t-butyl trifluoroacetate was detectable in the high-field region. The exchange experiment employing trifluoroacetic acid-*d* was carried out under the same conditions; half-life ~1 hr.

The reaction was also followed by ultraviolet spectroscopy with 10^{-4} *M* III in trifluoroacetic acid and in mixed solvents of the acid and carbon tetrachloride. The absorption of anthracene at 325 mμ increased steadily as an intermediate, λ_{max} 410 mμ, first increased and then decayed.

9-Hydroxy-10,10-diphenyl-9,10-dihydroanthracene (IV).—*o*-Benzoylbenzoic acid was converted to 10,10-diphenylanthrone.[11] The ketone was reduced to IV (mp 245–246°; lit.[12] mp 240–241°) with sodium borohydride in monoglyme.[13] Equal volumes of 2×10^{-3} *M* IV in carbon tetrachloride and trifluoroacetic acid were mixed. Aliquots were withdrawn over a 24-hr interval and diluted 1:25 with carbon tetrachloride, and the ultraviolet spectra were recorded. No absorptions were detected in the region (350–390 mμ) where 9,10-diphenylanthracene exhibits three intense bands (log ε >4). Control experiments established that 9,10-diphenylanthracene was stable under the reaction conditions and that yields of 2% were detectable.

(11) E. de Barnett, J. W. Cook, and I. G. Nixon, *J. Chem. Soc.*, 504 (1927). Phenyllithium replaced phenylmagnesium bromide.

(12) C. Liebermann and S. Lindenbaum, *Ber.*, **38**, 1804 (1905).

(13) H. C. Brown, E. J. Mead, and B. C. Subba Rao, *J. Am. Chem. Soc.*, **77**, 6209 (1955).

Deoxygenation of Pyridine N-Oxides with Sulfur Dioxide

FRANCIS A. DANIHER[1a] AND BRENNIE E. HACKLEY, JR.[1b]

Ash Stevens Inc., Detroit, Michigan, and U. S. Army Edgewood Arsenal, Edgewood Arsenal, Maryland

Received June 27, 1966

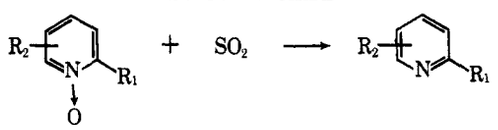
In recent years, synthetic manipulations on the pyridine nucleus have been greatly facilitated through the use of the N-oxide function, as pioneered by Ochiai and co-workers.[2] Consequently, a number of reagents have also been developed for the deoxygenation of pyridine N-oxides.[3]

In a study of the deoxygenation of pyridine N-oxides with various reducing agents, Relyea[3h] and co-workers reported that sulfur dioxide does not reduce pyridine N-oxide. We wish to report herein reaction conditions whereby sulfur dioxide is a useful agent for the deoxygenation of pyridine N-oxides.[4]

The addition of a slow stream of sulfur dioxide to a refluxing solution of the pyridine N-oxides in dioxane or water for a period of 3 hr[5] led to the formation of the corresponding free base in yields ranging from 21 to 78%. The results are summarized in Table I. The products were identified by comparison of their physical constants, chromatographic behavior (tlc), infrared spectra, and derivatives (picrate salts) with those of authentic samples.

TABLE I

DEOXYGENATION OF PYRIDINE N-OXIDES WITH SULFUR DIOXIDE



N-Oxide		Solvent		Free base, mp or bp (mm), °C	Picrate mp, °C
R_1	R_2	Dioxane	Water		
H	H	66		114[i]	166–167[i]
CH_3	H	34		126–127[i]	166–167[i]
H,	4-CH_3	31		141–142[i]	165–166[i]
H,	3-Cl[a]	21		54 (20)[i]	133–134[i]
CH_3	4-OCH_3[b]	62		89 (15)[k]	146–147[k]
CH_3	5-$CO_2C_2H_5$[c]	68	54	67 (0.5)[l]	167–168[l]
CH_3	6-$NHCOCH_3$[d]	65		88–89[d]	
CH_3	4-Cl[e]	41	38	61 (19)[m]	176–177[m]
CH_3	6-CH_3	67	78	142–143[i]	167–168[i]
CH_3	5-CH_3[f]	65		55 (17)[i]	167–169[i]
CH_3	5-C_2H_5[g]	63	74	72 (19)[n]	166–168[n]
CH_3	6-CH_3, 5-NO_2	31		36–38	
CH_3	4-NO_2[h]	NR	NR		
H,	4-$COOCH_3$[i]	NR			

