide⁵ (8.0 g.), in dry ether (100 c.c.) was added during 1½ hr. to a stirred suspension of lithium aluminium hydride (9.0 g.) in dry ether (800 c.c.). After 48 hr. at 20° the mixture was cooled to 0°, and water (50 c.c.) slowly added. The precipitate was removed by centrifugation and washed with ether (3 × 100 c.c.). The combined ethereal layers were dried (MgSO₄) and filtered, and the ether evaporated. The residue was distilled and sublimed to give **3,3,4,4-tetrafluoropyrrolidine** (3.5 g.), m. p. 42.5–43.5°, b. p. 106–107° (Found: C, 33.1; H, 3.4. C₄H₅F₄N requires C, 33.6; H, 3.5%), ν_{\max} . 3150 (>NH) and 1140–1180 cm.⁻¹ (>CF), mass-spectral analysis⁷ gave a molecule ion at 143 (C₄H₅F₄N) and a fragmentation pattern consistent with four fluorines on C-3 and C-4. The fluorine-19 magnetic resonance spectrum⁸ (n.m.r.) was also that expected for the structure allocated and contained a triplet signal of intensity ratio 1 : 2 : 1, probably due to the degeneration of one half of an A₄X₄ type spectrum.

The pyrrolidine (0.11 g.) in dry ether with hydrogen chloride gave a precipitate which was crystallised from ethanol to give the *hydrochloride* (0.12 g.), subliming rapidly at 210° (Found: C, 26.7; H, 3.4. C₄H₆ClF₄N requires C, 26.7; H, 3.3%). When benzoyl chloride (0.15 c.c.) was added to 10% w/v aqueous sodium hydroxide (3 c.c.) containing the above hydrochloride (0.12 g.), and the mixture shaken, a precipitate was formed which on recrystallisation from aqueous ethanol gave *1-benzoyl-3,3,4,4-tetrafluoropyrrolidine* (0.09 g.) m. p. 73° (Found: C, 53.6; H, 3.6. C₁₁H₉F₄NO requires C, 53.4; H, 3.6%). In a similar way the pyrrolidine (0.5 g.) and toluene-*p*-sulphonyl chloride (1.0 g.) at 100° gave **3,3,4,4-tetrafluoro-1-toluene-*p*-sulphonyl-pyrrolidine** (0.6 g.), m. p. 117° (Found: C, 44.2; H, 3.6. C₁₁H₁₁F₄NO₂S requires C, 44.4; H, 3.7%).

3,3,4,4,5,5-Hexafluoropiperidine. Hexafluoroglutarimide⁵ (9.0 g.) in dry ether (90 c.c.) was added to a stirred suspension of lithium aluminium hydride (9.5 g.) in dry ether (950 c.c.). After 48 hr. at ca. 20° the mixture was cooled to 0°, and water (50 c.c.) slowly added followed by sufficient 50% w/v sulphuric acid to dissolve the precipitate. The ether layer was separated and the aqueous phase extracted with ether (3 × 40 c.c.). The dried (MgSO₄) ether solution was filtered and evaporated to leave a liquid which was distilled to give a fraction (5.4 g.), boiling 78–138°, and a residue, which on distillation *in vacuo*, afforded a yellow paste (1.2 g.), ν_{\max} . 3250 (>NH) and 1725 cm.⁻¹ (>C=O). Gas chromatography (unit B, 140°, N₂ 3.4 l./hr.) of this fraction revealed three components which were separated on a preparative scale (column B, 138°, N₂ 50 l./hr.) to give: (i) an unidentified, very volatile liquid (0.3 g.); (ii) a volatile liquid (1.2 g.), b. p. 60–79°, ν_{\max} . 3020, 2990, 2920 (>CH), 1715, 1650 (>C=N* possibly), and 1150–1175 cm.⁻¹ (>CF), mass-spectral analysis⁷ of which showed a molecule ion at 191 (C₅H₃F₆N); (iii) **3,3,4,4,5,5-hexafluoropiperidine** (3.8 g.), b. p. 124–126° (Found: C, 31.3; H, 2.6. C₅H₃F₆N requires C, 31.1; H, 2.6%), ν_{\max} . 3300–3200 (>NH), 2900 and 2800 (>CH), 1175–1135 cm.⁻¹ (>CF). Mass spectral analysis⁷ gave a molecular weight of 193 (C₅H₃F₆N) and a fragmentation pattern consistent with the allocated structure. The fluorine-19 n.m.r. spectrum⁸ contained two broad peaks of relative intensities 2 : 1 and the proton spectrum two peaks of relative intensities 4 : 1.

