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AZAINDOLE DERIVATIVES

LIII.* NEW METHOD FOR THE SYNTHESIS OF 6-CHLORO-5-AZAINDOLINE

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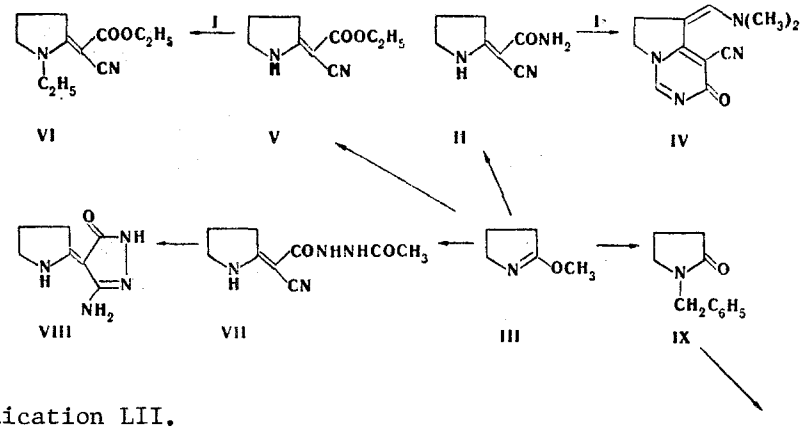
1-Benzyl-6-hydroxy-7-cyano-5-azaindoline, which was converted to 6-chloro-5-azaindoline through 6-hydroxy-5-azaindoline, was synthesized from O-methylbutyrolactim through 1-benzyl-2-pyrrolidone, 1-benzyl-2-cyano(carbamoylmethylene)pyrrolidine, and the product of its condensation with dimethylformamide diethylacetal.

The reaction of dimethylformamide diethylacetal (I) with 1-methyl-2-(cyanocarbamoylmethylene)pyrrolidine takes place at the amide NH_2 group to give the corresponding acylformamidine, which is readily cyclized to 1-methyl-6-hydroxy-7-cyano-5-azaindoline [2]. In order to synthesize pyrroline-nitrogen-unsubstituted 5-azaindoline derivatives by a similar method we studied the condensation with I of 2-(cyanocarbamoylmethylene)pyrrolidine (II), obtained by reaction of O-methylbutyrolactim (III) with cyanoacetamide.

However, the reaction of II with acetal I proceeded in a different way than the reaction with its N-methyl substituted derivative. Condensation took place at the amide nitrogen atom with closing of a pyrimidine ring through the NH group of the pyrrolidine ring and at the 3 position of the pyrrolidine fragment. The only reaction product, which was isolated in 74% yield, was 1-dimethylaminomethylene-7-oxo-8-cyano-1,2,3,7-tetrahydro-6-azaindolizine (IV).



*See [1] for communication LII.

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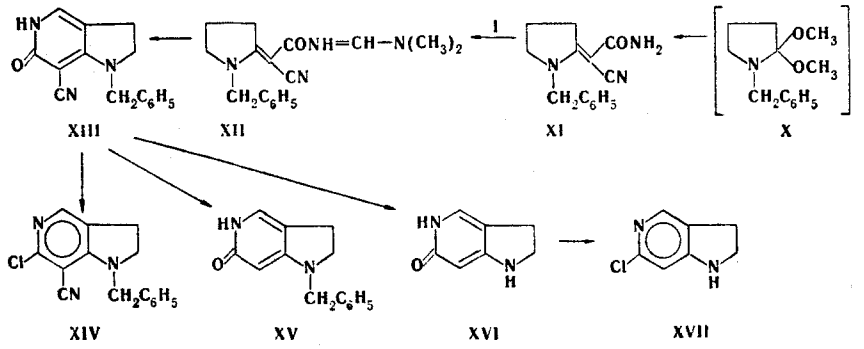

The ability of the ring-nitrogen-atom-unsubstituted pyrrolidine II to undergo condensation with I at the methylene group in the 3 position compelled us to check the possibility of the construction of a 5-azaindoline system on the basis of 2-(cyanocarbethoxymethylene)-pyrrolidine (V), in which closing of a pyrimidine ring of the IV type is excluded. Compound V was obtained by condensation of lactim III with cyanoacetic ester and was subjected to reaction with acetal I under various conditions — in refluxing xylene, in xylene under pressure at 180 and 200°C, and in tetralin at 200°C. We did not observe condensation at the 3 position of the pyrroline ring in any case, and pyrrolidine V underwent ethylation only to give 1-ethylpyrrolidine VI. In order to avoid alkylation of V we attempted to protect the NH group by acetylation with acetic anhydride (by refluxing for 6 h) or with acetyl chloride (by refluxing for 5 h) or by conversion to a urea derivative by reaction with methyl isocyanate [in dimethylformamide (DMF) at 20 and 100°C]. However, pyrrolidine V was recovered unchanged in all cases [according to the results of analysis by gas–liquid chromatography (GLC) and preparative isolation].

