Ring–Chain Tautomerism in 1,3-Diaza and 1,3-Oxaza Heterocycles

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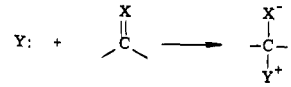
Abstract: The open-chain immonium tautomers (10–20%) are in equilibrium with the dominant ring form in CF_3CO_2H but are not present in CCl_4 for the five- and six-membered 1,3-diaza and 1,3-oxaza compounds **1–4**, which lack all carbon substituents. The alternative open-chain oxonium tautomer is suspected as a minor contributor for the five-membered oxaza heterocycle **3**. The proportion of open-chain form increases with temperature in all cases, usually achieving about the 50% level by 100 °C. The ring and chain forms of the five-membered diaza heterocycle **1** undergo rapid interconversion on the NMR time scale above 60 °C. This observation comprises the first DNMR coalescence for a nucleophilic attack on an sp^2 center (eq 1). The more rapid ring ⇌ chain interconversion for the diaza system than for the oxaza system results from the relative O/N nucleophilicities and C–O/C–N bond energies. The more rapid ring ⇌ chain interconversion for the five-membered ring (5-endo-trigonal) than for the six-membered ring (6-endo-trigonal) is an exception to the vectorial rules for ring closure. Either immonium ions or the ring–chain process itself may be a systematic exception to these rules.

The family of reactions between a nucleophile and a carbonyl group or its equivalent to produce a saturated carbon bonded to two heteroatoms is one of the most important and general in organic chemistry (eq 1, in which the usual acid



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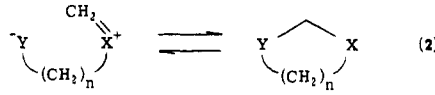
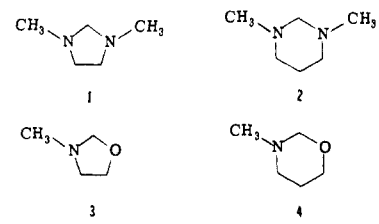
catalysis is not shown). When the nucleophile and the double bond are located within the same molecule, the process has been termed ring–chain tautomerism (eq 2). The kinetics and



(2)

equilibria for this process have been studied for dioxolanes (two oxygens, five members),[2a,b] oxazolidines (one oxygen, one nitrogen, five members),[2c-e] perhydrooxazines (one oxygen, one nitrogen, six members),[2f-h] thioxolanes (one oxygen, one sulfur, five members),[2i,j] and diazolidines (two nitrogens, five members),[2k] among others.

The reaction is central not only to organic reactions such as cyclic acetal formation/decomposition but also to biochemical processes such as the enzyme-catalyzed thymidylate synthetase reaction. The cofactor N^5,N^{10}-methylenetetrahydrofolic acid contains a diazolidine ring that undergoes ring–chain tautomerism while serving as a methylene transfer agent.[3] Baldwin[4] has classified the reaction in eq 2 as endo-trigonal, which is vectorially disfavored for five members but favored for six members. Studies have focused heretofore on systems in which the carbon between the two heteroatoms is either mono- or disubstituted.[2] Moreover, a steric effect on the ring–chain interconversion has been documented,[2b] whereby increased substitution at the 2 position slows the ring-opening process. Consequently, in the present study we have examined systems that carry no substituents on the carbon between the heteroatoms, or for that matter on any other carbons in the ring. The model is more appropriate for N^5,N^{10}-methylenetetrahydrofolic acid, which is unsubstituted on the carbon between the two nitrogens. We selected for study 1,3-dimethyl-1,3-diazolidine (or 1,3-dimethyl-1,3-imidazolidine) (**1**), 1,3-dimethyl-1,3-perhydrodiazine (or 1,3-dimethylperhydropyrimidine) (**2**), 1-methyl-1,3-oxazolidine (**3**), and 1-methyl-1,3-perhydrooxazine (**4**). Using nuclear magnetic resonance (NMR) techniques, we have examined the ring–chain equilibrium for all four systems in trifluoroacetic acid,



and we have determined the kinetics for the ring–chain interconversion when the rates fall within the NMR time scale.[5]

Results

The dinitrogen compounds (**1** and **2**) were prepared by the reaction of formaldehyde with the appropriate diamine, which in turn was prepared by the reaction of methylamine with 1,2-dibromoethane or 1,3-dibromopropane, respectively. Use of formaldehyde-d_2 resulted in placement of deuterium in the 2 position of **1** and **2**. 1,3-Dibromopropane-2,2-d_2 led to deuteration of the 5 position of **2**. The oxygen–nitrogen compounds (**3** and **4**) were prepared by the reaction of paraformaldehyde with the appropriate amino alcohol. The ^1H NMR spectra of **1–4** in neutral solvents (CCl_4, $CDCl_3$) showed resonances for only the ring structures.

