ACYLATION OF o-METHOXYBENZODIOXAHETEROCYCLES AND SYNTHESIS OF β-AMINO KETONES FROM ACETYL DERIVATIVES

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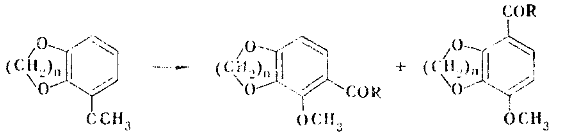
The sequences of the change in the relative rates of the formylation and acetylation of o-methoxybenzodioxaheterocycles and 1,2,3-trimethoxybenzene were established by the method of competitive reactions. It was shown that 4-methoxybenzo-1,3-dioxolane forms primarily 5-acyl derivatives, while 5-methoxybenzo-1,4-dioxane and 6-methoxybenzo-1,5-dioxepane form primarily 8- and 9-acyl derivatives, respectively. The acetyl derivatives were converted via the Mannich reaction to hydrochlorides of β-dimethylaminopropionyl derivatives, which have anti-inflammatory activity.

Acyl-substituted benzodioxaheterocycles are used in the synthesis of physiologically active substances [1]. In a continuation of our study of the electrophilic substitution reactions of o-methoxybenzodioxaheterocycles (I) [2] we therefore studied the compositions of the products of the formylation (IIa, IIIa) and acetylation (IIb, IIIb) of these compounds.



I　　II a-c　　IIIa-c

n = 1-3; II, III a R = H; b R = CH_3; c R = $CH_2CH_2N(CH_3)_2 \cdot HCl$

We found that the acylation of I gives isomeric acyl derivatives IIa, b and IIIa, b, the ratios of which depend on the number of methylene groups (n) contained in the heteroring. Thus when n = 1, primarily derivatives IIa, b are formed, whereas primarily isomers IIIa, b are formed when n = 2 or 3 (Table 1). The dominant acylation products are also more stable, since their percentages increase when the reaction time is increased, whereas the percentages of the alternative isomers decrease.

The steric effect of the methoxy group may hinder the formation of isomers IIa, b in the substitution of I (n = 2, 3), while the Mills–Nixon effect [2, 3] may hinder the formation of isomers IIIa, b in the substitution of I (n = 1). Possible reasons for the incorporation of certain substituents only in the positions of the aromatic ring that are adjacent to the alkoxy groups in the electrophilic substitution of I have been previously examined [4, 5].

The relative rates of formylation of I and their acyclic analog, viz., 1,2,3-trimethoxybenzene (IV), with dichloromethyl isopentyl ether in the presence of titanium tetrachloride determined by the method of competitive reactions decrease in the order I (n = 1) > I (n = 2) > I (n = 3) > IV. This is in agreement with the order of the decrease in the λ_{max}(log ε) values of the long-wave UV absorption band of these compounds due to a decrease in the electron donor character of the oxygen atoms with respect to the aromatic ring because of rotation of the alkoxy substituents about the C_{Ar}–O bond [2].

A somewhat different order of the decrease in the relative reaction rates is observed in the case of acetylation of I and IV with acetic anhydride in the presence of magnesium perchlorate or with acetyl chloride in the presence of stannic chloride: I (n = 2) > I (n = 3) > IV > I (n = 1), which corresponds to the order of the decrease in the rate constants for bromination of these compounds with bromine in acetic acid [6]. The decrease in the relative

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TABLE 1. Ratios of the Products of the Acylation Reactions of I

Compound	n		
	1	2	3
IIa	1	1	0
IIIa	0	9	1
IIb*	3	1	1
IIIb	1	4	4

*The ratios of isomers IIb and IIIb differ insubstantially in the case of acetylation with acetic anhydride or acetyl chloride.

rate of acetylation of I (n = 1) can evidently be explained by an increase in the role of steric hindrance of the methoxy group in its planar molecule [4] on passing from the formyl group to a more bulky substituent, viz., an acetyl group.

The hydrochlorides of β-amino ketones IIc and IIIc, which have moderate anti-inflammatory activity, were synthesized by the reaction of acetyl derivatives IIb and IIIb with paraformaldehyde and dimethylamine hydrochloride (via the Mannich reaction).

Compounds IIa (n = 1) [7] and IIb, c and IIIb, c (n = 2) [8] have been described. The structures of IIa-c and IIIa-c are confirmed by the presence of two doublets of aromatic protons (J = 9 Hz) in the PMR spectra. The signals of the methoxy groups of isomers IIa-c are shifted to weak field, while the signals of the alkylenedioxy groups are shifted to strong field as compared with the signals for isomers IIIa-c (Table 2).