The fluoropiperidine (1.0 g.) with hydrogen chloride in dry ether (15 c.c.) gave a precipitate of its *hydrochloride* (1.1 g.), decomp. at 165–170° (Found: C, 25.8; H, 2.6. C₅H₆ClF₆N requires C, 26.1; H, 2.6%). The piperidine (0.5 g.), benzoyl chloride (0.5 c.c.), and dry benzene (5 c.c.) were refluxed for 15 min., cooled, and washed with 10% w/v sodium carbonate solution, 10% v/v hydrochloric acid, and water. The benzene solution was evaporated and the residue crystallised from aqueous ethanol to give *1-benzoyl-3,3,4,4,5,5-hexafluoropiperidine* (0.45 g.), m. p. 72–74° (Found: C, 48.7; H, 3.0. C₁₂H₅F₆NO requires C, 48.5; H, 3.0%).

Pyrolysis of 3,3,4,4,5,5-hexafluoropiperidine over sodium fluoride. The piperidine (1.64 g.)

¹³ Schroeder, *J. Amer. Chem. Soc.*, 1960, **82**, 4115.

was slowly vaporised at 35° in a stream of nitrogen (1 l./hr.) passing through a glass tube (65 cm. × 45 mm. diam.) at 420° packed with sodium fluoride pellets (0.27 c.c. each). The volatile product (1.0 g.), trapped at -180°, was shown by gas chromatography (unit A, 107°, N₂ 1 l./hr.) to contain four components. The combined products (5.8 g.) of several runs were separated by gas chromatography (column A, 99°, N₂ 19 l./hr.) to give: fractions (i) and (ii) in trace amounts; (iii) 3,4,5-trifluoropyridine containing 2% of 2,3,4,5-tetrafluoropyridine (0.3 g.) according to mass spectrometry, with molecule ions at 133 and 151, respectively, and a fragmentation pattern consistent with the structures allocated, ν_{\max} . 3050 (\geq CH), 1610 and 1530 cm.⁻¹ (fluorinated pyridine nucleus), λ_{\max} . (in ethanol) 2540 Å (ϵ 2700, based on C₅H₂F₃N). After two weeks at 15–20° this fraction became largely solid, m. p. 188–190°, ν_{\max} . 1650, 1620, 1560, 1500 cm.⁻¹ (polyfluoropyridine nucleus), λ_{\max} . (in ethanol) 2880 Å; (iv) 3,3,4,4,5,5-hexafluoropiperidine (2.1 g.) (with correct i.r. spectrum). The trifluoropyridine fraction (0.2 g.) was refluxed for 5 hr. with hydrazine hydrate (0.2 g.) in ethanol (1 c.c.) and then extracted continuously with methylene chloride for 21 hr. The dried (MgSO₄) extract was filtered and evaporated and the residue sublimed (75°/30 mm.) twice to give a difluorohydrazinopyridine (0.2 g.), m. p. 134–135° (Found: C, 41.4; H, 3.6. C₅H₅F₂N₃ requires C, 41.4; H, 3.4%), ν_{\max} . 3340 and 3180 cm.⁻¹ (\geq NH).

We thank Dr. J. Majer for mass-spectrometric analyses, Dr. L. F. Thomas for the magnetic measurements, and the West Pakistan Education Department and the M.R.C. for maintenance awards (to M. T. C. and G. A. P., respectively).

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[Received, August 30th, 1963.]

169. Examination of C–H Stretching Absorptions in Aliphatic Carboxylic Acids.

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THE C–H stretching absorption of aliphatic carboxylic acids is obscured by the broad band at 2500–2700 cm.⁻¹ due to the bonded hydroxyl stretching vibration.¹ Deuterium exchange of the carboxyl hydrogen atom results in the expected isotopic shift,^{2,3} but it has not previously been pointed out that this is a convenient method of unmasking the C–H stretching absorptions.

In the course of other investigations we have studied deuterium exchange between several unsaturated carboxylic acids and deuterium oxide, and have thereby readily identified the saturated and olefinic C–H absorptions. This exchange may prove useful in the infrared examination of acidic natural products, and is preferable to the alternative technique of salt formation as the difficulties involved in exact neutralization of small quantities of acid are obviated.

A solution of the acid (25–250 mg.) in ether (5 ml.) is shaken three times, each with 1 ml. of deuterium oxide, for 1 min. The wet ethereal solution is rapidly transferred to a dried flask, and the volatile materials are removed by evacuation at room temperature.

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[Received, September 11th, 1963.]

¹ Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd edn., Methuen, London, 1958.

² Bratoz, Hadzi, and Sheppard, *Spectrochim. Acta*, 1956, **8**, 249.

³ Herman and Hofstadter, *J. Chem. Phys.*, 1939, **7**, 460.