INDOLE DERIVATIVES

LXXXIX.* SYNTHESIS OF SOME DIKETO ESTERS OF THE INDOLE SERIES AND OF INDOLYLPYRAZOLES FROM THEM

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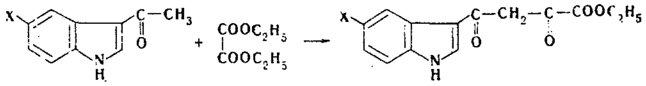
Diketo esters of the indole series have been synthesized by the condensation of 3-acetylindole, 3-acetyl-5-methoxyindole, and 3-acetyl-5-chloroindole with diethyl oxalate in the presence of sodium methoxide, and they have been converted into indolylpyrazolecarboxylic acids, some derivatives of these acids, and the corresponding indolylpyrazoles. It has been found previously that 3(5)-(indol-3-yl)pyrazole possesses a high antiinflammatory activity [2].

In the present work, in order to synthesize indolylpyrazoles, the diketo esters (Ia, b, c) have been obtained by the condensation of 3-acetylindole, 3-acetyl-5-methoxyindole, and 3-acetyl-5-chloroindole with diethyl oxalate.



I a-c

I a X=H; b X=OCH$_3$; c X=Cl

The following were used as condensing agents: sodium, sodium methoxide, and potassium tert-butoxide in tert-butanol. The best results were obtained with sodium methoxide in an excess of diethyl oxalate. In an alkaline medium the diketo esters (I) readily undergo solvolysis. Thus, compounds (Ia) and Ib) underwent partial cleavage even on recrystallization from ethanol, and therefore the unpurified substances were used for the subsequent stages.

The structure of the diketo esters (I) was confirmed by the results of elementary analysis and by IR spectroscopy (Table 1). The NMR spectrum of a 10% solution of (Ia) in deuterodimethylformamide showed that under these conditions the compound is approximately 50% enolized (Fig. 1).

The reaction of (Ia) with phenylhydrazine in the presence of traces of acetic acid gave the monophenylhydrazone of (II). An analysis of its IR spectrum gives grounds for considering that the reaction took place at the carbonyl group remote from the indole nucleus.

The same reaction of (Ia) but in boiling acetic acid led to ethyl 5-(indol-3-yl)-1-phenylpyrazole-3-carboxylate (III), the structure of which was confirmed by its IR spectrum and by its subsequent hydrolysis to the acid (IV), the decarboxylation of which led to the known 5-(indol-3-yl)-1-phenylpyrazole (V) [3].

The action of hydrazine hydrate on the ester (III) gave the hydrazide (VI) and the successive action on the acid (IV) of phosphorus pentachloride and ammonia gave the amide (VII).

The reaction of (Ia) with hydrazine hydrate (even in the cold) took place with the cleavage of a C–C bond and the formation of 3 -acetylindole, while on heating it gave a mixture of the hydrazone and the azine of the latter. However, when the reaction was performed in the presence of acetic acid, ethyl 5-(indol-3-yl)pyrazole-3-carboxylate (VIII) was obtained. The hydrolysis of this ester and the subsequent decarboxyl-

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* For Communication LXXXVIII, see [1].

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ation of the acid (IX) in the presence of a copper–chromium catalyst led to the known 3(5)-(indol-3-yl)pyrazole (Xa) [3]. The action on the ester (VIII) of hydrazine hydrate in ethanol yielded the hydrazide (XI). The amide of this acid (XII) was obtained from the hydrazide (XI) by its deamination with Raney nickel in ethanol.

3(5)-(5-Methoxyindol-3-yl)pyrazole (Xb) and 3(5)-(5-chloroindol-3-yl)pyrazole (Xc) (Table 2) were synthesized by the above-described method from the diketo esters (Ib) and (Ic).

EXPERIMENTAL

The IR spectra were recorded in paraffin oil on a UR-10 instrument and the PMR spectrum was taken on a JNM-4H-100 instrument with tetramethylsilane as internal standard.

Ethyl 4-(Indol-3-yl)-2,4-dioxobutanoate (Ia). With vigorous stirring, 7 g (0.13 mole) of sodium methoxide was added in portions to a mixture of 10 g (0.063 mole) of 3-acetylindole and 25 ml of diethyl oxalate. The mixture was stirred at room temperature for 1 h and was left to stand overnight, after which 300 ml of cold 3% acetic acid was added and the resulting mixture was stirred until a precipitate had formed. This was filtered off and washed with water acidified with acetic acid, and gave 15.8 g (96.5%) of (Ia) with mp 184-185°C (from ethanol). The individuality of (Ia) was established by TLC on "acid" alumina obtained by mixing 500 g of Al_2O_3 with 25 ml of glacial acetic acid. The eluent was ether and the spots were revealed by UV radiation.

