### [CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, TULANE UNIVERSITY]

# Alkylation of Organic Acids with Pyridotriazole<sup>1</sup>

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Ultraviolet absorption data suggested the presence of a pyridinium cation for pyridotriazole in acid solutions. Dilute acid and neutral solutions of 1-phenylpyridotriazole showed identical ultraviolet absorption patterns. At higher temperatures, pyridotriazole in carboxylic acids or phenol released nitrogen with the formation of corresponding esters of 2-pyridylmethanol or phenyl 2-pyridylmethyl ether, respectively. The less basic 1-phenylpyridotriazole required higher tempera-tures but also reacted with carboxylic acids to bring about the formation of corresponding esters of phenyl-2-pyridylcarbinol.

A resistance to decomposition by acids was a property of pyridotetrazole not shared with pyridotriazole.<sup>3</sup> Fortunately temperatures necessary for the release of nitrogen from the destabilized conjugate acid II (R = H) of the latter were high enough to allow certain investigations on its properties.

Neutral and alkaline solutions of pyridotriazole gave identical absorption in the ultraviolet (Table  $\overline{I}$ ). A band at 280 m $\mu$  grew weaker and finally disappeared as the acid strength of the solution increased and a new absorption at 267 m $\mu$  appeared and grew stronger. The latter was assigned to the conjugate acid II of pyridotriazole. Restoration of absorption at 280 m $\mu$  and disappearance of absorption at 267 m $\mu$  was brought about upon neutralization of a hydrochloric acid solution of I.<sup>4</sup> Stability of the conjugate acid II was demonstrated by no change in either the wave length or intensity of absorption in 1.2 N hydrochloric acid at room temperature for two weeks. It is suggested that this stability reflects the contribution of a pyridinium cation II  $(R = H)^5$  to the resonance hybrid ion II.



(Compare the absorption at 256 m $\mu$  ( $\epsilon$  5400) for

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(2) Texas Eastman Fellow, 1955-1956.

(3) J. H. Boyer, R. Borgers and L. T. Wolford, THIS JOURNAL, 79, 678 (1957).

(4) The less basic pyridotetrazole in alkaline, neutral and dilute acidic ethanol solutions absorbed at 260 m $\mu$  ( $\epsilon$  5290) (J. H. Boyer and R. F. Reinisch, unpublished data).

(5) A hypsochromic shift in absorption from 274 m<sub> $\mu$ </sub> ( $\epsilon$  7100) for its conjugate acid in 0.5 N hydrochloric acid to 262 m $\mu$  ( $\epsilon$  6000) with a peak remaining at 274 m $\mu$  ( $\epsilon$  5200) for benztriazole in neutral solution was also attributed to a change from a species with a certain degree of o-quinonoid properties to a benzenoid system (J. E. Fagel and G. W. Ewing, THIS JOURNAL, 73, 4360 (1951)). Supporting evidence was found in comparing absorption values from ethanol for quinonoid 2methylindazole at 284 m $_{\mu}$  ( $\epsilon$  6000) with benzenoid 1-methylindazole at 290 m $_{\mu}$  (s 5000) and 259 m $_{\mu}$  (3600) (I. M. Barclay, N. Campbell and G. Dodds, J. Chem. Soc., 113 (1941)).

pyridine in acidified ethanol.<sup>6</sup>) A similar stable cation was isolated for 1-phenyl-3-methyl-8-azaindazolium chloride.7 At higher temperatures a rearrangement of II, or its tautomer III, together with the associated anion occurred with triazole ring cleavage and was followed or accompanied with the usual decomposition of an intermediate diazonium salt into an ester or ether of 2-pyridylmethanol and nitrogen.



