REACTION OF INDOLES AND 2-KETOINDOLINES WITH SOME ALDEHYDES

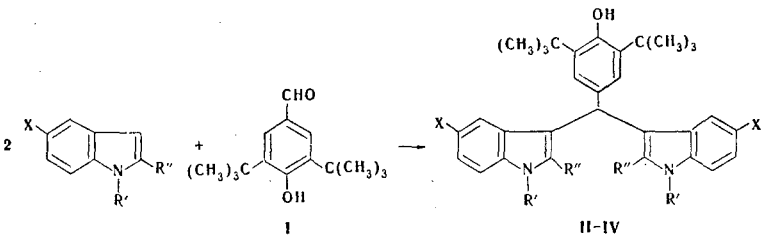
G. I. Zhungietu, G. A. Dragalina, and G. N. Dorofeenko

UDC 547.759.1'753'756

3,5-Di-tert-butyl-4-hydroxybenzaldehyde reacts with indole and 2-methylindole to give di(3-indolyl)methane derivatives but reacts with 2-ketoindoline and 1-methyl-2-ketoindoline to give 3-arylidene-2-ketoindoline derivatives. 2-Ketoindolines form 3-(o-hydroxybenzylidene)-2-ketoindolines with salicylaldehyde. They react with aryglyoxals to give 3-(2-ketoindolinyl)-aroylcarbinols, which are dehydrated to 3-phenacylidene-2-ketoindolines under the influence of acetic acid. Both the starting carbinols and these products form spiro[(2-ketoindoline)-3,5'-(3'-aryl-Δ^2-pyrazolines)] on reaction with hydrazine.

It is known that sterically hindered (shielded) phenols have a number of specific chemical and physicochemical properties, and this makes it possible to find broad practical applications for them [1-5].

In order to obtain indole derivatives of phenols of this type, we condensed indole and 2-ketoindoline with 3,5-di-tert-butyl-4-hydroxybenzaldehyde (I). When indole and aldehyde I are refluxed in benzene, they give 4-[di-(3-indolyl)methyl]-2,6-di-tert-butylphenol (II); 4-[di(2-methyl-3-indolyl)methyl]-2,6-di-tert-butylphenol (III) is obtained from 2-methylindole, while 4-[di(1,2-dimethyl-5-methoxy-3-indolyl)methyl]-2,6-di-tert-butylphenol (IV) is formed from 1,2-dimethyl-5-methoxyindole.

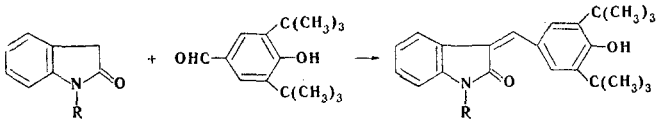


I II-IV

II R′=R″=X=H; III R′=X=H, R″=CH_3; IV R′=R″=CH_3, X=OCH_3

Pyrrole and 2-ketoindoline do not react with I under these conditions. However, 2-ketoindoline forms 3-(4-hydroxy-3,5-di-tert-butylbenzylidene)-2-ketoindoline (V) when it is refluxed in alcohol in the presence of piperidine, and 1-methyl-2-ketoindoline is also converted to a benzylidene derivative (VI).

The presence of the hydroxyl group of a sterically hindered phenol in II-IV is proved [2] by the pres-



V, VI

V R=H; VI R=CH_3

Institute of Chemistry, Academy of Sciences of the Moldavian SSR, Kishinev. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 40-44, January, 1973. Original article submitted November 10, 1971.

