SYNTHESIS OF UNSATURATED KETONES AND DERIVATIVES OF 2-PYRAZOLINE CONTAINING AN INDOLE NUCLEUS

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The crotonic condensation of 3-acetylindole, its N-methyl derivative, 3-formyl-1-methylindole, and 3-formyl-6-nitroindole with various aldehydes and methyl ketones in an alkaline medium has yielded a number of unsaturated ketones, some of which have been characterized as their 2,4-dinitrophenylhydrazones. The reaction of some of these unsaturated ketones with phenylhydrazine has yielded derivatives of 1-phenyl-2-pyrazoline, which possess luminescent properties.

In a preceding paper [1] we described the preparation of α,β-unsaturated ketones by the condensation of 3-formylindole with methyl ketones and discussed the causes of the low reactivity of the resulting carbonyl compounds of indole. In this work we have condensed 3-acetyl-, 3-acetyl-1-methyl-, 3-formyl-1-methyl-, and 3-formyl-6-nitroindoles with various carbonyl compounds (see Table 1).

We found that 3-acetylindole takes part in the crotonic condensation with considerably greater difficulty than 2-acetylpyrrole [2]; the reaction takes place in ethylene glycol on heating to 120–135° C for 20–30 min in the presence of small amounts of caustic potash (method A). After the experimental part of this investigation had been completed, we found out about a paper [3] which described the analogous synthesis of the indole chalcones I and II, but with boiling of the reactants in concentrated aqueous caustic potash for 24 hr. The same paper describes the crotonic condensation of 3-acetyl-1-methyl-indole with benzaldehyde, which gave an unsaturated ketone in the form of an oil. We were easily able to synthesize this chalcone analog VI (Table 1) in the crystalline state with mp 112.5–113° C, and also to effect the condensation of 3-acetyl-1-methylindole with other aromatic aldehydes (see VII–IX).

It must be mentioned that the N-methylated carbonyl compounds of indole generally take part in crotonic condensation in the presence of alkaline catalysts considerably more readily than the corresponding nonmethylated compounds. For example, chalcone VI was obtained in satisfactory yield both in ethylene glycol at 125–135° C and on brief boiling in ethanol in the presence of alkali (method B). The greater reactivity of 3-formyl-1-methylindole in comparison with the nonmethylated indolealdehyde is particularly striking. While the latter reacts with methyl ketones only at 160–180° C in the presence of piperidine, [1,4], 3-formyl-1-methylindole reacts readily even at 120–135° C, and caustic alkali can be used as condensing agent. This is due to the fact that the nonmethylated carbonyl compounds of indole (for example, the 3-acetyl- and 3-formylindoles) form the corresponding anions in the presence of strong bases [5], as a result of which the electron density on the carbonyl group is increased and their reactivity is lowered [6]. Furthermore, the 3-formyl- and 3-acetylindoles take part in the reaction with greater difficulty because of the possible formation of intermolecular hydrogen bonds of the N—H...O=C type, as has been reported previously for analogous pyrrole derivatives [7]. For this reason, it is characteristic that the methylated chalcones VI and VII have lower melting points than the nonmethylated ketones I and II.

In the condensation with acetophenone and its derivatives, the introduction of a nitro group into position 6 of 3-formylindole has no appreciable effect on the reaction, and the chalcones XVII–XIX were obtained by the same method as before [1] (method D). The introduction of a nitro group into the indole nucleus naturally increases the acidic properties of the hydrogen of the imino group and thereby facilitates the formation of the corresponding anions in an alkaline medium, and although it also increases the energy of the hydrogen bonds it simultaneously decreases the electron-donating influence of the indol-3-yl radical, which has an adverse effect on the reactivity of the formyl group.

We have also obtained two indole analogs of the para-dichalcones, XX and XXI, by reacting 3-formyl-1-methylindole with p-diacetylbenzene, and 3-acetylindole with terephthalic dialdehyde. In ethanolic solution, compound XX has a bright-green fluorescence, while the dichalcone XXI does not fluoresce. In general, all the chalcone analogs in which the carbonyl group is separated from the indole ring by a vinylene group, for example, X–XV, possess luminescent properties, while their isomers obtained from 3-acetyl- and 3-acetyl-1-methylindole do not possess this property. Thus, our previous conclusion [8] that a strong donor-acceptor interaction (indol-3-yl is a strong

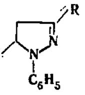
Table 1. Indole Chalcone Analogs RCOCH=CHR'

