RESEARCH ON IMIDAZO[1,2-a]BENZIMIDAZOLE DERIVATIVES

XIV.* α,β-UNSATURATED KETONES OF THE IMIDAZO[1,2-a]BENZIMIDAZOLE SERIES

V. A. Anisimova, N. I. Avdyunina,
A. M. Simonov, G. V. Kovalev,
and S. M. Gofman

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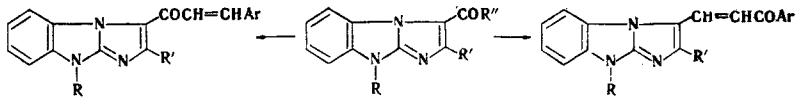
α,β-Unsaturated ketones of the imidazo[1,2-a]benzimidazole series were synthesized from 3-formyl- and 3-acetyl-substituted imidazo[1,2-a]benzimidazoles by crotonic condensation in the presence of alkaline catalysts. The α,β-unsaturated ketones can also be obtained by direct acylation of 3-unsubstituted imidazo[1,2-a]benzimidazoles with the chlorides of unsaturated acids. The properties and pharmacological activity of the ketones obtained were studied.

Chalcones contain a reactive α,β-unsaturated ketone grouping, which, as assumed in [2], is responsible for their antibacterial and fungicidal activity. The analogs of chalcones of some nitrogen heterocycles, namely, benzimidazole [3], pyridine [4], pyrimidine, etc., display a broad spectrum of pharmacological activity, including hypotensive and diuretic activity. In order to study the effect of this sort of keto group on the biological properties of imidazobenzimidazoles, we obtained α,β-unsaturated ketones III-VII from 3-acetyl- and 3-formyl-2,9-disubstituted imidazo[1,2-a]benzimidazoles (I and II).



III-V I, II VI, VII

I a R=R′=R″=CH_3; b R=R″=CH_3, R′=C_6H_5; c R=$CH_2CH_2N(C_2H_5)_2$, R′=C_6H_5, R″=CH_3; II a R=R′=CH_3, R″=H; b R=CH_3, R′=C_6H_5, R″=H; III R=R′=CH_3; a Ar=C_6H_5; b Ar=p-$CH_3OC_6H_4$; c Ar=p-$NO_2C_6H_4$; d Ar=m-$NO_2C_6H_4$; e Ar=2-furyl; f Ar=5-nitro-2-furyl; IV R=CH_3, R′=C_6H_5; a Ar=C_6H_5; b Ar=p-$CH_3OC_6H_4$; c Ar=p-$(CH_3)_2NC_6N_4$; d Ar=p-$NO_2C_6H_4$; e Ar=m-$NO_2C_6H_4$; f Ar=2-furyl; g Ar=5-nitro-2-furyl; V R=$CH_2CH_2N(C_2H_5)_2$, R′=C_6H_5, Ar=p-$CH_3OC_6H_4$; VI R=R′=CH_3; a Ar=C_6H_5; b Ar=p-$CH_3OC_6H_4$; VII R=CH_3, R′=C_6H_5; a Ar=C_6H_5; b Ar=p-$CH_3OC_6H_4$; c Ar=m-$NO_2C_6H_4$; d Ar=α-$C_{10}H_7$; e Ar=2-furyl

Despite the strong electron-donor character of the system, I and II quite readily undergo crotonic condensation under alkaline conditions. Condensation of I with aldehydes doe not take place in the presence of acid catalysts. This is probably explained by the sharp decrease in the nucleophilicity of the acetyl group upon protonation of the nitrogen atom in the 1 position of the heteroring. In this case only the salts of the starting imidazobenzimidazoles were isolated from the reaction mixture. Analogs of chalcones containing a nitrofuryl grouping, which is very sensitive to alkaline agents [5], therefore cannot be obtained by means of this condensation. Compounds of this type can be obtained by direct acylation of 3-unsubstituted imidazo-[1,2-a]benzimidazoles with chlorides of unsaturated acids [6]. The reaction takes place when the reagents are heated without a solvent or in pyridine. α,β-unsaturated ketones of the imidazo[1,2-a]pyridine series, the acetyl-substituted derivatives of which are unstable in acidic media [7], were also synthesized by this method. Nitration of ketone IVf in acetic anhydride also leads to nitrofuryl-substituted IVg, but the yield of the latter is considerably lower in this case.