Another possibility for directing the process to closing of a 5-azaindoline system and excluding the formation of **6-azaindolizine** derivatives of the IV type could be condensation with acetal I of acetylhydrazide VII instead of with amide II. Compound VII was obtained from lactim III and N-cyanoacetyl-N'-acetylhydrazine. However, when hydrazide VII was heated in DMF, it underwent cyclization to pyrazolone VIII considerably more readily than reaction with acetal I.

In this connection, for construction of 1-unsubstituted 5-azaindoline derivative we used benzyl protection of the nitrogen atom of the pyrrolidine ring. Lactim III was alkylated with benzyl chloride, and the resulting 1-benzyl-2-pyrrolidone (IX) was converted to acetal X by methylation with dimethyl sulfate and subsequent treatment with sodium methoxide; acetal X was converted, without isolation, to 1-benzyl-2-(cyanocarbamoylmethylene)pyrrolidine (XI) by reaction with cyanoacetamide. The condensation of XI with acetal I gave acylformamidine XII in quantitative yield, which was easily cyclized to 1-benzyl-6-hydroxy-7-cyano-5-azaindoline (XIII) in 83% yield by heating.

The production of 5-azaindoline derivative XIII with functional substituents in the 6 and 7 positions by a relatively simple scheme and in good yield opens up extensive possibilities for the preparation of various substituted 5-azaindoles. Thus, for example, the reaction of oxo cyano derivative XIII with phosphorus oxychloride gave chloro nitrile XIV in almost quantitative yield. The nitrile group is not saponified when azaindoline XIII is refluxed with 7% aqueous sodium hydroxide (for 5 h) or with 15% hydrobromic acid (for 5 h). However, refluxing the oxo nitrile with concentrated hydrobromic acid results not only in elimination of the cyano group as a result of saponification and subsequent **decarboxylation,** but also in simultaneous elimination of the benzyl group, which departs in the form of benzyl bromide. The products of this reaction were 1-benzyl-6-hydroxy-5-azaindoline (XV) and 6-hydroxy-5-azaindoline (XVI). It is interesting to note that cleavage of the benzyl group does not occur when decyanated 1-benzyl-5-azaindoline XV is treated under the same conditions with concentrated hydrobromic acid.

Reaction of 6-hydroxy-5-azaindoline (XVI) with phosphorus oxychloride gave 6-chloro-5-azaindoline (XVII), which we previously synthesized [3] by a more complex scheme from **butyrolactone and malonyl chloride.**

EXPERIMENTAL

The IR spectra were recorded with a UR-10 spectrometer. The PMR spectra were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. The molecular weights were determined with an MKh-1303 mass spectrometer with introduction of the samples into the ion source at 12 eV.

2-(Cyanocarbamoylmethylene)pyrrolidine (II). A mixture of 5.45 g (55 mmole) of lactim III and 4.2 g (50 mmole) of cyanoacetamide was heated at 120°C for 3 h, during which the mixture initially became homogeneous, after which it solidified. Treatment with dry isopropyl alcohol gave 4.85 g (55%) of colorless crystals of pyrrolidine II with mp 220-221°C (from DMF). The product was only slightly soluble in water, ether, benzene, acetone, and alcohols. IR spectrum: 3430, 3340, 3280 (NH, NH_2); 2200 (C≡N); 1645 cm^{-1} (C=O). Found, %: C 55.6; H 5.8; N 27.7. $C_7H_9N_3O$. Calculated, %: C 55.7; H 5.9; N 27.8.

1-Dimethylaminomethylene-7-oxo-8-cyano-1,2,3,7-tetrahydro-6-azaindolizine (IV). A solution of 1 g (6.6 mmole) of pyrrolidine II and 1.22 g (8.3 mmole) of acetal I in 25 ml of dry toluene was refluxed for 1 h, after which 0.4 g (2.7 mmole) of acetal I and 25 ml of toluene were added, and the mixture was refluxed for another 3.5 h. It was then cooled and filtered to give 1.06 g (74%) of azaindolizine IV with mp 284-285°C (from DMF). IR spectrum: 2200 (C≡N) and 1600 cm^{-1} (C=O). PMR spectrum (in d_6-DMSO), δ: 3.12 [s, $N(CH_3)_2$], 4.10 (m, 2-H, 3-CH_3), 7.86 (s, 1'-H), and 8.14 ppm (s, 5-H). Found, %: C 61.0; H 5.6; N 25.9. $C_{11}H_{12}N_4O$. Calculated, %: C 61.1 H 5.6; N 25.9.

