

271. *Alkylcyclohexanone Cyanohydrins.*

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When 4-methyl- and 4-*t*-butyl-cyclohexanone were converted into their cyanohydrins, only one cyanohydrin could be detected in each case, *e.g.*, *cis*-1-hydroxy-4-*t*-butylcyclohexanenitrile (III).^{*} The configuration of this was shown by conversion into the hydroxy-acid (II) obtained on oxidation of *trans*-1-ethynyl-4-*t*-butylcyclohexanol (I). Deamination of 4-alkyl-1-aminocyclohexanecarboxylic acids with nitrous acid yielded the cyclohexenyl acids, not the hydroxy-acids as claimed by Skita and Levi.¹ Dissociation constants of a number of 4-alkylcyclohexanone cyanohydrins have been measured.

THE investigation of cyanohydrin formation from alkylcyclohexanones has been carried out because of its similarity to the formation of α -amino-nitriles and spirohydantoins in the Strecker and the Bucherer synthesis, respectively. These latter reactions result in highly stereospecific additions to the carbonyl double-bond of the alkylcyclohexanones,²⁻⁴ with greater yields from the higher 4-alkyl compounds. These higher yields may be explained by the concept of "equatorial interference" advanced by Wheeler and Zabicky⁵ to explain the greater stability of 4-methylcyclohexanone cyanohydrin over that of cyclohexanone cyanohydrin. However, there is an alternative explanation for this difference in dissociation constants. Since the reported dissociation constant for the 4-methyl compound (3.15×10^{-4} mole l.⁻¹) is about half that given for cyclohexanone cyanohydrin (5.91×10^{-4} mole l.⁻¹), two epimeric cyanohydrins may be formed in about equal amounts, each with a dissociation constant about equal to that of the parent cyclohexanone cyanohydrin. It is necessary to know, therefore, if 4-alkylcyclohexanones do form two cyanohydrins.

2-Methylcyclohexanone was reported by Nazarov, Kamernitskii, and Akhrem⁶ to yield a mixture of cyanohydrins in which the *cis*-1-hydroxy-2-methylcyclohexanenitrile predominated. Godchot and Cauquil⁷ claimed that 3-methylcyclohexanone formed two cyanohydrins but, after hydrolysis of the crude product, they could only isolate one hydroxy-acid. Recently, Kamernitskii and Akhrem⁸ succeeded in isolating both isomeric hydroxy-acids, the *trans*-1-hydroxy-3-methylcyclohexanecarboxylic acid constituting 75% of the crude hydrolysis product. The 4-methyl derivative was investigated by Godchot and Cauquil⁹ who stated that two hydroxy-acids (m. p.s 115 and 82°) could be obtained by hydrolysis of the cyanohydrin. Tschoubar and Collin¹⁰ reported the m. p.s of these acids to be 122 and 95° although no analyses were reported; further, it was claimed that the cyanohydrin could be distilled at 126—130°/12 mm.

We found that 4-methylcyclohexanone cyanohydrin could not be distilled above 75° (at 10⁻⁶ mm.) without decomposition occurring, as Billimoria and MacLagan¹¹ found for cyclohexanone cyanohydrin itself. Chromatography of the crude undistilled cyanohydrin was carried out on alumina. The fractions were examined by infrared (i.r.) spectroscopy, and by conversion into the phenylurethanes. There was no evidence of more than one

* Throughout this Paper, except where otherwise stated, the terms "*cis*" and "*trans*" relate the position of the 4-substituent to that of the principal of the two groups in the 1-position, *i.e.*, the one which is used in the name as a suffix.

¹ Skita and Levi, *Ber.*, 1908, **41**, 2925.

² Munday, *J.*, 1961, 4372.

³ Brimelow, Carrington, Vasey, and Waring, *J.*, 1962, 2789.

⁴ Cremlyn, *J.*, 1962, 3977.

⁵ Wheeler and Zabicky, *Canad. J. Chem.*, 1958, **36**, 656.

⁶ Nazarov, Kamernitskii, and Akhrem, *Zhur. obshchei Khim.*, 1958, **28**, 1458.

