# DIHYDROPYRROLO[3,4-b]- AND DIHYDROPYRIMIDO[4,5-b]INDOLES

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Aromatic aldehydes react with indole-2-carboxylic acid azides under acid catalysis conditions to give the corresponding 3-(α-halobenzyl)indoles, which react with aliphatic and aromatic amines to give the corresponding aminobenzylindoles. The latter undergo intramolecular cyclization to dihydropyrrolo[3,4-b]indoles at room temperature and are converted to dihydropyrimido[4,5-b]indoles through the Curtius rearrangement when they are heated to 80-110°C. Acetylation of the latter products gives N- and O-acetyl derivatives.

We have previously demonstrated the possibility of the construction of three-ring indole-containing structures on the basis of the reaction of indole-2-carboxylic acid derivatives with aromatic aldehydes [1-3]. The addition of an aromatic aldehyde to indole-2-carboxylic acid azide with subsequent Curtius rearrangement would make it possible to obtain previously undescribed dihydropyrimido[4,5-b]indol-2-ones. 9H-Pyrimido[4,5-b]indoles are obtained by intermolecular cyclization of 3-benzylideneoxindoles with amidines [4] or of 2-chloro-3-formylindole with formamide [5].

We established that indole-2-carboxylic acid azides react with aldehydes by the method in [2] to give the corresponding 3-(α-halobenzyl)indoles I-VII in good yields; the latter in the presence of tertiary amines (evidently through the indolenine form) react with aliphatic and aromatic amines, as well as ammonia, to give 3-(α-aminobenzyl)indolecarboxylic acid azides VIII-X. 2-Ethylcarbamoyl-3-(α-ethylaminobenzyl)indole XI is formed in a large excess of ethylamine. The introduction of aliphatic amines in slight excesses in the reaction made it possible to obtain primarily VIII-X, which indicates the higher rate of addition to the double bond as compared with acylation. The acyl azide group is capable of acylating the amino group intramolecularly to give dihydropyrrolo[3,4-b]indoles XII-XVII. The degree of acylation depends on the time: dihydropyrroloindole XIII is formed in 15% yield in the reaction of bromobenzylindole III with ethylamine after 24 h but is formed in 40% yield afrer 3 days. The presence of a chlorine atom in the 5 position of indole intensifies the electrophilic properties of the carbonyl group to such an extent that indole VI reacts with ethylamine to give dihydropyrroloindole XIV in 63% after 24 h. The rate of intramolecular acylation is determined by the basicity of the added amino group: when $R^3$ = Ar, the reaction is slowed down by a factor of almost five (for example, for XVI). The process can be stopped at the amination step by carrying out the reaction in absolute ether, in which amino azides IX and X are insoluble and precipitate.

The electronic spectra of XII-XVII [$\lambda_{max}$ 303 nm (log ε 4.18-4.32)] are in agreement with the data in [2, 6] for dihydropyrrolo[3,4-b]indole-3-one derivatives; the IR spectra are similar to the spectra presented in [6, 7]. The PMR spectra are characterized by a singlet of a proton attached to $C_1$ at 5.6-6.2 ppm; the signals of the 2-$C_2H_5$ group of XIII and XIV are expressed in the form of a distinct three-proton triplet and a two-proton multiplet with eight lines, which indicates the magnetic nonequivalence of the protons of the $CH_2$ group, evidently due to hindrance to free rotation about the $N_2$—$C_2H_5$ bond.

Whereas the cyclization of VIII-X at room temperature leads to the formation of pyrroloindoles XII-XVII, rapid heating of 3-α-anilinobenzylindole-2-carboxylic acid azides to 80-110°C leads to Curtius rearrangement with subsequent acylation and the formation of dihydropyrimidoindoles XVIII-XXI. The alkylamines are acylated by the acyl azide group to give pyrroloindoles XII-XVII before the rearrangement occurs. As in [4], the product of cyclization of unsubstituted aminobenzylindole IX is isolated immediately in the form of the product of oxidation of 2-oxo-4-phenyl-1H-pyrimido[4,5-b]indole XXIV.

