

Synthesis of 5*H*-Pyrrolo[1,2-*c*]imidazole and 5*H*-Pyrrolo[1,2-*a*]imidazole

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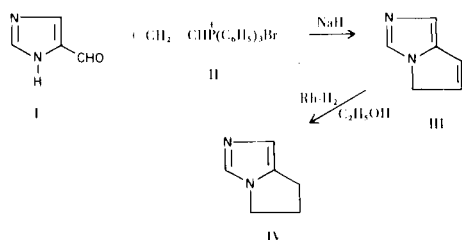
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The 5*H*-pyrrolo[1,2-*c*]imidazole (III) and 5*H*-pyrrolo[1,2-*a*]imidazole (VI) ring systems have been little explored and only hydrogenated derivatives are described in the chemical literature (1-10). A synthesis of 6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazole (IV), by intramolecular cyclization of 4-(3-bromo-*n*-propyl)imidazole has recently been reported from this laboratory (11). The present Note describes the synthesis of the parent compounds III and VI and their 6,7-dihydroderivatives.

When imidazole-4-aldehyde (I) was allowed to react with vinyltriphenylphosphonium bromide (II) in the presence of sodium hydride in a tetrahydrofuran suspension, a 64% yield of 5*H*-pyrrolo[1,2-*c*]imidazole (III) was obtained. The structure proof of compound III rests upon its conversion to the known 6,7-dihydro-5*H*-pyrrolo[1,2-*c*]imidazole (IV) (11) by catalytic hydrogenation with rhodium-on-carbon catalyst in ethanol solution (Scheme I).

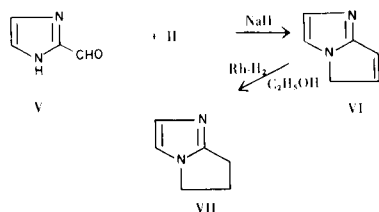
Scheme I



The 5*H*-pyrrolo[1,2-*c*]imidazole is a liquid which darkened on standing in the presence of air and rapidly converted into an unidentified compound.

In similar way by the reaction of imidazole-2-aldehyde (V) with the vinyl salt II the 5*H*-pyrrolo[1,2-*a*]imidazole (VI) was obtained in 35% yield (Scheme II).

Scheme II



Like III, the compound VI, which is solid below 28°, darkened rapidly in the presence of air and converted into an unidentified compound. The 5*H*-pyrrolo[1,2-*a*]imidazole could be hydrogenated at low pressure on rhodium to give 6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazole (VII).

The structure proposed for the synthesized products were confirmed by the elemental analyses and the ultraviolet, infrared and proton magnetic resonance spectra described in the experimental section.

EXPERIMENTAL

Melting and boiling points are uncorrected. Pmr spectra were obtained on a JEOL JNM C60-HL spectrometer (TMS as internal standard). The ir spectra were recorded with a Perkin Elmer Model 257 instrument. Uv spectra were obtained with a Unicam SP 800 spectrophotometer. Tlc was carried out on Merck F₂₅₄ silica gel plates. Spots were detected with a uv lamp ($\lambda = 254$ nm) or in iodine vapours. For column chromatography, silica gel Merck was used.

5*H*-Pyrrolo[1,2-*c*]imidazole (III).

To a suspension of 2.1 g. of sodium hydride (0.091 mole, 4.0 g. of a 53% dispersion in mineral oil) in 400 ml. of anhydrous tetrahydrofuran was added 8.55 g. (0.089 mole) of imidazole-4-aldehyde (12). The mixture was stirred and refluxed for 2 hours, then 39.7 g. (0.108 mole) of vinyltriphenylphosphonium bromide was added. The mixture was stirred and refluxed under nitrogen for 36 hours, after which the salts were removed by filtration. Removal of the organic solvent yielded a residue which was chromatographed on 2 kg. of silica gel eluting with a mixture of ethyl acetate-methanol (80:20). Evaporation of eluates containing the third component gave 6.0 g. (yield 64% based on aldehyde) of III as a tlc homogeneous oil. Distillation gave an analytical sample, b.p. 65° (0.25 mm), n_D^{20} 1.5570; uv λ max (ethanol): 273 nm ($\epsilon = 7,607$); ir ν max: 3095, 2915, 1590, 1470, 1377, 1220, 1155, 1080, 960 cm^{-1} ; nmr δ (deuteriochloroform): 4.3 (2, m, H₅), 6.3 (1, m, H₆), 6.4 (1, m, H₇), 6.5 (1, s, H₁) and 7.3 ppm (1, s, H₃).

Anal. Calcd. for C₆H₆N₂: C, 67.90; H, 5.70; N, 26.40. Found: C, 67.73; H, 5.85; N, 20.65.

Treatment of III free base with picric acid in ethanol gave the picrate which was recrystallized from ethanol, m.p. 164-165°.

Anal. Calcd. for C₁₂H₉N₅O₇: C, 42.99; H, 2.70; N, 20.89. Found: C, 43.08; H, 2.90; N, 20.65.

