Chemistry of Heterocyclic Compounds, Vol. 36, No. 12, 2000

THE DIRECTION OF RING FISSION OF UNSYMMETRICALLY SUBSTITUTED SUCCINIC ANHYDRIDES. 1. INTERACTION OF α-TETRAHYDROFURYLSUCCINIC ANHYDRIDE WITH BENZYLAMINE AND 2,5-XYLIDINE

G. G. Galust'yan, M. G. Levkovich, and N. D. Abdullaev

The reaction of α-tetrahydrofurylsuccinic anhydride with amines proceeds regiospecifically at room temperature with the formation of N-substituted 2-(α-tetrahydrofuryl)succinamic acids. On increasing the temperature the reaction direction is changed and the 3 isomer is mainly formed.

Keywords: amic acids, anilines, unsymmetrically substituted succinic anhydrides, double resonance, direction of nucleophilic attack, Overhauser effect.

Cyclic anhydrides of dicarboxylic acids react readily with ammonia, and with primary and secondary amines with ring fission forming dicarboxylic acid monoamides, but under more forcing conditions (high temperature, the presence of catalysts and water-removing agents) the latter are transformed into cyclic imides of the acids [1,2].

The process of acylation of amines by unsymmetrically substituted cyclic anhydrides of dibasic acids occurs in a more complex manner, since ring fission may occur with the formation of two (α- or α'-substituted) amidoacids depending on which of the two carbonyl carbon atoms is subject to nucleophilic attack by the amine. The literature data concerning the direction of opening of the anhydride ring in these reactions is extremely contradictory. Thus King and collaborators [3], studying the interaction of phthaloylglutamic anhydride with ammonia, amines, and amino acids, recorded exclusively the formation of γ-substituted amic acids. Other authors [4], investigating the reaction of anhydrides of substituted glutaric acids, particularly α-phenyl- and α-(*p*-nitrophenyl)glutaric anhydrides, with ammonia, recorded that in both cases exclusively α-substituted amic acids were formed, although with different yields.

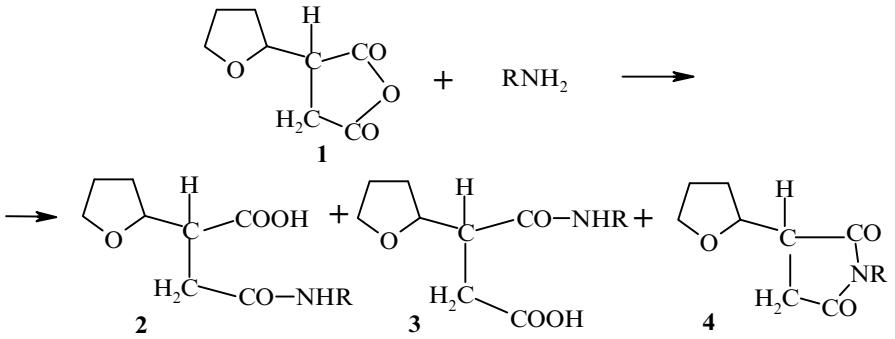
However these same authors later [5] had established the formation of a mixture of α- and γ-substituted amic acids separable with difficulty in reactions of alkylglutamic acid anhydrides with primary amines. The contradictory nature of the data presented may be caused by two reasons. Either the nature of the reactants, such as the character of the substituent in the anhydride or amine, has a significant effect on the direction of the reaction, or one of the two isomers formed is not always isolated from the reaction mixture, which leads to a mistaken conclusion on the composition and ratio of the isomers formed initially.

In view of the above it seemed of interest to investigate the acylation of amines with α-tetrahydrofurylsuccinic anhydride (**1**) under various conditions in order to clarify the direction of opening of the anhydride ring. Furthermore, the combination of a tetrahydrofuran ring, a peptide bond, and a carboxyl group in one molecule may lead to substances interesting in a practical sense.

Institute of the Plant Substances Chemistry, Uzbek Academy of Sciences, Tashkent 700170. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1634-1642, December, 2000. Original article submitted February 15, 1999.

