## INVESTIGATIONS IN THE IMIDAZOLE SERIES LXIII.\* SYNTHESIS OF IMIDAZO[1,2-a]IMIDAZOLE DERIVATIVES FROM 2-AMINOIMIDAZOLES

## B. A. Priimenko and P. M. Kochergin

A number of imidazo[1,2-a]imidazole derivatives were synthesized by the reaction of 1methyl-2-aminoimidazole with  $\alpha$ -bromoketones. The intermediate 1-methyl-3-acylmethyl-2-iminoimidazolines were isolated, and the conditions for their cyclization to imidazo-[1,2-a]imidazole derivatives were studied.

Derivatives of the heteroaromatic imidazo[1,2-a]imidazole system have received very little study. The preparation of several 2,5-disubstituted derivatives of this heterocycle by the condensation of  $\alpha$ -amino aldehydes with cyanamide has been described [2].

As we have already briefly communicated [3], in a study of the reaction of 1-substituted 2-aminoimidazole with  $\alpha$ -halo ketones we found a new simple synthesis of imidazo[1,2-a]imidazole derivatives. This paper is devoted to a more detailed discussion of the results.

As in the reaction of 1-ethyl-2-aminobenzimidazole with  $\alpha$ -halo ketones, [5], when 1-methyl-2aminoimidazole [4] was heated with phenacyl bromide and substituted phenacyl bromide, we isolated 1methyl-3-acylmethyl-2-iminoimidazolines (I-V, Table 1), which were characterized as their hydrobromides and picrates. The structures of these compounds were confirmed by the IR spectra, which contain absorption bands of the CO and NH groups at 1670-1715 and 3120-3260 cm<sup>-1</sup>, respectively.

It is interesting to note that the hydrobromides of bases I-V are less stable compounds than the hydrobromides of 1-ethyl-3-acylmethyl-2-iminobenzimidazolines [5] and on heating in lower alcohols or in water readily split out a molecule of water to give the hydrobromides of the corresponding imidazo-[1,2-a]imidazole derivatives. The cyclization of I-V proceeds still more rapidly when they are heated in organic or hydrohalic acids (HCOOH, CH<sub>3</sub>COOH, HCl, HBr) and also by the action of dehydrating agents (concentrated H<sub>2</sub>SO<sub>4</sub>, concentrated H<sub>3</sub>PO<sub>4</sub>, and POCl<sub>3</sub>) in the cold.

A simpler one-step method for the preparation of imidazo[1,2-a]imidazole derivatives (VI-XIV, Table 1) is heating of 1-methyl-2-aminoimidazole with  $\alpha$ -halo ketones in lower alcohols (methanol and ethanol).



\*See [1] for communication LXII.

Zaporozhe State Medical Institute. S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1692-1694. December, 1971. Original article submitted August 13, 1970.

© 1971 Consultants Bureau. a division of Plenum Publishing Corporation, 227 West 17th Street. New York, N. Y. 10011. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, microfilming, recording or otherwise, without written permission of the publisher. A copy of this article is available from the publisher for \$15,00.

