Facile Reduction of Pyridines with Nickel-Aluminum Alloy[1]

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Nickel-aluminum alloy in dilute base can be used to reduce a variety of pyridines, quinolines, and isoquinoline to the corresponding piperidines, 1,2,3,4-tetrahydroquinolines, and 1,2,3,4-tetrahydroisoquinoline in good yield. The reaction is simple to perform, and high temperatures, high pressures, or hydrogen atmospheres are not required. The reaction is accelerated by substituents in the 2-position and by electron-withdrawing groups in the 3- and 4-positions while electron-supplying groups in the 3- and 4-positions retard the reaction. The major product isolated from the reduction of 2-phenylpyridine was 2-cyclohexylpiperidine hydrochloride. With isoniazid (1) and iproniazid (4) the pyridine ring is hydrogenated before the hydrazine is cleaved.

The reduction of pyridines provides a simple and direct method for the synthesis of substituted piperidines but this process has generally been associated with high pressures and temperatures. For example, Adkins et al.[2] have shown that pyridines may be hydrogenated to piperidines over Raney nickel catalyst at high pressures (150–300 atm) and high temperatures (100–200 °C), and similar extreme conditions seem to be the general expectation[3,4] when nickel is used as the catalyst. In view of these observations we were surprised to observe that pyridine, used as an internal standard during recent work on the reductive degradation of *N*-nitroso compounds,[5] was rapidly reduced to piperidine when the reducing system was nickel–aluminum alloy in potassium hydroxide solution. A previous report[6] did mention the treatment of pyridines with nickel–aluminum alloy but made no mention of reduction of the ring (possibly because the previous study used a much higher pyridine:alloy ratio). Schwenk et al. have reported[7] the reduction of bromopyridines, but, as they were interested only in quantitative halogen determination, they made no attempt to determine the nature of the organic products. We found that the reaction worked well, and that pyridine could be reduced to piperidine hydrochloride in 74% yield. On extending the reaction it was found that a wide variety of pyridine-containing compounds could be reduced to the corresponding piperidines in good yield as shown in Table I. During the reaction the aluminum in the alloy reacts with the base to generate hydrogen and leave behind a very active form of nickel. The hydrogenation of the pyridine takes place on this nickel surface.

The reaction is simple to carry out and does not require special apparatus, hydrogen atmospheres, or particularly harsh conditions. For example, 2-picoline was stirred at room temperature in potassium hydroxide solution (0.5 M) and nickel–aluminum alloy added in portions over about an hour. After stirring for 3.75 h the reaction mixture was filtered through Celite and washed through with water and the filtrate distilled. Acidification (with dilute hydrochloric acid) of the distillate, evaporation, and recrystallization gave 2-methylpiperidine hydrochloride as white crystals in 77% yield. In some cases it was possible to extract the product (e.g., 1,2,3,4-tetrahydroquinoline) from the filtrate and so avoid the distillation step.

Monitoring the course of the reaction by gas chromatography is helpful for establishing completion. Thus it was found that quinoline required about 1 h whereas pyridine took about 28 h to give essentially complete reduction. The reduction times are shown in Table I. A variety of reduction times were observed, in accord with previous reports in the literature. Thus Adkins et al.[2] have observed that the reduction of pyridines at high temperatures and pressures is accelerated by substituents in the 2-position. The authors ascribed this to a steric effect in which the tendency of the pyridine nitrogen to poison the catalyst is reduced because of the presence of the substituent. Freifelder[8] has observed a similar effect when a rhodium catalyst was used. It has also been shown[9] that at high temperatures and pressures 2-methylpyridine is hydrogenated over nickel in preference to 3- and 4-methylpyridine although it has been stated[10] that pyridine is reduced more quickly than 2-methylpyridine. In our work we have observed that the reaction is accelerated by substituents in the 2-position; for example 2-methyl- and 2-ethylpyridine are reduced much more quickly than pyridine itself. On the other hand bulky groups, as in 2,2′-bipyridyl, retard the reaction presumably because, although poisoning of the nickel by the ring nitrogen is lessened, the twisted conformation[11] interferes with adsorption on the nickel surface. In fact the pyridine ring of 2-phenylpyridine (which is also reported to have a nonplanar conformation[12]) was reduced so slowly that the phenyl group was also reduced, a reaction which is not normally observed. The isolated product was 2-cyclohexylpiperidine hydrochloride. A particularly noteworthy example of the acceleration due to substituents in the 2-position is quinoline (2,3-substitution) which was reduced so rapidly that it was not necessary to add the usual amount of nickel–aluminum alloy. The planarity of quinoline, compared with 2,2′-bipyridyl, for example, may also have helped adsorption and thus accelerated the reaction. The reduction of isoquinoline (3,4-substitution), however, was much more sluggish. In some cases more