The Phenylhydrazone (II). This was obtained from (Ia) and phenylhydrazine in the presence of a drop of CH_3COOH at room temperature. Found: N 11.9%. $C_{20}H_{19}N_3O_3$. Calculated: N 12.0%. IR spectrum, cm^{-1}: 3310, 3290 (N–H of an indole ring of a hydrazone); 1680 (ester C=O); 1640, 1590 (C=O attached to an indole ring, C=N).

Ethyl 5-(Indol-3-yl)-1-phenylpyrazole-3-carboxylate (III). To a mixture of 3 g (0.012 mole) of (Ia) and 30 ml of glacial acetic acid was added 1.2 ml (0.012 mole) of phenylhydrazine, and the resulting mixture was boiled under reflux for 30 min and was then cooled and poured into 200 ml of water. The precipitate was filtered off and recrystallized from dilute ethanol, giving 3.4 g (87%) of (III) with mp 144°C. Found: C 72.5; H 5.6; N 12.4%. $C_{20}H_{17}N_3O_2$. Calculated: C 72.5; H 5.2; N 12.7%. IR spectrum, cm^{-1}: 3390 (N–H), 1695 (C=O).

5-(Indol-3-yl)-1-phenylpyrazole-3-carboxylic Acid (IV). To a solution of 1.75 g (5.3 mmoles) of (III) in 20 ml of ethanol was added 20 ml of a 2 N

TABLE 1. Characteristics of the Compounds Obtained

Compound	X	mp, °C	Empirical formula	Found, %				Calc., %				IR spectrum, ν, cm^{-1}				Yield, %
				C	H	Cl	N	C	H	Cl	N	N–H	$C=O_{ester}$	$C=O^*_{carbonyl}$	C–O–C	
Ia	H	184—185	$C_{14}H_{13}NO_4$	65,0	5,03	—	5,9	64,9	5,05	—	5,4	3280	1720	1615—1590	1280 1140	96,5
Ib	OCH_3	180—182	$C_{15}H_{15}NO_5$	62,3	5,22	—	4,8	62,3	5,2	—	4,8	3280	1720	1630—1585	1280 1140	97,6
Ic	Cl	214—215 (dec.)	$C_{14}H_{12}ClNO_4$	57,5	4,4	12,0	4,4	57,2	4,1	12,0	4,8	3280	1723	1610—1575	1280 1135	75,0†

*Broad multiplet or band.

†After washing with ethanol to chromatographic purity.

TABLE 2. Characteristics of the Compounds Synthesized

Compound	mp, °C	Empirical formula	Found, %				Calc., %				IR spectrum, ν, cm^{-1}			Decomp. pt. of the hydrochloride	Cl, %	
			C	H	Cl	N	C	H	Cl	N	N–H	N–H	C=N		found	calc.
Xa	160—161*	—	—	—	—	—	—	—	—	—	3330	3200	1608	216—218	—	—
Xb	161—162	$C_{12}H_{11}N_3O$	68,1	5,8	—	19,5	67,6	5,2	—	19,8	3340	3180	1608	218—220	14,3	14,2
Xc	142,5—143	$C_{11}H_8ClN_3$	60,5	3,95	15,9	19,3	60,7	3,7	16,3	19,3	3330	3180	1608	245—251	27,2	27,9

*According to the literature [3], mp 159-160°C.

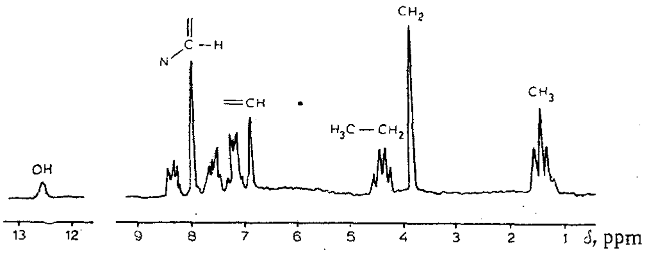

Fig. 1. PMR spectrum of ethyl 4-(indol-3-yl)-2,4-dioxobutanoate (Ia).

solution of NaOH. The mixture was boiled for 2 h and was then cooled, poured into 100 ml of water, and neutralized with 2 N hydrochloric acid. This gave 1.45 g (90%) of (IV) with mp 234-236°C (from dilute ethanol). Found: C 71.5; H 4.6; N 13.3%. $C_{18}H_{13}N_3O_2$. Calculated: C 71.3; H 4.3; N 13.8%. IR spectrum, cm^{-1}: broad band at 3250-3280 (N−H), 2600-2800 (OH of an acid, ass.), 1695 (C=O).

5-(Indol-3-yl)-1-phenylpyrazole (V). Compound (IV) (0.8 g) was heated at 230-240°C until the evolution of CO_2 ceased. The residue was crystallized from a mixture of benzene and n-octane, giving 0.46 g of (V) with mp 109-111°C [3].

