Synthesis and Hydrolysis of Hindered 2,2-Disubstituted 5-Cyanocyclopentanoneimines[1a]

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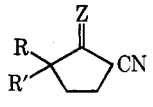
Previous attempts to hydrolyze 2,2-diphenyl-5-cyanocyclopentanoneimine (Ia, 2-amino-1-cyano-3,3-diphenylcyclopentene) to 2,2-diphenyl-5-cyanocyclopentanone (Ib) were unsuccessful.[2,3] The products isolated were the corresponding iminoamide, ketoamide, or decarboxylated ketone. Thus, the normally observed preferential hydrolysis of ketimine before nitrile was reversed in this case. The steric hindrance of the gem phenyl groups adjacent to the carbimino function was suggested to explain this anomaly since the desired selectivity was found in the dimethyl, diethyl, and ethylphenyl compounds.[3] Others have ascribed the decrease in reactivity of substituted ketimines toward hydrolysis to be related to increasing bulk of the groups attached to the carbon of the >C=NH.[4] We recently hydrolyzed the next higher homolog of Ia to 2,2-diphenyl-6-cyanocyclohexanone by using dioxane as the major solvent.[5] Since the 2,2-diphenyl groups did not prevent hydrolysis in the six-membered ring, the five-membered-ring case and related compounds were examined.

The synthesis and acid hydrolysis of these compounds were studied to determine the applicability of Newman's "six number." This concept has been



a, Z = NH
b, Z = O

Compd no.	R	R′
I	Ph	Ph
II	*i*-C_3H_7	Ph
III	*i*-C_3H_7	*i*-C_3H_7
IV	*c*-C_6H_{11}	Ph

effective in rationalizing data for addition–elimination reactions such as the ketimine hydrolyses considered here. The six numbers for Ia, IIa, IIIa, and IVa are 4, 8, 12, and 6, respectively.[6] The equality of phenyl and isopropyl groups for shielding effects is well known[7] as well as their opposite electronic effects. However, phenyl does not exert a constant steric effect[8] and there may occasionally be compensation by some polar effect. If the steric effect is controlling, the conversion of all but IIIa to the corresponding keto nitriles would be anticipated in reasonable yields.

Compounds Ia, IIa, IIIa, and IVa were synthesized by our previously developed route.[3] Acid hydrolysis of these iminonitriles (existing mainly as 1-amino-2-cyanocyclopentene tautomers[3,5,9]) proceeded in the order of difficulty predicted. Whereas type a compounds with R and R′ = hydrogens, dimethyls, diethyls, and ethylphenyl were hydrolyzed readily to their keto nitriles,[3] similar conditions were ineffective with the compounds reported here. However, changing the major solvent to dioxane and refluxing for several hours was quite satisfactory for the diphenyl Ia and cyclohexylphenyl IVa compounds which have six numbers of 4 and 6, respectively. A prolonged reaction time, 5 or 6 days, in refluxing dioxane gave some diisopropyl keto nitrile IIIb and a 62% yield of the isopropylphenyl keto nitrile IIb, six numbers of 12 and 8, respectively. The reexamination of the diphenyl and related compounds initiated by consideration of the "six number" again confirms the generalization that really large steric effects are observed only in compounds containing nine or more atoms in the 6 position.[6]

Experimental Section[10]

Disubstituted Acetonitriles.—The diphenyl compound was available.[3] The diisopropyl compound was obtained by extending the alkylation reaction reflux time to 18 hr for the preparation of ethyl diisopropylcyanoacetate,[11] saponification[12] for 44 hr followed by acidification to pH 2, and decarboxylation[12] in 57% overall yield. The phenylisopropyl compound was prepared by adding dropwise over 2 hr a solution of 146.4 g (1.25 mol) of phenylacetonitrile and 162 g (1.31 mol) of isopropyl bromide in 200 ml of anhydrous ether to 1.25 mol of lithium diethylamide[11] at a rate which allowed control of the exothermicity. The mixture was refluxed for 16 hr and worked up to give 167.5 g (84%) of isopropylphenylacetonitrile, bp 124–134° (15 mm) [lit.[13] 128–130° (15 mm)]. The cyclohexylphenyl compound was obtained by modifications of reported procedures.[13] To a solution of 32.6 g (0.2 mol) of bromocyclohexane in 200 ml of dimethyl sulfoxide was added simultaneously and separately 40 ml of 50% aqueous sodium hydroxide and 23.4 g (0.2 mol) of phenylacetonitrile at a rate that maintained the exothermic reaction between 45 and 50°. After the additions, stirring at 45° was continued for 3 hr. The cooled mixture was then diluted with water and extracted with three 100-ml portions of benzene and then two 100-ml portions of ether The Taranko work-up[13c] gave 25.6 g (64%) of product after vacuum distillation and solidification, mp 54–56.5° from hexane (lit.[14] 56–58°).

5-Chloro-2,2-disubstituted Pentanenitriles.—Adaptation of a published procedure for homologous compounds[3] gave the 2,2-diisopropyl compound, bp 131–140° (9 mm) (64%), the 2-isopropyl-2-phenyl compound, bp 167–173° (6 mm) (43%), and the 2-phenyl-2-cyclohexyl compound, bp 163–168° (0.8 mm) (52%) [lit.[14] 163° (0.7 mm)].

