6.9, 7.3, 7.8, 8.2, 8.9, 9.7, and 10.8; *m/e* 184 (parent peak). The isomers were best separated by glpc (8 ft Carbowax 20 *M* 10% on Chromosorb).

**2,2-Dimethyl-1,3-dioxacyclohept-5-ene.** A mixture of 8.8 g (0.1 mol) of 2-butene-1,4-diol, 20.0 g of anhydrous copper sulfate, 50 mg of *p*-toluenesulfonic acid, and 50 ml of anhydrous acetone was placed in a pressure bottle which was sealed and heated to 50° for a period of 2 weeks. Fractional distillation gave a 50% yield of the desired product: bp 18–20° (1 Torr); ir (neat) 3.3, 3.5, 6.9, 9.9, 11.6, 13.1; *m/e* 128 (parent peak).

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## References and Notes

(1) A. J. Jones, E. L. Eliel, D. M. Grant, M. C. Knoeber, and W. F. Bailey, *J. Amer. Chem. Soc.*, **93**, 4772 (1971).
(2) W. E. Willy, G. Binsch, and E. L. Eliel, *J. Amer. Chem. Soc.*, **92**, 5394 (1970).
(3) M. H. Gianni, J. Saavedra, and J. Savoy, *J. Org. Chem.*, **38**, 3971 (1973).
(4) M. H. Gianni, J. Saavedra, J. Savoy, and H. G. Kuivila, *J. Org. Chem.*, **39**, 804 (1974).
(5) M. Christl, H. J. Reich, and J. D. Roberts, *J. Amer. Chem. Soc.*, **93**, 3462 (1971).
(6) M. Christl and J. D. Roberts, *J. Org. Chem.*, **37**, 3443 (1972).
(7) E. F. Mooney, Ed., "Annual Reports on NMR Spectroscopy," Vol. 4, Academic Press, New York, N. Y., p 129; (b) B. Pesce, Ed., "Nuclear Magnetic Resonance in Chemistry," Academic Press, New York, N. Y., 1965, p 128; (c) S. Kabuss, H. Friebolin, and H. Schmid, *Tetrahedron Lett.*, 469, (1965). (d) The C2 carbon-13 hydrogen coupling constants for a series of 1,3-dioxacycloalkanes are recorded here because they provided the original indication that twist-boat conformations might be more common in these compounds than was previously believed. It was expected that the double bond in 1,3-dioxacyclohept-5-ene would spread the dioxamethylene (OCO) bond angle with respect to 1,3-dioxacycloheptane. In so far as these coupling constants relate to the dioxamethylene bond angle the data suggest that the angle is not larger but smaller. This observation is not inconsistent with a twist-boat conformation for 1,3-dioxacyclohept-5-ene. The coupling constants have an accuracy of 0.5 Hz at best and the change in values is small and therefore not conclusive. The values for diethoxymethane, which is assumed to be strain free, and 1,3-dioxacyclooctane, which was expected to be strain free, give testimony to the idea that the coupling constants are sensitive to bond angle. The $^{13}C$–H coupling constants are as follows: 1,3-dioxacyclopentane, 164; 1,3-dioxacyclohexane, 163; 1,3-dioxacycloheptane, 164; 1,3-dioxacyclooctane, 161; 1,3-dioxacyclohept-5-ene, 164.5; and diethoxymethane, 161 Hz.
(8) R. Knoor, C. Ganter, and J. D. Roberts, *Angew. Chem.*, **79**, 577 (1967); *Angew. Chem., Int. Ed. Engl.*, **6**, 556 (1967).
(9) (a) M. H. Gianni and R. Mohan, unpublished data; (b) K. L. Servis, E. A. Noe, N. R. Easton, and F. A. Anet, *J. Amer. Chem. Soc.*, **96**, 4185 (1974).
(10) M. H. Gianni, J. Saaverdra, R. Myhalyk, and K. Wursthorn, *J. Phys. Chem.*, **74**, 210 (1970).
(11) D. K. Dalling and D. M. Grant, *J. Amer. Chem. Soc.*, **94**, 5318 (1972).
(12) (a) G. M. Kellie and F. G. Riddell, *J. Chem. Soc. B*, 1030 (1971). (b) These values do not exclude a twist–diequatorial chair equilibrium.
(13) N. L. Allinger and J. T. Sprague, *J. Amer. Chem. Soc.*, **94**, 5734 (1972).
(14) E. L. Eliel and M. C. Knoeber, *J. Amer. Chem. Soc.*, **88**, 5347 (1966); (b) F. G. Riddell, *Quart. Rev., Chem. Soc.*, 3646 (1967).
(15) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 209.
(16) The difference between the chemical shift for an axial and equatorial methyl carbon is greater than 1 ppm for 1,3-dioxacyclohexanes and 3 ppm for cyclohexanes: ref 1 and 11.
(17) K. C. Brannock and G. R. Lappin, *J. Org. Chem.*, **21**, 1366 (1956).
(18) We use the Beilstein system of nomenclature (see also IUPAC Bulletin 35, June 1969) for cis–trans isomers with rings with more than two substituents whose stereochemistry must be indicated. The lowest number substituent of specified stereochemistry (equatorial 2-*tert*-butyl) is used as a reference point and given the prefix *r*. See also *J. Org. Chem.*, **35**, 2849 (1970).