⁷ Godchot and Cauquil, *Compt. rend.*, 1936, **203**, 1043.

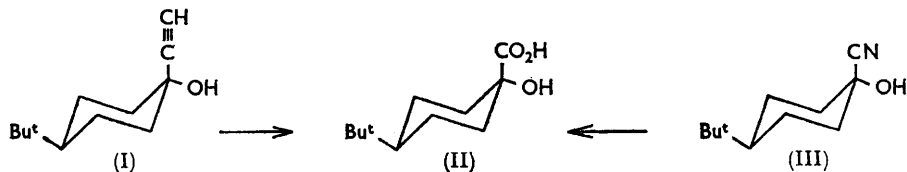
⁸ Kamernitskii and Akhrem, *Zhur. obshchei Khim.*, 1960, **30**, 754.

⁹ Godchot and Cauquil, *Compt. rend.*, 1937, **204**, 77.

¹⁰ Tschoubar and Collin, *Bull. Soc. chim. France*, 1947, **14**, 680.

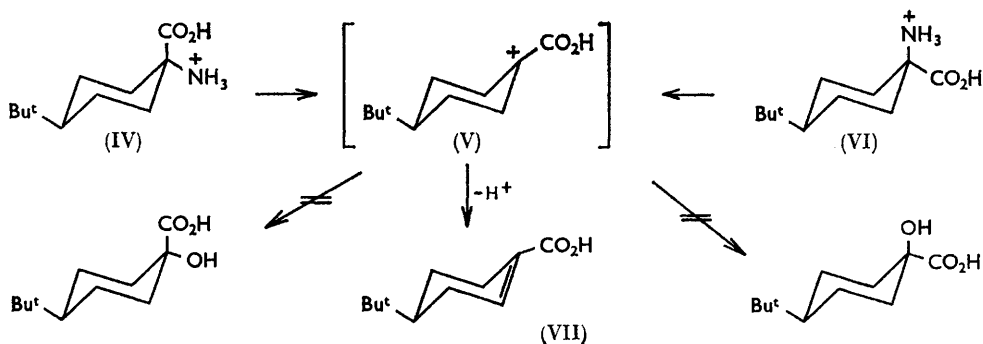
¹¹ Billimoria and MacLagan, *J.*, 1951, 3069.

isomer. Crude 4-*t*-butylcyclohexanone cyanohydrin was a solid and was similarly examined by chromatography. Again only one isomer could be found. The assignment of configuration was made by hydrolysing the 4-*t*-butylcyclohexanone cyanohydrin to the corresponding hydroxy-acid, m. p. 142—143°. Another product from the hydrolysis was a solid whose analysis suggested it to be the ester formed from the hydroxy-acid and the enol form of 4-*t*-butylcyclohexanone. A similar product was obtained by Godchot and Cauquil from the 4-methyl analogue.⁹ Hennion and O'Shea¹² obtained *cis*- and *trans*-1-ethynyl-4-*t*-butylcyclohexanol by the ethynylation of 4-*t*-butylcyclohexanone, and assigned the configurations from the relative rates of hydrolysis of their *p*-nitrobenzoates, and from the order of their elution from an alumina column. Oxidation of these acetylenic alcohols with potassium permanganate afforded the corresponding hydroxy-acids. The *cis*-1-hydroxy-4-*t*-butylcyclohexanecarboxylic acid (II) had m. p. 142.5—143°, and was identical with the product from the cyanohydrin. The *trans*-hydroxy-acid had m. p.



158—160°. The cyanohydrin therefore has its 4-*t*-butyl and nitrile groups in a *cis*-relationship. It is interesting to note that 2- and 4-alkylcyclohexanone cyanohydrins exist predominantly in the form with the alkyl groups *trans* to the hydroxyl group, whereas the 3-methyl compounds exist predominantly in the *cis*-configuration. This would suggest that the hydroxyl group, rather than the nitrile group, tends to be equatorial in the stable chair form. It could be that the effective bulk of the hydroxyl group is enlarged by solvation (cf. Eliel¹³).

