REGIOSELECTIVE DEUTERIATION KINETICS OF 2-, 4-, AND 6-METHYL GROUPS IN D_2O SOLUTIONS OF PYRYLIUM AND N-METHYLPYRIDINIUM PERCHLORATES POSSESSING ALSO 3-METHYL OR 3-PHENYL GROUPS

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SUMMARY

By ^{1}H-NMR it was found that 2,3,4,6-tetramethylpyrylium perchlorate (I) in D_2O undergoes isotopic exchange at the 2, 4, and 6-methyl groups with relative rates 5 : 40 : 1, respectively (assignments of α-methyl NMR signals were substantiated by unambiguous synthesis). If the 3-methyl group is replaced by a 3-phenyl group, the relative rates for the pyrylium salt III are 2.5 : 49 : 1, respectively (in D_2O + CD_3OD). On the other hand, the relative rates for the 2, 4, and 6-methyls in 1,2,4,6-tetramethyl-3-phenylpyridinium perchlorate are 12 : 1 : 4, respectively (in D_2O + CD_3OD + NaOD). These rate differences allow the preparation of selectively deuteriated pyrylium or pyridinium salts, and of other aromatic or heterocyclic compounds starting from pyrylium salts with selectively deuteriated side-chains.

Key Words : Deuterium isotope exchange, ^{1}H-NMR, Selectively methyl--deuteriated pyridines, pyrylium and pyridinium salts.

Previous papers in this series (1), which were reviewed recently (2, 3), evidenced that methyl side-chains of pyrylium salts are deuteriated faster in γ than in α-positions because γ-methylenepyran intermediates (anhydrobases) are formed more

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readily than α-methylenepyrans. So far, either symmetrical pyrylium cations such as 2,4,6-trimethyl- (4, 5), 2,3,5,6-tetramethyl- (6) and 2,3,4,5,6-pentamethylpyrylium (3, 7) were examined, or non-symmetrical pyrylium cations were investigated in which an α-methyl group was compared by intramolecular relative kinetics with an α-ethyl (8) or α-isopropyl group (9). The only non-symmetrical pyrylium salt so far discussed, 2,3,6-trimethyl-4-phenylpyrylium (6), had a small separation (0.03 ppm) between the two α-methyl groups ; at that time we had not investigated the difference in deuteriation rates between the two α-methyl groups since we were primarily interested to see whether the 3-methyl group underwent any deuteriation, and found that it does not ; this pyrylium salt is now being reinvestigated, and results will be presented in a future paper.

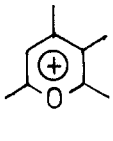
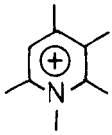
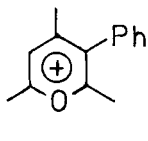
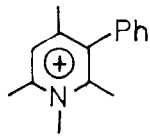
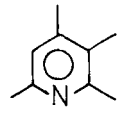
We decided to use other structures for evidencing whether, and how much, two α-methyl groups differ in their deuteriation rate when a 3-substituent is present. In some of these structures we use the ^{1}H-NMR shielding effect exerted by a phenyl group in position 3 on the two neighbouring methyl groups for an easier assignment of NMR signals and for spreading apart the two α-methyl peaks.

In the present paper we compare the deuteriation kinetics both between α- and γ-methyl groups, and between two α-methyl groups, in pyrylium and pyridinium cations with non-symmetrical substitution patterns : 2,3,4,6-tetramethylpyrylium I (10) and its N-methylpyridinium congener, 1,2,3,4,6-pentamethylpyridinium II (11, 12) ; 2,4,6-trimethyl-3-phenylpyrylium III (13) and its N-methylpyridinium congener, 1,2,4,6-tetramethyl-3-phenylpyridinium IV (13), all salts being perchlorates.

The ^{1}H-NMR spectra of these salts and of 2,3,4,6-tetramethylpyridine V are presented in Table 1. In all cases the methyl peaks and the ring proton peak appear as singlets under the usual recording conditions. Assignments rely on the fact that α-methyl protons

(positions 2 and 6) appear at the lowest fields, γ-methyl protons (position 4) at higher field, and ß-methyl protons (position 5) at the highest field in all these six-membered heterocycles (2, 8, 14) while the presence of a perpendicularly tilted 3-phenyl group shifts upfield the two flanking methyl peaks with 0.2 - 0.3 ppm from their normal position (6, 13).

