OXIDATION OF 2,5-DIMETHYLPYRAZINE WITH OXYGEN IN THE VAPOR PHASE ON OXIDE CATALYSTS AND IN THE LIQUID PHASE IN THE PRESENCE OF BASES

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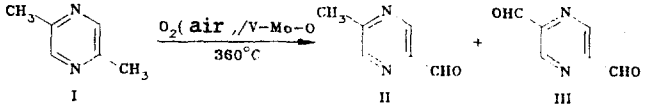
The vapor-phase oxidation of 2,5-dimethylpyrazine with oxygen on vanadium–molybdenum oxide catalysts modified with silver oxide gives 5-methyl-2-formylpyrazine and 2,5-diformylpyrazine in 37% and 35% yields, respectively. Pyrazine-2,5-dicarboxylic acid was obtained in 53% yield by the liquid-phase oxidation of 2,5-dimethylpyrazine with oxygen in the presence of a strong base and an interphase catalyst.

Aldehydes and acids of the pyrazine series are valuable intermediates in syntheses of biologically active substances [1-7]. We have previously proposed a one-step method for obtaining 5-methyl-2-formylpyrazine and 2,5-diformylprazine by catalytic vapor-phase oxidation of 2,5-dimethylpyrazine with air oxygen on vanadium–molybdenum oxide catalysts:



I II III

The maximum yields of aldehydes II and III were 25% and 23%, respectively [8, 9]. To increase the yields of these compounds in the present research we studied the effect of the introduction into V–Mo–O catalysts with V:Mo = 3:1 and 1:1 of silver, cadmium, and nickel oxides and sodium dihydrophosphate, which, as demonstrated in [10], increase the yield of formylpyrazine in the oxidation of monomethylpyrazine. The investigations were carried out by a pulse microcatalytic method and in a flow catalytic apparatus at 360-450°C at a contact time of 0.04-0.3 sec. The methods used to prepare the catalysts and to study their activities were previously described in [9, 11]. The physicochemical characteristics of the catalysts were presented in [11, 12].

The results of a study of the oxidation of I with air oxygen on vanadium–molybdenum oxide catalysts with various additives are presented in Table 1. The use of a catalyst with V:Mo:Ag = 1:1:0.02 (0.7% Ag_2O) makes it possible to obtain aldehydes II and III in 37% and 35% yields, respectively, which are greater by a factor of 1.5 than the maximum yields of these aldehydes on unmodified V–Mo–O catalysts. The overall yield of aldehydes achieved on the catalyst with V:Mo:Ag = 3:1:0.06 (1.2% Ag_2O) was 67%, as compared with 68% on the catalyst with V:Mo:Ag = 1:1:0.2 (6.2% Ag_2O). An increase in the percentage of silver oxide to 10.7% (catalyst with V:Mo:Ag = 3:1:0.6) does not lead to a further increase in the activity. It is apparent from Table 1 that the introduction of Ag_2O into V–Mo–O catalysts makes it possible to increase the reaction temperature without a significant increase in the conversion of I; as a result, the yield of aldehydes increases, since the energy of activation of the partial oxidation is higher than for the side processes (resinification, profound oxidation). This effect of the addition of Ag_2O to V–Mo–O catalysts is possibly due to the formation of vanadium–silver bronzes [13, 14]. In contrast to the oxidation of monomethylpyrazine [10], the introduction of other additives does not lead to a positive effect (Table 1).