 0009-3122/00/3612-1402$25.00

The reaction of anhydride **1** with benzylamine and with 2,5-xylidine was carried out at a reactant ratio of 1 : 1 in various solvents (chloroform, toluene, dioxane) under cooling, at room temperature, and at the temperature of the boiling solvent. From the known data the formation of acids **2** and **3** and imide **4** may be expected.



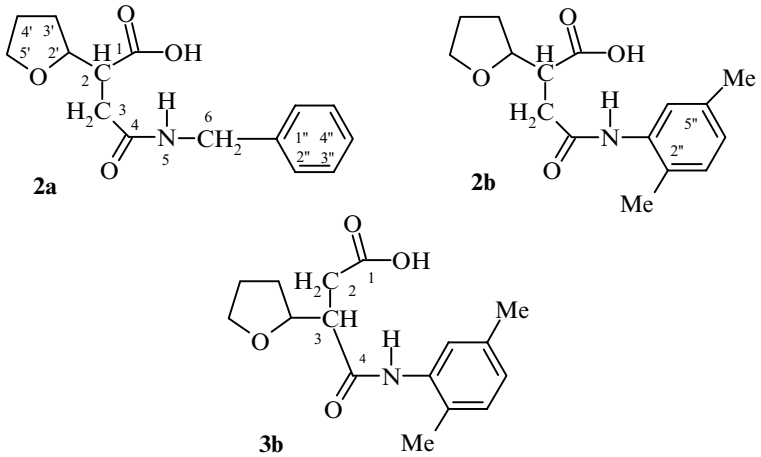
a R = $PhCH_2$, **b** R = 2,5-$Me_2C_6H_3$

Boiling anhydride **1** with benzylamine in the solvents indicated leads to the formation of an uncrystallizable oil, from which no individual products were successfully isolated. Varying the conditions enabled the reaction to be carried out with the formation of one of the two possible isomers. Thus, on slowly mixing solutions of anhydride **1** and benzylamine in chloroform (previously cooled in ice) and then maintaining the reaction mixture at room temperature for a day, a single acid (constant melting point after several recrystallizations, ^{1}H NMR spectrum) with mp 115-116°C was isolated (82% yield). It was not possible to assign the obtained acid to structure **2a** or **3a** on the basis of the usual ^{1}H NMR spectrum, so a more profound investigation was undertaken, the results of which indicated the formation of isomer **2a**, *viz*. N-benzyl-2-(α-tetrahydrofuryl)succinamic acid.

An acid with mp 124-125°C (65% yield) was isolated from the reaction of anhydride **1** with 2,5-xylidine under analogous conditions. Investigation of this acid enabled it to be assigned the structure of N-(2,5-dimethylphenyl)-2-(α-tetrahydrofuryl)succinamic acid (**2b**). However under more forcing reaction conditions (boiling a mixture of reactants in the solvents indicated for 4-6 h) isomer **3b**, N-(2,5-dimethylphenyl)-3-(α-tetrahydrofuryl)succinamic acid (60% yield) was formed preferentially, although acid **2b** was also isolated in small yield.

Imides **4** were not isolated from any experiment.

According to the data of ^{1}H and ^{13}C NMR spectra the molecules of compounds **2a**, **2b**, and **3b** exist in CD_3OD in two, three, and one conformation respectively. The reasons for the existence of several conformers may be the presence of two chiral centers ($C_{(2')}$ and $C_{(2)}$ for compounds **2a** and **2b**, $C_{(2')}$ and $C_{(3)}$ for **3b**), the planarity of the CO–NH grouping, and also intramolecular hydrogen bonds, for which there are several possibilities in these molecules. Analysis of the coupling constants (CC) will be considered in a separate publication. Only the position of substituents in these three compounds is analyzed in the present work.



