The Use of Periodate-oxidised Glycosides in the Robinson–Schöpf Condensation: Some Analogues of 9-Methyl-3-oxagranatan-7-one

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The periodate-oxidised methyl glycosides of β -L-arabinopyranose and α -L-rhamnopyranose and periodate-oxidised benzyl β -L-arabinopyranoside have been used as the dialdehyde components in the Robinson-Schöpf condensation, yielding analogues of 9-methyl-3-oxagranatan-7-one. Comment is made on the ultraviolet spectra of these compounds.

THE behaviour of periodate-oxidised monosacchardei derivatives as the dialdehyde component in the Robinson-Schöpf^{1,2} synthesis of tropinone and its analogues has been investigated. Reaction of the general type shown, using a periodate-oxidised glycoside,* would give products closely related structurally to the known⁴ 9-methyl-3-oxagranatan-7-one (II).



The first periodate-oxidised compound used was that from methyl β -L-arabinopyranoside (III). This contains no hydroxyl group so there is no complication due to hemiacetal formation; it also has one asymmetric centre, so two products (IX) and (X) are possible in which the methoxyl group is equatorial or axial.

The condensation with acetonedicarboxylic acid and methylamine hydrochloride was carried out in the usual way. The product was separated into three fractions. The first, a crystalline compound (A), was isolated in about 40% yield. The second was a syrup from which an isomer (B) was isolated as its methiodide in about 6% yield. The third was a dark, optically inactive, nitrogencontaining syrup which was not further investigated. All attempts at isolating the free base (B) from the mixture failed. Small differences in pH and temperature, and different methods of processing, were without effect. Isomer (A) was characterised as its oxime, methiodide, hydriodide, and perchlorate; in the latter form it could be obtained in 36% yield from the crude reaction mixture. The molecular rotations of the perchlorate $(+271^{\circ})$ and of the hydriodide $(+272^{\circ})$ confirmed the presence of a common cation in them. The presence of the \cdot CH₂·COCH₂· group in isomer (A) was confirmed by conversion into two diarylidene derivatives. Attempted hydrolysis of the acetal methoxyl group with dilute aqueous hydrochloric acid was unsuccessful, presumably because of the presence of the MeO-C-C-N- group. Protonation of the nitrogen atom provides an electrostatic shield as in methyl 2-amino-2-deoxy-glycosides which are not hydrolysed in these conditions.⁵

(A) and (B) were also isolated from reaction of periodate-oxidised methyl α -D-xylopyranoside, and the enantiomer of (A) was prepared from methyl β -D-xylopyranoside [isomer (B) was not isolated]. The analogue (VII) from benzyl β -L-arabinopyranoside (IV) was also synthesised; thin-layer chromatography suggested that in this only one isomer was formed and it was isolated as its crystalline perchlorate in 51% yield, and further characterised as its dibenzylidene derivative.

Periodate-oxidised methyl α -L-rhamnopyranoside (V) was also used as the dialdehyde component giving a product (VIII) which thin-layer chromatography suggested was the predominant component in the reaction mixture. The product was characterised as above.

The structures of these new tropinone analogues follow from their method of preparation and are supported by their derivatives and physical properties. The infrared spectra of 9-methyl-3-oxa-granatan-7-one (II) and the product (A) were very similar suggesting that they had a similar skeleton.

The ultraviolet spectra of the new compounds are compared with those of ψ -pelletierine (I) and 9-methyl-3-oxagranatan-7-one (II) in Table 1. The absorption maxima depended on the concentration of the solutions. Ultraviolet data on bicyclic amino-ketones containing an N-methylpiperidone ring are scarce. Leonard and his co-workers ⁶ measured the spectrum of ψ -pelletierine in absolute ether (λ_{max} . 213 and 246 m μ ; ε_{max} . 977 and 851) but did not record the concentration. In the same solvent we find a band at λ_{max} . 246 m μ with ε_{max} . 887 (c

- C. L. Zirkle, F. R. Gerro, A. M. Pavloff, and A. Burger, J. Org. Chem., 1961, 26, 395.
 A. B. Foster and D. Horton, Adv. Carbohydrate Chem., 1959,
- ⁵ A. B. Foster and D. Horton, Adv. Carbohydrate Chem., 1959, 14, 240, and references therein.

