INDOLE DERIVATIVES

XXXV.* SYNTHESIS OF 12H-6,7-DIHYDROBENZ[2',3'] OXEPINO[4,5-b]INDOLES

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A new heterocyclic system -12H-6,7-dihydrobenz[2',3']oxepino[4,5-b] indole - and a number of its substituted derivatives were synthesized by Fischer cyclization of 5-homochromanone arylhydrazones.

Continuing our investigations of the synthesis of condensed indole systems with 5-, 6-, and 7-membered sulfur and nitrogen heterocycles and with six-membered oxygen heterocycles [2], we have investigated the possibility of the Fischer condensation of 5-homochromanone (4,5-dihydro-1-benzoxepin-5-one) with various arylhydrazines.

By selecting the reaction conditions in each separate case we synthesized 12H-6,7-dihydrobenz[2',3']-oxepino[4,5-b]indole (I) itself, its derivatives (II-XI), and 8,9-benzo-12H-6,7-dihydrobenz[2,3]oxepino[4,5-b]-indole (XII).



1 R=R'=H; II $R=CH_3$, R'=H, III $R=OCH_3$, R'=H; IV R=H, $R'=CH_3$; V R=H, $R'=CH_2C_6H_5$; VI $R=COOC_2H_5$, $R'=CH_2C_6H_5$; VII $R=COOC_2H_5$, R'=H; VIII R=CI, R'=H; IX $R=B_T$, R'=H; X R=8 (OT 10)=CF₃, $R'=CH_2CH_2N(CH_3)_2$; XI $R=NO_2$, R'=H

The cyclization of 5-homochromanone arylhydrazones is facilitated by the introduction of electrondonating substituents in the para position and hindered by the presence of electron-accepting substituents $(NO_2, COOC_2H_5)$. In the latter case, the reaction does not proceed on heating with HCl in ethanol and requires the application of a mixture of glacial acetic acid and concentrated sulfuric acid. Indoles I and II were converted to the corresponding $12-\beta$ -cyanoethyl-substituted compounds (XIII and XIV) by the action of acrylonitrile, and indoles VI and VII were converted to the diethylaminoethyl esters (XV and XVI). Nitro compound XI is reduced over Raney nickel to aminooxepinoindole XVII. The UV spectra of oxepinoindoles I, II, and XI confirm the structures of these compounds. It is well known that unsubstituted indole has absorption maxima at 225 nm (log ε 4.39) and 270-290 nm (log ε 3.77). The introduction of alkyl substituents in the 2- and 3-positions of the indole system has a slight effect on the absorption curve, but the introduction of a phenyl radical into the 2-position leads to a significant bathochromic shift of the long-wave maximum (by 20 nm) due to the increase in the conjugation chain length in the molecule (decrease in the $\pi \rightarrow \pi^*$ transition energy). A certain hypsochromic shift of this maximum with a decrease in its intensity is observed in the spectrum of 2-phenyl-3-methylindole [3], which indicates partial deflection of the phenyl radical from the plane of the indole ring as a result of steric interaction of the phenyl radical with the methyl group. Deviation of the phenyl group from the plane is also observed for 6,7-dihydro[1]benzocyclohepteno-

*See [1] for communication XXXIV.

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TABLE 1. 12H-6,7-Dihydrobenz[2',3']oxepino[4,5-b]indoles

Com- pound	Cyclization con-	mp, °C	Empirical formula	Found, %			Calculated, %			eld, %
	ditions			C	Н	N	C	н	N	Yi
I II IV VV VI VII VIII IX XI XII	1 h (33%) 15 min (15%) 40 min (15%) 30 min (15%) 30 min (15%) 1 h (30%) 2 min ⁷ 1 h 30 min (30%) 1 h (30%) 13 h (30%) 20 min ¹⁹ 1 h (15%)	$\begin{array}{c} 135 - 137 & {}^{2,3} \\ 152 - 153 & {}^{4,5} \\ 171 - 172 & {}^{79 - 80^4} \\ 166 - 167 & {}^{4} \\ 145 - 146 & {}^{197 - 198} \\ 197 - 198 & {}^{4} \\ 167 - 167 , {}^{5} \\ 159 - 160^4 & {}^{223 - 224 11} \\ 223 - 224 {}^{11} \\ 199 - 199 , {}^{5} \\ 252 - 252 , {}^{5} \end{array}$	$\begin{array}{c} C_{16}H_{13}NO\\ C_{17}H_{15}NO\\ C_{17}H_{15}NO\\ C_{17}H_{15}NO\\ C_{23}H_{19}NO\\ C_{28}H_{23}NO_{3}\\ C_{26}H_{23}NO_{3}\\ C_{19}H_{17}NO_{3}\\ 9\\ C_{16}H_{12}CINO \\ 10\\ C_{21}H_{22}CIN_{2}O\\ C_{16}H_{12}N_{2}O_{3}\\ C_{20}H_{15}NO \end{array}$	81,7 81,9 76,4 81,6 84,5 78,8 74,7 	5,6 6,1 5,8 6,1 6,0 5,9 5,9 5,9 4,3 5,4	6,4 5,7 5,6 5,0 4,0 4,6 5,2 4,7 6,5 10,0 5,3	81,7 81,9 77,0 81,9 78,6 74,3 	5,6 6,1 5,7 6,9 5,8 5,6 1 4,3 5,3	5,9 5,6 5,3 4,9 3,5 4,6 5,5 4,5 6,5 10,0 4,9	97 82 81 58 43 60 86 76 58 15 57 50