2-(Cyanocarbethoxymethylene)pyrrolidine (V). A mixture of 11.89 g (130 mmole) of lactim III and 14.0 g (124 mmole) of cyanoacetic ester was heated at 120°C for 3 h, after which it was cooled, and the crystallized reaction mass was treated with a mixture of 20 ml of benzene and 10 ml of heptane and filtered to give 13.1 g (61%) of pyrrolidine V with mp 159-160°C (from benzene). IR spectrum: 3340 (NH), 2210 (C≡N), and 1670 cm^{-1} (C=O). Found, %: C 60.1; H 6.8; N 15.6%. $C_9H_{12}N_2O_2$. Calculated, %: C 60.0; H 6.7; N 15.6.

1-Ethyl-2-(cyanocarbethoxymethylene)pyrrolidine (VI). A solution of 5.61 g (31.2 mmole) of pyrrolidine V and 4.3 g (29 mmole) of acetal I in 150 ml of dry xylene was refluxed in a stream of argon for 5 h, during which the reaction was monitored by GLC [with a Pye-Unicam 104 chromatograph with a catharometer and a 2.1 m by 4 mm column filled with 10% SE-30 silicon elastomer on silanized diatomaceous earth (100-120 mesh); the helium flow rate was 30 ml/min, the temperature was 250°C, and the retention times were 3 min for V and 4 min for VI]. Another 2.56 g (17.4 mmole) of acetal I was added, the mixture was refluxed for 8 h, another 0.85 g (5.8 mmole) of acetal I was added, the mixture was refluxed for 5 h, and the xylene was then removed by vacuum distillation. The residue was sublimed at 120-125°C (3 mm) to give 5.25 g of pyrroldine VI with mp 64-65°C. IR spectrum: 2192 (C≡N) and 1685^{-1} (C=O). Found, %: C 63.0; H 7.9; N 13.4; M 208. $C_{11}H_{16}N_2O_2$. Calculated, %: C 63.4; H 7.7; N 13.4; M 208.

2-(Cyanocarbacetylhydrazidomethylene)pyrrolidine (VII). A mixture of 4 g (40 mmole) of lactim III and 4.44 g (31.5 mmole) of N-cyanoacetyl-N'-acetylhydrazine was heated at 120°C for 3 h, after which it was cooled, and triturated with 30 ml of absolute alcohol to give 4 g (61%) of hydrazide VII with mp 192-193°C (from DMF). IR spectrum: 3430, 3250, 3050 (NH); 2210 (C≡H); 1688 ($COCH_3$); 1645 cm^{-1} (CO). Found, %: C 48.2; H 6.1; N 25.2; H_2O 7.2. $C_9H_{12}N_4O_2 \cdot H_2O$. Calculated, %: C 47.8; H 6.2; N 24.8; H_2O 8.0.

When the reaction was carried out in DMF, 5-amino-4,2-(pyrrolidinylidene)-3-pyrazolone (VIII), with mp 294-295°C (dec., from DMF), was obtained. IR spectrum: 3370, 3305, 3215, 3140 (NH, NH_2); 1625 cm^{-1} (C=O). PMR spectrum (in CF_3COOH): 2.48 (m, 4-H), 3.42 (m, 3-H), and 4.09 ppm (m, 5-H). Found, %: C 50.8; H 6.4; N 33.8; M 166. $C_7H_{10}N_4O$. Calculated, %: C 50.6; H 6.1; N 33.8; M 166.