# Synthesis and Enol Determinations of 2,2-Disubstituted 6-Cyanocyclohexanones

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A series of 14 new 2-R-2-R′-6-cyanocyclohexanones was synthesized. The enol–keto contents of 19 compounds of this type were determined by quantitative ir study of conjugated CN (enol) and unconjugated (keto) absorbances. Application of the concept that steric inhibition of enolization was important in this system seemed appropriate. The per cent enol found for the R, R′ compounds were 37 (H, H), 24 (Ph, Ph), 20 (Me, Me), 18 (Et, Et), 19 (Me, Ph), 13 ($CH_2CH_2Ph$, Ph), 10 (Et, Ph), 10 (Pr, Ph), 10 (Am, Ph), 6 (*i*-Bu, Ph), 6 (c-Hex, Ph), 5 (*i*-Pr, Ph), 4 ($CH_2Ph$, Ph), and 5 (*n*-Bu, Ph). The series can be classified in four categories by percentage: A, only parent compound, ~37; B, four compounds, ~20; C, four compounds, ~10; and D, five compounds, ~5. The equivalency or extent of dissimilarity (branching) of substituents, number of conformations, and the 2-alkyl ketone effect rationalize the data with one exception and support the view that steric interference decreases enolization in these β-keto nitriles.

Large differences in the relative rates of hydrolysis of a series of α,α-disubstituted α′-cyanocycloalkanone imines (**1**) to their corresponding cyano ketones (**2**) have been observed.[2-4] The results were qualitative and the availability of a number of these β-keto nitriles or extension of the series by their ready synthesis suggested that quantitative date on the enolization of the latter might be useful.

The imines were more difficult to hydrolyze as their steric requirements increased. The isoelectronic imine (>C=N) and carbonyl bonds (>C=O) are not only chemically similar[5] but are also subject to similar steric limitations on the degree of enolization.[6,7] Whereas steric hindrance afforded a satisfactory explanation for the conversion of >C=N to >C=O in our previous work, this is an irreversible reaction. The enolization process, however, is an equilibrium condition. The concept that there can be steric inhibition of enolization has been employed to account for decreased enol contents in a series of compounds with increasing steric requirements[8a] but exceptions are also known.[8b] Steric requirements can have a profound effect.[8c] Studying our compounds seemed to offer an opportunity to contribute to the developing knowledge of enol–keto equilibria.[8d] Therefore, the percentage enol in a series of 2,2-disubstituted 6-cyanocyclohexanones ($2_K$) was obtained.

