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# SYNTHESIS OF 5H-PYRIDAZO[4,5-b]INDOLES BY CONDENSATION OF 2-ACYLINDOLE-3-CARBOXYLIC ACIDS WITH HYDRAZINE

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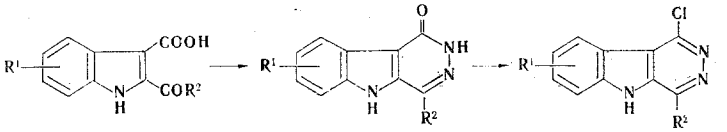
5H-Pyridazo[4,5-b]indol-1-ones were obtained by heating 2-acetylindole-3- or 2-aroylindole-3-carboxylic acids with hydrazine hydrate in ethylene glycol or alcohol. 1-Chloro-5H-pyridazo[4,5-b]indoles are formed by treatment of 5H-pyridazo[4,5-b]indol-1-ones with phosphorus oxychloride.

Some pyridazine derivatives have found practical application as medicinals. In particular, this is true of Apressin and Nepressol, which have strong hypotensive action. In our search for new compounds of this type we turned to condensed indole and pyridazone systems; such compounds can be regarded as aza analogs of carbolines, the ring system of which lies at the foundation of many substances with high physiological activity.

Only a few methods are known for the synthesis of condensed indole and pyridazine systems; a small number of papers in which 2,3- or 2-carbonyl derivatives of indole are used as the starting compounds have been published [1-8]. Up until now, 5H-pyridazo[4,5-b]-indol-1-ones (I-XII) have remained undescribed; this is evidently explained by the lack of convenient methods for the synthesis of the starting compounds. We have found that I-XII can be obtained by condensation of the recently described 2-acylindole-3-carboxylic acids [9-11] with hydrazine hydrate. Their structures were confirmed by reaction with phosphorus oxychloride, as a result of which 1-chloro-5H-pyridazo[4,5-b]indoles (XIII-XVII) are formed, and also by data from their IR spectra.



I–XII XIII–XVII

I, XIII $R^1$=H, $R^2$=$C_6H_5$; II, XIV $R^1$=H, $R^2$=$C_6H_4Cl$-*p*; III, XV $R^1$=H, $R^2$=$C_6H_4Br$-*p*; IV, XVI $R^1$=8-Br, $R^2$=$C_6H_5$; V, XVII $R^1$=6-$CH_3$, $R^2$=$C_6H_5$; VI $R^1$=8-Br, $R^2$=$C_6H_5Cl$-*p*; VII $R^1$=8-$OCH_3$, $R^2$=$C_6H_5$; VIII $R^1$=H, $R^2$=$CH_3$; IX $R^1$=8-$CH_3$, $R^2$=$CH_3$; X $R^1$=6-$CH_3$, $R^2$=$CH_3$; XI $R^1$=8-Br, $R^2$=$CH_3$; XII $R^1$=8-Cl, $R^2$=$CH_3$

The IR spectra of I-XII contain intense peaks of an amide carbonyl group at 1635-1645 $cm^{-1}$. The intensities of the bands in the indicated region are weak in the spectra of the products of treatment of I-VII with phosphorus oxychloride (these bands are evidently due to absorption of the pyridazine ring C=N bond); this is due to disappearance of the absorption of the carbonyl group and makes it possible to conlude that I-XII have lactam (rather than lactim) structures. The stretching vibrations of the NH group of the indole ring of I-IX, XI, and XII are found at 3130-3170 $cm^{-1}$, which corresponds to the intervals presented for the absorption of the NH group of 3-acylindoles [12]. The methyl group attached to the $C_6$ atom

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TABLE 1. Principal Characteristics of the Pyridazo[4,5-b]-indol-1-ones