The literature does not contain information on the oxidation of alkylpyrazines to acids by oxygen. It has been recently shown that pyridinecarboxylic acids can be obtained by the auto-oxidation of picolines in the liquid phase [dimethoxyethane (DME), THF] under conditions of generation of carbanions under the influence of strong bases (KOH, tert-BuOK) in the presence of an interphase catalyst – 18-crown-6 [15, 16]. Under these conditions, des-

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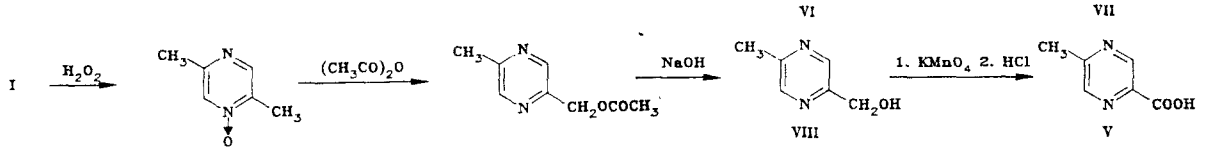
TABLE 1. Vapor-Phase Oxidation of 2,5-Dimethylpyrazine on Modified V–Mo–O Catalysts

Catalyst composition (ion ratio)	T, °C	Contact time, sec	Conversion (GLC), %	Yield of aldehydes (GLC), %			Selectivity with respect to aldehyde, %		
				II	III	II+III	II	III	II+III
V-Mo-O (V:Mo=3:1)*	360	0,10	60	15	11	26	25	18	43
V-Mo-O (V-Mo=1:1)*	360	0,10	50	25	23	48	50	46	96
	405	0,10	75	23	21	44	30	28	58
V-Mo-Ag-O	360	0,10	47	18	10	28	38	21	59
(V:Mo:Ag=3:1:0,06)	400	0,04	58	26	30	56	45	52	97
	420	0,04	60	30	26	56	50	43	93
	420	0,06	75	35	32	67	47	43	90
	450	0,04	65	31	19	50	48	29	77
V-Mo-Ag-O	420	0,04	55	26	24	50	47	44	91
(V:Mo:Ag=3:1:0,6)	450	0,04	62	33	25	58	53	40	93
	450	0,10	70	23	26	49	33	37	70
V-Mo-Ag-O	420	0,10	65	37	27	64	57	41	98
(V:Mo:Ag=1:1:0,02)	420	0,13	71	30	35	65	42	49	91
	450	0,10	80	28	35	63	35	44	79
V-Mo-Ag-O	420	0,10	65	30	22	52	46	34	80
(V:Mo:Ag=1:1:0,2)	450	0,10	72	35	33	68	48	46	94
V-Mo-Cd-O (V:Mo:Cd=3:1:0,1)	360	0,10	90	10	11	21	11	12	23
V-Mo-Ni-O (V:Mo:Ni=3:1:0,1)	360	0,10	97	8	4	12	8	4	12
V-Mo-O+5% NaH_2PO_4 (V:Mo=3:1)	360	0,10	69	14	10	24	20	14	34

*Data from [9].

pite the low CH acidities of picolines (pK_a 29-31 [17]), one can carry out the rate-determining step of detachment of a proton from the CH_3 group with the generation of the $[C_5H_4NCH_2^-]$ carbanion, which is oxidized to the corresponding pyridinecarboxylic acids by the action of molecular oxygen. The literature does not contain data on the CH acidities of alkylpyrazines; however, condensation reactions with the participation of methyl-substituted diazines that include deprotonation of the methyl group in the first step with the formation of the $[C_4H_3N_2CH_2^-]$ anion are known [18].

Considering this, we attempted to generate a carbanion from I by the action of bases (KOH, tert-BuOK) with subsequent oxidation with oxygen in the liquid phase (THF, DME) in the presence of 18-crown-6. The experiments were carried out in an autoclave in an oxygen atmosphere (1-7 atm) at 20-60°C (somewhat lower than the boiling points of the solvents). Samples were selected periodically, and the conversion of starting I was determined by GLC. At the end of the process the reaction mixture was acidified with hydrochloric acid, as a result of which pyrazine-2,5-dicarboxylic acid (IV) precipitated. 5-Methylpyrazine-2-carboxylic acid (V) is not formed under the investigated conditions. An authentic sample of acid V was obtained by the method in [19] by oxidation of 2-hydroxymethyl-5-methylpyrazine (VIII), synthesized from I through 2,5-dimethylpyrazine N-oxide (VI) and 2-acetoxymethyl-5-methylpyrazine (VII) by the method in [20]. The presence of acid IV and the absence of acid V in the reaction solutions and the final solid product were proved by high-performance liquid chromatography (HPLC) and PMR and mass spectrometry.



