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FORMATION OF 1-HYDROXYCYCLOPROPANECARBONITRILE RING IN BICYCLIC SYSTEMS.

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ABSTRACT. Reaction of α-methanesulfonyloxycycloalkanones with KCN in dimethylformamide is examined; this proceeds, with high yield, to give in some cases 1-hydroxybicyclocarbonitriles and in other cases 2-cyanooxiranes. Open chain α-methanesulfonyloxyalkanones afford 2-cyanooxiranes.

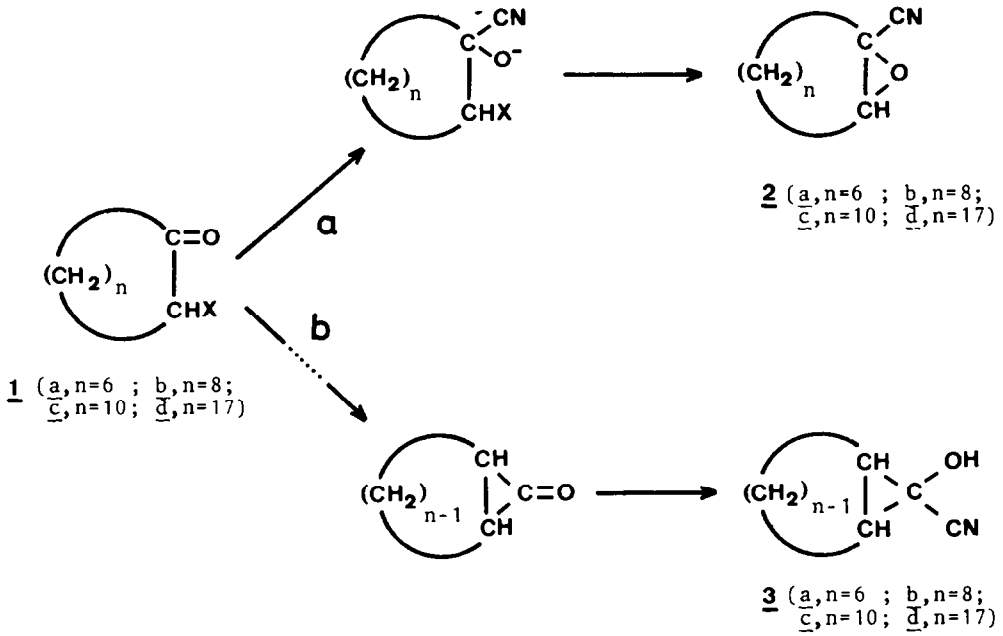
1-Hydroxycyclopropanecarbonitriles may be obtained by addition of hydrogen cyanide to cyclopropanone[1a], cyclization of β-chloroaldehydecyanohydrins,[1b] addition of lithium cyanide to the magnesium salt of the ethyl hemiketals of cyclopropanones,[1c] addition of carbenes to 2-acetoxyacrylonitriles or to 2-((trimethylsilyl)oxy)acrylonitriles[1d], and 1,3-dipolar addition of the last two to diazoalkanes[1d].

In this paper we wish to report the reaction of α-halocycloalkanones and α-methanesulfonyloxycycloalkanones with potassium cyanide in dimethylformamide. As a result we propose a new method to prepare 2-cyanooxiranes and 1-hydroxycyclopropanecarbonitriles attached to another ring, and at the same time we define the scope and limitations of the reaction. A point of interest is based on the possible enlargement of the cyclopropane cyanohydrin ring into cyclobutanone[1b], which opens the way to the preparation of other bicyclic compounds.