1-Benzyl-2-(cyanocarbamoylmethylene)pyrroldine (XI). A mixture of 107 g (0.62 mole) of 1-benzyl-2-pyrrolidone (IX) [bp 110-120°C (3 mm) and n_D^{20} 1.5484; obtained in 64% yield by refluxing lactim III with benzyl chloride] and 78 g (0.62 mole) of dimethyl sulfate was heated at 100°C for 2 h, after which it was cooled to 0°C and treated, with vigorous stirring, with a cooled (to 0°C) solution of sodium methoxide, obtained from 14.1 g (0.62 mole) of sodium and 200 ml of methanol. The cooling bath was removed, the reaction mixture was stirred for 2 h, and the precipitate was removed by filtration and washed with 200 ml of methanol. A 52-g (0.62 mole) sample of cyanoacetamide was added to the combined filtrates,

and the reaction mixture was heated to the boiling point, cooled, and allowed to stand overnight at 20°C. The red solution was then evaporated *in vacuo*, and the residue was treated with 150 ml of water and 100 ml of ether. The mixture was shaken for 30 min, and the colorless precipitate was removed by filtration and washed with 200 ml of water and 100 ml of ether to give 37 g (25%) of pyrrolidine XI with mp 155-156°C (from alcohol). IR spectrum: 3370, 3170 (NH_2); 2180 (C≡N); 1660 cm^{-1} (C=O). Found, %: C 69.8; H 6.4; N 17.6%. $C_{14}H_{15}N_3O$. Calculated, %: C 69.8; H 6.3; N 17.4. The ether layer in the water–ether filtrate was separated, the aqueous layer was extracted with ether, and the combined ether extracts were dried and vacuum distilled to give 16 g (15%) of pyrrolidone IX with bp 110-120°C (3 mm) and n_D^{20} 1.5484.

1-Benzyl-2-[cyano(N-dimethylaminomethylene)carbamoylmethylene]pyrrolidine (XII). A mixture of 58 g (0.24 mole) of pyrrolidine XI and 99 g (0.67 mole) of acetal I was refluxed for 3 h, after which it was cooled, and the crystals were removed by filtration and washed with benzene to give 52.6 g of formamidine XII. Evaporation of the mother liquor gave an additional 19.65 g of XII for an overall yield of 100%. The product had mp 144.5-145.5°C (from xylene). IR spectrum: 2180 (C≡N) and 1628 cm^{-1} (C=O). Found, %: C 68.8; H 6.9; N 19.1%. $C_{17}H_{20}N_4O$. Calculated, %: C 68.8; H 6.8; N 18.9.

1-Benzyl-6-hydroxy-7-cyano-5-azaindoline (XIII). A molten 52.6 g (0.177 mole) sample of formamidine XII was maintained at 175°C in an argon atmosphere for 10 min and at 200°C for 30 min, after which it was cooled and triturated with 50 ml of absolute isopropyl alcohol to give 37.1 g (83%) of azaindoline XIII with mp 295-296°C. IR spectrum: 3260, 3130 (NH); 2220 (C≡N); 1630 cm^{-1} (CO). Found, %: C 71.7; H 5.3; N 16.7. $C_{15}H_{13}N_3O$. Calculated, %: C 71.7; H 5.2; N 16.7.

1-Benzyl-6-chloro-7-cyano-5-azaindoline (XIV). A mixture of 10 g (40 mmole) of hydroxyazaindoline XIII and 50 ml of distilled phosphorus oxychloride was refluxed for 5 h, after which it was evaporated *in vacuo*, and the residue was treated with 20 ml of water and 50 ml of chloroform. The mixture was made alkaline with potassium carbonate, and the aqueous layer was separated and extracted with chloroform (three 20-ml portions). The combined chloroform extracts were dried with magnesium sulfate and vacuum evaporated to give 10.65 g (99%) of XIV with mp 131-132°C. IR spectrum: 2210 cm^{-1} (C≡N). Found, %: C 67.0; H 4.6; Cl 12.8; N 15.8%. $C_{15}H_{12}ClN_3$. Calculated: C 66.8; H 4.5; Cl 13.1; N 15.6%.

6-Hydroxy-5-azaindoline (XVI). Concentrated hydrobromic acid (80 ml) was added to 7.25 g (29 mmole) of nitrile XIII, and the mixture was refluxed for 5.5 h with slow removal of the hydrobromic acid by distillation [extraction of the distillate with ether gave 4.1 g (83%) of benzyl bromide, which was identified by comparison of its IR spectrum with the spectrum of an authentic sample]. The residue after removal of the hydrobromic acid by distillation (the last portions were removed by vacuum distillation) was mixed with 30 ml of water, 50 ml of chloroform, and 5 ml of 50% aqueous potassium carbonate solution. After 3 h, the precipitate was removed by filtration and washed with 50 ml of water and 30 ml of chloroform. The chloroform layer was separated, and the aqueous layer was extracted with chloroform (three 50-ml portions). The combined chloroform extracts were dried with magnesium sulfate and vacuum evaporated to give 0.5 g (8%) of azaindoline XV, which was identified by direct comparison with an authentic sample of 1-benzyl-6-hydroxy-5-azaindoline [3]. The precipitate remaining after washing with water and chloroform was identified as azaindoline XVI [3 g (76%)] with mp 287-288°C (dec., from DMF). IR spectrum: 3210, 3140 (NH); 1620 cm^{-1} (C = O). Found, %: C 61.4; H 5.7; N 20.6; M 136. $C_7H_8N_2O$. Calculated, %: C 61.7; H 5.9; N 20.6; M 136.