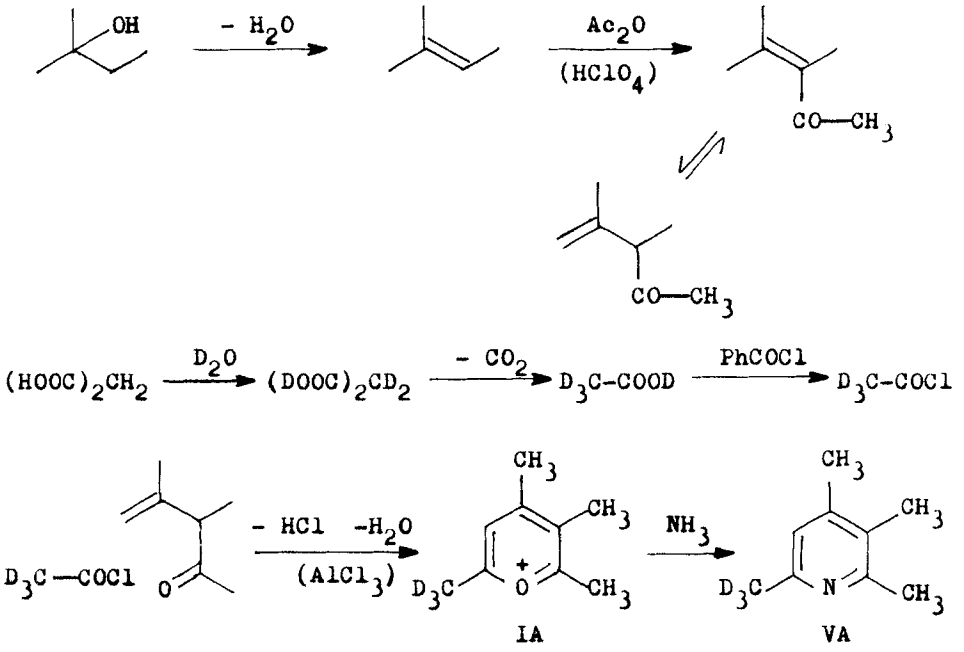
Table 1. ^{1}H-NMR chemical shifts (in F_3CCOOH unless otherwise stated, with internal TMS), δ values, ppm.

Compound / Peak	 I	 II	 III	 IV	 V [a]
1-Me	-	4.16	-	4.20	-
2-Me	2.92	2.83 [b]	2.74	2.60	2.39
3-Me	2.42	2.49	-	-	2.12
4-Me	2.70	2.60	2.52	2.32	2.17
5-H	7.63	7.58	7.81	[c]	6.65
6-Me	2.87 [d]	2.83 [b]	2.98	2.90	2.34 [d]

[a] In CCl_4 ; [b] Accidentally degenerate peaks both in D_2O and in F_3CCOOH ; [c] Masked by the phenyl multiplet (which is not included in the table) ; [d] This peak has low intensity in synthetic 6-CD_3-derivatives A, allowing the assignment of NMR peaks.

For the 3-phenyl-derivatives III and IV there is no ambiguity in the ^{1}H-NMR assignments. In order to make correct assignments for the methyl peaks of the 3-methyl-derivatives I, II and V, the following approach was used : (i) partly deuteriated 2,3,4,6-tetramethylpyrylium perchlorate I was converted into II and V, noting that the order of peaks with lower intensities was the same in these three compounds ; in particular, one of the α-methyl peaks which is deuteriated faster appears at the lowest field both in I

and in V ; (ii) for discriminating between the two α-methyl peaks (positions 2 and 6), we synthesized unambiguously 2,3,4-trimethyl-6-(d_3-methyl)-pyrylium (IA) and the corresponding pyridine (VA), as outlined in Scheme 1. Owing to the high solubility of the perchlorate I in water, the pyrylium salt was not isolated from the reaction mixture but was converted into the corresponding pyridine whose ^{1}H-NMR spectrum showed that the α-methyl peak undergoing slower deuteriation had a very low intensity (corresponding to the isotopic purity of 85-90 % of the acetyl chloride used in the synthesis presented in Scheme 1). Thus it was found that the 2-methyl peak in I appears at lower field and is deuteriated faster than the 6-methyl peak. The order of chemical shifts in I and V is 2 > 6 > 4 > 3-methyl (δ-values). In the 1,2,3,4,6-pentamethylpyridinium cation II, obtained from I and methylamine, the two α-methyl peaks are accidentally degenerate (isochronous).