From a theoretical point of view α-halocycloalkanones and α-metanesulfonyloxy cycloalkanones (1) may undergo two competitive reaction types when treated with potassium cyanide, as occurs in the reaction of α-haloketimines[2] with KCN. The reaction may begin (see scheme) with nucleophilic addition of the cyanide ion at the carbonyl group, (pathway a) to yield and adduct anion, which subsequently undergoes intramolecular nucleophilic substitution and leads to a 2-cyanooxirane (2). Another possibility is the Favorskii-type reaction (pathway b), which is iniciated by α'-deprotonation of cycloalkanone, carried out by the CN^- base, and which is followed by an intramolecular nucleophilic substitution, that sets up a new cyclopropanone ring, and finally ends by nucleophilic addition of HCN to the carbonyl function.

A general procedure is described in the experimental part for the synthesys of 2-cyanooxiranes and 1-hydroxybicyclocarbonitriles and its results are shown in the table.

SCHEME



The best results were obtained with the α-methanesulfonyloxycycloalkanones 1b (X=OMs) and 1c (X=OMs) (entry 2 and 3) which lead exclusively to the hydroxynitriles 3b and 3c. When the ring size is smaller, as in 1a, only the 2-cyanooxirane is obtained (entry 1), but when the ring size is larger, as in 1d, a mixture of cyanohydrin and 2-cyanooxirane is obtained (entry 4). Open chain methanesulfonyloxy alkanones afforded only 2-cyanooxiranes[4], e.g.: 5-methanesulfonyloxy-4-octanone gave only 4,5-epoxyoctane-4-carbonitrile. Substitution of the mesyloxy group by chlorine in the α-substituted cyclododecanone (entry 5) leads to 11% of 2-cyanooxirane, and substitution by bromine (entry 6) leads to a mixture containing mostly 2-cyanooxirane[5].

Table.- Reaction of α-substituted cycloalkanones with KCN in DMF

Entry	Starting material[3]	Reaction time(h)	Cyanohydrin[a] 3 yield %	2-Cyanooxirane 2 yield %
1	1a (X=OMs)	1.5	0	94[b]
2	1b (X=OMs)	1.5	88	0
3	1c (X=OMs)	1.5	92	0
4	1d (X=OMs)	1.5	26	47[c]
5	1c (X=Cl)	16.0	72	11[d]
6	1c (X=Br)	1.0	35	56[d]

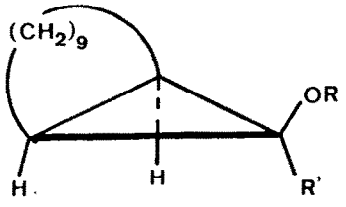
a) The corresponding trimethylsilylderivatives and acetates gave only one peak in gas chromatography. b) ^{1}H-NMR indicated a single isomer. c) Mixture of *cis* and *trans* isomers (inseparable by gas chromatography) indicated by ^{1}H-NMR. d) Mixture of *cis* and *trans* isomers (^{1}H-NMR) separated by combined gas chromatography-mass spectrometry.

These results may patially be explained in terms of I-strain (internal strain)[6]. Addition of cyanide ion to the carbonyl group (pathway a) in the medium rings 1b and 1c is accompained by an increase in I-strain and therefore the reaction is disfavoured. In the larger rings (as in 1d) which more closely resemble aliphatic derivatives the net change in strain accompanying cyanide ion addition is much less significant and the reaction is not disfavoured, the cyanooxirane being the major product.

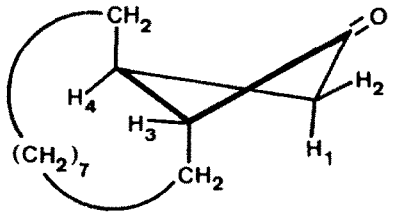
An unexpected result was obtained with the cyclooctanone 1a; presumably this is a result of the much greater rigidity of the 8-membered ring preventing the α-substituent from adopting an orientation suitable for the Favorskii-type reaction to take place.