^{*} Periodate-oxidised glycosides generally exist in hemiacetal and/or hemialdal forms.³ Throughout this Paper they will however be written in the dialdehyde form which exists in equilibrium in solution.

¹ R. Robinson, J. Chem. Soc., 1917, 111, 762, 876.

² C. Schöpf, Angew. Chem., 1937, 50, 779, 797.

^a R. D. Guthrie, Adv. Carbohydrate Chem., 1961, 16, 105.

⁶ N. J. Leonard, D. F. Morrow, and M. T. Rogers, J. Amer. Chem. Soc., 1957, **79**, 5476.

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0.132), though this value could be changed by varying the concentration.

The ultraviolet maximum for unconjugated ketones is usually in the region 280—310 mµ with ε_{max} generally less than 100. Saturated amines generally have one maximum at about 200 mµ with an extinction coefficient which varies with environment, but is generally above 1500.7 The spectra of ψ -pelletierine (I) and 9-methyl-3-oxagranatan-7-one (II), compounds of established structure, are not predictable from the above information but the values found are similar to those of the remaining compounds in Table 1, suggesting that they all have a common molecular skeleton. We suggest that the peaks observed may be the result of some interaction between

TABLE 1 Ultraviolet spectra

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Compounds	Free base in water "		Free base in MeOH ª		Perchlorate in water ^b	
R^{2} O $NMe = O$ R^{1} $R^{1} = H = R^{2} (II) \dots$ $R^{1} = OMe, R^{2} = H (IX)$ $R^{1} = OCH Pb, R^{2} = H (IX)$	λ _{max} 227 234 233	ε _{max} 1408 1479 1492	λ _{max} 235 236 238	ε _{max} 1017 1136	λ _{max} 236	ε _{max} 114
$R^1 = OMe, R^2 = Me \dots$ ψ -Pelletierine (I)	$\frac{233}{240}$	$\frac{1454}{1037}$	$\begin{array}{c} 236\\ 236\\ \end{array}$	1171 807	234	98
a 0.01-0.015	% solı	ations.	٥ 2%	solutio	ons.	

TABLE 2

	N	fass :	spectra	*		
 	~				-	

2(5)- α -Me	thoxy-)-meth	y1-3-0X	agranat	an-7-0	ne (IX))
m/e	39	41	42	43	44	54	55	56
I (%)	8	25	65	7	18	6	18	16
m e	57	68	69	70	71	75	82	83
I(%)	21	5	5	7	16	7	32	12
m e	84	96	97	98	110	111	112	124
I(%)	19	10	8	23	100	8	11	7
m e	125	126	128	154	155	170	185	186
I(%)	41	4	8	37	5	10	79(N	A) 8
$2R-\alpha(\text{or }\beta)$ -Methoxy- $4\beta(\text{or }\alpha)$ -9-dimethyl-3-oxagranatan-7-one								
m e	39	41	42	43	44	54	55	56
I(%)	9	24	94	11	5	6	25	12
m e	57	58	61	70	71	81	82	83
I(%)	50	5	10	11	27	6	18	5
m e	84	89	94	96	97	98	110	111
I(%)	37	17	5	19	6	57	100	11
m e	124	126	139	168	199			
I(%)	5	ß	90	20	94/N	4T)		

* All peaks with relative abundance greater than 5% of the base peak are given.

the amino- and the carbonyl functions. The low extinction coefficient of the perchlorates would then reflect the reduced availability of the nitrogen's electrons for such an interaction. Further work is in progress on the ultraviolet spectra of these compounds.

The mass spectra of derivatives (A) and (VIII) (Table 2) were extremely similar to those of compounds (I) and

⁷ A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Pergammon Press, Oxford, 1964.

(II).⁸ The molecular ions showed clearly and both spectra were dominated by peaks at m/e 110 and 42 and showed smaller peaks at M - 31 (loss of CH₃O) and M - 60 (loss of the CH₃·OCHO group).