The compounds listed in Table I were either on hand from earlier work or were synthesized from the appropriate disubstituted acetonitriles by alkylation with 5-chloropentanenitrile and cyclization in one reaction to the cyanocyclohexanone imines[3] (eq 1) which were subsequently hydrolyzed to keto nitriles. The effectiveness of the two-step,

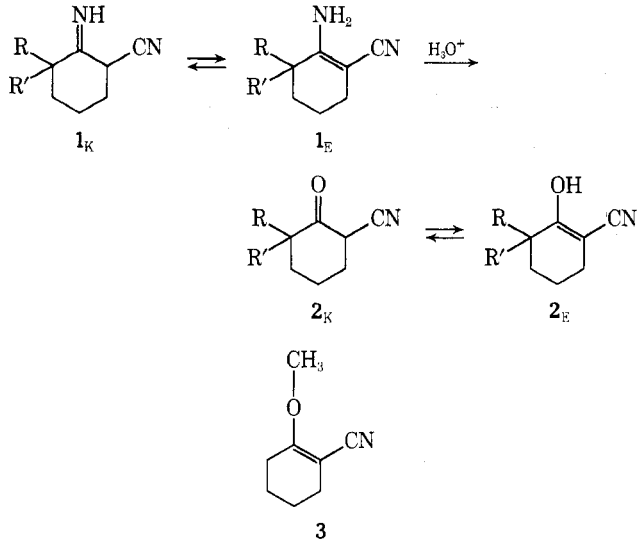
**Table I**
**Enol Contents of 2,2-Disubstituted 6-Cyanocyclohexanones (2)**

| Compd | R | R' | % enol (2210 cm$^{-1}$ CN conj) | % keto (2250 cm$^{-1}$ CN unconj) | Total % (E + K) | % enol nmr |
|---|---|---|---|---|---|---|
| **2a** | H | H | 37 | 60 | 97 | 30 |
| **2b** | Me | Me | 20 | 74 | 94 | 19 |
| **2c** | Ph | Ph | 24 | 77 | 101 | |
| **2d** | $CH_3$ | Ph | 19 | 79 | 98 | |
| **2e** | Et | Et | 18 | 79 | 97 | 23 |
| **2f** | $CH_2CH_2Ph$ | Ph | 13 | 90 | 103 | 15 |
| **2g** | Et | Ph | 10 | 86 | 96 | 10 |
| **2h** | $n$-$C_3H_7$ | Ph | 10 | 96 | 106 | |
| **2i** | $n$-$C_5H_{11}$ | Ph | 10 | 94 | 104 | |
| **2j** | $c$-$C_6H_{11}$ | Ph | 6 | 106 | 112 | 6 |
| **2k** | $i$-$C_4H_9$ | Ph | 6 | 98 | 104 | |
| **2l** | $i$-$C_3H_7$ | Ph | 5 | 95 | 100 | 4 |
| **2m** | $n$-$C_4H_9$ | Ph | 5 | 102 | 107 | |
| **2n** | $CH_2Ph$ | Ph | 4 | 103 | 107 | |

$$RR'CHCN + Cl(CH_2)_4CN \longrightarrow RR'C(CN)[CH_2]_4CN \longrightarrow 1 \quad (1)$$

one-batch, alkylation–cyclization was readily monitored by running the infrared spectrum. The presence of any uncyclized substituted adiponitrile was indicated by unconjugated nitrile absorption at ~2250 cm$^{-1}$ whereas the cyclic cyanoimine (mainly existing as its tautomeric $\beta$-amino vinyl cyanide, $H_2N$—C=C—CN)[2,9] showed a strong, sharp peak at ~2210 cm$^{-1}$ for conjugated nitrile.

The classical Kurt Meyer titration method and modification[10] for determining enol contents of these alicyclic compounds were found to be nonreproducible. Others have reported similar unreliability.[11] Ultraviolet spectroscopic determinations of enol content[12] did not correlate with ir and nmr values due to solvent and concentration differences and this technique is not the method of choice.




$1_K$ $1_E$ $2_K$ $2_E$




3

Quantitative infrared spectroscopy was examined next. Preliminary attempts to use either the C=C or C—OH region were inconclusive.