Scheme 1. Unambiguous synthesis of 6-methyl-deuteriated 2,3,4,6-tetramethylpyrylium (IA) and 2,3,4,6-tetramethylpyridine (VA).

Isotopic exchange experiments were carried out in the ^{1}H-NMR vials by dissolving the compound in the corresponding solvent and maintaining the vial at the required temperature ; integrated intensities were recorded every 5 minutes during 1-2 hours ; the intensity decrease was plotted semilogarithmically versus time. To minimize errors, the kinetic results are presented in Table 2 only as relative rates (intramolecular comparisons) and not as absolute values (time^{-1} for intermolecular comparisons). From previous parts of this series it should be recalled that polymethylpyrylium and -pyridinium perchlorates are soluble in warm water, but the presence of a phenyl group lowers the solubility so that D_2O + methanol-d_4 had to be used. The deuteriation rate is higher in phenyl-substituted than in polymethyl-substituted pyrylium salts, so that convenient temperatures had to be chosen. For pyrylium salts the deuteriation takes place in neutral or slightly acidic medium because at pH > 7 pyrylium salts are ring-opened to pseudobases which undergo condensation and resinification. The pyridinium salts are deuteriated too slowly under similar conditions, but since they are resistant towards bases, addition of low concentrations of NaOD enhances the deuteriation rate to a convenient value for NMR experiments.

Table 2. Kinetic results

Cation	Temp.	Solvent	Relative deutern. rates		
			2-Me	4-Me	6-Me
I, $Me_4\Pi^+$	80°	D_2O	5.0	40	1
III, $Me_3Ph\Pi^+$	60°	D_2O (45%) + D_3COD (55%)	2.5	49	1
II, Me_5Py^+	40°	D_2O + NaOD [a]	(13)[b]	1	(2)[b]
IV, Me_4PhPy^+	40°	D_2O + D_3COD + NaOD [a]	12	1	4.0

[a] NaOD concentration between 0.1 and 1 mmol/l ; [b] Data in brackets are imprecise because α-methyls are isochronous (see text).

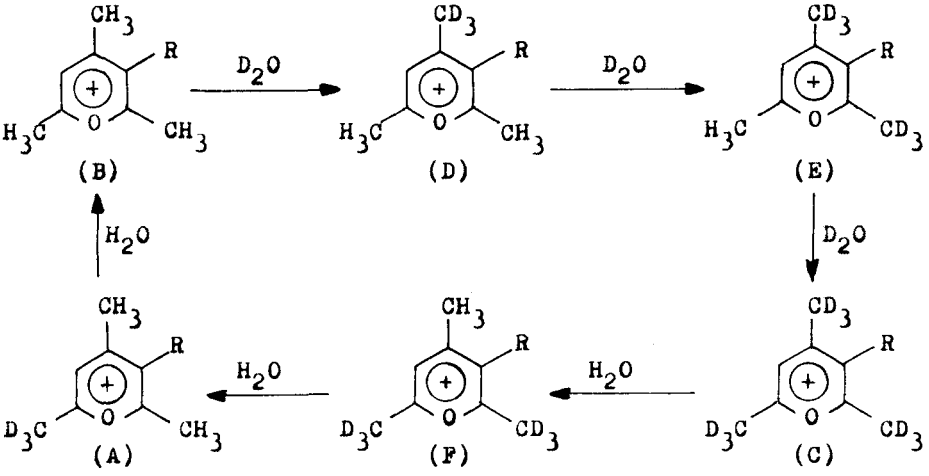
The 1,2,3,4,6-pentamethylpyridinium perchlorate II posed a special problem because the two α-methyl groups are isochronous (accidentally). In the kinetic semilogarithmic plot for this salt, the deuteriation of the 4-methyl group gives rise to a straight line, but a curved plot is obtained for the composite α-methyl peak. The latter curve was considered to be the sum of two processes with different rates (similarly to the radioactive decay of a mixture of two radioisotopes with different half-lives). However, the calculated relative deuteriation rates have lower precision than the other data from Table 2, therefore these values are given in brackets. For all compounds presented in Table 2, the substrate concentration was low enough for assuming pseudo-unimolecular kinetics. Abbreviations in Table 2 : Π^+ = pyrylium ; Py^+=pyridinium.

