# CYCLOCONDENSATION OF 2-PHENACYL-1H-BENZIMIDAZOLE
WITH ACYLHYDRAZINES: SYNTHESIS AND TAUTOMERISM
OF 2-(PYRAZOL-4-YL)-1H-BENZIMIDAZOLES

I. B. Dzvinchuk, A. V. Vypirailenko, V. V. Pirozhenko, and M. O. Lozinsky

The previously unknown 2-(pyrazol-4-yl)benzimidazoles containing aryl groups in the pyrazolyl ring have been obtained by the reaction of 2-phenacyl-1H-benzimidazole with aroylhydrazines. The compounds with nitrophenyl and pyridyl substituents in the pyrazole ring show pyrazolyl tautomerism with differences in the ^1H NMR spectra. A semi-empirical method is proposed to determine the tautomeric composition of the synthesized pyrazoles.

2-Phenacyl-1H-benzimidazole (I) has become an accessible compound thanks to our research [1]. Its arylhydrazones [2, 3] on acylation undergo recyclization with closing of the pyrazole ring and opening of the benzimidazole ring. For example phenylhydrazone II gave 5-[o-benzoylaminophenyl)amino]-1,3-diphenylpyrazole (III) with benzoyl chloride:
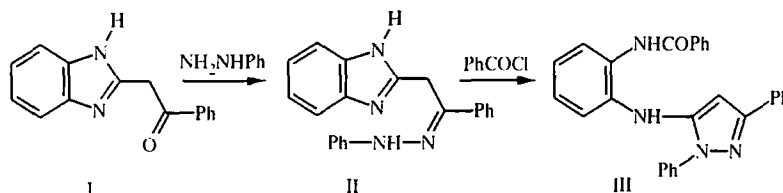

Other uses of ketone I in the synthesis of heterocyclic compounds are not known. The objective of the present study was to determine the possibility of obtaining new functionalized pyrazoles from the reaction of compound I with aroylhydrazines.

We have found that the initial compound I reacts slowly with benzoylhydrazine IVa. The benzoylhydrazone V was formed in 82% yield when the reagents were boiled in *n*-butanol for 2 h with acetic acid as catalyst. Taking recyclization into account [2, 3] and also the tendency of N-acyl groups in polyamino compounds to thermal migration [4], we expected that the hydrazone V would isomerize to the pyrazole VI at high temperature. However we did not succeed in finding conditions for this conversion apparently as a result of the low nucleophilicity of the nitrogen atom in the benzoyl fragment. On boiling in ethylene glycol intramolecular cyclocondensation occurred with participation of the active methylene group. As a result the pyrazole ring opened but the initial benzimidazole ring was retained to give 2-(3,5-diphenylpyrazol-4-yl)-1H-benzimidazole (VIIa):
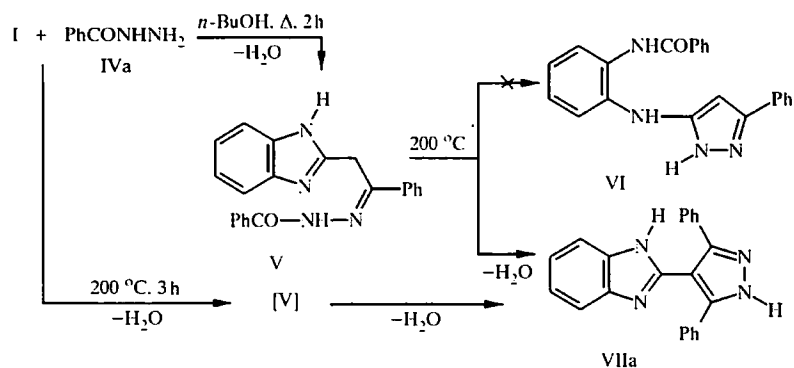

