(150 mg) in dry ethanol (15 ml) was refluxed for 3.5 hr. Water (25 ml) was added and the mixture was extracted with chloroform. The solvent was removed and the residue was crystallized from acetone–petroleum ether to give 1-carbethoxy-3-oxo-1,8-dehydropyrrolizidine (11): yield 69 mg (94%); mp 89–90° (lit.[7] mp 88.9–90°). Ir, nmr, and mass spectra confirmed the structure of the product. Decoupling studies revealed a long-range coupling of 1.2 cps between the protons in 2 and 7 positions. When the tosylate of **5** (25 mg) and potassium acetate (29 mg) were kept in 2 ml of ethanol at room temperature for 26 hr and worked up as described, thin layer chromatography of the product showed the presence of starting material and some of the 1,8 olefin 11 (*ca.* 30%). No reaction occurred if acetic acid was added to the mixture under conditions of room temperature for 4 days or 100° for 8 hr. The tosylate of **4** was treated with potassium acetate in ethanol similarly and gave the olefin 11 in good yields.

Conversion of 9 into (±)-Heliotridane.—The diol **9** (425 mg) was added to freshly distilled thionyl chloride (10 ml) at 0° and the solution was refluxed for 90 min. After removal of excess thionyl chloride under reduced pressure, the residue was taken up in water and the solution was washed with chloroform, made alkaline with potassium carbonate, and extracted with chloroform to give a colorless oil (244 mg). The oil was dissolved in ethanol (8 ml) and reduced with hydrogen and Raney nickel. The catalyst was removed and the filtrate was diluted with 0.5 *N* sulfuric acid, washed with chloroform, basified with ammonia, and extracted with light petroleum ether (bp 30–40°). The product was distilled in a bulb tube, giving a liquid (80 mg) which formed a picrolonate, needles from ethanol; mp 146–147°, undepressed on admixture with (+)-heliotridane picrolonate; mp 155°, prepared from (+)-isoretronecanol by a similar procedure. The ir spectrum of the free base was identical with that of (−)-heliotridane[11] and its nmr spectrum (100 Mcps, $CDCl_3$) was identical with that of (+)-heliotridane and different from that of (+)-pseudoheliotridane prepared from (+)-trachelanthamidine by the above procedure.

Reduction of 2 with Sodium Borohydride.—A solution of **2** (434 mg) in dimethoxyethane (5 ml) was added dropwise to sodium borohydride (93 mg) in dimethoxyethane (5 ml). After 5 min, excess hydride was destroyed with a few drops of acetic acid and the mixture was poured into water (60 ml) and extracted with chloroform. Removal of solvent left a gum (368 mg) which crystallized from acetone–light petroleum ether, giving **4**; yield 179 mg, mp 103°, undepressed on admixture with an authentic sample. The mother liquor was submitted to preparative tlc (silica gel, 5% methanol in chloroform), giving additional **4**, yield 59 mg, R_f 0.67, together with **5**, yield 38 mg, R_f 0.60, mp 128°, undepressed on admixture with an authentic sample and with the same ir spectrum.

Registry No.—**3**, 21850-63-5; **4**, 21823-71-2; **6**, 15211-07-1; **7**, 21823-73-4; **8**, 21850-64-6; **9**, 21823-78-9; **10**, 21823-74-5; **10** (picrolonate), 21823-75-6; (±)-1-carbomethoxy-2,3-dioxo-8α-pyrrolizidine, 21823-76-7; (±)-1α-carbethoxy-2β-hydroxy-3-oxo-8α-pyrrolizidine tosylate, 21823-77-8.

(11) C. C. J. Culvenor and L. W. Smith, *Aust. J. Chem.*, **12**, 255 (1959).

N,N'-Dinitrosopiperazine

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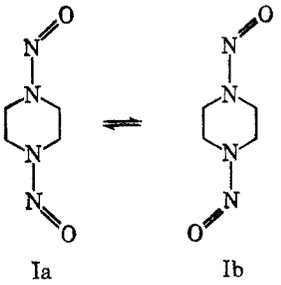
The conformational properties of N,N'-dinitrosopiperazine have been investigated in detail. In solution, both *syn* and *anti* forms are present, with a predominance of the latter. Only the *anti* form appears to be present in the solid. The *R* value obtained from the nmr spectrum of the *anti* form indicates that the molecule is either a boat form or a flattened chair in solution. The ir and Raman spectra (4000–50 cm^{-1}) have been examined in the solid to obtain information concerning molecular symmetry.