¹Refluxing time (HCl concentration in absolute alcohol).
²From aqueous alcohol.
³λ_{max} 322-324 nm (log ε 4.70).
⁴From \$6% alcohol.
⁵λ_{max} 324-328 nm (log ε 4.43).
⁶From absolute alcohol.
⁷ In glacial acetic acid-concentrated sulfuric acid (9:1).
⁸From heptane.
⁹Found %: Cl 13.1. Calc. %: Cl 13.1.
¹⁰Found %: Br 25.2. Calc. %: Br 25.4.
¹¹From absolute alcohol-ether.
¹²In glacial acetic acid-concentrated sulfuric acid (6:1).
¹³From benzene.
¹⁴λ_{max} 294 (log ε 4.53), 312 nm (log ε 4.57).

[b]indole. The conjugation of the benzene ring with indole is reinforced in the corresponding benzycyclopenteno[b]indole due to the substantially more planar structure of the molecule, and this is reflected in the UV spectrum: $\lambda_{max} 320-330$ nm (log $\varepsilon 4.2$) [3]. The same dependence in the character of the UV spectrum can be observed on passing from the indole (I) that we synthesized [$\lambda_{max} 322-324$ nm (log $\varepsilon 4.70$)] to benzopyrano[4,3-b]indole [2] [$\lambda_{max} 338$ nm (log $\varepsilon 4.24$)]. In addition, the bathochromic shift of the long-wave maxima of oxygen-containing heterocyclic systems, as compared with their carbon analogs, can be explained by the effect of the auxochromic oxygen-containing grouping in the ortho position of the phenyl radical.

Two triplets at 3.13 and 4.20 ppm (J \simeq 5 Hz) due to the protons of the two methylene groups of the seven-membered ring are manifested in the PMR spectrum of I (in CDCl₃). The corresponding triplet signals from the protons of XII (in pyridine) are observed at 3.53 and 4.27 ppm.

Esters XV and XVI do not manifest appreciable antiserotonin activity.

EXPERIMENTAL

The UV spectra in alcohol (c 10^{-5} M, d 1 cm) were obtained with an SF-4 spectrometer. The PMR spectra were obtained with an RS-60 spectrometer with an operating frequency of 60 MHz with hexamethyl-disiloxane as the internal standard.

<u>9-Methyl-12H-6,7,-dihydrobenz[2',3']oxepino[4,5-b]indole(I)</u>. A mixture of 3 g (17 mmole) of 5-homochromanone [4] and 2.7 g (17 mmole) of p-tolylhydrazine hydrochloride was refluxed for 15 min in 30 ml of 15% HCl in alcohol and then poured into 120 ml of water. The resulting oil crystallized on trituration, and the crystals were filtered, washed with water, and dried.

Indoles I-VI, VIII-X, and XII were similarly obtained (see Table 1).

5-Homochromanone p-Carbethoxyphenylhydrazone. A solution of 3.6 g (25 mmole) of 5-homochromanone and 4 g (25 mmole) of p-carbethoxyphenylhydrazine in 25 ml of absolute alcohol was refluxed with 1 ml of glacial acetic acid. The precipitate that formed on cooling was filtered and washed with a small amount of cold alcohol to give 6.3 g (88%) of a hydrazone with mp 151-152.5° (from alcohol). Found %: C 70.6; H 6.3; N 8.8. $C_{19}H_{20}N_2O_3$. Calc. %: C 70.3; H 6.2; N 8.6.