[a] M. P. Cava and B. Weinstein, *J. Org. Chem.*, **23**, 1616 (1958). [b] E. Ochiai and I. Suzuki, *J. Pharm. Soc. Japan*, **67**, 158 (1947). [c] F. A. Daniher and B. E. Hackley, Jr., unpublished results. [d] R. Adams and S. Miyano, *J. Am. Chem. Soc.*, **76**, 2785 (1954). [e] E. Profft and W. Rolle, *Z. Tech. Hochsch. Chem. Leuna-Nersburg*, **2**, 187 (1959); *Chem. Abstr.*, **55**, 1609*i* (1961). [f] Y. Arata and K. Achiwa, *Yakugaku Zasshi*, **79**, 108 (1959); *Chem. Abstr.*, **53**, 10211*g* (1959). [g] J. A. Berson and T. Cohen, *J. Am. Chem. Soc.*, **78**, 416 (1956). [h] E. Ochiai, K. Arima, and M. Ishikawa, *J. Pharm. Soc. Japan*, **63**, 79 (1943). [i] R. L. Bixler and C. Niemann, *J. Am. Chem. Soc.*, **80**, 2716 (1958). [j] R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley and Sons Inc., New York, N. Y., 1964, p 235. [k] M. Endo and T. Nakashima, *Yakugaku Zasshi*, **80**, 875 (1960); *Chem. Abstr.*, **54**, 24705*c* (1960). [l] P. A. Plattner, W. Keller, and A. Boller, *Helv. Chim. Acta*, **37**, 1379 (1954). [m] T. Kato, *J. Pharm. Soc. Japan*, **75**, 1228 (1955); *Chem. Abstr.*, **50**, 8665*i* (1956). [n] C. P. Farley and E. L. Eliel, *J. Am. Chem. Soc.*, **78**, 3477 (1956).

Of the 14 pyridine N-oxides employed in this study, only two, 4-nitro-2-picoline N-oxide and methyl isonicotinate N-oxide, were not deoxygenated even under forcing conditions (6 to 12 hr at reflux). The unreactivity of the nitro compound is not unexpected since 4-nitropyridine N-oxide is not deoxygenated by other reducing agents.[3a,d]

Yields of 60 to 78% were obtained with electron-releasing substituents such as alkyl, acetamido, and methoxyl, with the exception of 2- and 4-picoline N-oxide, the yields being 34 and 31%, respectively.

In general, electron-withdrawing groups such as 3- and 4-chloro and 5-nitro gave somewhat lower yields ranging from 21 to 41%. On the other hand, ethyl 6-methylnicotinate N-oxide gave a 68% yield of product in dioxane so that factors other than electronegativity are operative.

The reaction proceeds with the formation of 1 mole of sulfur trioxide. For example, the reduction of 2,6-lutidine N-oxide in water led to the formation of 0.78 mole of 2,6-lutidine and 0.82 mole of sulfur trioxide, determined as sulfate. In many cases in dioxane sol-

(1) (a) Ash Stevens Inc.; (b) U. S. Army Edgewood Arsenal.

(2) For a summary, see E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953).

(3) (a) M. Hamana, *J. Pharm. Soc. Japan*, **75**, 121, 135, 139 (1955); (b) K. Takeda and K. Tokuyama, *ibid.*, **75**, 620 (1955); (c) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **77**, 3164 (1955); (d) F. Furukawa, *Pharm. Bull. Japan*, **3**, 230 (1955); (e) E. Howard, Jr., and W. F. Olszewski, *J. Am. Chem. Soc.*, **81**, 1483 (1959); (f) E. Hayashi, H. Yamanaka, and K. Shimizu, *Chem. Pharm. Bull.* (Tokyo), **7**, 141 (1959); (g) T. R. Emerson and C. W. Rees, *J. Chem. Soc.*, 1917 (1962); (h) D. I. Relyea, P. O. Tawney, and A. R. Williams, *J. Org. Chem.*, **27**, 477 (1962); (i) E. E. Schweizer and G. J. O'Neill, *ibid.*, **28**, 2460 (1963); (j) W. Hoefling, D. Eilhauer, and G. Reckling, East German Patent 36,422 (1965); *Chem. Abstr.*, **63**, 18047*d* (1965); (k) R. A. Abramovich and K. A. H. Adams; *Can. J. Chem.*, **39**, 2134 (1961).

