ACETYLATION, BROMINATION, AND NITRATION OF BENZOXAHETEROCYCLES AND SYNTHESIS OF β-AMINOKETONES FROM ACETYL DERIVATIVES

V. K. Daukshas, O. Yu. Pyatrauskas,
É. B. Udrenaite, P. G. Gaidyalis,
and G. A. Gasperavichene

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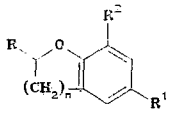
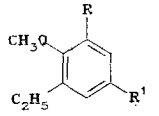
The method of competing reactions was used to establish the sequence of variation of the relative rates of acetylation, bromination, and nitration reactions of 2-methylcoumaran, chroman, 2,3,4,5-tetrahydrobenzo-1-oxepan, and 1-methoxy-2-ethylbenzene. The isomeric composition of the substitution products formed was determined. The acetyl derivatives were converted according to a Mannich reaction to hydrochlorides of β-dimethylaminopropionyl derivatives, possessing antiinflammatory activity.

Acyl-, halo-, and nitrosubstituted benzodioxaheterocycles are used in the synthesis of drugs [1, 2]. Continuing searches for methods of obtaining new compounds suitable for this purpose [2], we studied the composition of the reaction products of acetylation, bromination, and nitration of benzoxaheterocycles I, IV, and their acyclic analog 1-methoxy-2-ethylbenzene (VI).



I – V



VI – VIII

I n=2.3, R=R¹=R²=H; IIa—d n=2.3, R=R²=H; III n=2.3, R=R¹=H, R²=NO₂; IV n=1, R=CH₃, R¹=R²=H; Va—d n=1, R=CH₃, R²=H; VI R=R¹=H; VIIa—d R=H; VIII R=NO₂, R¹=H; II, V, VII a R¹=COCH₃, b R¹=Br, c R¹=NO₂, d R¹=$=COCH_2CH_2N(CH_3)_2 \cdot HCl$

In the acetylation of compounds I, IV, and VI with acetyl chloride in methylene chloride in the presence of aluminum chloride or in bromination with bromine in CCl_4, as well as in the case of nitration of compound IV with a mixture of nitric and acetic acids, the corresponding products of substitution in the para-position to the alkoxy group (IIa, b, Va-c, and VIIa, b), which, according to the data of gas–liquid chromotography and the PMR spectra, contain practically no impurities of other isomers, are formed. However, in the nitration of compounds I (n = 2, 3) and VI, mixtures of isomers IIc with III and VIIc with VIII are formed in a ratio of 4:1, 2:1, and, correspondingly, 2:1.

The production of the nitro-derivatives III and VIII, products of substitution in the ortho-position to the alkoxy group of compounds I and VI, may be due to the higher reactivity and, consequently, reduced positional selectivity of the nitration agent in comparison with agents of acetylation and bromination [3]. The formation of ortho-nitro-derivatives by alkoxybenzenes with a relatively high yield was described earlier [4]. Substitution of the ortho-position to the alkoxy group in a compound IV may be prevented by the Mills–Nixon effect [2, 5].

The relative rates of the reactions of acetylation, bromination, and nitration of compounds I, IV, and VI, determined by the method of competing reactions, decrease in the sequence: IV >> I (n = 2) > VI >> I (n = 3). This corresponds to the sequence of decreasing values of $\lambda_{max}(\varepsilon)$ of the long-wave UV absorption band of these compounds in hexane: 282 (2950), 277 (2090), 272 (1990), 265 nm (1020), due to the decrease in electron donor capacity of the oxygen atom with respect to the aromatic ring on account of rotation of the alkoxy

V. Kapsukas Vil'nyus State University, Vil'nyus, 232734. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1035-1038, August, 1984. Original article submitted June 24, 1983.

