Chemistry of Heterocyclic Compounds, Vol. 33, No. 2, 1997

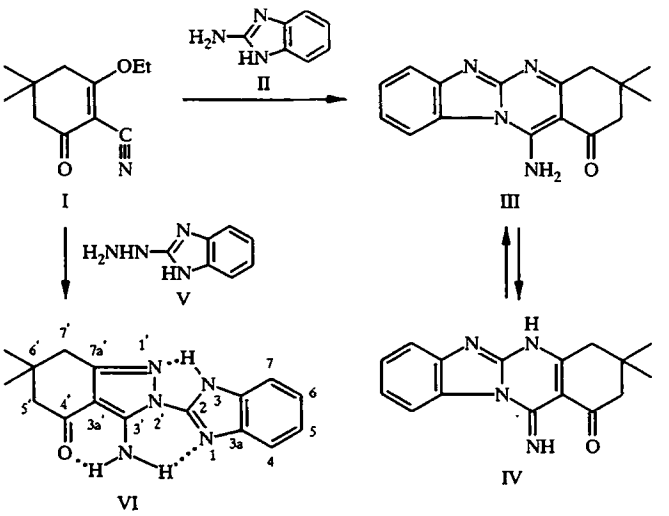
REACTIONS OF 2-CYANO-3-ETHOXY-5,5-DIMETHYL-2-CYCLOHEXEN-1-ONE WITH 2-AMINO- AND 2-HYDRAZINOBENZIMIDAZOLES

A. Ya. Strakov, M. V. Petrova, A. Dishs, Yu. Popelis, and N. N. Tonkikh

The reactions of 2-cyano-3-ethoxy-5,5-dimethyl-2-cyclohexen-1-one with 2-amino- and 2-hydrazinobenzimidazoles gave 1-oxo-3,3-dimethyl-11-amino-1,2,3,4-tetrahydroquinazolino[3,2-a]benzimidazole and 2-(2-benzimidazolyl)-3-amino-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydroindazole, respectively.

Both cyclic reaction products (the respective derivatives of 3-aminoindazole and 4-aminoquinazoline [1]) and 2-cyano-3-hydrazino-5,5-dimethyl-2-cyclohexen-1-ones [2, 3] were obtained in the reactions of the enol ether of 2-cyanodimedone (I) with bifunctional nucleophiles. In a continuation of these researches (see also [4]) we studied the reaction of compound (I) with 2-amino- and 2-hydrazinobenzimidazoles (II, V). In reaction with the enol ether (I) the amine (II), which is a heterocyclic amidine analog, forms 1-oxo-3,3-dimethyl-11-amino-1,2,3,4-tetrahydroquinazolino[3,2-*a*]benzimidazole (III). Several tautomeric forms are possible for quinazolino[3,2-*a*]benzimidazole (III). Of these we chose the imine structure (IV) as more likely, since the presence of the benzimidazoline structures is less likely. The absence of the characteristic frequencies of the C≡N group in the IR spectrum and the presence of a series strong maxima in the region of 3450-3100 cm^{-1} favor a mixture of forms, as indicated earlier [1].

In the reaction of the enol ether (I) with 2-hydrazinobenzimidazole (V) the formation of the dibenzo[*c*,*d*]-1,2,4-triazepino[4,3-*a*]imidazole derivative (VII) in addition to 2-(2-benzimidazolyl)-3-amino-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydroindazole (VI) is possible.



Riga Technical University, Riga LV-1658. Latvian Institute of Organic Synthesis, Riga LV-1006. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 234-240, February, 1997. Original article submitted March 23, 1996.