As shown in Table 2 and as known previously, the 4-methyl group is deuteriated faster than α-methyl groups in pyrylium salts, but this order is reversed in N-methylpyridinium salts (2, 7, 15, 16). Table 2 also presents a result which had not been investigated experimentally till now, namely that in pyrylium or pyridinium salts having 3-methyl or 3-phenyl substituents, the two α-methyl groups are deuteriated with different rates : in both types of cations the more crowded (buttressed) 2-methyl group is deuteriated 2.5 - 5 times faster than the non-hindered 6-methyl group.

The mechanism of isotopic exchange at "benzylic" positions of α- or γ-standing side-chains of pyrylium or pyridinium cations is known to involve deprotonation to anhydrobases (methylenepyrans and methylene-dihydropyridines, respectively) followed by addition of deuterons from the solvent (2, 3, 17, 18). Theoretical calculations accounting for the regioselectivity evidenced here will be reported in a separate paper.

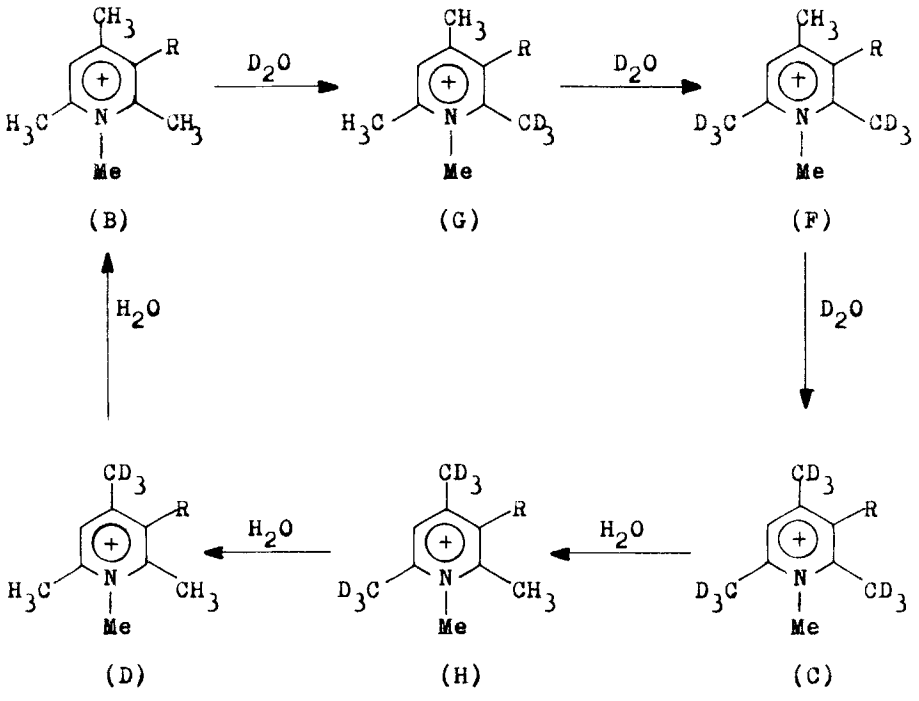
One may conclude from Table 2 that by monitoring and by stopping the isotope exchange at the right moment (e. g. through cooling), one may deuteriate predominantly the faster reacting methyl

group(s) without having to resort to the more fastidious synthetic approaches. Alternatively, one may deuteriate completely all the α and γ-methyl groups, and de-deuteriate some of them selectively in H_2O, namely again the faster reacting methyl(s). Thus one may obtain selective enrichment in deuterium differentiating not only α- from γ-positions as we had done before (γ more reactive in pyrylium, less reactive in pyridinium), but also 2- from 6-methyl groups in 3-substituted salts (2-methyl always more reactive). These ideas are presented in more detail in Schemes 2 and 3.



Scheme 2. Deuteriation and de-deuteriation of 2,4,6-trimethylpyrylium salts having R = Me or Ph groups in position 3.

Starting from pyrylium or N-methylpyridinium salts which are non-deuteriated (B) or are completely deuteriated at the 2, 4, and 6-methyl groups (C), one may obtain predominantly monomethyl-deuteriated (A, D, G) or dimethyl-deuteriated compounds (E, F, H). It will be observed that in both Schemes 2 and 3, structures B, F, C, and D are present, but structures A, E, G, and H appear only in one scheme. It should be stressed that according to the rate differences presented in Table 2 the enrichment in deuterium will be only partial, and that other deuteriated species will also be present in the mixture.