The ^{1}H NMR spectrum of compound **3b** in CD_3OD is represented by separate well resolved signals. The four β-protons of the tetrahydrofuran ring are displayed as three complex multiplets in the most high field part of the spectrum. Only two signals at 2.017 and 1.068 ppm overlap one another. These belong to the geminal protons 4H and 4H* of the tetrahydrofuran ring (here and subsequently the more high field proton of a geminal pair is denoted by an asterisk). The values of their chemical shifts were established from a homocorrelation spectrum (COSY). Protons in the positions α to the oxygen atom of the tetrahydrofuran ring are displayed as three well marked quartets with CC J = 7.5 Hz for 2'-H and 5'-H and J = 7.2 Hz for 5'-H* (Table 1). The protons of the linear portion of the molecule 2-H, 2-H*, 3-H form a well resolved first order spectrum with readily measurable values of the chemical shift. The aromatic part of the molecule is displayed as a spectrum usual for such a fragment with an ABC system of aromatic protons and two singlets for the methyl groups. It was possible only to note some broadening of signals for the aromatic protons preventing measurement of the *meta* and *para* coupling constants. A feature of the ^{1}H NMR spectrum for compound **3b** was the residual small signal of the NH proton (8.75 ppm) on recording the spectrum in deuteromethanol. The signal was retained for at least several days while the spectral investigation of the compound was being carried out. This is probably caused by the formation of a strong intramolecular hydrogen bond which may slow down the NH → ND exchange in CD_3OD significantly and therefore reduce the mobility of the benzene ring leading to an insignificant broadening of the lines for the aromatic proton signals.

The ^{13}C NMR spectrum of compound **3b** in CD_3OD was interpreted on the basis of an HMQC experiment (two-dimensional heterocorrelation spectra using long range CC). Values of the chemical shifts in the ^{13}C NMR spectrum are given in Table 2. The spectrum is represented by single signals from one conformation of the compound. The position of substituents on the carbonyl carbon atoms was established by analysis of the long range ^{1}H–^{13}C CC. The residual weak signal of the NH proton in this spectrum displays responses to the $C_{(1")}$, $C_{(2")}$, and $C_{(6")}$ carbon atoms and to one of the carbonyl atoms at 172.59 ppm. The same carbonyl carbon also has responses to the 2-H, 2-H*, 2'-H, and 3-H protons. Consequently it must be carbon $C_{(4)}$. The $C_{(1)}$ carbonyl carbon atom has responses only to the geminal proton pair 2-H and 2-H* and the signal at 174.91 ppm belongs to it.

When investigating the ^{1}H NMR spectrum of acid **3b** in $CDCl_3$ it was possible to observe a weak Overhauser effect (NOE ~2.5-3%) on the signal of the 3-H proton under irradiation of the sample at the frequency of the NH proton signal, which also confirms the structure of acid **3b**. The chemical shifts of the protons and of the carbon nuclei of compound **3b** in $CHCl_3$ are given in Tables 1 and 2 respectively. The appearance in the spectrum of two conformers A and B at an approximate ratio of 3 : 1 was the most notable feature in difference to the ^{1}H NMR spectrum of this substance in CD_3OD. The greatest changes in the values of the proton chemical shifts of the conformers were observed for the NH group (0.52 ppm) and the hydrogen atoms of both chiral centers 2-H* and 2'-H (~0.10 ppm). A fairly large change in the chemical shift values (0.074 ppm) was displayed by one further proton of the tetrahydrofuran ring 5-H*. No significant differences in chemical shift were observed in the ^{13}C NMR spectra of these conformers.

The ^{1}H NMR spectrum of compound **2b** in CD_3OD shows that it exists in three conformations A : B : C at a ratio of 5 : 3 : 1. The spectrum of the aliphatic part of the molecule is represented in this case by very complex overlapping multiplets.

An interpretation of signals for the 2-H, 3-H, and 3-H* protons which are most important for the spectral investigation is given in Fig. 1. Their assignment to conformers A, B, and C is also shown. The interpretation and assignment were carried out on the basis of a series of double resonances, differential variants of tickling, INDOR, and the Overhauser effect (NOE). The chemical shifts for the three conformers in CD_3OD are given in Table 1.

