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REACTIONS OF 2-AMINO- AND 2-HYDRAZINO-BENZIMIDAZOLES WITH 2-ACYLDIMEDONES

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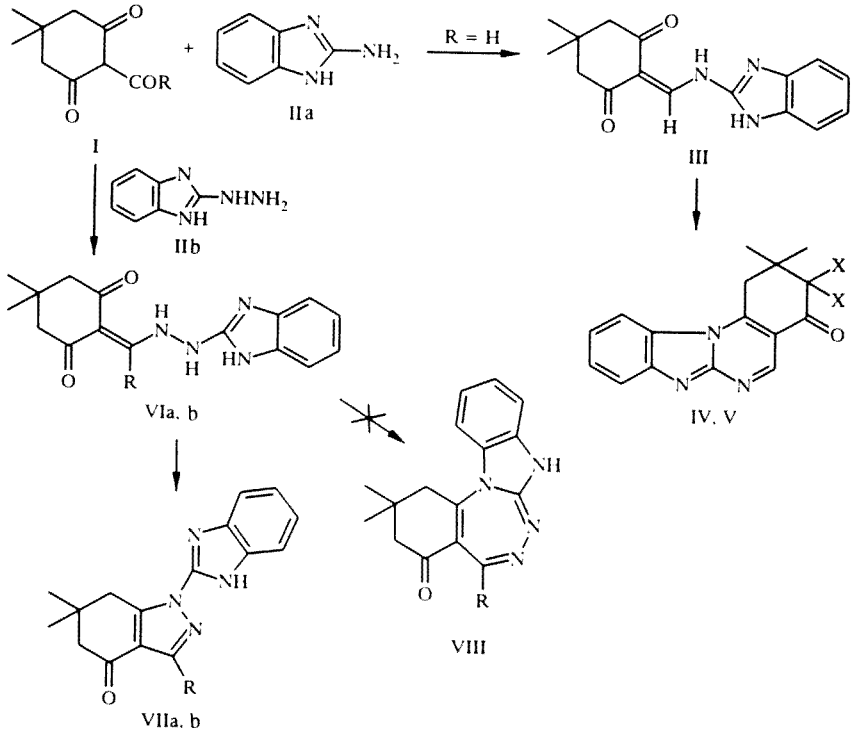
The reaction of 2-formyldimedone with 2-amino- and 2-hydrazinobenzimidazoles at 20°C in ethanol gave 2-(2-benzimidazolyl)aminomethylene- and 2-[2-(2-benzimidazolyl)hydrazinomethylene]-5,5-dimethylcyclohexanediones, while this reaction carried out in ethanol at reflux in the presence of acid gave 2,2-dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolino[1,2-a]benzimidazole and 1-(2-benzimidazolyl)-6,6-dimethyl-4-oxo-4,5,6,7-tetrahydroindazole, respectively.

In a continuation of work on the synthesis of heterocycles using 2-acyl-1,3-cyclanediones [1, 2], we studied the reaction of 2-acyldimedones (Ia, Ib) with 2-amino- (IIa) and 2-hydrazinobenzimidazoles (IIb) (Scheme 1).

Scheme 1



I, VI, VII a R = H, bR = Me; IV X, X = H, H; V X, X = O

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TABLE 1. ^{13}C NMR Spectral Data for VIIa in Various Solvents

Solvent	T, K	^{13}C NMR chemical shifts, ppm				
		2	3a	4	5	6
$CDCl_3$	303	†	142,29	119,46	122,34	122,80
DMSO	303	145,26	†	†	†	†
DMSO	367	145,34	135,17*	118,52*	122,18*	
DMSO + D_2O	303	145,17	137,07	114,93	122,27	
DMSO + CF_3COOH	303	145,43	137,29	115,19*	122,52*	
		7	7a	3'	4'	5'
$CDCl_3$	303	110,59	131,65	†	118,30	151,22
DMSO	303	†	†	149,36	117,28	150,98
DMSO	367	111,45	135,17*	149,65	117,46	151,26
DMSO + D_2O	303	114,93	137,07	149,66	117,29	151,02
DMSO + CF_3COOH	303	115,19	137,29	149,96	117,60	151,26

*Broad signal.

†Signal could not be detected due to its considerable width and low solubility of VIIa.