It was hoped that a correlation might also be achieved with *cis*- and *trans*-1-amino-4-*t*-butylcyclohexanecarboxylic acid (cf. IV and VI), prepared by the Bucherer and the Strecker synthesis, by deamination with nitrous acid to the corresponding hydroxy-acids. (The amino-group of an α -amino-acid is replaced by the hydroxyl group with retention of configuration.¹⁴) Unfortunately, with nitrous acid, both these amino-acids yield the same product, namely 4-*t*-butylcyclohex-1-enecarboxylic acid (VII). It seems that the



carbonium ion (V) postulated as an intermediate in nitrous acid deaminations undergoes, in these cases, loss of a β -proton to yield an olefinic acid, rather than solvation to produce the hydroxy-acid.

Godchot and Cauquil⁹ had claimed that the main product from the hydrolysis of

¹² Hennion and O'Shea, *J. Amer. Chem. Soc.*, 1958, **80**, 614.

¹³ Eliel, *J. Chem. Educ.*, 1960, **37**, 130.

¹⁴ Brewster, Hiron, Hughes, Ingold, and Rao, *Nature*, 1950, **166**, 178.

4-methylcyclohexanone cyanohydrin was a hydroxy-acid, m. p. 115°, identical with that prepared by Skita and Levi¹ by deamination of 1-amino-4-methylcyclohexanecarboxylic acid prepared by the Strecker reaction. However, we could not repeat these results. The m. p. of our hydroxy-acid, produced by hydrolysis of the cyanohydrin, was 124—126°. (An additional product was the enol ester of 4-methylcyclohexanone with the hydroxy-acid.) When the Strecker amino-acid was treated with nitrous acid, following exactly the procedure of Skita and Levi, the product had m. p. 133—134° and an analysis corresponding to the unsaturated acid. The hydantoin product also underwent deamination to the same acid.

We have extended Wheeler and Zabicky's studies⁵ to higher homologues substituted in the 4-position, and, in keeping with their theory, the cyanohydrins become progressively more stable as the alkyl group is enlarged. Because of the low dissociation constants in

Dissociation constants of cyanohydrins at 21°.

| | 96% ethanol | | 94% ethanol | |
|--------------------------------|--|----------|--|----------|
| | 10 ⁴ K (mole l. ⁻¹) | σ | 10 ⁴ K (mole l. ⁻¹) | σ |
| Cyclohexanone | 6.21 | ±0.57 | 45.6 | ±2.8 |
| 4-Methylcyclohexanone | 3.73 | ±0.22 | 31.1 | ±2.1 |
| 4-Ethylcyclohexanone | 3.12 | ±0.51 | 24.0 | ±2.8 |
| 4-Isopropylcyclohexanone | 2.72 | ±1.09 | 23.6 | ±3.1 |
| 4-t-Butylcyclohexanone | 2.32 | ±1.7 | 22.2 | ±1.1 |

σ = standard deviation.

96% alcohol, concordant results could not be achieved. By reducing the percentage of alcohol to 94 the degree of dissociation was increased about ten-fold, and the relative error thereby reduced.

EXPERIMENTAL

4-Methylcyclohexanone Cyanohydrin.—This was prepared by the method used by Billimoria and MacLagan¹¹ for cyclohexanone cyanohydrin. To 4-methylcyclohexanone (57.0 g.) in ether (150 ml.) was added finely powdered potassium cyanide (50 g.). The suspension was cooled to -10°, concentrated hydrochloric acid (75 ml.) was added slowly during 1 hr., and the temperature was then kept below 0° for 6 hr. The ether layer was separated and the aqueous layer washed twice with ether (100 ml.). The combined ether extracts were washed with saturated sodium hydrogen sulphite solution and sodium hydrogen carbonate solution, and dried (Na₂CO₃). The ether was removed under reduced pressure, and the temperature of the oil-bath raised to 70°. The residue was distilled at 65—70°/10⁻⁶ mm., to yield the *cyanohydrin* as a viscous colourless oil which did not crystallise on standing at -70° for several hours (Found: C, 69.2; H, 9.5; N, 9.5. C₈H₁₃NO requires C, 69.0; H, 9.8; N, 10.1%).

