SYNTHESIS OF CHALCONE ANALOGS AND DERIVATIVES OF 2-PYRAZOLINE FROM 3-FORMYLINDOLE

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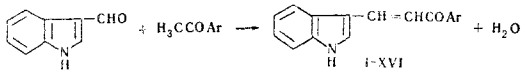
By the crotonic condensation in an alkaline medium of 3-formylindole with various aromatic and heterocyclic methyl ketones, and also with cyclopentanone, cyclohexanone, and 1,4-diacetylbenzene, we have synthesized nineteen α,β-unsaturated ketones. The majority of them were characterized as the 2,4-dinitrophenylhydrazones, the absorption maxima of which in chloroform are given. Some considerations are expressed concerning the reactivity of 3-formyl- and 3-acetylindoles. Ten 3-aryl-1-phenyl-5-(indol-3-yl)-2-pyrazolines and their analogs with a 3-heterocyclic residue have been synthesized by the reaction of 3-aryl-1-(indol-3-yl)propen-3-ones and the corresponding analogs with phenylhydrazine. Some of the compounds synthesized possess a bright luminescence.

In spite of the fact that indole derivatives have been widely studied, α,β-unsaturated ketones of the chalcone type containing this heterocycle have not yet been investigated. Only one paper is known [1] in which products of the crotonic condensation of 3-formylindole with acetophenone, 4-methylacetophenone, and 4-methoxyacetophenone are described.

Continuing a series of investigations of the synthesis of α,β-unsaturated ketones and their derivatives and on the study of their properties, we decided to effect the crotonic condensation of 3-formylindole with various aromatic and heterocyclic methyl ketones:



Condensation takes place with satisfactorily yields in ethylene glycol in the presence of piperidine on heating to from 160 to 180° C for 5–30 min. The reaction of 3-formylindole takes place somewhat more readily and with higher yields when electron-accepting substituents (chlorine, nitro group) are present in the aromatic nucleus of the ketonic component. Conversely, electron-donating groups inhibit the crotonic condensation. Thus, in spite of repeated attempts under various conditions, we were unable to isolate products of the reactions with 4-amino-, 4-dimethylamino-, and 2,4,6-trimethoxyacetophenones in adequately pure form. Attempts to perform the crotonic condensation of 3-acetylindole with various aromatic and heterocyclic aldehydes also proved unsuccessful. The latter circumstance is apparently due to features of the conjugation of the carbonyl group with the electron pair of the nitrogen atom of the indole ring. Because of this, some authors regard 3-acylindoles as vinylogs of of amides, which is confirmed to a certain extent by a study of their IR spectra [3,4]. 3-Formylindole takes part in condensation with considerably greater difficulty than 2-formylpyrrole [5], and the latter with considerably greater difficulty than its furan [6], thiophene [7], and selenophene [8] analogs.

The lower reactivity of 2-formylpyrrole as compared with its isologs has been explained by the strong electron-donating nature of the pyrrole nucleus [9] and by the existence of hydrogen bonds [10]. Both these factors must apply to an even greater extent to 3-formylindole, which is confirmed, on the one hand, by the IR spectra [11] and, on the other hand, by the fact that the reactivity of 1-acetyl-3-formylindole is considerably higher [12]. It is interesting that attempts to use solutions of caustic alkalis in place of piperidine, as has been done in the case of 2-formylpyrrole [5], for the crotonic condensation of 3-formylindole with methyl ketones proves unsuccessful. This must be due to the fact that in a strongly alkaline medium the formylindole can form the corresponding anion, and as a result of this, the electron density on the carbonyl group is increased, and its reactivity is decreased, still further [13]. At the same time, of course, because of the greater possibilities for the delocalization of the negative charge, indole must possess a more acidic nature than pyrrole.

All the indole analogs of the chalcones that we synthesized, **I–XVI** (Table 1), are crystalline substances readily soluble in ethanol, acetic acid, chloroform, and other organic solvents. Order and Lindwal [1] gave mp 164–165° C for 1-(indol-3-yl)-3-(4-tolyl)propen-3-one (**II**); however, in all cases of our synthesis of **II**, including synthesis under the conditions described by Order and Lindwal, only a substance with mp 171–172° C was obtained the analytical data of which corresponded to its empirical formula. Compounds **I–XVI** possess halochromic properties, and in mineral acid solutions their color deepens to orange or red-violet. In addition to this, on dissolution in alcoholic solutions of alkalis they form the corresponding anions, the color of which is also deeper than in a neutral solvent. Some of the chalcone analogs obtained luminescence under the influence of untraviolet radiation in the solid state or in solutions. Thus, crystals of **III** and **VIII** give a green, **XII** a yellow, and **XV** an orange luminescence. Alcoholic solutions of almost all the indole chalcones possess a green or blue luminescence.

The 2,4-dinitrophenylhydrazones of the chalcones synthesized are formed with some difficulty when the substances are boiled for a long time (1–3 hr) with ethanolic solutions of 2,4-dinitrophenylhydrazine in the presence of small amounts of hydrochloric acid (Table 1). In some cases (**XI**, **XII**), resinification takes place under these conditions.