The conversion of hydrazone V to the pyrazole VIIa occurred in quantitative yield. In this connection it was of interest to combine the formation of the hydrazone and its cyclocondensation in a single step. However, fusion of compound I with benzoylhydrazine at 200°C for 3 h was even more expedient from a preparative point of view since it gave the pyrazole directly in quantitative yield. The process was readily carried out in the presence of a small amount of diglyme which inhibited the reaction interruption at the stage of the high melting formation pyrazone. Use of ethylene glycol as diluent was ineffective – the reaction occurred unselectively, probably because of concurrent alcoholysis of compound I to 2-methyl-1H-benzimidazole. Cyclocondensation of compound I with benzoylhydrazone proceeded in quantitative yield on prolonged boiling in dimethylformamide.

Compound I underwent analogous cyclocondensation with aroylhydrazines IVb-f, which have more electrophilic carbonyl groups than benzoylhydrazine. However fusion of the reactants is complicated by formation of by-products. The reactions occur more readily by prolonged boiling of the reagents in dimethylformamide. It is possible that the low selectivity of the reaction in these cases is caused by the tendency of the acylhydrazones to undergo self condensation at high temperatures to give triazoles [4]. Nevertheless, the reaction has preparative value since it gives the valuable products VIIb-f (74-80% yield), which, in distinction from compound VIIa, contain various substituents in positions 3 and 5 of the pyrazole ring and which may exist in two tautomeric forms, A and B:

IV, VII b R = 4-BrC$_6$H$_4$, c R = 3-NO$_2$C$_6$H$_4$, d R = 4-NO$_2$C$_6$H$_4$,
e R = 3-pyridyl, f R = 4-pyridyl
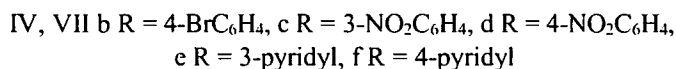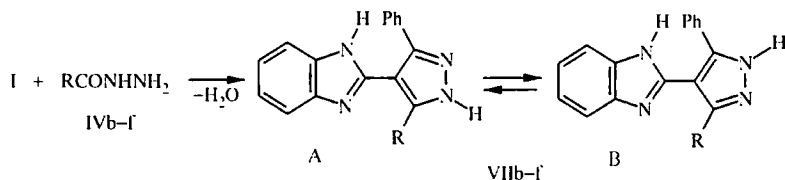
The synthesized compounds V and VIIa-f are high melting crystalline solids. The nitro compounds VIIc,d are yellowish, the rest colorless. The pyrazolylbenzimidazoles have a tendency to form strong solvates. To obtain the pure compounds it was necessary to dry the crystals at high temperature and low pressure. Some physicochemical properties of the compounds are given in Table 1.

The IR and ^{1}H NMR spectra of hydrazone V were in agreement with data for the previously described benzoylhydrazone of 2-acetonyl-1H-benzimidazole [5]. However, compound V, in distinction from its structural analog, only exists in DMSO-d$_6$ solution as one tautomeric form of the enhydrazone structure C (about 5% in the tautomeric mixture):
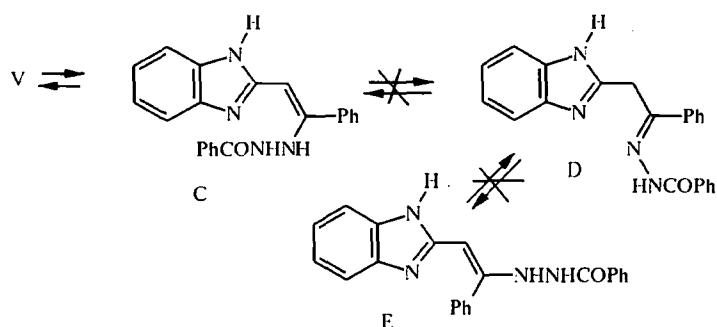
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TABLE 1. Physicochemical Characteristics of the Synthesized Compounds

