STUDY OF TAUTOMERISM IN ALLOPURINOL AND ITS METHYL DERIVATIVES BY ^{13}C SPECTROSCOPY

T. A. Babushkina, T. S. Leonova,
A. I. Chernyshev, and V. G. Yashunskii

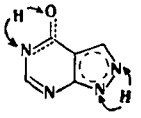
UDC 541.623:543.422.25:547.857

One of the most promising methods for studying the tautomerism of the purines is ^{13}C NMR spectroscopy [1, 2]. In the present work this method has been used for studying the tautomerism of close analogs of the purines, pyrazolo[3,4-d]pyrimidines, and in particular the known hyperuricemia preparation 4-hydroxypyrazolo[3,4-d]pyrimidine (I, allopurinol) and some of its methyl derivatives.

Application of the NMR method for studying the tautomerism is based on the following propositions. At room temperature the rate of the tautomeric reaction is quite large in the time scale of NMR; therefore, for each carbon atom a single signal is observed with a chemical shift which is averaged for the tautomeric forms. In order to evaluate the chemical shifts of the different tautomeric forms, model compounds were studied in which the hydrogen atom is replaced by a substituent which does not participate in the exchange, for example the methyl group. The effect of the methyl group on the chemical shifts of the studied carbon atoms, as a rule, is not very great [1].

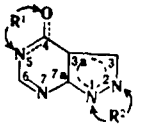
Previously by means of ^{13}C NMR spectroscopy it has been shown that the predominant form of amine–imine tautomerism in 4-aminopyrazolo[3,4-d]pyrimidines is the amino form [3, 4]. By studying the protropic tautomerism by this method it was found that in 7-hydroxypyrazolo-[4,3-d]pyrimidine the population of the $N_{(2)}$–H form was 26 ± 6% [5].

For allopurinol, which is a close analog of hypoxanthine, two types of tautomerism are possible: lactam–lactim in the pyrimidine ring and prototropic in the pyrazole ring.



I

The following compounds were chosen as model systems:



II–IX

II R^1=1-CH_3, R^2=H; III R^1=2-CH_3, R^2=H; IV R^1=1-CH_3, R^2=5-CH_3; V R^1=H, R^2=5-CH_3; VI R^1=H, R^2=4-CH_3; VII R^1=1-CH_3, R^2=4-CH_3; VIII R^1=2-CH_3, R^2=5-CH_3; IX R^1=2-CH_3, R^2=4-CH_3

In this case in order to ascertain the mutual effect of both studied processes it was necessary to study separately the lactam–lactim tautomerism in compounds II and III (by using the triads II, IV, VII and III, VIII, IX, respectively) and the prototropic tautomerism in compounds V and VI (triads V, IVa, VIII and VI, VII, IX, respectively). Unfortunately compound IX could not be synthesized, and compound VIII was insufficiently soluble to permit recording the ^{13}C NMR spectra. Therefore, the lactam–lactim tautomerism was studied only for compound II, and in studying the prototropic tautomerism certain assumptions had to be made.

The chemical shifts of the ^{13}C NMR signals for allopurinol and its methyl compounds II–VII are given in Table 1.

Institute of Biophysics of the Ministry of Public Health USSR, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1543-1546, November, 1979. Original article submitted January 9, 1979.

 0009-3122/79/1511-1240$07.50

TABLE 1. ^{13}C NMR Chemical Shifts in Allopurinol and Its Methyl Derivatives in Hexametapol Solution

Compound	Substituent	Chemical shifts of the carbon atoms, ppm					
		$C_{(3)}$	$C_{(3a)}$	$C_{(4)}$	$C_{(6)}$	$C_{(7a)}$	CH_3 groups
I		132,8	106,0	157,5	147,3	154,5	
II	1-CH_3	133,5	106,2	156,7	147,7	152,2	33,5
III	2-CH_3	129,2	107,9	159,5	146,2	158,2	39,3
IV	1,5-$(CH_3)_2$	133,3	105,0	156,6	151,2	151,8	33,5; 32,2
V	5-CH_3	132,8	104,7	157,3	150,4	154,1	32,0
VI	4-OCH_3	130,4	101,5	163,4	154,3	156,6	53,4
VII	1-CH_3, 4-OCH_3	130,4	101,9	163,5	154,9	154,5	33,6; 53,8