We have also carried out the crotonic condensation of 3-formylindole with cyclopentanone, cyclohexanone, and 1,4-diacetylbenzene. Under conditions analogous to those described above, we obtained 2,5-di(indol-

Table 1

Characteristics of the Compounds Obtained

Compound	Ar	Mp, °C	External form	Time of heating	Empirical formula	N, % found	N, % calculated	Yield, %	2,4-Dinitrophenylhydrazones mp, °C	λ_{max}, nm	empirical formula	N, % found	N, % calculated
I	Phenyl	166[1]*	Yellow plates	5	$C_{17}H_{18}NO$	— —	—	64	249	441	$C_{23}H_{17}N_5O_4$	16.40; 16,51	16.37
II	4-Tolyl	171—172[1]*	Yellow needles	30	$C_{18}H_{15}NO$	5.49; 5.55	5.32	61	235	426	$C_{24}H_{19}N_5O_4$	16.13; 16.14	15.87
III	4-Anisyl	170[1]*	Yellow needles	5	$C_{18}H_{15}NO_2$	— —	—	68	232	427	$C_{24}H_{19}N_5O_5$	15.34; 15.47	15.31
IV	2,4-Dimethoxyphenyl	172—173	Yellow plates	20	$C_{19}H_{17}NO_3$	4.72; 4.72	4.56	31	184	380	$C_{25}H_{21}N_5O_6$	14.63; 14.66	14.37
V	4-Chlorophenyl	192—193	Yellow needles	10	$C_{17}H_{12}ClNO$[2]*	4.92; 4.98	4.98	75	228—229	420	$C_{23}H_{16}ClN_5O_4$	15.36; 15.41	15.18
VI	4-Bromophenyl	194	Yellow needles	20	$C_{17}H_{12}BrNO$[3]*	4.35; 4.45	4.29	54	230	418	$C_{23}H_{16}BrN_5O_4$	13.73; 13.81	13.83
VII	4-Nitrophenyl	228—229	Red plates	6	$C_{17}H_{12}N_2O_3$	9.60; 9.79	9.59	55	—	—	—	— —	—
VIII	1-Naphthyl	214	Yellow-green prisms	30	$C_{21}H_{15}NO$	4.70; 4.79	4.71	62	250	430	$C_{27}H_{19}N_5O_4$	14.56; 14.72	14.67
IX	2-Naphthyl	218	Yellow-green plates	25	$C_{21}H_{15}NO$	4.65; 4.71	4.71	70	227—228	425	$C_{27}H_{19}N_5O_4$	14.57; 14,65	14.67
X	4-Biphenylyl	253	Yellow-green plates	30	$C_{23}H_{17}NO$	4.29; 4.30	4.33	80	232—233	428	$C_{29}H_{21}N_5O_4$	13.83; 13.87	13.91
XI	2-Pyrryl	266	Colorless plates	15	$C_{15}H_{12}N_2O$	11.89; 11.89	11.85	30	—	—	—	— —	—
XII	2-Furyl	168	Yellow needles	20	$C_{15}H_{11}NO_2$	6.12; 6.20	5.90	58	—	—	—	— —	—
XIII	2-Thienyl	164	Orange-yellow prisms	30	$C_{15}H_{11}NOS$[4]*	5.62; 5.75	5.53	40	232	426	$C_{21}H_{15}N_5O_4S$	16.19; 16.37	16.15
XIV	2-Selenienyl	167	Orange prisms	20	$C_{15}H_{11}NOSe$[5]*	— —	—	50	243	422	$C_{21}H_{15}N_5O_4Se$	14.74; 14.83	14.59
XV	3-Pyridyl	191	Yellow plates	10	$C_{16}H_{12}N_2O$	11.11; 11.15	11.20	56	—	—	—	— —	—
XVI	4-Pyridyl	257—258	Yellow plates	5	$C_{16}H_{12}N_2O$	11.19; 11.26	11.20	48	244	416	$C_{22}H_{16}N_6O_4$	19.53; 19.56	19.62

[1]* According to the literature [1], for I mp 166° C, for II mp 164—165° C, for III mp 170° C. [2]* Found, %: Cl 11.46, 12.83. Calculated, %: Cl 11.60. [3]* Found, %: Br 24.48, 24.60. Calculated, %: Br 24.50. [4]* Found, %: S 12.60, 12.64. Calculated, %: S 12.65. [5]* Found, %: Se 26.23, 26.44. Calculated, %: Se 26.30.