Compound	Empirical Formula	Found, % Calculated, %			mp, °C*	Yield, %
		C	H	N		
V	$C_{22}H_{18}N_4O$	74.8 / 74.6	5.2 / 5.1	16.0 / 15.8	215-215.5	82
VIIa	$C_{22}H_{16}N_4$	78.6 / 78.6	4.5 / 4.8	16.8 / 16.7	275.5-277	100*[2]
VIIa	$C_{22}H_{15}BrN_4$	63.4 / 63.6	3.4 / 3.6	13.3 / 13.5	264-265.5	80
VIIa	$C_{22}H_{15}N_5O_2$	69.3 / 69.3	3.8 / 4.0	18.6 / 18.4	265.5-267	75
VIIa	$C_{22}H_{15}N_5O_2$	69.3 / 69.3	3.9 / 4.0	18.4 / 18.4	310-312	75
VIIa	$C_{21}H_{15}N_5$	74.6 / 74.8	4.6 / 4.5	20.8 / 20.8	274.5-276	74
VIIa	$C_{21}H_{15}N_5$	74.5 / 74.8	4.4 / 4.5	20.8 / 20.8	318-319	76

* From mixtures of dimethylformamide-water, 3:1 (V, VIIe,f), ethanol-water,2:1 (VIIa), acetone-water,1:1 (VIIb), and 1-propanol-water, 3:1 (VIIc,d).

*[2] By methods A, B, and C.

Forms with structures D and E were not observed. Their instability is evidently caused by steric hindrance created by the tendency of the phenyl group to become coplanar with the conjugated C=N bond (in form D) or the C=C bond (in form E).

The structures of the pyrazolylbenzimidazoles VIIa-f were confirmed by IR and ^1H NMR spectroscopy (Table 2). The vibrational spectra are not informative since the compounds show only one general characteristic NH absorption band. The ^1H NMR spectra are complicated, the interpretation of which requires a definite sequence. The methylene signal characteristic of the starting hydrazone is absent in the ^1H NMR spectrum of compound VIIa. The signal for proton 4 of the pyrazole ring, which would be expected for compound VI, is also absent (it was observed in spectra of compound III [2]). Two one-proton singlets appear at low field and disappear on addition of D_2O and consequently correspond to protons of the NH groups of the pyrazole and benzimidazole rings. Their chemical shifts are practically coincident with those known for both heterocycles [2, 3, 6]. The integrated intensity of the aromatic proton signals (14H) corresponds to structure VIIa. It is notable that one of the aromatic protons appears as a broad multiplet separate from the signals of the other aromatic protons at lower field (7.68 ppm). It is possible that, on the ^1H NMR time scale (300 MHz), migration of this proton between the nitrogen atom of the benzimidazole ring is hindered and the 4-H signal appears practically as in 1-alkyl-1H-benzimidazoles [7]. On increasing the temperature to 70°C the monoproton aromatic signal shifts to higher field where it is overlapped by the signals of the remaining aromatic protons which is expected with an increase in rate of the exchange processes. One of the aromatic protons in the spectra of compounds VIIb-f behaves similarly.

TABLE 2. IR and ^{1}H NMR Spectra of the Synthesized 2-(pyrazol-4-yl)-benzimidazoles VIIa-f

