Crystal Structure and Absolute Configuration of (*R*)-(−)-3-Acetoxyquinuclidine Methiodide

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The structure and absolute configuration of the title compound has been determined by single-crystal *X*-ray diffraction. Crystals are triclinic with $Z = 1$ in a unit cell of dimensions $a = 7{\cdot}610(4)$, $b = 7{\cdot}410(4)$, $c = 6{\cdot}909(3)$ Å, $\alpha = 69{\cdot}75(3)$, $\beta = 111{\cdot}88(3)$, $\gamma = 112{\cdot}38(3)°$, space group $P1$. The structure was solved by Patterson and Fourier methods and refined by least-squares by use of 1637 observed three-dimensional diffractometer data to R 0·045. The absolute configuration was determined by use of the anomalous scattering effect of the iodine atom. The quinuclidine cage is twisted by *ca.* 12° and the ester group is planar.

THE absolute configurations of (+)- and (−)-3-acetoxy quinuclidine were first reported by Robinson, Belleau, and Cox.[1] Later Belleau and Pauling [2] concluded that the original assignment was incorrect and that the dextrorotatory enantiomer possesses the (*S*)- rather than the (*R*)-configuration. The absolute configuration of the laevorotatory enantiomer has now been established by *X*-ray diffraction techniques and we report here the results of the analysis.

EXPERIMENTAL

Crystals of the methiodide compound provided by Professors Belleau and Robinson are irregular plates which give a biaxial interference figure with an optic axis almost perpendicular to the plate.

Crystal Data.—$C_{10}H_{18}INO_2$, $M = 311{\cdot}16$. Triclinic, $a = 7{\cdot}610(4)$, $b = 7{\cdot}410(4)$, $c = 6{\cdot}909(3)$ Å, $\alpha = 69{\cdot}75(3)$, $\beta = 111{\cdot}88(3)$, $\gamma = 112{\cdot}38(3)°$, $U = 325$ Å^3, $D_m = 1{\cdot}59(1)$ (by flotation), $Z = 1$, $D_c = 1{\cdot}59$. Space group $P1$. Mo-K_α radiation, $\lambda = 0{\cdot}7107$ Å; $\mu(\text{Mo-}K_\alpha) = 26{\cdot}2$ cm^{-1}. All parameters were determined from Weissenberg and precession photographs. Refined parameters and associated standard deviations were determined using the methods described in ref. 3.

Intensity Measurements.—Three-dimensional *X*-ray diffraction data from a small single crystal fragment (*ca.* 0·34 × 0·14 × 0·07 mm) were collected on a computer controlled [3] four-circle diffractometer by use of Mo-K_α radiation with graphite monochromator (002). A coupled θ—2θ step-scan with $\Delta 2\theta$ 0·04°, a counting time of 5 s per step and a peak-width of 1·8° were used. In the range 2θ 6—45° two hemispheres of data were collected, (i) $+h \pm k \pm l$ and (ii) $-h \pm k \pm l$. All 846 unique reflections possible in each hemisphere were observed with $I \geqslant 3\sigma(I)$. A further 1102 unique reflections ($+h \pm k \pm l$) in the region 2θ 45—60° gave 791 observed intensities. The data were corrected for Lorentz and polarisation effects but not for absorption or extinction.

Structure Solution and Refinement.—A three-dimensional Patterson synthesis was carried out [4] using the 846 data from set (i), and from this synthesis the positions of all atoms in the quinuclidine nucleus together with the *N*-methyl carbon atom were found. The atoms in the acetoxy-group were found from a Fourier synthesis [4] using data (i) phased with the iodine atom and the *N*-methylquinuclidine nucleus. Successive cycles of full-matrix least-squares [5] using 1637 data ($+h \pm k \pm l$) with all atoms anisotropic and normal scattering factors gave R 0·052. At this stage the effect of anomalous scattering of the iodine atom was taken into account. Four separate refinements were carried out using each hemisphere of 846 data in turn, together with the two possible molecular configurations. Anisotropic thermal parameters for iodine, positional and isotropic thermal parameters for all other atoms, and an overall scale factor were refined until all shifts were $\leqslant 0{\cdot}1\sigma$. The reversion to isotropic thermal parameters for atoms other than iodine appeared to be justified since refinement of 1637 data using anisotropic thermal parameters for iodine only and normal scattering factors also produced R 0·052. Furthermore, reducing the number of parameters saved computing time.