*See [1] for communication XIII.

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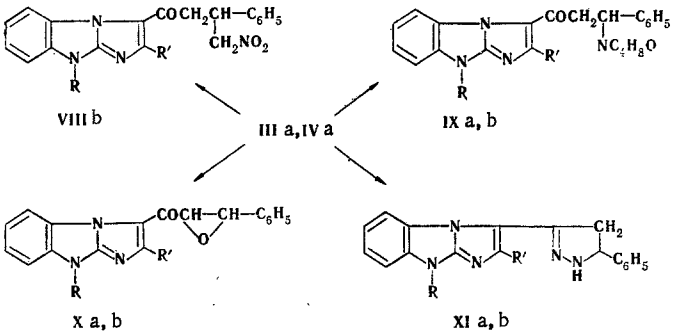
All of the α,β-unsaturated ketones obtained by us are characterized by a trans orientation of the substituents attached to the double bond, as attested to by the presence in their IR spectra of intense absorption bands of out-of-plane and in-plane deformation vibrations of the hydrogen atoms of the vinyl group at 980-1000 and 1290-1310 cm^{-1}, respectively [8]. The stretching vibrations of the C=C and C=N bonds appear in the form of two intense bands at 1580-1620 cm^{-1}. A weak band of carbonyl group absorption is observed in the spectra of ketones VI and VII at 1650-1660 cm^{-1}, whereas in the spectra of ketones III and IV it is shifted to the lower-frequency region (1635-1645 cm^{-1}); this can be explained by simultaneous conjugation of the C=O group with the electron-donor imidazobenzimidazole ring and the ethylene bond. The low intensity of the absorption band of the carbonyl group as compared with the band of the stretching vibrations of the C=C bond indicates their s-cis-orientation relative to one another [9, 10].

The electronic spectra of IIIa and IVa are characterized by two absorption bands of approximately equal intensity (log ε 4.25-4.4) at 300 and 366-370 nm due to π-electron transitions in the conjugated system of bonds. The long-wave band in the spectra of ketones VIa and VIIa is shifted to 415-420 nm, evidently due to lengthening of the conjugation chain. The introduction of a nitro group in the para position of the phenyl ring or replacement of the phenyl group by an electron-donor furyl grouping in ketones III, IV, and VII leads to a bathochromic shift of the long-wave band of 15-20 nm. Halochromic properties are characteristic for III-VII: The absorption maxima of the long-wave bands of sulfuric acid solutions of these compounds are shifted by 100-150 nm to the red region as compared with the spectra of alcohol solutions.

Ketones III and IV undergo characteristic reactions involving addition to the double bond to give γ-nitro ketones VIII and morpholides IX. Treatment of them with an alkaline solution of hydrogen peroxide leads to keto oxides X.



VIII-XI a R=R′=CH_3; b R=CH_3, R′=C_6H_5

The reaction of ketones III and IV with hydrazines is hindered; this can be explained by the combined effect of electronic and steric factors. No reaction occurs with phenylhydrazine even under the most severe conditions. We were able to isolate the corresponding hydrazones in low yields when IIIa and IVa were refluxed for a long time with the more reactive 2,4-dinitrophenylhydrazine. The absorption bands of CH=CH and CO groups vanish in the IR spectra of the hydrazones; the vibrations of ring C=C and C=N bonds appear at 1600 and 1620 cm^{-1}, the nitro groups give doublet absorption bands at 1318, 1340 and 1510, 1525 cm^{-1}, and a ν_{NH} band at 3280 cm^{-1} and a band of medium intensity at 1680 cm^{-1}, which is characteristic for the vibrations of the out-of-plane C=N bond of α,β-unsaturated compounds [8], appear in the spectra.

