

Continued elution of the aluminum oxide column with ethyl acetate and methanol afforded an oily product, 2.94 g., which proved to be unstable even in the cold and in the absence of light. The total recovery was 8.01 g.

In the experiment described above, the ratio of the butadiene to the ring-closed pyridine derivative was approximately 1:1. In another experiment which was carried out in the same manner, except that the dehydration in polyphosphoric acid was performed at 240–250° for 30 min., the ratio of butadiene to pyridine was approximately 2:1 (3.74 g. and 1.70 g., respectively). In a third experiment, in which the dehydration was allowed to proceed at 240° for 20 min., the ratio of the open and ring closed products was found to be about 10:1.

**Oxidative Degradation of 6-(3-Pyridyl)-7-methyl-5H-4-pyridine.**—To a stirred, hot suspension of the above pyridine (416 mg., 2 mmoles) in water was added in portions 1.90 g. (0.012 mole) of potassium permanganate. Manganese dioxide began to precipitate immediately. Boiling and stirring were continued for 15 min. after the addition of the oxidizing agent, the excess of which was then decomposed by the addition of 1 ml. of methanol. The hot reaction mixture was filtered and the manganese dioxide washed twice with warm water. The clear, straw-colored filtrate was acidified with dilute hydrochloric acid and evaporated to dryness under reduced pressure. The salt-like residue was taken up in 3 ml. of water the acidity was adjusted to approximately

pH 2–3 with crystalline sodium carbonate, and the crystalline precipitate was collected, washed twice with 1 ml. of cold water, and dried. The product weighed 35 mg. and melted with decomposition at 233–240°. After one recrystallization from water, the melting point was 235–241°. A paper chromatogram of this material indicated only one spot, inseparable from that of pyridine-2,3-dicarboxylic acid,  $R_f$  value 0.40, developed with a mixture of butanol-acetic acid-water (4:1:5) and stained with bromophenol blue indicator. The infrared absorption spectrum of the product was superimposable on that of an authentic specimen of pyridine-2,3-dicarboxylic acid in Nujol mull.

A second crop of product was obtained upon concentration of the aqueous filtrate. This material exhibited two spots on the paper chromatogram,  $R_f$  values 0.40 and 0.70, respectively, whereas the residue obtained after complete evaporation of the mother liquor showed only the rapidly migrating component, which proved to be inseparable from added nicotinic acid.

**Acknowledgment.**—We wish to express our appreciation to Dr. Emil Schlittler for his continued interest and encouragement throughout this project. We are grateful to Mr. Louis Dorfman and his staff for the microanalyses and the spectral data.

## Hydroxylamine Chemistry. II. The Abnormal Michael Reaction of *N,N*-Disubstituted Hydroxylamines with 2- and 4-Vinylpyridines<sup>1</sup>

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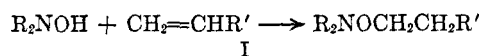
The application of the pyridylethylation reaction to *N,N*-disubstituted hydroxylamines affords unexpected products which do not contain oxygen. They have been identified as the compounds resulting from the addition of the corresponding amine (*i.e.*, the hydroxylamine without its oxygen atom) to the unsaturated system. Several different types of hydroxylamines have been investigated with consistent results.

The prediction by Doering and Weil<sup>2</sup> on theoretical grounds that the  $\alpha$ - and  $\gamma$ -pyridyl groups should be classified with the other well known electron-deficient systems ( $>C=O$ ,  $-CN$ ,  $-NO_2$ ,  $>SO_2$ , etc.) which activate a double bond to attack by nucleophilic reagents has been extensively substantiated. No report prior to 1947 on the pyridylethylation reaction had appeared, but in the last fourteen years this synthetic method has been widely exploited.

The facts that a wide variety of pyridylethylated products possess significant pharmacologic activity<sup>3–7</sup> and that *N,N*-disubstituted hydroxylamines

had never been subjected to the pyridylethylation reaction prompted us to investigate this area in an effort to obtain useful pharmacologic agents.

A number of *N,N*-disubstituted hydroxylamines have been successfully condensed in a Michael-type reaction with various electron-deficient systems to produce "normal" products such as I ( $R' = CN, COCH_3, COOR$ ).<sup>8</sup>



On the other hand, the reaction of *N*-hydroxypyrrolidine<sup>9</sup> and 2-vinylpyridine without solvent in the presence of a trace of Triton B does not give the expected Michael adduct but rather leads to 2-(2-pyrrolidinoethyl)pyridine, characterized as its dipicrate. This material was prepared by an

(1) E. L. Schumann, L. A. Paquette, R. V. Heinzelman, D. P. Wallach, J. P. DaVanzo, and M. E. Greig, *J. Med. Pharm. Chem.*, **5**, 464 (1962), may be considered Part I of this series.