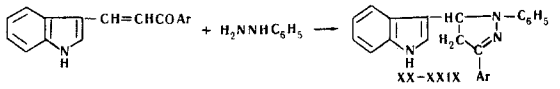
Table 2

3-Aryl-5-(indol-3-yl)-1-phenyl-2-pyrazolines and Their 3-Heterocyclic Analogs

Compound	Aryl (heteryl)	Mp, °C	Time of boiling, hr	Luminescence		Empirical formula	N, %		Yield, %
				crystals	solution in toluene		found	calculated	
XX	Phenyl	176—177	2.5	Blue	Blue	$C_{23}H_{19}N_3$	12.36; 12.61	12.46	62
XXI	4-Tolyl	177—178	2	Blue	Blue	$C_{24}H_{21}N_3$	12.06; 12.14	11.99	70
XXII	4-Anisyl	156	2.5	Blue	Fairly deep blue	$C_{24}H_{21}N_3O$	11.63; 11.67	11.44	65
XXIII	4-Chlorophenyl	160—161	8	Violet	Violet blue	$C_{23}H_{18}ClN_3$	11.22; 11.30	11.32	35
XXIV	4-Bromophenyl	180—181	5	Violet	Violet blue	$C_{23}H_{18}BrN_3$	9.79; 9.96	10.07	34
XXV	1-Naphthyl	172—173	3	Green	Green	$C_{27}H_{21}N_3$	10.77; 10.85	10.88	63
XXVI	2-Naphthyl	206	5	Green	Blue	$C_{27}H_{21}N_3$	11.06; 11.15	10.88	60
XXVII	4-Biphenylyl	147	6	Violet	Blue-violet	$C_{29}H_{23}N_3$	10.06; 10.20	10.16	40
XXVIII	2-Thienyl	174—175	2	Green	Blue	$C_{21}H_{17}N_3S$	12.43; 12.47	12.27	67
XXIX	2-Selenienyl	198	2	Yellow-green	Blue	$C_{21}H_{17}N_3Se$	10.86; 11.05	10.77	58

3-ylmethylene)cyclopentanone (**XVII**), 2,6-di(indol-3-ylmethylene)cyclohexanone (**XVIII**), and 1,4-di[β-(indol-3-yl)acryloyl]benzene (**XIX**). Compounds **XVII–XIX** are characterized by particularly deep colorations in solutions of strong acids and alkalis. Thus, for example, in acetic acid solution containing a small amount of sulfuric acid, **XVII** has a blue-violet color, and in an alkaline caustic soda solution it has a cherry-red color.

Up to the present time, no 2-pyrazolines containing an indole radical have been known. We have treated a number of our α,β-unsaturated ketones with phenylhydrazine and isolated the corresponding 3-aryl-5-(indol-3-yl)-1-phenyl-2-pyrazolines or their 3-heterocyclic analogs (**XX–XXIX**, Table 2).



The 2-pyrazolines synthesized are high-melting crystalline substances soluble in ethanol, toluene, and benzene. They all possess a bright luminescence both in the solid state and in solutions.

EXPERIMENTAL

The 3-formylindole was obtained by Smith's method [14] and the 1,4-diacetylbenzene as described by Sladkov and Vitt [15].

3-Aryl-1-(indol-3-yl)propen-3-ones (I–XVI, Table 1). Stoichiometric amounts of 3-formylindole (0.01 mole) and the appropriate methyl ketone were dissolved in 10–15 ml of ethylene glycol, 0.5 ml of piperidine was added, and the mixture was heated under reflux at 160–180° C for 5–30 min. After cooling, 5–10 ml of water and 0.5–1 ml of acetic acid were added to the flask. The crystals that deposited were filtered off and recrystallized: **I–VIII** and **X–XV** from ethanol and **IX** and **XVI** from dioxane.

2,5-Di(indol-3-ylmethylene)cyclopentanone (XVII). A solution of 0.2 mole of 3-formylindole and 0.01 mole of cyclopentanone in 10 ml of ethylene glycol was treated with 0.5 ml of piperidine and was then heated at 175–180° C for 10 min. After cooling, 5 ml of water and 0.5 ml of acetic acid were added. The crystals that deposited were filtered off and recrystallized from ethanol. Orange prisms with mp 316–318° C. Yield 53%. Found, %: N 8.54, 8.59. Calculated for $C_{23}H_{18}N_2O$, %: N 8.28.

2,6-Di(indol-3-ylmethylene)cyclohexanone (XVIII). Obtained in a similar manner to **XVII**. Orange plates with mp 296° C (from ethanol). Yield 56%. Found, %: N 8.12, 8.27. Calculated for $C_{24}H_{20}N_2O$, %: N 7.95.

1,4-Di[β-(indol-3-yl)acryloyl]benzene (XIX). Obtained in a similar manner to **XVII** with heating for 20 min. Red needles with mp 320° C. Yield 51%. Found, %: N 6.49, 6.70. Calculated for $C_{28}H_{20}N_2O$, %: N 6.73.

3-Aryl-5-(indol-3-yl)-1-phenyl-2-pyrazolines (XX–XXIX, Table 2). A solution of 0.005 mole of the appropriate ketone and 0.006 mole of phenylhydrazine (or phenylhydrazine hydrochloride in the case of compounds **XXIII** and **XXIV**) in 10–15 ml of methanol was treated with 0.5 ml of acetic acid and boiled under reflux for 2–8 hr. The crystals that deposited after cooling were filtered off and recrystallized from ethanol.

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