5-(Indol-3-yl)-1-phenylpyrazole-3-carbohydrazide (VI). To a solution of 0.5 g of (III) in 15 ml of ethanol was added 0.8 ml of hydrazine hydrate and the mixture was boiled until a chromatographic check showed the absence of (III) from the reaction mixture. The ethanol was distilled off and the residue was washed with water and recrystallized from dilute ethanol to give 0.3 g of (VI) with mp 201°C. Found: C 68.3; H 4.7; N 21.9%. $C_{18}H_{15}N_5O$. Calculated: C 68.1; H 4.8; N 22.1%. IR spectrum, cm^{-1}: 3420, 3320, 3215 (N−H), 1680 (C=O).

5-(Indol-3-yl)-1-phenylpyrazole-3-carbonamide (VII). With ice cooling, 0.5 g of PCl_5 was added to a suspension of 0.74 g of (IV) in 200 ml of absolute ether, and the mixture was stirred at room temperature until the solid matter had dissolved; the resulting ethereal solution of the acid chloride was added by drops to 20 ml of a 20% solution of ammonia cooled with a mixture of ice and salt. The precipitate that deposited was filtered off, washed with water, and recrystallized from dilute ethanol, giving 0.57 g of (VII) with mp 211°C. Found: C 71.6; H 4.6; N 18.3%. $C_{18}H_{14}N_4O$. Calculated: C 71.5; H 4.7; N 18.5%. IR spectrum, cm^{-1}: 3465, 3300, 3180 (N−H), 1680, 1655 (amide C=O groups).

Ethyl 5-(Indol-3-yl)pyrazole-3-carboxylate (VIII). To a mixture of 100 ml of isopropanol, 40 ml of glacial acetic acid, and 20 ml of hydrazine hydrate at 20-22°C, 10 g (0.04 mole) of (Ia) was added in portions, and the resulting mixture was slowly heated to 60-70°C, held at this temperature until the yellow color had disappeared, and it was then poured into 500 ml of water. The precipitate was filtered off, washed with water, and recrystallized from dilute ethanol, giving 8.5 g (86%) of (VIII) with mp 183-185°C. Found: C 66.1; H 5.2; N 16.4%. $C_{14}H_{13}N_3O_2$. Calculated: C 65.9; H 5.1; N 16.5%. IR spectrum, cm^{-1}: 3440 (N−H of an indole ring), 3145 (N−H of a pyrazole ring), 1715 (C=O).

5-(Indol-3-yl)pyrazole-3-carboxylic Acid (IX). A solution of 8.5 g (0.033 mole) of (VIII) in 65 ml of hot ethanol was treated with 65 ml of 20% NaOH solution, and the mixture was boiled for 1 h 30 min. After cooling and acidification with hydrochloric acid, the precipitate was filtered off and washed with water to give 7.3 g (95%) of (IX) with mp 315-316°C (decomp; from water). IR spectrum, cm^{-1}: 3390 (N−H), 3180 (N−H), 2540-2780 (OH of a carboxy group, ass.), 1695 (C=O).

3(5)-(Indol-3-yl)pyrazole (Xa). A mixture of 2 g of (IX) and 0.05 g of copper−chromium catalyst was heated in a current of nitrogen at 310-300°C until the evolution of CO_2 ceased. The residue was dissolved in hot ethanol, diluted with a fivefold amount of water, and extracted with ether, and the ethereal solution was dried with potassium carbonate. The ether was distilled off and the residue was recrystallized from benzene, giving 1.0 g (62%) of (Xa) with mp 160-161°C [3].

5-(Indol-3-yl)pyrazole-3-carbohydrazide (XI). From 1 g of (VIII) and 1.3 ml of hydrazine hydrate was obtained 0.75 g of (XI). mp 288 290°C (from ethanol). Found: C 59.6; H 4.7; N 28.5%. $C_{12}H_{11}N_5O$. Calculated: C 59.7; H 4.6; N 29.0%. IR spectrum, cm^{-1}: 3420, 3350, 3200 (N−H), 1635, 1645 (C=O).

5-(Indol-3-yl)pyrazole-3-carbonamide (XII). A suspension of 1 g of (XI) in 60 ml of ethanol was treated with 10 g of Raney nickel. The mixture was boiled until the evolution of ammonia ceased (about three days). The nickel was filtered off and washed with ethanol. The ethanolic solution was evaporated and the residue was recrystallized from water to give 0.32 g of (XII) with mp 268-269°C. Found: C 63.7; H 4.5; N 24.0%. $C_{12}H_{10}N_4O$. Calculated: C 63.7; H 4.5; N 24.8%. IR spectrum, cm^{-1}: 3468, 3405, 3375, 3190, (broad) (N–H), 1690, 1660 (amide C=O groups).

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