An sp^2 atom in an otherwise saturated six-membered ring generally flattens the surrounding portion of the molecule, as has been demonstrated for a number of simple cyclohexanones.[2] A pair of adjacent sp^2 atoms, as in cyclohexene, force a six-membered ring into the half-chair conformation. Trigonal atoms at opposite (1, 4) corners of the ring produce either a severely flattened chair or, if the methylene–methylene torsional strain is too great, a twist boat. The latter circumstance has been found to be the case for 1,4-cyclohexanedione[3] for some of its derivatives, and possibly for 1,4-dimethylenecyclohexanes.[4] Additional trigonal centers, *e.g.*, in cyclohexadienes, serve to flatten the ring even more.[5,6]

The factors that contribute to these conformational alterations are not fully understood. We have chosen to investigate the conformational properties of N,N'-dinitrosopiperazine (I) because of its formal resem-



Ia Ib

blance to the dione and because it possesses several modes of conformational flexibility. The amine nitrogen in a nitrosamine such as I is probably very close to being trigonally hybridized, because of delocalization of the lone pair into the nitroso group. Chow and Colón[7] have calculated that the polar form is present to

(1) (a) Alfred P. Sloan Fellow, 1968–1970. This work was supported by the National Science Foundation (Grants GP-6611 and GP-9257) and by the donors of the Petroleum Research Fund, administered by the American Chemical Society (Grant 2970-A4, 5); (b) NDEA Fellow, 1966–1969; (c) National Science Foundation Undergraduate Research Participant, 1968–present.

(2) (a) J. B. Lambert, R. E. Carhart, and P. W. R. Corfield, *J. Amer. Chem. Soc.*, **91**, 3567 (1969); (b) J. B. Lambert, R. E. Carhart, P. W. R. Corfield, and J. H. Enemark, *Chem. Commun.*, 999 (1968); (c) N. L. Allinger and M. A. DaRooge, *J. Amer. Chem. Soc.*, **84**, 4561 (1962).

(3) See, among others, (a) P. Groth and O. Hassel, *Acta Chem. Scand.*, **18**, 923 (1964); (b) A. Mossel and C. Romers, *Acta Crystallogr.*, **17**, 1217 (1964); (c) N. L. Allinger, H. M. Blatter, L. A. Freiberg, and F. M. Karkowski, *J. Amer. Chem. Soc.*, **88**, 2999 (1966).

(4) F. Lautenschlaeger and G. F Wright, *Can. J. Chem.*, **41**, 1972 (1963); A. Aihara, C. Kitazawa, and F. Iwasaki, *Bull. Chem. Soc. Jap.*, **41**, 1034 (1968).

(5) H. Oberhammer and S. H. Bauer, *J. Amer. Chem. Soc.*, **91**, 10 (1969).

(6) M. Traetteberg, *Acta Chem. Scand.*, **22**, 2294 (1968).

(7) Y. L. Chow and C. J. Colón, *Can. J. Chem.*, **46**, 2827 (1968).

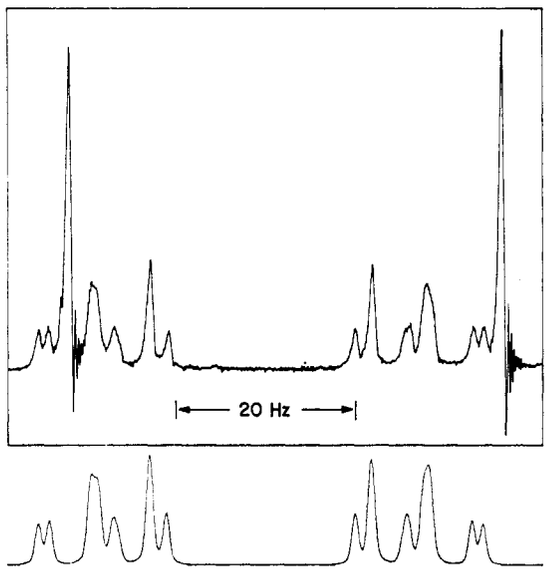


Figure 1.—(a) Upper: nmr spectrum of N,N′-dinitrosopiperazine at 60 MHz and 40° in dimethyl sulfoxide; the high-field *syn* resonance is 1.25 ppm downfield from the solvent. (b) Lower: calculated spectrum for the *anti* isomer using the parameters listed in Table II.

the extent of 49% in the ground state. The barrier to N–N bond rotation (21–23 kcal/mol) is close to the