The nitrile region of the infrared spectrum of these compounds in dioxane solution offers an excellent method for determining their enol contents. There are two sharp peaks for the keto and enol structures appearing at ~2250 cm$^{-1}$ for the nonconjugated keto nitrile ($2_K$) and ~2210 cm$^{-1}$ for the conjugated enol nitrile ($2_E$). These peaks occur in a region of the spectrum where there is virtually no interference from other absorptions. Thus, there are two independent means of checking the equilibrium values. The per cent keto is obtained by comparing the nitrile absorbance at ~2250 cm$^{-1}$ to a calibrated related standard, *e.g.*, $2a_E$ to 4-cyanocyclohexene (**5**). The complementary per cent enol isomer is obtained by comparing the nitrile absorbance at ~2210 cm$^{-1}$ to a different calibrated related standard, *e.g.*, $2a_K$ to 1-cyano-2-methoxycyclohexene (**3**). The total of enol and keto isomers should account for 100% composition of the equilibrium system. The E + K column in Table I shows that the results generally strike total material balance. It was found that at least two sets of standards were necessary. For hydrogen or alkyl substituents, the reference compounds were 1-cyano-2-methoxycyclohexene (**3**) and 4-cyanocyclohexene (**5**). For compounds containing at least one aryl substituent, the reference compounds were 1-cyano-2-methoxy-3,3-diphenylcyclohexene (**4**) and 2-cyano-2-methyl-6,6-diphenylcyclohexanone (**6**). Obviously an enol and a keto standard for *each* compound would be preferable. The per cent enol, keto, and total for the 14 compounds studied are listed in Table I.

An alternative keto–enol analysis procedure was employed: high resolution nuclear magnetic resonance spectrometry.[13] The compound selected for initial intensive study was 6-cyano-2,2-diethylcyclohexanone (**2c**). The carbon-bound enolizable proton ($\delta$ 3.71 ppm) appeared as a distinct and deshielded multiplet well separated from the complex envelope of cyclohexyl ring and ethyl group methylene hydrogens ($\delta$ 1.2 to 2.7 ppm). The oxygen-bound enolizable proton (in the enol tautomer) could not be located in the spectrum even at very low field. There is ample precedent for similar enol OH's to be difficult to locate or apparently absent.[14] The only other clearly distinguishable resonances were the two overlapping methyl triplets at $\delta$ 0.78 ppm.

The keto–enol sample, prepared in $CDCl_3$, was allowed to obtain equilibrium distribution of isomers at probe temperature (34°) but there was essentially no further change in the spectrum after 5 min. Integration of the 3.71 ppm multiplet with reference to the two overlapping methyl resonances taken as six proton units was used to calculate the keto percentage as 77 ± 5%.

In order to firmly establish that the 3.71 downfield multiplet (which resembled two overlapping triplets of $J$ = 4 Hz under high resolution scale expansion) was indeed due to the carbon-bound enolizable proton, two experiments were devised. A spectrum of a methyl enol ether (**3**) showed no such downfield proton. Furthermore, the $CDCl_3$ solution of the original 6-cyano-2,2-diethylcyclohexanone was treated with $D_2O$ and with periodic shaking underwent slow diminution of the 3.71 ppm resonance until at the end of 16 days it had almost vanished.

The nmr method was then applied to six other compounds and gave the results found in Table I. The enolizable H was centered between 3.45 (*i*-Pr, Ph) and 3.9 (Me, Me) ppm in all cases. An attempt to use dioxane-$d_8$ as solvent failed due to impurity resonance at 3.56 ppm. The nonequivalence of methyls was clearly evidenced by two singlets at 2.23 and 2.31 for **2b** and two doublets at 0.49 and 0.88 for **2l**. The tabulated nmr data presented involve judicious choices in interpretation and calculation. Furthermore, at best these nmr data are ±5% reliable for quantitative work.

Alkylation experiments which were carried out to pre-

pare potential standards gave unanticipated results. Ethyl iodide was reacted with the sodium salt of 2,2-diphenyl-6-cyanocyclohexanone (2c) in an attempt to obtain the corresponding carbon ethylated product. However, the *O*-ethyl compound, 1-cyano-2-ethoxy-3,3-diphenylcyclohexene (6), was isolated. Others have shown that this type of alkylation is highly dependent upon reagents and conditions.[15] The reaction of the diphenyl keto nitrile (2c) under similar conditions with methyl iodide gave the *C*-alkylated product, 2-cyano-2-methyl-6,6-diphenylcyclohexanone (7). Repetition of the methylation on the phenyl isopropyl compound (2l) also gave *C*-alkylation. The nmr spectrum of 2-cyano-6-isopropyl-2-methyl-6-phenylcyclohexanone (8) showed two doublets of equal intensity and spacing at 0.45 ppm (3 H) and 0.94 ppm (3 H) due to the restricted rotation of the isopropyl group and its nonequivalent methyls.