A particularly interesting question is the cis- or trans-fusion of three- and higher membered rings of hydroxybicyclocarbonitriles. This was shown to be cis- at least in the case of the fused three- and eleven-membered rings. The cyanohydrin 3c was transformed[1d] into bicyclo[9.2.0]tridecan-12-one in which the cyclobutanone was certainly cis-attached to the cycloundecane ring since this compound was epimerized to the more stable trans-stereoisomer[7] (5) by treatment with sodium methoxide. The cis-attachment of the fused three- and eleven-membered rings in 3c explains the fact that the cyclopropane hydrogens in 3c appear at lower field than is typical (between 1.0-2.0 ppm) due to the deshielding effect of the CN group. In fact, when the compound 3c is converted into 4b or 4c the influence of the CN group disappears and both protons are registered at δ 0.5 ppm in 4b and δ 0.8 ppm in 4c. In addition a NOE of 20% was observed between cyclopropane hydrogens and CH_3 group in 4c. Solvolysis of 4c in AcOH/NaOAc gave the acetate of 2-methylcyclo dodec-cis-2-enol, which contains an olefinic proton on the same side as the CH_3 group (a NOE of 11% between the olefinic proton and the CH_3 group was registered); this agrees with a disrotatory opening of cyclopropane ring in 4c concerted with loss of the leaving group[8], with the cyclopropane hydrogens and the CH_3 group being on the same side.

The same arrangement of rings is found in compound 3b.



4 a: R=-CH(CH$_3$)OCH$_2$CH$_3$, R'=CN
b: R=-CH(CH$_3$)OCH$_2$CH$_3$, R'=CH$_3$
c: R=p-CH$_3$C$_6$H$_4$SO$_2$-, R'=CH$_3$



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EXPERIMENTAL PART

General Methods.- Melting points were determined on a Kofler apparatus and are uncorrected. I.R. spectra were recorded as liquid films for oils and in KBr discs for solids in a Perkin-Elmer model 281 spectrophotometer. The ^{1}H spectra were registered on a Varian X120 (200 MHz) and a Perkin-Elmer R12B (60 MHz) spectrometers, using tetramethylsilane as internal standard and $CDCl_3$ as solvent. Mas spectra were performed at 70 eV on a Varian 166 machine, using a direct inlet systems. Gas chromatography was carried out on a Perkin-Elmer model 3920B, using

helium as carrier gas and a Minigrator to integrate the areas. The R_t (retention time) values are given for a column of EGA 5% on chromosorb W-AW, 2m long and 3mm o.d., using helium as carrier gas at a flow rate of 30 ml min^{-1} with θinj. 250°C and θdet 250°C (column temperatures indicated). Column chromatography was performed on Merck silica gel (0.063-0.200 mm) and thin layer chromatography on Merck silica gel (G.60 and 60 HF_{254}; 0.25 mm layer thickness).

General procedure for the synthesis of 2-cyanooxiranes and 1-hydroxybicyclocarbonitriles. A solution of 3.0 mmol of α-methanesulfonyloxycycloalkanone (1, X=OMs) or α-halocycloalkanone (1c, X=Br or Cl) in dimethylformamide(5.0 ml) was added dropwise to a suspension of 6.0 mmol of KCN in dimethylformamide (13.0 ml) at room temperature with continuous stirring, which was continued until reaction was complete. The reaction mixture was poured into water and extracted with ether, washed with 5% hydrochloric acid, aqueous sodium hydrogencarbonate and brine. Drying over Na_2SO_4 and evaporation of the solvent afforded the crude product. This was chromatographed on silica gel, from which hexane:ether/9:1 eluted cyanooxiranes and hexane:ether/7:3 eluted hydroxybicyclocarbonitriles. The results are given in the table.

Selected physical data

2a, 1-cyano-1,2-epoxycyclooctane: Oil; MS: m/z 123.0677 ($M^+-C_2H_4$), $C_9H_{13}ON-C_2H_4$ requires 123.0684; ν_{max} 2240(CN), 1220(oxirane) cm^{-1}; ^{1}H-NMR (200 MHz) δ 3.29 ppm (dd, J=10.3 and J=4.1 Hz, 1H, -CHC(CN)-).