 $c, A = C_6 H_5 CO_2$  $\begin{array}{l} c, A = C_{6}H_{5}CO_{2}^{-} \\ d, A = p-NO_{2}C_{6}H_{4}CO_{2}^{-} \\ e, A = 3,5(NO_{2})_{2}C_{6}H_{3}CO_{2}^{-} \\ f, A = C_{6}H_{5}O^{-} \\ g, A = B-C_{10}H_{7}O^{-} \\ h, A = C_{6}H_{5}CH=-CHCO_{2}^{-} \end{array}$ 

Upon heating pyridotriazole and carboxylic acids with or without an added inert solvent, nitrogen was released between 70 and  $100^{\circ}$  and corresponding esters of 2-pyridylmethanol were obtained in moderate yields. A similar alkylation of phenol required higher temperature (140°) and brought about the formation of phenyl 2-pyridylmethyl ether (IV,  $A = C_6H_5O^-$ , R = H). The identity of 2-pyridylmethyl acetate (IV,  $A = CH_3CO_2^-$ , R = H) was established through its known picrate derivative.<sup>8</sup> Acid hydrolysis of 2-pyridylmethyl 3,5-dinitrobenzoate afforded known 3,5-dinitro-benzoic acid and 2-pyridylmethanol. The method appears to be general for the synthesis of esters of 2-pyridylmethanol, hitherto unknown except for

(6) M. L. Swain, A. Eisner, C. F. Woodward and B. A. Brice, THIS JOURNAL, 71, 1341 (1949).

(7) R. Kuhn and W. Munzing, Ber., 85, 29 (1952).

(8) V. Boekelheide and W. J. Linn, THIS JOURNAL, 76, 1286 (1954).

| Ultraviolet Maximum Absorption Values |           |     |              |  |  |
|---------------------------------------|-----------|-----|--------------|--|--|
| Compound                              | Solvent   | mμ  | e            |  |  |
| Pyridotriazole                        | Water     | 280 | 7600         |  |  |
|                                       | 1 N NaOH  | 279 | 7000         |  |  |
|                                       | 0.1 N HCl | 280 | 4900         |  |  |
|                                       |           | 269 | 5200         |  |  |
|                                       | 0.6 N HC1 | 267 | 5600         |  |  |
|                                       | 1.2 N HCl | 267 | 5800         |  |  |
|                                       | 6.0 N HCl | 267 | <b>58</b> 00 |  |  |
| 1-Phenylpyridotriazole                | Ethanol   | 298 | 9700         |  |  |
|                                       |           | 282 | 10000        |  |  |
|                                       |           | 969 | 11700        |  |  |

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#### Experimental<sup>10</sup>

Pyridotriazole and 1-phenylpyridotriazole were prepared according to a previous report.

Alkylation of Organic Acids .- Two methods, comparable in yields afforded, were employed for the reaction between pyridotriazoles and organic acids In one (A) the triazole was heated in an excess of the acid and in the other (B) equimolar portions of triazole and acid were heated in an inert solvent. Isolation of product varied within each method.

Method A1.---A solution of 2.38 g. (0.02 mole) of pyridotriazole in 4 ml. of acetic acid was warmed gently. Vigor-ous evolution of nitrogen occurred at 60-70° and after fur-ther heating at 100° for 15 minutes gas evolution had ceased. Upon distillation the mixture gave acetic acid at 1 atm., crude 2-pyridylmethyl acetate, 1.10 g., b.p. 105-110°

| Compound             | Solvent   | mμ  | e            |
|----------------------|-----------|-----|--------------|
| yridotriazole        | Water     | 280 | 7600         |
|                      | 1 N NaOH  | 279 | 7000         |
|                      | 0.1 N HCl | 280 | 4900         |
|                      |           | 269 | 5200         |
|                      | 0.6 N HC1 | 267 | 5600         |
|                      | 1.2 N HCl | 267 | 5800         |
|                      | 6.0 N HCl | 267 | <b>58</b> 00 |
| Phenylpyridotriazole | Ethanol   | 298 | <b>97</b> 00 |
|                      |           | 282 | 10000        |
|                      |           | 262 | 11700        |
|                      |           |     |              |

