

New Synthesis of Condensed Hydropyridazine Derivatives V.

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The reactivity of pyrrole derivatives towards the semicarbazone of ω -bromoacetophenone has been reported. Substituents at position 1 of the pyrrole ring greatly affect the course of the reaction. 1,4,4a,4b,5,8,8a,8b-Octahydro-9H-pyrrolo[2,3-c:4,5-c']dipyridazine derivative or α - and α,α -pyrrolyl derivatives were obtained depending on the substituents. The structures reported were assigned on the basis of satisfactory analytical and spectroscopic data.

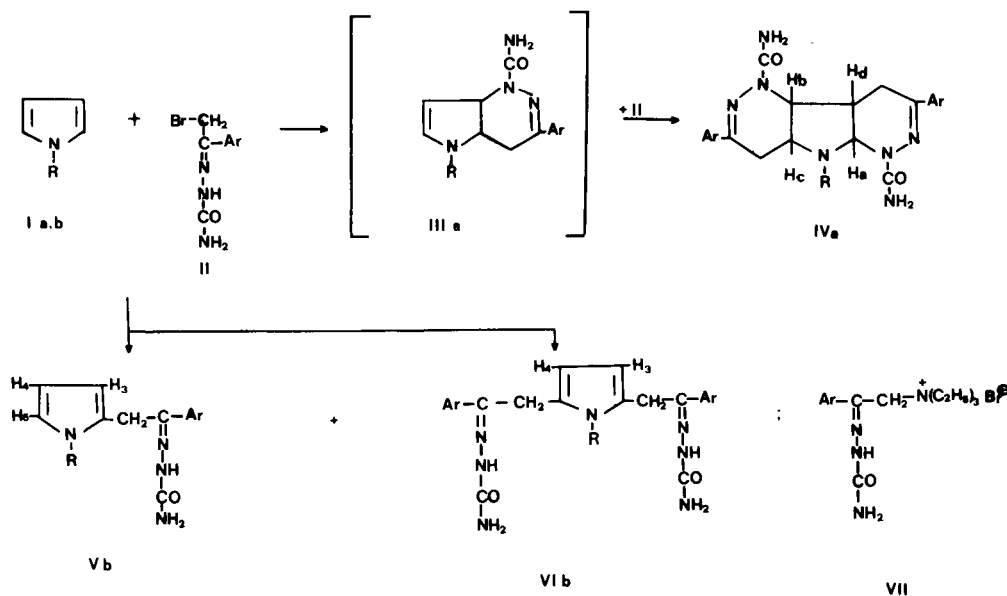
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The synthetic utility of the semicarbazone of ω -bromoacetophenone in obtaining condensed hydropyridazine derivatives is documented by a number of recent publications (1-4) from these laboratories.

We wish to report here the isolation of some reaction products obtained from pyrroles Ia,b and II, whose structures were established by spectroscopic and analytical

means. We have found that *N*-methylpyrrole and II react in chloroform in the presence of triethylamine to give, as a major side-reaction, a product formulated as the semicarbazone of phenacyltriethylammonium bromide (VII). However, after the removal of VII and concentration *in vacuo*, the filtrate afforded a mixture from which a compound of formula $C_{23}H_{25}N_7O_2$ and $M^+ = 431$ was iso-

Scheme



lated to which we assigned structure IVa. In the nmr spectrum the low δ value of N-CH₃ protons at 2.36, compared with that of the same protons of *N*-methylpyrrole (3.50 δ) (5) indicated the absence of a ring current. The four protons of the pentatomic ring showed different chemical shifts: H_a (d) at 5.50 δ , H_b (t) at 4.35 δ , H_c (m) at 3.40 δ and H_d (m) at 2.88 δ . This fact can be explained by supposing the four protons were in different chemical environments. Moreover, double resonance experiments were employed for determining the relative positions of protons H_a, H_b, H_c, and H_d in IVa.

Thus, by irradiating at 2.88 δ the doublet at 5.50 δ and the triplet at 4.35 δ were simplified to a singlet and doublet respectively, so that the doublet at 5.50 δ must be the H_a absorption downfield since this proton was the most deshielded by the nitrogen atoms and the triplet at 4.35 δ must be the H_b absorption. In fact this triplet became a doublet by irradiating at 3.40 δ that must be regarded as the H_c shift.

Then the signal at 2.88 δ must be the H_d absorption. The ir spectrum showed carbonyl bands at 1670-1680 cm⁻¹ and the multiple bands in the 3 μ region (NH₂).

The formation of IVa can be outlined as follows: (See scheme).

In the intermediate IIIa, that can be formed by initial electrophilic attack of II in the α -position of the *N*-methylpyrrole nucleus, the β position of the cyclic enamine double bond, that became very reactive, undergo further reaction with II to form IVa.

Pyrrole Ib, when treated with II, afforded a complex reaction mixture from which products Vb and VIb have been isolated.

Attempts made to obtain tricyclic material of the pyrrolopyridazine structure failed. The assigned structures Vb and VIb are based upon elemental data and spectroscopic evidence (nmr, ms, ir).

Both products showed pyrrole CH signals indicating an α and an α,α' substitution and a NH absorption at 9.30 δ , exchangeable with deuterium oxide, unequivocally attributable at the -N=NH of a semicarbazone structure.