|                          | Vield             | Yield,            |              | 2                    | 65                  | 77  | 13           | 0                          | 1 0  | 16  | 70   | : [                 | 12          |                         | 84   | - 9                               | 69   | 8 [                               | 72          | 29   | 80                  | 1                   | 53  | 58   |  | 2                             |
|--------------------------|-------------------|-------------------|--------------|----------------------|---------------------|---|--------------|----------------------------|--|---|--|---------------------|-------------|-------------------------|--|-----------------------------------|--|-----------------------------------|-------------|--|---------------------|---------------------|---|--|--|-------------------------------|
|                          |                   | z                 |              | 18,9                 | 18,3                | 12,0                                      | 11,1         |                            | 0,0  | 191   | 1  | 19,7                | 14,4        | 1,61                    | 13.0   | t a                               | 2 C.   | 18,2                              | 15,2        | 12,0   |                     | 0.01                | 22.2  | 14,4   |  | +,  <br>+,                    |
|                          | olo               | Br                |              |                      |                     | 24,5                                      |              | 7+7                        | 19.64  | 15.3  |  |                     | 27,3        | 1                       | 25,9   | 1 11                              | 35.9   | 7.7                               | 28,9        | 1  |                     | 0.01                | #   | 27,3   |  | 27,3                          |
|                          | Calc.,            | H                 |              | 3,6                  | 4.0                 | 4 c                                       | 0.0          | 0                          | o c<br>V r   | 500   |  | 3,3                 | 4<br>8,1    | 3,7                     | ©,∪<br>+ c                                       | 0 T<br>0 C                        | 0 00<br>F 00   | 58                                | 3.5         | 4<br>53  |                     | 0,0                 | 3.7   | 4,8  |  | 4.<br>ν,                      |
|                          |                   | J                 |              | 48,6                 | 49,8                | 47,9                                      | 40,1         | 1                          | 38.4   | 41.3  | -  | 50,7                | 53,4        | 2. I.C.                 | 50.7   | 0,00                              | 44.8   | 46,9                              | 52,2        | 41,3   | 0 01                | 20.74               | 44.4  | 53,4   |  | 53,4                          |
|                          |                   | z                 |              | 19,0                 | 17,9                | 13,1                                      | 1,1          | 120                        | о ю<br>2 Е   | 15.9  | 1  | 19,8                | €<br>1<br>1 | 0,61                    | 13,2   | 10,0                              | 13.4   | 18,2                              | 15,5        | 12,5   | 101                 | 10,4                | 22,1  | 14,2   | 1                                      | ۶,41<br>                      |
| <sup>1</sup> 3 v1 - x1 v | ₀⁄₀ •pur          | Br                |              | l                    |                     | 25,1                                      | 1 10         | 7<br>7<br>7<br>7<br>7<br>7 | 43 1   | 15,6  |  |                     | 27.1        |                         | 20,7   | 100                               | 35,8   | 7,5                               | 29,0        | ]  | 131                 | 10,1<br>96.6        | 0.04  | 27,4   |  | 71,2                          |