(2) W. E. Doering and R. A. N. Weil, *J. Am. Chem. Soc.*, **69**, 2461 (1947).

(3) A. H. Sommers, M. Freifelder, H. B. Wright, and A. W. Weston, *ibid.*, **75**, 57 (1953).

(4) L. A. Walter, R. H. Barry, and J. R. Clark, U.S. Patent 2,713,051, July, 1955.

(5) A. R. Katritsky, *J. Chem. Soc.*, 2581 (1955).

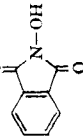
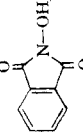
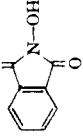
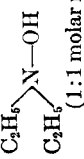
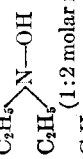
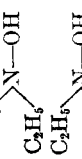
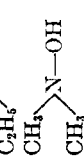
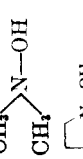
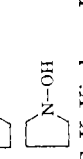
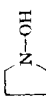
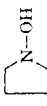
(6) B. Elpern, L. N. Gardner, and L. Grumbach, *J. Am. Chem. Soc.*, **79**, 1951 (1957).

(7) S. L. Shapiro and co-workers, *ibid.*, **79**, 2811 (1957); **80**, 1648 (1958); *J. Org. Chem.*, **26**, 1323 (1961); U.S. Patent 2,993,905 (July 25, 1961).

(8) G. Zinner, *Angew. Chem.*, **71**, 311 (1959); *cf.*, also, L. A. Paquette, *J. Org. Chem.*, to be published.

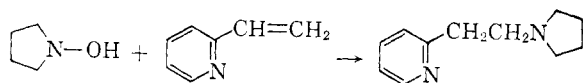
(9) J. Thesing and W. Sirrenberg, *Chem. Ber.*, **92**, 1748 (1959).

TABLE I  
ABNORMAL PYRIDYLETHYLATION OF N,N-DISUBSTITUTED HYDROXYLAMINES

Hydroxylamine	Vinyl- pyridine	Catalyst	Reaction time, hr.	B.p., °C.	Yield, %	Characterized as	Literature m.p. and ref.	Formula	Calcd.			Found		
									C	H	N	C	H	N
1. 	2-VP	Triton B	0.5	...	32.2	Base, m.p. 86-87°	95-97° <sup>a</sup>	C <sub>15</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub>	71.41	4.80	11.11	71.35	4.77	10.86
2. 	2-VP	HOAc	0.5	...	39.0	Same as above	Same as above							
3. 	4-VP	Triton B	0.5	..	20.0	Base, m.p. 147-151°	138° <sup>b</sup> 157-158° <sup>c</sup>	C <sub>15</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub>	71.44	4.80	11.11	71.08	4.86	11.12
4. 	2-VP	Triton B	3	112-116° (13 mm.)	28.4	Dipicrate, m.p. 163-165°	163.5-165° <sup>d</sup>	C <sub>23</sub> H <sub>36</sub> N <sub>2</sub> O <sub>4</sub>	43.40	3.80	17.61	43.60	3.44	17.59
5. 	2-VP	Triton B	3	115-119° (12 mm.)	26.1	Same as above								
6. 	2-VP	None	3	112-122° (11 mm.)	25.8	Same as above								
7. 	4-VP	HOAc	3	125-128° <sup>e</sup> (17 mm.)	28.4	Dihydrochloride, m.p. 233-234°	234-235° <sup>f</sup>	C <sub>11</sub> H <sub>20</sub> Cl <sub>2</sub> N <sub>2</sub>	52.59	8.02	11.15	52.22	8.23	11.00
8. 	4-VP	HOAc	3	114-123° <sup>e</sup> (11 mm.)	47.0	Dihydrochloride, m.p. 232.5-234°	223-224° <sup>f</sup>	C <sub>9</sub> H <sub>18</sub> Cl <sub>2</sub> N <sub>2</sub>	48.44	7.23	12.56	48.66	7.77	12.22
9. 	2-VP	Triton B	1	95-110° (12 mm.)	20.8	Dipicrate, m.p. 182-184°	177-178° <sup>g</sup>	C <sub>21</sub> H <sub>30</sub> N <sub>2</sub> O <sub>4</sub>	41.45	3.31	18.42	41.89	3.23	18.19
10. 	2-VP	Triton B	3	129-144° (10 mm.)	34.1	Dipicrate, m.p. 161-161.5°	157-158° <sup>h</sup>	C <sub>23</sub> H <sub>22</sub> N <sub>2</sub> O <sub>4</sub>	43.54	3.50	17.66	43.71	3.86	17.62
11. 	4-VP	HOAc	3	134-145° (10 mm.)	47.6	Dihydrochloride, m.p. 223-225°	216-217° <sup>i</sup>	C <sub>11</sub> H <sub>18</sub> Cl <sub>2</sub> N <sub>2</sub>	53.02	7.28	11.46	52.79	7.33	11.42