TABLE II

ALKYLATION OF ORGANIC ACIDS WITH PYRIDOTRIAZOLES

| Triazole I,<br>R ≈ | Acid  | Method        | Temp., °C.<br>Time, hr. | Product          | Yield,<br>% | M.p. or<br>b.p., °C.<br>(mm.) | Picrate m.p., °C.,<br>picrolonate,<br>dec. °C. |
|--------------------|---|---------------|-------------------------|------------------|-------------|-------------------------------|--|
| Н                  | $CH_3CO_2H$   | A1            | 100                     | IVa              | $20^{a}$    | 105-110 <sup>b</sup>          | $167 - 168^{b}$                                |
|                    |   |               | 0.25                    | R = H            |             | (8.5)                         |  |
| H                  | $CH_{3}CH_{2}CO_{2}H$   | B2            | 90-100                  | IVb <sup>e</sup> | $19^a$      | 89                            | $137 - 138^{d}$                                |
|                    |   |               | 1                       | R = H            |             | (2.5)                         | 132-134°                                       |
| H                  | $C_6H_5CO_2H$   | B3            | 90-100                  | $IVc^{f}$        | 29          | 93                            | 161–162 <sup>g</sup>                           |
|                    |   |               | 1                       | R = H            |             | (0.04)                        | $156 - 157^{h}$                                |
| H                  | p-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H | B1            | 100-110                 | IVd              | 25          | 89–91 <b>'</b>                |  |
|                    |   |               | 2                       | R = H            |             |                               |  |
| н                  | $3,5-(O_2N)_2C_6H_3CO_2H$   | B1            | 90-100                  | IVe <sup>i</sup> | 33          | 100-101                       |  |
|                    |   |               | 1                       | R = H            |             |                               |  |
| н                  | C <sub>6</sub> H <sub>5</sub> OH                                  | $\mathbf{A4}$ | 140 - 150               | $IVf^k$          | 22          | 92 - 93                       | 173-174  |
|                    |   |               | $^{2}$                  | R = H            |             | (0.1)                         |  |
| H                  | $\beta$ -C <sub>10</sub> H <sub>7</sub> OH                        | A4            | 140 - 150               | IVg              |             |                               |  |
|                    |   |               | 5                       | R = H            |             |                               |  |
| $C_6H_5$           | CH <sub>3</sub> CO <sub>2</sub> H                                 | A2            | 120                     | IVa              | 44          | 101-104                       | 154-155 <sup>m</sup>                           |
|                    |   |               | 5                       | $R = C_6 H_5$    |             | (0.04)                        | 125-126 <sup>n</sup>                           |
| $C_6H_5$           | $C_6H_5CO_2H$   | A3            | 190 - 210               | IVe°             | 69          | 92 - 93                       |  |
|                    |   |               | 0.33                    | $R = C_6 H_b$    |             |                               |  |
| $C_6H_5$           | $C_6H_5CH=CHCO_2H$  | A3            | 190 - 210               | IVh              |             |                               |  |
|                    |   |               | 0.33                    | $R = C_6 H_5$    |             |                               |  |