The compounds appear to fall into four main categories: (A) 2a (H, H) is clearly the most highly enolized at ~37%; (B) four compounds (**2b, 2c, 2d, 2e**) [($Me_2$), ($Ph_2$), (Ph, $CH_3$), ($Et_2$)] are ~20% enolized; (C) four compounds (**2f, 2g, 2h, 2i**) [(Ph, $(CH_2)_2$Ph), (Ph, Et), (Ph, *n*-$C_3H_7$), (Ph, *n*-$C_5H_{11}$)] are ~10% enolized and (D) five compounds (**2j, 2k, 2l, 2m, 2n**) [(Ph, c-$C_6H_{11}$), (Ph, *i*-$C_4H_9$), (Ph, *i*-$C_3H_7$), (Ph, *n*-$C_4H_9$), (Ph, $CH_2$Ph)] are ~5% enolized.

Among effects which influence keto–enol equilibrium are resonance, hydrogen bonding, solvation, induction, steric requirements, and entropy. The structures of the alicyclic $\beta$-keto nitriles included in this work are quite complex mainly due to conformational possibilities of the cyclohexane system. Compounds of type A and B, except **2d,** have equivalent substituents. The change from hydrogens (**2a**) to other groups involves a change in steric requirement. Thus, these compounds have one enol form of cyclohexene, since pseudo axial and pseudo equatorial are equivalent, and two keto forms, CN equatorial (eclipsed to carbonyl) and CN axial (hydrogen eclipsed to carbonyl). Type C and D compounds, with different substituents adjacent to the carbonyl, present a more complicated situation. There are now two enol forms (ethyl pseudo axial, phenyl pseudo equatorial, and *vice versa* which can interconvert) leading *via* ketonization by hydrogen attachment above or below the plane of the cyclohexene nitrile to four arrangements of the keto nitrile (CN eclipsed to carbonyl with either phenyl or ethyl cis and CN staggered to carbonyl with either phenyl or ethyl cis). Examination of molecular models shows a preference for carbonyl-CN staggered conformations. Furthermore, the distinctions between type C and D compounds on steric grounds are emphasized. Type C compounds are alkyls with $\alpha$ *and* $\beta$ methylene carbons but type D compounds, with the exception of **2m,** are branched either on the $\alpha$ or $\beta$ carbon. The enigma introduced by **2m** eludes definitive comment but models suggest the *n*-butyl has more freedom of rotation than *n*-amyl and encounters considerable 1,3-diaxial interference similar to other type D compounds.

The major factors influencing enol–keto equilibria in this series appear to be population of the number of possible configurations and conformations and the "2-alkyl ketone effect."[16] The latter indicates some stabilization difference in going from methyl to ethyl but a large difference in comparing 2-ethyl to 2-isopropylcyclohexanone.

In summary, for enol values in this series the ir method of comparing conjugated nitrile absorbance with the corresponding easily prepared methyl enol ether standard absorbance curve is recommended for ±1% reliability. Although the population and steric effects discussed offer a reasonable interpretation of the data, it is difficult to disentangle all contingencies.[8c,17]

**Table II**
**Properties of 2,2-Disubstituted 6-Cyanocyclohexanones (2)**

| Compd | Mp,[a] deg | % yield | Formula[b] |
|---|---|---|---|
| **2d** | 64–64.5 | 90 | $C_{14}H_{15}NO$ |
| **2f** | 128–130 | 100 | $C_{21}H_{21}NO$ |
| **2h** | 104–104.5 | 100 | $C_{16}H_{19}NO$ |
| **2i** | 40.5–42 | 90 | $C_{18}H_{23}NO$ |
| **2j** | 149–151 | 85 | $C_{19}H_{23}NO$ |
| **2k** | 71–72 | 80 | $C_{17}H_{21}NO$ |
| **2l** | 94–95 | 94 | $C_{16}H_{19}NO$ |
| **2m** | 52–53 | 70 | $C_{17}H_{21}NO$ |
| **2n** | 122.5–123 | 93 | $C_{20}H_{19}NO$ |

[a] Recrystallized from $Et_2O$ (**2n**), 50% MeOH (**2l**), petroleum ether (**2d, 2i, 2k, 2m**), MeOH (**2f, 2j**), and 80% MeOH (**2h**). [b] Satisfactory analytical data (±0.4% for C, H, and N) were reported for all new compounds listed in the table.

