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SYNTHESIS OF NEW CONDENSED HETEROCYCLES BY THE FISCHER METHOD

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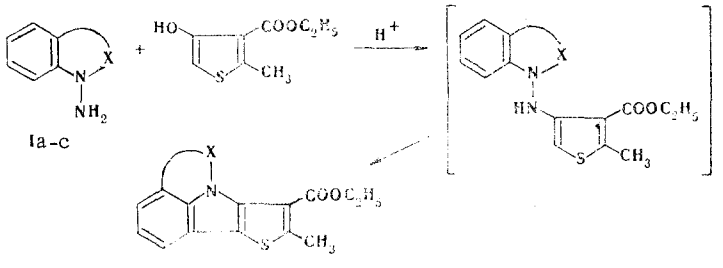
Derivatives of thienoindolopyridine, thienoindolopyrazine, and thienoindolodiazepine derivatives were obtained by Fischer condensation of 2-methyl-3-carbethoxy-4-hydroxythiophene with 1-amino derivatives of tetrahydroquinoline, tetrahydroquinoxaline, and dihydro[1,5]benozodiazepin-4-one. Derivatives of indoloindolopyridine and indoloindolodiazepine were obtained in the reaction of N-acetylindoxyl with 1-amino derivatives of tetrahydroquinoline and dihydro[1,5]benzodiazepin-4-one under similar conditions.

The Fischer method, which is the most nearly universal method for the synthesis of diverse derivatives of indole, has found application for the preparation of condensed heterocycles [1, 2]. The method has made it possible to also obtain thieno[3,2-b]indole derivatives by condensation of 2-methyl-3-carbethoxy-4-hydroxythiophene with phenylhydrazine [3]. This is an unusual example of the Fischer reaction. The hydroxythiophene derivative exists in the hydroxy form, and its reaction with phenylhydrazine probably leads to a thienylphenylhydrazine derivative, which then undergoes a rearrangement similar to the o-benzidine rearrangement [4].

Further developments in research dealing with the synthesis of new condensed heterocycles are presented in the present paper. Derivatives of thieno[3',2'-2,3]indolo[1,7a,7-ab]pyridine (IIa), thieno[3',2'-2,3]indolo[1,7a,7-ab]pyrazine (IIb), and thieno[3',2'-2,3]indolo[1,7a,7-ab]diazepine (IIc) were obtained in the reaction of 1-amino derivatives of tetrahydroquinoline, tetrahydroquinoxalin-3-one, and dihydro[1,5]benzodiazepin-4-one with 2-methyl-3-carbethoxy-4-hydroxythiophene.



I, II a X=—$(CH_2)_3$—; b X=—NH—C(=O)—CH_2—; c X=—NH—C(=O)—$(CH_2)_2$—

The reaction of 1-amino-1,2,3,4-tetrahydroquinoline (Ia), which was obtained by the method described in [5], with 2-methyl-3-carbethoxy-4-hydroxythiophene was carried out in acetic acid in the presence of concentrated hydrochloric acid at 70-80°C; the product was IIa. In other cases 1-amino-3-keto-1,2,3,4-tetrahydroquinoxaline (Ib) and 1-amino-2,3-dihydro[1,5]benzodiazepin-4-one (Ic), which were obtained by reduction of the corresponding nitroso derivatives [6, 7] with zinc in acetic acid, were subjected, without isolation from the reaction solution, to condensation with 2-methyl-3-carbethoxy-4-hydroxythiophene. As a result, we obtained IIb, c. Concentrated hydrochloric acid was also used as the catalyst.