(1) Presented in part at the 187th National Meeting of the American Chemical Society, St. Louis, MO, April 1984; Abstr. ORGN 187.
(2) Adkins, H.; Kuick, L. F.; Farlow, M.; Wojcik, B. *J. Am. Chem. Soc.* **1934**, *56*, 2425.
(3) Freifelder, M.; Stone, G. R. *J. Org. Chem.* **1961**, *26*, 3805.
(4) Rylander, P. "Catalytic Hydrogenation in Organic Syntheses"; Academic Press: New York, 1979; p 214.
(5) Lunn, G.; Sansone, E. B.; Keefer, L. K. *Carcinogenesis (London)* **1983**, *4*, 315.
(6) Finlayson, A. C.; Krishna, R.; Kallury, M. R.; Prager, R. H. *Aust. J. Chem.* **1979**, *32*, 189.
(7) Schwenk, E.; Papa, D.; Ginsberg, H. *Ind. Eng. Chem., Anal. Ed.* **1943**, *15*, 576.
(8) Freifelder, M.; Robinson, R. M.; Stone, G. R. *J. Org. Chem.* **1962**, *27*, 284.
(9) Ushakov, M. I.; Yakovleva, E. V. *J. Gen. Chem. USSR (Engl. Transl.)* **1937**, *7*, 753; *Chem. Abstr.* **1937**, *31*, 5799.[7]
(10) Bagdasarova, I. A.; Safaev, A.; Alovidinov, L. *Deposited Doc.* **1974**, VINITI 753-74; *Chem. Abstr.* **1977**, *87*, 21964d.
(11) Cheng, C. L.; Murthy, D. S. N.; Ritchie, G. L. D. *J. Chem. Soc., Faraday Trans. 2* **1972**, *68*, 1679.
(12) Galasso, V.; DeAlti, G.; Bigotto, A. *Tetrahedron* **1971**, *27*, 991.

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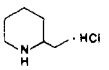
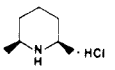
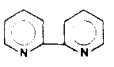
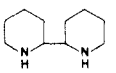
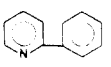
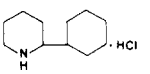
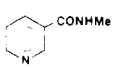
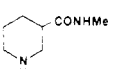
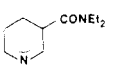
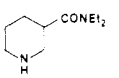
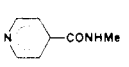
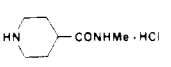
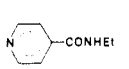
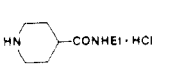
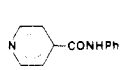
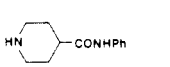
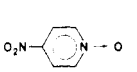
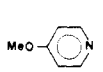
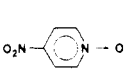
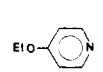
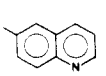
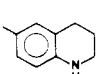
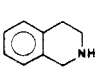
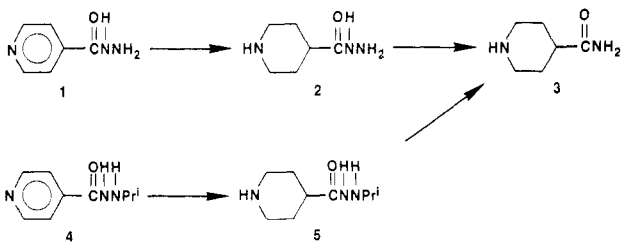
Table I. Reduction of Pyridines, Quinolines, and Isoquinoline

Starting Material	Product	Yield (%)	Ni/Al (g)	Time (h)	mp/bp	Lit.mp/bp	Ref.
		74	45	28.5	246-7	244.5-6	44
		77	30	4.2	211-2	210	45
		79	25	4.3	182-3	181-2	46
		53[a]	45	23.7	289-91	280-2	47
		83[b]	25	66	92-3/2	259	48
		63[b,c]	50	148.3	249-51	251-2.5	49
		58	50	20.9	246-8	244.5-6	44
		56	25	21.2	69-70[d]		
		75[b]	50	140.6	112-4/2	127-8/3	3
		72[b]	25	2.5	199-201	200-3	50
		79[b]	9[e]	3.3	160-2	162-3	51
		57[b]	25	18.1	137-8[f]	121-7	52
		90	11.5	1.2	63-4/2	94-5/9	53
		59	50	18.3	246-7	244.5-6	44
		74[b]	25	19	155-63/200	102/40	54
		51	15[g]	20.2	164-70/200	94/14	55
		84[b]	17	0.9	79-83/2	251	56
		89[b]	16.3	0.8	116-7/3	131-3/9	57
		74[b]	50	42.6	75-7/2	234/763	58