The spectra in trifluoroacetic acid showed clear evidence for an equilibrium between the ring and chain forms. The spectrum of 1-methyl-1,3-perhydrooxazine (**4**) is given in Figure 1. The large doublet at δ 2.7 comes from the methyl group on nitrogen in the ring form, split by the proton on nitrogen. When the temperature is raised, this doublet collapses to a singlet, as NH proton exchange becomes fast on the NMR time scale. The AB quartet centered at δ 4.5 is from the 2 protons in the ring form. The upfield (axial) half of the AB quartet is further split into a triplet from the axial–axial HNCH coupling. At higher temperatures, fast NH proton exchange removes this coupling and converts the triplet to the normal doublet half of the AB quartet. The broad peak at δ 7.5 that disappears at higher temperatures is from the proton on nitrogen. Other multiplets in the δ 1.5–2.5 and 3–4 regions are from the remaining ring protons. The sharp peak at δ 7.9 cannot be assigned to any of the protons in the ring structure. Use of CF_3CO_2D results in the disappearance only of the broad peak at δ 7.5. We assign the δ 7.9 peak to the CH_2= protons in the chain form **4c**. The extremely low field position is the result of the diamagnetic anisotropy of the carbon–nitrogen double bond, by analogy with the well-known effect of the aldehyde carbon–oxygen double bond. The chain form accounts for about 10% of the mixture at room temperature. Raising the

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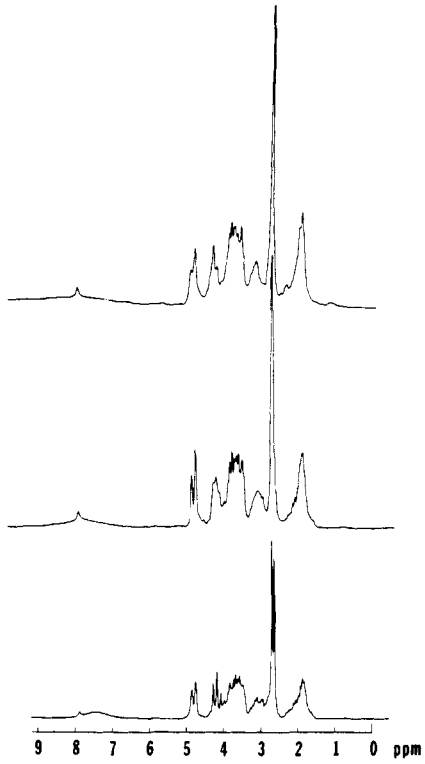
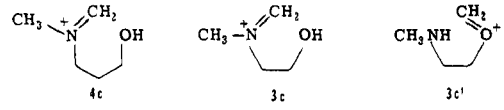


Figure 1. The 60-MHz ^1H spectrum of 1-methyl-1,3-perhydrooxazine (**4**) in CF_3CO_2H as a function of temperature: (bottom to top) 34, 80, and 104 °C.



temperature removes all HNCH couplings and broadens most of the peaks but does not lead to coalescence of the ring and chain resonances. By 115 °C, the AB quartet has collapsed to a broad singlet. At the extreme of fast NH exchange, the NCH_2O protons are no longer diastereotopic.