Compound	R	R′	Mp, °C	Method of synthesis	Empirical formula	N, %		Yield, %
						found	calculated	
I	Indol-3-yl	Phenyl	232—233	A	$C_{17}H_{13}NO$	5.86; 5.79	5.66	56
II	Indol-3-yl	Anisyl	204—205	A	$C_{18}H_{15}NO_2$	5.02; 4,92	5,00	54
III	Indol-3-yl	2,4-Dimethoxyphenyl	184—185	A	$C_{19}H_{17}NO_3$	4.85; 4,76	4.56	46
IV	Indol-3-yl	4-Dimethylaminophenyl	257—258	A	$C_{19}H_{18}N_2O$	9.70; 9.58	9.65	40
V	Indol-3-yl	2-Furyl	183	A	$C_{15}H_{11}NO_2$	5.98; 5.98	5.90	60
VI	1-Methylindol-3-yl	Phenyl	112,5—113	A, B	$C_{18}H_{15}NO$	5.53; 5.46	5.36	62
VII	1-Methylindol-3-yl	Anisyl	138—138,5	A, B	$C_{19}H_{17}NO_2$	5,02; 4.88	4.81	59
VIII	1-Methylindol-3-yl	2,4-Dimethoxyphenyl	182	A	$C_{20}H_{19}NO_3$	4,62; 4,60	4.36	50
IX	1-Methylindol-3-yl	1-Methylindol-3-yl	189—190	C	$C_{21}H_{18}N_2O$	8,87; 8.85	8,91	30
X	Phenyl	1-Methylindol-3-yl	143,5	A, B	$C_{18}H_{15}NO$	5.59; 5.36	5.36	66
XI	4-Tolyl	1-Methylindol-3-yl	154	B	$C_{19}H_{17}NO$	5.18; 5.06	5.09	55
XII	4-Anisyl	1-Methylindol-3-yl	129,5	A, D	$C_{19}H_{17}NO_2$	5.07; 4.92	4,81	50
XIII	2,4-Dimethoxyphenyl	1-Methylindol-3-yl	137,5	B	$C_{20}H_{19}NO_3$	4.46; 4,42	4.36	25
XIV	4-Chlorophenyl	1-Methylindol-3-yl	167	B	$C_{18}H_{14}ClNO$	4.87; 4.77	4.74	48
XV	4-Nitrophenyl	1-Methylindol-3-yl	232	B	$C_{18}H_{14}N_2O_3$	9.36; 9.35	9.11	35
XVI	Pyrid-4-yl	1-Methylindol-3-yl	154,5—155	A, D	$C_{17}H_{14}N_2O$	10.95; 10.81	10,87	50
XVII	Phenyl	4-Dimethylaminophenyl	227	D	$C_{17}H_{12}N_2O_3$	9,68; 9.73	9.58	40
XVIII	4-Chlorophenyl	4-Dimethylaminophenyl	293,5	D	$C_{17}H_{11}ClN_2O_3$	8,77; 8,73	8.59	55
XIX	4-Nitrophenyl	4-Dimethylaminophenyl	320	D	$C_{17}H_{11}N_3O_5$	12,59; 12.40	12,46	60

electron donor) at a definite length of the conjugation chain is necessary for the luminescence of α-β-unsaturated ketones is confirmed.

Only very recently has information appeared in the literature on the preparation of 2-pyrazolines containing an indol-3-yl substituent in position 3 [9]. Nevertheless, such indolyl-substituted heterocycles are of definite interest for a study of their optical properties. By boiling some of the indole chalcones that we have synthesized with phenylhydrazine in ethanolic solution in the presence of glacial acetic acid we succeeded in synthesizing a number of 2-pyrazolines, XXII–XXVI (Table 2). The 2-pyrazolines obtained consisted of high-melting colorless or yellow crystals readily soluble in the usual organic solvents. We confirmed their structure by means of their IR spectra, which clearly showed the absorption bands at ~1600 cm^{-1} (stretching vibrations of a C=N bond), at ~1500 cm^{-1} (stretching vibrations of a phenyl group) and at ~1325 cm^{-1} (stretching vibrations of Ar—N) that are characteristic for 1, 3, 5-triarylpyrazolines and their heterocyclic analogs [10, 11]. In addition to this, in carbon tetrachloride solution compound XXIII lacked the band of the stretching vibrations of an N—H group in the 3200–3500-cm^{-1} region. The Knorr reaction [12] (the formation of a blue coloration on the addition of concentrated sulfuric acid and ferric chloride) was positive for all the 2-pyrazolines obtained. Toluene solutions of compounds XXII–XXVI have a bright blue luminescence, which is also characteristic for pyrazolines [13].