[a] Recrystallized yield of 95% cis. Crude yield = 71% from which this and 41:59 cis/trans mixture (12%) could be isolated. [b] Methanol was cosolvent. [c] Initially isolated as an oil bp 95–6 °C(3 mmHg) (lit.[49] 80–85 °C (0.8–1 mmHg)) which was 83% 2-cyclohexylpiperidine and contained ca. 5% 2-phenylpiperidine and other unknown compounds. The hydrochloride was recrystallized from ethanol and washed with ether. GC showed only one compound. [d] Anal. Calcd for $C_7H_{14}N_2O$: C, 59.13; H, 9.92; N, 19.59. Found: C, 58.83; H, 9.68; N, 19.59. [e] Performed in reduced scale. The compound (1.71 g) in 35 mL of methanol and 35 mL of 1 M potassium hydroxide solution was reduced by 9 g of nickel–aluminum alloy. [f] Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.32; H, 7.73; N, 13.78. [g] Performed on a reduced scale. The compound (2.07 g) in 50 mL of ethanol and 50 mL of 1 M potassium hydroxide solution was reduced by 15 g nickel–aluminum alloy.

Scheme I



alloy had to be added to move the reaction to completion.

The literature does not contain many studies on the influence of substituents on the rate of hydrogenation of aromatics but, in general, substitution by electron-supplying groups appears to retard hydrogenation. Thus it has been found, for the hydrogenation of benzene[13] and pyridine[14] derivatives, that the rate decreases with increasing methyl group substitution. In work on the hydrogenation of substituted benzenes over ruthenium[15] and platinum[16] it was concluded that both steric and electronic factors are important in determining the relative rates. In our work we found that electron-withdrawing groups in the 3- and 4-positions accelerated the reaction while electron-supplying groups retarded it. It seems likely that an electronic effect must be involved to explain why, for example, *N*-methyl-4-pyridinecarboxamide was completely reduced after 2.5 h while only 13% of 4-methylpyridine was reduced after 168 h. Similarly only 27% of 3-methylpyridine was reduced after 1 week while *N*-methyl-3-pyridinecarboxamide was reduced in 21.2 h. *N,N*-Diethyl-3-pyridinecarboxamide, however, did require 140.6 h for complete reduction. (Friefelder et al.[17] have observed similar sluggish behavior over rhodium for this compound. They attribute this behavior to the large bulk of the substituent.) Possibly the electron-deficient nucleus is adsorbed more efficiently on the nickel surface and this allows the reaction to proceed more quickly. In addition, the π-electrons of the carbonyl of the carboxamido group may help adsorption on the surface and thus speed the reaction.

In connection with a project on the disposal of potentially carcinogenic hydrazines we had occasion to treat the tuberculostatic drug isoniazid (**1**) with nickel–aluminum alloy. We observed that it was reduced initially to 4-piperidinecarboxylic acid hydrazide (**2**) although prolonged reaction eventually gave 4-piperidinecarboxamide (**3**). In other words the pyridine ring is reduced before the N–N bond. The products were identified by GC/MS. In the case of the more hindered hydrazide iproniazid (**4**) the piperidine hydrazide (**5**) could be isolated and the structure confirmed by ^{15}N NMR as well as GC/MS (Scheme I). With prolonged reaction times (4 days) complete reduction to the amide (**3**) was obtained.

Attempts to reduce 4-acetyl and 4-cyanopyridine gave mixtures of products because of competitive reductions of the substituents. 1-Methyl-2-pyridone was reduced in 1 h although this compound is not aromatic. When 3-chloropyridine was reduced, it was found that there was an initial very rapid (ca. 1 h) reduction to pyridine (at one stage 81% of the theoretical amount of pyridine was detected) followed by a much slower reduction to piperidine. After 21 h the reaction was stopped and piperidine hydrochloride isolated in 58% yield. In no cases were any traces of partially reduced pyridines detected.