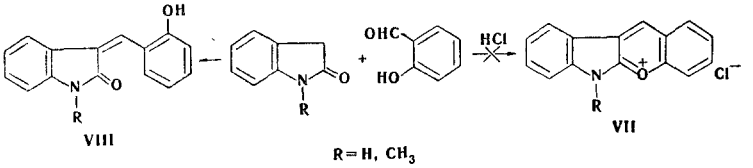
TABLE 1. Characteristics of the Compounds Obtained

Compound	mp, °C	Empirical formula	Found, %			Calc. %			IR spectrum,[c] ν, cm⁻¹	UV spectrum,[d] λmax, nm (log ε)	Yield, %
			C	H	N	C	H	N			
II	226[a]	$C_{31}H_{34}N_2O$	83,0	7,7	6,3	82,7	7,6	6,2	3651	225 (4,51), 284 (3,83)	38
III	239[a]	$C_{33}H_{38}N_2O$	83,8 83,4	8,4 8,2	5,9 5,8	82,8	8,0	5,8	3651	211 (4,37), 284 (3,81) 229 (4,41)	36
IV	186[a]	$C_{37}H_{46}N_2O_3$	78,3	8,3	5,0	78,4	8,1	4,9	3651	212 (4,44), 288 (3,9)	53
V	227[b]	$C_{23}H_{27}NO_2$	78,9	7,3	4,3	78,9	7,4	4,0	3651	211 (4,41), 254 (4,20)	28
VI	134[b]	$C_{24}H_{29}NO_2$	78,3	8,0	4,0	79,3	8,0	3,9	3651	211 (4,24), 254 (3,98)	31

[a]Crystallized from benzene. [b]Crystallized from petroleum ether. [c]In KBr pellets with a UR-10 spectrometer. [d]In methanol with a Specord spectrometer.

ence of a narrow single peak at 3651 cm^{-1} in their IR spectra. The UV spectra contain characteristic absorption bands at 210-220 nm (the B band with a higher extinction coefficient) and 260-280 nm (the C band with a lower extinction coefficient) [2]. The shift of the C band to the short-wave region on passing to V and VI is apparently explained by the presence of conjugation with the 2-ketoindolinyl residue, the characteristic absorption band of which lies at 248 nm (3.74).

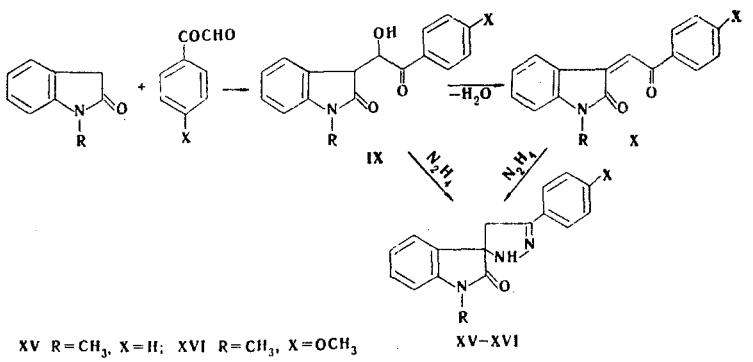
One might have expected the formation of indolo[3,2-e]pyrylium chlorides (VII) in the reaction of 2-ketoindolines with salicylaldehyde in the presence of hydrogen chloride. However, when a mixture of the reagents in methanol is saturated with hydrogen chloride, 3-(o-hydroxybenzylidene)-2-ketoindolines (VIII), which are also obtained when the reaction is carried out in alcohol in the presence of piperidine, are formed in high yield in place of the expected VII.



VIII VII

R = H, CH_3

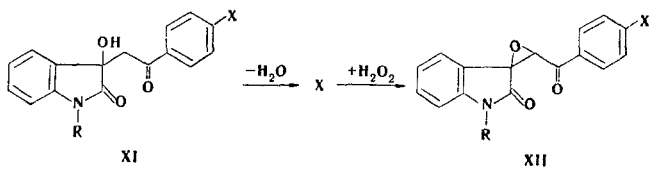
It was recently found that 2-ketoindolines react with arylglyoxals to give 3-(2-ketoindolinyl)aroylcarbinols (IX) [6]. These compounds are readily dehydrated to 3-phenacylidene derivatives (X) in acetic acid at room temperature or on refluxing for 2-3 min. Thus 1-methyl-3-(p-methoxyphenacylidene)-2-ketoindoline (X, R = CH_3, X = OCH_3) and 1-methyl-3-phenacylidene-2-ketoindoline (X, R = CH_3, X = H) were obtained in high yields in this manner. 3-(1-Methyl-2-ketoindolinyl)(p-bromobenzoyl)carbinol (IX, R = CH_3, X = Br) is dehydrated particularly readily to 1-methyl-3-(p-bromophenacylidene)-2-ketoindoline (X, R = CH_3, X = Br), even during recrystallization from boiling alcohol.



