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N-ACETYLINDOXYL IN THE SYNTHESIS OF NEW CONDENSED HETEROCYCLES

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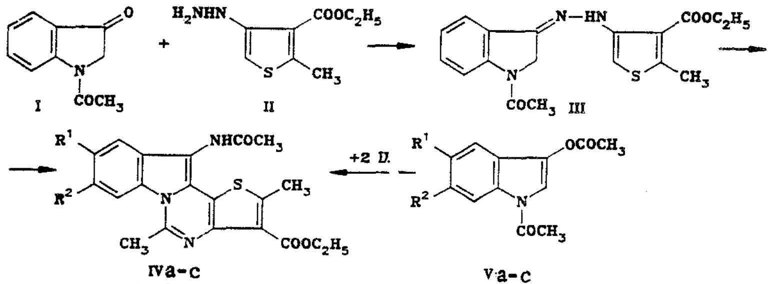
Derivatives of a new heterocyclic system thieno[2',3':5,6]pyrimido[3,4-a]indole, were obtained by the reaction of substituted N,O-diacetylindoxyls with excess N-(2-methyl-3-ethoxycarbonyl-4-thienyl)hydrazine. The reaction of N-acetylindoxyl and 4-hydrazinouracil forms 12-amino-1,3-dioxo-2,4,6-trimethylpyrimido[5',4':5,6]pyrimido[3,4-a]indole.

The reaction of N-acetylindoxyl with arylhydrazines forms arylhydrazones, which when heated in acetic acid in the presence of acetic anhydride undergo rearrangement and cyclocondensation to derivatives of 12-acetylaminoindolo[1,2-c]quinazoline [1]. In the present work the heterocyclization of hydrazines by this reaction has been studied.

The reaction of N-acetylindoxyl (I) with N-(2-methyl-3-ethoxycarbonyl-4-thienyl)hydrazine (II) gives the N-(2-methyl-3-ethoxycarbonyl-4-thienyl)hydrazone of N-acetylindoxyl (III). When the last-named is treated with a mixture of acetic anhydride and acetic acid it is converted by the scheme previously proposed [1, 2] to 11-acetylamino-2,5-dimethyl-3-ethoxycarbonylthieno[2',3':5,6]pyrimido[3,4-a]indole (IVa) in 66% yield. Compound IVa and other derivatives of thieno[2',3':5,6]pyrimido[3,4-a]indole (IVb, c) are also obtained by the reaction of a twofold excess of thienylhydrazine II with N,O-diacetylindoxyl (V) under conditions analogous to the synthesis of 12-acetylaminoindolo[1,2-c]quinazolines [1].



IV, V a $R^1=R^2=H$; b $R^1=Br$, $R^2=H$; c $R^1=H$, $R^2=NO_2$

A derivative of a new heterocyclic system, 12-amino-1,3-dioxo-2,4,6-trimethylpyrimido[5',4':5,6]pyrimido[3,4-a]indole (VI) is formed by the prolonged heating of N-acetylindoxyl with 4-hydrazinouracil VII in alcohol.

We were unable to isolate the corresponding hydrazone.

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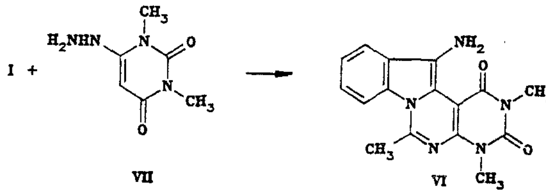

The structures of compounds IVa-c and VI were confirmed by the mass spectra, which show molecular ion peaks with m/z values corresponding to the molecular weights of these compounds.

EXPERIMENTAL

IR spectra were obtained in mineral oil with a Perkin-Elmer spectrometer, UV spectra in ethanol with a Perkin-Elmer 575 instrument. Mass spectra were obtained with a Varian MAT-112 mass spectrometer (70 eV) by direct introduction of sample into the ion source. PMR spectra were recorded with a JNM-4H-100 instrument; the internal standard was HMDS for compound III, TMS for compounds IVa, b. The course of the reaction was monitored and the individuality of substances was determined on Silufol UV-254 plates in 1:1 heptane—acetone.