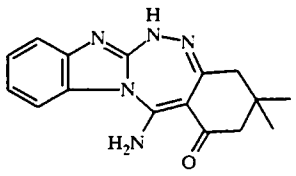
 0009-3122/97/3302-0202$18.00

TABLE 1. ^{13}C NMR Spectra of Solutions of Compounds (VI) and (VIIIb) in DMSO

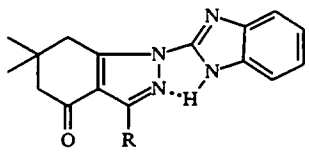
Compound	Chemical shifts, δ, ppm (spin—spin coupling constants, $^nJ_{(^{13}C,^1H)}$, Hz)			
	$C_{(3')}$	$C_{(3a')}$	$C_{(4')}$	$C_{(5')}$
VI	148,1	110,3	191,2 (^3J = 6,4)	51,4 (^1J = 128,1) (^3J = 4,5)
VIIIb†	149,7 (^2J = 6,4)	117,3	192,9 (^2J = 4,5)	51,8 (^1J = 126,9) (^3J = 4,5)
Compound	$C_{(6')}$	$C_{(7')}$	$C_{(7a')}$	$C_{(2Me)}$
VI	34,4 (^2J = 4,2)	36,2 (^1J = 131,4) (^2J = 3,6)	156,5 (^3J = 6,4)	27,9 (^1J = 126,1) (^3J = 3,2)
VIIIb†	34,9 (^2J = 4,1)	36,9 (^1J = 129,4) (^3J = 4,5)	150,9 (^3J = 6,4)	27,9 (^1J = 124,5) (^3J = 4,2)
Compound	$C_{(2)}$	$C_{(5)}C_{(6)}$	$C_{(4)}C_{(7)}$	$C_{(3a)}C_{(7a)}$
VI	145,6	122,1, 121,9 (^1J = 163,4)	117,8, 111,2 (^1J = 163,4)	141,2, 132,1 ($^{2,3}J$ = 4,2)
VIIIb†	145,3	122,18*	118,5*, 111,5*	137,3*

*The signals are broadened.

†Published data [4].



VII



VIII a, b

VIII a R = H, b R = Me

In order to answer the question concerning the structure of the reaction product [(VI) or (VII)] we used the data from IR and ^1H and ^{13}C NMR spectroscopy and quantum-chemical calculations by the semiempirical AM1 method [5]. An index of the preference for one or the other compound can be obtained from its relative thermodynamic stability. The heat of formation ΔH_f, which we calculated for compounds (VI) and (VII) (with full optimization of the geometry of the latter), amounts to 91.54 and 91.32 kcal/mole respectively. This shows that energetically the two structures are equally probable.

In the PMR spectra of the reaction product (I, V) in DMSO the signals of 7-H and 4-H of the benzimidazole fragment are observed at 7.43 and 7.59 ppm. Increase in the temperature of the sample leads to broadening and coalescence of the signals, while decrease in the temperature leads to restoration of the initial spectral pattern, indicating the dynamic nature of the observed effect.

The addition of a few drops of water or acid to the solution averages the signals of the nonequivalent hydrogen atoms 7-H and 4-H, which are transformed into a multiplet, recorded at 7.51 ppm. Earlier [4] similar features in the PMR spectra were observed for compounds (VIIIa, b). Here it was shown that the reason for the observed dynamic effects in compounds (VIIIa, b) can be both inter- and intramolecular N—H proton migrations and also restricted rotation about the $C_{(2)}$—$N_{(1')}$ bond. Application of the previously proposed interpretation to the present investigation proves that the formation of the triazepine structure (VII) is impossible.

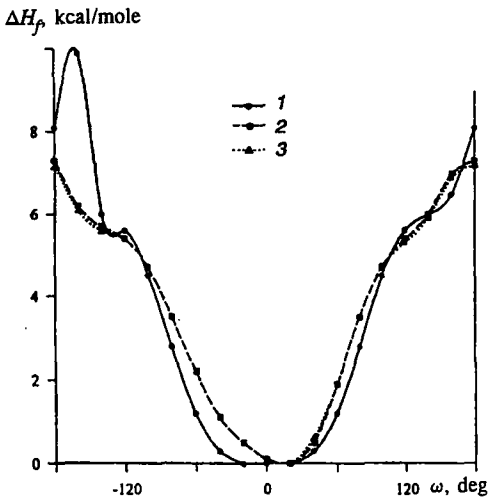


Fig. 1. Dependence of the heat of formation (ΔH_f) of compounds (VI) (1), (VIIIa) (2), and (VIIIb) (3) on the dihedral angles $N_{(1')}N_{(2')}C_{(2)}N_{(3)}$ (VI) and $N_{(2')}N_{(1')}C_{(2)}N_{(3)}$ (VIII).