The remaining problem is the orientation of the methoxyl group. Unfortunately only one pair of epimers was isolated, (A) and (B), and then only as methiodides. These have been examined in deuterium oxide solution in which the acetal proton in (A) gave a signal at higher field (τ 4.97) than that in (B) (τ 4.63). Axial protons generally resonate at higher fields than equatorial protons so we tentatively suggest that in (A), the predominant isomer, the acetal proton is axial and in (B) equatorial; thus (A) is (IX) and (B), (X). In the other cases in which only one isomer was isolated we presume that this will have the acetal proton axial and the aglycone group equatorial.

Since Robinson-Schöpf condensations possibly take place via the di-(1-hydroxyalkyl)amine (XI) it was of



interest to try and isolate this intermediate. Several reactions of periodate-oxidised carbohydrates with nitrogenous bases give such compounds.³ For example, Khym⁹ treated periodate-oxidised adenosine with methylamine to give a product that was reduced with borohydride to yield a compound believed to have structure (XII), but now shown ¹⁰ to have structure (XIII). Experiments with periodate-oxidised methyl β-L-arabinopyranoside and methylamine gave only dark material, which with borohydride gave a colourless, intractable syrup. An attempt to isolate an oxygen analogue of (VI) by reaction of the oxidised arabinoside (III) with acetonedicarboxylic acid was not successful; no dark material was formed. One of the characteristics of Robinson-Schöpf condensations is the formation of large amounts of dark material, presumably owing to condensation between the amine and the dialdehyde.

Reduction of isomer (A) with lithium aluminium hydride gave a nearly quantitative yield of an alcohol (homogeneous by thin-layer chromatography) to which, by analogy with much-studied reductions on related systems,⁴ we assign the α -configuration; the product was characterised by esterification. Methods used to reduce compounds (I) and (II) to the β -alcohol ⁴ gave only mixtures of ketone and alcohol with isomer (A). The best reagent was sodium and 2-methylpropan-1-ol in

⁸ (a) R. D. Guthrie and J. F. McCarthy, J. Chem. Soc. (C), 1966, 1207; (b) M. Spiteller-Friedmann and G. Spiteller, Monatsh., 1966, **96**, 104. In ref. (a) the peak at m/e 155 in the spectrum of ψ -pelletierine should be one-tenth that shown.

⁹ J. X. Khym, Biochemistry, 1963, 2, 344.

¹⁰ D. M. Brown and A. P. Read, J. Chem. Soc., 1965, 5072.

toluene, which gave the β -alcohol as its *p*-nitrobenzoate in 15% yield.

EXPERIMENTAL

Compounds were identified where necessary by mixed m. p. and infrared spectrometry. Optical rotations were measured in chloroform unless stated otherwise. Alumina was of type H, 100—200 mesh, supplied by P. Spence Limited. DMF refers to NN-dimethylformamide. Perchloric acid was used as 60% aqueous solution. Thinlayer chromatography (t.l.c.) was on silica (Kieselgel G nach Stahl), with either iodine vapour or concentrated sulphuric acid as the location reagent. Unless stated otherwise, the solvent system was ethanol-chloroform (7:93). All evaporations were at reduced pressure on a rotary evaporator, below 50° .

 $2(S)\alpha$ - and - β -Methoxy-9-methyl-3-oxagranatan-7-one. Methyl B-L-arabinopyranoside 11 (4.92 g.) was added gradually with shaking during 15 min. to sodium metaperiodate (12.85 g.) in water (100 ml.) at 5–10°. The solution was allowed to warm to room temperature during 0.5 hr. in the dark and then aqueous N-sodium hydrogen carbonate (27 ml., 90% theory) was added to raise the pH to ca. 5. After standing for 1 hr. in the dark with occasional shaking (test for periodate negative), barium chloride dihydrate (7.3 g.) was added and the mixture poured into ethanol (600 ml.). The inorganic precipitate was filtered off and sodium sulphate added. Filtration and evaporation to about 100 ml. gave a clear solution, to which were added methylamine hydrochloride (4.05 g.), sodium acetate trihydrate (8.16 g.), and acetonedicarboxylic acid (8.76 g.). The solution was kept at room temperature for 5 days, during which it became brown, carbon dioxide was evolved, the pH rose from 3.5 to 4.8 and the optical rotation changed. Sodium carbonate was added (pH 10) and the solution was extracted continuously with chloroform for 4 days. Evaporation, and co-distillation with benzene, gave a dark brown syrup (P) (5.03 g.). T.l.c. in ethanol-chloroform (1:49) showed one large spot and five fainter ones. By using ethanol-chloroform (7:93), the large spot was resolved into two closely-moving spots which corresponded with the isomers (IX) and (X). Elution of the syrup from a column of alumina with chloroform and evaporation yielded a brown syrup (3.40 g.) which deposited crystals on standing. Recrystallisation (charcoal) from cyclohexane afforded long white spears (2.18 g., 39%), m. p. 96-98°, which were recrystallised further to give 2(S)-a-methoxy-9-methyl-3-oxagranatan-7-one (IX) [designated isomer (A)], m. p. 99—100°, $[\alpha]_{D}^{24} + 133^{\circ}$ (c 0.93 in H₂O); see Table 1 for ultraviolet data [Found: C, 58.1; H, 7.9; N, 7.8%; M (vapour pressure in water), 186. C₉H₁₅NO₃ requires C, 58.4; H, 8.2; N, 7.6%; M, 185].