Table 2. 1-Phenyl-3-R-5-R'-2-pyrazolines



Compound	R	R′	Mp, °C	Empirical formula	N, %		Yield, %
					found	calculated	
XXII	Indol-3-yl	Phenyl	197	$C_{23}H_{20}N_3$	12.41; 12.37	12.46	65
XXIII	1-Methylindol-3-yl	Phenyl	235	$C_{24}H_{21}N_3$	11.95; 11.91	11.68	55
XXIV	Phenyl	1-Methylindol-3-yl	146,5	$C_{24}H_{21}N_3$	11.88; 11.64	11.68	60
XXV	Tolyl	1-Methylindol-3-yl	145,5	$C_{25}H_{23}N_3$	11.73; 11.62	11.50	62
XXVI	Pyrid-4-yl	Indol-3-yl	233	$C_{22}H_{19}N_4$	16.67; 16.56	16.56	70

EXPERIMENTAL

3-Acetylindole was obtained by the acetylation of indole with N, N-dimethylacetamide in the presence of phosphorus oxychloride by the Vilsmeier reaction [14], mp 191° C. 3-Acetyl-1-methylindole was obtained by methylating 3-acetylindole with dimethyl sulfate [15], mp 96° C. 1-Methylindole-3-aldehyde was synthesized as described by Rodionov and Veselovskaya [16]. 3-Formyl-6-nitroindole was obtained by nitrating the indolealdehyde [17].

Crotonic condensation. Method A. A solution of equimolecular amounts (0.01 mole) of the appropriate aldehyde and methyl ketone in 8–10 ml of ethylene glycol was treated with 1 ml of a 40% solution of potassium hydroxide and the mixture was heated at 120–135° C for 20–30 min. The cooled solution was treated dropwise with 1–2 ml of glacial acetic acid, until it was feebly acid, and the precipitate that had deposited was filtered off. It was recrystallized from ethanol or some other organic solvent.

Method B. A solution of equimolecular amounts of aldehyde and methyl ketone (0.01 mole) in 7–10 ml of ethanol was boiled for 15–25 min in the presence of 1 ml of 20% caustic soda solution. The product was worked up as in method A.

Method C. Similar to method A but the reaction was carried out at 180–190° C for 40 min.

Method D. A solution of stoichiometric amounts of aldehyde and ketone (0.01 mole) in 8–10 ml of ethylene glycol was treated with 1 ml of piperidine and heated under reflux at 170–185° C for 20–30 min. After cooling, 5–10 ml of water and 1 ml of acetic acid were added; the crystals that deposited were recrystallized from ethanol.

Some of the indole analogs of the chalcones were characterized by means of their 2, 4-dinitrophenylhydrazones, whose absorption maxima in the visible region of the spectrum were measured in chloroform solution on an SF-10 spectrophotometer (see Table 3).

1,4-Di[3'-(1"-Methylindol-3"-yl)acryloyl]benzene (XX). A solution of 0.01 mole of 1,4-diacetylbenzene and 0.02 mole of 1-methylindole-3-aldehyde in 10 ml of ethylene glycol was treated with 1 ml of 40% caustic soda solution and heated under reflux at 120–135° C for 20 min. The crystals that deposited were boiled with ethanol. Yellow-orange plates with mp 277–278° C. Yield 70%. Found, %: N 6.28. Calculated for $C_{30}H_{24}N_2O_2$, %: N 6.30.

Table 3. 2,4-Dinitrophenylhydrazones of Indole Chalcones

Chalcone	Mp, °C	λ_{max}, nm	Empirical formula	N, %	
				found	calculated
I	244	424	$C_{23}H_{17}N_5O_4$	16.50; 16.57	16.37
II	215–216	428	$C_{24}H_{19}N_5O_6$	15.24; 15.46	15.31
X	237–238	438	$C_{24}H_{19}N_5O_4$	15.92; 16.00	15.87
XI	227,5	431	$C_{25}H_{21}N_5O_4$	15.43; 15.62	15.38
XII	235	441	$C_{25}H_{21}N_5O_5$	14.76; 15.09	14.86
XIV	233	442	$C_{24}H_{18}ClN_5O_4$	14.64; 14.67	14.73
XVI	226	418	$C_{23}H_{18}N_6O_4$	19.08; 19.19	19.02

1,4-Di[1'-(indol-3"-yl)-3'-acryloyl]benzene (XXI). This was obtained in a manner similar to the preceding compound from terephthalic dialdehyde and 3-acetylindole. Yellow plates with mp 372° C. Yield 45%. Found, %: N 6.93. Calculated for $C_{28}H_{20}N_2O_2$, %: N 6.73.

2-Pyrazolines. A solution of 0.005 mole of the appropriate ketone and 0.007 mole of phenylhydrazine in 10–15 ml of methanol was treated with 0.5–1 ml of acetic acid and was boiled under reflux for 1.5–2 hr. The crystals that deposited after cooling were filtered off and recrystallized from ethanol.

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