Assignment of substituents to the appropriate position in acid **2b** was confirmed by the presence of heterocorrelation responses in the HMQBC spectra of carbon $C_{(1)}$ on protons 2-H, 3-H, 3-H*, and 2'-H. The $C_{(4)}$ carbonyl displays a good response in this experiment to protons 3-H and 3-H* and weak responses to the 2-H and NH protons.

A NOE of ~4-5% was observed in the ^{1}H NMR spectrum of acid **2b** measured in $CDCl_3$ at the methylene pair of 3-H protons on irradiating the sample by a field with the frequency of the NH proton signal. The methyl group at position $C_{(2")}$ displayed a good Overhauser effect of 6-8% on the same irradiation. In its turn this also confirms the fixed disposition of the benzene ring in space, leading as in the case of isomer **3b** to some broadening of the aromatic proton signals. The multiplicity and the order of disposition of the signals in the spectrum of compound **2b** were in good agreement with the signals of compound **3b**.

TABLE 1. Chemical Shifts (ppm) in the ^{1}H NMR Spectra of Compounds **2a**, **2b**, and **3b** in $CDCl_3$ and CD_3OD

Proton in conformations A, B, C	**2a**		**2b**		**3b**	
	$CDCl_3$	CD_3OD	$CDCl_3$	CD_3OD	$CDCl_3$	CD_3OD
2-H (A) 2-H (B) 2-H (C)	2.905 3.050	2.930 3.022	3.101 3.032 2.915	3.088 2.979 2.985	2.826 2.859	2.819
2-H* (A) 2-H* (B) 2-H* (C)					2.678 2.572	2.528
3-H (A) 3-H (B) 3-H (C)	2.646 2.646	2.647 2.401	2.783 2.823 2.836	2.805 2.812 2.764	2.915 2.912	2.696
3-H* (A) 3-H* (B) 3-H* (C)	2.447 2.609	2.625 2.587	2.654 2.775 2.616	2.564 2.747 2.463		
6-H (A) 6-H (B) 6-H (C)	4.385 4.390	4.376 4.376				
6-H* (A) 6-H* (B) 6-H* (C)	4.385 4.390	4.322 4.322				
2'-H (A) 2'-H (B) 2'-H (C)	4.054 4.092	4.023 4.048	4.140 4.150 4.039	4.120 4.091 4.015	4.047 3.945	4.076
3'-H (A) 3'-H (B) 3'-H (C)	2.079 2.046		2.06-2.02	1.99-2.09	2.210 2.210	2.098
3'-H* (A) 3'-H* (B) 3'-H* (C)	1.706 1.671	1.67-2.05	1.766 1.744 1.625	1.73-2.09	1.652 1.652	1.652
4'-H 4'-H*	1.83-1.94		1.85-2.03	1.87-1.99	2.017 1.968	1.995 1.957
5'-H (A) 5'-H (B) 5'-H (C)	3.807 3.880	3.818 3.818	3.955 3.862 3.845	3.883 3.850 3.933	3.988 4.007	3.969
5'-H* (A) 5'-H* (B) 5'-H* (C)	3.710 3.762	3.701 3.701	3.915 3.790 3.773	3.747 3.738 3.781	3.895 3.811	3.845
2"-H 3"-H (A) 3"-H (B) 4"-H 5"-H 6"-H (A) 6"-H (B) 6"-H (C)	7.22-7.34	7.19-7.32	7.014 7.025 6.864 7.508 7.467	6.928 7.073 7.109 7.109 7.164	7.054 6.875 7.731 7.764	7.062 6.891 7.472
NH (A) NH (B) NH (C)	6.60 6.50		7.661 7.652 7.700		8.70 8.18	8.751
2"-Me (A, B) 2"-Me (C) 5"-Me (A, B, C)			2.158 2.161 2.267	2.177 2.206 2.269	2.217 2.207 2.310	2.222 2.295

The interpretation of the ^{13}C NMR spectrum for acid **2b**, in difference to its ^{1}H NMR spectrum, was not complex since the sequence of signals in this spectrum corresponds to the sequence of signals for compound **3b**, and assignment of the signals to a conformation was readily carried out from their relative intensity.

