Dehydration of Primary Amides with Sodium Borohydride

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Because anomalous results were noted regarding the type of product (amine or alcohol) resulting from reaction of primary fluorinated amides with sodium borohydride in refluxing diethylene glycol dimethyl ether (diglyme), an investigation of the behavior of nonfluorinated primary amides with this system became of interest.

Although the latter class of compounds has generally been reported to be nonreducible with sodium borohydride at normal temperatures,[2] the four amides studied were quite reactive in refluxing diglyme, giving nitriles and hydrogen as the major products.

Limited data obtained during 1 hr for the reaction of equimolar quantities of benzamide and sodium borohydride indicated the consumption of about 0.25 mole of the hydride per mole of amide, accompanied by the formation of about 1 mole of hydrogen with an isolated yield of benzonitrile of about 50%. Newman and Fukunaga[3] reported that the dehydration of primary amides with *deficient* amounts of lithium aluminum hydride (excess hydride produces amines) proceeds according to the following equation.

$$RCONH_2 + 0.5LiAlH_4 \longrightarrow RCN + 2H_2 + LiAlO$$

A search was made for amines among the reaction products but these were detected only in the case of acetamide, from which both ammonia and ethylamine were formed. In separate experiments it was ascertained that acetonitrile, benzonitrile, and phenylacetonitrile were not appreciably affected by the hydride under the same reaction conditions, allowing recoveries in the range of 71–98%.

Although the yields of nitriles are not so high as might be hoped for, this reaction may have utility in the synthesis of nitriles containing acid-labile groups which might be attacked by the usual acidic reagents, *i.e.*, phosphorus pentoxide, thionyl chloride, or phosphorus oxychloride, used in amide dehydrations. Since excess hydride may be used, this reaction should be helpful in bringing about nitrile formation simultaneously with reduction of other groups which are attacked by sodium borohydride.

A useful feature of sodium borohydride as the dehydrating agent is its ability to bring about a partial reduction of the aromatic nucleus in nicotinamide[4] as well as dehydration of the carboxamido group. One of the products from this reaction was 3-cyano-1,4,5,6-tetrahydropyridine (I). The structure of I was derived from elemental analysis, infrared spectrum (NH at 3344, C≡N at 2179,[6] and C=C at 1621 cm^{-1}, KBr disk), and its nmr spectrum (Table I).

Table I

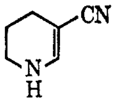
Nmr Spectrum of 3-Cyano-1,4,5,6-tetrahydropyridine (I)

Ring position	τ (multiplicity)[a,b] CCl$_4$	CCl$_4$–D$_2$O	Integral
2	3.12 (d)	3.09 (s)	1
1	4.48 (b)	...	1
6	6.81 (m)	6.78 (t)	2
4	7.77 (t)	7.74 (t)	2
5	8.15 (m)	8.12 (m)	2

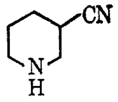
[a] s, singlet; d, doublet; t, triplet; m, multiplet; b, broad. [b] Similar nmr spectra are reported for the substituted 1,4,5,6-tetrahydropyridines of ref 4b.

A second product isolated from the reaction was 3-cyanopiperidine (II), the structure of which was assigned on the basis of elemental analysis, infrared spectrum (NH at 3344 and C≡N at 2252 cm^{-1}, in CCl_4), equivalent weight (titration with aqueous HCl), and nmr spectrum. The nmr spectrum of II in CCl_4 consisted of two complex groups of peaks in the ranges τ 6.9–7.6 and 7.9–8.8. Before deuteration the two groups were of equal area; after deuteration, a previously sharp signal (apparently a singlet) centered at τ 8.27 disappeared and the area ratio was 5:4.

The reaction of nicotinamide and sodium borohydride must involve intermediates other than (or in addition to) nicotinonitrile since the latter compound under similar conditions with sodium borohydride is transformed into a tarry mixture containing I (low yield) and unchanged nicotinonitrile, but no II was detected by gas chromatography.



I



II

Experimental Section[8]

Infrared spectra were run on the Perkin-Elmer Models 21 and 137B spectrophotometers with NaCl optics. Nmr spectra were taken on the Varian A-60 and A-60A spectrometers using TMS as internal standard. Gas chromatographic analyses were carried out on the Aerograph Model A-700 instrument using a silicone high-vacuum grease column. Product composition was determined from uncorrected area ratios.