In addition to the similarity in the spectral behavior of compounds (VIIIa, VI) in the ^1H and ^{13}C NMR spectra it is also necessary to note certain differences. Thus, in the PMR spectra of compound (VI) the signals of the 7-H and 4-H protons are two fairly well resolved signals, the coalescence temperature of which is 65°C. In compounds (VIIIa, b) the signals are substantially broadened even at room temperature, and their coalescence begins in the region of 35-45°C. By means of Eyring's formula [6] we determined the free energies of activation (ΔG^*) of restricted internal rotation about the $C_{(2)}$—N bond at the coalescence temperature, which amounted to 19.1 kcal/mole for compound (VI) and did not exceed 15.5 kcal/mole for (VIIIa, b). The obtained values of the free energy of activation of restricted internal rotation are comparable with those observed in the series of aminomethylene derivatives of dicarbonyl compounds [7] and the amides of carboxylic acids [8]. This demonstrates the double-bond character of the $C_{(2)}$—N bond, resulting from the conjugation between the heterocycles.

In order to confirm the suggestion above in light of the generality of the observed process in the investigated compounds we used the AM1 method [5] to calculate the geometry and electronic structure of compounds (VI, VIIIa, b) (Tables 2 and 3). We also carried out a comparative analysis of these compounds. The activation barrier of the rotation of the benzimidazole fragment about the $C_{(2)}$—N bond (see Fig. 1) was determined as the difference between the heats of formation of the most stable and unstable rotamers with variation of the torsion angles $N_{(1')}N_{(2')}C_{(2)}N_{(3)}$ (VI) and $N_{(2')}N_{(1')}C_{(2)}N_{(3)}$ (VIIIa, b) from 0 to 360° in steps of 30°.

The results of the calculations, like the PMR spectroscopic data, indicate that the barrier of the exchange process in the molecules of compounds (VIIIa, b) is low in comparison with (VI). However, the value of this difference (< 1 kcal/mole), like incidently the sizes of the barriers themselves (~ 8-9 kcal/mole), is substantially smaller than the experimental values. The length of the $C_{(2)}$—N bond in compounds (VI, VIIIa, b) (Table 2) is less in value (1.418 Å) than the standard length characteristic of a single C—NH_2 bond (1.479 Å) [9]. However, it is also problematical to speak of its double bond character (C=N 1.339 Å). Moreover, in spite of the absence of appreciable steric hindrances to the realization of a planar structure in compounds (VI) and (VIIIa, b) the most stable conformations in all three compounds are not planar. The torsion angles $N_{(1')}N_{(2')}C_{(2)}N_{(3)}$ (VI) and $N_{(2')}N_{(1')}C_{(2)}N_{(3)}$ (VIIIa, b), due to rotation of the benzimidazole fragment about the $C_{(2')}$—N bond, in the most stable conformation are 14.22 (VI), 14.35 (VIIIb), and 15.11° (VIIIa). In turn, the indazole fragment in compound (VI) is at an angle of 11° in relation to the remainder of the molecule. In solution the analogous nitrogen-containing bis-heterocyclic systems can have a nonplanar conformation, determined by a combination of electronic and steric factors [10, 11].

The presented arguments show that the degree of conjugation between the heterocycles in compounds (VI) and (VIIIa, b) is comparatively low on account of the nonplanar structure of the molecules. This does not in the present case make it possible to speak of a determining effect from conjugation between the heterocycles on the energetics of the restricted rotation

TABLE 2. Bond Lengths (Å) in the Molecules of Compounds (VI, VIIIa, b)

