AUTOOXIDATION OF METHYLHETEROCYCLES UNDER PHASE TRANSFER CATALYSIS CONDITIONS

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The autooxidation of methyl- and dimethyl-substituted N-, S-, and O-heterocyclic compound derivatives has been studied in 1,2-dimethoxyethane—t-BuOK in the presence of 18-crown-6. Mono- and dicarboxylic acid derivatives of pyrazine, pyridine, pyrimidine, and thiophene have been synthesized.

Autooxidation of carbanions, prepared by action of strong bases on C—H acids under phase transfer catalysis conditions, offers a method for the preparation of a variety of oxygen-containing organic compounds [1, 2]. For instance, pyridinedicarboxylic acids have been prepared via oxidation of picolines by oxygen in benzene—t-BuOK—PEG-6000 [3] and 1,2-dimethoxyethane—KOH—18-crown-6 [4, 5] phase transfer systems. We have also demonstrated recently that 2,5-dimethylpyrazine (I) is oxidized by oxygen in 1,2-dimethoxyethane—t-BuOK solvent system in the presence of 18-crown-6, to give pyrazine-2,5-dicarboxylic acid [6].

In the present paper we have explored the potential applications of this method for the preparation of a variety of hetarylcarboxylic acids; in particular, we have examined the autooxidation behavior of methyl- and dimethyl-substituted pyrazine, pyridine, pyrimidine, thiophene and furan derivatives. The pertinent reactions were studied under conditions developed previously for the preparation of the diacid product from compound I [6]: initial starting material concentration in 1,2-dimethoxyethane 0.5 mole/liter; mole ratio of methylheterocycle—t-BuOK—18-crown-6 equal to 1:2.5 (per one CH_3 group): 0.05; oxygen pressure 5 atm; temperature 60°C (Table 1). In the oxidation of monomethyl derivatives of mono- and diazines, namely methylpyrazine (II), 4-methylpyridine (III), and 4-methylpyrimidine (IV), the corresponding hetarylcarboxylic acids were obtained in 64, 75, and 32% yields, respectively. The relatively low yield of 4-pyrimidinecarboxylic acid is probably due to partial destruction of the diazine ring upon treatment with base; this is characteristic of pyrimidine compounds [7]. The reactivity of methylpyrazine II is higher than that of dimethylpyrazine I, while picoline III is more reactive than methylpyrazine II.

In the case of the oxidation of 2,4-, 2,6-, 3,4-, 2,5-, and 3,5-lutidines (V-IX), the corresponding acid product was obtained in only one case, from 2,4-lutidine (V). Compound V, in analogy with the behavior of compound I [6], was converted to dicarboxylic acid (methylpyridinecarboxylic acid was not detected in the reaction mixture), indicating that a singular or identical mechanism is operating in the oxidation of compounds I and V (the proposed mechanism for this transformation under phase transfer catalysis conditions has been discussed in the previous paper [6] for the oxidation of compound I as an example). The reactivity of dimethylpyridine V is lower than that of dimethylpyrazine I, and considerably lower than that observed for methylpyridine III. Azinecarboxylic acid products are not formed in the oxidation of 2,6-dimethylpyridine or 2,6-dimethylpyrazine; these heterocycles undergo ring destruction under the reaction conditions, as evidenced by the observation of acetic acid among the reaction products (the latter was identified by GLC and chromatography-mass spectrometry). This behavior can be explained on the basis of the instability of the intermediate carbanions generated in the reaction mixture; it is known from the literature [8] that carbanion instability represents an obstacle to the preparation of oxidation products from weak C—H acids via reaction with oxygen. Compounds VII-IX, which contain β-CH_3 groups, are practically inert under phase transfer catalyzed-autooxidation conditions; it is not possible to prepare mono- or dicarboxyic acids from these substrates via this reaction pathway

2-Thiophenecarboxylic acid was obtained in 67% yield upon oxidation of 2-methylthiophene (XI); the corresponding acids were not formed, however, from 3-methyl- and 2,5-dimethylthiophenes (XII and XIII) under these reaction conditions. The reactivity of compound XI is substantially lower than for N-heterocyclic methyl derivatives II-IV. It was found that in all cases involving the formation hetarylcarboxylic acid conversion of the

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TABLE 1. Autooxidation of Methyl- and Acetyl-Substituted N-, S-, and O-Heterocycle Derivatives under Phase Transfer Catalysis Conditions (c_0 = 0.5 mole/liter heterocycle in 1,2-dimethoxyethane; heterocycle: t-BuOK—18-crown-6 = 1:2.5 (per CH_3 group): 0.05 moles; 5 atm O_2, 60°C)