## Experimental[13] Section

**1-Cyano-2-methoxycyclohexene (3).** To 0.086 mol of 2-cyanocyclohexanone in 30 ml of dry ether was added excess diazomethane in ether (HOOD). Evolution of nitrogen occurred slowly and the mixture was allowed to stand at room temperature overnight. The excess diazomethane was destroyed by cautiously adding hydrochloric acid. The ethereal solution was washed with water then aqueous sodium hydroxide. After drying ($MgSO_4$), filtration, and concentration, the residue distilled cleanly at 114–116° (9 mm), 83% yield.

*Anal.* Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.90; H, 8.24; N, 10.15.

**1-Cyano-2-methoxy-3,3-diphenylcyclohexene (4).** This compound was prepared as described above from 2,2-diphenyl-6-cyanocyclohexanone (**2c**). Recrystallization from methanol gave mp 102–103.5°, 87% yield.

*Anal.* Calcd for $C_{29}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 83.03; H, 6.49; N, 4.87.

**4-Cyanocyclohexene (5)** was obtained from K & K Laboratories, Inc., and distilled, bp 70–72° (17 mm).

**2-Amino-1-cyano-3,3-disubstituted Cyclohexenes ($1_E$).** These compounds were available or prepared by the method previously described.[3] The crude reaction mixtures obtained by alkylation of the disubstituted acetonitriles were heated under vacuum only to remove unreacted starting materials and the remaining undistilled dinitriles (which contained some cyclic enamines) were then cyclized. The enamines were obtained in 75–100% yields and had the following melting points: **1d,** 95–97°; **1f,** 114–115°; **1h,** 113–113.5°; **1i,** 64.5–66°; **1j,** 100–102°; **1k,** 77–80°; **1l,** 121–123°; **1m,** 64–67°; **1n,** 143–144°. The infrared spectra of all these compounds showed two NH stretch peaks and one conjugated CN peak as found earlier.

**2,2-Disubstituted 6-Cyanocyclohexanones ($2_K$).** These compounds were available or prepared as previously described.[3] The properties of the new ketones are listed in Table II.

**Calibration Data for Infrared Determinations.** Compound **3** in solutions of 0.131–1.314 mmol/10 ml of dioxane was used to run a calibration curve for conjugated nitrile absorbances (2210 $cm^{-1}$) for aliphatic compounds. Similarly compound **4** in dioxane at 0.344–1.552 mmol/10 ml of dioxane was used for compounds which contained at least one aryl substituent. The unconjugated nitrile absorbances at 2240 $cm^{-1}$ were obtained from **5** in 2.643–4.748 mmol/10 ml of dioxane for aliphatic compounds and similar data were obtained with compound **6** for compounds with aryl substituent(s).

**Enol and Keto Contents in Dioxane.** The enol contents of 14 compounds (**2a–n**) in concentrations of ~3.5 mmol/10 ml of dioxane (0.35 *M*) were determined by comparing the nitrile absorbances to **3** for aliphatic substituents or **4** for aryl substituent(s) in matched 0.189-mm cells with dioxane in the reference cell. Keto contents were obtained similarly but the reference compounds were **5** and **6**. The percentages are listed in Table I. Most of the $\beta$-keto nitriles equilibrated almost instantaneously but **2l, 2m,** and **2n** required 10 days to equilibrate.

**1-Cyano-2-ethoxy-3,3-diphenylcyclohexene (6).** In a dry apparatus 4.8 g (0.0175 mol) of **2c** was dissolved in 210 ml of absolute

ethanol at 65°. An ethanol solution of 0.0175 mol of sodium ethoxide was added and the mixture was cooled to room temperature. To this was added 13.70 g (0.0875 mol) of ethyl iodide and after refluxing 1.5 hr an additional 5.26 g of ethyl iodide was added and reflux was continued another 1.5 hr. By this time the solution was neutral and it was allowed to cool and stand overnight. About two-thirds of the ethanol was removed by distillation, then 80 ml of water and 40 ml of ether were added. The separated ethereal solution was washed repeatedly until a negative test for iodide was observed. Evaporation of the ether left 4.7 g (91%) of crude product. Recrystallization from absolute methanol then 70% ethanol gave 1.1 g (21%) of very pure product, mp 116–117°. The infrared spectrum had nitrile absorption at 2210 $cm^{-1}$ characteristic of conjugated CN as in **4**. The nmr spectrum in $CDCl_3$ had a triplet (3 H) at 0.93 ppm and a quartet (2 H) at 4.14 ppm showing an ethyl bonded to an oxygen.