 $0.33 \qquad R = C_6H_6$ <sup>•</sup> Yield determined from picrate. <sup>b</sup> V. Boekelheide and W. J. Linn, THIS JOURNAL, **76**, 1286 (1954), reported b.p. 115-118° (22 mm.), picrate m.p. 168-168.5°. • Calcd. for C<sub>3</sub>H<sub>11</sub>NO<sub>2</sub>: C, 65.43; H, 6.71; N, 8.48. Found: C, 65.33; H, 6.49; N, 9.86. An unidentified liquid, b.p. 118-125° (2.9 mm.), was also obtained. <sup>d</sup> Calcd. for C<sub>15</sub>H<sub>14</sub>N<sub>4</sub>O<sub>6</sub>: C, 45.70; H, 3.58; N, 14.21. Found: C, 45.65; H, 3.63; N, 14.42. • Calcd. for C<sub>19</sub>H<sub>19</sub>N<sub>4</sub>O<sub>7</sub>: C, 53.14; H, 4.46; N, 16.31. Found: C, 52.68; H, 4.71; N, 16.00. <sup>f</sup> n<sup>24</sup>D 1.5711. Calcd. for C<sub>13</sub>H<sub>11</sub>NO<sub>2</sub>: C, 73.22; H, 5.20; N, 6.57. Found: C, 72.42; H, 5.56; N, 7.09. An unidentified liquid, b.p. 144-145° (2.9 mm.), was also obtained. <sup>g</sup> Calcd. for C<sub>18</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>: C, 51.60; H, 3.12; N, 12.67. Found: C, 51.82; H, 3.37; N, 12.94. <sup>h</sup> Calcd. for C<sub>28</sub>H<sub>19</sub>N<sub>5</sub>O<sub>4</sub>: C, 57.85; H, 4.01; N, 14.67. Found: C, 57.88; H, 4.17; N, 14.68. <sup>c</sup> R. Graf, G. Perathoner and M. Tatzel, *J. prakt. Chem.*, 146, 88 (1936), reported m.p. 92°. <sup>j</sup> Calcd. for C<sub>18</sub>H<sub>9</sub>N<sub>5</sub>O<sub>6</sub>: C, 51.48; H, 2.99; N, 13.86. Found: C, 51.38; H, 3.15; N, 14.05. <sup>\*</sup> An alcoholic solution of the ether gave a brown color with ferric chloride solution. <sup>l</sup> Calcd. for C<sub>18</sub>H<sub>14</sub>N<sub>4</sub>O<sub>5</sub>: C, 52.19; H, 3.41; N, 13.52. Found: C, 52.09; H, 3.60; N, 13.59. <sup>m</sup> Calcd. for C<sub>29</sub>H<sub>15</sub>N<sub>4</sub>O<sub>5</sub>: C, 52.62; H, 3.53; N, 12.28. Found: C, 52.89; H, 3.81; N, 12.74. <sup>n</sup> Calcd. for C<sub>24</sub>H<sub>21</sub>N<sub>5</sub>O<sub>7</sub>: C, 58.64; H, 4.31; N, 14.25. Found: C, 58.51; H, 4.27; N, 14.54. <sup>o</sup> Calcd. for C<sub>19</sub>H<sub>16</sub>N<sub>4</sub>O<sub>5</sub>: C, 78.86; H, 5.24; N, 4.84. Found: C, 78.90; H, 5.38; N, 4.87.

the *p*-nitrobenzoate (see Experimental) and for the acetate which was reported recently from the action of acetic anhydride upon 2-picoline-N-oxide8 and for the diacetate of 2-hydroxymethylpyridol-3 from 2-dimethylaminomethylpyridol-3 and acetic anhydride.9

Neutral and acidic solutions of 1-phenylpyridotriazole (I,  $R = C_6 H_5$ ) gave identical absorption in the ultraviolet. Accordingly, reactions between carboxylic acids and 1-phenylpyridotriazole required temperatures from 120 to 200° for the release of nitrogen. The benzoate ester IV ( $R = C_6H_5$ ,  $A = C_6H_5CO_2^-$ ) was identified through saponification to benzoic acid and phenyl 2-pyridylmethanol.

(8.5 mm.), an unidentified basic fraction, 0.35 g., b.p. 80° (0.1 mm.), and a tar residue. From 0.1 g. of crude ester, 0.13 g. of a picrate derivative was obtained, m.p. 167-168°.<sup>§</sup> Based upon quantitative picrate formation, the minimum yield of 2-pyridylmethyl acetate was 20%.

The following variations were used for product isolation. A2: Excess acid was neutralized with sodium carbonate solution and the product ester extracted with ether. A3: The reaction mixture was dissolved in ether which was then extracted with dilute hydrochloric acid. The product ester precipitated upon neutralizing the acid layer. A4: The reaction mixture was dissolved in ether, unreacted acids were removed by extraction with 5% sodium hydroxide, and the ether layer was distilled.

Method B1.—A mixture of 1.19 g. (0.01 mole) of pyrido-triazole and 2.12 g. (0.01 mole) of 3,5-dinitrobenzoic acid in 75 ml. of toluene was heated at 90–100° for one hour or until gas evolution had ceased. From the cooled mixture, 0.30 g. of an unidentified black solid was isolated by thorough

<sup>(9)</sup> G. Ginsburg and I. B. Wilson, THIS JOURNAL, 79, 481 (1957); A. Stempel and E. C. Buzzi, ibid., 71, 2969 (1949); T. Urbanski, J. Chem. Soc., 1104 (1946).