TABLE 1

(*a*) Residual values from different refinements

	Data set	Molecular confgn.	R	R'
(i)	$(+h \pm k \pm l)$ 846 data	(*R*)	0·0419	0·0560
		(*S*)	0·0425	0·0580
(ii)	$(-h \pm k \pm l)$ 846 data	(*R*)	0·0477	0·0606
		(*S*)	0·0485	0·0622
(iii)	$(+h \pm k \pm l)$ 1637 data	(*R*)	0·0519	0·0599
		(*S*)	0·0525	0·0618

(*b*) Observed and calculated structure factors for the Friedel pairs most affected by anomalous scattering

	Structure factors		
	Calc.		
Index	(*R*)	(*S*)	Obs.
0 0 1	33·5	30·5	33·7
0 0 $\bar{1}$	30·5	33·4	28·4
0 1 0	35·0	32·9	32·6
0 $\bar{1}$ 0	32·8	34·9	29·1
1 0 $\bar{1}$	18·1	16·1	19·4
$\bar{1}$ 0 1	14·9	16·8	17·3
1 $\bar{3}$ 0	23·7	21·9	24·0
$\bar{1}$ 3 0	21·0	22·9	22·0
1 0 0	44·4	45·4	30·5
$\bar{1}$ 0 0	46·5	45·5	40·7
2 1 0	45·1	44·7	46·5
$\bar{2}$ $\bar{1}$ 0	43·1	43·4	43·8
3 $\bar{1}$ 0	35·4	35·4	38·0
$\bar{3}$ 1 0	33·1	33·1	33·6

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[1] J. B. Robinson, B. Belleau, and B. Cox, *J. Med. Chem.*, 1969, **12**, 848.

[2] B. Belleau and P. J. Pauling, *J. Med. Chem.*, 1970, **13**, 737.

[3] W. R. Busing, R. D. Ellison, H. A. Levy, S. P. King, and R. T. Roseberry, 'The Oak Ridge Computer-Controlled *X*-ray Diffractometer,' U.S. Atomic Energy Commission, Report ORNL 143, 1968.

[4] J. Dollimore, A Fourier Program for LUNA, University of London Institute of Computer Science, Circular No. 1.2.

[5] G. Shearing, A Crystallographic SFLS Program in AA, University of Manchester, 1965.

The function minimised in the refinement was $\Sigma w(|F_o| - |F_c|)^2$ with $w = 4I/\sigma^2$ where $\sigma = \sigma(I) + 0{\cdot}02I$. The term $0{\cdot}02I$, which was added to the statistical standard deviation, was included because the long-term fluctuation of the standard reflection collected after every 25 reflections was *ca.* ±2%. A further two refinements using 1637 data with the (*R*)- and (*S*)-configuration were also carried out. The results obtained frim these six refinements are given in Table 1. Significance tests [6] were carried out on the three pairs of R' by use of the hypothesis: H_0: The (*S*)-(absolute)-configuration is correct. This is a three-dimensional hypothesis since it involves changing the co-ordinates of all atoms from x,y,z to $\bar{x},\bar{y},\bar{z}$; however the choice of the signs of x,y,z for one atom of the quinuclidine molecule determines the signs for all the rest. The values for the three R' factor ratios are:

TABLE 2

Fractional co-ordinates (×10⁴) and thermal motion parameters (U_{ij} in Å² × 10⁴) for non-hydrogen atoms derived from the least squares refinement, with estimated standard deviations in parentheses. The Debye–Waller factor is defined as $T = \exp[-2\pi^2 \sum_i \sum_j a_i^* a_j^* h_i h_j U_{ij}]$