Compound	IR spectra, ν_{NH} cm^{-1} (KBr)	^{1}H NMR Spectra, δ, pp (DMSO-d₆)				
		T, °C	5-, 6-, 7-H, 4-H, C₆H₅	R*	Benzimidazole NH (1H)	Pyrazole NH (1H)
VIIa	3390	20	7.19-7.48 (13H); 7.68 m (1H)	—	12.51	13.73 s
		70	7.19-7.50m (14H)	—	12.26	13.51
VIIb	3380	20	7.15-7.46m (8H); 7.70 m(1H)	7.42-7.59 m (4H, C₆H₄Br)	12.51	13.83 s
VIIc	3410	20	7.20-7.46m (8H); 7.70m (1H)	7.60 m (1H, 5-H); 7.88 m (1H, 6-H); 8.13 m^B; 8.19 m^A (1H, 4-H); 8.46 s^B; 8.53 s^A(1H)	12.57	14.01 s^B, 14.15 s^A
VIId	3630	20	7.20-7.46m (8H); 7.70 m(1H)	7.73 m (2H, 2-H); 8.18 m^B; 8.25 m^A (2H, 3-H)	12.59	14.07 s^B 14.12 s^A
		20*²	7.17-7.45 (8H); 7.66m (1H)	7.69 m (2H, 2-H); 8.16 m (2H, 3-H)	12.54	14.03
VIIe	3410	20	7.20-7.48m (8H); 7.57 m (1H)	7.49 m (1H, 5-H); 7.86 d (1H, 6-H); 8.49 br.d$^{A·B}$ (1H, 4-H); 8.62 s^B 8.64 s^A (1H, 2-H)	12.56	13.91 s
VIIf	3460	20	7.20-7.42m (8H); 7.59 m (1H)	7.46 m (2H, 2-H); 8.49 m^B; 8.56 m^A (2H, 3-H)	12.60	14.03 s^B, 14.12 s^A

* Order of numbering of the H atoms in the fragment R: from the point of attachment to the pyrazole ring in the direction of the closest substituent in the ring.

*² Experiment in DMSO-d₆ with an increased water content.

Migration of the NH bond proton in the pyrazole ring is hindered. In compounds VIIc,d,f, which contain the most electron accepting substituents R, the effect is sufficiently clearly expressed that it is possible to identify the separate signals of the tautomeric forms A and B and to determine the tautomeric composition from their intensities. We note that this method of quantitative investigation of pyrazole tautomers by ^{1}H NMR spectroscopy is not known – in previous studies the problem of the relative stabilities of isomers was decided qualitatively [8, 9]. Therefore the facts are analyzed in detail here.

In the ^{1}H NMR spectra of compounds VIIc,d,f the proton of the NH bond of the pyrazole ring appears as two singlets of different intensity. An analogous doubling with the same intensity ratio is characteristic for the aromatic protons closest to the nitro group or the terminal nitrogen atom of the R fragment. The ratio of the integral intensities of these protons depends on the nature of the R group and corresponds to the tautomeric composition of compounds in solutions. The differences in the chemical shifts of these signals in forms A and B are evidently explained by the different electron donor effects of the nitrogen atom at position 1 of the pyrazole ring along the conjugated chain to the electron acceptor substituent R. Transmission of the electronic effect may occur if the substituent R is at position 3 or 5. However at position 3 the chain of conjugation is one bond shorter and consequently it is energetically preferable. As a result tautomer B for compounds VIIc,d,f is the more stable. Spectroscopically this is evident in that the high field signal for fragment R of the different forms is the more intense, i.e., in this tautomer the increased electron donor effect of the pyrazole ring leads to a large increase in electron density at the carbon atoms of the aromatic substituent R.

According to the theory of tautomerism as an acid-base equilibrium (Kabachnik [10]), any tautomeric equilibrium is shifted in the direction of the less dissociated product. Consequently for compounds VIIc,d,f, fom A, in which the fragment R and the proton of the pyrazole NH are closer together than in form B, is the more acid. It follows that the electronic influence of the substituent R on the acidity of the pyrazoles occurs basically or completely via an inductive mechanism. In the ^{1}H NMR spectra the less intense signal of the NH pyrazole ring proton (corresponding to the more acidic form) is in fact shifted to lower field.

In the spectra of compounds VIIb,e the signal of the pyrazole NH proton appears as a unique singlet and the signals of the tautomeric forms of the substituent R overlap. In this case, determination of the tautomeric composition by the ^{1}H NMR method either gives large errors (for compound VIIe there is a discontinuity in one of the signals of the 3-pyrazyl fragment) or is quite impossible.