The spectrum of 1-methyl-1,3-oxazolidine (**3**) is presented in Figure 2. The methyl resonance again begins as a doublet and becomes a singlet at higher temperatures. The 2 protons of the ring form give a pair of triplets (δ 4.2 and 4.8) at room temperature (mutual AB coupling plus coupling to NH). Both halves of the AB quartet show the HNCH coupling because of the similarity of $^3J_{cis}$ and $^3J_{trans}$ in five-membered rings, in contrast to the situation in six-membered rings such as **4**. The pair of triplets becomes a pair of doublets at higher temperatures, as proton exchange becomes rapid on the NMR time scale. The low-field region again displays the NH (δ 8.5, br) and the CH_2= (δ 7.8–7.9) resonances. The most remarkable difference between the spectra of **3** and **4** is the presence of *two* singlets in the CH_2= region for **3**. One possible explanation is that both the immonium (**3c**) and the oxonium (**3c'**) forms are present, since syn-anti isomerism of **3c** is unlikely. Previous studies have discussed these equilibria in terms of the immonium tautomer only.[2c,f-h] In fact, the NMR spectra alone give no information on the question of immonium vs. oxonium structure, since there is no reliable distinction between CH_2=N^+ and CH_2=O^+. We will adhere to the literature precedents[2] and write the major chain tautomer with the immonium structure.

At higher temperatures, the two CH_2= resonances at δ 7.8–7.9 coalesce into a singlet. If both immonium and oxonium forms are present, their interconversion would take place through the ring form, so that the peak coalescence may be the result of fast chain-ring-chain isomerism. The coalescence of the CH_2= peaks would occur at lower temperatures because

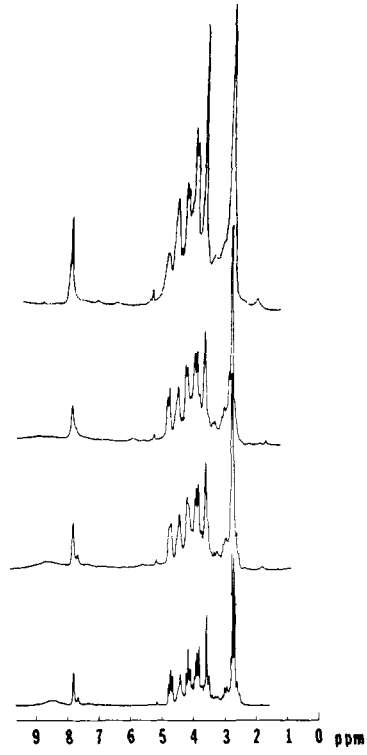


Figure 2. The 60-MHz ^1H spectrum of 1-methyl-1,3-oxazolidine (**3**) in CF_3CO_2H as a function of temperature: (bottom to top) 36, 61, 80, and 104 °C.

of the closeness of the resonances. Integration of CH_2= (chain) and NCH_2O (ring) resonances indicates that the chain form represents about 10% of the mixture at room temperature. Raising the temperature produces a decided increase in the chain proportion, to about 20% at 80 °C and 30% at 104 °C. The relative decrease of the ring methyl and the 2 proton (AB) resonances and the increase of a presumed methyl resonance at δ 3.7 and of other peaks from the chain form, particularly at δ 4.4, are consonant with this shift in the equilibrium.

The relatively complex ^1H spectrum of 1,3-dimethylperhydropyrimidine (**2**) in trifluoroacetic acid was simplified by deuteration at the 5 position. As a result, the 4,6 resonance is a singlet at δ 3.3 (Figure 3). In contrast to the oxaza compounds, NH exchange in **2** is fast at room temperature, so that the CH_3 and 2-CH_2 resonances are singlets. Apparent monoprotonation leaves one unprotonated amine center that inverts rapidly and interconverts the cis-trans isomers.[6] Further deuteration at the 2 position eliminates both the CH_2= resonance from the chain form (δ 7.8) and the 2 proton resonance from the ring form (4.4). Again, an increase in temperature clearly favors the chain structure (resonances at δ 3.5–3.9). The proportion of the chain form goes from about 31% at 40 °C to 36 (50 °C), 41 (60 °C), 46 (70 °C), and 54% (80 °C). The proportions are not strictly reproducible at a given temperature, possibly because of failure to attain equilibrium, but all spectral changes are reversible.