| Compound | mp, °C | IR spectrum, $cm^{-1}$ | Found, % | | | | Empirical formula | Calculated, % | | | | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | C | H | Hal | N | | C | H | Hal | N | |
| I | 301—302 | 3170, 3080, 1640 (s) | 73,7 | 3,9 | — | 16,1 | $C_{16}H_{11}N_3O$ | 73,6 | 4,2 | — | 16,1 | 66 |
| II | 358—360 | 3170, 3070, 1645 (s) | 64,7 | 3,3 | 12,3 | 14,1 | $C_{16}H_{10}ClN_3O$ | 65,0 | 3,4 | 12,0 | 14,2 | 67 |
| III | 362—364 | 3150, 3050, 1645 (s) | 56,1 | 2,8 | 23,1 | 12,2 | $C_{16}H_{10}BrN_3O$ | 56,5 | 2,9 | 23,5 | 12,3 | 72 |
| IV | 347—348 | 3170, 3070, 1645 (s) | 56,1 | 2,7 | 23,2 | 12,2 | $C_{16}H_{10}BrN_3O$ | 56,5 | 2,9 | 23,5 | 12,3 | 54 |
| V | 330—332 | 3160, 3070, 1645 (s) | 73,9 | 4,6 | — | 15,0 | $C_{17}H_{13}N_3O$ | 74,2 | 4,7 | — | 15,3 | 59 |
| VI | 363—366 | 3170, 3080, 1645 (s) | 51,0 | 2,3 | 30,5 | 11,0 | $C_{16}H_9BrClN_3O$ | 51,3 | 2,4 | 30,8 | 11,2 | 50 |
| VII | 320—321 | 3150, 3070, 1640 (s) | 70,3 | 4,5 | — | 14,2 | $C_{17}H_{13}N_3O_2$ | 70,1 | 4,5 | — | 14,4 | 71 |
| VIII | 295 | 3130, 3080, 1635 (s) | 66,1 | 4,5 | — | 21,3 | $C_{11}H_9N_3O$ | 66,3 | 4,6 | — | 21,1 | 64 |
| IX | 350 | 3130, 1635 (s) | 67,8 | 5,2 | — | 19,8 | $C_{12}H_{11}N_3O$ | 67,6 | 5,2 | — | 19,7 | 49 |
| X | 320 | 3230, 1640 (s) | 67,6 | 5,3 | — | 20,1 | $C_{12}H_{11}N_3O$ | 67,6 | 5,2 | — | 19,7 | 75 |
| XI | 360 | 3420, 3380, 3140, 1640 (s) | 47,3 | 3,0 | 29,3 | 15,2 | $C_{11}H_8BrN_3O$ | 47,5 | 2,9 | 28,7 | 15,1 | 62 |
| XII | 330 | 3130, 1635 (s) | 56,7 | 3,5 | 15,2 | 18,1 | $C_{11}H_8ClN_3O$ | 56,5 | 3,4 | 15,2 | 18,0 | 64 |
| XIII | 254—255 | 3150, 3060, 1620 (w) | 68,8 | 3,7 | 12,8 | 15,1 | $C_{16}H_{10}ClN_3$ | 68,7 | 3,6 | 12,7 | 15,0 | 54 |
| XIV | 278—280 | 3150, 1650 (w) | 61,1 | 2,7 | 22,2 | 13,5 | $C_{16}H_9Cl_2N_3$ | 61,1 | 2,9 | 22,6 | 13,4 | 80 |
| XV | 281—282 | 3150, 1650 (w) | 53,8 | 2,7 | 31,9 | 11,6 | $C_{16}H_9BrClN_3$ | 53,6 | 2,5 | 32,2 | 11,7 | 66 |
| XVI | 272—274 | 3160, 1650 (w) | 53,7 | 2,7 | 31,9 | 11,5 | $C_{16}H_9BrClN_3$ | 53,6 | 2,5 | 32,2 | 11,7 | 67 |
| XVII | 268—270 | 3160, 1650 (w) | 69,8 | 4,3 | 11,8 | 14,1 | $C_{17}H_{12}ClN_3$ | 69,5 | 4,1 | 12,1 | 14,3 | 43 |

of X gives rise to an appreciable hypsochromic shift of the absorption band of the indole NH group to 3230 $cm^{-1}$. The absorption bands at 3050-3080 $cm^{-1}$ in the spectra of I-VIII can be assigned to the associated form of the pyridazine ring NH group; this is confirmed by the absence of absorption in this region in the spectra of XIV-XVII. The absorption bands of the indole and pyridazine NH groups are overlapped in the spectra of IX, X, and XII. Weak bands at 3380 and 3420 $cm^{-1}$, which we assign, respectively, to the absorption of the NH group of the associated and unassociated forms of the pyridazine ring, appear in the spectrum of 8-bromo derivative XI.

## EXPERIMENTAL

The melting points of the synthesized compounds were determined with a Boëtius apparatus and were not corrected. The IR spectra of mineral oil suspensions of the compounds were recorded with a Specord-71 IP spectrometer. The individuality of the compounds was confirmed by chromatography on Silufol plates (with development with iodine vapors).