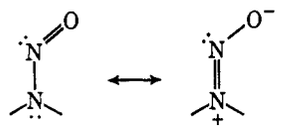


figure for amide rotation.[8,9] The question arises whether the constraints of two trigonal centers in N,N′-dinitrosopiperazine can force the molecule to assume the twist-boat conformation, as is the case for 1,4-cyclohexanedione. Several years ago, George and Wright[10] suggested that the flexible form predominates, although the conclusion was based on dipole-moment data that did not take into account the existence of *syn* and *anti* isomers (Ia and Ib). The goals of the present study thus were twofold: (1) to determine the amounts of *syn* and *anti* isomers present in solution and in the solid state; and (2) to determine the shape of the six-membered ring in the solid and in solution.

The *syn–anti* Question.—In solution, the *syn* (Ia) and *anti* (Ib) forms may be readily distinguished at their equilibrium concentrations by nmr spectroscopy. In both cases the strong nitrosamine resonance interaction precludes the existence of axial–equatorial isomerism. The nmr spectrum in dimethyl sulfoxide is presented in Figure 1a.[11] The *syn* isomer produces two sharp singlets: an A_4 pattern at high field due to the protons *cis* to the oxygen atoms;[12] and a B_4 pattern at low field due to the *trans* protons. The cross-ring coupling between the A and B protons is negligible. The *anti* isomer gives an $(AA'BB')_2$ pattern (see the next section). Direct integration shows that, under these equilibrium conditions, the *anti* form is favored over the *syn* by a factor of up to about 2. Data for several solvents are given in Table I.

TABLE I
THE *anti/syn* PROPORTION FOR N,N′-DINITROSOPIPERAZINE IN SOLUTION AT 40°

Solvent	% *anti*
CH_3COCH_3	62
CH_3SOCH_3	63.5
CH_2Cl_2	64
CH_3CN	65.5
$HCON(CH_3)_2$	67

The question of conformation in the solid cannot usually be answered without recourse to X-ray data. Under certain circumstances,[13] nmr experiments can give information about the form molecules assume in the solid by examination of the spectrum before sufficient time has elapsed for the mixture of isomers to reach thermodynamic equilibrium. To this end, in a typical experiment, a sample of solid N,N′-dinitrosopiperazine is dissolved in acetone-d_6 at −10°. After it has been ascertained that no solid is present, the nmr spectrum is recorded at the same temperature. In contrast to the equilibrium situation depicted in Figure 1a, the observed spectrum is essentially that of the *anti* form alone (<5% *syn*). Therefore, only the *anti* form, or a derived dimer, could have been present in the solid. The resonances of the *syn* form gradually increase in intensity. After several minutes at 0°, or almost immediately at 40°, the *anti/syn* equilibrium ratio is reached. The interesting conclusion from this experiment is that the predominant geometry of the molecule in the solid (*anti*) can be determined by nmr experiments in solution.[14]

At a given temperature, the rate of appearance of the sharp peaks from the *syn* isomer in the nonequilibrium spectrum may be measured by classical methods of kinetics. From the rate at 7° ($\sim 10^{-4}$ sec^{-1}) and at 16.5° ($\sim 1.6 \times 10^{-4}$ sec^{-1}), a crude free energy of activation was found to be 22 kcal/mol for the isomerization of the *anti* to the *syn* form. Although these rates are not very accurate, the agreement with previous nmr methods[8,9] under equilibrium conditions and at high temperatures is quite good.

The high-temperature behavior was examined in dimethylformamide and in benzyl acetate. As expected, the entire spectrum in Figure 1a collapses to a broad singlet above 180°. At this temperature, the *syn–anti* interconversion is rapid on the nmr time scale. Because the rate process involves an eight-spin system (four spins if symmetry is taken into account), no attempt has yet been made to determine the high-temperature kinetics.

In summary, both the *syn* and the *anti* forms of N,N′-dinitrosopiperazine are present in solution, with a predominance of the latter. In the solid, the centrosymmetric *anti* form appears to be present exclusively, although a few per cent of the *syn* cannot be discounted.

(8) C. E. Looney, W. D. Phillips, and E. L. Reilly, *J. Amer. Chem. Soc.*, **79**, 6136 (1957).

(9) R. K. Harris and R. A. Spragg, *Chem. Commun.*, 362 (1967).

(10) M. V. George and G. F Wright, *J. Amer. Chem. Soc.*, **80**, 1200 (1958).