Knowing the tautomeric composition of the three compounds from experiment and using the Hammet equation, we have calculated the tautomeric composition of compounds VIIb,e, starting from two postulates: first, compound VIIa contains two identical substituents at positions 3 and 5, consequently the probability of finding the proton at either ring nitrogen atom is 50%. Secondly the effects of the R substituents on the tautomeric equilibrium is determined by their σ-constants [11, 12]. The proposal that it is more acceptable to use the σ$^+$-constants (taking into account direct polar conjugation of the substituent R with the electron donor reaction center) was excluded for the following reasons. We observed experimentally that the tautomeric compositions of the p- and m-nitrophenyl compounds were practically the same, and this, coupled with the first postulate, indicates that nitro groups in p- and m-positions have similar constants which is only possible within the limits of σ-scales.

The percentage contents of tautomer A, determined by calculation (in brackets) and experimentally for compounds VIIb-f are respectively (40), 22, 20, (31) or 24-32, and 21.

The fact that the equilibria studied correlate with σ-constants and not with σ$^+$-constants probably indicates that interconversion of tautomers occurs without dissociation and intermediate formation of ions. Most probably the transfer of a proton from one ring nitrogen atom to the other occurs synchronously, perhaps via a six-centered transition state in dimeric associates of pyrazoles in which the molecules interact by pairs via intermolecular hydrogen bonds with participation of both ring nitrogen atoms (such a mechanism has already been discussed for pyrazoles [8]). In our opinion it is more probable that the mechanism occurs via participation of solvent water. A molecule of water bonded to a molecule of substrate via hydrogen bonds to both ring nitrogen atoms facilitates proton transfer via a five-centered transition state (interconversion of A' and B'):
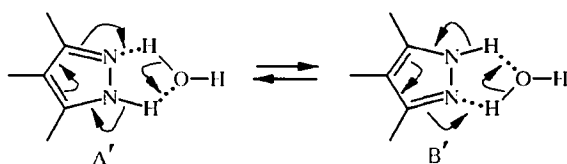
When the ^{1}H NMR spectrum of compound VIId was recorded in DMSO-d$_6$ containing an increased water content we observed that the tautomeric interconversion increased so much that the signals of the individual tautomeric forms were not observed. This confirmed the role of water in proton transfer in the tautomers. It also showed that the compounds were indeed tautomers and not impurities in the synthetic products.

It should be noted that only unsubstituted 2-(pyrazol-4-yl)-1H-benzimidazole [13] and its derivatives with amino groups in the pyrazole ring [14] were known until now. They were all prepared by the reaction of hydrazine with difficult to obtain 1H-benzylimidazoles containing diformylmethyl or (arylaminothiocarbonyl)cyanomethyl units at position 2.

Thus the interaction of 2-phenacyl-1H-benzimidazole with aroylhydrazines at elevated temperatures is a suitable preparative method for the previously unknown 2-(pyrazol-4-yl)-1H-benzimidazoles containing aryl substituents in the pyrazole ring. The reaction products exist in tautomeric equilibrium in solutions, shifted in the direction of the form in which the more electron acceptor substituent is at position 3 of the pyrazole ring.

EXPERIMENTAL

The course of the reaction and the purity of the products were monitored by TLC on Silufol UV-254 strips with 9:1 benzene-ethanol as solvent (spots revealed by UV light). Synthesized samples were dried for 1 h in a Fisher drying tube under water vapor pressure at 150°C before determination of the melting point, elemental analysis, and spectroscopy. IR spectra of KBr discs were recorded on UR-20 spectrometer. ^{1}H NMR spectra were recorded on a Varian VXR-300 spectrometer (working frequency 300 MHz) in MSO-d_6 edistilled and dried over 4A molecular sieves) with TMS as internal standard.