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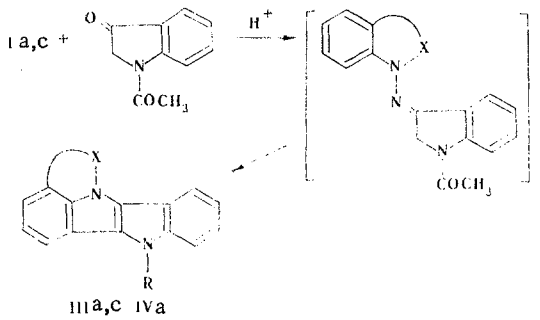
In contrast to the hydroxythiophene, N-acetylindoxyl exists in the keto form [8], and the formation of indoloindole derivatives can be represented in accordance with the usual scheme of the Fischer reaction.



IIIa,c IVa

IIIa X=—$(CH_2)_3$—, R=—$COCH_3$; IIIc X=—NH—C(=O)—$(CH_2)_2$—, R=—$COCH_3$; IVa X=—$(CH_2)_3$—, R=H

N-Acetylindoxyl was subjected to reaction with Ia, c under the conditions described above with p-toluenesulfonic acid as the catalyst. As a result, we obtained representatives of new heterocyclic systems, viz., derivatives of indolo[3,2-b]indolo[1,7a,7-ab]pyridine (IIIa) and indolo[3,2-b]indolo[1,7a,7-ab]diazepine (IIIc). In connection with the difficulty involved in the isolation of individual IIIa, it was subjected to alkaline hydrolysis, as a result of which we obtained indolo[3,2-b]indolo[1,7a,7-ab]pyridine (IVa).

The IR and UV spectroscopic data confirm the structures of the compounds obtained.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with UR-10 and Perkin-Elmer spectrometers. The UV spectra of solutions in dioxane were obtained with Hitachi EPS-3T and Perkin-Elmer 575 spectrophotometers.

8-Methyl-9-carbethoxy-2,3-dihydrothieno[3',2'-2,3]indolo[1,7a,7-ab]pyridine (IIa). A 7.5-g (0.05 mole) sample of 1-amino-1,2,3,4-tetrahydroquinoline was added with stirring to a suspension of 4.7 g (0.04 mole) of 2-methyl-3-carbethoxy-4-hydroxythiophene in 75 ml of 50% acetic acid, after which the mixture was heated on a boiling-water bath for 2 h. It was then cooled with ice, and the precipitate was removed by filtration and washed with water to give 9 g (30%) of a product with mp 107-109°C (from methanol). IR spectrum: 790 (thiophene ring) and 1690 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 220 (4.42), 240 (4.56), 270 (3.90), and 315 nm (4.03). Found: C 68.4; H 5.7; N 4.8; S 10.6%. $C_{17}H_{17}NO_2S$. Calculated: C 68.2; H 5.7; N 4.7; S 10.7%.

8-Methyl-9-carbethoxy-2,3-dihydrothieno[3',2'-2,3]indolo[1,7a,7-ab]pyrazin-2(3H)-one (IIb). A 6.5-g (0.1 mole) sample of zinc dust was added in small portions with stirring and ice cooling to a suspension of 3.5 g (0.02 mole) of 1-nitroso-3-keto-1,2,3,4-tetrahydroquinoxaline in 35 ml of glacial acetic acid (the zinc dust was added at such a rate that the temperature did not rise above 25°C). The precipitate (unchanged zinc and zinc acetate) was removed by filtration and washed on the filter with 10 ml of acetic acid. A 3.7-g (0.02 mole) sample of 2-methyl-3-carbethoxy-4-hydroxythiophene and 2 ml (0.02 mole) of concentrated hydrochloric acid were added to the combined filtrate (a solution of 1-amino-3-keto-1,2,3,4-tetrahydroquinoxaline in acetic acid), and the resulting reaction solution was heated with stirring on a boiling-water bath for 2 h. It was then cooled with ice and diluted with 75 ml of water, and the precipitate was removed by filtration and washed with water to give 2.4 g (38%) of a product with mp 291-293°C (from dioxane). IR spectrum: 800 (thiophene ring); 1680, 1710 (C=O); 3060, 3250 cm^{-1} (amide NH). UV spectrum, λ_{max} (log ε): 225 (4.48), 400 (4.34), and 420 nm (4.26). Found: C 60.9; H 4.5; N 8.9; S 9.9%. $C_{16}H_{14}N_2O_3S$. Calculated: C 61.1; H 4.5; N 8.9; S 10.2%.