6,7-Dihydro-5*H*-pyrrolo[1,2-*c*]imidazole (IV).

One g. of III (9.4 mmoles) in 40 ml. of ethanol and 0.2 g. of 5% rhodium/carbon was hydrogenated at atmospheric pressure. After 5 hours the catalyst was removed by filtration and the ethanol was

evaporated. The residue was chromatographed on a silica gel column eluting with a mixture of ethyl acetate-methanol (80:20). Evaporation of eluates containing the second component gave the product in 85% yield. The structure of compound IV was confirmed by comparison (ir, nmr, tlc) with an authentic sample obtained by a different synthetic route (11).

5*H*-Pyrrolo[1,2-*a*]imidazole (VI).

This compound was prepared from imidazole-2-aldehyde (13) and vinyltriphenylphosphonium bromide using the same method as for compound III. The mixture of reaction was stirred and refluxed under nitrogen for 3 hours. The salts formed were removed by filtration; removal of the solvent yielded a residue which was chromatographed on a silica gel column with a mixture of ethyl acetate-methanol (90:10). Evaporation of eluates containing the second component gave a 35% yield of VI as oil. Distillation under nitrogen gave an analytical sample, b.p. 85° (0.55 mm), which rapidly solidifies, m.p. 28-29°: uv λ max (ethanol): 267 nm ($\epsilon = 7,350$); ir ν max: 3100, 2920, 1570, 1520, 1485, 1435, 1410, 1270, 1170, 1122, 1080, 965, 930, 740, 670 cm^{-1} ; nmr δ (deuteriochloroform): 4.25 (2, pseudo s, H₅), 6.06 (2, pseudo s, H₆ and H₇), and 7.03 ppm (2, pseudo s, H₂ and H₃).

Anal. Calcd. for C₆H₆N₂: C, 67.90; H, 5.70; N, 26.40. Found: C, 67.71; H, 5.58; N, 26.13.

6,7-Dihydro-5*H*-pyrrolo[1,2-*a*]imidazole (VII).

To a solution of 1 g. of VI (9.4 mmoles) in 40 ml. of ethanol was added 0.2 g. of 5% rhodium/carbon. The mixture was hydrogenated at atmospheric pressure for 48 hours. The catalyst was removed by filtration and the ethanol was evaporated. The residue was chromatographed on a silica gel column eluting with a mixture of ethyl acetate-methanol (80:20). Evaporation of eluates containing the second component gave an hygroscopic solid (0.7 g., 68% yield);

m.p. 43-44°: ir ν max (nujol): 3090, 1520, 1500, 1290, 1267, 1140, 1100, 1055, 940, 720, 665 cm^{-1} ; nmr δ (deuteriochloroform): 2.60 (4, m, H₆ and H₇); 3.88 (2, t, H₅), 6.80 and 6.95 ppm (2, dd, J = 1.5 Hz, H₂ and H₃).

Treatment of VII free base with picric acid in ethanol gave the picrate which was recrystallized from ethanol, m.p. 156-158°.

Anal. Calcd. for C₁₂H₁₁N₅O₇: C, 42.73; H, 3.28; N, 20.76. Found: C, 42.56; H, 3.08; N, 20.51.

REFERENCES

- (1) N. M. Bortnick and M. F. Fegley, U.S. Patent 2,957,885 (1960); *Chem. Abstr.*, 55, 4535 h (1933).
- (2) R. G. Glushkov and O. Y. Magidson, *Zh. Obshch. Khim.*, 31, 1906 (1961).
- (3) D. W. Henry and D. R. Hoff, Belgian Patent 661,262 (1965); *Chem. Abstr.*, 64, 20944 (1966).
- (4) M. W. Gittos and W. Wilson, *J. Chem. Soc.*, 877 (1962).
- (5) J. R. Geigy A.-G. Belgian Patent 659,530 (1965); *Chem. Abstr.*, 64, 6664f (1966).
- (6) W. J. Houlihan, U.S. Patent 3,334,099 (1967); *Chem. Abstr.*, 69, 96769f (1968).
- (7) H. Wollweber, *Angew. Chem. Int. Ed. Engl.*, 8, 69 (1969).
- (8) H. Wollweber, J. Kurz, W. Naegele, *Arch. Pharm.*, 304, 774 (1971).
- (9) C. A. Grob and P. Ankli, *Helv. Chim. Acta*, 33, 658 (1950).
- (10) N. A. Kogan, I. M. Nurova; I. Kh Fel'dman, *Khim. Farm. Zh.*, 3, 12 (1969).
- (11) P. Franchetti, M. Grifantini, S. Martelli and M. L. Stein, *Farmaco, Ed. Sci.*, 29, 309 (1974).
- (12) W. Hubball and F. L. Pyman, *J. Chem. Soc.*, 21 (1928).
- (13) H. Schubert and H. C. Rudolf, *Angew. Chem. Int. Ed. Engl.*, 5, 674 (1966).