TABLE 2. Chemical Shifts (ppm) in the ^{13}C NMR Spectra of Compounds **2a**, **2b**, and **3b** in $CDCl_3$ and CD_3OD

Carbon atom in conformations A, B, C	**2a**		**2b**		**3b**	
	$CDCl_3$	CD_3OD	$CDCl_3$	CD_3OD	$CDCl_3$	CD_3OD
$C_{(1)}$ (A)	172.42	174.10	176.14	176.53	174.02	174.91
$C_{(1)}$ (B)	171.59	173.65	176.06	176.59		
$C_{(1)}$ (C)			175.91	175.39		
$C_{(2)}$ (A)	46.91	47.98	46.24	47.97	33.64	33.68
$C_{(2)}$ (B)	46.02	48.20	46.74	48.28	33.50	
$C_{(2)}$ (C)			47.68	47.97		
$C_{(3)}$ (A)	34.53	35.89	35.44	35.70	47.87	48.53
$C_{(3)}$ (B)	34.31	35.50	35.32	36.18	47.87	
$C_{(3)}$ (C)			33.31	34.05		
$C_{(4)}$ (A)	175.00	176.59	169.83	172.68	172.27	172.59
$C_{(4)}$ (B)	175.19	176.55	170.64	173.11		
$C_{(4)}$ (C)			171.28	174.30		
$C_{(6)}$ (A)	68.07	69.06				
$C_{(6)}$ (B)	68.45	69.24				
$C_{(2')}$ (A)	78.36	80.54	78.80	80.75	78.82	79.92
$C_{(2')}$ (B)	78.78	80.75	75.58	80.58	79.58	
$C_{(2')}$ (C)			78.83	81.00		
$C_{(3')}$ (A)	29.85	30.62	25.58	26.70	25.44	26.12
$C_{(3')}$ (B)	29.08	29.81	25.58	26.62	25.69	
$C_{(3')}$ (C)			25.42	26.70		
$C_{(4')}$ (A)	25.58	26.57	29.69	29.80	31.04	30.48
$C_{(4')}$ (B)	25.62	26.65	29.26	30.71	29.71	
$C_{(4')}$ (C)			30.61	30.59		
$C_{(5')}$ (A)	43.83	44.15	68.57	69.32	68.45	68.83
$C_{(5')}$ (B)	43.80	44.20	68.21	69.12	68.26	
$C_{(5')}$ (C)			68.32	69.32		
$C_{(1'')}$ (A)	137.68	140.05	135.04	136.65	135.52	136.05
$C_{(1'')}$ (B)	137.81	139.98	134.93	136.71	135.52	
$C_{(1'')}$ (C)			135.59	136.80		
$C_{(2'')}$ (A)	128.69	129.48	126.20	127.93	125.69	128.03
$C_{(2'')}$ (B)	128.69	129.51	126.33	127.50	125.69	
$C_{(2'')}$ (C)			125.57	127.06		
$C_{(3'')}$ (C)	127.72	128.53	130.23	131.39	130.22	130.79
$C_{(3'')}$ (A)	127.75	128.58	130.19	131.30	130.22	
$C_{(3'')}$ (B)			130.10	131.22		
$C_{(4'')}$ (A)	127.56	128.12	126.68	128.08	125.86	126.76
$C_{(4'')}$ (B)	127.53	128.16	126.87	128.04	125.86	
$C_{(4'')}$ (C)			125.61	127.83		
$C_{(5'')}$ (A)	127.72	128.53	136.23	137.03	136.44	136.62
$C_{(5'')}$ (B)	127.75	128.58	136.23	137.00	136.44	
$C_{(5'')}$ (C)			136.27	136.89		
$C_{(6'')}$ (A)	128.69	129.48	124.03	127.57	123.23	125.05
$C_{(6'')}$ (B)	128.69	129.51	124.22	127.60	122.76	
$C_{(6'')}$ (C)			123.08	127.44		
2"-Me (A)			17.34	17.66	21.14	21.32
2"-Me (B)			17.29			
2"-Me (C)			17.34			
5"-Me (A)			21.04	20.96	17.33	17.65
5"-Me (B)			21.02			
5"-Me (C)			21.10			