The crude cyanohydrin (8.0 g.) remaining after removal of the ether in the above preparation, in light petroleum (b. p. 40—60°; 50 ml.) was adsorbed on to a column of alumina (240 g.; 100—200 mesh; Spence grade H). The column was eluted successively with light petroleum (40—60°; 400 ml.), light petroleum-chloroform (9 : 1; 400 ml.), and light petroleum-methanol (4 : 1; 400 ml.). Fractions (10 ml.) were collected and the solvent was removed under reduced pressure, while the tubes were warmed to no more than 50°. 22 fractions yielding residues were obtained. Fractions 1, 2, and 3 (total weight, 1.95 g.) gave i.r. spectra identical with that of 4-methylcyclohexanone, and no band at 2220 cm.⁻¹ characteristic of the nitrile group was observed. Fraction 4 was negligible. Fractions 5—19 (total weight, 5.93 g.) were also liquid and gave identical i.r. spectra. Portions of these fractions, on warming with phenyl isocyanate and a trace of triethylamine, all yielded the same *phenylurethane derivative* as needles, m. p. 183—185° (from ethanol) (Found: C, 69.7; H, 6.3; N, 11.2. C₁₅H₁₈N₂O₂ requires C, 69.7; H, 7.0; N, 10.8%). Fractions 20—22 gave a trace of a solid on evaporation, whose analysis indicated that it was probably *1-hydroxy-4-methylcyclohexanecarbonamide*, plates, m. p. 158—160° [from light petroleum (b. p. 60—80°)-benzene] (Found: C, 60.6; H, 9.5. C₈H₁₅NO₂ requires C, 61.1; H, 9.6%). Chromatography of the cyanohydrin was carried out 6 times without detection of a second isomer, even when 60 g. of cyanohydrin was used.

Hydrolysis of 4-Methylcyclohexanone Cyanohydrin.—The crude cyanohydrin (6.0 g.) and concentrated hydrochloric acid (20 ml.) were set aside for 2 weeks at room temperature, and were

then heated on a water-bath for 24 hr. After evaporation of the water, the residue was extracted with benzene. Concentration of the benzene extract, and addition of light petroleum (b. p. 40—60°) afforded 1-hydroxy-4-methylcyclohexanecarboxylic acid, needles, m. p. 124—126° [from benzene—light petroleum (b. p. 40—60°)] (Found: C, 59.6; H, 9.3. $C_8H_{14}O_3, \frac{1}{2}H_2O$ requires C, 59.1; H, 8.7%). The mother-liquors, on evaporation, left a gummy solid which, after chromatography on alumina, yielded 4-methylcyclohex-1-enyl 1-hydroxy-4-methylcyclohexanecarboxylate, prisms, m. p. 118—119° (lit.,⁹ 119°).

Deamination of cis-1-Amino-4-methylcyclohexanecarboxylic Acid.—The amino-acid (2.0 g.) in dilute sulphuric acid (5%; 10 ml.) was treated with sodium nitrite (1.0 g.) in small portions during $\frac{1}{2}$ hr. The solution was set aside for 4 hr., and then extracted with ether. Removal of the solvent afforded 4-methylcyclohex-1-enecarboxylic acid, needles, m. p. 133—134° [from benzene—light petroleum (b. p. 40—60°)] (Found: C, 68.4; H, 9.0. $C_8H_{12}O_2$ requires C, 68.5; H, 8.6%).

Deamination of trans-1-Amino-4-methylcyclohexanecarboxylic Acid.—The amino-acid (1.9 g.) was treated exactly as in the previous case, to yield 4-methylcyclohex-1-enecarboxylic acid, needles, m. p. 133° [from benzene—light petroleum (b. p. 40—60°)] (Found: C, 68.7; H, 8.6. $C_8H_{12}O_2$ requires C, 68.5; H, 8.6%).