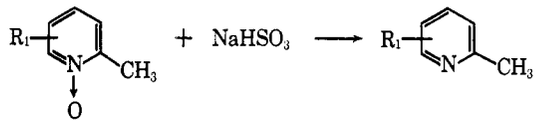
(4) However, nonaromatic tertiary amine N-oxides have been reduced with SO_2: (a) E. C. Taylor and N. E. Boyer, *J. Org. Chem.*, **24**, 275 (1959); (b) W. Wiewiorowski and P. Baranowski, *Bull. Acad. Polon. Sci.*, **10**, 549 (1962).

(5) The yields reported for ethyl 6-methylnicotinate N-oxide and 3-nitro-2,6-lutidine N-oxide were those obtained at 4 and 6 hr, respectively.

vent a solid formed during the course of the reaction. This is believed to be a pyridine–sulfur trioxide complex.

The use of aqueous sodium bisulfite was also investigated in a few selected cases with moderate success. This work is summarized in Table II. Further studies

TABLE II
DEOXYGENATION OF PYRIDINE N-OXIDES WITH AQUEOUS SODIUM BISULFITE



R_1	% yield
4-OCH_3	44
5-$COOC_2H_5$	19
6-$NHCOCH_3$	27
5-C_2H_5	66

with this reagent may be warranted since significant amounts of starting material were recovered in most cases investigated. Thus, the reaction of ethyl 6-methylnicotinate N-oxide with a mole excess of aqueous sodium bisulfite at reflux for 6 hr led to the formation of a 19% yield of the deoxygenated product and the recovery of 25% of the starting N-oxide.

Experimental Section

Melting points and boiling points are uncorrected. The starting pyridine N-oxides were either commercially available or prepared according to literature procedures. In the latter case, the physical constants of the materials were in agreement with those reported in the literature. Gas chromatographic studies were performed with an F and M Model 810 Chromatograph (hydrogen flame detector) using a 4-ft, 3.8% SE 30 on 80–100 mesh Diatoport S column.

3-Nitro-2,6-lutidine N-oxide was prepared from 3-nitro-2,6-lutidine[6] by treatment with 30% hydrogen peroxide in acetic acid, according to the method of Ochiai.[7] Using this procedure the product was obtained in 64% yield, mp 101–102°.

Anal. Calcd for $C_7H_8N_2O_3$: C, 49.99; H, 4.79; N, 16.66. Found: C, 50.12; H, 4.54; N, 16.50.

General Procedure for the Reduction of Pyridine N-Oxides. A. Dioxane Solvent.—A slow stream of sulfur dioxide was introduced into a refluxing solution containing 0.1 mole of the N-oxide in 100 ml of dioxane for 3 hr (see ref 5). The solution was cooled and solvent was removed at aspirator pressure. The residue was made alkaline by the addition of 20% potassium carbonate solution and the product was removed by ether extraction. The ether extract was dried over potassium carbonate, filtered, and evaporated to yield the product. The product was purified by either distillation or recrystallization. The results are reported in Table I.

B. Water Solvent.—A slow stream of sulfur dioxide was introduced into a refluxing solution containing 0.1 mole of N-oxide in 100 ml of water for 3 hr. The solution was cooled and made alkaline by the addition of solid potassium carbonate. The product was removed by ether extraction. The ether extract was treated as in A to yield the product.