Atom	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
I	0	0	0	461(5)	588(4)	570(4)	164(2)	161(2)	−130(2)
N(1)	6649(12)	0765(12)	3296(14)	389(39)	498(43)	631(49)	119(33)	129(36)	−214(38)
C(2)	8731(14)	2172(15)	3700(17)	366(44)	487(52)	566(57)	113(59)	113(39)	−186(45)
C(3)	8672(20)	4335(23)	3018(27)	412(58)	489(72)	668(88)	104(49)	160(64)	−109(70)
C(4)	6552(17)	4425(17)	1803(20)	495(58)	568(61)	717(73)	202(48)	045(52)	−109(52)
C(5)	5211(16)	3260(18)	3301(22)	433(53)	651(67)	965(90)	186(50)	116(55)	−321(62)
C(6)	5483(15)	1183(17)	4378(18)	461(53)	642(63)	672(65)	138(47)	211(48)	−235(51)
C(7)	5691(16)	1161(19)	0907(20)	414(51)	846(79)	766(75)	203(52)	030(49)	−453(64)
C(8)	5900(19)	3379(21)	−0023(21)	563(67)	826(83)	640(73)	204(60)	−057(55)	−210(62)
O(9)	9242(12)	5140(12)	4868(14)	468(42)	471(43)	733(53)	123(34)	142(36)	−176(38)
C(10)	11,263(22)	5688(23)	5880(33)	616(81)	384(67)	888(122)	088(55)	138(86)	−238(83)
C(11)	11,782(28)	6545(29)	7732(32)	1014(127)	844(112)	1092(138)	288(95)	100(98)	−482(107)
O(12)	12,428(13)	5443(15)	5270(16)	431(44)	888(61)	957(65)	147(41)	171(42)	−274(49)
C(13)	6721(19)	−1368(16)	4186(23)	692(72)	446(56)	986(92)	146(51)	314(67)	−183(57)

$$R(\text{i}) = 0{\cdot}0580/0{\cdot}0560 = 1{\cdot}038$$

$$R(\text{ii}) = 0{\cdot}0622/0{\cdot}0606 = 1{\cdot}026$$

$$R(\text{iii}) = 0{\cdot}0618/0{\cdot}0599 = 1{\cdot}032$$

For cases (i) and (ii) 59 parameters were refined using 846 data. The number of degrees of freedom is 787. From ref. 6 $R_{3,787,0\cdot005}$ is 1·008. For case (iii) with 1637 observations and 59 parameters $R_{3,1578,0\cdot005}$ is 1·004. Hence the hypothesis may be rejected at the 0·005 level of significance and so the correct conformation is (*R*). An independent test using the Friedel pairs of reflections most affected by anomalous scattering was carried out. Seven pairs of reflections for which the difference in calculated structure factors was ⩾2 e were examined. In most cases the observed structure amplitudes were in better agreement with the (*R*) than with the (*S*)-configuration. The results are given in Table 1(*b*). From this point on the (*R*)-configuration was accepted to be correct and the structure further refined with anisotropic thermal parameters for all atoms and including anomalous scattering effects. The residual dropped significantly to *R* 0·048 at which stage a difference-Fourier synthesis was carried out. From this synthesis all hydrogen atoms except those on C(11) were located. Hydrogen atom contribution to the calculated structure factors was included and the non-hydrogen atoms further refined. The final *R* was 0·045 Atomic scattering factors for neutral carbon, nitrogen and oxygen and for I⁻ were taken from ref. 7, for hydrogen from ref. 8, and anomalous dispersion corrections for iodine from ref. 9. Positional and thermal parameters are listed in Tables 2 and 3 and bond distances and angles [10] in Table 4. Observed and calculated structure factors are listed in Supplementary Publication No. SUP 20533 (6 pp., 1 microfiche).*

TABLE 3

Fractional co-ordinates (×10³) for hydrogen atoms derived from a difference-Fourier synthesis

Atom	x	y	z	Atom	x	y	z
H(2,1)	955	182	550	H(7,1)	409	060	100
H(2,2)	955	227	275	H(7,2)	590	046	000
H(3,1)	955	546	200	H(8,1)	460	318	−100
H(4,1)	659	614	100	H(8,2)	682	455	−100
H(5,1)	364	318	250	H(13,1)	522	−227	350
H(5,2)	560	400	450	H(13,2)	772	−180	400
H(6,1)	591	091	600	H(13,3)	682	−182	550
H(6,2)	409	000	400				

Hydrogen atoms are numbered according to the atom to which they are bonded. A thermal motion parameter U = 0·045 Å² is assumed for all hydrogen atoms.