Extraction with ethanol of the charcoal used in the recrystallisation of (IX), and evaporation of the extracts and of the recrystallisation mother-liquors, afforded a dark brown syrup (Q) (0.95 g.). Dissolving this in ethanol (2 ml.) and adding a slight excess of perchloric acid gave crystals which were recrystallised from water to yield the perchlorate of isomer (IX) (0.25 g., 2.9%), m. p. 245° (decomp.) (see below). Basifying the mother-liquors from this preparation with dilute aqueous sodium hydroxide solution and extraction with chloroform gave a yellow syrup (R) (0.46 g., 8%). T.l.c. indicated that it consisted almost entirely of the title compounds, the majority being (X) [designated]

isomer (B)]. Attempts to purify this further by crystallisation or by conversion into the hydrochloride or perchlorate were unsuccessful. This syrup (R) was used for the preparation of derivatives of (X).

A substantial quantity of dark, optically inactive material, which still had characteristic infrared absorption bands in the 1700 and 900—1200 cm.⁻¹ regions, was also eluted from the column. T.l.c. gave only a long streak and no derivative could be obtained with either methyl iodide or perchloric acid, even though a Middleton test for nitrogen was positive.

In a parallel experiment, the brown syrup (Q) (1·28 g.) was dissolved in methyl iodide (3 ml.) and kept for 24 hr. Evaporation of the excess of methyl iodide and recrystallisation of the product from aqueous alcohol gave the *methiodide* of (X) (0·78 g., 6%), m. p. 236—237° (decomp.), $[\alpha]_{\rm D}^{24} - 0.6^{\circ}$ (c 0·89 in H₂O) [Found: C, 36·9; H, 5·5; I, 38·8; N, 4·4%; M (vapour pressure in water), 333. C₁₀H₁₈INO₃ requires C, 36·7; H, 5·5; I, 38·7; N, 4·3%; M, 327].

Isolation of the "dialdehyde" before condensation, by either solvent extraction of the evaporated residue, or by de-ionisation of the solution with ion-exchange resin followed by freeze-drying, had little or no effect on the condensation. Similarly, use of different quantities of sodium acetate, change of concentrations, vigorous stirring during the condensation, or allowing the solution to stand at 25° had negligible effect. The crude product could be sublimed at *ca.* $130^{\circ}/0.1$ mm. pressure to give white crystals, but some loss occurred owing to charring and spitting.

Compound (IX), m. p. $98-99^{\circ}$, $[\alpha]_{D}^{23} + 132^{\circ}$ (c 1.06 in $H_{2}O$), and compound (X), as its methiodide, m. p. $233-234^{\circ}$ (decomp.), were obtained in similar yield from periodate-oxidised methyl α -D-xylopyranoside.

Reactions of Compound (IX).—(a) With methyl iodide. Treatment of (IX) with methyl iodide as described above afforded the methiodide (86%), m. p. 229—230° (decomp.) (from ethanol), $[a]_p^{22}$ +87·1 (c 0.94 in H₂O) (Found: C, 36·6; H, 5·65; N, 4·45%). When the crude syrup (P) was treated similarly a 58% yield of material, m. p. 225— 227° (decomp.), was obtained.