The lactam–lactim tautomerism was studied in compound II by utilizing the chemical shifts of the $C_{(4)}$ atoms in the triad II, IV, and VII. A correlation diagram of the changes in the chemical shifts of these compounds is shown in Fig. 1. The relative position of the $C_{(4)}$ signal enables the amount of the $N_{(3)}$–H tautomer to be calculated from the following equation (4) given in [2]:

$$[\%N_{(5)}H] = \frac{\delta C_{(4)}(II) - [\delta C_{(4)}(VII) - y]}{[\delta C_{(4)}(IV) - z] - [\delta C_{(4)}(VII) - y]} \cdot 100\%, \quad (1)$$

where $\delta C_{(4)}$ is the chemical shift of the $C_{(4)}$ atom in compounds II, IV, VIII, and y and z are the correction factors for the chemical shift of the $C_{(4)}$ atom due to the effect of the substituents OCH_3 and NCH_3. In [2] for hypoxanthine derivatives the value of z was taken to be 0.5 ppm; the parameter y was not determined.

The population of the lactam form $N_{(3)}$–H in compound II was $\geqslant$91% taking account of z or 100% without allowing for this coefficient.

The prototropic tautomerism in the pyrazole part of the allopurinol molecule affects the valency structure of the five-membered ring. As indicated elsewhere [5] the presence of a hydrogen atom or a substituent in position $N_{(2)}$ reduces the degree of delocalization of electron density, which increases the energy of this isomer compared with the energy of the $N_{(1)}$ isomer. In addition it is not possible to take into account the fact that the prototropic tautomerism can affect the lactam–lactim tautomeric equilibrium. An increase in the population of the $N_{(2)}$–H isomer can result in an increase in the lactim form; that is, the difference in the chemical shifts of the atoms $C_{(3)}$ and $C_{(7a)}$ in compounds II and III (Table 1) can be caused not only by a change in the position of the CH_3 group in the five-membered ring, but also by an increase in the content of the lactim form in III, which changes the chemical shift in the same direction (cf. the chemical shifts of $C_{(3)}$ and $C_{(7a)}$ in IV and VII).

Further examination of the chemical shifts of $C_{(3)}$ and $C_{(7a)}$ shows that the signal of the $C_{(7a)}$ atom is more sensitive to prototropic tautomerism than to lactam–lactim tautomerism since the position of the signal due to this atom on passing from compound II to compound III ($\Delta\delta$ = 6 ppm) changes by twice as much as on passing from IV to VII ($\Delta\delta$ = 2.7 ppm). The corresponding differences for the chemical shifts of the $C_{(3)}$ atoms are nearer to each other ($\Delta\delta$ = 4.3 and 2.9 ppm). Therefore, in studying the prototropic tautomerism the chemical shifts of the $C_{(7a)}$ atom were examined.

In order to calculate the population of the $N_{(2)}$–H tautomeric form in compounds V and VI, in which the lactam or the lactim configuration is fixed, the following equations can be used, which are similar to equation (1) found in [2]:

$$[\%N_{(2)}H] = \frac{\delta C_{(7a)}(V) - [\delta C_{(7a)}(IV) - \alpha]}{[\delta C_{(7a)}(VIII) - \beta] - [\delta C_{(7a)}(IV) - \alpha]} \cdot 100\%, \quad (2)$$

$$[\%N_{(2)}H] = \frac{\delta C_{(7a)}(VI) - [\delta C_{(7a)}(VII) - \alpha]}{[\delta C_{(7a)}(IX) - \beta] - [\delta C_{(7a)}(VII) - \alpha]} \cdot 100\%, \quad (3)$$

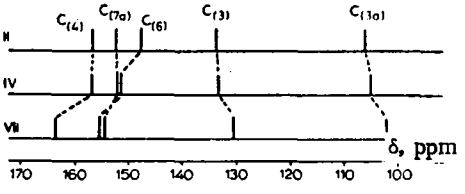


Fig. 1

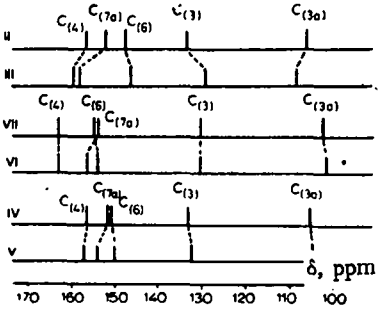


Fig. 2

Fig. 1. Correlation diagram of the chemical shifts in compounds II, IV, VII.