IX XV–XVI

XV R = CH_3, X = H; XVI R = CH_3, X = OCH_3

α,β-Unsaturated ketones X are intensely red compounds that are identical to samples obtained by dehydration of carbinols XI [7, 10].



XI XII

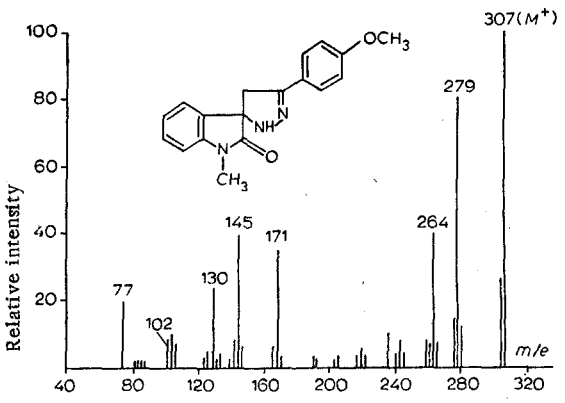
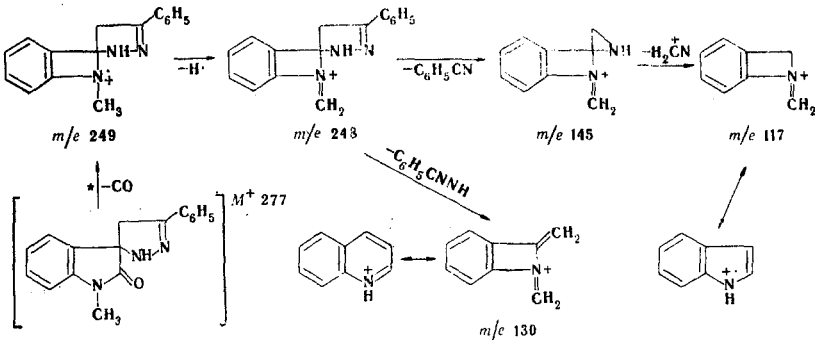


Fig. 1. Mass spectrum of XVI.

Epoxidation of ketones X gives the previously described [8, 9] epoxy ketones (XII). Both carbinols IX and ketones X on refluxing in alcohol with hydrazine hydrate form the same colorless crystalline products, to which the spiro[(1-methyl-2-ketoindoline)-3,5'-(3'-aryl-Δ^2-pyrazoline)] structure can be assigned on the basis of the mass spectra. This route was used to obtain 3'-phenyl- (XV) and 3'-(p-anisyl) (XVI) derivatives.

The mass spectrum of XVI is presented in Fig. 1. The mass spectrum of XV, the disintegration of which is similar to the disintegration of XVI, contains a molecular ion peak with m/e (relative intensity in percent) 249 (100), 248 (30), 145 (57), 130 (45), 117 (30), the presence of which makes it possible to assume the following order of disintegration: as in the case of other 2-ketoindoline derivatives [11], carbon monoxide is initially ejected, as proved by the presence of a metastable peak with m/e 223.5 ($249^2/277 = 223.8$). This is followed by normal disintegration according to the scheme



EXPERIMENTAL

Reaction of Indoles with 3,5-Di-tert-butyl-4-hydroxybenzaldehyde. A solution of 2.34 g (20 mmole) of indole and 2.34 g (10 mmole) of 3,5-di-tert-butyl-4-hydroxybenzaldehyde in 50 ml of benzene was refluxed for 1.5 h. It was then cooled to precipitate pale-rose crystals of 4-[di(3-indolyl)methyl]-2,6-di-tert-butylphenol (II). Similarly, 4-[di-(2-methyl-3-indolyl)methyl]-2,6-di-tert-butylphenol (III) and 4-[di(1,2-dimethyl-5-methoxy-3-indolyl)methyl]-2,6-di-tert-butylphenol (IV) (Table 1) were obtained from 2-methylindole and 1,2-dimethyl-5-methoxyindole.