(11) The nmr spectrum has also been examined by R. K. Harris, *J. Mol. Spectrosc.*, **15**, 100 (1965).

(12) G. J. Karabatsos and R. A. Taller, *J. Amer. Chem. Soc.*, **86**, 4373 (1964); H. W. Brown and D. P. Hollis, *J. Mol. Spectry.*, **13**, 305 (1964).

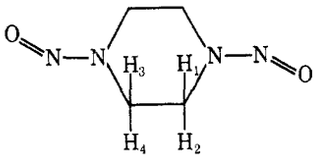
(13) C. H. Bushweller, *J. Amer. Chem. Soc.*, **90**, 2450 (1968); F. R. Jensen and C. H. Bushweller, *ibid.*, **88**, 4279 (1966).

(14) The magnitude of the nitrosamine barrier has been used to similar advantage by Mannschreck, *et al.*, who separated the isomers of an aromatic nitrosamine; see A. Mannschreck, H. Münsch, and A. Mattheus, *Angew. Chem. Intern. Ed. Engl.*, **5**, 728 (1966).

The Chair–Boat Question.—The method of coupling-constant ratios[15] has been found to be extremely useful in determining the nature of distortions in six-membered rings.[2a,b] As a first step in the conformational analysis of *anti*-N,N'-dinitrosopiperazine, the $(AA'BB')_2$ spectrum was therefore analyzed to obtain the averaged vicinal coupling constants, J_{trans} and J_{cis}. The symmetry of the *syn* isomer precludes analysis of its spectrum unless ^{13}C satellites are examined. Both the Swalen–Reilly and the Castellano–Bothner-By methods[16] were used; the results are listed in Table II and

TABLE II

NMR SPECTRAL PARAMETERS FOR *anti*-N,N'-DINITROSOPIPERAZINE AT 60 MHZ AND 40°[a]



	NMRENIT	LAOCN3
Chemical-shift difference $(\delta_{1,2} - \delta_{3,4})$[b]	34.7 ± 0.1	34.7
$J_{trans} = J_{1,4} = J_{2,3}$	7.45 ± 0.1	7.43
$J_{cis} = J_{1,2} = J_{2,4}$	4.94 ± 0.1	4.95
J_{gem}	−14.6 ± 0.1	−14.6
J'_{gem}	−15.1 ± 0.1	−15.1

[a] Because ring inversion is rapid at this temperature, only one J_{trans} and one J_{cis} are observed. [b] All units are hertz.

illustrated in Figure 1b.[17] The R value[15] (J_{trans}/J_{cis}), which depends only on the conformation of the molecule and is independent of the nature of the atoms attached to the $-CH_2CH_2-$ fragment, was found to be 1.5. Such a number is diagnostic for flattened conformations, *i.e.*, ones in which the adjacent methylene groups are more nearly eclipsed than in cyclohexane.[2a] Flattened chairs and most boat forms fall into this category. The observed R value is lower than that of cyclohexanes (2.2),[2a,15] but not so low as that of 1,4-cyclohexanedione (1.3).[15] Since the R values for N-methyl-N-nitrosopiperazine and N-nitrosomorpholine[18] are in the range of 1.7–1.95, these molecules, in contrast to N,N'-nitrosopiperazine, must be only slightly flattened from the shape of cyclohexane, much as in typical cyclohexanones.[2a,b]

Vibrational spectra of N,N'-dinitrosopiperazine have been examined to obtain information about the conformation in the solid. The nmr evidence presented in the previous section showed that little or no *syn* isomer is present in the crystal. The ir spectrum of N,N'-dinitrosopiperazine is substantially different in solution (methylene chloride, acetonitrile) from that in the solid (KBr pellet).[19] Not only are intensities radically altered, but frequencies of absorption also change. Information concerning molecular symmetry may be obtained by comparison of ir and Raman spectra. For centrosymmetric molecules, there should be no absorption coincidences between the ir and Raman spectra.[19] Molecules lacking such symmetry should exhibit a coincidence in the ir spectrum for each Raman absorption. The chair conformation of the *anti* form (but not the *syn*) is centrosymmetric and may thus be differentiated from all-boat and twist-boat forms. By experiments of this type, Allinger[3c] showed that 1,4-cyclohexanedione is in a boat form.