When 4-nitropyridine *N*-oxide was reduced under these conditions, the isolated product was 4-methoxypyridine. The methyl group comes from the methanol which was used as a cosolvent, and when we used ethanol as a cosolvent, we isolated 4-ethoxypyridine. When no cosolvent was used (i.e., an entirely aqueous system), then the only product was 4-aminopyridine (identified by GC/MS). This reaction is known to occur under anhydrous and strongly basic conditions[18–22] (e.g., sodium benzyloxide in benzyl alcohol gave 4-benzyloxypyridine *N*-oxide in 80% yield[17]). Control experiments showed that dissolving 4-nitropyridine *N*-oxide in a 1:1 mixture of methanol/1 M potassium hydroxide solution caused displacement of the nitro group. Addition of nickel–aluminum alloy then removed the *N*-oxide in line with our earlier observation[23] of the reduction of trimethylamine *N*-oxide to trimethylamine. It was also found that 4-methoxypyridine *N*-oxide was reduced to 4-methoxypyridine. We would not expect the electron-rich 4-methoxypyridine to be further reduced.

Nickel–aluminum alloy in base is a powerful reducing system and this should be borne in mind when planning syntheses. Halogens[24] and nitriles[25] (although not amides) are reduced. In addition we have shown[23] that this is a general method for the cleavage of N–N and N–O bonds (e.g., azo and azoxy compounds). Ketones and double[26] and triple[27] bonds are hydrogenated and benzylic compounds are hydrogenolyzed.[26] Ring-opening reactions have been demonstrated with furans,[28] thiophenes,[29] and methylenedioxy compounds.[30] We have observed the partial reduction of polycyclic aromatic hydrocarbons,[31] and the partial reduction of naphthalenes[32] has been reported.

In conclusion we believe that nickel–aluminum alloy in base furnishes another useful technique for reducing pyridine-containing compounds, a technique that is characterized by simplicity and ease of operation.

Experimental Section

Warning. These reductions generate hydrogen and should be done in an efficient hood. The nickel which is removed by filtration is potentially pyrophoric and should not be sucked dry for extended periods. It should be allowed to dry on a metal tray in the absence of flammable solvents for 24 h before disposal.

General. Nickel–aluminum alloy and all other reagents were obtained from Aldrich Chemical Co., Milwaukee, WI. Melting points were determined on an Electrothermal melting point apparatus. NMR spectra were obtained by using a Nicolet NT300 machine operating at 300 MHz for proton, 75.4 MHz for carbon,

(13) Smith, H. A. *Ann N. Y. Acad. Sci.* **1967**, *145*, 72.
(14) Smith, H. A. In "Catalysis"; Emmett, P. H., Ed.; Reinhold: New York, 1957; Vol. 5, p 238.
(15) Kieboom, A. P. G. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 331.
(16) Mochida, I.; Yoneda, Y. *J. Catal.* **1968**, *11*, 183.
(17) Brady, L. E.; Freifelder, M.; Stone, G. R. *J. Org. Chem.* **1961**, *26*, 4757.
(18) Taylor, E. C.; Crovetti, A. J. *J. Am. Chem. Soc.* **1956**, *78*, 214.
(19) Ochiai, E. *J. Org. Chem.* **1953**, *18*, 534.
(20) Profft, E.; Krueger, W.; Kuhn, P.; Lietz, W. *Ger. (East) Pat.* 69126; *Chem. Abstr.* **1970**, *72*, P90309w.
(21) Raucher, S.; Macdonald, J. E. *Synth. Commun.* **1980**, *10*, 325.
(22) Murto, J.; Kaariainen, L. *Suom. Kemistil. B* **1966**, *B39*, 40.
(23) Lunn, G.; Sansone, E. B.; Keefer, L. K. *Synthesis*, in press.
(24) Schwenk, E.; Papa, D.; Whitman, B.; Ginsberg, H. *J. Org. Chem.* **1944**, *9*, 1.
(25) Staskun, B.; van Es, T. *J. Chem. Soc. C* **1966**, 531.
(26) Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; p 718 and references therein.
(27) Schwenk, E.; Papa, D.; Whitman, B.; Ginsberg, H. F. *J. Org. Chem.* **1944**, *9*, 175.
(28) Schwenk, E.; Papa, D.; Hankin, H.; Ginsberg, H. In "Organic Syntheses", Horning, E. C. Ed.; Wiley: New York, 1955; Collect. Vol. III, p 742.
(29) Papa, D.; Schwenk, E.; Ginsberg, H. F. *J. Org. Chem.* **1949**, *14*, 723.
(30) Schwenk, E.; Papa, D. *J. Org. Chem.* **1945**, *10*, 232.
(31) G. Lunn, unpublished observations.
(32) Papa, D.; Schwenk, E.; Breiger, H. *J. Org. Chem.* **1949**, *14*, 366.