The results of a study of the liquid-phase oxidation of 2,5-dimethylpyrazine with oxygen in the presence of bases are presented in Table 2. The optimum conditions for obtaining acid IV are as follows: DME as the solvent, tert-BuOK as the base, molar ratio I:tert-BuOK:18-crown-6 = 1:5:0.03, oxygen pressure 5 atm, and reaction temperature 60°C. Under these conditions the conversion of starting I reaches 68% after 24 h, after which the reaction ceases. In the oxidation of picolines with oxygen in the benzene/tert-BuOK/PEG-6000 system it was observed [17] that the reaction does not go to completion even when a large excess of the base is used. Neumann and Sasson [17] explain this by the fact that during the reaction tert-BuOK is replaced by KOH, which is ineffective. It might also be assumed that the complete

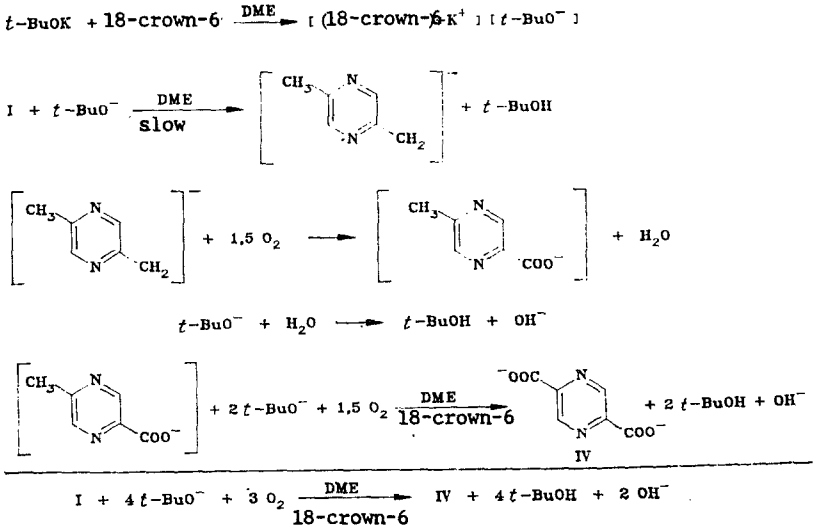
TABLE 2. Oxidation of 2,5-Dimethylpyrazine by the Action of Bases in Dimethoxyethane at an Oxygen Pressure of 5 atm at 60°C (with 18-Crown-6 as the Catalyst $[I]_\alpha$ = 0.5 mole/liter)

Base	I:base molar ratio	Amt. of catalyst, mole %	Time, h	Conversion (GLC), %	Yield of IV, %
t-BuOK	1:2	3	40	52	37
t-BuOK	1:5	3	24	68	53
t-BuOK	1:7	3	24	70	50
t-BuOK	1:5	0	24	44	30
t-BuOK	1:5	5	24	68	53
t-BuOK*[1]	1:5	3	24	42	30
t-BuOK*[2]	1:5	3	24	50	36
t-BuOK*[3]	1:5	3	24	70	52
t-BuOK*[4]	1:5	3	40	36	—
KOH	1:5	3	24	12	—
KOH	1:10	3	48	22	—
KOH	1:10	0	24	5	—

*[1]In THF.
*[2]At 1 atm.
*[3]At 7 atm.
*[4]At 24°C.

conversion of the methyl azines does not occur because of the formation of tert-butyl alcohol, which dilutes the reaction mixture and is a proton donor. Under the investigated conditions the maximum preparative yield of acid IV achieved was 53% (with a selectivity of 79%). The use of THF as the solvent and KOH as the base is considerably less effective (Table 2). The 18-crown-6 catalyst accelerates the oxidation process both in the case of tert-BuOK, and, particularly, solid KOH; this constitutes evidence in favor of the role of interphase transfer in this process (tert-BuOK is partially soluble in DME and THF, while the solubility of KOH is very low). The oxidation of I to acid IV also takes place at 20°C with oxygen at atmospheric pressure. An increase in the temperature to 60°C and the O_2 pressure to 5 atm accelerates the reaction (Table 2).