We have illustrated the variation of the spectrum of 1,3-dimethyl-1,3-diazolidine (**1**) with temperature elsewhere.[5] The spectrum contains singlets for the ring resonances of CH_3N, NCH_2N, and NCH_2CH_2N, so that NH exchange is fast. At lower field are the resonances for NH and CH_2=. The most extraordinary difference from the other three systems is the complete coalescence of the ring and chain resonances, most dramatically illustrated by the CH_2= (chain) and NCH_2N (ring) resonances. These begin to broaden at about 40 °C and are fully coalesced by 100 °C. The remaining ring protons also clearly pass through coalescence, but with less broadening

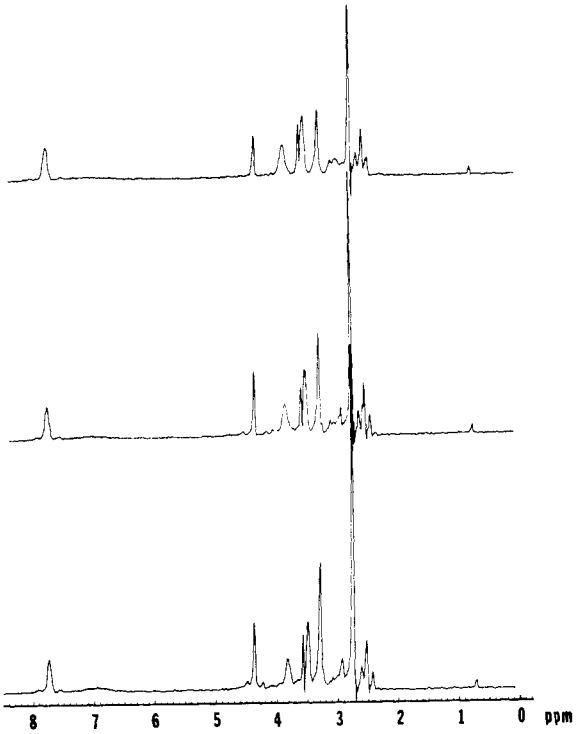


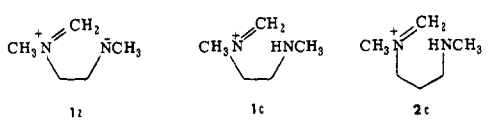
Figure 3. The 60-MHz ^1H spectrum of 1,3-dimethylperhydropyrimidine-*5,5-d*$_2$ (**2**-*d*$_2$) in CF_3CO_2H as a function of temperature: (bottom to top) 40, 70, and 90 °C.

because of shorter distances between exchanging resonances. Thus at 120 °C, the spectrum contains only three peaks, an average methyl resonance, an average NCH_2CH_2N resonance, and an average $CH_2{=}/NCH_2N$ resonance.

Application of standard coalescence temperature methods gives a free energy of activation of 16.9 ± 0.3 kcal/mol at 90 °C for the ring–chain interconversion in **1**. The failure to observe coalescence in the other systems is consistent with barriers of at least 18 kcal/mol. To confirm the spin interchange of the $CH_2{=}$ and NCH_2N protons in **1**, we carried out Forsén–Hoffman-type experiments.[7] Irradiation of the $CH_2{=}$ resonance at 70 °C reduced the intensity of the NCH_2N resonance significantly without affecting the CH_3N and NCH_2CH_2N resonances.

Discussion

The spectra of the neutral heterocycles show no evidence of the chain tautomer at room temperature in CCl_4, whereas in the acidic medium of CF_3CO_2H the protonated heterocycles consistently show 10–20% of the chain form in equilibrium. Simple electrostatic forces may be the cause of these observations. The chain tautomer would be a zwitterion in neutral media, e.g., **1z**. Re-formation of the ring appears to be a very



favorable process, since the negative charge cannot be neutralized by reaction with any easily accessible protons. Consequently, the neutral closed form **1** is much more stable than the open dipolar form **1z**. On the other hand, if the ring is initially protonated, as in CF_3CO_2H, the chain form has a net positive charge (see **1c**, **2c**, **3c**, **3c′**, and **4c**) with much less impetus to reclose the ring. Thus the ring and chain forms are more closely balanced in energy. At higher temperatures the open and closed forms tend toward more nearly equal energies. It should be emphasized that these considerations are purely thermodynamic and only pertain to the relative stabilities of the corresponding ring and chain forms. Furthermore, the well-known acid catalysis of acetal formation and related reactions is not relevant, since the protonation preequilibrium step serves to enhance the electrophilicity of the carbon atom that receives the nucleophile. In these heterocycles, the immonium and oxonium chains already carry a positive charge on the heteroatom and do not need further activation.