or 30.4 MHz for nitrogen. IR spectra were obtained on a Perkin-Elmer 467 spectrometer. Mass spectra were obtained on a Finnigan 3300 mass spectrometer equipped with a Finnigan 6000 MS data system. The gas chromatograph was a Hewlett-Packard HP5830A fitted with a 1.8 m × 2 mm internal diameter silanized glass column using flame ionization detection. Peak areas were integrated by means of a built-in electronic integrator. The column packings were 10% Carbowax 20 M + 2% KOH on 80/100 Chromosorb W AW and 2% Carbowax 20 M + 1% KOH on 80/100 Supelcoport, and column temperatures ranged from 100 to 200 °C. The carrier gas was nitrogen flowing at about 30 mL/min. The samples were injected directly onto a precolumn, which was changed periodically to protect the main column.[5] Analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

Preparation of Substrates. *N*-Methyl-4-pyridinecarboxamide was prepared by using the method of Libermann et al.,[33] mp 112–4 °C (EtOH) (lit.[34] mp 116.5–7 °C). *N*-Phenyl-4-pyridinecarboxamide was prepared according to Miller et al.,[35] mp 169–171 °C (lit.[35] mp 170–172 °C). *N*-Ethyl-4-pyridinecarboxamide was prepared by a modification of the method of Meltzer et al.[34] Thus, isonicotinoyl chloride hydrochloride (4.03 g, 23 mmol) and ethylamine hydrochloride (4.01 g, 49 mmol) in pyridine (20 mL) were boiled under reflux for 2 h. The reaction mixture was cooled, basified with potassium hydroxide solution (10 M), acidified with acetic acid, and evaporated. Potassium hydroxide solution (5 M) was added and the mixture extracted three times with dichloromethane. The extracts were dried over anhydrous sodium sulfate, evaporated, and distilled at 144–7 °C (1.5 mmHg) to give an oil which rapidly solidified to a pale yellow solid, *N*-ethyl-4-pyridinecarboxamide (2.16 g, 64%, mp 69–70 °C, lit.[36] mp 65–7 °C) which exhibited satisfactory spectroscopic characteristics.

Typical Reduction Procedures. (a) 2-Picoline (5.04 g, 54 mmol) was dissolved in water (100 mL), and potassium hydroxide solution (1 M, 100 mL) was added. This mixture was stirred in a 500-mL round-bottom flask fitted with a reflux condenser, and nickel–aluminum alloy (30 g) was added in portions over 1 h. After a further 2 h 47 min gas chromatography showed that the reaction had gone to completion so the contents of the flask were filtered through Celite 545 (Fisher Scientific Co., Fairlawn, NJ). The mixture was washed through with a further portion of water (300 mL) and the entire filtrate distilled under a stream of nitrogen almost to dryness. The nitrogen entered at the still head and exited through a trap filled with dilute hydrochloric acid. The distillate and the contents of the trap were combined and evaporated under reduced pressure to give a mass of white crystals (6.78 g, 92% after azeotropic drying with ethanol). Recrystallization from ethanol/acetone gave 2-methylpiperidine hydrochloride as white crystals (5.22 g, 77%): MS, *m/e* (%) 99 (11), 98 (10), 85 (8), 84 (100), 71 (7), 70 (15), 57 (13), 56 (45), 55 (9), 44 (11), 43 (23), 42 (40), 41 (17), 39 (12), 38 (21), 36 (56).

(b) Quinoline (5.05 g, 39 mmol) was taken up in methanol (100 mL) and potassium hydroxide solution (1 M, 100 mL) added. The mixture was stirred in a 500-mL round-bottom flask fitted with a reflux condenser. Nickel–aluminum alloy (17 g) was added over 37 min whereupon gas chromatography indicated that the reduction was substantially complete (>99.9%). After stirring for a further 16 min the mixture was filtered through a pad of Celite and washed through with dichloromethane (400 mL). The aqueous layer was extracted 3 times with the organic layer and the extracts were dried over Na_2SO_4. Evaporation and distillation gave 1,2,3,4-tetrahydroquinoline as a pale yellow oil (4.39 g, 84%): MS, *m/e* (%) 133 (85), 132 (100), 130 (18), 118 (26), 117 (28), 105 (11), 104 (23), 103 (10), 91 (12), 78 (14), 77 (20). NMR[37] and IR[38] were identical with published examples.

(c) Pyridine (5.07 g, 64 mmol) in potassium hydroxide solution (0.5 M, 200 mL) was reduced by nickel–aluminum alloy (25 g). After 24 h reduction was 81% so a second batch (10 g) was added. After a further 3.5 h reduction was 93% so a third batch (10 g) was added. After another hour reduction was 97% so the reaction mixture was processed as in a above to give piperidine hydrochloride as white crystals (5.80 g, 74%): MS, *m/e* (%) 85 (55), 84 (100), 70 (13), 57 (42), 56 (56), 55 (11). Alternatively it was found that pyridine (1.89 g, 24 mmol) in potassium hydroxide solution (100 mL, 0.5 M) could be reduced by nickel–aluminum alloy (15 g) over 22 h to give 95% reduction. Piperidine hydrochloride (1.87 g) was isolated in 64% yield.