EXPERIMENTAL

The UV spectra of solutions of the compounds in ethanol were recorded with a Specord UV-vis spectrophotometer. The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in CCl_4 were recorded with a Tesla BS-487C spectrometer (80 MHz) with tetramethylsilane as the internal standard. The determination of the ratios of the compounds was accomplished by GLC as in [5]. The relative reaction rates were established by GLC determination of the ratios of the concentrations of the starting I and IV and the acylation products formed under the preparative conditions indicated below but with the use of one equivalent each of two compounds to be compared per equivalent of the acylating agent.

Formylation. A 0.38-g (20 mmole) sample of $TiCl_4$ was added at 0°C to a mixture of 10 mmole of I, 2.6 g (15 mmole) of dichloromethyl isopentyl ether, and 15 ml of anhydrous CH_2Cl_2, and the mixture was stirred at 20°C for 3 h. It was then poured over ice, and the organic layer was washed with water and concentrated.

Acetylation. A) A mixture of 10 mmole of I, 5.1 g (50 mmole) of acetic anhydride, and 0.1 g (0.5 mmole) of magnesium perchlorate was heated at 80°C for 10 h (n = 1) or at 70°C for 7 h (n = 3), after which it was stirred with water at 50°C for 30 min. It was then cooled and extracted with dichloroethane, and the extract was washed with water, dried with $MgSO_4$, and concentrated. The residue was recrystallized from hexane. Isomer IIIb was isolated first.

B) A 2.6-g (10 mmole) sample of $SnCl_4$ was added at 5°C to a mixture of 10 mmole of I, 7.8 g (10 mmole) of acetyl chloride, and 8 ml of anhydrous CH_2Cl_2, and the mixture was stirred at 10°C for 10 min. It was then poured over ice, and the aqueous mixture was extracted with dichloroethane. The extract was washed with dilute (1:4) HCl and water and worked up as in variant A.

Synthesis of the Hydrochlorides of Amino Ketones IIc and IIIc. A mixture of 10 mmole of ketones IIb or IIIb, 0.45 g (15 mmole) of paraformaldehyde, 1.0 g (12 mmole) of dimethyl-