(b) With perchloric acid. To a solution of (IX) (0.11 g.) in water (2 ml.) in an ice-bath was added perchloric acid (0.07 ml.). The white crystals (0.15 g., 88%), m. p. 245° (decomp.), were recrystallised from water to yield the perchlorate, m. p. 245—246° (decomp.), $[\alpha]_{\rm p}^{25}$ +94.8° (c 1.04 in H₂O) (Found: Cl, 12.15; N, 4.8. C₉H₁₆ClNO₇ requires Cl, 12.4; N, 4.9%). Similar treatment of the crude syrup (P) gave identical material (36% based on the dialdehyde), m. p. 246° (decomp.). See Table 1 for ultraviolet data.

(c) With hydriodic acid. Hydriodic acid (containing 53% hydrogen iodide; 10 drops) was added to a solution of (IX) (0.10 g.) in water (2 drops). The crystalline precipitate (0.15 g., 89%), m. p. 238° (decomp.), was kept for 0.5 hr. and then diluted with a little acetone, filtered off, and recrystallised from methanol to give cubes of the hydriodide, m. p. 238° (decomp.), $[\alpha]_{\rm D}^{21} + 86.7^{\circ}$ (c 0.82 in H₂O) (Found: C, 34.8; H, 5.4; I, 41.2. C₉H₁₆INO₃ requires C, 34.5; H, 5.2; I, 40.5%).

(d) With benzaldehyde. A mixture of (IX) (0.148 g.), benzaldehyde (0.19 g.), aqueous sodium hydroxide (10%; 0.2 ml.), water (4.5 ml.), and ethanol (2 ml.) was shaken at

¹¹ J. W. Pratt, N. K. Richtmyer, and C. S. Hudson, J. Amer. Chem. Soc., 1952, 74, 2200.

room temperature for 60 hr. The yellow precipitate was recrystallised from propan-2-ol to give the 6,8-*dibenzylidene derivative*, m. p. 132—133°, $[\alpha]_{\rm D}^{22}$ +113° (*c* 0.71), $\lambda_{\rm max}$. (MeOH) 236 and 315 mµ [$\varepsilon_{\rm max}$ 13,240 (*c* 0.0180) and 28,880 (*c* 0.0090)] (Found: C, 76.6; H, 6.4; N, 4.3. C₂₃H₂₃NO₃ requires C, 76.4; H, 6.4; N, 3.9%).

(e) With p-nitrobenzaldehyde. Reaction of (IX) and p-nitrobenzaldehyde as in (d) gave the 6,8-di-p-nitrobenzylidene derivative (from nitromethane) (70%), m. p. 261--262° (decomp.), $[\alpha]_{p}^{26} + 99 \cdot 5^{\circ}$ (c 0.98), λ_{max} (MeOH), 225 and 313 mµ [ε_{max} 17,930 (c 0.0146) and 39,580 (c 0.0073)] (Found: C, 61.0; H, 4.9; N, 9.4. C₂₃H₂₁N₃O₇ requires C, 61.2; H, 4.7; N, 9.3%).

(f) With hydroxylamine. Compound (IX), hydroxylamine hydrochloride, and aqueous potassium hydroxide gave a colourless gum which resisted all attempts at crystallisation. T.l.c. showed only one spot. The material was dissolved in a little ethanol and treated with perchloric acid to give the oxime perchlorate (80%) (from ethanol), m. p. 215-216° (decomp.), $[\alpha]_D^{21} + 98\cdot3°$ ° (c 0.88) (Found: Cl, 11.7; N, 8.95. C₃H₁₇ClN₂O₇ requires Cl, 11.8; N, 9.3%).

(g) With hydrochloric acid. A solution of (IX) (0.201 mg.) in aqueous 4N-hydrochloric acid (10 ml.) was heated on a boiling-water bath for 3 hr. The solution was cooled, basified (pH 10) with concentrated aqueous sodium hydroxide, and extracted with ethyl acetate to give starting material (0.183 g., 99%), m. p. 98.5—100°.