Heating ketones IIIa, IVa, VIa, and VIIa with hydrazine hydrate leads to pyrazoline derivatives XI and XII. It was noted that the formation of the latter occurs more readily in the case of ketones VI and VII, in which the electron-donor imidazobenzimidazole ring has a lesser effect on the carbonyl group. Bands of vibrations of ring C=C and C=N bonds at 1610 and 1628 cm^{-1} are observed in the IR spectra of XI and XII, and the stretching vibrations of the NH group appear at 3200-3250 cm^{-1}.

Tests of the substances obtained in this research for fungicidal activity did not give interesting results.

The effect of some of the chalcone analogs (IVa, b, f, V, and VII) on the arterial pressure level was studied in experiments on Numbutal-narcotized rats. The systemic arterial pressure was recorded int he carotid by the usual method. Since the investigated compounds are insoluble in water, they were administered intravenously in the form of alcohol solutions. The investigation showed that all of the compounds have a clearly expressed hypotensive effect (Table 1). Ketone IVf, which markedly lowered the blood pressure in doses of 2.5 mg/kg, was found to be the most active compound. A hypotensive effect of IVb and VIIe was noted in the case of administration of larges doses (10 mg/kg) than for ketone IVf. Ketones IVa and V displayed the lowest activity:

TABLE 1. Effect of α,β-Unsaturated Ketones of the Imidazo[1,2-a] benzimidazole Series on the Arterial Pressure

Compound	Dose, mg/kg	Depression of the SAP* after injection of the preparation in percent relative to the starting values after:				
		5 min	15 min	30 min	45 min	60 min
IVa	20	0	9	18	23	23
IVb	10	20	30	20	20	20
IVf	2,5	5	36	47	52	52
V	20	18	34	44	47	50
VIIe	10	25	15	20	30	30

*The systemic arterial pressure. The average results are presented.

TABLE 2. Imidazo[1,2-a]benzimidazole α,β-Unsaturated Ketones

Compound	mp, °C	Empirical formula	Found, %			Calculated, %			Yield, %
			C	H	N	C	H	N	
IIIa	179—180	$C_{20}H_{17}N_3O$	76,3	5,6	13,0	76,2	5,4	13,3	90
IIIb	181	$C_{21}H_{19}N_3O_2$	73,3	5,4	12,0	73,1	5,5	12,2	91
IIIc	292	$C_{20}H_{16}N_4O_3$	66,4	4,5	15,4	66,6	4,5	15,5	95
IIId	243—244*	$C_{20}H_{16}N_4O_3$	66,6	4,8	15,3	66,6	4,5	15,5	94
IIIe	185—186	$C_{18}H_{15}N_3O_2$	70,7	5,1	13,9	70,8	4,9	13,8	50
IIIf	253—254*	$C_{18}H_{14}N_4O_4$	61,3	3,9	16,1	61,7	4,0	16,0	20
IVa	225	$C_{25}H_{19}N_3O$	79,8	5,2	11,1	79,6	5,1	11,3	94
IVb	211—212	$C_{26}H_{21}N_3O_2$	77,0	5,4	10,4	76,7	5,2	10,3	90
IVc	208	$C_{27}H_{24}N_4O$	77,2	5,5	13,3	77,1	5,8	13,3	73
IVd	288	$C_{25}H_{18}N_4O_3$	71,0	4,5	13,3	71,1	4,3	13,3	95
IVe	323*	$C_{25}H_{18}N_4O_3$	70,8	4,3	13,1	71,1	4,3	13,3	90
IVf	210*	$C_{23}H_{17}N_3O_2$	75,4	4,7	11,4	75,2	4,7	11,4	83
IVg	304—305*	$C_{23}H_{16}N_4O_4$	66,8	3,8	13,6	67,0	3,9	13,6	53
V	149—150	$C_{31}H_{32}N_4O_2$	75,8	6,3	11,5	75,6	6,6	11,4	88
VIa	204—205*	$C_{20}H_{17}N_3O$	76,1	5,7	13,4	76,2	5,4	13,3	80
VIb	216—217*	$C_{21}H_{19}N_3O_2$	73,0	5,4	12,0	73,1	5,5	12,2	88
VIIa	168—169*	$C_{25}H_{19}N_3O$	79,8	5,2	11,1	79,6	5,1	11,3	85
VIIb	178—179*	$C_{26}H_{21}N_3O_2$	76,8	5,5	10,6	76,6	5,2	10,3	89
VIIc	272—273*	$C_{25}H_{18}N_4O_3$	71,3	4,3	13,5	71,1	4,3	13,3	34
VIId	164—165	$C_{29}H_{21}N_3O$	81,2	5,3	9,4	81,5	5,0	9,8	84
VIIe	221—222	$C_{23}H_{17}N_3O_2$	75,3	4,7	11,2	75,2	4,7	11,4	98