Bond	VI	VIIIa	VIIIb	Bond	VI	VIIa	VIIIb
$N_{(1)}—C_{(2)}$	1,368	1,336	1,367	$C_{(3')}—R$	1,348	·	1,476
$N_{(1)}—C_{(7a)}$	1,405	1,406	1,397	$C_{(3')}—C_{(3a')}$	1,427	1,447	1,454
$N_{(3)}—C_{(2)}$	1,421	1,422	1,423	$C_{(7a')}—C_{(3a')}$	1,451	1,411	1,412
$N_{(3)}—C_{(3a)}$	1,398	1,393	1,406	$C_{(4')}—C_{(3a')}$	1,432	1,447	1,448
$N_{(2')}—C_{(2)}$	1,418			$C_{(4')}=O$	1,243	1,236	1,237
$N_{(1')}—C_{(2)}$		1,419	1,419	$C_{(4')}—C_{(5')}$	1,507	1,509	1,510
$N_{(2')}—C_{(3')}$	1,438	1,349	1,359	$C_{(5')}—C_{(6')}$	1,530	1,529	1,520
$N_{(2')}—N_{(1')}$	1,376	1,364	1,362	$C_{(7a')}—C_{(7')}$	1,536	1,474	1,474
$N_{(1')}—C_{(7a')}$	1,347	1,404	1,403				

process. On the whole the characteristics presented in Table 2 show qualitatively that the AM1 method accurately conveys the steric and geometric structure of compounds (VI, VIIIa, b). The optimized bond lengths are close to the standard values (Table 2). In the dimedone fragment of compound (VI) the $C_{(3')}$, $C_{(3a')}$, $C_{(4')}$, and O atoms lie in one plane. This promotes conjugation within this fragment and is reflected in the shortening of the single bonds $C_{(4')}—C_{(3a')}$ and $C_{(3')}—N_{(2')}$ and lengthening of the double bonds $C_{(4')}=O$ and $C_{(3a')}=C_{(3')}$ compared with their standard values [9]. The $C_{(6')}$ atom of the dimedone fragment is withdrawn from the plane of the ring by 25°, which agrees with the data from x-ray crystallographic investigations of the dimedone derivatives [12].

In addition, we note that the experimentally determined characteristics of the barrier to rotation about the $C_{(2)}—N$ bond substantially exceed their calculated values. Among the possible reasons for the observed discrepancy may be: determination of the free energy of activation of the rotation process only at the coalescence temperature without analysis of the total line form of the aromatic protons; comparison of the experimental and calculated characteristics for different states of aggregation; limitations of the AM1 method in the determination of intramolecular contacts; no allowance for intermolecular interactions, which may be determining in their effect on the dynamics of internal rotation and proton exchange.

According to the calculations, the intramolecular distances $R(N_{(1')}\cdots N_{(3)})$ (2.89 Å), $R(N_{(3)}H\cdots N_{(1')})$ (2.72 Å), and $R(N_{(2')}\cdots N_{(3)})$ (2.91 Å), $R(N_{(3)}H\cdots N_{(2')})$ (2.73 Å), characterizing the intramolecular hydrogen bonds of compounds (VI, VIIIa, b), somewhat exceed the values usually found in systems with intramolecular hydrogen bonds, while the angle $\alpha(N_{(3)}HN_{(1')})_{VI}$ or $\alpha(N_{(3)}HN_{(2')})_{VIIIa,\ b}$ is significantly smaller than required for the formation of an intramolecular hydrogen bond [13]. At the same time the downfield absorption of the $N_{(3)}—H$ protons, observed at 12.95 (VI) and 13.07 (VIIIa, b) ppm and weakly dependent on the temperature and concentration, does not exclude the possibility of intramolecular $N_{(3)}H\cdots N'$ contact. Moreover, the ability of the amino group of compound (VI) to form an additional stabilizing intramolecular hydrogen bond with the $N_{(1)}$ atom of the benzimidazole fragment may provide an explanation for the fact that the rotation process is hindered in the given compound.