(h) With lithium aluminium hydride. To a stirred solution of lithium aluminium hydride (0.38 g.) in refluxing ether (15 ml.) was gradually added a solution of (IX) (0.927 g.) in ether (50 ml.) during 20 min. After stirring and refluxing for 6 hr., water (0.8 ml.) followed by wet ether (20 ml.) was cautiously added to the mixture cooled in ice. The solid was filtered off through kieselguhr and washed with ether. The solution was dried (K_2CO_3) and evaporated to a colourless, mobile syrup (0.898 g., 96%) which showed no infrared carbonyl absorption; t.l.c. showed only one intense spot (iodine vapour). Puri fication was attempted by stirring an ether solution of the product with charcoal for 24 hr. to give 2(S)-a-methoxy-9-methyl-3-oxagranatan-7 α -ol, $n_{\rm D}^{23}$ 1.4874, $\left[\alpha\right]_{\rm D}^{25}$ +143° (c 0.78 in H₂O) (Found: C, 56.8; H, 9.4. C₉H₁₇NO₃ requires C, 57.7; H, 9.15%).

Use of sodium borohydride (six equivs.) in methanolwater (19:1) for this reduction gave a product containing a large amount of unchanged material.

The α -alcohol was benzoylated with benzoyl chloride in pyridine to give a pale yellow syrup, which could not be crystallised. Conversion into the methiodide by the method given previously gave 2(S)- α -methoxy-9-methyl-3-oxagranatan-7 α -ol benzoate methiodide (from propan-2-ol), m. p. 204—205° (decomp.), $[\alpha]_{D}^{25} + 68.0°$ (c 0.74 in H₂O) (Found: C, 46.8; H, 5.6; I, 28.9; N, 3.2. C₁₇H₂₄INO₄ requires C, 47.1; H, 5.6; I, 29.3; N, 3.2%).

The α -alcohol was converted into the p-*nitrobenzoate* (73%), m. p. 112—113° (from propan-2-ol), $[\alpha]_D^{21} + 96\cdot5°$ (c 1·13) (Found: C, 57·2; H, 5·9; N, 8·3. $C_{16}H_{20}N_2O_6$ requires C, 57·1; H, 6·0; N, 8·3%).

The p-nitrobenzoate gave a methiodide, m. p. 223° (decomp.) (from aqueous ethanol), $[\alpha]_D^{23} + 55 \cdot 6^\circ$ (c 0.52 in MeNO₂) (Found: C, 42.4; H, 4.9; I, 25.3; N, 5.45. $C_{17}H_{23}IN_2O_6$ requires C, 42.7; H, 4.9; I, 26.5; N, 5.9%).

(i) With sodium and 2-methylpropan-1-ol. A solution of (IX) (0.927 g.) in anhydrous toluene (7 ml.) and 2-methylpropan-1-ol (0.47 g.) was added dropwise with vigorous

stirring during 0.25 hr. to a refluxing mixture of sodium (0.23 g.) and anhydrous toluene (7 ml.). The red-brown mixture was stirred and refluxed for 3 hr., cooled, and residual sodium decomposed by addition of a few drops of ethanol and then water. After standing overnight, the mixture was acidified with dilute hydrochloric acid and the aqueous layer separated from the toluene, which was washed with two small portions of dilute hydrochloric acid. The combined aqueous solution was washed with ether, neutralised with concentrated aqueous potassium hydroxide, concentrated to a small volume (about 25 ml.), and extracted continuously with chloroform. Evaporation of the extracts afforded a yellow oil (0.665 g.) which still showed much infrared carbonyl absorption. The syrup was dissolved in pyridine and treated with p-nitrobenzoyl chloride, to yield a light brown oil which was crystallised twice from propan-2-ol to give $2(S)-\alpha$ -methoxy-9-methyl-3-oxagranatan-7 β -ol p-nitrobenzoate (15%), m. p. 93–94° (mixed m. p. with the epimeric α -p-nitrobenzoate 74—94°), $[\alpha]_{D}^{21} + 76.6^{\circ} (c \ 0.70)$ (Found: C, 57.1; H, 6.0; N, 8.4%).

Reactions of Compound (X).—With p-nitrobenzaldehyde. Reaction of the syrup (R) (0.185 g.) with p-nitrobenzaldehyde (0.30 g.) as described for (IX) gave a yellow solid (0.349 g.) which after recrystallisation from ethyl acetate and then butan-1-ol yielded the 6,8-di-p-nitrobenzylidene derivative of (X), m. p. 267—268° (mixed m. p. with its isomer 238—239°) $[\alpha]_{\rm D}^{23}$ +139° (c 0.42), $\lambda_{\rm max}$ (MeOH) 246 and 317 mµ $[\varepsilon_{\rm max}$ 10,560 (c 0.0372) and 33,380 (c 0.0104)] (Found: C, 61·2; H, 4·8; N, 9·4%).