<sup>a</sup> F. K. Kirehner, J. R. McCormick, C. J. Cavallito, and L. C. Miller, *J. Org. Chem.*, **14**, 388 (1949). <sup>b</sup> E. Profft, *J. prakt. Chem.*, **4**, 19 (1956). <sup>c</sup> A. P. Gray, W. L. Archer, E. E. Spinner, and C. J. Cavallito, *J. Am. Chem. Soc.*, **79**, 3805 (1957). <sup>d</sup> See ref. 10. <sup>e</sup> G. Magnus and R. Levine, *J. Am. Chem. Soc.*, **78**, 4127 (1956) and A. J. Matuszko and A. Taurins, *Can. J. Chem.*, **32**, 538 (1954) have also reported these bases. <sup>f</sup> A. P. Phillips, *J. Am. Chem. Soc.*, **78**, 4441 (1956).

alternate unequivocal route<sup>10</sup>; the identity of the



infrared spectra and physical properties of the two substances served to confirm the structure. A mixed melting point of the dipicrates was undepressed. Similarly, N-hydroxypyrrolidine condensed readily with 4-vinylpyridine to afford 4-(2-pyrrolidinoethyl)pyridine. The "abnormal" pyridylethylation reaction was likewise extended to include N,N-dimethylhydroxylamine,<sup>11</sup> N,N-diethylhydroxylamine,<sup>12</sup> and N-hydroxyphthalimide<sup>13</sup> (cf. Table I).

Various attempts to condense acetone oxime (N-isopropylidenehydroxylamine) with 2- and 4-vinylpyridines under a large assortment of conditions failed to give any pyridylethylated product, starting materials being recovered in all instances.

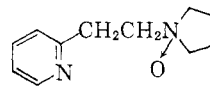
Additional studies were undertaken at this point in an effort to gain some insight into the mechanism of this oxidation-reduction reaction. Initially, determination of whether the oxygen atom of the hydroxylamines is sufficiently loosely bound to be transferred either to the nitrogen atom of a pyridine ring or to an electron-deficient double bond seemed desirable. Equimolar quantities of N,N-diethylhydroxylamine and pyridine were refluxed for five hours and subsequently carefully fractionally distilled to give virtual quantitative recovery of the starting materials. An identical experiment with 1,1-diphenylethylene gave similar negative results.

Additional information was obtained when the discovery was made that the pyridylethylation proceeded equally as well in the absence of catalyst as it did in the presence of either an acidic or a basic catalyst (cf. Table I, expt. 5-7).

In order to establish whether the yield of abnormal product could be affected by the concentration of 2-vinylpyridine, a twofold molar excess of this reagent was employed in one run; however, the yield remained unchanged (cf. Table I, expt. 4, 5). It is also noteworthy that the yields in all the reactions attempted never exceeded 50%.

Conceivably, the nitrogen atom of the hydroxylamines could be the nucleophilic species which attacks the electron-deficient terminal carbon atom of the polarized vinylpyridine. This process would be followed by a 1,4-prototropic shift from oxygen to carbon resulting in the mono-N-oxide II, which

could then undergo oxidation-reduction to yield an oxygen-free product. In an attempt to give substance to this theory, 2-(2-pyrrolidinoethyl)-



II

pyridine was treated with ethanolic hydrogen peroxide to give II, characterized as its dihydrochloride. Pyrolytic decomposition of II under reduced pressure afforded, in addition to some polymeric material, 2-vinylpyridine and N-hydroxypyrrolidine.<sup>14</sup> Efforts to simulate more closely reaction conditions by heating II in N-hydroxypyrrolidine and in 2-vinylpyridine did, however, not alter the product composition. Although the products obtained in the pyrolysis do not support the theory outlined above, they are not totally unexpected in view of the large accumulation of data<sup>15</sup> concerning the pyrolysis of N-oxides containing  $\beta$ -hydrogen atoms.