We previously studied the reactions of 2-aminobenzimidazole IIa with α,β-unsaturated ketones leading to pyrimido-[1,2-*a*]benzimidazoles [3, 4].

The reaction of 2-formyldimedone Ia with amine IIa in ethanol at 20°C initially gives aminomethylene derivative III, which then gradually cyclizes. Hence, only the first crystals of the compound could be isolated in pure form by decantation of the reaction mixture. We should note that, as a rule, quinazoline derivatives are immediately obtained in the reactions of 2-acyl-1,3-cyclohexanediones and their enol ethers with amines and heterocyclic amine analogs [5-7], while intermediates such as dione III could not be isolated. Heating Ia and IIa in ethanol at reflux in the presence of catalytic amounts of *p*-toluene-sulfonic acid leads exclusively to the product of the cyclization of III, namely, tetrahydroquinazolinobenzimidazole IV. The conversion of III to IV also proceeds upon simply heating. Crystals of III melt at 170°C. The melt then hardens to give IV and remelts upon heating to 289-292°C. This sample did not give a depressed melting point when mixed with an authentic sample of IV.

The oxidation of tetrahydroquinazolinobenzimidazole IV by selenious acid according to the method of Gudrinietse [8] leads to α-diketone V.

The structure of 4-oxo- (IV) and 3,4-dioxo-2,2-dimethyl-1,2,3,4-tetrahydroquinazolino[1,2-*a*]benzimidazoles (V) was indicated by PMR and IR spectroscopy. The methylene group protons for IV, in contrast to the case of dione III, differ strongly and are found at 2.62 and 3.53 ppm, respectively. The methylene group protons of diketone V are not magnetically equivalent and appear as singlets at 4.42 and 5.80 ppm. The IR spectrum of this compound shows carbonyl group bands at 1758 and 1720 cm^{-1}.

The reaction of 2-acyldimedones Ia and Ib with 2-hydrazinobenzimidazole IIb proceeds similarly. At room temperature, the reaction of IIb and formyldimedone Ia gives hydrazinomethylene derivative VI, while heating Ia and Ib with IIb in 2-propanol at reflux in the presence of HCl leads exclusively to VIIa and VIIb, respectively. The formation of 2-pyrazolylbenzimidazoles from hydrazine IIb and acyclic 1,3-dicarbonyl compounds has been noted by Singh [9] and Youssef [10, 11].

The cyclization of substituted hydrazines VI gives indazole derivatives VII and possibly, isomeric dibenzo-[*b*,*e*]imidazo[1,2-*c*]-1,2,4-triazepines (VIII). Such a cyclization variant has been discussed for the reaction of 2-hydrazino-benzimidazole and acetylacetone [9], which yields a product with benzimidazolylpyrazole structure.

Structure VII was assigned to the products obtained using NMR spectroscopy. Thus, the PMR spectra of VIIa and VIIb in $CDCl_3$ have characteristic singlets for the methyl and methylene protons as well as an AA'BC' multiplet for the aromatic protons (see Experimental section and Fig. 1a). The downfield signal for the NH group protons at 10.05 ppm indicate participation of this group in intramolecular $=N-H\ldots N\equiv$ hydrogen bonding.

The addition of a few drops of DMSO or D_2O to a solution of VIIa in $CDCl_3$ leads to significant broadening of the signals of the benzimidazole fragment, while the signals for 7-H and 4-H in DMSO solution are two broad unresolved bands (Fig. 1b), which approach each other and finally coalesce upon heating to 90°C. These changes are reversible and the initial spectral pattern is restored upon lowering the temperature. Similar effects are seen in the ^{13}C NMR spectra, in which broad signals of all the aromatic carbon nuclei are similarly temperature-dependent.

The addition of a few drops of CF_3CO_2H or D_2O to a solution of the condensation products (VII or VIII) in DMSO transforms the aromatic part of the PMR spectrum into a symmetric AA'BB' multiplet (Fig. 1d), averaging pairs of signals of nonequivalent carbon atoms: C_4 and C_7, C_5 and C_6, C_{3a} and C_{7a} (Table 1).