Fig. 2. Correlation diagram of the changes in the chemical shifts for the compounds II—III, V—IV, VI—VIII.

where $\delta_{C_{(7a)}}$ is the chemical shift of atom $C_{(7a)}$ of the corresponding compound; α and β are correction factors for the methyl substituent at $N_{(1)}$ for the adjacent and remote carbon atoms. The values of these factors $\alpha = 0.4$ and $\beta = 0.1$ ppm were taken from [1].

Since the ^{13}C NMR spectra of compounds VIII and IX were not recorded, it was assumed that

$$\delta_{C_{(7a)}}(\mathrm{III}) - \delta_{C_{(7a)}}(\mathrm{II}) = \delta_{C_{(7a)}}(\mathrm{IX}) - \delta_{C_{(7a)}}(\mathrm{VII}) = \delta_{C_{(7a)}}(\mathrm{VIII}) - \delta_{C_{(7a)}}(\mathrm{IV}),$$

i.e., that the effect of the lactam—lactim tautomerism on the chemical shift of the $C_{(7a)}$ atom is not very great, which is not absolutely correct. The correlation diagram of the chemical shifts of the carbon atoms in compounds II—III, V—IV, VI—VIII is shown in Fig. 2. From Eqs. (2) and (3) we find that the population of the $N_{(2)}$—H form in compound V $\leqslant$ 43%, and in compound VI $\leqslant$ 40%.

Allopurinol (I) participates in two tautomeric processes, the cross effects of which are difficult to evaluate from the experimental data. However, the closeness of the chemical shifts of all the carbon atoms (except the $C_{(6)}$ atom, on the position of the signal of which the 5-CH_3 substituent exerts a strong effect) of compounds I and V suggests that the tautomeric forms in these compounds are also closely similar. In particular for allopurinol the content of the tautomer $N_{(1)}H$—$N_{(3)}H$ $\geqslant$ 60%, and of the tautomer $N_{(2)}H$—$N_{(3)}H$ $\leqslant$ 40%.

EXPERIMENTAL

The investigated substances were prepared by published methods: II, mp 300° (from water) [6], R_f 0.30; III, mp 294° (from water) [7]; IV, mp 187-189° (from alcohol) [8], R_f 0.60; V, mp 253-254° (from water) [8], R_f 0.24; VI, mp 197-199° (from methanol) [6]; VII, mp 105-106° (from methanol) [6]; VIII, mp 291-292° (from alcohol) [8], R_f 0.19. Compound I was characterized by its UV spectrum. The system used for thin-layer chromatography was ethyl acetate—methanol—chloroform (6:1:2) on Silufol UV-254 plates.

The ^{13}C NMR spectra were recorded on a Bruker WH-90 instrument using saturated solutions in Hexametapol under conditions of complete and incomplete suppression of the proton spin—spin interaction. Assignment of the signals was made by means of selective suppression of the interaction, as well as by comparison with the data in [3], in which the spectrum of compound I in a solution of DMSO-d_6 is given. Chemical shifts were measured with respect to the high-field line of Hexametapol; in Table 1 they are given with respect to TMS δ_{meas} + 36.2 ppm = δ.

LITERATURE CITED

1. M. T. Chenon, R. J. Pugmire, D. M. Grant, R. P. Panzika, and L. B. Townsend, J. Am. Chem. Soc., 97, 4627 (1975).
2. M. T. Chenon, R. J. Pugmire, D. M. Grant, R. P. Panzika, and L. B. Townsend, J. Am. Chem. Soc., 97, 4636 (1975).
3. M. T. Chenon, R. J. Pugmire, D. M. Grant, R. P. Panzika, and L. B. Townsend, J. Heterocycl. Chem., 10, 431 (1973).