To make this conformational distinction, we have examined the ir and Raman spectra of solid N,N'-dinitrosopiperazine over the range of 4000–50 cm^{-1}. The results are outlined in Table III. The peak positions

TABLE III

INFRARED AND RAMAN FREQUENCIES[a] FOR SOLID N,N'-DINITROSOPIPERAZINE

Infrared[b]	Raman[c]	Infrared[b]	Raman[c]
77 (m)			1072
	99	1144 (m)	
181 (m)	179		1156
286 (m)		1163 (s)	
326 (m)	322	1182 (s)	1186
	341	1266 (m)	
384 (w)	388	1278 (s)	1278
396 (w)		1290 (s)	
	431	1347 (s)	1351
579 (m)		1366 (vs)	
670 (w)			1413
683 (w)	683	1429 (s)	
	807	1444 (sh)	
813 (w)		1460 (m)	
960 (s)		2870 (w)	
979 (vs)		2934 (w)	2934
	999		3004
1047 (w)	1047	3018 (w)	
1065 (w)			

[a] In cm^{-1}. [b] KBr pellet. [c] Neat pellet.

were measured to within 2 cm^{-1}. Six Raman bands (99, 341, 431, 999, 1413, 3004) clearly lack an ir coincidence and another three (807, 1072, 1156) are at least 6 cm^{-1} from the nearest ir peak. Five bands (179, 683, 1047, 1278, 2934) appear to have a coincidence (within 3 cm^{-1}) in the ir, and four others have borderline (4 cm^{-1}) coincidences (322, 388, 1186, 1351). For comparison,[20] 1,4-dioxane, which is certainly in a chair conformation, has three coincidences (1109, 1443, 2966) and one borderline coincidence (1396) out of 21 observed Raman absorptions; 1,4-cyclohexanedione, thought to be a boat,[3c] has a coincidence for each of nine Raman bands.

Since the coincidences and noncoincidences are evenly divided for N,N'-dinitrosopiperazine, it would seem that this method does not permit a conformational distinction. The weight of the argument may lean slightly in favor of the chair for two reasons, although we

(15) J. B. Lambert, *J. Amer. Chem. Soc.*, **89**, 1836 (1967); J. B. Lambert, R. G. Keske, and D. K. Weary, *ibid.*, **89**, 5921 (1967); J. B. Lambert and R. G. Keske, *Tetrahedron Lett.*, 4755 (1967).

(16) J. D. Swalen and C. A. Reilly, *J. Chem. Phys.*, **37**, 21 (1962); S. Castellano and A. A. Bothner-By, *ibid.*, **41**, 3863 (1964).

(17) Our values of the vicinal coupling constants are in reasonable agreement with those of Harris.[11] There is substantial disagreement, however, in the values of the geminal coupling constants. The small peaks 10 Hz from the center and on either side of the *anti* spectrum in Figure 1a are very sensitive to the sum of the two J_{gem} values. The difference between the J_{gem} values is determined by the width of the small peaks 15 Hz from the center. It is interesting that the former pair of peaks (10 Hz from the center) are only present in dimethyl sulfoxide and dimethylformamide. In the other solvents of Table I, the spectrum resembles that reported by Harris.[11]

(18) R. K. Harris and R. A. Spragg, *J. Mol. Spectry.*, **23**, 158 (1967).

(19) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, pp 149–150.

(20) F. E. Malherbe and H. J. Bernstein, *J. Amer. Chem. Soc.*, **74**, 4408 (1952).

shall not offer a decision. First, the presence of so many noncoincidences may have more import than do the corresponding number of coincidences, which can[20] occur fortuitously. Second, four of the five coincidences in the ir are weak bands that might be expected to be forbidden. It is not impossible that these coincidences arise from a second conformation, although there is no discernible pattern in the alteration of their intensities in going from the solid to solution. More likely, the overabundance of coincidences points toward the weakness of this technique as a straightforward method of conformational analysis.[21]

In summary, nmr evidence is consistent with a very flattened chair or with certain boat forms in solution. The method of ir–Raman coincidences does not provide a clear choice between the alternatives in the solid. The question cannot be fully answered without X-ray evidence, which we hope to obtain in the future.

(21) The question of dimers in nitrosamines is still somewhat controversial.[8,22] By dilution experiments, we saw no evidence for dimers from the ir spectra in solution.

(22) S. D. Christian and P. Klaeboe, *Acta Chem. Scand.*, **21**, 2293 (1968).

Experimental Section

The nmr spectra were taken on Varian Model T-60 and A-60 spectrometers. Spectral analyses were carried out on the Control Data Corp. 6400 computer equipped with a Calcomp plotting accessory. The ir spectra were obtained from Beckman IR-9, IR-10, and IR-11 spectrometers. Raman spectra[23] were recorded on a Spex 1400-II double monochromator with a 6328 He–Ne laser and photon-counting detectors.