Other compounds were reduced as detailed above. Hydrochlorides were isolated as in (a) and identified by melting point and MS, and liquids were isolated as in (b) and identified by NMR, IR, and MS. All compounds exhibited the correct spectroscopic characteristics.

In general ca. 5 g of substrate was reduced by 25 g of nickel–aluminum alloy in an overnight reaction. In some cases monitoring of the reactions by GC revealed that the reduction was essentially complete before all the nickel–aluminum alloy was added or that shorter reaction times were sufficient. In these cases the reactions were terminated although adding the full amount of alloy and/or allowing the reaction to proceed overnight probably would not have affected the yields. If the reaction mixture is hot, it is advisable to cool it in an ice bath before filtering through Celite.

In other cases it was found that reduction was not complete after adding 25 g of nickel–aluminum alloy and allowing the reaction to proceed overnight. In these cases more alloy was added as detailed in (c) above and the reaction allowed to proceed to completion. Amounts of alloy added and reaction times are shown in Table I.

Reduction of 2,6-Lutidine. 2,6-Lutidine (5.03 g, 47 mmol) in potassium hydroxide solution (0.5 M, 200 mL) was reduced by nickel–aluminum alloy (25 g). After 19.7 h GC showed that reduction was only 93% complete, so more alloy (10 g) was added. After 21.8 h reduction was 97% complete, and another batch of alloy (10 g) was added. After 23.5 h little change was observed so the reaction mixture was filtered, distilled, acidified, and evaporated as described above to give a cis/trans mixture of 2,6-dimethylpiperidine hydrochloride (5.00 g, 71%). Recrystallization from ethanol gave *cis*-2,6-dimethylpiperidine hydrochloride (3.70 g, 53%, mp 289–291 °C, (95% cis by GC)) and a cis/trans mixture (0.84 g, 12%, mp 235–240 °C (41:59 cis/trans by GC)): MS, *m/e* (%) 113 (4), 112 (4), 99 (9), 98 (100), 84 (7), 82 (3), 81 (7), 72 (2), 71 (8), 70 (35), 69 (3), 68 (3), 67 (2). The first isomer to elute by GC was assigned cis and the second was assigned trans (retention times were 1.05 and 1.39 min, respectively, using a 10% Carbowax 20 M + 2% KOH column at 100 °C). The isomers were identified by ^{13}C NMR (of the hydrochlorides in $NaOD/D_2O$); for the first compound shifts were 18.71, 21.99, 29.69, and 53.34 ppm and for the second they were 16.27, 16.41, 28.53, and 47.60 ppm. The lower values were assigned to the more crowded trans molecule (axial, equatorial) rather than the less crowded cis molecule (diequatorial) by analogy with *cis*- and *trans*-1,3-dimethylcyclohexanes.[39,40]

Reduction of Iproniazid (4). Iproniazid phosphate (2.47 g, 8.0 mmol) was reduced by nickel–aluminum alloy (20 g) in potassium hydroxide solution (0.5 M, 200 mL) for 30 min. The reaction was filtered, and the filtrate was distilled almost to dryness. The residue was extracted with dichloromethane. After drying, the piperidine hydrazide (**5**) was obtained as an amorphous white solid (0.80 g, 49%): ^1H NMR ($CDCl_3$) δ 0.96 (d, J = 6.3 $(CH_3)_2$), 1.54, 1.75 (two m, $CHCH_2$), 2.15 (m, $COCH$), 2.55, 3.05 (t(J = 12.3 Hz), m, $NHCH_2$), 3.0 (m, $(CH_3)_2CH$), 7.7 (s, NH). ^{15}N NMR ($CDCl_3$) (relative to NH_3) 339.90 (COHN), 138.98 (*i*-PrNH), 85.57 (piperidine NH). The structure seems best assigned as $C_5H_{10}NC(OH)$=NNHPr-*i* by analogy with PhCH=NNHPh for which the shifts[41] are 326 and 143 ppm, respectively. Shift for