6-Chloro-5-azaindoline (XVII). A mixture of 2 g (16 mmole) of hydroxyazaindoline XVI and 30 ml of phosphorus oxychloride was refluxed for 3.5 h, after which it was vacuum evaporated, and the residue was treated with 30 ml of water and 30 ml of chloroform, and the mixture was made alkaline with respect to phenolphthalein with potassium carbonate. The mixture was filtered, and the aqueous layer was separated, washed with chloroform, and acidified to pH 1 with hydrochloric acid. The acidic aqueous solution was heated to the boiling point, cooled, and carefully made alkaline to pH 7 with potassium carbonate. The precipitated XVII was removed by filtration and recrystallized from ethyl acetate to give 0.8 g (35%) of product with mp 115-116°C. No melting-point depression was observed for a mixture of a sample of the product with an authentic sample [3]. The IR spectra of the two samples were identical.

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RESEARCH ON 1-AZA TWO-RING SYSTEMS.

XVII.* SYNTHESIS OF 5-(γ-HYDROXYPROPYL)-1,2-DIHYDROPYRROLIZINES AND PROPERTIES OF THEIR INTRAMOLECULAR π-HYDROGEN BONDS

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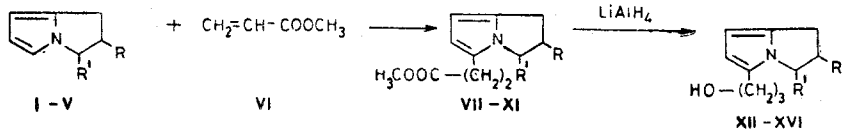
Reduction of 5-[2-(methoxycarbonyl)ethyl]-1,3-dihydropyrrolizines with lithium aluminum hydride gave 5-(γ-hydroxypropyl)-1,2-dihydropyrrolizines (in 70-90% yields), which have intramolecular π-hydrogen bonds in dilute solutions. The parameters of the π-hydrogen bonds were determined in the IR spectra, and their enthalpies were found. The data obtained ($\Delta\nu_{OH}$ 95-99 cm^{-1}, $-\Delta H$ 3.05 $kJ \cdot mole^{-1}$) show that among compounds with an aliphatic hydroxyl group and a system of π electrons, 5-(γ-hydroxypropyl)-1,2-dihydropyrrolizines have some of the strongest intramolecular π-hydrogen bonds.

We have previously obtained and investigated 5-hydroxymethyl- [2] and 5-(β-hydroxyethyl)-1,2-dihydropyrrolizines [3, 4]. In the present communication we describe the synthesis of 5-(γ-hydroxypropyl)-1,2-dihydropyrrolizines and the results of a study of the properties of their intramolecular π-hydrogen bonds.

Instances of nonselective substitution reactions of 1,2-dihydropyrrolizines are known [3, 5]. In the present research we therefore monitored the isomeric purity of the products of the reaction of 1,2-dihydropyrrolizines I-V with methyl acrylate (VI) — 5-[2-(methoxycarbonyl)-ethyl]-1,2-dihydropyrrolizines VII-XI (Table 1) — which are starting compounds for the synthesis of 5-(γ-hydroxypropyl)-1,2-dihydropyrrolizines XII-XVI.



I, VII, XII R = R' = H ; II, VIII, XIII R = CH_3, R' = H ; III, IX, XIV R = H, R' = CH_3 ; IV, X, XV R = C_2H_5, R' = H ; V, XI, XVI R = H, R' = $C(CH_3)_3$

Analysis of the PMR spectra of the products of the first reaction shows that, in contrast to the cases described in [3, 5], a substituent is incorporated virtually only in the 5 position of the dihydropyrrolizines.

In order to investigate the intramolecular π-hydrogen bonds in 1,2-dihydropyrrolizine systems with a hydroxyl group three methylene links away from the ring we subjected VII-XI to reduction with lithium aluminum hydride to alcohols XII-XVI (Table 2). A study of the

*See [1] for communication XVI.

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