Scheme 3. Deuteriation and de-deuteriation of 1,2,4,6-tetramethylpyridinium salts having an R = Me or Ph group in position 3 of the ring.

In pyridinium salts II or IV the N-methyl group does not undergo isotopic exchange under the mild conditions described in Table 2 ; for deuteriation of the N-methyl group, the formation of the N-ylid intermediate requires more concentrated alkali and longer heating. The 3-methyl group in the pyrylium (I) or pyridinium salts (II) does not exchange its hydrogens under any condition.

As an alternative to Scheme 3, one may first prepare a pyrylium salt with desired deuteriation pattern according to Scheme 2, and then convert it by reaction with a primary amine into the corresponding deuteriated pyridinium salt.

By using the selectively deuteriated pyrylium salts as synthons (2, 19), a wide variety of heterocyclic (pyridines, thio-

phenes, furans, pyrazolines, isoxazolines, 1,2-diazepines, etc.) or carbocyclic compounds with deuteriated side-chains may be prepared (derivatives of benzene, naphthalene, phenol, nitrobenzene, benzonitrile, azulene, etc.). The deuteriation of side-chains in such compounds does not proceed under such mild conditions as those described above, since deprotonation of pyrylium or pyridinium cations is assisted by the positive charge of the heteroatom.

Finally, all the above discussion may be transposed and applied to the preparation of side-chain tritiated compounds if tritiated water (HTO) is employed instead of deuterium oxide (D_2O).

EXPERIMENTAL

The preparation of pyrylium salts I (10) and III (13), of pyridinium salts II (11, 12) and IV (13), and of 2,3,4,6-tetramethylpyridine V (10-12) was described previously.

^{1}H-NMR Spectra were recorded with a Varian A-60A spectrometer using tetramethylsilane (TMS) as standard for solutions in trifluoroacetic acid or in carbon tetrachloride ; no TMS was used for D_2O solutions. Kinetic determinations were performed in the ^{1}H-NMR vial using the nitrogen flush thermal regulator system of the instrument or an external thermostated bath ; in the former case, NMR spectra were recorded while the deuteriation was progressing (at regular intervals during 1 - 2 hours) ; in the latter case, which applied only to I and III,the deuteriation was stopped during the recording of the NMR spectra at a lower temperature. Since only relative rates are discussed in the present paper for intramolecular comparisons, we have not used buffered solutions as in previous parts of this series. For the compounds included in Table 2, the temperature (with I and III) and NaOD concentration (with II and IV) were chosen so that the deuteriation proceeded with a convenient rate, i. e. with a half-life between 40 and 80 minutes. For each compound several integral curves in the ^{1}H-NMR spectrum were recorded at a

sweep width 50 Hz, then the kinetic plots were obtained by averaging these integrated intensities and by recording them semilogarithmically versus time for one temperature.

Preparation of 2,3,4-trimethyl-6-(d_3-methyl)-pyrylium (IA) and the corresponding pyridine (VA). The preparation of acetyl chloride-d_3 will be described first. Acetic acid-d_3 was obtained by decarboxylating deuteriated malonic acid (20). Malonic acid was deuteriated by isotopic exchange with D_2O (99.5 %) admixed with dioxane (1 : 4 vol.), using 50 ml D_2O/mol of malonic acid. After three equilibrations of 24 hrs. each at room temperature, the product (about 90 % isotopic purity) was dried in vacuum and decarboxylated by heating for 6 hrs. with a reflux condenser. Acetic acid-d_3 fractionated at atmospheric pressure was mixed with benzoyl chloride (1 : 2.5 molar ratio), and D_3C-COCl was distilled off from this mixture on a Vigreux column (21), b. p. 45-50°, overall yield 50 %, final isotopic purity between 85 and 90 %.