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TABLE 1. 3-(α-X-Benzyl)indole-2-carboxylic Acid Azides (I-X)

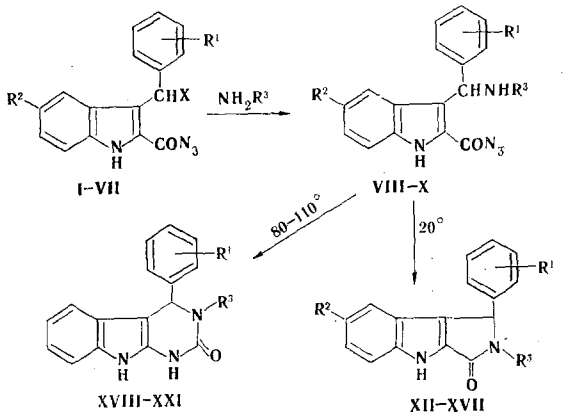
| Compound | R¹ | R² | X | mp, °C | Found, % | | Empirical formula | Calc., % | | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | halogen | N | | halogen | N | |
| I | H | H | Cl | 170—172 | 11,4 | 18,1 | $C_{16}H_{11}ClN_4O$ | 11,4 | 18,0 | 61 |
| II | *o*-Cl | H | Cl | 178—179 | 20,4 | 16,2 | $C_{16}H_{10}Cl_2N_4O$ | 20,6 | 16,2 | 66 |
| III | H | H | Br | 132—134 | 22,4 | 15,8 | $C_{16}H_{11}BrN_4O$ | 22,5 | 15,8 | 70 |
| IV | *o*-Cl | H | Br | 157—159 | 29,5 | 14,5 | $C_{16}H_{10}BrClN_4O$ | 29,6 | 14,4 | 77 |
| V | *p*-$NO_2$ | H | Cl | 145—148 | 9,8 | 19,7 | $C_{16}H_{10}ClN_5O_3$ | 9,9 | 19,7 | 73 |
| VI* | H | Cl | Br | 142—144 | 29,5 | 14,3 | $C_{16}H_{10}BrClN_4O$ | 29,6 | 14,4 | 69 |
| VII | *p*-$NO_2$ | $OCH_3$ | Cl | 152—156 | 9,1 | 18,3 | $C_{17}H_{12}ClN_5O_4$ | 9,2 | 18,2 | 76 |
| VIII* | *o*-Cl | H | $NHC_6H_5$ | 140—141 | 8,8 | 17,5 | $C_{22}H_{16}ClN_5O$ | 8,8 | 17,4 | 87 |
| IX* | H | H | $NH_2$ | 160—162 | | 24,3 | $C_{16}H_{13}N_5O$ | | 24,0 | 74 |
| X* | H | Cl | $NHC_2H_5$ | 160—162 | 9,9 | 19,9 | $C_{18}H_{16}ClN_5O$ | 10,0 | 19,8 | 75 |

*IR spectra: VI, 1680, 3405; VIII, 1687, 3430; IX, 1675; X, 1680, 3440, 3485 $cm^{-1}$.

TABLE 2. 1-Oxo-3-phenyl-1,2-dihydropyrrolo[3,4-b]indoles (XII-XVII)

| Compound | R¹ | R² | R³ | mp, °C | IR spectrum, $cm^{-1}$ | | Found, % | | | Empirical formula | Calc., % | | | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | CO | NH | C | H | N | | C | H | N | |
| XII | H | H | $CH_3$ | 309—310 | 1670 | 3090, 3170 | 77,9 | 5,3 | 10,8 | $C_{17}H_{14}N_2O$ | 77,9 | 5,3 | 10,7 | 14 |
| XIII | H | H | $C_2H_5$ | 268—270 | 1662 | 3090, 3165 | 78,4 | 5,8 | 10,2 | $C_{18}H_{16}N_2O$ | 78,3 | 5,8 | 10,1 | 15 |
| XIV* | H | Cl | $C_2H_5$ | 289—290 | 1662 | 3040, 3160 | 69,5 | 4,8 | 9,2 | $C_{18}H_{15}ClN_2O$ | 69,6 | 4,8 | 9,0 | 63 |
| XV | *p*-$NO_2$ | H | $C_2H_5$ | 276—278 | 1660 | 3180 | 67,2 | 4,7 | 13,2 | $C_{18}H_{15}N_3O_3$ | 67,3 | 4,7 | 13,1 | 28 |
| XVI | H | H | *p*-$CH_3OC_6H_4$ | 308—310 | 1668 | 3090, 3195 | 77,8 | 5,1 | 8,0 | $C_{23}H_{18}N_2O_2$ | 77,9 | 5,1 | 7,9 | 15 |
| XVII | *p*-$NO_2$ | $OCH_3$ | $C_2H_5$ | 284—285 | 1663 | 3155 | 65,0 | 4,8 | 12,0 | $C_{19}H_{17}N_3O_4$ | 64,9 | 4,8 | 11,9 | 30 |

*Found: Cl 11.3%. Calculated: Cl 11.4%.