3b, 10-cyanobicyclo[7.1.0]decan-10-ol: m.p. 92-93°C (hexane); ν_{max} 3350 (OH), 2235 (CN) cm^{-1}; ^{1}H-NMR (60 MHz) δ3.69 (br s, 1H, OH), 2.1-1.0 ppm (m, 16H, $7CH_2$ + 2CH). Acetate: m.p. 71-72°C (hexane); MS: m/z 221.1411 (M^+), $C_{13}H_{19}O_2N$ requires 221.1418; ν_{max} 2235 (CN) and 1766 (OAc) cm^{-1}; ^{1}H-NMR (60 MHz) δ 2.1 ppm (s, 3H, $OCOCH_3$).

3c, 12-cyanobicyclo[9.1.0]dodecan-12-ol: m.p. 107-108°C (hexane); ν_{max} 3350 (OH), 2235 (CN) cm^{-1}; ^{1}H-NMR (60 MHz) δ 3.55 (br s, 1H, OH), 2.0-1.0 ppm (m, 20H, $9CH_2$+ 2CH). Acetate: m.p. 92.5-93.5°C (hexane); MS: m/z 249.1718 (M^+), $C_{15}H_{23}O_2N$ requires 249.1729; ν_{max} 2235 (CN) and 1760 (OAc) cm^{-1}; ^{1}H-NMR (60 MHz) δ 2.1 ppm (s, 3H, $OCOCH_3$).

3d, 19-cyanobicyclo[16.1.0]nonadecan-19-ol: m.p. 122-123°C (hexane); ν_{max} 3350(OH) and 2235 (CN) cm^{-1}; ^{1}H-NMR (60 MHz) δ 3.50 (br s, 1H, OH), 1.8-1.0 ppm (m, 34H, 16 CH_2+ 2CH). Acetate: m.p. 42-42.5°C (methanol); MS: m/z 347.2809 (M^+), $C_{22}H_{37}O_2N$ requires 347.2824; ν_{max} 2235 (CN) and 1760 (OAc) cm^{-1}; ^{1}H-NMR (60 MHz) δ 2.1 ppm (s, 3H, $OCOCH_3$).

1-Ethoxyethyl ether of 12-methylbicyclo[9.1.0]dodecan-12-ol (4b). A mixture of 3c (1.219 g, 5.888 mmol), ethyl vinyl ether (0.636 g, 8.833 mmol) and pyridinium toluene-4-sulfonate (0.148 g) in anhydrous dichloromethane (40 ml) was allowed to react for 2h at room temperature. The reaction mixture was washed with brine, dried over Na_2SO_4 and the residue obtained after solvent removal chromatographed(hexane:ether/8:2 eluant) to provide the 1-ethoxyethyl ether of 12-cyanobicyclo[9.1.0]dodecan-12-ol 4a (1.547 g, 94.2%) as an oil.

Compound 4a (1.547 g, 5.554 mmol) was dissolved in anhydrous ether (6.7 ml) and treated with sodium bis(2-methoxyethoxy)aluminium hydride[9] (1.2 ml, 70% in toluene, 6.96 mmol) at -30°C under argon. The mixture was stirred for 2h, poured into cold water and neutralized with cold 5% sulphuric acid. The ethereal layer was washed with brine and dried over Na_2SO_4 at -30°C. The residue obtained after evaporation of solvent under reduced pressure (ν_{max} 1710 cm^{-1}(CHO)) was mixed with diethyleneglycol (20.6 ml) and hydrazine hydrate (1.7 ml) and heated with stirring for 1h at 100°C. After addition of KOH (1.566 g) the temperature was raised to 210°C and the reaction mixture stirred for 1h at this temperature. The reaction mixture was cooled, diluted with water and worked up as usual to provide the crude product. Chromatography (hexane:ether/9:1) gave 4b (1.210 g, 81.5% from 4a) as an oil; MS: m/z 268.2402 (M^+), $C_{17}H_{32}O_2$ requires 268.2411; ν_{max} 1380 (CH_3) and 1080 (C-O) cm^{-1}; ^{1}H-NMR (200 MHz), δ 4.81 (q, J=5.2 Hz, 1H, -OCHOEt), 3.51 (two overlapping q, J=7.2 Hz, 2H, $-OCHOCH_2CH_3$), 1.35 (s, 3H, CH_3 on cyclopropane ring) 1.24 (d, J=5.3 Hz, 3H, $-OCHCH_3$), 1.16 (t, J=7 Hz, 3H, $-OCHOCH_2CH_3$), 0.54 ppm (complex, 2H, both hydrogens on cyclopropane ring).