Compound **2b** exists in CD_3OD in two conformations with a ratio A : B of ~3 : 2. The sequence of signals and the main spectral characteristics of the ^1H NMR spectrum corresponds to the case considered above for compounds **2b** and **3b**. In difference to the previous a new group of signals appeared in the ^1H NMR spectrum for the protons of the NCH_2 group at ~4.35 ppm and the aromatic part of the spectrum was changed due to the absence of substituents in the aromatic nucleus.

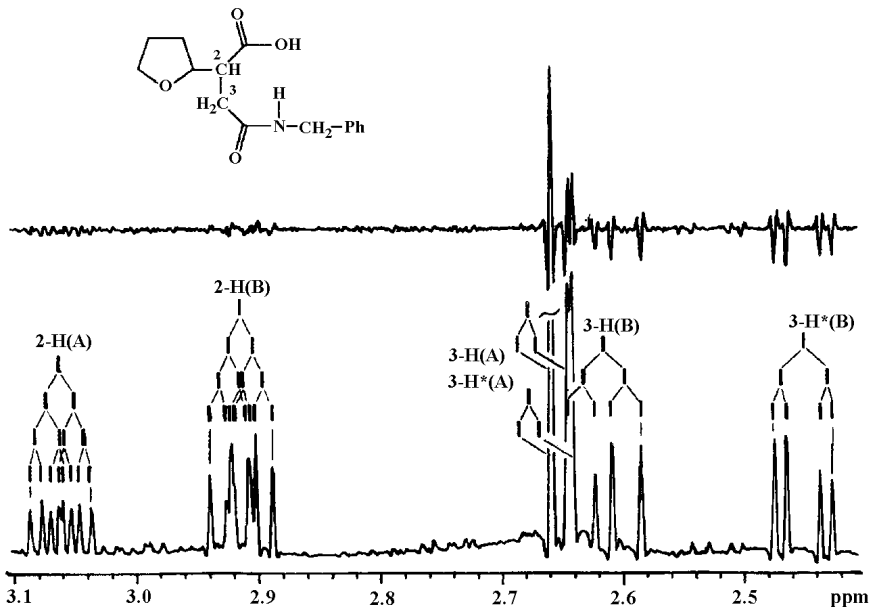


Fig. 1. ^{1}H NMR spectrum of the aliphatic part of compound **2b** in CD_3OD.

In the ^{1}H NMR spectrum of compound **2a** recorded in $CDCl_3$ the NH protons formed two broadened singlets at 23°C [NH(A)- 6.6 and NH(B)- 6.5 ppm] or two poorly resolved triplets with CC J = 5.7 Hz at 10°C [NH(A)- 6.7 and NH(B)- 6.6 ppm]. These two signals are convenient for establishing the position of substituents. On sequential irradiation of the sample at their frequencies and subtraction of the spectra from one another, the signals of the 3-H and 3-H* methylene protons displayed both an Overhauser effect and also a small unresolved CC from the NH proton which is seen in the differential spectrum in Fig. 2. The NOE for conformer A is directed upwards and for conformer B downwards. The value of the NOE was about 4% and analysis of the shape of the signal allowing for the Overhauser effect shows the presence of a hidden constant equal to 0.1-0.2 Hz. It was possible to establish one further small CC of approximately 0.08-0.15 Hz at the 3-H and 3-H* protons by the same method on irradiating the sample at the frequencies of the methylene pair of protons in the benzylic fragment, which determines completely unequivocally position 5 for the benzyl substituent in compound **2a**.