Singlets of a 9-H proton at 9.75, a 1-H proton at 8.3, a 4-H proton at 6.65, and a $CH_3$ group at 2.36 ppm are observed in the PMR spectrum of pyrimidoindole XXI, in addition to a multiplet of aromatic protons at 6.8-7.4 ppm (12H).

Treatment of XXI with refluxing acetic anhydride leads to the formation of $N_1$-(XXII, νCO 1670 $cm^{-1}$) and O-acetyl (XXIII, νCO 1710 $cm^{-1}$) derivatives. The signal of the 9-H proton is shifted 0.5 ppm to strong field in the spectrum of XXII and 0.6 ppm to weak field in the spectrum of derivative XXIII as compared with starting XXI. A singlet of a 1-H proton is absent in the spectra of XXII and XXIII. The doubled number of signals in the spectrum of a solution of pyrimidoindole XVIII in $CD_3COOD$ makes it possible to assume that the enol form is simultaneously present in up to 10% amounts along with the keto form.

## EXPERIMENTAL

The UV spectra of solutions of the compounds in ethanol (c $0.2\text{-}0.3 \cdot 10^{-4}$ M) were recorded with an SF-16 spectrophotometer. The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions in $CDCl_3$ were obtained with a Tesla-80 spectrometer with hexamethyldisiloxane as the internal standard. The purity of the products was verified by thin-layer chromatography (TLC) on Silufol in an ethyl acetate–hexane system (5:1).

The indole-2-carboxylic acid azides were obtained by the method in [8]; their characteristics were in agreement with the literature data.

3-(α-Bromobenzyl)-5-chloroindole-2-carboxylic Acid Azide (VI). A 5-ml sample of acetic acid saturated with HBr was added with cooling (ice water) to a mixture of 1.1 g (5 mmole) of 5-chloroindole-2-carboxylic acid azide and 1.1 g (10 mmole) of benzaldehyde. The components gradually dissolved. The precipitate of VI that formed 5-10 min after the components dissolved was removed by filtration, washed with heptane, and crystallized from benzene to give 1.34 g (69%) of a product with with mp 142-144°C (explosively). IR spectrum: 1680 (C=O) and 3405 $cm^{-1}$ (NH). Compounds I-V and VII were similarly obtained (Table 1).

3-(α-Anilino-o-chlorobenzyl)indole-2-carboxylic Acid Azide (VIII). A 0.5-ml (3.5 mmole) sample of triethylamine was added to a suspension of 0.78 g (2 mmole) of indole IV in 30 ml of dry benzene, as a result of which the solution took on a characteristic yellow color. A solution of 0.23 g (2.5 mmole) of aniline in 10 ml of dry ether was added dropwise with cooling (ice water) to the solution at such a rate that the drops had time to decolorize. The mixture was then maintained at room temperature for 2 h, after which it was neutralized with 50 ml of 2% HCl. The solution was dried over $Na_2SO_4$ and evaporated to dryness in vacuo at no higher than 40°C.

Azides IX and X were similarly obtained, except that 6 mmole of $(NH_4)_2CO_3$ was used for 2 mmole of III and 6 mmole of ethylamine in a mixture of 4 ml of pyridine and 20 ml of absolute ether was used for 6 mmole of ethylamine hydrobromide. The precipitated amines IX and X were immediately removed by filtration, washed with water, and dried. Compounds VIII-X were unstable during storage.