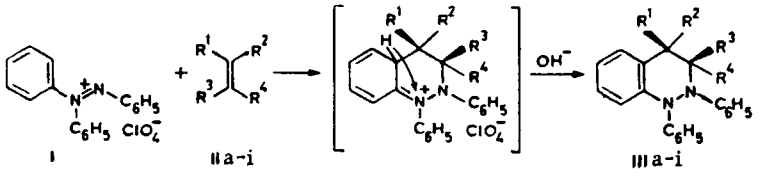
4. R. A. Earl, R. J. Pugmire, G. R. Revankar, and L. B. Townsend, J. Org. Chem., 40, 1822 (1975).
5. M. T. Chenon, R. P. Panzika, J. C. Smith, R. J. Pugmire, D. M. Grant, and L. B. Townsend, J. Am. Chem. Soc., 98, 4736 (1976).
6. C. C. Cheng and R. K. Robins, J. Org. Chem., 23, 852 (1958).
7. P. Schmidt, K. Eichenberger, and J. Druey, Helv. Chim. Acta., 42, 763 (1959).
8. P. Schmidt, K. Eichenberger, M. Wilhelm, and J. Druey, Helv. Chim. Acta, 42, 349 (1959).

SYNTHESIS OF 1,2-DIPHENYL-1,2,3,4-TETRAHYDROCINNOLINES FROM ALKENES AND THE CATION OF TRIPHENYLDIAZENE

K. M. Zelenin and V. N. Verbov

UDC 541.623:547.852.7:543.422.25.4

It is well-known that [1] the cation of triphenyldiazene, obtained by the electrochemical oxidation of triphenylhydrazine, reacts with ethyl vinyl ether, with closing of the tetrahydrocinnoline cycle. It would be timely to investigate the preparational possibilities of this reaction, since methods for the synthesis of cinnoline derivatives, including tetrahydrocinnolines, are extremely limited [2, 3], and to obtain information on the stereochemical special characteristics of this process, which is important for an understanding of its mechanism. To these ends, we have examined the interaction of triphenyldiazene perchlorate (I) with alkenes of different types: vinyl ethers IIa-d, enamines IIe, and styrenes IIf-i, as well as with acrylonitrile and methyl acrylate.



I IIa-i IIIa-i

II, III a $R^1=OCH_3$; b $R^1=OC_2H_5$; c $R^1=OC_2H_5$, $R^4=D$; d $R^1=OCH_3$, $R^3=R^4=CH_3$; e $R^1=N(CH_2)_5$, $R^3=R^4=CH_3$; f $R^1=C_6H_5$; g $R^1=C_6H_5$, $R^3=D$; h $R^1=C_6H_5$, $R^4=D$; i $R^1=C_6H_5$, $R^2=CH_3$ (unindicated R=H)[3]

It was found that, from vinyl ethers and enamine, the corresponding 1,2-diphenyl-1,2,3,4-tetrahydrocinnolines (IIIa-e) are formed with a high yield even cold, while from styrenes they are formed only with prolonged heating. The latter was found possible due to the fact that salt I, in contrast to other diazene salts [1, 4, 5], remains practically unchanged with long-term boiling of an acetonitrile solution of it. Under these same conditions, there was no kind of reaction between the cation of I with acrylonitrile or methyl acrylate. Thus, the cation of triphenyldiazene reacts only with olefins with a nucleophilic character, and this reaction can serve as a method for the synthesis of 1,2-diphenyl-1,2,3,4-tetrahydrocinnolines (IIIa-i, Tables 1 and 2), having an electron-donor substituent R^1.

In the IR spectra of compounds III there are no characteristic frequencies of any kind of short bonds or functional groups, except for the usual frequencies of the aromatic rings, and their UV spectra are similar to the spectra of triphenylhydrazine. The PMR spectra of the derivatives III (Table 1) have a corresponding set of signals, reflecting the structure ascribed to them.

A conclusion with respect to the position of the substituent R^1 in the ring can be drawn from the mass spectroscopy of typical representatives of the compounds III: derivatives IIIa and IIIf with a methoxy or phenyl group, respectively.* In the mass spectra of these compounds (Table 3) there are intense peaks of molecular ions (m/e 316 for IIIa and 362 for IIIf), which attests to their stability with respect to electron impact. A lowering of the

*The mass spectrum of the compound IIIe could not be obtained due to the thermal destruction of the substance under the conditions of the recording of the spectrum.

S. M. Kirov Military Medical Academy, Leningrad 195009. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1547-1551, November, 1979. Original article submitted January 5, 1979.

0009-3122/79/1511-1243$07.50