This point brings us to the second major area of consideration, the relative rates of ring–chain tautomerization for the four compounds, **1–4**. By NMR coalescence, we observed that the five-membered dinitrogen heterocycle **1** has the fastest rate of tautomerization. The barrier of 16.9 kcal/mol is the first measured for this type of process by the NMR method. Reactions studied by DNMR techniques heretofore have included proton transfers, sigmatropic shifts, bond rotations, and a variety of other conformational processes. The observed coalescence of the ring and chain resonances for **1** may be the first example of the broad class of nucleophilic addition reactions (eq 1) that in particular includes additions to carbonyl groups. Consequently, it would seem worthwhile to search for other examples. Certainly ring–chain tautomerism is particularly favorable, since it is unimolecular in both directions and (in the protonated form) the equilibrium is reasonably well balanced, i.e., the rate in one direction is not appreciably different from the rate in the opposite direction.

The rate of tautomerization appears to be faster for the diazolidine **1** than for the oxazolidine **3**. In the ring-closure direction, the nucleophile for the diazolidine is amino, whereas that for the oxazolidine is hydroxyl. The higher nucleophilicity of nitrogen in comparison to oxygen is well established in other systems and is consistent with the lower tautomerization barrier for the diazolidine. (The higher nucleophilicity of N may also explain why the oxonium form **3c′**, with its N nucleophile, is less stable than the immonium salt **3c**, with its O nucleophile.) In the reverse direction the diazolidine ring may open more rapidly than the oxazolidine ring because of the lower average bond energy of C–N (72.8 kcal/mol) compared to C–O (85.5 kcal/mol).[8]

Perhaps the most puzzling observation was that the five-membered diazolidine **1** tautomerizes more rapidly than the six-membered perhydropyrimidine **2**. According to Baldwin's vectorial rules, the 5-endo-trigonal process is much less favorable than the 6-endo-trigonal process, at least for first-row systems.[4,9] Two other authors, however, have also observed rapid 5-endo-trigonal processes recently.[2d,e] It may be significant that their systems, as well as ours, involve attack of the first-row nucleophile on an immonium double bond. Pelletier and Mody suggested that the immonium bond is much more accessible than the carbonyl bond and hence is less subject to vectorial constraints.[2e] Although such considerations may absolve these five-membered heterocycles of the venial sin of undergoing the tautomerization in the first place, they do not speak to the more serious offense of tautomerizing faster than the six-membered heterocycle. Like second-row systems (those containing sulfur, phosphorus, etc.), the immonium systems may have to be excluded from the vectorial considerations. Alternatively, it should be borne in mind that there is an entropic favoring of five-membered over six-membered ring formation, because of the shorter chain length, and this entropic component must be weighed against the other factors. Furthermore, there may be special considerations in our specific system of ring–chain tautomerism. Because the reaction is occurring rapidly at equilibrium, the chains with their adhering solvent molecules may not fully relax into extended conformations. Vectorial considerations may be less important if the solvent maintains the reacting ends of the chain very close to the site of nucleophilic attack.

Summary and Conclusions

Five- and six-membered saturated heterocycles containing nitrogen at the 1 position and either oxygen or another nitrogen at the 3 position exist as a mixture of ring and open-chain tautomers in trifluoroacetic acid. In neutral solvents, only the ring form is observed. In the acidic solvent the chain form is readily discerned by the low-field CH_2= resonance. The five-membered oxygen/nitrogen ring may be in equilibrium with both the immonium and the oxonium chain tautomers, although the existence of an oxonium tautomer must be demonstrated by further experimentation before its existence can be accepted. Coalescence of the ring and chain resonances for the five-membered dinitrogen system provides the first kinetics of a nucleophilic addition by the dynamic NMR method. The more rapid tautomerization reaction of the dinitrogen heterocycle than of the oxygen/nitrogen heterocycle is consistent with known relative N and O nucleophilicities and C–N and C–O bond energies. The more rapid 5-endo-trigonal tautomerization for the five-membered dinitrogen system in comparison with the 6-endo-trigonal tautomerization in the six-membered dinitrogen system is in contradiction with the Baldwin vectorial rules for ring closure. Addition to immonium salts may be less subject to vectorial constraints than are additions to carbonyl groups, or the ring–chain tautomerization process itself may be exempted because of incomplete relaxation of the solvent shell during the rapid ring opening/ring closing process. The four systems studied (**1–4**) were chosen because they lack substituents at the electrophilic site (the 2 position) and hence more closely resemble naturally occurring methylene transfer reagents such as N^5,N^{10}-methylenetetrahydrofolic acid than do the more easily studied mono- and disubstituted heterocycles.