|                          | Fot               | Н                 | 1            | 3,5 .                | 4,1                 | 4,0                                       |              | 10                         | - 1<br>- 1   | 2,9   | .  | 3,2                 | 0.0<br>0    | χ,<br>Ωι                | 4, 6<br>0, 0                                     | 4<br>4<br>4                       | 3.8  | 3,0                               | 00 :<br>m • | 4,0  | с<br>С              | 2.4                 | 4,1   | 4,9  |  | 4,0<br>                       |
|                          |                   | c                 |              | 48,9                 | 49,6                | 48,3<br>18,3                              | 1,01         | 151                        | 38.2   | 41,6  | 1  | 50,8                | 53.4        | 01,4<br>2,1,4           | 50,9<br>6,03                                     | 62.5                              | 45,1   | 47,2                              | 52,4        | 41,0   | 19.6                | 30.0                | 44,6  | 53,3   |  | 03,0                          |
| CH-R<br>CH-R<br>CH-R     | Empirical formula | Empirical formula |              | C12H13N3O · C6H3N3O7 | CI3HISN3O · C6H3N3O | C13H15N3O2 + HDT<br>C13H15N3O2 • C6H3N3O5 | C.H.CINO HBr | CieHeCINSO · CeHeNsO       | C <sub>12</sub> H <sub>12</sub> BrN <sub>3</sub> O · HBr | $C_{12}H_{12}BrN_{3}O \cdot C_{6}H_{3}N_{3}O_{7}$ | $C_{12}H_{11}N_3 \cdot IIBr \cdot II_2O^*$ | C12H11N3 · C6H3N3O7 |             | CI31113.V3 • C6113.V3C7 | CisularsO . C.H., N.O.                           | Civilia Civilia                   | C <sub>12</sub> H <sub>10</sub> ClN <sub>3</sub> · HBr · 0,5H <sub>2</sub> O | C12H10CIN3 · C6H3N3O7             | CI2HI0BEN3  | $C_{10}H_{10}BIN_3 \cdot HC_{1} \cdot Z_{112}OT$ | C.,H.,BrN, C.H.N.O. | CoHnNS · HBr · H.Ot | C <sub>8</sub> H <sub>11</sub> N <sub>3</sub> · C <sub>6</sub> H <sub>3</sub> N <sub>3</sub> O <sub>7</sub> | C <sub>13</sub> H <sub>13</sub> N <sub>3</sub> · HBr | $C_{13}H_{13}N_3 \cdot C_6H_3N_3O_7^*$ | C13H13N3 · C6H3N3O7*          |
|                          | mp, °C            | (dec.)            | 234-236      | 215-216              | 185-186             | 243-244                                   | 993-994      | 157-158                    | 233-234*   | 184-185   | 207208                                     | 222-223             | 239240      | 012 018                 | 1017-1017  | 160-161                           | 228-229  | 224-225                           | 102-103     | 994205   | 010-210-220         | 233-234             | 206-207   | 284-285  | 209-210                                | 162-163                       |
|                          | à                 | Ŕ                 |              | C <sub>6</sub> H5    | p-CH3C6H4           | p-CH3OC6H4                                | p-CICkH4     | p-CICeH                    | p-BrC <sub>6</sub> H <sub>4</sub>                        | p-BrC <sub>6</sub> H <sub>4</sub>                 | $C_{eH_5}$                                 | CeH5                | //-CH3C6H4  | n.CH.OC.H.              | p-CH <sub>0</sub> OC <sub>6</sub> H <sub>4</sub> | p-CIC <sub>6</sub> H <sub>4</sub> | p-CIC <sub>6</sub> H <sub>4</sub>  | p-CIC <sub>6</sub> H <sub>4</sub> | p-BrCent    | p-BrCeH  | p-BrCeH,            | C.H.S               | CH3   | CH <sub>3</sub>                                      | CH <sub>3</sub>                        | C <sub>6</sub> H <sub>5</sub> |
| :                        | • ~               | ſ                 | H            | ΗI                   |                     | ΞΞ  | H            | Н                          | Н  | H:  | Ξ:   | = =                 | ΞI          | : 1                     | : II   | Н                                 | =:   | 32                                |             | ΞΞ   | H                   | Н                   | CH3   | Cens.  | CH,                                    | CH3                           |
|                          | Com -             | hinod             | а <u>1</u> , | 9 1                  |                     | dII                                       | IVa          | IVb                        | Va   | ٩٨  | VIa  |                     | VIIb        | VIIIa                   | VIIID  | XI                                | IXa  | dV.I                              | < *×        | xb<br>Xb   | Xc                  | Xla                 | XIIa  | VIIIa  | XIVa                                   | XIVb                          |