2,2-Disubstituted Hexanedinitriles.—The sodium cyanide–dimethyl sulfoxide method[15] gave the 2,2-diisopropyl compound,

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bp 176–178° (9 mm) (82%), the 2-isopropyl-2-phenyl compound, mp 71–72° from methanol, bp 183–185° (3 mm) (72%), and the 2-cyclohexyl-2-phenyl compound, mp 74–75° (lit.[14] mp 71–72°).

2,2-Disubstituted 5-Cyanocyclopentanoneimines.—The sodium hydride–dioxane procedure[8] gave the following compounds.

IIIa had mp 121–122° from 85% methanol; distilled at 155–165° (5 mm) (~100% yield of crude); ir ($CHCl_3$) 3500, 3400 (NH), 2190 (CN), and 1610 cm^{-1} (C=C).

Anal. Calcd for $C_{12}H_{20}N_2$: C, 74.95; H, 10.48, N, 14.57. Found: C, 74.92; H, 10.49; N, 14.57.

IIa had mp 119–119.5° (75%) from ethanol–water; ir ($CHCl_3$) 3495, 3400 (NH), 2195 (CN), and 1595 cm^{-1} (C=C).

Anal. Calcd for $C_{15}H_{18}N_2$: C, 79.60; H, 8.02; N, 12.38. Found: C, 79.78; H, 8.11; N, 12.35.

IVa had mp 110–112° (lit.[14] 106–107°) (74%) from methanol; ir ($CHCl_3$) 3480, 3380 (NH), 2190 (CN), and 1640 cm^{-1} (C=C).

2,2-Disubstituted 5-Cyanocyclopentanones.—Ib was obtained by the hydrochloric acid–dioxane procedure[5] previously used for the cyclohexanone homolog. The product had mp 105–106.5° from ethyl acetate and was identical (mixture melting point not depressed and infrared spectrum) with a sample[16] available from an alternate synthesis.

A similar hydrolysis mixture of 4.0 g of IIa was refluxed with stirring for 5 days. To the cooled mixture was added 50 ml of water and three extractions with 60-ml portions of ether were carried out. The combined ether extracts were washed six times with equal volumes of water and then five times with fresh 50-ml portions of 10% sodium hydroxide. The mixture was shaken vigorously for about 3–4 min each. The combined basic extracts were cooled in ice, acidified to pH 2 with 6 *N* HCl, and allowed to stand in ice. The filtered, air-dried product weighed 2.5 g (62%) and melted at 68–70°. The analytical sample after four recrystallizations from ethanol had mp 68–69°; ir ($CHCl_3$) 2250 (CN) and 1755 cm^{-1} (CO).

Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.08; H, 7.62; N, 6.06.

Numerous other hydrolysis attempts for shorter time periods in dioxane or in other solvents (toluene, methanol, polyphosphoric acid, glacial acetic acid, sulfuric acid) were ineffective or considerably less efficient as determined by infrared spectra of crude reaction product mixtures by nitrile absorption peaks for conjugated CN (IIa tautomer) and nonconjugated CN (IIb).

Refluxing IVa in hydrochloric acid–dioxane for 5 hr gave 91% crude IVb which after sublimation and recrystallization from hexane melted at 115–116°; ir ($CHCl_3$) 2245 (CN) and 1745 cm^{-1} (CO).

Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.98; H, 7.96; N, 5.24.

The diisopropyl compound IIIb was obtained by the same procedure as IIb but the reaction time was 6 days. Final distillation of the mixture gave 30% 2,2-diisopropylcyclopentanone, bp 54° (1 mm), and 40% IIIb, bp 103° (1 mm), ir (neat) 2250 (CN) and 1750 cm^{-1} (CO).

Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.42; H, 9.77; N, 7.04.

The final product, 2,2-diisopropylcyclopentanone, had an infrared peak (neat) at 1735 cm^{-1} and no absorptions for NH or CN.

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.32; H, 11.71.

Many other hydrolyses of IIIa were attempted by varying solvents, concentrations, and times but were less satisfactory than the above procedure.

2,2-Diisopropylcyclopentanoneimine-5-carboxamide.—Polyphosphoric acid treatment[17] of IIIa gave a 60% yield of iminoamide: mp 154.5–155.5° from benzene; ir 3500, 3400, and 1760 cm^{-1}.

Anal. Calcd for $C_{12}H_{22}N_2O$: C, 68.53; H, 10.55; N, 13.31. Found: C, 68.55; H, 10.70; N, 13.32.

2,2-Diisopropylcyclopentanone-5-carboxamide.—To 32 ml of 80% sulfuric acid at 100° was added 1 g of IIIa with stirring. After 1 hr the mixture was cooled and poured over crushed ice. The tan solid was unstable in air, in light, and at room temperature. Repeated crystallization by partially evaporating an ether solution and storage of the compound under nitrogen at −10° gave a white solid, mp 109° dec. Its ir was comparable with that of 2-ethyl-2-phenyl-6-carbamoylcyclohexanone.[5]

Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.60; H, 10.00; N, 6.64. Found: C, 68.93; H, 9.67; N, 6.73, 6.69.

Registry No.—IIa, 29411-08-3; IIb, 29411-09-4; IIIa, 29411-10-7; IIIb, 29411-11-8; IVa, 5358-98-5; IVb, 29411-13-0; 2,2-diisopropylcyclopentanone, 29411-14-1; 2,2-diisopropylcyclopentanoneimine-5-carboxamide, 29411-15-2; 2,2-diisopropylcyclopentanone-5-carboxamide, 29411-16-3.

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