Experimental Section

Proton magnetic resonance spectra were obtained at 60 MHz on a Perkin-Elmer R20B spectrometer and at 80 MHz on a Varian CFT20 spectrometer. The double resonance ^1H experiments were carried out on the R20B. Carbon-13 spectra were obtained at 20 MHz on the CFT20. Infrared spectra were recorded on a Perkin-Elmer 283 spectrometer. NMR samples were obtained by adding the compound to a tube containing frozen trifluoroacetic acid; the tube was warmed slowly and the layers were mixed.

1,3-Dimethyl-1,3-diazolidine (1) and 1,3-dimethyl-1,3-perhydrodiazine (2) were obtained by condensing formaldehyde (30% aqueous solution) with the corresponding di(methylamino)alkane according to the method of Riddell.[10] The di(methylamino)ethane is commercially available (Aldrich), and the di(methylamino)propane was prepared by the reaction of 1,3-dibromopropane with methylamine. The characteristics of the diazolidine **1** were bp 107–110 °C (760 mmHg); ^{13}C NMR (CF_3CO_2H) δ 42.70 (CH_3N), 55.18 (NCH_2CH_2N), 74.48 (NCH_2N). The characteristics of the perhydropyrimidine were bp 137–138 °C (760 mmHg); ^{13}C NMR (CF_3CO_2H) δ 21.97 (CCH_2C), 43.65 (CH_3N), 53.72 (NCH_2C), 70.54 (NCH_2N).

1-Methyl-1,3-oxazolidine (3) was obtained by heating 2-(methylamino)ethanol with paraformaldehyde in refluxing benzene according to the method of Jones et al.[11] Its characteristics were bp 97–99 °C (760 mmHg); ^{13}C NMR (CF_3CO_2H) δ 41.61 (CH_3N), 54.45 (NCH_2C), 68.11 (CCH_2O), 88.62 (NCH_2O).

1-Methyl-1,3-perhydrooxazine (4) was similarly obtained by heating 3-(methylamino)propanol with paraformaldehyde in refluxing benzene.[12] Its characteristics were bp 124–126 °C (760 mmHg); ^{13}C NMR (CF_3CO_2H) δ 23.56 (CCH_2C), 39.36 (CH_3N), 54.95 (NCH_2C), 68.19 (CCH_2O), 86.20 (NCH_2O).

Formaldehyde-d_2. Paraformaldehyde-d_2 was placed in a 25-mL round-bottomed flask connected via glass tubing to a small beaker containing 10 mL of 99.4% D_2O. The tubing was immersed in the D_2O, the beaker was cooled to 0 °C, and the flask and glass tubing were heated with a gas burner. The resulting formaldehyde-d_2 gas was dissolved in the D_2O as it was formed.

1,3-Dimethyl-1,3-diazolidine-2,2-d_2. 1,2-Di(methylamino)ethane (0.02 mol) was mixed carefully with 0.022 mol of formaldehyde-d_2 (25% D_2O solution) for 0.5 h. The product was isolated by addition of NaOH pellets (until basic) and extraction with ethyl ether. The organic portion was dried (Na_2CO_3), the ether was evaporated, and the residue was distilled (bp 107–109 °C (760 mmHg)) to give a 33% yield of the product. A similar procedure was used to prepare 1,3-dimethyl-1,3-perhydrodiazine-2,2-d_2 in 53% yield.

References and Notes

(1) (a) This work was supported by the National Science Foundation (Grants CHE77-08384 and CHE79-05542), by the donors of the Petroleum Research Fund, administered by the American Chemical Society, and by the National Institutes of Health (Grant 1 RO1 GM26124-01). (b) Petroleum Research Fund Postdoctoral Fellow, 1977–1978, on leave of absence from the Institute of Drug Research. Pharmaceutical Faculty of the Medical Academy, Łodź, Poland.
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