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[1] One of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

[2] N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, p 592. H. P. Johnson [U. S. Patent 3,026,355 (1962)] reported the reduction of acetamide and benzamide to the amines with sodium borohydride in a *solvent-free* system.

[3] M. S. Newman and T. Fukunaga, *J. Am. Chem. Soc.*, **82**, 693 (1960).

[4] (a) Reaction of sodium borohydride with several substituted 3,5-dicyanopyridines near room temperature gave 1,2-, 1,4-, or 1,6-dihydro-3,5-dicyanopyridines[5] but apparently neither tetrahydro derivatives nor piperidines were observed.[5a] (b) P. M. Quan and L. D. Quin [*J. Org. Chem.*, **31**, 2487 (1966)] reported the formation of 1,4,5,6-tetrahydropyridines upon catalytic hydrogenation of pyridines bearing carbonyl functions in the 3 position.

[5] J. Kuthan and E. Janeckova, *Collection Czech. Chem. Commun.*, **29**, 1654 (1964); **30**, 3711 (1965).

[5a] Note Added in Proof.—Nicotinamide was unchanged by the hydride in refluxing ethanol, but nicotinonitrile was converted into I: S. Yamada and Y. Kikugawa, *Chem. Ind.* (London), 2169 (1966).

[6] Several enaminonitriles have been observed to have C≡N stretching frequencies 17–38 cm^{-1} below the usual lower limit of 2215 cm^{-1} for α,β-unsaturated nitriles.[7]

[7] S. Baldwin, *J. Org. Chem.*, **26**, 3288 (1961).

[8] All boiling points and melting points are uncorrected. Analyses were by Galbraith Laboratories, Inc., Knoxville, Tenn. Mention of a company or a product does not imply endorsement by the Department of Agriculture to the exclusion of others which may be equally suitable.

Benzonitrile.—A mixture of 12.1 g (0.10 mole) of benzamide, 4.18 g (0.11 mole) of sodium borohydride (Metal Hydrides, Inc.), and 80 ml of diglyme (dried on an alumina column) was stirred and refluxed for 1 hr. Evolution of hydrogen caused considerable foaming for about 45 min as the mixture became light yellow. The cooled mixture was poured into 500 ml of ice water, acidified with 100 ml of 20% acetic acid, and saturated with salt prior to extraction with ether. After drying and evaporation of the ether, the residue was analyzed by gas chromatography and contained 6.1 g (59% yield) of benzonitrile, in addition to diglyme and acetic acid. Distillation gave 4.90 g of the nitrile which was identified by its infrared spectrum and by hydrolysis to benzoic acid. From the distillation residue a trace of 2,4,5-triphenylimidazole, mp 275–276°[9] from aqueous ethanol, was isolated and identified by comparison of its infrared spectrum with that published.[10] Under similar conditions benzonitrile was recovered to the extent of 71% after treatment with excess hydride.

In a similar manner slow addition of phenylacetamide to a refluxing slurry of sodium borohydride in diglyme gave a 58% yield (by gas chromatography) of phenylacetonitrile. The latter compound was recovered (75%) unchanged upon treatment with excess sodium borohydride.

Upon reaction of acetamide and sodium borohydride in a 1:1 molar ratio, acetonitrile (98% pure) was obtained in 66% yield by distillation from the crude reaction mixture. Reaction with hydrochloric acid of the gases evolved during the reaction gave a small amount of ammonium chloride and ethylamine hydrochloride which were separated and identified by their infrared spectra. Acetonitrile was nearly quantitatively recovered under the same conditions.

3-Cyano-1,4,5,6-tetrahydropyridine (I) and 3-Cyanopiperidine (II).—To a well-stirred slurry of 3.78 g (0.1 mole) of sodium borohydride in 50 ml of diglyme maintained at 90–100° was added over 10 min 12.21 g (0.1 mole) of solid nicotinamide. Upon heating to 140° a vigorous reaction began and an orange semisolid separated and slowly solidified as the mixture was cooled to about 100° with a water bath. The yellow suspension was then refluxed for 1 hr and cooled, and 200 ml of ether was added, whereupon the solid which separated was filtered.