TABLE 2. Characteristics of the Synthesized Compounds

Compound	n	mp, °C	IR spectrum, C=O, cm-1	UV spectrum		PMR spectrum, ppm				Found, %				Empirical formula	Calc., %				Yield, %
				λmax, nm	lg ε	OCH_3	$O(CH_2)_nO$	COR	H_{Ar}[a]	C	H	Cl	N		C	H	Cl	N	
IIa	2	—[b]	—	—	—	3,88 (s)	4,15 (s)	10,00 (s)	6,44 (d, 8-H); 7,10 (d, 7-H)	—	—	—	—	$C_{10}H_{10}O_4$	—	—	—	—	—
IIIa	2	133—134[c]	1695	226, 238, 294	4,01; 4,13; 4,12	3,84 (s)	4,30 (s)	10,11 (s)	6,44 (d, 6-H); 7,31 (d, 7-H)	61,7	5,2	—	—	$C_{10}H_{10}O_4$	61,8	5,2	—	—	49
IIIa	3	88—89[c]	1695	214, 237, 290	3,87; 4,01; 3,92	3,81 (s)	2,23 (q, CH_2)[d], 4,17 (t, OCH_2)[d], 4,24 (t, OCH_2)[d]	10,17 (s)	6,54 (d, 7-H); 7,36 (d, 8-H)	63,4	5,8	—	—	$C_{11}H_{12}O_4$	63,4	5,8	—	—	43
IIb	1	37—38[e]	1670	223, 237, 279	4,06; 4,20; 4,03	4,02 (s)	5,96 (s)	2,40 (s)	6,47 (d, 7-H); 7,25 (d, 6-H)	61,8	5,1	—	—	$C_{10}H_{10}O_4$	61,8	5,2	—	—	52[f], 56[g]
IIIb	1	100—101[e]	1675	237, 277, 314	4,27; 4,15; 3,48	3,90 (s)	6,02 (s)	2,44 (s)	6,49 (d, 5-H); 7,32 (d, 6-H)	61,6	5,3	—	—	$C_{10}H_{10}O_4$	61,8	5,2	—	—	20[f], 21[g]
IIb	3	—[b]	—	—	—	3,85 (s)	2,08 (q, CH_2)[d], 4,12 (t, OCH_2)[d], 4,19 (t, OCH_2)[d]	2,44 (s)	6,58 (d, 9-H); 7,20 (d, 8-H)	—	—	—	—	$C_{12}H_{14}O_4$	—	—	—	—	—
IIIb	3	75—76[e]	1690	230, 278	4,10; 3,95	3,79 (s)	2,20 (q, CH_2)[d], 4,13 (t, OCH_2)[d], 4,23 (t, OCH_2)[d]	2,43 (s)	6,50 (d, 7-H); 7,29 (d, 8-H)	64,7	6,2	—	—	$C_{12}H_{14}O_4$	64,8	6,3	—	—	41[f], 55[g]
IIc	1	127—128[h]	1675	223, 238, 284	3,88; 4,00; 3,81	4,02 (s)[i]	5,94 (s)	2,80 (s, NCH_3); 3,38 (s, $COCH_2CH_2N$)	6,55 (d, 7-H); 7,29 (d, 6-H)	54,1	6,3	12,1	5,1	$C_{13}H_{17}NO_4 \cdot HCl$	54,3	6,3	12,3	4,9	65
IIIc	1	168—169[h]	1675	238, 281, 314	3,82; 3,71; 3,10	3,84 (s)[i]	6,01 (s)	2,86 (s, NCH_3); 3,43 (s, $COCH_2CH_2N$)	6,46 (d, 5-H); 7,31 (d, 6-H)	54,2	6,4	12,2	5,0	$C_{13}H_{17}NO_4 \cdot HCl$	54,3	6,3	12,3	4,9	78
IIIc	3	175—176[h]	1665	234, 283	3,79; 3,71	3,84 (s)[i]	2,26 (q, CH_2)[d], 4,19 (t, OCH_2)[d], 4,38 (t, OCH_2)[d]	2,85 (s, NCH_3); 3,48 (s, $COCH_2CH_2N$)	6,84 (d, 7-H); 7,60 (d, 8-H)	56,8	6,8	11,4	4,1	$C_{15}H_{21}NO_4 \cdot HCl$	57,0	7,0	11,2	4,4	90

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[a] J = 9 Hz. [b] This compound was not isolated in individual form. The spectrum was established from the spectrum of a mixture of both isomers. [c] From ethanol. [d] J = 6 Hz. [e] From hexane. [f] Acetylation with acetic anhydride. [g] Acetylation with acetyl chloride. [h] From 2-propanol. [i] In deuteromethanol.

amine hydrochloride, 10 ml of ethanol, and two drops of concentrated HCl was refluxed for 8 h, after which it was concentrated to half its original volume, and the product was precipitated by the addition of hot acetone.

The characteristics of the compounds synthesized for the first time are presented in Table 2.

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SYNTHESIS AND SOME TRANSFORMATIONS OF BENZO[b]THIOPHENE DERIVATIVES

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A number of 3-chloro-2-chlorocarbonylbenzo[b]thiophenes with alkyl substituents in various positions of the benzene ring were synthesized by arylation of acrylic acid with the corresponding alkyl-substituted iodobenzenes under the influence of catalytic amounts of palladium acetate and subsequent oxidation of the resulting arylacrylic acids with thionyl chloride. Replacement of the pyridine added in the oxidation reaction by triethylbenzylammonium chloride led to substantial increases in the yields of the desired products. The possibility of conversion of the resulting benzo[b]thiophene derivatives to thiophene ring-unsubstituted benzo[b]thiophenes was shown in the case of 3-chloro-2-chlorocarbonylbenzo[b]thiophene as a result of successive saponification of the 2-chlorocarbonyl group, decarboxylation, and dechlorination.

The research on condensed heteroaromatic compounds that contain a thiophene ring has thus far been quite limited in connection with the synthetic difficulties and the complexity involved in the study of the behavior of such compounds. A knowledge of the principal chemical properties of such structures is necessary for the development of effective methods for the isolation of the sulfur-containing compounds of petroleum and the selection of efficient methods for their chemical refining and skillful utilization. In addition, condensed sulfurous heteroaromatic compounds, particularly benzo[b]thiophenes, may be of practical interest as standard compounds for the study of the composition of the sulfurous components of the heavy fractions of petroleum and petroleum residues.

The known methods for the preparation of benzo[b]thiophenes [1] have a number of disadvantages, the chief of which are the use of difficult-to-obtain starting reagents and the overall low yields of the desired products.

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