(33) Libermann, D.; Rist, N.; Grumbach, F.; Cals, S.; Moyeux, M.; Rouaix, A. *Bull Soc. Chim. Fr.* **1958**, 694.
(34) Meltzer, R. I.; Lewis, A. D.; King, J. A. *J. Am. Chem. Soc.* **1955**, *77*, 4062.
(35) Miller, P. E.; Oliver, G. L.; Dann, J. R.; Gates, J. W., Jr. *J. Org. Chem.* **1957**, *22*, 664.
(36) Prijs, B.; Gall, R.; Hinderling, R.; Erlenmeyer, H. *Helv. Chim. Acta* **1954**, *37*, 90.
(37) Pouchert, C. J. "The Aldrich Library of NMR Spectra", 2nd ed.; Aldrich Chemical Company: Milwaukee, WI, 1983; Vol. 1, Spectrum 1114D.
(38) Pouchert, C. J. "The Aldrich Library of Infrared Spectra", 2nd ed.; Aldrich Chemical Company: Milwaukee, WI, 1975; Spectrum 695B.
(39) Stothers, J. B. "Carbon-13 NMR Spectroscopy"; Academic Press: New York, 1972; p 64.
(40) Dalling, D. K.; Grant, D. M. *J. Am. Chem. Soc.* **1967**, *89*, 6612.

piperidine is reported[42] to be 37 ppm. Cf. $PhNHNH_2$ for which the shifts are 87 and 62 ppm, respectively.[43] The mass spectrum was obtained by GC/MS, *m/e* (%) 185 (19), 170 (10), 129 (7), 127 (7), 113 (9), 112 (100), 87 (14), 85 (7), 84 (44), 83 (10), 82 (22), 74 (17), 68 (6). After 4 days, only 4-piperidinecarboxamide (3) was detected by gas chromatography. It was identified by using an authentic standard.

Reduction of Isoniazid. Isoniazid (1) was reduced as above, and 4-piperidinecarboxylic acid hydrazide (2) was identified by GC/MS as an intermediate after 6.3 h: MS, *m/e* (%) 143 (10), 127 (25), 125 (5), 113 (15), 112 (95), 111 (5), 110 (5), 109 (5), 98 (10), 94 (10), 87 (30), 85 (35), 84 (100), 83 (20), 82 (75). After 20 h, only the amide (3) was found. It was identified by comparison with an authentic standard.

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Registry No. 1, 54-85-3; 2, 42596-58-7; 3, 39546-32-2; 4, 305-33-9; 5, 99706-49-7; pyridine, 110-86-1; 2-methylpyridine, 109-06-8; 2-ethylpyridine, 100-71-0; 2,6-dimethylpyridine, 108-48-5; 2,2'-bipyridine, 366-18-7; 2-phenylpyridine, 1008-89-5; 3-chloropyridine, 626-60-8; *N*-methyl-3-pyridinecarboxamide, 114-33-0; *N,N*-diethyl-3-pyridinecarboxamide, 59-26-7; *N*-methyl-4-pyridinecarboxamide, 6843-37-4; *N*-ethyl-4-pyridinecarboxamide, 41116-48-7; *N*-phenyl-4-pyridinecarboxamide, 3034-31-9; *N*-methyl-2-pyridinone, 694-85-9; pyridine oxide, 694-59-7; *p*-nitropyridine oxide, 1124-33-0; quinoline, 91-22-5; 6-methylquinoline, 91-62-3; piperidine hydrochloride, 6091-44-7; 2-methylpiperidine hydrochloride, 5119-88-0; 2-ethylpiperidine hydrochloride, 1484-99-7; cis-2,6-dimethylpiperidine hydrochloride, 32166-02-2; 2,2'-bipiperidyl, 531-67-9; 2-cyclohexylpiperidine hydrochloride, 51523-81-0; *N*-methyl-3-piperidinecarboxamide, 5115-98-0; *N,N*-diethyl-3-piperidinecarboxamide, 3367-95-1; *N*-methyl-4-piperidinecarboxamide hydrochloride, 1903-75-9; *N*-ethyl-4-piperidinecarboxamide hydrochloride, 1981-39-1; *N*-phenylpiperidinecarboxamide, 73415-85-7; *N*-methyl-2-piperidinone, 931-20-4; 4-methoxypyridine, 620-08-6; 4-ethoxypyridine, 33399-46-1; 1,2,3,4-tetrahydroquinoline, 635-46-1; 6-methyl-1,2,3,4-tetrahydroquinoline, 91-61-2; nickel, 7440-02-0; aluminum, 7429-90-5; 2-cyclohexylpiperidine, 56528-77-9; isonicotinoyl chloride hydrochloride, 39178-35-3; isoquinoline, 119-65-3; 1,2,3,4-tetrahydroisoquinone, 91-21-4.