*Anal.* Calcd for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62. Found: C, 83.19; H, 7.05; N, 4.60.

**2-Cyano-2-methyl-6,6-diphenylcyclohexanone (7).** Repetition of the above reaction with methyl iodide gave 33% pure product after vacuum sublimation and recrystallization from ether, mp 134.5–135°. The infrared spectrum in dioxane showed unconjugated nitrile at 2240 $cm^{-1}$ and a shoulder at 2250 $cm^{-1}$. The nmr spectrum in $CDCl_3$ had a singlet (3 H) at 1.42 ppm, an aromatic (10 H) at 7.23 ppm, and methylenes (6 H) at ~2.85 ppm.

*Anal.* Calcd for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 83.06; H, 6.68; N, 4.64, 4.77.

**2-Cyano-6-isopropyl-2-methyl-6-phenylcyclohexanone (8).** Similarly **2l** and methyl iodide gave an oil which was vacuum distilled and crystallized with difficulty. Recrystallization from 30–60 petroleum ether gave a 40% yield, mp 77.5–78.5°. The nmr spectrum ($CDCl_3$) had a doublet (3 H) at 0.45 ppm, a doublet (3 H) at 0.94 ppm, a singlet (3 H) at 1.12 ppm, a singlet (1 H) at 1.99 ppm, a septet (6 H) at 2.56 ppm, and an aromatic (5 H) at 7.32 ppm.

*Anal.* Calcd for $C_{17}H_{21}NO$: C, 79.92; H, 8.29; N, 5.49. Found: C, 80.14; H, 8.12; N, 5.65.

**Acknowledgment.** We thank Lehigh University, Dr. Ned Heindel, and Mr. Richard Conley for running and assistance in interpreting the nmr spectra.

**Registry No.**—**1d,** 53586-66-6; **1f, 53586-67-7; 1h,** 18072-65-6; **1i,** 18072-67-8; **1j,** 53586-68-8; **1k,** 53586-69-9; **1l,** 53586-70-2; **1m,** 18072-66-7; **1n,** 18072-68-9; **2a** enol form, 53586-71-3; **2a** keto form, 4513-77-3; **2b** enol form, 53586-72-4; **2b** keto form, 10219-83-7; **2c** enol form, 53586-73-5; **2c** keto form, 15719-03-6; **2d** enol form, 53586-74-6; **2d** keto form, 53586-75-7; **2e** enol form, 53586-76-8; **2e** keto form, 15595-78-5; **2f** enol form, 53586-77-9; **2f** keto form, 53586-78-0; **2g** enol form, 53586-79-1; **2g** keto form, 15595-79-6; **2h** enol form, 53586-80-4; **2h** keto form, 53586-81-5; **2i** enol form, 53586-82-6; **2i** keto form, 53586-83-7; **2j** enol form, 53586-84-8; **2j** keto form, 53586-85-9; **2k** enol form, 53586-86-0; **2k** keto form, 53586-87-1; **2l** enol form, 53586-88-2; **2l** keto form, 53586-89-3; **2m** enol form, 53586-90-6; **2m** keto form, 53586-91-7; **2n** enol form, 53586-92-8; **2n** keto form, 53586-93-9; **3,** 53586-94-0; **4,** 53586-95-1; **6,** 53586-96-2; **7,** 53586-97-3; **8,** 53586-93-4.