<sup>(10)</sup> Semi-micro analyses by Alfred Bernhardt, Microanalytisches Laboratorium, Mülheim (Ruhr), Germany.

extraction with water, 0.73 g. of 3,5-dinitrobenzoic acid was recovered upon acidification of extractions obtained using sodium bicarbonate solution, and 2-pyridylmethyl 3,5-dinitrobenzoate was obtained upon neutralizing with sodium carbonate the extractions obtained using 5% hydrochloric acid. The ester recrystallized from ethanol as colorless needles, m.p. 100–101°, 1.00 g. (33%).

Anal. Calcd. for  $C_{13}H_9N_3O_6$ : C, 51.48; H, 2.99; N, 13.86. Found: C, 51.38; H, 3.15; N, 14.05.

An unidentified dark oil, 0.16 g., was isolated from the neutralized acid extractions by further extraction with ether.

The following variations were used in product isolation. B2: Toluene and a low boiling acid were removed by normal distillation and the product ester distilled *in vacuo*. B3: The reaction mixture in toluene was extracted with 5%sodium bicarbonate solution and then distilled. Table II contains summarizing data for reactions between two different triazoles and eight different organic acids. Intractable material obtained in experiments with  $\beta$ -naphthol and with cinnamic acid was not further identified.

Upon hydrolysis with hydrochloric acid, 3,5-dinitrobenzoic acid, m.p. and mixture m.p. 203-208°, and 2-pyridylmethanol were obtained from 2-pyridylmethyl 3,5-dinitrobenzoate. A picrate derivative, m.p. 160.5-161°,<sup>8</sup> was prepared from 2-pyridylmethanol.

Saponification of phenyl-2-pyridylmethyl benzoate afforded phenyl-2-pyridylcarbinol, m.p. 74-77°,<sup>11</sup> picrate m.p. 170-171°,<sup>11</sup> and benzoic acid, m.p. and mixture m.p. 121-122°.

(11) A. E. Tschitschibabin, Ber., **37**, 1370 (1904); M. R. F. Ashworth, R. P. Daffern and D. L. Hammick, J. Chem. Soc., 809 (1939). NEW ORLEANS 18, LA.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE U. S. VITAMIN CORPORATION]

## Antihypertensive Agents. I. Dialkylaminoalkoxyalkylpiperidines and Pyrrolidines

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A series of 2-dialkylaminoalkoxyalkyl-1-methylpiperidines and pyrrolidines have been synthesized in the search for bistertiary amines with hypotensive activity. Such activity has been found with the 2-(2'-dialkylaminoethoxy)-methyl-1met hyl- and the 2-(3'-dimethylaminopropoxy)-methyl-1-methylpiperidines.

The wide therapeutic usage of hexamethonium and pentapyrrolidinium has indicated irregularities in the oral absorption of these drugs<sup>1</sup> which have been associated in part with the quaternary character of the compounds.

The report by Phillips and his associates<sup>2</sup> of potent hypotensive action in bis-tertiary amines of the type 1-methyl-3-(4'-dimethylaminobutyl)-piperidine dihydrochloride, suggested structural variation of amines of this type. As a result of such studies it was hoped that bis-tertiary amines retaining the hypotensive potential of the clinically useful bis-onium salts without the side effects of these salts, could be obtained.

The scope of the study included variations of the structure I,  $A_1$ -Y- $A_2$ ·2RX, wherein  $A_1 = 2$ -pyridyl, 4-pyridyl, N-methyl-2-piperidyl, N-methyl-4-piperidyl and N-methyl-2-pyrrolidyl; Y =  $(CH_2)_n$ - and  $-(CH_2)_nO(CH_2)_n'$ -;  $A_2$  = dimethylamino, diethylamino, pyrrolidino, piperidino, morpholino, hexamethylenimino and tetrahydroquinolino; R = hydrogen and lower alkyl.

The extension of investigations in certain of these directions stimulated work not only by our laboratories, but by others,<sup>3</sup> and particularly by Phillips<sup>4</sup> and his associates, and a large group of the compounds in the category I,  $Y = -(CH_2)_n$ , have since been reported in the literature.<sup>5</sup>

(1) L. S. Goodman and A. Gilman, "The Pharmacological Basis of Therapeutics," 2nd ed., The Macmillan Co., New York, N. Y., 1955, p. 636.