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TABLE 1. Characteristics of the Compounds Synthesized

Compound	n	mp, °C	IR spectrum, C=O, cm⁻¹	UV spectra λ, nm	UV spectra lg ε	PMR spectrum, δ, ppm	Found, % C	Found, % H	Found, % Hal	Found, % N	Gross formula	Calculated, % C	Calculated, % H	Calculated, % Hal	Calculated, % N	Yield, %
IIb	3	—[a]	—	225, 266, 305 sh	4,06; 3,44;	1,43—2,03 (4H, m, CH_2CH_2); 2,60—2,73 (2H, m, CH_2Ar); 3,84 (2H, t, CH_2O)[b] 6,70 (1H, d, 9-H)[c] 7,08 (1H, e,e, 8-H)[d]; 7,10 (1H, e, 6-H)[e,f]	53,2	5,0	35,0	—	$C_{10}H_{11}BrO$	52,9	4,9	35,2	—	78
IIc	3	—	—	—	—	1,55—2,11 (4H, m, CH_2CH_2); 2,73—2,98 (2H, m, CH_2Ar); 4,00 (2H, t, CH_2O)b 6,91 (1H, e, 9-H)[c] 7,85 (1H, e,e, 8-H)[d], 7,89 (1H, e, 6-H)[e,f]	—	—	—	—	$C_{10}H_{11}NO_3$	—	—	—	—	—
IId	2	153—154	1670	208, 228, 289	4,09; 3,98; 4,10	1,55—1,80 (2H, m, CH_2); 2,36—2,58 (2H, m, CH_2Ar); 2,71 (6H, s, CH_3N); 3,28 (4H, s, $COCH_2CH_2N$); 3,88—4,10 (2H, m, CH_2O); 6,50 (1H, e, 8-H)[c]; 7,29—7,48 (2H, m, 7-H, 8-H)[g]	62,2	7,4	13,2	5,2	$C_{14}H_{19}NO_2 \cdot HCl$	62,3	7,5	13,1	5,2	76
IId	3	160—161	1670	218, плечо 266	4,09	1,25—1,88 (4H, m, CH_2CH_2); 2,48—2,65 (2H, m, CH_2Ar); 2,68 (3H, s, CH_3N); 2,76 (3H, s, CH_3N); 3,34 (4H, s, $COCH_2CH_2N$); 3,83—4,00 (2H, m, CH_2O); 6,80 (1H, e, 9-H)[c]; 7,48 (1H, d,d, 8-H)[d]; 7,53 (1H, e, 6-H)[e,g]	63,3	7,9	12,3	4,9	$C_{15}H_{21}NO_2 \cdot HCl$	63,5	7,7	12,5	4,9	78
III	2	—	—	—	—	1,95 (2H, qu CH_2)[b]; 2,75 (2H, t, CH_2Ar)[b], 4,18 (2H, t, CH_2O)[b]; 6,69 (1H, t, 6-H)[c]; 7,11 (1H, e,e, 5-H) ; 7,40 (1H, e,e, 7-H)[d,f]	—	—	—	—	$C_9H_9NO_3$	—	—	—	—	—
III	3	—	—	—	—	1,55—2,11 (4H, m, CH_2CH_2); 2,73—2,98 (2H, m, CH_2Ar); 4,00 (2H, t, CH_2O)b; 6,98 (1H, t, 7-H)[c] 7,24 (1H, e,e, 6-H)[d]; 7,36 (1H, e,e, 8-H)[d,f]	—	—	—	—	$C_{10}H_{11}NO_3$	—	—	—	—	—
Vc	—	59—60[h]	—	209, 237, 328	4,00; 3,82; 3,98	1,48 (3H, e, CH_3)[b]; 2,83 (1H, e,e, CHAr)[i] ; 3,39 (1H, e,d, CHAr)[i] ; 4,80—5,24 (1H, m CHO); 6,65 (1H, d, 7-H)[c]; 7,93 (1H, d, 4-H)[d]; 7,95 (1H, e,e 6-H)[d,e]	60,6	5,3	—	7,9	$C_9H_9NO_3$	60,3	5,1	—	7,8	51
Vd	—	152—153	1655	208, 229, 293	4,13; 4,04; 4,11	1,18 (3H, e, CH_3)[b], 2,55 (1H, e,e, CHAr)[i]; 2,68 (3H, s, CH_3N); 2,75 (3H, c, CH_3N); 3,11 (1H, d,d CHAr)[i]; 3,31 (4H, s, $COCH_2CH_2N$); 4,59—5,00 (1H, m, CHO); 6,53 (1H, d, 7-H) ; 7,49 (1H, d, 4-H)[d]. 7,52 (1H, d,d, 6-H)[d,g]	62,0	7,8	13,0	5,4	$C_{14}H_{19}NO_2 \cdot HCl$	62,3	7,5	13,1	5,2	72
VIIc	—	—	—	—	—	1,16 (3H, t, CH_3)b; 2,61 (2H, qu, CH_2Ar)[b]; 3,91 (3H, s, CH_3O); 6,79 (1H, d, 6-H)[c]; 7,89 (1H, d, 3-H)[d]. 7,94 (1H, d,d, 5-H)[d,f]	—	—	—	—	$C_9H_{11}NO_3$	—	—	—	—	—
VIId	—	141—142	1655	208, 226, 280	4,10; 4,14; 4,17	0,84 (3H, t, CH_3)[b]; 2,31 (2H, qu, CH_2Ar)b; 2,68 (3H, s, CH_3N); 2,74 (3H, s, CH_3N); 3,19 (4H, s, $COCH_2CH_2N$); 3,55 (3H, s, CH_3O); 6,60 (1H, d, 5-H)[c]; 7,43 (1H, d, 2-H)[d] ; 7,51 (1H, d,d, 6-H)[d,g]	61,6	8,2	12,7	5,3	$C_{14}H_{21}NO_2 \cdot HCl$	61,8	8,2	13,0	5,2	73
VIII	—	—	—	—	—	1,20 (3H, t, CH_3)b; 2,70 (2H, qu, CH_2Ar)b; 3,85 (3H, s, CH_3O); 7,03 (1H, t, 5-H)[c]; 7,33 (1H, d,d 4-H)[d]; 7,50 (1H, d,d, 6-H)[d,f]	—	—	—	—	$C_9H_{11}NO_3$	—	—	—	—	—