4-Aryl-5H-pyridazo[4,5-b]indol-1-ones (I-VII). A solution of 0.012 mole of hydrazine hydrate in 10 ml of alcohol was added to a solution of 0.01 mole of 2-aroylindole-3-carboxylic acid in 190 ml of ethanol, and the mixture was refluxed on a water bath. After 20-30 min, a white crystalline precipitate began to form. Refluxing was discontinued after 3 h, and the crystalline precipitate was removed by filtration in hot form, washed on the filter with alcohol (three 10-ml portions), and dried at 80°C for 1 h. Where necessary, the substance could be crystallized from water–dimethylformamide (1:2). The principal characteristics of the compounds obtained are presented in Table 1.

4-Methyl-5H-pyridazo[4,5-b]indol-1-ones (VIII-XII). A 0.376-g (7.5 mmole) sample of hydrazine hydrate was added at 100°C to a suspension of 7.4 mmole of finely ground 2-acetylindole-3-carboxylic acid in a mixture of 75 ml of ethylene glycol and 5 ml of water. When the mixture was heated slowly (up to the boiling point), it became homogeneous. It was then refluxed for 30-40 min, after which it was cooled and diluted with water. The crystalline precipitate was removed by filtration, air dried, and crystallized from butyl alcohol. The principal characteristics of the compounds obtained are presented in Table 1.

The 5H-pyridazo[4,5-b]indol-1-ones (I-XII) are characterized by high melting points (above 300°C) and low solubilities in protic and aprotic solvents such as water, alcohols, acetone, benzene, chloroform, etc.

1-Chloro-5H-pyridazo[4,5-b]indoles (XIII-XVII). A 32-g sample of phosphorus oxychloride was added at 150°C to a mixture of 0.01 mole of 4-substituted 5H-pyridazo[4,5-b]indol-1-one in 140 ml of nitrobenzene, and the reaction mixture was heated for 20 min. The excess phosphorus oxychloride was removed by vacuum distillation, the residue was cooled and diluted with 100 ml of ether, and the precipitated 4-substituted 1-chloro-5H-pyridazo[4,5-b]-

indole hydrochloride was removed by filtration and washed with ether. The hydrochloride was dissolved in a small amount of cold water and neutralized with pyridine, after which the precipitated base was removed by filtration, washed on the filter with cold water, dried over $P_2O_5$, and crystallized from benzene. For complete removal of the crystallization benzene, the substance was heated at 100°C in vacuo for 3 h. The principal characteristics of the compounds obtained are presented in Table 1.

As compared with the 1-oxo derivatives, lower melting points and high solubilities in ordinary organic solvents are characteristic for XIII-XVIII.

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# SYNTHESIS AND PROPERTIES OF 1-SUBSTITUTED DERIVATIVES OF DIETHYL 4-ARYL-1,4-DIHYDRCPYRIDINE-3,5-DICARBOXYLIC ACID ESTERS


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1-Unsubstituted 4-aryl-3,5-diethoxycarbonyl-1,4-dihydropyridines in the presence of NaH form anions that react with alkyl halides, acid chlorides, and halo acid esters to form the corresponding 1-substituted derivatives of 1,4-dihydropyridine. Hydrolysis of one or both ethoxycarbonyl groups in the 3 and 5 positions, as well as hydrolysis of ethyl 4-phenyl-3,5-diethoxycarbonyl-1,4-dihydropyridinyl-1-acetate, occur upon reaction with alkali, but 1,3,5-triethoxycarbonyl-4-phenyl-1,4-dihydropyridine gives the corresponding unsubstituted 1,4-dihydropyridine.


Only a few reactions involving substitution at the nitrogen atom in series of 1,4-dihydropyridine derivatives are known: there are individual examples of acylation [1, 2] and more detailed studies of the alkylation of esters of 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acids [3, 4] and 2,6-dimethyl-3,5-dicyano-1,4-dihydropyridines [5, 6]. In the present research we accomplished the synthesis of 1-substituted derivatives of 4-aryl-3,5-diethoxycarbonyl-1,4-dihydropyridine (unsubstituted in the 2 and 6 positions) and studied their reactivities.

1-Unsubstituted 1,4-dihydropyridines I and II were obtained by the reaction of an aromatic aldehyde with propiolic acid ester (with the use of stoichiometric ratios of the reagents, in contrast to the method in [7]) in the presence of ammonium acetate.


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