Reaction of 2-Ketoindolines with 3,5-Di-tert-butyl-4-hydroxybenzaldehyde. A mixture of 1.33 g (10 mmole) of 2-ketoindoline, 2.34 g (10 mmole) of 3,5-di-tert-butyl-4-hydroxybenzaldehyde, and several drops of piperidine in 50 ml of alcohol was refluxed for 8-10 h. The mixture was cooled, and a brown oil was isolated. Chromatography of the oil with a column filled with aluminum oxide and elution by petroleum ether–benzene (1:1) gave 3-(4-hydroxy-3,5-di-tert-butylbenzylidene)-2-ketoindoline (V) (yellow crystals). 1-Methyl-3-(4-hydroxy-3,5-di-tert-butylbenzylidene)-2-ketoindoline (VI) (Table 1) was obtained from 1-methyl-2-ketoindoline.

Reaction of 2-Ketoindolines with Salicylaldehyde. A solution of 1.33 g (10 mmole) of 2-ketoindoline and 1.22 g (10 mmole) of salicylaldehyde in 20 ml of methanol was saturated in the cold with hydrogen chloride. The yellow precipitate of 3-(o-hydroxybenzylidene)-2-ketoindoline (VIII, R=H) was removed by filtration and crystallized from benzene to give 1.2 g (51%) of a product with mp 196°. Found: N 5.5%. $C_{15}H_{11}NO_2$. Calculated: N 5.9%. IR spectrum (in mineral oil), cm^{-1}: 1685, 1605. UV spectrum (in alcohol): λ_{max} 246 nm, log ε 4.30. Similarly, 1.47 g (10 mmole) of 1-methyl-2-ketoindoline gave 1.8 g (72%) of a yellow precipitate of 1-methyl-3-(o-hydroxybenzylidene)-2-ketoindoline (VIII, $R=CH_3$) with mp 208°. Found: C 76.7; H 5.3; N 5.3%. $C_{16}H_{13}NO_2$. Calculated: C 76.5; H 5.2; N 5.5%. IR spectrum (in mineral oil), cm^{-1}: 1675, 1630, and 1600. UV spectrum (in alcohol): λ_{max} 247 nm, log ε 4.36. Both compounds VIII (R=H and $R=CH_3$) were also obtained by refluxing (for 3 h) a methanol solution of the corresponding 2-ketoindoline and salicylaldehyde in the presence of a few drops of piperidine.

Preparation and Dehydration of Aroylcarbinols. A. 3-(1-Methyl-2-ketoindolinyl)(p-bromobenzoyl)-carbinol (IX, R = CH_3, X = Br). A mixture of 3.47 g (15 mmole) of p-bromophenylglyoxal hydrate and 2.2 g (15 mmole) of 1-methyl-2-ketoindoline in 15 ml of benzene was refluxed for 3 h, after which the solvent was removed by vacuum distillation to about half the original volume and allowed to stand for crystallization to give 1.1 g (20%) of a product with mp 142°. Found: C 56.6; H 4.2; N 3.8%. $C_{17}H_{14}BrNO_3$. Calculated: C 56.7; H 3.9; N 3.9%.

B. 1-Methyl-3-(p-bromophenacylidene)-2-ketoindoline (X, R = CH_3, X = Br). 3-(1-Methyl-2-ketoindolinyl)(p-bromobenzoyl)carbinol was refluxed for 30 min in alcohol, and the mixture was then cooled to give brick-red crystals with mp 192° in 100% yield. Found: C 60.1; H 3.7; N 4.0%. $C_{17}H_{12}BrNO_2$. Calculated: C 59.7; H 3.5; N 4.1%.