C. Aqueous Sodium Bisulfite.—A solution of 0.1 mole of the N-oxide and 0.2 mole of sodium bisulfite in 100 ml of water was refluxed for 6 hr. The solution was allowed to cool and made alkaline by the addition of solid potassium carbonate. The product was isolated by ether extraction and purified by either distillation or recrystallization. Unreacted starting material could be recovered by extraction of the aqueous layer with chloroform. Using this procedure the amounts of recovered starting material in the cases examined were as follows: 4-methoxy-2-picoline N-oxide, 10%; ethyl 6-methylnicotinate N-oxide, 25%; 6-acetamdo-2-picoline N-oxide, 28%; 5-ethyl-2-picoline N-oxide, 0%. Yield data are reported in Table II.

(6) Aldrich Chemical Co., Inc.

(7) E. Ochiai and R. Sai, *J. Pharm. Soc. Japan*, **65B**, 18 (1945).

5H-1,4-Benzodiazepin-5-ones from Substituted *o*-Aminobenzamides

ARTHUR A. SANTILLI AND T. S. OSDENE

Research and Development Division, Wyeth Laboratories, Inc., Radnor, Pennsylvania

Received June 10, 1966

A previous attempt by us to prepare 5H-1,4-benzodiazepin-5-ones by cyclodehydration of substituted *o*-amino-N-(2-hydroxyalkyl)benzamides resulted in the formation of 2-oxazolines.[1] This observation was independently substantiated by Field and co-workers.[2] We now wish to report a successful synthesis of this type of benzodiazepinone starting from *o*-aminobenzamides substituted in such a way as to preclude the possibility of oxazoline formation. The reaction scheme is given in Chart I.

Treatment of *o*-benzylaminobenzamide (Ia) with ethylene oxide in acetic acid at room temperature afforded *o*-[benzyl(2-hydroxyethyl)amino]benzamide (IIa). The product was demonstrated by a melting point comparison to be different from the isomeric *o*-benzylamino-N-(2-hydroxyethyl)benzamide prepared from N-benzylisatoic anhydride and 2-hydroxyethylamine. Replacement of the hydroxy group in IIa with a chloro group was accomplished by mild treatment with thionyl chloride to minimize the possibility of dehydrating the carbamoyl group to a nitrile group.[3] Cyclodehydrochlorination of the resulting product (IIIa) with sodium hydride in benzene proceeded smoothly to afford 1-benzyl-1,2,3,4-tetrahydro-5H-1,4-benzodiazepin-5-one (IVa) in good yield.

Apart from the aromatic protons, the nmr spectrum of IVa in deuteriochloroform revealed the presence of the benzylic CH_2 protons (singlet at δ 4.45). A single exchangeable lactam proton was noted as a broad singlet at δ 8.05. The four CH_2 protons of the diazepine ring appeared as a compact multiplet, centered at δ 3.38, that collapsed to a singlet on deuteration of the sample. The development of this singlet was somewhat unexpected, since an apparent magnetic equivalence is thereby indicated for the protons of the two chemically nonequivalent CH_2 groups. On protonation of IVa with trifluoroacetic acid in benzene, however, the chemical shifts for the two CH_2 groups of the diazepine ring became distinctly separated from each other, a triplet appearing δ 3.25 and a multiplet at 2.80. The triplet was assigned to the CH_2 protons adjacent to the quaternized nitrogen, and the multiplet to the CH_2 protons adjacent to the lactam nitrogen. On treatment with sodium deuterium oxide the two methylene patterns merged to a singlet.[4]

The structure of IVa was confirmed unequivocally by the following experiments. Reduction with lithium aluminum hydride ($LiAlH_4$) afforded 1-benzyl-2,3,4,5-

(1) A. A. Santilli and T. S. Osdene, *J. Org. Chem.*, **30**, 2100 (1965).

(2) G. F. Field, W. J. Zally, and L. H. Sternbach, *ibid.*, **30**, 2098 (1965).

(3) An attempt to prepare the tosylate ester of IIa was unsuccessful. The compound proved to be surprisingly unreactive to tosyl chloride in pyridine.

(4) S. Shiotani and K. Mitsuhashi [*J. Pharm. Soc. Japan*, **84**, 656 (1964)] reported a singlet at δ 3.04 (four protons) for the protons of the two chemically nonequivalent CH_2 groups bridging the nitrogen atoms in 2,3,4,5-tetrahydro-1H-1,4-benzodiazepine.