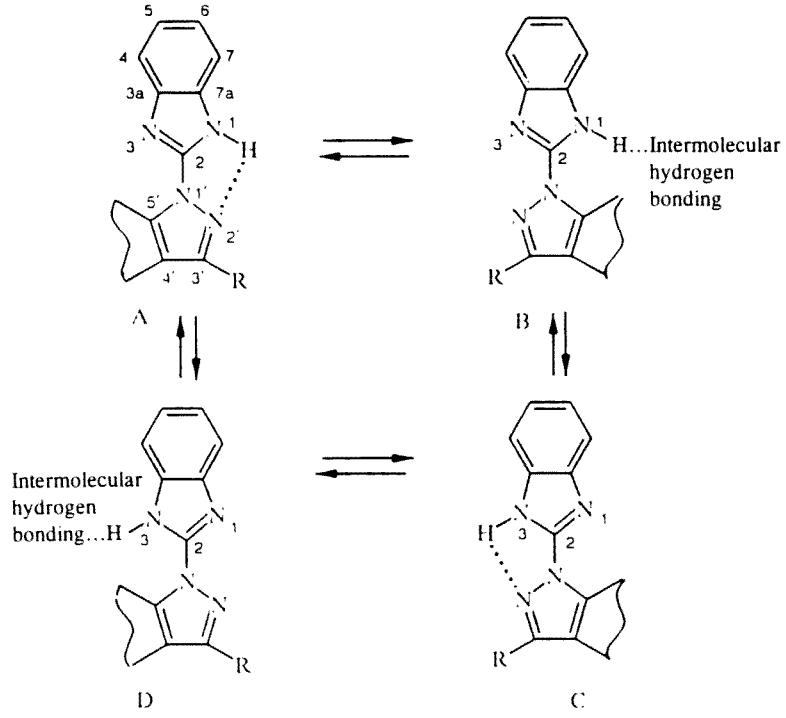
As a consequence of the extremely low solubility of VII in $CDCl_3$, we could not record the signals of all the carbon atoms in the ^{13}C NMR spectrum, although the signals of the aromatic carbon nuclei (Table 1) unequivocally indicate asymmetric structure for its 2-benzimidazolyl fragment. As in the PMR spectrum, the pattern of the signals of all the aromatic carbon nuclei is temperature-dependent.

The following interpretation is possible for the observed spectral behavior of VIIa. In the presence of acid or water as well as upon an elevation of the temperature, degenerate migrations of the NH group proton, which are rapid on the NMR time scale, lead to averaging of the spectral parameters. This produces the apparent symmetrical structure of the benzimidazole fragment. The rate of the exchange processes depends on the solvent, indicating the possibility of an intermolecular mechanism for proton exchange, which occurs by formation of self-aggregates and aggregates with the solvent (Scheme 2).

In addition to the above, we note inhibited rotation of the partially conjugated heterocyclic fragments of VIIa about the C–N bond (equilibria AB, AD, BC, and CD, Scheme 2). Kolodyazhnyi et al. [12-14] have noted that such nitrogen-containing bisheterocyclic systems in solution may have a nonplanar configuration related to twisting of the heterocyclic fragments about single bonds. The three-dimensional structure was postulated in this case to depend not only on steric factors but also the extent of conjugation between the heterocycles.

The stabilization of the planar form of VIIa in relatively inert $CDCl_3$ and at low concentrations may be attributed to intramolecular =N–H···N= hydrogen bonding (A and C in Scheme 2) as well as some conjugation between the heterocycles. Evidence for this hypothesis is found in the possibly nonplanar structure of VII in DMSO, which is a strongly solvating solvent, in which there is no intramolecular hydrogen bonding due to stronger intermolecular hydrogen bonding with the solvent molecules (B and D in Scheme 2). In this case, some of the molecules may acquire a sterically more favorable conformation with location of the benzimidazole and indazole fragments in different planes.