C. 1-Methyl-3-(p-methoxyphenacylidene)-2-ketoindoline (X, R = CH_3, X = OCH_3). A 1-g sample of 3-(1-methyl-2-ketoindolinyl)(p-anisoyl)carbinol [6] was dissolved with slight heating in 10 ml of acetic acid, and the solution was allowed to stand at 20° for 10 h. The mixture was then diluted with water, and the brick-red crystalline precipitate was removed by filtration, washed with water, and crystallized from alcohol to give 0.6 g (67%) of a product with mp 121° (mp 119-123° [10]).

D. 1-Methyl-3-phenacylidene-2-ketoindoline (X, R = CH_3, X = H). This compound was similarly obtained in 100% yield from 3-(1-methyl-2-ketoindolinyl)benzoylcarbinol and had mp 126° (mp 127-128° [7]). No melting-point depression was observed for a mixture of this product with a sample obtained by the method in [7].

Reaction of Aroylcarbinols with Hydrazine. A. Spiro[(1-methyl-2-ketoindoline)-3,5'-(3'-phenyl-Δ^2-pyrazoline)] (XV). A solution of 1.4 g (5 mmole) of 3-(1-methyl-2-ketoindolinyl)benzoylcarbinol in 10 ml of ethanol was refluxed with 0.16 g (5 mmole) of hydrazine hydrate for 1 h. Colorless needles [0.48 (35%)] with mp 220° precipitated from the mixture on standing. Found: C 73.7; H 5.6; N 14.5%. $C_{17}H_{15}N_3O$. Calculated: C 73.6; H 5.4; N 15.1%. IR spectrum (in mineral oil), cm^{-1}: 3300, 3040, 1710, and 1610. UV spectrum (in alcohol): λ_{max} 265 nm, log ε 3.33. The same compound was obtained in 69% yield by reaction of hydrazine with 1-methyl-3-phenacylidene-2-ketoindoline.

B. Spiro(1-methyl-2-ketoindoline)-3,5'-[3'-(p-anisyl)-Δ^2-pyrazoline] (XVI). This compound was similarly obtained as colorless needles [0.58 g (38%)] with mp 206° from 1.55 g (5 mmole) of 3-(1-methyl-2-ketoindolinyl)(p-anisoyl)carbinol. Found: C 70.7; H 5.6; N 13.4%. $C_{18}H_{17}N_3O_2$. Calculated: C 70.4; H 5.5; N 13.7%. IR spectrum (KBr pellets), cm^{-1}: 3340, 2970, 1710, 1610. UV spectrum (in alcohol): λ_{max} 290 nm, log ε 3.28. The same compound was obtained by reaction of hydrazine with 1-methyl-3-(p-methoxyphenacylidene)-2-ketoindoline in alcohol (in 86% yield).

LITERATURE CITED

1. L. M. Strigun, L. S. Vartanyan, and N. M. Émanuél', Usp. Khim., 37, 969 (1968).
2. G. A. Nikiforov and V. V. Ershov, Usp. Khim., 39, 1369 (1970).
3. L. R. Mahoney, Angew. Chem., 81, 555 (1969).
4. N. M. Émanuél', in: Methods for the Synthesis of and Search for Antitumorigenic Preparations [in Russian], Medgiz, Moscow (1962), p. 22.
5. D. Harman, Agents' Actions, 1, 3 (1969).
6. G. I. Zhungietu and G. A. Dragalina, Khim. Geterotsikl. Soedin., 996 (1971).
7. H. G. Lindwall and J. S. Maclennan, J. Am. Chem. Soc., 54, 4739 (1932).
8. G. Kobayashi, S. Furucawa, and I. Matsuda, J. Pharm. Soc. Japan, 86, 1156 (1966); Ref. Zh. Khim., 23G365 (1967).
9. A. D. Ainley and R. Robinson, J. Chem. Soc., 1508 (1934)
10. G. Kobayashi and S. Furukawa, Chem. Pharm. Bull., 12, 1129 (1964).
11. T. Hino, M. Nakagawa, K. Tsuneoka, S. Misawa, and S. Akaboshi, Chem. Pharm. Bull., 17, 1651 (1969).