The results obtained and allowance for the literature data [15, 16] make it possible to propose the following scheme of the processes that occur:



EXPERIMENTAL

The PMR spectra of solutions of the compounds in $CDCl_3$ or d_6-DMSO were recorded with a Bruker WH-90/DS spectrometer (90 MHz) with tetramethylsilane (TMS) as the internal standard. The mass spectra were recorded with a Kratos MS-25 chromatographic mass spectrometer and an MS-50 mass spectrometer (70 eV). Analysis by GLC was carried out with a Chrom-4 chromato-

graph with a flame-ionization detector and a glass column (2.4 m by 3 mm) filled with 10% E-301 and 2.5% Reoplex-400 on a Chromosorb A/AW support (60-80 mesh); the carrier gas was helium (60 ml/min), and the column temperature ranged from 120°C to 180°C as a function of the composition of the reaction mixture.

The analysis of the mixtures containing acids IV and V was carried out with a Du Pont 880 Prep liquid chromatograph with a Silasorb-600 column (125 by 4.6 mm); the eluent was 20% acetonitrile and 80% 0.05 M ammonium acetate buffer solution (pH 6) with the addition of 0.01 mole/liter cetyltrimethylammonium bromide, the flow rate was 2 ml/min, and the detector was a UV detector (254 nm). The retention times of acids V and IV were 5.5. min and 7 min, respectively.

2,5-Dimethylpyrazine, potassium tert-butoxide, and 18-crown-6 obtained from Fluka, potassium hydroxide obtained from Chemapol, and analytical-grade ammonium metavanadate and paramolybdate, silver, cadmium, and nickel nitrates, and sodium dihydrophosphate were used in the research.

The PMR and mass spectra of II-VI are presented in Table 3.

The V–Mo–Ag–O Catalyst (V:Mo:Ag = 1:1:0.02). A 2.8-g (2.26 mmole) sample of ammonium paramolybdate tetrahydrate $[(NH_4)_6Mo_7O_{24}\cdot 4H_2O]$ was dissolved in 0.5 liter of water in a porcelain dish, and 1.85 g (15.8 mmole) of ammonium metavanadate (NH_4VO_3) and a solution of 0.054 g (0.32 mmole) of silver nitrate in 20 ml of water was added. The water was then evaporated to half the original volume by stirring the mixture on a water bath at 80-85°C, and 37.6 g (20 ml) of corundum with a specific area of ~0.1 m^2/g was added. Prior to completion of the evaporation 5 ml of furfural was added, and the mixture was evaporated to dryness. The residue was placed in a drying chamber at 120°C for 2 h, after which it was calcined for 6 h in a muffle furnace with access to the air at 470°C. This procedure gave 40 g (24 ml) of catalyst, the active phase of which contained 33.1% V_2O_5, 66.2% MoO_3, and 0.7% Ag_2O.

5-Methyl-2-formylpyrazine (II) and 2,5-Diformylpyrazine (III). A flow catalytic reactor was charged with 20 ml of the V–Mo–Ag–O catalyst (V:Mo:Ag = 1:1:0.02) applied to corundum. Air oxygen was fed into the reactor at a rate of 35 liters/h, the catalyst was heated to 420°C, and a 3% aqueous solution of 2,5-dimethylpyrazine (I) was fed in at a rate of 200 ml/h with a peristaltic pump. The products that emerged from the reactor were condensed in ice-cooled traps. The experimental time was 3 h, and 560 ml of catalysate was obtained. The catalyzate was removed from the catalyst particles by filtration. A total of 70% of the volume of the catalysate was removed by distillation with a rotary vacuum evap-