Analysis of the data of the ^{13}C NMR spectra of compounds (VI, VIIIb) in DMSO also indicates that the dynamic effects in compound (VI) have higher energy than in (VIIIb). In contrast to compound (VIIIb), we were able to record all the carbon signals in the ^{13}C NMR spectrum of compound (VI), in DMSO solution at room temperature. It is possible to see some proximity in the chemical shifts of the carbon atoms in compounds (VI) and (VIIIb), in spite of the difference in their structures; the $\Delta\delta$ value for the $C_{(7a')}$ and $C_{(3a')}$ atoms amounts to 6.5-7 ppm, while the value for the $C_{(3')}$, $C_{(4')}$, and $C_{(2')}$ atoms does not exceed 1.5 ppm. The other chemical shifts are practically identical. It is known that in some cases the screening of the carbon nuclei correlates with the electron density at these atoms, while the downfield shift of the NMR signal indicates a decrease in the electron density at the atom [14]. Comparison of the calculated effects of the charges (Δq) with the chemical shifts of the carbon atoms showed that the last statement is only fulfilled for the $C_{(2)}$ and $C_{(3a')}$ atoms. The results of the calculations here indicate that the effect of the nature of the substituents on the nature of the electron density distribution in compounds (VI, VIIIa, b) shows up in the following way: The transition from compounds (VIIIa, b) to (VI) is accompanied by an increase of the electron density at the $N_{(1')}$, $N_{(2')}$, $C_{(3a')}$, O, and $C_{(7a')}$ atoms and a decrease at $C_{(3')}$, $C_{(4')}$, $C_{(2')}$, and $N_{(1)}$ (Table 3).

The obtained data on the electronic structure of compound (VI) make it possible to suppose that it will interact with electrophiles at the nitrogen atom of the amino group, since its contribution to the HOMO and the size of the negative charge are substantially larger than at the alternative $N_{(3)}H$ group.

TABLE 3. Effective Charges (q) at the Atoms in Compounds (VI, VIIIa, b)

Compound	$N_{(1')}$	$N_{(2')}$	$C_{(3')}$	$C_{(3a')}$	O	$C_{(4')}$
VI	-0,114 (0,063)	-0,124 (0,112)	0,252 (0,041)	-0,389	-0,357	0,321
VIIIa	-0,078 (0,084)	-0,099 (0,010)	-0,071 (0,039)	-0,280 (0,042)	-0,299 (0,007)	0,312
VIIIa	-0,074 (0,097)	-0,107 (0,001)	-0,012 (0,049)	-0,281 (0,049)	-0,306 (0,007)	0,312
Compound	$C_{(7a')}$	NH_2	$N_{(1)}$	$C_{(2)}$	$N_{(3)}$	$C_{(3a)}$
VI	0,008 (0,045)	-0,335 (0,095)	-0,114 (0,081)	0,163 (0,09)	-0,211 (0,006)	-0,027
VIIIb	-0,061 (0,006)	—	-0,154 (0,093)	0,152 (0,141)	-0,218 (0,002)	-0,024
VIIIb	0,061 (0,008)	—	-0,156 (0,093)	0,152 (0,131)	-0,218 (0,003)	-0,024

*The squares of the contributions from the AOs of the atoms to the HOMO of compounds (VI, VIIIa, b) are given in parentheses.

EXPERIMENTAL

The IR spectra were recorded on a Specord 75-IR instrument for suspensions of the substances in Vaseline oil (1800-1500 cm^{-1}) and hexachlorobutadiene (3600-2000 cm^{-1}, without the stretching vibrations of the C—H bonds in the region of 3050-2800 cm^{-1}).

The ^1H and ^{13}C NMR spectra were recorded on Bruker WH-90/DS and Bruker AM-360 spectrometers in DMSO-d_6 solutions with TMS as internal standard. The assignment of the signals of the carbon atoms in the ^{13}C NMR spectra was made by analysis of the characteristic spin—spin coupling with the protons $^nJ(^{13}C,^1H)$.

The computations were carried out with the MOPAC 6.0 software [15].

1-Oxo-3,3-dimethyl-11-amino-1,2,3,4-tetrahydroquinazolino[3,2-*a*]benzimidazole (III). We boiled 0.96 g (5 mmole) of the enol ether (I) and 0.66 g (5 mmole) of 2-aminobenzimidazole for 6 h in 40 ml of *n*-butanol in the presence of catalytic amounts of *p*-toluenesulfonic acid. After cooling the yellow precipitate was filtered off. We obtained 0.58 g (41%) of (III); mp 336-337°C (ethanol—DMSO). IR spectrum, cm^{-1}: 1655, 1620, 1590, 3450, 3340, 3120. PMR spectrum (DMSO, δ, ppm): 1.07 (6H, s, $2CH_3$); 2.51 (2H, s, CH_2); 2.88 (2H, s, CH_2); 7.42-7.81 (3H, m, arom.); 8.43 (1H, m, arom.); 9.0 (1H, NH); 10.73 (1H, NH). Found, %: C 68.4; H 5.8; N 20.1. $C_{16}H_{16}N_4O$. Calculated %: C 68.5; H 5.8; N 20.0.