[a] Mp 150-151°C (17 gPa); n_D^{20} 1.5785. [b] J = 5-6 Hz. [c] J = 9 Hz. [d] J = 3 and 9 Hz. [e] J = 3 Hz. [f] In CCl_4. [g] In CF_3COOH. [h] From hexane. [i] J = 8 and 16 Hz.

substituent around the C_{Ar}—O bond. An analogous pattern is also observed for the rates of the bromination of benzoxaheterocycles in acetic acid [6].

Hydrochlorides of the aminoketones IId, Vd, and VIId, possessing pronounced antiinflammatory activity and low toxicity, were synthesized by the reaction of acetyl derivatives IIa, Va, and VIIa with paraform and dimethylamine hydrochloride (according to Mannich). Compound Vd, was the most active.

EXPERIMENTAL

Spectroscopic investigations and a determination of the relative reaction rates were conducted analogously to [2], while the determination of the ratio of the compounds according to gas—liquid chromatography was conducted as in [17].

Derivatives IIa (n = 2, 3) [6, 7], Va [8], VIIa [9], IIb (n = 2) [10], Vb [11], VIIb [12] and IIc (n = 2, 3) [13, 14] were described earlier. The structures of compounds II, V, and VII is confirmed by the presence in the PMR spectrum of the signals of the aromatic protons in the form of a system consisting of a doublet (J = 9 Hz), a doublet (J = 3 Hz), and a doublet of doublets (J = 3 and 9 Hz).

Nitroderivatives IIc (n = 3), III (n = 2, 3), VIIc, and VIII could not be isolated in individual form. Their structure was assigned according to the PMR spectrum of mixtures of isomers in which the aromatic protons of compounds III and VIII appear in the form of a system consisting of a triplet (J = 9 Hz) and two doublets of doublets (J = 3 and 9 Hz).

The initial chroman (I, n = 2) and 2-methylcoumaran (IV) were synthesized according to the methods of [7, 15]. 2,3,4,5-Tetrahydrobenzo-1-oxepan (I, n = 3) was produced by Clemmensen reduction of the 5-oxo-derivative for 40 h; the absence of the solvent (toluene) increased the yield from 61 [14] to 76%.

Compound I (n = 3) melts at 28-29°C [6], although it was described as a liquid in [14, 16]. The boiling point [6, 14, 16] and the PMR spectrum [16] correspond to those cited.

Acetylation. Over a period of 15 min at —20°C we added 20 g (0.15 mole) $AlCl_3$ to a solution of 0.10 mole of compounds I, IV, or VI and 8 g (0.10 mole) acetyl chloride in 70 ml anhydrous CH_2Cl_2; cooling was stopped, and after 1 h the mixture was poured out onto ice. The organic layer was washed with a dilute solution of hydrochloric acid, with water, dried over Na_2SO_4, and redistilled. In the case of compound IV the reaction mixture was exposed for about 30 min, while in the case of compound I (n = 3) $AlCl_3$ was added at 5°C. Yield of IIa (n = 2, 3), Va, and VIIa 65, 76, 54, and 68%, respectively.