Scheme 2



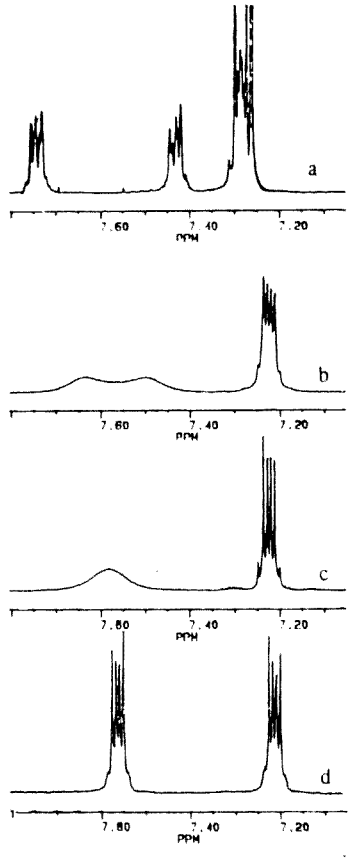


Fig. 1. Dependence of the PMR spectra of the benzimidazole fragment in VIIa on solvent and temperature: a) in $CDCl_3$ at 303 K; b) in DMSO at 303 K; c) in DMSO at 367 K; and d) in DMSO containing traces of acid or water.

An elevation in the temperature, similar to the addition of traces of acid, increases the rate of proton migrations and weakens the hydrogen bond stabilizing the specific conformation of VIIa. In turn, this leads to the removal of steric hindrance to rotation of the benzimidazole fragment about the C–N bond, and the corresponding hydrogen and carbon atoms become completely indistinguishable in the NMR spectra.

Since these effects would be impossible for VIII, all the spectral features noted above, in our opinion, unequivocally indicate that the products of the reactions of 2-hydrazinobenzimidazole with 2-acyldimedones have structure VII.

EXPERIMENTAL

The IR spectra were taken on a Specord 75-IR for suspensions in Nujol (1800-1500 cm^{-1}) and hexachlorobutadiene (3600-2000 cm^{-1}). The CH stretching bands at 3050-2800 cm^{-1} are not given.

The ^1H NMR spectra were taken on a Bruker 90/DS spectrometer at 90 MHz and Bruker AM-360 spectrometer at 360 MHz in a pulse mode with subsequent Fourier transformation. The ^{13}C NMR were taken on a Bruker AM-360 at 90.5 MHz. TMS served as the internal standard. The carbon signals in the ^{13}C NMR by analyzing the coupling constants with protons ^nJ (^{13}C, ^1H).

2-(2-Benzimidazolyl)aminomethylene-5,5-dimethyl-1,3-cyclohexanedione (III). A solution of 0.67 g (5 mmoles) 2-aminobenzimidazole in 20 ml ethanol was added to a solution of 0.84 g (5 mmoles) 2-formyldimedone in 15 ml ethanol at 20°C. The formation of large crystals began after 5-10 min. The reaction solution was decanted upon the appearance of these crystals to give 0.1 g yellow crystalline III, mp 170°C (the melt solidifies above 175°C and then remelts at 275-280°C). IR

spectrum: 1680, 1646, 1632, 1612, 1552, 1540, 3300, 3200 cm^{-1}. PMR spectrum in $CDCl_3$: 1.09 (6H, s, $2CH_3$), 2.42 (2H, s, CH_2), 2.46 (2H, s, CH_2), 7.13-8.10 (5H, br.m, NH, C_6H_4), 9.02 (1H, =CH−N), 12.80 ppm (1H, NH). Found: C, 67.60: H, 6.20; N, 14.60%. Calculated for $C_{16}H_{17}N_3O_2$: C, 67.82; H, 6.05; N, 14.83%. After 2 h, 0.50 g crystals were isolated from the decanted solution. These crystals were heated in 20 ml ethanol containing 2-3 drops of hydrochloric acid to give 0.40 g product, which proved identical to IV in its mp and IR and PMR spectra (see below).

2,2-Dimethyl-4-oxo-1,2,3,4-tetrahydroquinazolino[1,2-*a*]benzimidazole (IV). A mixture of 0.84 g (5 mmoles) 2-formyldimedone, 0.67 g (5 mmoles) 2-aminobenzimidazole, and 0.05 g *p*-toluenesulfonic acid in 30 ml ethanol was heated at reflux for 3 h and cooled. After 24 h, product IV was obtained by filtration and recrystallized from ethanol. The yield of IV was 0.63 g (55%), mp 289-292°C. IR spectrum: 1695, 1630, 1600, 1550, 1515 cm^{-1}. PMR spectrum in $CDCl_3$: 1.29 (6H, s, $2CH_3$), 2.62 (2H, s, CH_2), 3.53 (2H, s, CH_2), 7.42-8.04 (4H, br.m, C_6H_4), 9.22 ppm (1H, s, =CH−N). Found: C, 72.40; H, 5.65; N, 15.80%. Calculated for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84%.