*With decomposition.

They had a hypotensive effect only in doses of 20 mg/kg. The toxicity of the investigated preparations was low. However, a true evaluation of the activity is hindered by the use of ethanol as the solvent, since, as noted in [1], it lowers the blood pressure level and also may intensify the hypotensive effect of the investigated compounds.

EXPERIMENTAL

The IR spectra of mineral oil suspensions and chloroform solutions of the compounds were obtained with a UR-20 spectrometer. The electronic absorption spectra of solutions in methanol and concentrated sulfuric acid (c 10^{-4}-10^{-5} M) were recorded with an SF-4A spectrophotometer.

Imidazo[1,2-a]benzimidazole α,β-Unsaturated Ketones (III-VII). A) One to two drops of 40% sodium hydroxide solution were added to a hot alcohol solution of a mixture of equimolar amounts of 3-acetyl(formyl)-imidazo[1,2-a]benzimidazole (I, II) and the corresponding aryl- or hetarylcarbonyl compound. After a few hours, the precipitated α,β-unsaturated ketone was removed by filtration and washed with alcohol and ether. Lemon-yellow to orange-red crystalline substances were obtained. Compounds IIIb, IVb, c, f, V, VIa, b and VIId were crystallized from alcohol, IIIa, d, e, IVa, and VIIb were crystallized from dimethylformamide (DMF)—alcohol, and the remaining compounds were recrystallized from DMF. The yields, melting points, and results of analysis of the compounds are presented in Table 2.

B) A thoroughly ground mixture of equimolar amounts of 2,9-disubstituted imidazo[1,2-a]benzimidazole and the α,β-unsaturated acid chloride was heated on a glycerol bath until it solidified completely. Fusion with cinnamoyl chloride was carried out at 40-50°, with furylacryloyl chloride at 70-80°, and with 5-nitrofuryl-acryloyl chloride at 100-120°. The fused mass was treated with a small amount of saturated sodium acetate solution or ammonia and ether. The precipitate was removed by filtration, washed with water and ether, and purified by recrystallization. This method was used to obtain IIIa and IVa, f, g.

2,4-Dinitrophenylhydrazone of IIIa. This compound was obtained as dark-claret crystals, with mp 228-229° (dec., from DMF), in 45% yield after heating a mixture of saturated alcohol solutions of ketone IIIa and 2,4-dinitrophenolhydrazine for 8 h. Found: N 19.6%. $C_{26}H_{21}N_7O_4$. Calculated: N 19.8%.

2,4-Dintrophenylhydrazone of IVa. This compound, with mp 259-260° (dec., from DMF), was obtained as bright-blood-red crystals in 30% yield after refluxing the starting components in alcohol for 18 h. Found: N 17.5%. $C_{31}H_{23}N_7O_4$. Calculated: N 17.6%.