All computational work was carried out on the University of London ATLAS computer and University College IBM 360 computer.

DISCUSSION

Description of the Molecular Structure.—The configuration of the molecule and the atom numbering

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* For details see Notice to Authors No. 7 in *J. Chem. Soc.* (*A*), 1960, Issue No. 20 (items less than 10 pp. are sent as full size copies).

[6] W. C. Hamilton, *Acta Cryst.*, 1965, **18**, 502.

[7] D. T. Cromer and J. T. Waber, *Acta Cryst.*, 1965, **19**, 104.

[8] 'International Tables for *X*-Ray Crystallography,' vol. III, Kynoch Press, Birmingham, 1962.

[9] C. H. Dauben and D. H. Templeton, *Acta Cryst.*, 1955, **8**, 841.

[10] J. Dollimore, A Distance Angle Program for LUNA, University of London Institute of Computer Science, Circular No. 4.

TABLE 4

Interatomic distances (Å) and bond angles (°), with estimated standard deviations in parentheses

(*a*) Distances

N(1)–C(2)	1·51(1)	C(2)–H(2,1)	1·15(10)
N(1)–C(6)	1·52(2)	C(2)–H(2,2)	1·03(10)
N(1)–C(7)	1·51(2)	C(3)–H(3,1)	1·07(10)
N(1)–C(13)	1·50(2)	C(4)–H(4,1)	1·19(10)
C(2)–C(3)	1·52(2)	C(5)–H(5,1)	1·11(10)
C(3)–C(4)	1·53(2)	C(5)–H(5,2)	1·04(10)
C(3)–O(9)	1·45(2)	C(6)–H(6,1)	1·01(10)
C(4)–C(5)	1·53(2)	C(6)–H(6,2)	1·10(10)
C(4)–C(8)	1·53(2)	C(7)–H(7,1)	1·15(10)
C(5)–C(6)	1·52(2)	C(7)–H(7,2)	1·03(10)
C(7)–C(8)	1·51(2)	C(8)–H(8,1)	0·96(10)
O(9)–C(10)	1·39(2)	C(8)–H(8,2)	1·09(10)
C(10)–C(11)	1·48(3)	C(13)–H(13,1)	1·10(10)
C(10)–O(12)	1·20(2)	C(13)–H(13,2)	0·99(10)
		C(13)–H(13,3)	0·84(10)

(*b*) Angles

C(2)–N(1)–C(6)	109(1)	C(3)–C(4)–H(4,1)	108(5)
C(2)–N(1)–C(7)	108(1)	C(5)–C(4)–H(4,1)	116(5)
C(2)–N(1)–C(13)	109(1)	C(8)–C(4)–H(4,1)	107(5)
C(6)–N(1)–C(7)	109(1)	C(4)–C(5)–H(5,1)	114(5)
C(6)–N(1)–C(13)	110(1)	C(4)–C(5)–H(5,2)	110(5)
C(7)–N(1)–C(13)	111(1)	C(6)–C(5)–H(5,1)	111(5)
N(1)–C(2)–C(3)	110(1)	C(6)–C(5)–H(5,2)	108(5)
C(2)–C(3)–C(4)	110(1)	H(5,1)–C(5)–H(5,2)	104(7)
C(2)–C(3)–O(9)	111(1)	C(5)–C(6)–H(6,1)	113(5)
C(4)–C(3)–O(9)	106(1)	C(5)–C(6)–H(6,2)	112(5)
C(3)–C(4)–C(5)	110(1)	N(1)–C(6)–H(6,1)	118(5)
C(3)–C(4)–C(8)	105(1)	N(1)–C(6)–H(6,2)	99(5)
C(5)–C(4)–C(8)	109(1)	H(6,1)–C(6)–H(6,2)	105(7)
C(4)–C(5)–C(6)	110(1)	N(1)–C(7)–H(7,1)	96(5)
C(5)–C(6)–N(1)	110(1)	N(1)–C(7)–H(7,2)	120(5)
N(1)–C(7)–C(8)	110(1)	C(8)–C(7)–C(7,1)	100(5)
C(7)–C(8)–C(4)	109(1)	C(8)–C(7)–H(7,2)	115(5)
C(3)–O(9)–C(10)	115(1)	H(7,1)–C(7)–H(7,2)	112(7)
O(9)–C(10)–C(11)	114(2)	C(4)–C(8)–H(8,1)	123(5)
O(9)–C(10)–O(12)	121(2)	C(4)–C(8)–H(8,2)	97(5)
C(11)–C(10)–O(12)	125(2)	C(7)–C(8)–H(8,1)	95(5)
N(1)–C(2)–H(2,1)	110(5)	C(7)–C(8)–H(8,2)	132(5)
N(1)–C(2)–H(2,2)	116(5)	H(8,1)–C(8)–H(8,2)	103(7)
C(3)–C(2)–H(2,1)	109(5)	N(1)–C(13)–H(13,1)	105(5)
C(3)–C(2)–H(2,2)	99(5)	N(1)–C(13)–H(13,2)	121(5)
H(2,1)–C(2)–H(2,2)	112(7)	N(1)–C(13)–H(13,3)	115(5)
C(2)–C(3)–H(3,1)	120(5)	H(13,1)–C(13)–H(13,2)	110(7)
C(4)–C(3)–H(3,1)	104(5)	H(13,1)–C(13)–H(13,3)	101(7)
O(9)–C(3)–H(3,1)	104(5)	H(13,2)–C(13)–H(13,3)	103(7)