N,N′-Dinitrosopiperazine was prepared by treatment of piperazine dihydrochloride with sodium nitrite and hydrochloric acid according to the same procedures used by George and Wright.[10] The product was recrystallized from water to give cream-colored crystals, mp 156–158° (lit.[10] 156–156.5°).

Registry No.—N,N-Dinitrosopiperazine, 140-79-4.

(23) The authors are deeply grateful to Dr. D. F. Shriver and Mr. B. I. Swanson for assistance in the operation of the IR-11 and the Raman spectrometers. We also wish to thank the National Science Foundation for a departmental instrument grant that permitted purchase of the IR-11.

Oxidation of Pyridineacetic Acid Derivatives with Peracids. An Unusual α Hydroxylation

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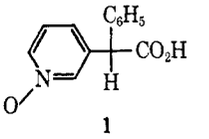
Oxidation of various isomeric methyl α-phenylpyridineacetates with peracids is described. The 3- and 4-pyridyl isomers reacted "normally" to give the corresponding N-oxides in high yields. However, with the 2-pyridyl isomer, the main product was the corresponding glycolate derivative, the net result being hydroxylation at the α carbon. Similar results were obtained with some related compounds having in common a –CHR′COR grouping at the 2 position of the pyridine ring. The second-order rate constants measured for this reaction are compared with those of peracid oxidation of olefins and pyridyl nitrogen. The much higher rate of the α oxidation as compared with oxidation of pyridine nitrogen shows that rearrangement of an initially formed N-oxide is not involved; rather, a mechanism is suggested in which the rate-determining step is epoxidation of a tautomeric form, followed by fast opening of the oxirane ring.

It is well documented that 2- and 4-pyridineacetic acids are generally less stable than their phenyl counterparts;[1,2] indeed, α-phenyl-substituted derivatives decarboxylate below room temperature.[3,4] However, the N-oxides of both α-phenyl-2- and -4-pyridineacetic acids have been prepared in high yields from reactions of the respective N-phenacetylpyridinesulfonamide 1-oxide with sodium hydroxide.[5] Since these acids or their N-oxides were needed for another study, attempts were made to prepare the latter by a more classical route: peracid oxidation of the respective esters or amides followed by hydrolysis. The 4-pyridyl derivatives were indeed successfully prepared this way; however, in the case of the 2-pyridyl isomers oxidation at the α carbon was the predominant reaction path. A study of this unusual reaction constitutes the main part of the present paper.

In contrast to its two isomers, α-phenyl-3-pyridineacetic acid could be prepared by saponification of the ester. Subsequent oxidation of the acid with peracetic acid gave the N-oxide **1** in good yield. In a similar fashion, oxidation of methyl α-phenyl-4-pyridineacetate with either peracetic acid or *m*-chloroperbenzoic acid yielded the liquid N-oxide **2**, characterized as its picrate.[5] Saponification gave the corresponding acid **3** in 85% yield. However, treatment of the 2-pyridine isomer **4** under the same conditions gave a crystal-



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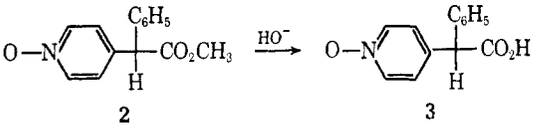

2 **3**

line product, which according to thin layer chromatography consisted of three compounds besides the starting material. Attempts to get some quantitative data as to their relative amounts using gas chromatography were unsuccessful because of decomposition.

Two of the compounds were successfully separated by chromatography on silica gel. The major product analyzed correctly for the expected N-oxide of **4**, but the infrared spectrum exhibited no significant absorp-

(1) J. C. Godfrey in "Pyridine and Derivatives," Part III, E. Klingsberg, Ed., Interscience Publishers, New York, N. Y., 1962, Chapter XI.

(2) W. von E. Doering and V. Z. Pasternak, *J. Amer. Chem. Soc.*, **72**, 143 (1950).

(3) D. Singh, *J. Chem. Soc.*, 2445 (1925).

(4) L. Panizzon, *Helv. Chim. Acta*, **27**, 1748 (1944).

(5) T. Naito, R. Dohmori, and T. Kotake, *Chem. Pharm. Bull.* (Tokyo), **12**, 588 (1964); R. Dohmori, *ibid.*, **12**, 595 (1964).