3-(5-Nitrofuryl-2-acryloyl)-2-phenylimidazo[1,2-a]pyridine. This compound was obtained in 55% yield by fusing equimolar amounts of 2-phenylimidazo[1,2-a]pyridine and 5-nitrofurylacryloyl chloride at 100-120°. Workup gave yellow-orange needles with mp 239-241° (dec., from alcohol). Found: C 66.9; H 3.8; N 11.7%. $C_{20}H_{13}N_3O_4$. Calculated: C 66.9; H 3.7; N 11.7%.

2-Phenyl-3-cinnamoylimidazo[1,2-a]pyridine. A mixture of 0.2 g (1 mmole) of 2-phenylimidazo[1,2-a]-pyridine, 1 ml of dry pyridine, and 0.17 g (1 mmole) of cinnamoyl chloride was heated at 70-80° for 3 h, after which it was cooled and treated with water. The liberated oil was separated, dried in a desiccator, and chromatographed with a column filled with aluminum oxide [elution with chloroform–ether (1 : 2)] to give a product with R_f 0.87. Evaporation of the solvent gave yellow crystals with mp 182-183° (from alcohol) in 40% yield. Found: C 81.4; H 5.2; N 8.9%. $C_{22}H_{16}N_2O$. Calculated: C 81.5; H 5.0; N 8.6%.

9-Methyl-3-(5-nitrofuryl-2-acryloyl)-2-phenylimidazo[1,2-a]benzimidazole (IVg). A solution of 0.37 g (1 mmole) of ketone IVf in 3 ml of acetic anhydride was added with vigorous stirring to a cooled (to −17°) nitrating mixture prepared from 5.1 ml of acetic anhydride and 1.3 ml of concentrated HNO_3 (sp. gr. 1.52) at no higher than −10° at such a rate that the temperature of the reaction mixture did not rise above −14°. The mixture was stirred at this temperature for 1 h, after which it was poured over 50 g of crushed ice. After the acetic anhydride had decomposed (~2 h), the solution was neutralized with sodium carbonate and extracted with chloroform–ether (2 : 1). The solvents were evaporated from the organic layer, and the residue was chromatographed with a column filled with aluminum oxide (elution with chloroform) with collection of the yellow fraction with R_f 0.9 to give 0.15 g (35%) of a product with mp 304-305° (dec.). The product was identical to ketone IVg obtained by direct acylation of 9-methyl-2-phenylimidazo[1,2-a]benzimidazole with 5-nitrofuryl-acryloyl chloride.

1-(9-Methyl-2-phenylimidazo[1,2-a]benzimidazol-3-yl)-4-nitro-3-phenyl-1-butanone (VIII). A mixture of 0.1 g (0.26 mmole) of ketone IVa, 2 ml of nitromethane, and 0.2 ml of diethylamine was heated on a boiling-water bath for 20 h, during which the completion of the reaction was followed by means of thin-layer chromatography (TLC). The excess nitromethane and diethylamine were evaporated, and the residue was crystallized from alcohol to give 0.1 g (91%) of pale-yellow crystals with mp 168-169° (dec.). Found: C 71.1; H 5.1; N 12.7%. $C_{26}H_{22}N_4O_3$. Calculated: C 71.2; H 5.1; N 12.8%.

1-(9-Methyl-2-phenylimidazo[1,2-a]benzimidazol-3-yl)-3-morpholino-3-phenyl-1-propanone (IXb). A mixture of 0.38 g (1 mmole) of ketone IVa and 1.5 ml of morpholine was heated in a sealed ampul on a boiling-water bath for 8 h, after which it was cooled, and the resulting precipitate was removed by filtration and washed with a small amount of alcohol and ether to give 0.45 g (93%) of colorless crystals with mp 176-177° (dec., from alcohol). Found: C 75.1; H 6.2; N 12.1%. $C_{29}H_{28}N_4O_2$. Calculated: C 75.0; H 6.1; N 12.1%.