Of the several possible remaining mechanistic interpretations of this interesting reaction, the possibility that the N,N-disubstituted hydroxylamine is itself undergoing oxidation-reduction is not without analogy. Hydroxylamine, as the free base, is subject to rapid oxidation-reduction above 15°; it is also readily oxidized and possesses powerful reducing properties.<sup>16,17</sup> In addition, several reports of this type of chemical behavior among the N-alkylhydroxylamines can be found in the early literature.<sup>18a</sup> Finally, evidence for the autoxidation of aliphatic hydroxylamines, both primary and secondary, has been clearly demonstrated.<sup>18b</sup> Although this type of phenomenon may well explain the "abnormal" Michael reaction, we have not directed studies to elucidate this point.

## Experimental<sup>19</sup>

**General Procedure.**—A mixture of 0.10 mole of the N,N-disubstituted hydroxylamine, 0.10 mole of the vinylpyridine and 2-3 drops of catalyst (if employed) was refluxed for a period of time (cf. Table I). The dark liquid was directly distilled under reduced pressure to give the diamines.

When N-hydroxyphthalimide was employed, a vigorously exothermic reaction was observed as the refluxing began.

(14) These materials were identified by vapor phase chromatography and a comparison of the retention times of the two components with those of authentic samples. An F and M Model 500 gas chromatograph equipped with a 20% silicone rubber-packed column (1/4 in.  $\times$  2 ft.) was employed.

(15) For a review of N-oxide pyrolyses see A. C. Cope and E. R. Trumbull, *Org. Reactions*, **XI**, 317 (1960).

(16) N. V. Sidgwick, "Chemical Elements and Their Compounds," Oxford University Press, 1950, Vol. I, p. 681.

(17) R. E. Steiger, *Org. Syntheses*, Coll. Vol. III, John Wiley & Sons, New York, 1955, p. 91.

(18)(a) Cf., *inter alia*, C. Kjellin, *Ber.*, **30**, 1891 (1897); J. Stieglitz and P. N. Leech, *J. Am. Chem. Soc.*, **36**, 272 (1914); (b) M. A. T. Rogers, *J. Chem. Soc.*, 2784 (1956), and earlier papers in this series.

(19) All melting points and boiling points are uncorrected. Florisil is a magnesia-silica gel adsorbent manufactured by Floridin Co., Tallahassee, Florida.

(10) H. E. Reich and R. Levine, *J. Am. Chem. Soc.*, **77**, 4913 (1955).

(11) T. C. Bissot, R. W. Parry, and D. H. Campbell, *ibid.*, **79**, 796 (1957).

(12) Purchased from the Aldrich Chemical Co., Milwaukee, Wisconsin.

(13) W. R. Orndorff and D. S. Pratt, *Am. Chem. J.*, **47**, 89 (1912).

At the end of the reaction time, the contents were cooled to 110° and 30 ml. of chloroform was added. The dark brown-maroon solution was chromatographed directly on Florisil<sup>19</sup> (elution with acetone-hexane, 1:1) to give the colorless products as the only identifiable materials.

In all cases a substantial amount of red-brown polymer was produced, and quantities of the hydroxylamines and vinylpyridines were recovered in the early fractions of the distillations.

**2-[2-(1-Pyrrolidinyl)ethyl]pyridine N-Oxide Dihydrochloride (II·2HCl).**—A solution of 7.9 g. (0.045 mole) of 2-(2-pyrrolidinylethyl)pyridine and 5.4 g. of 30% hydrogen peroxide (0.0475 mole) in 30 ml. of absolute ethanol was allowed to stand at room temperature with occasional swirling for 4 days. Platinum-on-charcoal (5%) was added to decompose any residual peroxide. After filtration, the filtrate was evaporated under reduced pressure to give an uncrystallizable yellow oil. This material was treated with ethereal hydrogen chloride in the usual manner and the precipitated white solid was filtered and dried to afford 6.8 g. (57.1%) of II dihydrochloride, m.p. 165–166°. Three recrystallizations of the salt from ethanol-ether (Darco G-60)

gave pure N-oxide dihydrochloride as pale yellow blades m.p. 166–167.5°.

*Anal.* Calcd. for C<sub>11</sub>H<sub>18</sub>Cl<sub>2</sub>N<sub>2</sub>O: C, 49.82; H, 6.84; N, 10.57; equiv. wt. 133. Found: C, 49.74; H, 6.95; N, 10.38; equiv. wt. 133.