<u>9-Carbethoxy-12H-6,7-dihydrobenz[2',3']oxepino[4,5-b]indole (VII)</u>. 5-Homochromanone p-carbethoxyphenylhydrazone [1.5 g (4.6 mmole)] was heated for 2 min in 15 ml of glacial acetic acid-concentrated sulfuric acid (9:1). The mixture was poured into 150 ml of water, and the resulting precipitate was filtered and washed with water and dried.

Indole XI was similarly obtained.

<u>5-Homochromanone p-Nitrophenylhydrazone</u>. A mixture of 3 g (18 mmole) of 5-homochromanone and 2.9 g (18 mmole) of p-nitrophenylhydrazine in 30 ml of absolute alcohol was refluxed for 30 min in the presence of 1 ml of glacial acetic acid. The mixture was cooled and the resulting precipitate was filtered and washed with cold alcohol to give 4.6 g (82%) of a hydrazone with mp 204-206° (from absolute alcohol). Found %: N 14.2. $C_{16}H_{15}N_{3}O_{3}$. Calc. %: N 14.1.

9-Amino-12H-6,7-dihydrobenz[2',3']oxepino[4,5-b]indole (XVII). Nitro compound XI [1.7 g (6 mmole)] was hydrogenated in 50 ml of alcohol over 0.2 g of Raney nickel for 8 h until hydrogen absorption ceased. The catalyst was removed by filtration, and the solution was evaporated to give 1.2 g (80%) of amine XVII with mp 221-222.5° (dec., from alcohol) and R_f 0.66 (activity IV Al₂O₃, chloroform). Found %: C 77.0; H 5.7; N 10.9. C₁₆H₁₄N₂O. Calc. %: C 76.8; H 5.6; N 11.2.

<u>Hydrochloride of 9-(β -Diethylaminoethoxycarbonyl)-12H-6,7-dihydrobenz[2',3']oxepino[4,5-b]indole</u> (XVI). Absolute toluene (100 ml) was added to 2.7 g (88 mmole) of indole VII, the mixture was heated to the boiling point, and a solution of 3-4 mg of sodium in 5 ml of β -diethylaminoethanol was added to the solution. The mixture was refluxed for 2 h with slow distillation of the toluene, another 3 ml of β -diethylaminoethanol was added, and the mixture was refluxed with slow distillation of the toluene for another 2 h. The mixture was then evaporated in vacuo, and the residue was treated with water and extracted with ether. The extract was washed with a potassium carbonate solution and dried with anhydrous magnesium sulfate. The addition of an ether solution of hydrogen chloride precipitated 3.4 g (94%) of the hydrochloride of indole XVI with mp 242-243° (from absolute alcohol). Found %: N 6.8; Cl 8.5. C₂₃H₂₆N₂O₃ °HCl. Calc. %: N 6.7; Cl 8.5.

Hydrochloride of $9-(\beta-Diethylaminoethoxycarbonyl)-12H-benzyl-6,7-dihydrobenz[2',3']oxepino[4,5-b] indole (XV). This compound [1.95 g (57%)] was similarly obtained from 2.7 g (6.8 mmole) of indole VI and had mp 185-186° (from absolute alcohol). Found %: N 5.5; Cl 7.0. C₃₀H₃₂N₂O·HCl. Calc. %: N 5.5; Cl 7.0.$

<u>9-Methyl-12-(β -cyanoethyl)-6,7-dihydrobenz[2',3']oxepino[4,5-b]indole (XIV)</u>. Freshly prepared acrylonitrile (10 ml) and 1 ml of a freshly prepared solution of Rodionov catalyst were added to 2.15 g (8 mmole) of indole II, and the mixture was heated for 1 h on a boiling-water bath. The residue after distillation of excess acrylonitrile was triturated with alcohol to give 0.8 g (19%) of nitrile XIV with mp 126-128° (from heptane). Found %: C 79.2; H 6.3; N 9.5. C₂₀H₁₈N₂O. Calc. %: C 79.4; H 6.0; N 9.3.

 $\frac{12-(\beta-\text{Cyanoethyl})-6,7-\text{dihydrobenz}[2',3']\text{oxepino}[4,5-b]\text{indole (XIII).}}{\text{Similarly obtained from 1.9 g (8 mmole) of I and had mp 118-119.5° (from heptane). Found %: C 79.2; H 5.6; N 9.9. C₁₉H₁₆N₂O. Calc. %: C 79.2; H 5.6; N 9.7.$

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