Starting material	Reaction time, h	GLC Conversion, %	pH for acid formation	Acid product	T, °C		Yield, %
					Found	literature data	
I	20...24	68	2,0	2,5-Pyrazinedicarboxylic acid,	255...256*	253...260 [11]*	53
II	20...24	81	2,0	Pyrazinecarboxylic	220 dec.	225 [12]	64
III	15...18	87	3,6	4-Pyridinecarboxylic	315 subl.	311 [13]*	75
IV	16...18	92	2,5	4-Pyrimidinecarboxylic	240	238...240 [14]	32
V	45...48	65	3,2	2,4-Pyridinedicarboxylic acid,	248	248...250 [15]	52
VI	20...24	83	3,2	Acetic			Not determined
X	20...24	90	2,0	Acetic			Not determined
VII	48	15	3,2	—			—
VIII	48	12	3,2	—			—
IX	48	10	3,2	—			—
XI	55...60	76	2,5	2-Thiophenecarboxylic	128...130	128 [16]	67
XII	60	10	2,5	—			—
XIII	60	12	2,5	—			—
XVI	13...15	88	2,5	2-Thiophenecarboxylic	128...130	128 [16]	52
XVII	13...15	89	3,0	2-Furancarboxylic	133	130...134 [17]	48
XIV	24	7	3,0	—			—
XV	24	12	3,0	—			—

*In a sealed ampul.

TABLE 2. Spectral Characteristics of Azinecarboxylic Acids

Acid	NMR spectrum, δ, ppm	Mass spectrum*, m/e (I_{rel}, %)
Pyrazinecarboxylic**	9,11 (m, 3-H); 8,67...8,84 (m, 5-H, 6-H)	124 (M^+, 22), 80 (100), 79 (18), 53 (52), 52 (57), 51 (20), 28 (25)
4-Pyrimidinecarboxylic, hydrate**	9,27 (s, 2-H); 7,95 (m, 5-H); 9,00 (m, 6-H)	124 (M^+, 10), 80 (100), 79 (23), 53 (57), 52 (79), 51 (21), 27 (28)
(carboxyl group carbon atoms)	119,78, 121,97, 125,67, 138,59, 149,76 (ring carbon atoms); 159,95, 166,28 (carboxyl group carbon atoms)	137 (100), 120 (10), 109 (11), 93 (19), 92 (29), 91 (11), 69 (31), 65 (27), 57 (21), 55 (23), 51 (23), 50 (13)

*Only peaks with $I_{rel} \geq 10\%$ are listed.
**δ_H values are given for this NMR spectrum.
***δ_C values are given for this NMR spectrum.

methyl- and dimethylheterocycle starting materials was terminated once a certain conversion level had been reached. This is probably due to dilution of the reaction mixture by tert-butyl alcohol, which is formed during the reaction process, and which as a solvent is much less effective than 1,2-dimethoxyethane in this type of reaction process.

2-Methylfuran (XIV) and 2,5-dimethylfuran (XV) are essentially unreactive with oxygen under these phase transfer catalysis conditions; the corresponding acids cannot be prepared by this method, apparently due to the extremely low C—H acidity of these compounds. For comparison purposes we also examined the autooxidation of 2-acetylthiophene and furan derivatives (XVI and XVII), which are readily deprotonated by solid base under phase transfer catalyzed conditions to form carbanions capable of undergoing alkylation by alkyl halides [9]. Autooxidation of these acetylheterocyclic derivatives in 1,2-dimethoxyethane—t-BuOK in the presence of 18-crown-6 leads to C—C bond cleavage in the acetyl group; the corresponding hetarylcarboxylic acids are formed in about 50% yield. Ketoacids are not formed under these reaction conditions.

EXPERIMENTAL

NMR spectra were recorded on Bruker WH-90/DS (^1H, 90 MHz) and WH-360/DS (^{13}C, 90.5 MHz) spectrometers using solutions in DMSO-D_6 or $CDCl_3$ versus TMS as internal standard. Mass spectra were measured on an MS-50 spectrometer (at 70 eV). GLC analyses were carried out on a Chrom-4 gas chromatograph equipped with a flame ionization detector using a glass column (1.2 m × 3 mm) filled with 10% SE-30 silicone elastomer and 2.5% Reoplex-400 on W/AW Chromosorb support (60-80 mesh). The helium carrier gas flow rate was 60 cm^3/min, the column temperature 100-200°C, depending on the starting material used. The reagents used in this study, 18-crown-6, potassium tert-butoxide, and all of the oxidizable substrates, were obtained from Fluka. Pure grade 1,2-dimethoxyethane was dried carefully according to a literature procedure [10] prior to use, and was stored over calcined 4 Å molecular sieves.