Benzoyl Hydrazone of 2-Phenacyl-1H-benzimidazole (V). A mixture of compound I (0.24 g, 1 mmol) and benzoylhydrazine IVa (0.17 g, 1.2 mmol) in n-butanol (1 ml) was boiled for 2 h in the presence of 1 drop of glacial acetic acid. After cooling the precipitated product was filtered off, washed with ethanol, and dried at 100°C. Yield 0.29 g (82%). IR spectrum: 1655 (CO), 3180 cm^{-1} (NH). ^{1}H NMR spectrum: 4.49 (2H, s, H$_2$), 7.16-8.15 (14H, m, 4,5,6,7-H + 2Ph), 12.76 (1H, s, NHCO), 12.84 (1H, s, 1-H); signals of enhydrazine form B (about 5%): 5.47 (1H, s, CH=C-NN), 10.48 (1H, s, C=C-NHN), 12.13 (1H, s, NHCO).

2-(3,5-Diphenylpyrazol-4-yl)-1H-benzimidazole (VIIa). A. Compound V (0.46 g, 1.3 mmol) was boiled for 15 min in ethylene glycol (2 ml). After cooling, the residue was filtered off, washed with 1:1 aqueous ethanol, and dried at 150°C at the water pump. Yield 0.44 g (100%).

B. A mixture of compound I (0.24 g, 1 mmol), benzoylhydrazine IVa (0.15 g, 1.1 mmol), and diglyme (0.2 ml) was heated on an oil bath for 3 h at 195-200°C. After cooling to 80°C ethanol (1 ml) was added. Water was added dropwise with stirring to the hot solution until crystallization began. After cooling the product was separated and treated as in method A. Yield 0.34 g (100%).

C. A solution of compound I (0.24 g, 1 mmol) and benzoylhydrazine IVa (0.15 g, 1.1 mmol) in dimethylformamide (1 ml) was boiled for 10 h. Then water (0.5 ml) was added carefully and the mixture was stirred at boiling point until crystallization began. After cooling the precipitated product was treated as in method A. Yield 100%. Compounds VIIb-f were obtained analogously from compound I and aroylhydrazines IVb-f.

REFERENCES

1. I. B. Dzvinchuk, M. O. Lozinsky, and A. V. Vypirailenko, *Zh. Org. Khim.*, **30**, 909 (1994).
2. I. B. Dzvinchuk, A. V. Vypirailenko, and M. O. Lozinsky, *Zh. Org. Khim.*, **32**, 1759 (1996).
3. I. B. Dzvinchuk, A. V. Vypirailenko, and M. O. Lozinsky, *Zh. Org. Khim.*, **33**, 116 (1997).
4. K. T. Potts, *Chem. Rev.*, **61**, 87 (1961).
5. I. B. Dzvinchuk and M. O. Lozinsky, *Zh., Org. Khim.*, **34**, 782 (1998).
6. N. V. Gorbulenko, M. S. Frasinyuk, and V. P. Khilya, *Khim. Geterotsikl. Soedin.*, No. 4, 464 (1994).
7. I. I. Popov, *Khim. Geterotsikl. Soedin.*, No. 8, 1067 (1996).
8. J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, *The Tautomerism of Heterocycles. Advances in Heterocyclic Chemistry. Suppl. 1*, Academic Press, New York (1976), pp. 34, 41, and 269.
9. L. G. Tensmeyer and C. Ainsworth, *J. Org. Chem.*, **31**, 1878 (1966).
10. A. N. Nesmeyanov and N. A. Nesmeyanov, *Introductory Organic Chemistry*, [in Russian], Vol. 1, Khimiya, Moscow (1969).
11. A. Gordon and R. Ford, *Handbook of Chemistry* [Russian translation], Mir, Moscow (1967).
12. A. F. Pozharskii, *Theoretical Bases of the Chemistry of Heterocycles* [in Russian], Khimiya, Moscow (1985).
13. N. A. Naik, V. Purnapraina, and S. Seshadri, *Indian J. Chem.*, **15B**, 338 (1977).
14. G. Nawwar, L. M. Chabaka, and M. T. Omar, *Phosphorus, Sulfur, Silicon, Relat. Elem.*, **57**, 65 (1991).