Further investigation of the scope and limitations of these reactions is in progress.

EXPERIMENTAL

Melting points were determined on Buchi-Tottoli apparatus and are uncorrected. Ir spectra were determined in nujol mulls with a Perkin-Elmer Infracord 137 spectrophotometer; the nmr spectra (DMSO-d₆) were obtained with a Jeol C-60 H spectrometer (TMS as internal reference). A 270 Perkin-Elmer mass spectrometer was employed for determination of low resolution 70 ev mass spectra.

4,8-Dicarbamoyl-2,6-diphenyl-9-methyl-1,4,4a,4b,5,8,8a,8b-octa-hydropyrrolo[2,3-*c*:4,5-*c'*]dipyridazine (IVa).

N-Methylpyrrole (20 mmoles) was dissolved in 200 ml. of dry chloroform and 40 mmoles of the semicarbazone of ω -bromoacetophenone (II) was added. Triethylamine (40 mmoles) was added in one portion and the mixture was then refluxed for 1½ hours. After cooling, the precipitate, the semicarbazone of phenacyltriethylammonium bromide (7.2 g.), was collected and recrystallized, m.p. 178-180° dec., (ethanol-ether); ir: 1720 cm⁻¹ (CO) and multiple bands in the 3 μ region (NH, NH₂); nmr δ : 1.00-1.40 (9H, m, 3 x CH₃) 3.00-3.50 (6H, m, 3 x CH₂) 4.40 (2H, s, CH₂) 6.58 (2H, s, NH₂) 7.50-7.80 (5H, m, C₆H₅) 9.00 (1H, s, NH).

Anal. Calcd. for C₁₅H₂₅BrN₄O: C, 50.75; H, 7.05; N, 15.68. Found: C, 50.69; H, 6.67; N, 15.55.

The filtrate was concentrated under reduced pressure and 50 ml. of methanol-water (4:1) was added. After standing overnight IVa as a white crystalline product (370 mg.) was obtained, m.p. 274-276° (ethanol); molecular weight by mass spectrometry *m/e*, 431; ir: 1670-1680 cm⁻¹ (CO) and multiple bands in the 3 μ region (NH₂); nmr δ : 2.36 (3H, s, CH₃) 2.10-3.00 [5H, m, (2 x CH₂ + H_d)] 3.40 (1H, m, H_c) 4.35 (1H, t, H_b; [J_{bd} + J_{bc}] = 11.5 Hz) 5.50 (1H, d, H_a; J = 8.5 Hz) 6.50 (2H, s, NH₂) 6.70 (2H, s, NH₂) 7.30-7.80 (10H, m, 2 x C₆H₅).

Anal. Calcd. for C₂₃H₂₅N₇O₂: C, 64.02; H, 5.84; N, 22.72. Found: C, 63.95; H, 5.84; N, 22.57.

The mother liquors were concentrated to dryness under reduced pressure and a mixed product lacking the elements of *N*-methylpyrrole was obtained. However, purification and rigorous proof of the byproducts were not pursued.

2,5-Diphenacylpyrrole Disemicarbazone (VIb) and 2-Phenacylpyrrole Semicarbazone (Vb).

Pyrrole (20 moles) and the semicarbazone of ω -bromoacetophenone (II) (40 mmoles) were reacted in the same manner as described above. In this case formation of bromide VII was not observed. The resultant solution was evaporated under reduced pressure and 50 ml. of methanol-water (4:1) was added. After standing overnight a white crystalline product (VIb) (830 mg.) was obtained, m.p. 233-235° (ethanol); molecular weight by mass spectrometry *m/e*, 417; ir: 1670-1690 cm⁻¹ (CO) and multiple bands in the 3 μ region (NH, NH₂); nmr δ : 4.00 (4H, s, 2 x CH₂) 5.40 (2H, d, H₃ + H₄; J = 2.2 Hz) 6.47 (4H, s, 2 x NH₂) 7.00-8.00 (10H, m, 2 x C₆H₅) 9.30 (2H, s, 2 x =N-NH) 10.35 (broad, NH).

Anal. Calcd. for C₂₂H₂₃N₇O₂: C, 63.27; H, 5.56; N, 23.50. Found: C, 63.56; H, 5.37; N, 23.47.

The mother liquors were concentrated to dryness under reduced pressure and the resultant yellow-brown gum was chromatographed on a column (25 x 3 cm) of silica gel with 15% of water (80 g.). Elution with ethyl-acetate (F₅₋₁₀, each 50 ml.) removed 2-phenacylpyrrole semicarbazone (Vb) as a white crystalline product after several recrystallizations from benzene (80 mg.), m.p. 184-187° (benzene); molecular weight by mass spectrometry *m/e*, 242; ir: 1680 cm⁻¹ (CO) and multiple bands in the 3 μ region (NH, NH₂); nmr δ : 4.03 (2H, s, CH₂) 5.50-5.92 (2H, m, H₃ + H₄) 6.50 (3H, m, H₅ + NH₂) 7.20-8.20 (5H, m, C₆H₅) 9.30 (1H, s, =N-NH) 10.50 (broad, NH).

Anal. Calcd. for C₁₃H₁₄N₄O: C, 64.43; H, 5.83; N, 23.14. Found: C, 64.59; H, 5.86; N, 23.12.

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