In a three-necked round-bottomed flask provided with an efficient mechanical stirrer and immersed thermometer, the D_3C-COCl - - $AlCl_3$ complex was prepared by adding gradually 50 mmol $AlCl_3$ into 100 mmol D_3C-COCl at -5° - 0°C. Then 50 mmol of 3,4-dimethyl-3-penten-2-one (10), which becomes equilibrated with its unconjugated isomer in the presence of $AlCl_3$, was added under stirring at 0°. After 2 hrs' stirring at 0° and 2 hrs at room temperature, the flask was left overnight. The reaction mixture was decomposed by pouring into 100 ml water acidified with 2 ml hydrochloric acid. After extraction with ether, the aqueous layer containing the pyrylium chloroaluminate (IA) was poured into excess of aqueous ammonia containing crushed ice, with good stirring for conversion into the pyridine VA. The resulting mixture was filtered with suction, the aluminium hydroxide was washed on the filter with ether, and the filtrate was extracted with ether. The pyridine VA was purified

from ketonic by-products by extraction with dilute hydrochloric acid, separation of the aqueous layer, and treatment of this layer with sodium hydroxide solution. Finally, after extraction with ether, the pyridine VA was distilled under reduced pressure.

REFERENCES

1. To be considered as Part XIV in the series "Isotopic Exchange of Active Methyl Hydrogens". The preceding part is ref. 3.
2. Balaban, A. T., Dinculescu, A., Dorofeenko, G. N., Fischer, G. W., Koblik, A. V., Mezheritskii, V. V., and Schroth, W.- "Pyrylium Salts. Syntheses, Reactions and Physical Properties", Adv. Heterocyclic Chem. Suppl. 2, Academic Press, New York, 1982.
3. Balaban, A. T.- J. Labelled Comp. Radiopharm. 18: 1621 (1981).
4. Gârd, E., Vasilescu, A., Mateescu, G. D. and Balaban, A. T.- J. Labelled Comp. 3 : 169 (1967).
5. Gârd, E., Stănoiu, I., Chiraleu, F. and Balaban, A. T.- Rev. Roumaine Chim. 18 : 257 (1973).
6. Gârd, E., Stănoiu, I., Balaban, A. T. and Chiraleu, F.- Rev. Roumaine Chim. 14 : 247 (1969).
7. Balaban, A. T., Bota, A., Oniciu, D., Klatte , G., Roussel, C. and Metzger,J.- J. Chem. Res. (S) 44 (1982) ; (M) 559 (1982).
8. Stănoiu, I. I., Gârd, E., Uncuţa, C., Chiraleu, F. and Balaban, A. T.- Rev. Roumaine Chim. 24 : 209 (1979).
9. Stănoiu, I. I., Gârd, E., Uncuţa, C., Chiraleu, F. and Balaban, A. T.- Rev. Roumaine Chim. 22 : 1359 (1977).
10. Balaban, A. T. and Bota, A.- Org. Prep. Proc. Internat. (under press).
11. Balaban, A. T. and Nenitzescu, C. D.- J. Chem. Soc. 3553 (1961).
12. Praill, P. F. G. and Whitear, A. L.- J. Chem. Soc. 3573 (1961).
13. Bota, A., Balaban, A. T. and Chiraleu, F.- Rev. Roumaine Chim. 21 : 101 (1976).

14. Balaban, A. T., Bedford, G. R. and Katritzky, A. R.- J. Chem. Soc. 1646 (1964).

15. Zatsepina, N. N., Kaminsky, L. Yu. and Tupitsyn, I. F.- Organic Reactivity (Reaktsionnaya sposobnosti org. soedin.) 6 : 442 (1969) ; 7 : 667 (1970) ; Zatsepina, N. N., Kirova, A. V., Tupitsyn, I. F.- ibid. 5 : 70 (1968) ; Zatsepina, N. N., Tupitsyn, I. F. and Efros, L. S.- Zhurn. Obshchei Khim. 33 : 2703 (1963) ; 34 : 4065, 4072 (1974).

16. Zatsepina, N. N. and Tupitsyn, I. F.- Khim. Geterotsikl. Soed. 1587 (1974).

17. Boyd, G. V.- Rev. Roumaine Chim. 12 : 1133 (1967).

18. Boyd, G. V. and Balaban, A. T.- Rev. Roumaine Chim. 14 : 1575 (1969).

19. Balaban, A. T.- in "New Trends in Heterocyclic Chemistry", Studies in Organic Chemistry No. 3, edited by Mitra, R. B. et al., Elsevier, Amsterdam, 1979, p. 79.

20. Shiner, V. J. Jr. and Smith, M. L.- J. Am. Chem. Soc. 80 : 4095 (1958).

21. Brown, H. C.- J. Am. Chem. Soc. 60 : 1325 (1938).