2(R)-a-Methoxy-9-methyl-3-oxagranatan-7-one.---

Oxidation of methyl β -D-xylopyranoside with sodium metaperiodate and reaction of the product with methylamine and acetonedicarboxylic acid, as described for its enantiomorph, gave the title compound, $[\alpha]_D^{26} - 135 \cdot 5^{\circ}$ (c 0.93 in H₂O) (Found: C, 58.2; H, 8.25; N, 7.55%), in the same yield and with the same m. p. as for (IX), mixed m. p. 68—96°. The infrared spectra of the enantiomorphs were identical.

2(S)-a-Benzyloxy-9-methyl-3-oxagranatan-7-one. Benzyl β -L-arabinopyranoside ¹² (4.80 g.) was oxidised with sodium metaperiodate (8.56 g.) in water (70 ml.) as described for the methyl glycoside. Methylamine hydrochloride (2.7 g.), sodium acetate trihydrate (8.2 g.), and acetonedicarboxylic acid (5.84 g.) were added to the "dialdehyde," and the solution made up to 200 ml.; after 7 days the solution was decanted from oil (which was optically inactive), basified (pH 10) with sodium carbonate, and extracted continuously with chloroform for 2 days to give a brown syrup (4.17 g.). T.l.c. showed one intense spot and six faint ones having lower $R_{\rm F}$ values. The material could not be crystallised and was therefore eluted from a column of alumina with chloroform-benzene (2:3) giving a pale yellow syrup (S) * (3.10 g.). A dark brown, optically inactive, intractable syrup was obtained by eluting the column with methanol.

Perchloric acid (1 ml.) was added to a cold solution of the syrup (S) (1.05 g.) in absolute ethanol (4 ml.). The white crystals (1.01 g. 41%), m. p. 86—90°, were recrystallised from ethanol to give the *perchlorate*, m. p. 77—94°, $[a]_p^{18}$ +116° (c 0.69, H₂O) (Found: N, 4.1. C₁₅H₂ClNO₄ requires N, 3.9%). Repeated recrystallisation did not sharpen the m. p.

A slurry of the perchlorate (0.496 g.) in water (5 ml.) * Percentage yields of products from the syrup (S) are based on benzyl β -t-arabinopyranoside.

¹² F. Wold, J. Org. Chem., 1961, 26, 197.

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was basified (pH 10) by the addition of dilute aqueous sodium hydroxide. Continuous chloroform extraction gave a colourless syrup (0.326 g., 91%). T.l.c. of the syrup and of its aqueous solution before extraction showed only one component. The *free base*, $[\alpha]_D^{22} + 201^\circ$ (c 0.85) (Found: C, 68.7; H, 7.6. C₁₅H₁₉NO₃ requires C, 68.95; H, 7.3%), was purified by stirring a benzene solution with charcoal. See Table 1 for ultraviolet data.

Methyl iodide (3 ml.) was added to a solution of the syrup (S) (0.493 g.) in acetone (3 ml.) to give the *methiodide*, m. p. 226—227° (decomp.) (from methanol), $[\alpha]_D^{22} + 88.9°$ (c 0.54 in DMF) (Found: C, 47.6; H, 5.5; N, 3.4. C₁₆H₂₂INO₃ requires C, 47.65; H, 5.5; N, 3.5%).

The syrup (S) was converted into its 6,8-dibenzylidene derivative, m. p. 170–171° (from ethanol), $[\alpha]_D^{23} + 114°$ (c 0.66), λ_{max} . (MeOH) 243 and 317 mµ [ϵ_{max} 15,660 (c 0.0232) and 30,200 (c 0.0166)] (Found: C, 79.5; H, 6.3; N, 3.25. C₂₉H₂₇NO₃ requires C, 79.6; H, 6.2; N, 3.2%).