Tosylate of 12-methylbicyclo[9.1.0]dodecan-12-ol (4c). A solution of 4b (0.200 g, 0.746 mmol) in tetrahydrofuran (2 ml), water (0.5 ml) and concentrated HCl(0.125 ml) was stirred for 1h at 0°C. Dilution with water and work-up gave an oil (ν_{max} 3240 cm^{-1}) which was dissolved in pyridine (1.2 ml), treated with toluene-4-sulfonyl chloride (0.139 g, 0.730 mmol) and the mixture stirred for 30 min at 60°C. The mixture was transferred to ice-5% hydrochloric acid and ether. The ethereal layer

was washed with aqueous sodium hydrogencarbonate and worked up as usual to provied an oil which was chromatographed (hexane:ether/1:1) to provide 4c (0.110 g, 42%); ν_{max} 1600 (Ph), 1370 and 1189(SO_2)cm^{-1}; ^{1}H-NMR (200 MHz) δ 7.77 and 7.32 (two d, J=8.6 Hz, 4H, Ph-H), 2.44(s, 3H, SO_2CH_3), 1.52(s, 3H, CH_3 on cyclopropane ring), 1.0-2.2 (m, 18H, 9 CH_2), 0.8 ppm (m, 2H, both hydrogens on cyclopropane ring); MS: m/z 350 (M^+, 0.5%), 195(3.5%), 194(7.5%), 179(100%), because of low intensity of M^+ a reliable high resolution mass measurement was not possible.

Acetate of 2-methylcyclododec-cis-2-enol. To the above tosylate 4c (0.105 g, 0.3 m mol) in acetic acid (5.8 ml) under argon was added acetic anhydride (1.4 ml) and sodium acetate (69 mg), and the mixture stirred for 48h at 100°C. Work-up provided an oil which was purified by preparative thin layer chromatography (silica gel; hexane:ether/8:2), to afford 0.030 g (42%) of acetate of 2-methylcyclododec-cis-2-enol, g.l.c. analysis of which (180°C) showed a major peak (R_t 2.42 min; 97.3%); MS: m/z 238.1940 (M^+), $C_{15}H_{26}O_2$ requires 238.1933; ν_{max} 1735 (OAc), 1662(C=C)cm^{-1}; ^{1}H-NMR (200 MHz) δ 5.64 (m, 1H, CH=C), 5.20 (dd, J=9.8 and 5.6 Hz, 1H, CHOAc), 2.18 (m, 2H, CH_2=), 2.02 (s, 3H, CH_3CO_2), 1.64 (s, 3H, CH_3C=), 2.0-1.0 ppm (m, 16H, 8CH_2).