2-Ethylcarbamoyl-3-(α-ethylamino-o-chlorobenzyl)indole (XI). This compound was obtained in the same way as VIII, except that ethylamine was used in the form of a saturated ether solution, and the reaction was carried out at room temperature. The product was crystallized from benzene to give 0.52 g (74%) of a product with mp 214-215°C. IR spectrum: 1635 (C=O) and 3375 $cm^{-1}$ (NH). PMR spectrum: 10.35 (1H, s, 1-H), 7.0-7.5 (8H, m, Ar), 5.85 (1H, s, 3-CH), 3.4 (2H, q, 2-$C_2H_5$), 2.7 (2H, q, 3-$C_2H_5$), 0.95-1.2 (6H, m, $CH_3$), and 1.85 ppm (1H, t, NH). Found: C 67.3; H 6.1; Cl 9.8; N 11.9%. $C_{20}H_{22}ClN_3O$. Calculated: C 67.5; H 6.2; Cl 10.0; N 11.8%.

3-Phenyl-2-ethyl-5-chloro-1-oxo-2,3-dihydropyrrolo[3,4-b]indole (XIV). A benzene solution prepared from indole VI and triethylamine (1:2.2) was added with cooling (ice water) to a suspension of 0.75 g (6 mmole) of ethylamine hydrobromide in 30 ml of $CH_2Cl_2$, and the mixture was stirred at room temperature for 4 h, after which it was allowed to stand overnight. The mass was diluted with ether, and the mixture was washed with 2% HCl, sodium carbonate solution, and water and dried over $Na_2SO_4$. It was then evaporated to a volume of 5-7 ml, and the precipitate was removed by filtration and crystallized from acetonitrile. The yield was 0.39 g. PMR spectrum: 10.17 (1H, s, 8-H), 7.21-7.54 (8H, m, Ar), 5.84 (1H, s, 3-H), 3.99 (1H, q, 2-$CH_2$), 3.46 (1H, q, 2-$CH_2$), and 0.84 ppm (3H, t, 2-$CH_3$).

Compounds XII, XIII, and XV-XVII were similarly synthesized. The reaction time was 1 day in the preparation of XII, XIII, XV, and XVII and 5 days in the preparation of XVI (Table 2). PMR spectra: XII 7.09-7.54 (9H, m, Ar), 5.56 (1H, s, 3-H), 3.17 (3H, s, 2-$CH_3$); XIII 9.82 (1H, s, 8-H), 7.0-7.54 (9H, m, Ar), 5.6 (1H, s, 3-H), 3.62 (1H, q, 2-$CH_2$), 3.14 (1H, q, 2-$CH_2$), 0.89 ppm (3H, t, 2-$CH_3$); XVI 7.01-7.63 (13H, m, Ar), 6.19 (1H, s, 3-H), 3.99 ppm (3H, s, $CH_3O$).

2-Oxo-3-(p-methoxyphenyl)-4-phenyl-3,4-dihydropyrimido[4,5-b]indole (XVIII). A benzene solution prepared from indole III and triethylamine was added dropwise with cooling (ice water) to a solution of 0.31 g (2.5 mmole) of p-anisidine in 10 ml of ether, and the mixture was maintained at room temperature for 2 h. It was then washed with a 2% solution of HCl in ether, sodium carbonate solution, and water until the wash waters were neutral and evaporated

TABLE 3. 2-Oxo-4-phenyl-3,4-dihydropyrimido[4,5-b]indoles (XVIII-XXI)

| Compound | $R^1$ | $R^3$ | mp, °C | UV spectrum $\lambda_{max}$, nm (log ε) | IR spectrum, $cm^{-1}$ | | Found, % | | | | Empirical formula | Calc., % | | | | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | CO | NH | C | H | Cl | N | | C | H | Cl | N | |
| XVIII | H | *p*-$CH_3OC_6H_4$ | 279—280 | 235 (4,63), 277 (4,08), 302 (4,11) | 1643 | 3205, 3250, 3360 | 74,6 | 5,1 | | 11,5 | $C_{23}H_{19}N_3O_2$ | 74,8 | 5,1 | | 11,4 | 66 |
| XIX | *o*-Cl | *p*-$CH_3OC_6H_4$ | 278—280 | 277 (3,98), 303 (3,96) | 1648 | 3190, 3395 | 68,2 | 4,5 | 8,7 | 10,5 | $C_{23}H_{18}ClN_3O_2$ | 68,4 | 4,5 | 8,8 | 10,4 | 70 |
| XX | *o*-Cl | H | 271—273 | 277 (3,77), 302 (3,88) | 1653 | 3338, 3375 | 70,6 | 4,3 | 9,4 | 11,2 | $C_{22}H_{16}ClN_3O$ | 70,7 | 4,3 | 9,5 | 11,2 | 75 |
| XXI | *o*-Cl | *p*-$CH_3C_6H_4$ | 286—288 | 277 (3,85), 303 (3,92) | 1648 | 3210, 3260, 3375 | 71,2 | 4,6 | 9,2 | 10,9 | $C_{23}H_{18}ClN_3O$ | 71,2 | 4,6 | 9,2 | 10,8 | 62 |