TABLE 3. Spectral Characteristics of 2,5-Disubstituted Pyrazines

Compound	PMR spectrum,* δ, ppm				Mass spectrum, m/z (I_{rel}, %)**
	3-H, s	6-H, s	2-H, s	5-H, s	
II	9,04	8,60	10,11 (1H, CHO)	2,69 (3H, CH_3)	122 (M^+, 100), 94 (66), 93 (33), 67 (43), 66 (41), 53 (40), 52 (33), 42 (47), 40 (42), 39 (72), 38 (25), 29 (15), 28 (47)
III	9,25 (s, 2H)		10,53 (s, 2H, CHO)		136 (M^+, 96) 108 (67), 80 (13), 79 (23), 54 (13), 53 (75), 52 (100), 50 (31), 29 (53), 28 (75)
IV	9,24 (s, 2H)		—	—	168 (M^+, 30), 150 (14), 140 (16), 124 (92), 123 (10), 122 (10), 95 (16), 80 (18), 79 (14), 78 (5), 70 (24), 67 (20), 53 (40), 52 (52), 51 (22), 45 (22), 44 (52), 40 (18), 32 (28), 28 (100)
V	9,04	8,67	—	2,59 (3H, CH_3)	138 (M^+, 26), 120 (5), 94 (21), 93 (8), 86 (14), 66 (11), 57 (11), 44 (14), 43 (10), 42 (28), 41 (11), 39 (15), 30 (83), 29 (100), 28 (54)
VI	8,29	8,00	2,40 (3H, CH_3)	2,45 (3H, CH_3)	124 (M^+, 100), 108 (23), 107 (48), 80 (60), 66 (35), 53 (22), 42 (50), 39 (98), 28 (20)

*The spectra of II and VI were recorded in $CDCl_3$, while the spectra of III-V were recorded in d_6-DMSO.
**The peaks of the characteristic ions and the peaks with intensities ≥10% are indicated.

orator; a solution of pyrazine I in water, by the addition to which of I in up to 3% concentration one could again feed it into the reactor for oxidation, was removed by distillation during this procedure. The residual solution (30% by volume of the catalysate) was extracted with methylene chloride (five 40-ml portions; the degree of extraction was monitored by GLC), and the extract was dried with anhydrous $MgSO_4$ and filtered. The CH_2Cl_2 was removed, and the residue was fractionated in vacuo at 38-40°C (1 mm) to give 4.8 g of aldehyde II (mp 10-15°C, n_D^{20} 1.536). The still residue was recrystallized from dioxane to give 3.1 g of aldehyde III with mp 96-98°C; the bis(phenylhydrazone) had mp 265°C (mp 266°C [21].

Pyrazine-2,5-dicarboxylic Acid (IV). A 20-ml sample of dimethoxyethane, 1 ml (10 mmole) of I, 0.08 g (0.3 mmole) of 18-crown-6, and 5.6 g (50 mmole) of potassium tert-butoxide were placed in a 120 ml stainless steel autoclave with a jacket, and oxygen was fed in at a pressure of 5 atm with stirring with a magnetic stirrer at 60°C for 24 h. The conversion of I was 68% (GLC). Water (15 ml) was added to the resulting reaction mixture, and all of the volatile organic substances and the water were removed by distillation with a rotary vacuum evaporator until a precipitate began to form. The residual mixture was acidified with concentrated hydrochloric acid (with ice cooling) to pH 1.5 (according to the data in [22], acid IV was obtained from solutions at pH 1-2) and allowed to stand at 10°C for 10-12 h. The resulting precipitate was recrystallized from hot water and dried in vacuo (1 mm) over P_2O_5 to give 0.89 g (53%) of acid IV with mp 255°C (mp 255-260°C [23]).