## References and Notes

(1) Taken in part from the Honors Papers of R.W.S. (1965), D.E.F. (1968), and J.B. (1970).
(2) S. S. Kulp, V. B. Fish, and N. R. Easton, *Can. J. Chem.*, **43,** 2512 (1965).
(3) S. S. Kulp, *Can. J. Chem.*, **45,** 1981 (1967).
(4) S. S. Kulp, J. Molnar, P. J. Miller, and S. T. Herman, *J. Org. Chem.*, **36,** 2203 (1971).
(5) M. M. Spring, *Chem. Rev.*, **26,** 297 (1940).
(6) G. K. Schweitzer and E. W. Benson, *J. Chem. Eng. Data,* **13,** 452 (1968).
(7) R. C. Fuson, J. Corse, and C. H. McKeever, *J. Amer. Chem. Soc.*, **62,** 3250 (1940).
(8) (a) M. S. Newman, "Steric Effects in Organic Chemistry," Wiley, New York, N.Y., 1956, p 237; (b) G. S. Hammond, W. G. Borduin, and G. A. Guter, *J. Amer. Chem. Soc.*, **81,** 4682 (1959); (c) L. N. Ferguson, "The Modern Structural Theory of Organic Chemistry," Prentice-Hall, Englewood Cliffs, N.J., 1963, p 376; (d) M. T. Rogers and J. L. Burdett, *Can. J. Chem.*, **43,** 1516 (1965).
(9) E. C. Taylor and A. McKillop, "The Chemistry of Cyclic Enaminonitriles and *o*-Aminonitriles," Wiley, New York, N.Y., 1970, p 4.
(10) (a) A. Gero, *J. Org. Chem.*, **26,** 3156 (1961); *ibid.*, **19,** 1960 (1954); (b) O. Riobe and L. Gouin, *C. R. Acad. Sci.*, **234,** 1889 (1952).
(11) N. L. Allinger, L. W. Chow, and R. A. Ford, *J. Org. Chem.*, **32,** 1994 (1967).
(12) P. B. Russell and J. Mentha, *J. Amer. Chem. Soc.*, **77,** 4245 (1955).
(13) Ir spectra were run on a Perkin-Elmer Model 237-B. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were by Dr. George I. Robertson, Jr., Florham Park, N.J. Nmr spectra were obtained on a Perkin-Elmer Hitachi R20A calibrated against tetramethylsilane.
(14) N. D. Heindel, V. B. Fish, M. F. Ryan, and A. R. Leplay, *J. Org. Chem.*, **32,** 2678 (1967).
(15) M. E. Kuehne and J. A. Nelson, *J. Org. Chem.*, **35,** 161 (1970).
(16) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N.Y., 1962, p 240.
(17) S. Forsén and M. Nilsson, "The Chemistry of the Carbonyl Group," Vol. 2, J. Zabicky, Ed., Interscience, New York, N.Y., 1970, p 198 and 203.

# Aminocyclitols. 31. Synthesis of Dideoxystreptamines[1]

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All four predicted positional isomers of dideoxystreptamine have been synthesized. From the two mesylates (**10a** and **10b**), 2,4-(**4a**) and 4,6-dideoxystreptamine (**7a**), together with the acetyl derivatives of two other diaminocyclohexanediols (**11** and **12**), were obtained. 2,5-Dideoxystreptamine (**5a**) was synthesized regioselectively in good yield *via* an intermediate 1,3-hydrazino compound (**15a**) obtained by hydrazinolysis of 1,4-*cis*-diepoxycyclohexane (**14**). 4,5-Dideoxystreptamine (**6a**) was prepared from the dimesylates **17** and **19**.

In 1969, Rinehart and his coworkers[2] described the first successful bioconversion of streptamine (**1**)[3] and 2-epistreptamine (**2**)[4] to semisynthetic neomycin A and B using mutants of *Streptomyces fradiae* in a fermentation media containing **1** and **2**. Very recently, two papers[5,6] on the bioconversion of aminocyclitols to antibiotics have been published. Rinehart and collaborators[5] have tested 29 analogs of 2-deoxystreptamine (**3**) as to whether they are incorporated into antibiotics and it has been found that only two compounds (**1** and **2**) undergo bioconversion to active antibiotics. Structural features of the aminocyclitols which allow the bioconversion were limited to a minor modification of 2-deoxystreptamine; their results suggested guidelines for subsequent synthesis of 2-deoxystreptamine analogs. Along this line, we have attempted to synthesize dideoxystreptamines. In the neomycins,[7] paromomycins,[8] and ribostamycin[9] an aminohexose and D-ribose are linked to the hydroxyl groups at C-4 and C-5 of 2-deoxystreptam-