Bicyclo[9.2.0]tridecan-12-one (5). To a stirred suspension of lithium aluminium hydride (0.200 g, 5.263 mmol) in anhydrous ether (10 ml) under argon was added a solution of 4a (0.445 g, 1.595 mmol) in ether (2 ml) and the mixture heated to reflux for 1.5h. After addition of water (0.2 ml) the mixture was transferred to an aqueous solution of sodium potassium tartrate and extracted with ether. The solid residue obtained after drying and solvent removal was dissolved in acetic acid (2 ml) and water (1 ml), the solution was cooled in an ice-water bath, treated dropwise with a solution of sodium nitrite (0.320 g, 4.636 mmol) in water (0.70 ml) and stirred for 1h at 5°C. After neutralization with solid sodium carbonate the mixture was poured into water and extracted with light petroleum. The organic layer was washed with brine followed by drying and removal of the solvent to afford and oil, which was chromatographed on silica gel (hexane:ether/9:1) to give the cis isomer of bicyclo[9.2.0]cyclotridecan-12-one (0.247 g 80%); g.l.c. analysis (170°C) showed two peaks due to cis (R_t 8.46 min, 90%) and trans (R_t 7.75 min, 10%) isomers of bicyclo[9.2.0]cyclotridecan-12-one; ν_{max} 1775 cm^{-1} (CO cyclobutanone); ^{1}H-NMR (60 MHz) δ 2.2-3.5 (m, 3H, CHCO + CH_2CO), 2.0-2.2 (m, 1H, CH), 0.9-2.0 ppm (m, 18H, 9 CH_2).

Isomerization of the above product was effected by treatment with sodium methoxide in methanol at room temperature; g.l.c. analysis of isomerized product (170°C) showed a major peak due to trans-isomer 5 (R_t 7.75 min, 96%). ν_{max} 1775 cm^{-1} (CO); ^{1}H-NMR (200 MHz) δ 3.10 (two dd, J_{12}=17.6, J_{14}=8.7, J_{13}=2.8 Hz, 1H, H_1), 2.92 (m, 1H, H_3), 2.63 (two dd, J_{21}=17.6, J_{24}=7.3, J_{23}=3.1 Hz, 1H, H_2), 2.16 (m, 1H, H_4), 1.90 (m, 2H, CH_2CH), 1.65-1.26 ppm (m, 16H, 8 CH_2); MS: m/z 194.1676 (M^+), $C_{13}H_{22}O$ requires 194.1670.

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REFERENCES AND NOTES

1. (a) W.J.M. van Tilborg, S.E. Schaafsma, H, Steinberg and T.J. De Boer, Recl.Trav.Chim.Pays-Bas, 86, 419 (1967). (b) G. Stotk, J.C. Depezay and J. d'Angelo, Tetrahedron Lett., 389 (1975). (c) J. Salaiin, F. Bennani, J.C. Compain, A. Fadel and J. Olliver, J.Org.Chem., 45, 4129 (1980). (d) A. Oku, T. Yokoyama and T. Harada, J.Org.Chem., 48, 5333 (1983).

2. N. De Kimpe, P. Sulmon, R. Verhé, L. De Buyck and N. Schamp, J.Org.Chem., 48, 4320 (1983).

3. For the preparation of starting material see A.Abad, M.Arnó, J.R.Pedro and E.Seoane, J.Chem.Soc.Perkin Trans. I, 2471 (1983) and papers cited therein.

4. For other examples of 2-cyanooxiranes from α-haloketones see: K.Takahashi, T. Nishizuka and H. Iida, Tetrahedron Letrer, 2389 (1981), and K.Takahashi,

T. Nishizuja and H. Iida, Synth.Commun., 757 (1981).

5. If the low solubility of KCN in dimethylformamide is increased by the use of other solvents, such as dimethylsulfoxide, the amount of 2-cyanooxirane also increases.

6. (a) H.C. Brown and K.Ichikawa, Tetrahedron, 1, 221 (1957). (b) Michael Hanack, "Conformation theory", Organic Chemistry, a series of monographs, Academic Press, London, 1965, Vol.3, chap.3, p. 164-171.

7. J.L. Gras, R. Maurin and M. Bertrand, Tetrahedron Lett., 3533 (1969).

8. P.v.R. Schleyer, W.F. Sliwinski, G.W. Van Dine, V. Schölkopf, J. Paust and K. Fellenberger, J.Amer.Chem.Soc.,94, 125 (1972).

9. M. Schlosser and Z. Brich. Helv.Chim.Acta, 61, 1903 (1978).