(3) F. H. McMillan, K. A. Kun, C. B. McMillan and J. A. King, *ibid.*, **78**, 4077 (1956).

(4) (a) A. P. Phillips, *ibid.*, **78**, 4441 (1956); (b) **79**, 2836 (1957); (c) **79**, 5754 (1957).

(5) We prepared along parallel synthetic lines and evaluated as hypotensives the following of the Phillips compounds. Good agreement in the physical constants and analyses were obtained in all instances: ref. 4a, Table I, expt. 1, 2; ref. 4b, Table I, empd. 10, 11, 12, This paper will be confined to derivatives of I, Y = oxa-alkylene. The 1-methyl-2-piperidine (and pyrrolidine) alkanols were treated with an excess of the dialkylaminoalkyl halide in the presence of an alkaline condensing agent to yield the desired compounds in moderate yields. The compounds which were prepared, as well as their bis-quaternary salts, have been detailed in Table I.

The required heterocyclic aminoalcohols were accessible through a variety of procedures reported in the literature,<sup>6</sup> and the reactant alkanol amines were prepared following these procedures; 1methyl-2-hydroxymethylpyrrolidine,<sup>6b</sup> 1-methyl-2-(2-hydroxyethyl)-piperidine,<sup>6f</sup> and the preparation

14, 15; ref. 4c, Table I, cmpd. 14, 15, 16, 20, 21, 24, 25, 26, 27. Utilizing procedures similar to those of Phillips, several new I,  $A_1 = N$ -methyl-4-piperidyl and  $Y = -(CH_2)_{I-}$ , were prepared and are reported in Table A.

TABLE A

#### N-METHYL-4-(3'-TERTIARYAMINOPROPYL)-PIPERIDINES

|                    | <b>D W</b> | Yield,          | M.p.,     | Nitrogen, % |       |
|--------------------|------------|-----------------|-----------|-------------|-------|
| A2                 | RA         | %               | ·C.       | Calca.      | Found |
| $2 \cdot MP^h$     | HC1        | 17              | 295-296   | 9.0         | 8.9   |
| $2 \text{-} MP^h$  | CH₃I       | 82 <sup>g</sup> | 296-297°* |             |       |
| нмі                | HC1        | 71              | 280-283°1 | 9.0         | 8.9   |
| HMI                | CH3I       | 96              | 265-267°4 | 5.4         | 5.3   |
| $\mathrm{THQ}^{i}$ | HCI        | 58              | 180-182°1 | 8.1         | 7.7   |
| $THQ^{i}$          | CH3I       | 84              | 133-137°1 | 5.0         | 4.9   |

The footnotes have the same significance as in Table I. <sup>9</sup> Calcd.: C, 39.1; H, 7.0. Found: C, 39.1; H, 7.1. <sup>h</sup> 2-MP = 2-methylpiperidino. <sup>i</sup> HMI = hexamethylenimino. <sup>j</sup> THQ = tetrahydroquinolino. None of these compounds showed significant hypotensive activity. We also noted that in the instance of the entire series reviewed in this footnote, the important hypotensive activity, if present, was confined to the bis-methodides, rather than to the bis-tertiary amines which confirmed Phillips' observation.<sup>40</sup>

tiary amines which confirmed Phillips' observation.<sup>40</sup>
(6) (a) F. F. Blicke and C.-J. Lu, THIS JOURNAL, **77**, 29 (1955);
(b) F. F. Blicke, U. S. Patent 2,695,301; (c) R. Paul and S. Tchelitchefi, Bull. soc. chim. France, 1139 (1954); (d) E. Profit, Chem. Tech. (Berlin), **8**, 378 (1956); (e) R. E. Feldkamp, U. S. Patent 2,657,211;
(f) S. L. Shapiro, H. Soloway and L. Freedman, J. Am. Pharm. Assoc., Sci. Ed., **46**, 333 (1957).

<sup>(2) (</sup>a) S. Norton and A. P. Phillips, Nature, **172**, 867 (1953); (b) A. P. Phillips, THIS JOURNAL, **76**, 2211 (1954).