9-Methyl-10-carbethoxy-1,2-dihydrothieno[3',2'-2,3]indolo[1,7a,7-ab][1,5]diazepin-3-one (IIc). This compound was obtained from 1-nitroso-2,3-dihydro[1,5]benzodiazepin-4-one by a method similar to that used to prepare IIb. Workup gave a product with mp 222-224°C (from dioxane) in 15% yield. IR spectrum: 785 (thiophene ring); 1660, 1690 (C=O); 3100, 3200

cm^{-1} (amide NH). UV spectrum, λ_{max} (log ε): 200 (4.15), 225 (4.53), 250 (4.34), and 310 nm (4.06). Found: C 62.4; H 5.3; N 8.4; S 9.9%. $C_{17}H_{16}N_2O_3S$. Calculated: C 62.2; H 4.9; N 8.5; S 9.8%.

8-Acetyl-1,2-dihydroindolo[3,2-b]indolo[1,7a,7-ab][1,5]diazepin-3(4H)-one (IIIc). This compound was obtained from 1-nitroso-2,3-dihydro[1,5]benzodiazepin-4-one and N-acetylindoxyl by a method similar to that used to prepare IIc. Workup gave a product with mp > 300°C (from acetic acid) in 12% yield. IR spectrum: 1650, 1685 (C=O); 3100, 3200 cm^{-1} (amide NH). Found: C 71.8; H 4.5; N 13.3%. $C_{19}H_{13}H_3O$. Calculated: C 71.9; H 4.8; N 13.2%.

2,3-Dihydroindolo[3,2-b]indolo[1,7a,7-ab]pyridine (IVa). Compound IIIa was obtained from 1-amino-1,2,3,4-tetrahydroquinoline and N-acetylindoxyl by a method similar to that used to prepare IIIa. The precipitated IIIa (1.33 g) was treated with 2.28 g (0.04 mole) of potassium hydroxide in 10 ml of methanol, and the mixture was refluxed for 10 min. It was then cooled and diluted with 30 ml of water to give 0.8 g (71%) of a product with mp 167-169°C (from dioxane). IR spectrum: 3380 cm^{-1} (indole ring NH). UV spectrum, λ_{max} (log ε): 213 (4.22), 240 (4.24), 264 (4.66), and 327 nm (4.33). Found: C 83.3; H 5.7; N 11.3%. $C_{17}H_{14}N_2$. Calculated: C 82.9; H 5.7; N 11.4%.

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INVESTIGATION OF THE REACTIVITIES AND TAUTOMERISM OF AZOLIDINES. 41.* "ANOMALOUS" PRODUCTS OF AMINOMETHYLATION OF 2-IMINOTHIAZOLIDIN-4-ONE WITH AQUEOUS FORMALDEHYDE AND PRIMARY AMINES

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The corresponding thiazolo[3,2-a]-1,3,5-triazines, which are substituted in the $C_{(7)}$ position of the condensed heterocyclic system, are formed as a result of aminomethylation of 2-iminothiazolidin-4-one with aqueous formaldehyde and several primary aliphatic amines. A 2,3-bis(aminomethyl)derivatives is formed when o-iodoaniline is used as the amino component.

In [1] we showed that the aminomethylation of 2-iminothiazolidin-4-one (Ia) and several of its 5-substituted derivatives with primary amines in the presence of an approximately threefold excess of formaldehyde leads to the formation of the corresponding 6-oxo-2,3,4,5,6,-7-hexahydrothiazolo[3,2-a]-1,3,5-triazines (II, R^3 = Alk, Ar; $R^1 = R^2 = H$, $R^1 = R^2 = CHAr$). Continuing our study of this reaction, we established that, in addition to the expected

*See [1] for Communication 40.

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