TABLE 5

Selected torsion angles (°)

N(1)–C(2)–C(3)–C(4)	−9
N(1)–C(2)–C(3)–O(9)	108
N(1)–C(6)–C(5)–C(4)	−12
N(1)–C(7)–C(8)–C(4)	−14
C(2)–N(1)–C(6)–C(5)	66
C(2)–N(1)–C(7)–C(8)	−52
C(2)–C(3)–C(4)–C(5)	63
C(2)–C(3)–C(4)–C(8)	−55
C(2)–C(3)–O(9)–C(10)	77
C(3)–C(2)–N(1)–C(6)	−54
C(3)–C(2)–N(1)–C(7)	65
C(3)–C(2)–N(1)–C(13)	−174
C(3)–C(4)–C(5)–C(6)	−51
C(3)–C(4)–C(8)–C(7)	68
C(3)–O(9)–C(10)–C(11)	179
C(3)–O(9)–C(10)–O(12)	−2
C(4)–C(3)–O(9)–C(10)	−164
C(5)–C(4)–C(3)–O(9)	−57
C(5)–C(4)–C(8)–C(7)	−50
C(5)–C(6)–N(1)–C(7)	−52
C(5)–C(6)–N(1)–C(13)	−174
C(6)–C(1)–C(7)–C(8)	67
C(6)–C(5)–C(4)–C(8)	64
C(8)–C(4)–C(3)–O(9)	−175
C(8)–C(7)–N(1)–C(13)	−172

is shown in Figure 1. The acetoxy-group joined to the quinuclidine cage is planar (Table 6), and the quinuclidine cage is slightly twisted in a way similar to that observed in quinuclidinyl di-α,α′-thienylglycollate (QT) [11] and quinuclidinyl benzilate hydrobromide, (QB).[12] A comparison of torsion angles for these structures is given in Table 7. From this limited amount of data it can be seen that the difference {τ[N(1)–C(2)–C(3)–O(9)] − τ[N(1)–C(2)–C(3)–C(4)]} tends to a constant value. This is to be expected, for if the quinuclidine cage was in a totally eclipsed form $\tau(4)$ would be *ca.* 120°. It is interesting to note that QT and 3AQ have anticlockwise twists viewed down the N(1) · · · C(4) axis while QB has a clockwise twist. The question of twist occurring in quinuclidine structures, bicyclo[2,2,2]octane derivatives and 1,4-diazabicyclo[2,2,2]octane derivatives

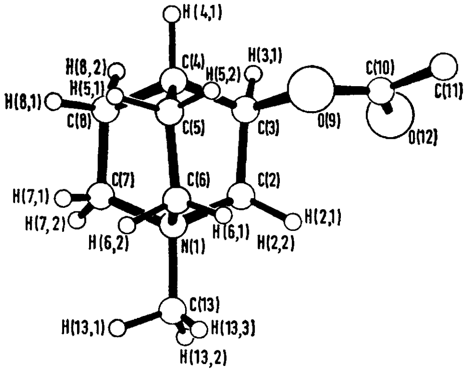

FIGURE 1 Conformation of 3-acetoxyquinuclidine as observed in crystals of the methiodide