N-(2-Methyl-3-ethoxycarbonyl-4-thienyl)hydrazone of N-acetylindoxyl (III). To a suspension of 3.32 g (19 mmoles) of N-acetylindoxyl in 60 ml of alcohol was added 3.8 g (19 mmoles) of N-(2-methyl-3-ethoxycarbonyl-4-thienyl)hydrazine (II) and the mixture was boiled for 4 h. Then it was cooled and the precipitate was filtered off and washed with alcohol. Yield 2.46 g (36%), mp 182°C (decomp., from methanol). IR spectrum: 3300 (NH), 1670 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 226 (4.45), 356 nm (4.34). PMR spectrum ($CDCl_3$): 2.27 (3H, s, $COCH_3$); 2.53 (3H, s, CH_3); 4.26 (2H, q, $\underline{CH_2}CH_3$); 1.35 (3H, t, $CH_2\underline{CH_3}$); 4.46 (2H, s, CH_2); 6.48 (1H, s, 5-H); 7.17, 7.65, 8.27 ppm (5H, m, arom. protons). Found, %: C 60.7; H 5.2; N 11.9; S 9.1. $C_{18}H_{19}N_3O_3S$. Calculated, %: C 60.5; H 5.4; N 11.8; S 9.0.

11-Acetylamino-2,5-dimethyl-3-ethoxycarbonylthieno[2',2':5,6]pyrimido[3,4-a]indole (IVa). (A). A mixture of 1.86 g (5.2 mmoles) of hydrazone III, 19 ml of glacial acetic acid, and 1.53 g (15 mmole) of acetic anhydride was boiled for 5-10 min, then cooled. The precipitate was filtered off and washed with acetic acid and methanol. Yield 1.3 g (66%), mp 286-287°C (from acetic acid). IR spectrum: 3300 (NH), 1675 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 246 (4.46), 276 (4.59), 310 shoulder (3.85), 350 nm (3.92). PMR spectrum (DMFA-D_7): 2.31 (3H, s, $COCH_3$); 2.75 (3H, s, 2-CH_3); 3.15 (3H, s, 5-CH_3); 4.42 (2H, q, $\underline{CH_2}CH_3$); 1.41 (3H, t, $CH_2\underline{CH_3}$); 7.35-8.2 (arom. protons); 9.85 ppm (1H, s, NH). Found, %: C 62.8; H 5.0; N 11.1; S 8.6; M^+ 381. $C_{20}H_{19}N_3O_3S$. Calculated, %: C 63.0; H 5.0; N 11.0; S 8.4; M 381.

(B). To a suspension of 0.54 g (2.5 mmole) of N,O-diacetylindoxyl Va in 5 ml of glacial acetic acid was added 1 g (5 mmole) of hydrazine II with stirring, and the mixture was heated to boiling. Then 1.53 g (15 mmole) of acetic anhydride was added and the mixture was boiled for 5 min. Then it was cooled and the precipitate was filtered off and washed with methanol. Yield 0.3 g (31.5%), mp 286-287°C (from DMFA). A mixture of this material with a sample obtained by procedure (A) did not show depression of melting point.

9-Bromo-11-acetylamino-2,5-dimethyl-3-ethoxycarbonylthieno[2'3';5,6]pyrimido[3,4-a]indole (IVb) was obtained analogously to compound IVa, starting from N,O-diacetylindoxyl Vb and hydrazine II (method B). Yield 58%, mp 305-307°C (from acetic acid). IR spectrum: 3280 (NH), 1657, 1705 cm^{-1} (C=O). PMR spectrum (DMFA-D_7): 2.31 (3H, s, $COCH_3$); 2.75 (3H, s, 2-CH_3); 3.14 (3H, s, 5-CH_3); 4.45 (2H, q, $\underline{CH_2}CH_3$); 1.43 (3H, t, $CH_2\underline{CH_3}$); 7.49 (1H, q, $J_{8,7}$ = 9, $J_{8,10}$ = 4 Hz, 8-H); 7.84 (1H, d, $J_{10,8}$ = 4 Hz, 10-H); 8.24 (1H, d, $J_{7,8}$ = 9 Hz, 7-H); 9.65 ppm (1H, s, NH). Found, %: C 52.4; H 3.6; Br 17.3; N 9.1; S 6.4; M^+ 460. $C_{20}H_{18}BrN_3O_3S$. Calculated, %: C 52.2; H 3.9; Br 17.4; N 9.1; S 7.0; M 460.