 $2(R)\alpha(or \beta)$ -Methoxy-4 β (or α)-9-dimethyl-3-oxagranatan-7-one.-Methyl a-L-rhamnopyranoside 13 (1.78 g.) was oxidised with sodium metaperiodate (4.26 g.) in water (30 ml.) and the product allowed to react with methylamine hydrochloride (1.35 g.), sodium acetate trihydrate (2.72 g.), and acetonedicarboxylic acid (2.92 g.); after 5 days, the dark brown solution was basified (pH 10) and extracted continuously with chloroform for 3 days, to give a dark brown syrup (1.95 g.). T.l.c. showed nine spots; all were of equal intensity except for one which had the largest $R_{\rm F}$ value and corresponded with the title compound. Attempted crystallisation was fruitless and the product was therefore eluted from alumina with chloroform-light petroleum (b. p. $60-80^{\circ}$) (1 : 1), giving another brown syrup (U) (1.50 g.) which also resisted all attempts at crystallisation.

The syrup (U) * treated as above gave a *perchlorate*, m. p. 204-205° (decomp.) (from ethanol) (46%), $[\alpha]_{0}^{26}$

* Percentage yields of products from the syrup (U) are based on methyl α -L-rhamnopyranoside. -78.0° (c 1.05 in H₂O) (Found: Cl, 11.4; N, 4.6. C₁₀H₁₈ClNO₇ requires Cl, 11.8; N, 4.7%). See Table 1 for ultraviolet data.

The perchlorate was converted, as described for (S), into the *free base*, m. p. 72—74° (from cyclohexane), $[a]_p^{24}$ -100° (c 0.51) (Found: C, 59.9; H, 8.6. C₁₀H₁₇NO₃ requires C, 60.3; H, 8.6%). See Table 1 for ultraviolet data.

The free base gave a methiodide, m. p. 208—209° (decomp.; sublimed) (from ethanol), $[\alpha]_{D}^{21} - 65 \cdot 5^{\circ}$ (c 1·1 in H₂O) (Found: C, 38·7; H, 5·9; N, 4·0. C₁₁H₂₀INO₃ requires C, 38·7; H, 5·9; N, 4·1%), and a 6,8-dibenzylidene derivative, m. p. 173—174° (from cyclohexane), $[\alpha]_{D}^{24} + 296^{\circ}$ (c 0·69), λ_{max} . (MeOH) 238 and 310 mµ [ε_{max} . 13,090 (c 0·0198) and 28,830 (c 0·0099)] (Found: C, 76·5; H, 6·9; N, 3·9. C₂₄H₂₅NO₃ requires C, 76·8; H, 6·7; N, 3·7%).

A solution of the pure free base (0.896 g.) in ether (60 ml.) was reduced, as described previously, with lithium aluminium hydride (0.34 g.) in ether (20 ml.) to give a colour-less syrup (0.831 g., 92%), which showed no infrared carbonyl absorption. T.l.c. showed only one spot, with a lower $R_{\rm f}$ than the parent ketone. The pure $2(R)\alpha({\rm or }\beta)$ -methoxy- $4\beta({\rm or }\alpha)$ -9-dimethyl-3-oxagranatan-7 α -ol $[\alpha]_{\rm p}^{21}$ -120° (c 0.63), $n_{\rm p}^{20}$ 1.4838 (Found: C, 59.6; H, 9.35. C₁₀H₁₉NO₃ requires C, 59.7; H, 9.5%), was obtained by stirring an ether solution with charcoal for 12 hr.

The α -alcohol was converted into the p-nitrobenzoate methiode, m. p. 213—214° (decomp.) (from methanol), $[\alpha]_D^{23} - 44 \cdot 1°$ (c 0.51 in MeNO₂) (Found: C, 44.2; H, 5.3; N, 5.3. C₁₈H₂₅IN₂O₆ requires C, 43.9; H, 5.1; N, 5.7%).

The mass spectra were determined by Mr. F. Bloss on an A.E.I. MS9 spectrometer. One of us (J. F. McC.) thanks Imperial Chemical Industries Limited (Pharmaceuticals Division) for financial support.

[6/773 Received, June 22nd, 1966]

¹³ W. T. Haskins, R. M. Harris, and C. S. Hudson, J. Amer. Chem. Soc., 1946, **68**, 628.