TABLE 6

Least-squares plane

Plane: C(3), O(9), C(10), C(11), O(12)

Equation of plane:*

$$-0{\cdot}024X + 0{\cdot}797Y - 0{\cdot}603Z = 7{\cdot}674$$

Displacements (Å) from plane: C(3) 0·01, O(9) −0·01, C(10) 0·00, C(11) 0·01, O(12) 0·00

* Based on orthonormalised co-ordinates: X is parallel to the crystallographic a axis, Y is perpendicular to X in the plane ab, and Z is perpendicular to the plane ab and completes a right-handed set of axes X, Y, Z.

TABLE 7

Comparison of torsion angles for quinuclidine structures

Torsion angle	QB[a]	QT[b]	3AQ
(1) N(1)–C(2)–C(3)–C(4)	+10·3	−5·4	−9·4
(2) N(1)–C(6)–C(5)–C(4)	+7·2	−8·7	−11·8
(3) N(1)–C(7)–C(8)–C(4)	+7·9	−9·3	−13·8
(4) N(1)–C(2)–C(3)–O(9)	+125·7	+111·8	+107·7
(5) Mean $\tau(1) + \tau(2) + \tau(3)$	+8·5	−7·8	−11·7
(6) $\tau(4) - \tau(1)$	115·4	117·2	117·1
(7) $\tau(4) - \tau(5)$	117·2	119·6	119·4

Torsion angles calculated from (*a*) ref. 10; (*b*) ref. 11.

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[11] A. Meyerhöffer and D. Carlström, *Acta Cryst.*, 1969, *B*, **25**, 1119.

[12] A. Meyerhöffer, *Acta Cryst.*, 1970, *B*, **26**, 341.

has been much discussed[11-14] already. It has been shown[14] that the symmetrically substituted bicyclo-[2,2,2]octane-1,4-dicarboxylic acid molecule possesses C_{2v} ($mm2$) symmetry and the bicyclo-octane skeleton D_{3h} ($\bar{6}m2$) symmetry. The quinuclidine structures are substituted in the 3-position and it could be this fact which leads to the reported twist. Further torsion angles for 3AQ are given in Table 5. The bond distances and angles of the quinuclidine nucleus (Table 4) do not differ significantly from those in QB or QT. Only two intermolecular contacts $<3{\cdot}6$ Å exist. These are C(13) $\cdots$ O(9) 3·59 [$O(9^{I})$ at $x, y-1, z$] and C(13) $\cdots$ O(12) 3·40 Å [$O(12^{II})$ at $x-1, y-1, z$]. The packing of the molecule projected on (001) is shown in Figure 2.

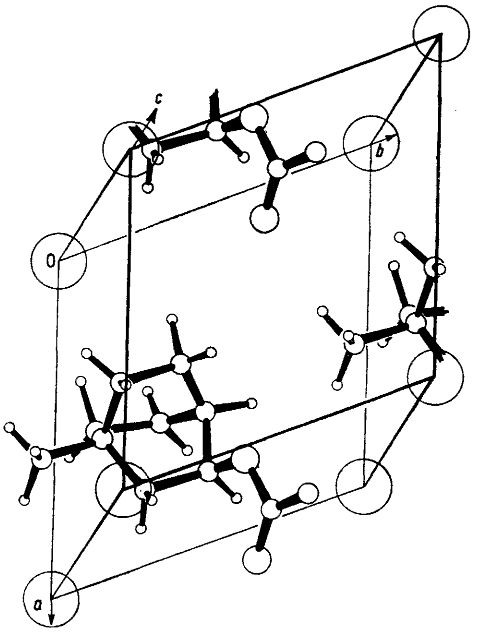

FIGURE 2 Molecular packing projected on (001)

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[2/1339 *Received*, 12*th June*, 1972]

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[13] A. F. Cameron, G. Ferguson, and D. G. Morris, *J. Chem. Soc.* (*B*), 1968, 1249.

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