5-Methylpyrazine-2-carboxylic Acid (V). The reaction of 1 ml of 2,5-dimethylpyrazine by the method in [24] gave 0.9 g of 2,5-dimethylpyrazine N-oxide (VI) with mp 107°C. The synthesized N-oxide VI was converted by the method in [20] to 2-acetoxymethyl-5-methylpyrazine (VII), which was identified by chromatographic mass spectrometry (m/z 166, M^+). From VII (without isolation) we obtained 2-hydroxymethyl-5-methylpyrazine (VIII) (m/z 124, M^+) by the action of solid sodium hydroxide at 20°C for 30 min. By oxidation of alcohol VIII with potassium permanganate by the method in [19] we synthesized acid V (0.3 g), which was purified by vacuum sublimation (140°C/2 mm) to give a product with mp 165°C.

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HETEROADAMANTANES AND THEIR DERIVATIVES.

9.* SYNTHESIS OF 1,5-DINITRO-3,7-DIAZABICYCLO[3.3.1]NONANE AND DERIVED 2,2-DISUBSTITUTED 5,7-DINITRO-1,3-DIAZAADAMANTANES

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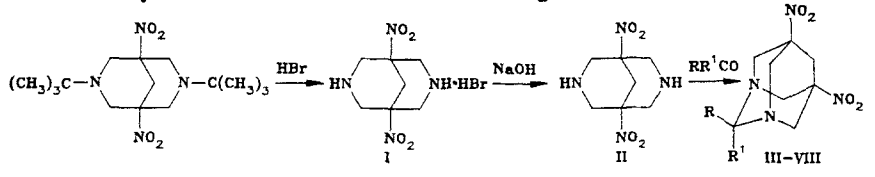
UDC 547.853.5.07;543.51

Heating 1,5-dinitro-3,7-di(tert-butyl)-3,7-diazabicyclo[3.3.1]-nonane with concentrated hydrobromic acid gives 1,5-dinitro-3,7-diazabicyclo[3.3.1]nonane. Cyclization of the latter with various aldehydes and ketones gave a series of 2,2-disubstituted 5,7-dinitro-1,3-diazaadamantanes. The behavior of the synthesized compounds under electron impact has been studied.

1,3-Diazaadamantanes with substituents at nodal positions have been little studied up to this time because of the absence of convenient methods of preparation.

2,2-Disubstituted 5,7-dinitro-1,3-diazaadamantanes have been synthesized from the bicyclic precursor 1,5-dinitro-3,7-di(tert-butyl)-3,7-diazabicyclo[3.3.1]nonane, which has been synthesized previously [2]. For the first time we have shown how to split off the N-tert-butyl substitutents from this compound using concentrated hydrobromic acid. Brief heating under these conditions leads to practically quantitative formation of the hydrobromide of 1,5-dinitro-3,7-diazabicyclo[3.3.1]nonane (I). The free base II was prepared by treatment of hydrobromide I with aqueous sodium hydroxide. A similar conversion of 2-(tert-butyl)-amino-5,6-dihydro-4H-1,3-thiazine to a 2-amino-5,6-dihydro-4H-1,3-thiazine salt using concentrated hydrobromic and hydrochloric acids has been given in [3].



I II

III R=R¹=H; IV R=R¹=CH_3; V R=C_2H_5, R¹=CH_3; VI R=R¹=C_2H_5; VII R=C_6H_5, R¹=H; VIII R=*p*-$NO_2C_6H_4$, R¹=H

The IR spectra of the dinitrobispidine II shows absorption bands for the stretching (3295) and deformation (1615) vibrations of the amino group and also the symmetric (1340) and asymmetric (1540 cm^{-1}) vibrations of the nitro group. The PMR spectra of II are characterized by an AB- spin coupled system for resonance absorption signals of the eight protons of the N—CH_2—C fragments (H_a 3.71, H_e 3.22 ppm, $^2J_{ae}$ = 12.0 Hz), a singlet signal at 2.85 ppm for the two protons of C—CH_2—C, and a broadened signal near 2.58 ppm corresponding to the absorption of the two amino group protons. The mass spectrum of II shows a characteristic ion peak at M^+ 216.

The dinitrobispidine II was used as starting material for synthesis of a series of 2,2-disubstituted 5,7-dinitro-1,3-diazaadamantanes III-VIII by cyclization with various aldehydes

*For Communication 8 see [1].

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