Bromination. A solution of 75 mmoles of compounds I, IV, or VI and 12 g (75 mmoles) bromine in 75 ml CCl_4 was exposed at 20°C until the color disappeared, washed with water, dried over $NaSO_4$, and redistilled. Yield of the compounds IIb, Vb, and VIIb 76-80%.

Nitration. We added 6.5 ml (75 mmoles) 56% HNO_3 at 10°C to a solution of 50 mmoles of compounds I (n = 2) or IV in 30 ml of acetic acid, mixed for 1 h at 20°C, poured out onto ice, extracted with chloroform, washed the extract with water, dried over Na_2SO_4, and distilled off the solvent. In the case of compound VI we added 3 ml (75 mmoles) of 99% HNO_3, while 5 g (34 mmoles) of compound I (n = 3) was added at 5°C in 30 ml (0.47 mole) of 70% HNO_3, and the mixture was mixed for 30 min at 20°C. The total yield of mixtures of the nitro derivatives IIc and III (n = 2, 3), VIIc and VIII was 64, 58, and 63%, respectively.

Hydrochlorides of Aminoketones IId, Vd, and VIId. A mixture of 30 mmoles of the ketones IIa, Va, or VIIa, 2.9 g (36 mmoles) dimethylamine hydrochloride, 1.4 g (45 mmoles) paraform, 60 ml ethanol, and 4 drops of conc. HCl was boiled for 5 h, then 0.5 g (15 mmoles) paraform was added, the mixture boiled for another 5 h, concentrated under vacuum, and the residue recrystallized from isopropanol.

The characteristics of the compounds are cited in Table 1.

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MOLECULAR COMPLEXES OF CHLOROFORM WITH METHYL-SUBSTITUTED 1,3-DIOXANES

L. F. Lapuka, I. G. Bresler,
T. A. Gorozhankina, R. S. Musavirov,
E. A. Kantor, and D. L. Rakhmankulov

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The ^{1}H NMR method was used to study the relative electron donor capacity of a number of methyl-substituted 1,3-dioxanes in complex formation with chloroform. The spectral and thermodynamic parameters of 1:1 H-complexes were determined. The values of the chemical shifts from the hydrogen bond in the complexes vary in correlation with the charges on the oxygen atoms of the investigated bases, calculated by the CNDO/2 method.

In studies of acid-catalyzed conversions of 1,3-dioxacycloalkanes it is suggested that the reactivity is largely determined by the basicity of the acetal [1, 2]. A study of the spectral and thermodynamic characteristics of hydrogen bonds with H-acids permits an estimation of the donor properties of the compounds and a characterization of the influence of the electronic and geometrical structure of the molecules on these properties [3, 4]. Earlier the relative basicity of 1,3-dioxane and some of its derivatives was determined in the reaction of complex formation with iodine [5], deuteromethanol [6], and phenol [7, 8] by the method of IR spectroscopy.

In this work the electron donor properties of 1,3-dioxane and its derivatives were investigated by the ^{1}H NMR method as a function of the number and position of the methyl substituents in the ring. Chloroform was used as the standard CH acid. The selection was due to the weakness of the autoassociates of chloroform [9] and its rather high ability to form molecular complexes with various bases [10-18].

When chloroform is diluted with an inert solvent, cyclohexane, the signal of the chloroform proton is shifted by 0.13 ppm in the strong-field direction, which is explained by the presence of weak autoassociates in the solutions [9]. In the region of chloroform concentrations below 0.10 mole fraction, the chemical shift (CS) of the proton (δ_M = 7.06 ppm) is unchanged. This is evidence of the absence of association of the molecules in $CHCl_3$ at high dilutions. In solutions of compounds I-XIII the signal of the proton of chloroform is shifted in the weak-field direction with increasing concentration of the base (Fig. 1), which is an indication of the formation of intermolecular associates through a hydrogen bond. In the series of 1,3-dioxanes studied (Table 1), the least changes in the CS of the $CHCl_3$ proton due

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