$\lambda_{\text{max}}^{\text{EtOH}}$  238sh (2,950), 243 (3,050), 254.5 (3,250), 261 (3,600), 268 (3,000), 277sh (1,150), 285sh (957), and 295sh m $\mu$  (432).

The free N-oxide was prepared by dissolving the dihydrochloride in ethanol and slowly adding two equivalents of a diluted ethanolic sodium hydroxide solution. The precipitated sodium chloride was filtered and the filtrate was concentrated to give a yellow oil.

**Pyrolysis of II.**—A 3.0-g. sample of II was placed in an oil bath at 180° under reduced pressure. A colorless liquid soon began to distil, b.p. 43–64° (13 mm.), 1.60 g. Raising of the bath temperature to 230° afforded no additional material; a dark red-brown polymer remained in the heel of the distilling flask. Vapor phase chromatography of the distillate<sup>14</sup> indicated that it was a two-component system. 2-Vinylpyridine and N-hydroxypyrrolidine had the same retention times as the constituents of the distillate.

## Polynuclear Heterocycles. II. Addition Reactions of Benzophenazines

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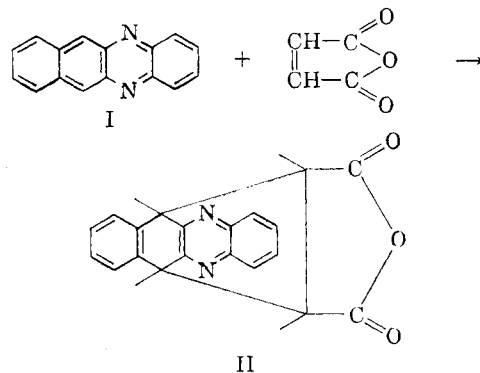
Benzo[*a*]-, benzo[*b*]-, dibenzo[*a,i*]-, and dibenzo[*f,i*]phenazine are utilized as diene components under typical Diels-Alder conditions, and structures are assigned to the adducts formed with maleic anhydride, diethyl maleate, benzoquinone, and dimethyl acetylenedicarboxylate. The reaction between these phenazine derivatives and nucleophilic agents such as benzenesulfonic acid, aromatic amines, and mercaptans is described, and the structure of the products was determined by the use of substituted phenazine derivatives. Spectral data, as they relate to the assignment of structures, are discussed.

Numerous attempts to use the double bond system of an aromatic nucleus as a diene component have been described in the literature. Attempts to add maleic anhydride to phenanthrene, chrysene, or pyrene were unsuccessful.<sup>1</sup>

Anthracene, its homologs and its derivatives, as well as numerous benzo derivatives of anthracene, such as naphthacene, add maleic anhydride readily across the *meso* positions.<sup>1</sup>

As a continuation of our studies<sup>2</sup> in the azanaphthacene series, we investigated the reaction of maleic anhydride with benzo[*b*]phenazine (I), which is structurally analogous to naphthacene.

These components react readily in an inert solvent to give benzo[*b*]phenazine-6,11-*endosuccinic* anhydride (II).<sup>3</sup> The latter structure is preferred to the alternative structures in which the maleic



anhydride has added either across the 1,4-positions or across the nitrogen atoms for the following reasons: A. The parent compound phenazine, which has essentially the same bond structure as I and differs only in the absence of the fused benzo group, does not add maleic anhydride.<sup>4</sup> B. If addition of maleic anhydride had occurred across the nitrogen atoms, the ultraviolet absorption spectrum of the adduct should be similar to that of the dihydrophenazines, whereas it is quite different. This point

(1) "Newer Methods of Preparative Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1948, p. 485, summarizes the work in this field.

(2) J. A. VanAllan, G. A. Reynolds, and R. E. Adel, *J. Org. Chem.*, **27**, 1659 (1962).

(3) According to the rules suggested by the International Union of Pure and Applied Chemistry, *J. Am. Chem. Soc.*, **82**, 5545 (1960), the generic name of II is 6,11-dihydro-6,11-ethano-5,12-diazaphthacene-13,14-dicarboxylic anhydride; IIa is diethyl 6,11-dihydro-6,11-ethano-5,12-diazaphthacene-13,14-dicarboxylate; IIb is 6,11,13,14-15,16-hexahydro-15,16-dioxo-5,11-diaza-13,14-benzenonaphthacene. For convenience and brevity, we have used the additive name.

(4) M. Lora Tomayo, R. Perez Ossaris, and M. Sanz Burati, *Anales real. soc. españ. fis. y quim.* (Madrid), **50B**, 865 (1954); *Chem. Abstr.*, **50**, 361 (1956).