2-(2-Benzimidazolyl)-3-amino-4-oxo-6,6-dimethyl-4,5,6,7-tetrahydroindazole (VI). We boiled 0.48 g (2.5 mmole) of the enol ether (I) and 0.37 g (2.5 mmole) of 2-hydrazinobenzimidazole for 20 min in 30 ml of ethanol. The mixture was cooled, and the precipitate was filtered off. We obtained 0.53 g (71%) of (VI); mp 284-286°C (ethanol—DMFA). IR spectrum, cm^{-1}: 1655, 1630, 1610-1600, 3405, 3290, 3200. PMR spectrum (DMSO, δ, ppm): 1.05 (6H, s, $2CH_3$); 2.26 (2H, s, CH_2); 2.26 (2H S, CH_2) [sic]; 7.19 (2H, m, arom.); 7.43 (2H, m, arom.); 7.84 (1H, NH); 12.95 (1H, NH). Found, %: C 65.1; H 5.7; N 23.7. $C_{16}H_{17}N_5O$. Calculated, %: C 65.1; H 5.8; N 23.7.

REFERENCES

1. A. Ya. Strakov, M. B. Andaburskaya, A. M. Moiseenkov, and A. A. Akhrem, Izv. Akad. Nauk Lat. SSR. Ser. Khim., No. 3, 330 (1973).
2. A. Ya. Strakov, N. N. Tonkikh, and M. V. Petrova, Latv. Ķim. Žurn, No. 2, 168 (1991).
3. A. Ya. Strakov, A. A. Krasnova, and M. V. Petrova, Khim. Geterotsikl. Soedin., No. 1, 81 (1996).

4. A. Y. Strakov, M. V. Petrova, Yu. Yu. Popelis, A. A. Krasnova, and I. A. Strakova, Khim. Geterotsikl. Soedin., No. 2, 247 (1996).
5. M. J. S. Dewar, E. G. Loebish, E. F. Hegly, and I. I. P. Stewart, J. Am. Chem. Soc., **107**, 3902 (1985).
6. Michinori Oki, Methods in Stereochemical Analysis, Part 4, 5 (1985).
7. É. É. Liepin'sh, M. V. Petrova, Ya. Ya. Paulin'sh, I. Ya. Gudele, and É. Yu. Gudrinietse, Izv. Akad. Nauk Latv. SSR. Ser. Khim., No. 4, 495 (1987).
8. W. E. Stewart and T. H. Siddal, Chem. Rev., **70**, 517 (1970).
9. F. H. Allen, O. Kennard, D. Watson., L. Brammer, and A. G. Orpen, J. Chem. Soc. Perkin Trans. II, No. 12, 51 (1987).
10. Yu. V. Kolodyazhnyi, A. D. Garnovskii, O. A. Osipov, V. I. Minkin, S. N. Kolodyazhnaya, and A. M. Simonov, Khim. Geterotsikl. Soedin., No. 4, 515 (1970).
11. S. N. Kolodyazhnaya, A. M. Simonov, Yu. V. Kolodyazhnyi, O. A. Osipov, V. A. Bren', and I. D. Sadekov, Khim. Geterotsikl. Soedin., No. 2, 238 (1970).
12. Yu. T. Struchkov, Yu. L. Slovokhotov, M. V. Petrova, Ya. Ya. Paulin'sh, T. F. Kozlovskaya, and É. Yu. Gudrinietse, Izv. Akad. Nauk SSR. Ser. Khim., No. 6, 726 (1986).
13. R. Taylor, O. Kennard, and W. Versichel, Acta Crystallogr., **B40**, 280 (1984).
14. I. P. Bangov, T. Steiger, and R. Radeglia, J. Phys. Chem. Leipzig, **268**, 891 (1987).
15. J. J. P. Stewart, MOPAC 6.0 A. General Molecular Orbital Package.