2,2-Dimethyl-3,4-dioxo-1,2,3,4-tetrahydroquinazolino[1,2-*a*]benzimidazole (V). A mixture of 0.55 g (2 mmoles) IV and 0.70 g (6 mmoles) selenious acid in 30 ml dioxane was heated at reflux for 8 h and cooled. The selenium residue as filtered off. A sample of 150 ml water was added to the filtrate. The precipitate of V was recrystallized from DMF. The yield of V was 0.28 g (50%), mp 300-303°C. IR spectrum: 1758, 1720, 1654, 1620, 1602, 1586, 1578, 1550 cm^{-1}. PMR spectrum in DMSO-d_6: 1.33 (6H, s, $2CH_3$), 4.42 (1H, s, $C_{(1)}H$), 5.80 (1H, s, $C_{(1)}H$), 7.50-8.29 (4H, br.m, C_6H_4), 9.35 ppm (1H, s, =CH−N). Found: C, 68.57; H, 4.58; N, 15.00%. Calculated for $C_{16}H_{13}N_3O_2$: C, 68.80; N, 4.69; N, 15.05%.

5,5-Dimethyl-2-[2-(2-(benzimidazolyl)hydrazinomethylene]-1,3-cyclohexanedione (VIa). A solution of 0.34 g (2.5 mmoles) 2-hydrazinobenzimidazole in 10 ml ethanol was added to a solution of 0.42 g (2.5 mmoles) 2-formyldimedone in 5 ml ethanol. After 1 h, crystalline VIa was filtered off. The yield of VIa was 41%, mp 265-267°C. IR spectrum: 1685, 1650, 1610, 1560, 1545, 1510, 3360, 3220, 3180 cm^{-1}. PMR spectrum in DMSO-d_6: 1.02 (6H, s, $2CH_3$), 2.29 (4H, s, $2CH_2$), 6.89-7.24 (5H, br.m, NH, C_6H_4), 8.09 (1H, s, =CH−N), 11.38 ppm (1H, NH). Found: C, 64.58; H, 6.15; N, 18.60%. Calculated for $C_{16}H_{18}N_4O_2$: C, 64.41; H, 6.08; N, 18.78%.

6,6-Dimethyl- (VIIa) and 3,6,6-Trimethyl-1-(2-benzimidazolyl)-4-oxo-4,5,6,7-tetrahydroindazoles (VIIb). A mixture of 2.5 mmoles 2-hydrazinobenzimidazole and 2.5 mmoles corresponding 2-acyldimedone in 20 ml 2-propanol with 0.2 ml hydrochloric acid was heated at reflux for 2 h. The reaction mixture was cooled. The crystalline precipitate of VII was filtered off and recrystallized from ethanol.

VIIa was obtained in 79% yield, mp 267-269°C. IR spectrum: 1668, 1625, 1552, 1505, 3100-3060 cm^{-1}. PMR spectrum in DMSO-d_6: 1.18 (6H, s, CH_3), 2.44 (2H, s, CH_2), 3.47 (2H, s, CH_2), 7.20-7.60 (4H, br.m, C_6H_4), 8.07 (1H, s, =CH−), 12.48 ppm (1H, NH). Found: C, 68.50; H, 5.66; N, 19.91%. Calculated for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.75; N, 19.99%.

VIIb was obtained in 75% yield, mp 260-263°C. IR spectrum: 1666, 1626, 1605, 1560, 1500, 3240, 3070 cm^{-1}. PMR spectrum in $CDCl_3$: 1.20 (6H, s, $2CH_3$), 2.40 (2H, s, CH_2), 2.56 (3H, s, CH_3), 3.42 (2H, s, CH_2), 7.20-7.67 (4H, br.m, C_6H_4); 11.60 ppm (1H, NH). Found: C, 69.40; H, 6.10; N, 19.10%. Calculated for $C_{17}H_{18}N_4O$: C, 69.36; H, 6.16; N, 19.04%.

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