(41) Westerman, P. W.; Botto, R. E.; Roberts, J. D. *J. Org. Chem.* **1978**, *43*, 2590.
(42) Duthaler, R. O.; Williamson, K. L.; Giannini, D. D.; Bearden, W. H.; Roberts, J. D. *J. Am. Chem. Soc.* **1977**, *99*, 8406.
(43) Yavari, I.; Roberts, J. D. *J. Am. Chem. Soc.* **1978**, *100*, 4662.
(44) Grave, T. B. *J. Am. Chem. Soc.* **1924**, *46*, 1460.
(45) Lipp, A. *Justus Liebigs Ann. Chem.* **1896**, *289*, 173.
(46) Lipp, A. *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 3513.
(47) Ferles, M. *Chem. Listy* **1958**, *52*, 668; *Chem. Abstr.* **1958**, *52*, 13724e.
(48) Smith, C. R. *J. Am. Chem. Soc.* **1928**, *50*, 1936.
(49) Von E. Doering, W.; Rhoads, S. J. *J. Am. Chem. Soc.* **1953**, *75*, 4738.
(50) Zenitz, B. L.; Albro, L. P. *U.S. Patent* 3 177 211; *Chem. Abstr.* **1965**, *63*, 616b.
(51) Swain, A. P.; Naegele, S. K. *J. Am. Chem. Soc.* **1957**, *79*, 5250.
(52) Campbell, S. F.; Danilewicz, J. C.; Greengrass, C. W.; Plews, R. M. *U.S. Patent* 4 243 666; *Chem. Abstr.* **1980**, *92*, 181222s.
(53) Fischer, E.; Bergmann, M. *Justus Liebigs Ann. Chem.* **1913**, *398*, 96.
(54) Leis, D. G.; Curran, B. C. *J. Am. Chem. Soc.* **1945**, *67*, 79.
(55) Ishii, T. *J. Pharm. Soc. Jpn.* **1951**, *71*, 1092; *Chem. Abstr.* **1952**, *46*, 5046b.
(56) Perkin, W. H. *J. Chem. Soc.* **1896**, *69*, 1025.
(57) Von Braun, J.; Petzold, A.; Seemann, J. *Ber. Dtsch. Chem. Ges.* **1922**, *55*, 3779.
(58) Short, W. F. *J. Chem. Soc.* **1925**, *127*, 269.

Conformational Studies by Dynamic NMR. 31.[1] Enantiotopomerization and Torsional Processes in sp^2-Carbon Diaryl-Substituted Hindered Compounds

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The stereodynamical processes in phenyl 2,4,6-triisopropylphenyl ketone and the analogues C=S, C=NH, and $C=CPh_2$ have been investigated by NMR. In all these compounds the plane of the triisopropylphenyl ring is perpendicular to the plane of the sp^2 carbon, as shown by anisochronous methyl groups for the pair of *o*-isopropyl groups. The enantiotopomerization processes that render these methyls isochronous at high temperature have free energies of activation that increase with the dimension of the X group. A second process, involving the rotation of the unsubstituted phenyl ring, which is coplanar to the C=X moiety, was observed by high-field ^{13}C NMR at low temperature. The free energies of activation of this second process were much lower than those for enantiotopomerization. It has been shown that the conformational arrangement of the two aromatic rings (triisopropylphenyl perpendicular and Ph coplanar to CO) is maintained in the intermediate radical produced in the photoreduction of 2,4,6-triisopropylbenzophenone.

Highly hindered aromatic ketones have relatively high barriers to internal rotation; some of these values have been determined recently by variable-temperature NMR spectroscopy.[2,3] The larger barriers of these hindered ketones compared to the less crowded ones are due to a change in the conformation of the ground state. In compounds like acetophenone[4] or benzaldehyde,[5] the phenyl ring and the carbonyl group are essentially coplanar in the

(1) Part 30. Casarini, D.; Lunazzi, L.; Macciantelli, D. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1839.
(2) Ito, Y.; Umeharo, Y.; Nakamura, K.; Yamado, Y.; Matsura, T.; Iamshiro, F. *J. Org. Chem.* **1981**, *46*, 4359.
(3) Staab, H. A.; Chi, C. S.; Dabrowski, J. *Tetrahedron* **1982**, *38*, 3499.
(4) Drakenberg, T.; Sommer, J. M.; Jost, R. *Org. Magn. Reson.* **1976**, *8*, 579.
(5) Drakenberg, T.; Jost, R.; Sommer, J. M. *J. Chem. Soc., Chem. Commun.* **1974**, 1011. Lunazzi, L.; Macciantelli, D.; Boicelli, A. C. *Tetrahedron Lett.* **1975**, 1205.

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