TABLE 1. 1-Methyl-3-acylalkyl-2-iminoimidazolines and Imidazo[1,2-a]imidazole Derivatives

\* The melting points were in agreement with the reported values [3].  $\ddagger$  Found: Cl 10.4%. Calculated: Cl 10.2%.  $\ddagger C_4H_3S$  is 2-thienyl. Found: S 10.5%. Calculated: S 10.6%.

1575

The structures of VI-XIV were confirmed by the IR spectra, in which, in contrast to the IR spectra of I-V, bands of the stretching vibrations of the CO group are absent.

## EXPERIMENTAL

1-Methyl-3-acylmethyl-2-iminoimidazolines (I-V, Table 1). A 0.02-mole sample of an  $\alpha$ -bromo ketone was added to a solution of 0.02 mole of 1-methyl-2-aminoimidazole [4] in 20 ml of acetone, and the mixture was refluxed for 30 min and cooled. The precipitated hydrobromide of I-V was removed by filtration and washed with acetone. The colorless crystalline substances were soluble in water and the lower alcohols. Bases I-V were oily substances. The picrates of bases I-V were obtained by the addition of an alcohol solution of picric acid to an alcohol solution of the hydrobromides of I-V.

Imidazo[1,2-a]imidazole Derivatives (VI-XIV, Table 1). A) A 0.01-mole sample of 1-methyl-2-aminoimidazole hydrochloride [4] was added to a solution of sodium ethoxide prepared from 0.01 g-atom of sodium and 20 ml of anhydrous ethanol. The solution was filtered away from the NaCl precipitate, 0.01-0.011 mole of  $\alpha$ -bromo ketone was added to the filtrate, and the mixture was refluxed for 3-4 h and cooled. The precipitated hydrobromides of bases VI-XIV were removed by filtration and washed with ether. Evaporation of the ether-alcohol mother liquors to dryness and washing of the residues with ether yielded an additional amount of the hydrobromides of VI-XIV. The colorless, crystalline substances were soluble in water and the lower alcohols. Bases IX and X were isolated by the addition of ammonium hydroxide to solutions of their hydrobromides (IXa and Xb) in methanol. The picrates of bases VI-XIV were obtained by the method used for the picrates of bases I-V.

B) A solution of 3.75 g of Va in 20 ml of ethanol, water, 85% formic acid, 98% acetic acid, 36% hydrochloric acid, or 42% hydrobromic acid was refluxed from 1.5-2 h, and the solvent (except in the case of water) was removed by vacuum distillation. The residue was dissolved in water, ammonium hydroxide was added, and the precipitate was removed by filtration and washed with water. The yield of X was 2.8-4.0 g (50-72%). Compound Va was similarly obtained in 70% yield from Ia by heating in concentrated hydrobromic acid.

C) A solution of 3.75 g of Va in 20 ml of 89% phosphoric acid, 92% sulfuric acid, or phosphorus oxychloride was allowed to stand for 24 h and poured into water. The solution was made alkaline with ammonium hydroxide, and the precipitate was removed by filtration and washed with water. The yield of X was 3.2-4.4 g (58-79%).

The compounds were purified for analysis by precipitation from ethanol solutions by the addition of ether (Ia-IIIb, IVb-Vb), from methanol by the addition of ether (XIa), from ethanol by the addition of ethyl acetate (IVa), or from methanol by the addition of ethyl acetate (VIIIa, IXa); by crystallization from ethanol (VIa, Xa-Xc, XIVa, XIVb), aqueous ethanol (XIIa), methanol (VIb-VIIb, XIIIa, and XIIIb), aqueous methanol (IX, X), or aqueous acetone (VIIIb, IXb). The  $\nu_{\rm CO}$ ,  $\nu_{\rm NH}$ , and  $\nu_{\rm OH}$  values (in reciprocal centimeters) in the IR spectra (recorded from mineral-oil suspensions with a UR-10 spectrometer) were as follows: Ia 1695 (CO), 3260 (NH); Ib 1690 (CO), 3280 (NH); IIIb 1670 (CO), 3120 (NH), 3400 (OH); IVb 1705 (CO), 3160 (NH), 3430 (OH); Va 1700 (CO), 3180 (NH); Vb 1715 (CO), 3150 (NH), 3415 (OH). We thank Yu. N. Sheinker, V. V. Kolpakova, and the co-workers of their laboratories for recording the IR spectra and performing the microanalyses.

## LITERATURE CITED

1. E. G. Knysh, A. N. Krasovskii, and P. M. Kochergin, Khim. Geterotsikl. Soedin., 1128 (1971).

- 2. A. Lawson, J. Chem. Soc., 307 (1956).
- 3. P. M. Kochergin and B. A. Priimenko, Khim. Geterotsikl. Soedin., 176 (1969).

4. B. T. Storey, W. E. Sullivan, and C. L. Moyer, J. Org. Chem., 29, 3118 (1964).

5. P. M. Kochergin and A. M. Simonov, Khim. Geterotsikl. Soedin., No. 1, 133 (1967).