4-t-Butylcyclohexanone Cyanohydrin.—This was prepared from 4-t-butylcyclohexanone in 70% yield, as described above for the 4-methyl derivative. The cyanohydrin formed needles, m. p. 53—54° [from light petroleum (b. p. 40—60°)] (Found: C, 72.9; H, 10.95; N, 7.8. $C_{11}H_{19}NO$ requires C, 72.9; H, 10.6; N, 7.7%). The crude cyanohydrin was analysed by chromatography on alumina, and only samples melting in the range 50—54° were obtained.

Hydrolysis of 4-t-Butylcyclohexanone Cyanohydrin.—The cyanohydrin (3.6 g.) and concentrated hydrochloric acid (10 ml.) were set aside for 1 week at room temperature, and then refluxed for 60 hr. After cooling the mixture, the semi-solid mass was filtered off, and fractionally crystallised from water—acetic acid (1:9). The first fraction, from its analysis, was presumed to be 4-t-butylcyclohex-1-enyl 1-hydroxy-4-t-butylcyclohexanecarboxylate and formed plates, m. p. 330° (from water—acetic acid) (Found: C, 75.1; H, 10.9. $C_{21}H_{36}O_3$ requires C, 74.9; H, 10.8%). The second fraction, *cis*-1-hydroxy-4-t-butylcyclohexanecarboxylic acid (II), formed plates, m. p. 142—143° (from water—acetic acid) (Found: C, 62.8; H, 9.9. $C_{11}H_{20}O_3, \frac{1}{2}H_2O$ requires C, 63.1; H, 10.1%).

Ethynylation of 4-t-Butylcyclohexanone.—The procedure of Hennon and O'Shea¹² was followed, to yield *cis*-1-ethynyl-4-t-butylcyclohexanol, m. p. 100—101° (lit.,¹² 101—102°), in 66% yield, and the *trans*-isomer (I), m. p. 60—61° (lit.,¹² 62—64°) in 4.5% yield.

trans-1-Hydroxy-4-t-butylcyclohexanecarboxylic Acid.—*cis*-1-Ethynyl-4-t-butylcyclohexanol (0.35 g.) and potassium permanganate (0.9 g.) in water (20 ml.) were shaken for 4 hr. The precipitated manganese dioxide was filtered off and sulphur dioxide passed through the filtrate to decolourise it. The hydroxy-acid was precipitated, and formed plates, m. p. 158—160° (from water—acetic acid) (Found: C, 63.80; H, 9.9. $C_{11}H_{20}O_3, \frac{1}{2}H_2O$ requires C, 63.1; H, 9.6%).

cis-1-Hydroxy-4-t-butylcyclohexanecarboxylic Acid (II).—*trans*-1-Ethynyl-4-t-butylcyclohexanol (I) was similarly oxidised to yield the corresponding hydroxy-acid, plates, m. p. 142.5—143° (from water—acetic acid) (Found: C, 62.8; H, 9.85. $C_{11}H_{20}O_3, \frac{1}{2}H_2O$ requires C, 63.1; H, 10.1%). When mixed with the hydroxy-acid produced by hydrolysis of 4-t-butylcyclohexanone cyanohydrin, the m. p. was not depressed.

Deamination of cis- and trans-1-Amino-4-t-butylcyclohexanecarboxylic Acid.—The *trans*-acid (0.45 g.) was suspended in hydrochloric acid (10%; 30 ml.), and sodium nitrite solution (0.2 g. in 5 ml. water) was slowly added. The solution was finally warmed to 50° for 5 min., and cooled, and the solid 4-t-butylcyclohex-1-enecarboxylic acid (VII) filtered off. It formed plates, m. p. 182—184° (from water—acetic acid) (Found: C, 71.2; H, 10.0. $C_{11}H_{18}O_2, \frac{1}{4}H_2O$ requires C, 70.9; H, 9.7%). An identical product was formed from the *cis*-amino-acid.

The determination of the cyanohydrin dissociation constants was carried out by the method of Wheeler and Zabicky.⁵ The 4-alkylcyclohexanones were purified by way of their semicarbazones, which were recrystallised to constant m. p. The ketones were liberated by steam-distillation with phthalic anhydride, and redistilled. The water content of the solvents was checked by the Karl Fischer method.