1-(2,9-Dimethylimidazo[1,2-a]benzimidazol-3-yl)-3-morpholino-3-phenyl-1-propanone (IXa). This compound, with mp 182-183° (dec., from alcohol) was obtained in 90% yield from ketone IIIa and morpholine by the method described above. Found: C 71.3; H 6.3; N 13.8%. $C_{24}H_{26}N_4O_2$. Calculated: C 71.6; H 6.5; N 13.9%.

1-(2,9-Dimethylimidazo[1,2-a]benzimidazol-3-yl)-3-phenyl-2,3-epoxy-1-propanone (Xa). A 1.5-ml sample of 28% hydrogen peroxide and 0.3 ml of 2 N NaOH solution were added in the course of 10 min with vigorous stirring and heating to 30° to a solution of 0.32 g (1 mmole) of ketone IIIa in 10 ml of acetone and 2.5 ml of methanol, after which the mixture was refluxed until the color vanished. It was then cooled, and the resulting precipitate was removed by filtration to give 0.33 g (95%) of snow-white silky needles with mp 179-180° (dec., from alcohol). Found: C 72.4; H 4.9%. $C_{20}H_{17}N_3O_2$. Calculated: C 72.5; H 5.2%.

1-(9-Methyl-2-phenylimidazo[1,2-a]benzimidazol-3-yl)-3-phenyl-2,3-epoxy-1-propanone (Xb). This compound, with mp 204° (dec., from alcohol), was obtained in 80% yield by oxidation of ketone IVa by the method used to prepare Xa. Found: C 76.4; H 4.7; N 10.5%. $C_{25}H_{19}N_3O_2$. Calculated: C 76.3; H 4.9; N 10.7%.

3-(9-Methyl-2-imidazo[1,2-a]benzimidazol-3-yl]-5-phenylpyrazoline (XIb). A 0.3-ml sample of hydrazine hydrate was added to a suspension of 0.38 g (1 mmole) of ketone IVa in 2 ml of alcohol, and the mixture was refluxed for 10 h. The solution was evaporated, the residue was treated with water, and the solid material was

removed by filtration and washed with water, alcohol, and ether to give 0.37 g (92%) of slightly yellowish crystals with mp 172.5° (dec., from alcohol). Found: C 77.0; H 5.2; N 18.1%. $C_{25}H_{21}N_5$. Calculated: C 76.6; H 5.4; N 17.9%.

5-(9-Methyl-2-phenylimidazo[1,2-a]benzimidazol-3-yl)-3-phenylpyrazoline (XIIb). This compound was obtained in 95% yield by refluxing an alcohol solution of ketone VIIa and hydrazine hydrate for 2 h. Workup gave pale-yellow crystals with mp 169-170° (dec., from alcohol). Found: C 76.5; H 5.5; N 17.7%. $C_{25}H_{21}N_5$. Calculated: C 76.7; H 5.4; N 17.9%.

Pyrazoline IIIa and IVa were also similarly obtained.

3-(2,9-Dimethylimidazo[1,2-a]benzimidazol-3-yl)-5-phenylpyrazoline (XIa). This compound was obtained in 90% yield as pale-yellow needles with mp 194-195° (dec., from alcohol). Found: C 72.7; H 5.8; N 21.2%. $C_{20}H_{19}N_5$. Calculated: C 72.9; H 5.8; N 21.3%.

5-(2,9-Dimethylimidazo[1,2-a]benzimidazol-3-yl)-3-phenylpyrazoline (XIIa). This compound was obtained in 87% yield as pale-yellow needles with mp 149-152° (dec., from petroleum ether). Found: C 72.9; H 5.7; N 21.3%. $C_{20}H_{19}N_5$. Calculated: C 72.9; H 5.8; N 21.3%.

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