Upon addition of 200 ml of ether to the filtrate more solid precipitated and was removed. The filtered solid was washed with ether and from the combined filtrates ether was distilled at atmospheric pressure and diglyme at 75 mm. The sticky residue was distilled at 83–100° (3–3.5 mm) to give 1.71 g of a mixture of 3-cyanopiperidine (II) (91% pure by chromatography, 14% yield) and diglyme, in addition to a tarry residue. The distilled product from several runs was combined in aqueous HCl and the diglyme was removed by careful ether extraction. Compound II was then obtained by ether extraction after rendering the solution alkaline. The dried product was distilled at 77° (2.5 mm), $n^{25}\mathrm{D}$ 1.4776.

Anal. Calcd for $C_6H_{10}N_2$: C, 65.40; H, 9.17; N, 25.43; equiv wt, 110.2. Found: C, 65.26; H, 9.35; N, 25.24; equiv wt, 111.

The tarry residue after removal of the above product was chromatographed in benzene solution on alumina (Alcoa F-20) and eluted with ether. The product was recrystallized from a mixture of ether–petroleum ether (bp 30–60°) containing Norit, yielding 1.82 g (17%) of 3-cyano-1,4,5,6-tetrahydropyridine (I), mp 38–39°. Further recrystallization gave an analytical sample, mp 39–40°.

Anal. Calcd for $C_6H_8N_2$: C, 66.62; H, 7.47; N, 25.91. Found: C, 66.41; H, 7.50; N, 25.69.

Registry No.—I, 7492-87-7; II, 7492-88-8; benzonitrile, 100-47-0; 2,4,5-triphenylimidazole, 484-47-9; phenylacetonitrile, 140-29-4.

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[9] B. Radziszewski. *Ber.*, **10**, 70 (1877).

[10] Sadtler Spectrum No. 14151.

Migration of the Benzyl Group in the Base-Catalyzed Rearrangement of 4′-Chloro-α-benzylbenzoin[1]

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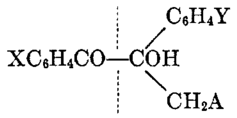
During the course of an investigation of base-catalyzed ether rearrangements,[3] we examined the behavior toward base of 4′-chloro-α-benzylbenzoin (I) and have found evidence for an unusually facile, base-catalyzed ketol rearrangement with migration of a benzyl group. Since work in this area has been temporarily discontinued we publish these results in their present state of completion.

Starting material I was prepared from α-oximinobenzyl 4-chlorophenyl ketone and benzylmagnesium chloride followed by hydrolysis of the oxime group (Scheme I). The isomer, 4-chloro-α-benzylbenzoin (II), was not prepared in a pure state. Addition of benzylmagnesium bromide to 4-chlorobenzil gave a mixture of I and II as shown by its infrared spectrum, nmr spectrum, and carbon–hydrogen analysis. It could not be separated into its constituents by the methods attempted. It was further characterized by mass spectrometry and by cleavage with periodic acid which showed that it consisted of I and II in a ratio of about 1.9.

The utility of mass spectrometry in the analysis of mixtures of α-alkylbenzoins stems from the fact that the major peaks are those with *m/e* corresponding to



$$XC_6H_4CO{-}\underset{CH_2A}{\overset{C_6H_4Y}{C}}OH$$

cleavage of the type shown below, as has been found previously with other α-hydroxy ketones.[4]

The α-benzylbenzoin (I) was treated with methanolic potassium hydroxide at 56°. Analyses of the product mixtures were carried out by cleavage with periodic acid and submission of the resulting ketone mixture to gas phase chromatography. The results were confirmed qualitatively by mass spectrometry of the original mixture. It was found that the initial ketol I after even 0.5 hr had rearranged significantly to the isomer II with benzyl migration and after 2 hr the ratio of I/II was nearly the same with a value of 1.9 as it was after 23 hr when it was 1.7. There was evidence that the product III was also produced but much more slowly. Phenyl migration was the reaction observed in a previous study of the reaction of the closely

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[1] Taken from the Ph.D. Thesis of A. C. Henry, University of Illinois, 1966.

[2] Roger Adams Fellow, 1962–1963. Grateful acknowledgment is made to the U. S. Army Research Office (Durham) for partial support of this work.

[3] For reviews of previous work, see H. E. Zimmerman, "Molecular Rearrangements," Vol. I, P. deMayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 372 ff; D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965, p 230 ff.

[4] See K. Biemann, "Mass Spectrometry," McGraw Hill Book Co., Inc., New York, N. Y., 1962, p 90.