8-Nitro-11-acetylamino-2,5-dimethyl-3-ethoxycarbonylthieno[2'3':5,6]pyrimido[3,4-a]indole (IVc) was synthesized from N,O-diacetylindoxyl Vc analogously to compound IVa (method B). Yield 66%, mp 330°C (from DMFA). IR spectrum: 3220 (NH), 1710, 1665 cm^{-1} (C=O). Found, %: C 56.3; H 4.3; N 13.1; S 7.2; M^+ 426. $C_{20}H_{18}N_4O_5S$. Calculated, %: C 56.3; H 4.3; N 13.1; S 7.5; M 426.

12-Amino-1,3-dioxo-2,4,6-trimethylpyrimido[5'4':5,6]pyrimido[3,4-a]indole (VI). To a hot solution of 0.68 g (4 mmole) of 4-hydrazino-1,3-dimethyluracil in 90 ml of alcohol was added 0.7 g (4 mmole) of N-acetylindoxyl. The mixture was boiled for 15 h, then cooled, and the precipitate was filtered off and washed with alcohol. Yield 0.4 g (32%), mp > 360°C (from DMFA). IR spectrum: 3400, 3370, 3310 (NH_2), 1690, 1650 cm^{-1} (C=O). Found, %: C 61.9; H 4.8; N 22.9; M^+ 309. $C_{16}H_{15}N_5O_2$. Calculated, %: C 62.1; H 4.9; N 22.6; M 309.

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SYNTHESIS OF 4-CHLOROSUBSTITUTED SPIROPYRANES OF THE INDOLE SERIES

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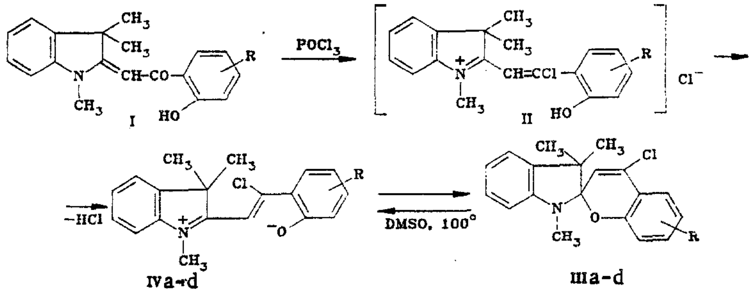
Enaminohydroxyketones, formed from 1,3,3-trimethyl-2-methyleneindoline and ortho-acetoxyaromatic acid chlorides, are converted by heating with phosphorus oxychloride in dichloroethane and subsequent treatment with alkali to 4-chlorosubstituted spiropyranes of the indole series; these, in contrast to the unsubstituted analogs, do not show photochromic properties.

The search for new photochromic compounds is intimately related to the structure—property problem. In the field of indoline spirobenzopyranes this problem has been solved, as evidence by the regularities already established of the effect of substituents in the indoline and benzopyrane segments on the spectral kinetic properties of photochromic compounds [1]. In spite of the large number of such investigations the problem of the relation between photochromic properties and chemical structure is far from its final solution. A substantial difficulty in this field is the absence of data on the photochromic properties of compounds with a substituent at position 4 of the pyrane ring. The method of Wizinger and Wenning [2] comprising condensation of a Fischer base with a salicyclic aldehyde is not applicable in this case.

The present work proposes a new synthesis of indoline spiropyranes with simultaneous introduction of a chlorine atom at position 4. It consists of heating an enaminohydroxyketone such as compound I with phosphorus oxychloride and cyclization of the resulting indolinium salt II by alkali to the spiro compound III.



III a R=H; b R=8-CH_3; c R=6-NO_2; d R=6,7-benzo

By means of this scheme we obtained the previously unknown indoline 4-chlorospiropyranes containing various substituents in the benzopyrane segment (IIIa-d). The structures were confirmed by PMR and mass spectra and elemental analysis. The chemical shifts of the most characteristic groups of the 4-chlorospiropyranes are shown in Table 1. Analysis of the

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