Synthesis of Hetarylcarboxylic Acids (General Procedure). A stainless steel, 120 ml-volume autoclave, equipped with a thermostating jacket and a manometer, was charged with 20 ml dimethoxyethane, 10 mmoles of the heterocyclic substrate, 0.13 g (0.5 mmoles) 18-crown-6, and 5.6 g (50 mmoles) or 2.8 g (25 mmoles) potassium tert-butoxide; the autoclave was sealed, pressurized with oxygen (5 atm), and heated to 60°C while being vigorously stirred with a magnetic stirrer. Samples were withdrawn periodically by microsyringe and analyzed by GLC. The reaction was continued until conversion of the heterocyclic starting material ceased. Water was then added to the reaction mixture to dissolve any unreacted potassium tert-butoxide. The mixture was evaporated under vacuum until a precipitate began to appear. The mixture was cooled with ice and acidified with concentrated HCl to pH 3.6-2.0 (cf. Table 1). In the case of N-heterocycles the onset of acid precipitate formation is observed, and the mixture was allowed to stand 10-12 h at 10°C. The precipitate was washed on the filter with a small amount of cold water and air dried. In the case of the oxidation of thiophene and furan derivatives, on the other hand, the resulting acid products were removed from the reaction mixture after acidification by extraction of the aqueous solution with ether (5 × 20 ml), and the extract was dried over anhydrous $MgSO_4$ and concentrated to remove the ether solvent. Thiophenecarboxylic acid was purified by recrystallization from petroleum ether, furancarboxylic acid by sublimation under vacuum at 140°C (20 mm Hg).

The acid products formed in this manner were identified based on comparison of their physicochemical properties with literature data (Table 1). The PMR and mass spectra of 2,5-pyrazinedicarboxylic acid were reported in [6]; 4-pyridine-, 2-thiophene-, and 2-furancarboxylic acids were consistent in their properties with the literature [18-22]. The NMR spectra of the new azinecarboxylic acids are reported herein (cf. Table 2) (PMR spectral signal assignments were made based on the data in [25, 26], while ^{13}C spectral assignments were made based on the data in the handbook [25]).

LITERATURE CITED

1. E. Demlow and Z. Demlow, *Phase Transfer Catalysis* [Russian translation], Mir, Moscow (1987).
2. G. A. Artamkina and I. P. Beletskaya, *ZhVKhO*, **31**, 196 (1986).
3. R. Neumann and Y. Sasson, *J. Org. Chem.*, **49**, 1282 (1984).
4. G. A. Artamkina, A. A Grinfel'd, and I. P. Beletskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, No. 10, 2284 (1984).
5. G. A. Artamkina, A. A. Grinfel'd, and I. P. Beletskaya, *Tetrahedron Lett.*, **25**, 4989 (1984).
6. I. G. Iovel', I. Ya. Yansone, Yu. Sh. Gol'dberg, and M. V. Shimanskaya, *Khim. Geterotsikl. Soedin.*, No. 4, 532 (1990).
7. J. Joule and H. Smith, *Principles of the Chemistry of Heterocyclic Compounds* [Russian translation], Mir, Moscow (1975), p. 142.
8. I. P. Skibida, A. M. Sakharov, and O. N. Emanuel', *Itogi Nauki i Tekhniki, Ser. Kinet. Katal.*, **15**, 118 (1986).
9. E. M. Abele, Yu. Sh. Gol'dberg, Yu. Yu. Popelis, and M. V. Shimanskaya, *Zh. Org. Khim.*, **26**, 1784 (1990).
10. A. Gordon and R. Ford, *The Chemist's Companion*, Wiley—Interscience, New York (1972).
11. D. Pitre, S. Boveri, and E. B. Grabitz, *Chem. Ber.*, **99**, 364 (1966).
12. H. Gainer, *J. Org. Chem.*, **24**, 691 (1959).
13. G. Black, E. Depp, and B. B. Corson, *J. Org. Chem.*, **14**, 44 (1949).
14. T. V. Gortinskaya, K. M. Murav'eva, and M. N. Shchukina, *Zh. Obshch. Khim.*, **25**, 2313 (1955).
15. R. Lukes, V. Galik, and J. Jizba, *Coll.*, **26**, 2727 (1961).
16. H. Gilman, *J. Am. Chem. Soc.*, **71**, 1870 (1949).
17. A. A. Ponomarev, *Synthesis and Reactions of Furan Derivatives* [in Russian], Saratov Univ. Press (1960).
18. W. Brügel, *Z. Elektrochem.*, **66**, 159 (1962).
19. D. J. Chadwick, J. Chambers, G. D. Meakins, and R. L. Snowden, *J. Chem. Soc., Perkin Trans. 1*, 201 (1973).
20. S. Gronowitz, J. Johnson, and A.-B. Hörnfeldt, *Chem. Scr.*, **7**, 211 (1975).
21. S. R. Heller and G. W. A. Miene, *EPA/NJH Mass Spectra Data*, Vol. 1, Washington (1978).
22. *Eight Peak Index of Mass Spectra*, 2nd edn., Mass Spectrometry Data Centre, Aldermaston (1974).
23. G. S. Marx and P. E. Spoerri, *J. Org. Chem.*, **37**, 111 (1972).
24. T. J. Batterham, *NMR Spectra of Simple Heterocycles*, Wiley—Interscience, New York (1975).
25. G. Levy and G. Nelson, *Carbon-13 Nuclear Magnetic Resonance for Organic Chemists*, Wiley—Interscience, New York (1972).