to dryness. Toluene (10 ml) was poured over the residue, and the mixture was refluxed for 40 min. The precipitate that formed when the mixture was cooled was removed by filtration and crystallized from acetonitrile. The yield was 0.44 g. PMR spectrum (in $CD_3COOD$): 7.07-7.52 (13H, m, Ar), 6.78 (1H, s, 4-H), 3.67 (3H, s, $CH_3O$); enol form: 5.47 (1H, s, 4-H), 3.62 ppm (3H, s, $CH_3O$).

Compounds XIX-XXI were similarly synthesized, except that the Curtius rearrangement was carried out in benzene with refluxing for 3 h. PMR spectrum of XXI: 9.75 (1H, s, 9-H), 8.3 (1H, s, 1-H), 6.83-7.4 (12H, Ar), 6.5 (1H, s, 4-H), and 2.31 ppm (3H, s, $CH_3$). The characteristics of XVIII-XXI are given in Table 3.

2-Oxo-4-phenylpyrimido[4,5-b]indole (XXIV). A 0.87-g (3 mmole) sample of IX was refluxed in 15 ml of toluene for 40 min, after which it was cooled, and the resulting precipitate was removed by filtration and crystallized from dioxane to give 0.26 g (33%) of a substance with mp > 360°C. UV spectrum, $\lambda_{max}$ (log ε): 271 (439) and 303 nm (3.77). IR spectrum: 1650 (C=O); 3060, 3140 $cm^{-1}$ (NH). Found: C 73.3; H 4.1; N 16.1%. $C_{16}H_{11}N_3O$. Calculated: C 73.5; H 4.2; N 16.1%.

Reaction of XXI with Acetic Anhydride. A 1.16-g (3 mmole) sample of XXI was refluxed in 15 ml of acetic anhydride for 1 h, after which the acetic anhydride was removed by distillation to dryness in vacuo. The residue was triturated in ether, and the 1-acetyl-2-oxo-3-(p-tolyl)-4-(o-chlorophenyl)-3,4-dihydropyrimido[4,5-b]indole (XXII) was removed by filtration and crystallized from ethanol to give 0.25 g (19%) of a substance with mp 257-259°C. UV spectrum, $\lambda_{max}$ (log ε): 302 nm (3.83). IR spectrum: 1660 (C=O), 1670 ($COCH_3$), and 3427 $cm^{-1}$ (NH). PMR spectrum: 9.25 (1H, s, 9-H), 6.95-7.58 (12H, m, Ar), 6.54 (1H, s, 4-H), 2.78 (3H, s, $COCH_3$), and 2.25 ppm (3H, s, p-$CH_3$). Found: C 69.6; H 4.6; Cl 8.2; N 9.9%. $C_{25}H_{20}ClN_3O_2$. Calculated: C 69.8; H 4.6; Cl 8.3; N 9.8%.

The ether solution after separation of XXII was evaporated to dryness, and the residue was triturated in water. The solid was removed by filtration and crystallized from ethanol to give 0.84 g (65%) of 2-acetoxy-3-(p-tolyl)-4-(o-chlorophenyl)-3,4-dihydropyrimido[4,5-b]-indole (XXIII) with mp 158-160°C. UV spectrum, $\lambda_{max}$ (log ε): 293 nm (3.99). IR spectrum: 1710 ($OCOCH_3$) and 3458 $cm^{-1}$ (NH). PMR spectrum: 10.35 (1H, s, 9-H), 6.85-7.4 (12H, m, Ar), 6.54 (1H, s, 4-H), 2.76 (3H, s, $COCH_3$), and 2.26 ppm (3H, s, p-$CH_3$). Found: C 69.5; H 4.7; Cl 8.2; N 9.9%. $C_{25}H_{20}ClN_3O_2$. Calculated: C 69.8; H 4.6; Cl 8.3; N 9.8%.

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