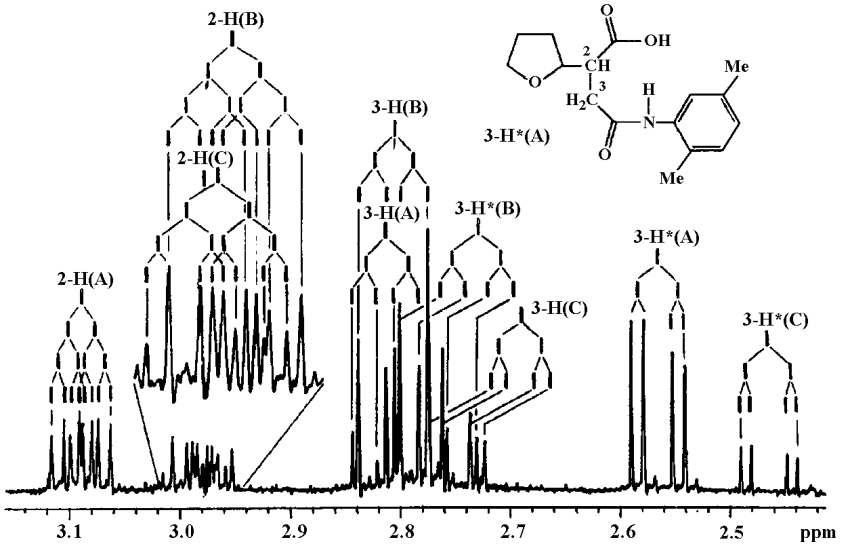


Fig. 2. Differential NOE spectrum for the aliphatic part of compound **2a** in $CDCl_3$.

The presence of two conformers was also observed in the ^{13}C NMR spectrum of acid **2a** with a ratio A : B = 3 : 2. Assignment of the sp^3-hybridized carbon atoms was similar to the two previous cases. Assignment of the carbon signals of the benzene ring was made on the basis of a HMQC experiment.

The investigation carried out has shown that the direction of opening of the anhydride ring in reactions of the unsymmetrically substituted succinic anhydride **1** is regiospecific at temperatures no greater than room temperature. On increasing the temperature the reaction becomes regioselective.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Unity 400 spectrometer in CD_3OD and $CDCl_3$ with an operating frequency of 400 MHz for protons and 100 MHz for ^{13}C nuclei. As internal standard TMS was used.

Anhydride **1** was obtained by homolytic addition of tetrahydrofuran to maleic anhydride in the presence of benzoyl peroxide (ratio in the order named 40 : 1 : 0.3) while boiling for 6 h according to the modified procedure of [6]. Benzylamine, 2,5-xylidine, and the solvents were dried and redistilled before the experiment.

Reaction of Anhydride 1 with Benzylamine. A cooled solution of benzylamine (1.07 g, 0.01 mol) in chloroform (15 ml) was added gradually to an ice-cooled solution of anhydride **1** (1.7 g, 0.01 mol) in chloroform (15 ml) permitting no significant heating. The mixture was left at room temperature for 25 h. After removing chloroform the residue, a viscous clear oil (crude acid **2a**), was treated with saturated sodium bicarbonate solution. The resulting homogeneous solution of acid **2a** sodium salt was washed three times with benzene, after which it was carefully acidified with hydrochloric acid solution (1 : 1). Crystals gradually separated on standing. After recrystallization from hot water, acid **2a** (2.3 g: 82%) was obtained as snow-white crystals; mp 115-116°C. Found, %: C 64.65; H 7.09; N 5.35. $C_{15}H_{19}NO_4$. Calculated, %: C 64.98; H 6.86; N 5.05. No products other than acid **2a** residues were detected in the mother liquor after evaporation to dryness. Benzylamine (0.13 g) was isolated from the benzene extracts.

Reaction of Anhydride 1 with 2,5-Xylidine. A. An oil was obtained similarly to the previous experiment from anhydride **1** (1.7 g, 0.01 mol) and 2,5-xylidine (1.21 g, 0.01 mol). The oil was also treated with sodium bicarbonate solution. On acidifying the benzene-washed bicarbonate solution an oily substance was precipitated, which slowly crystallized from aqueous alcohol. Crystals of acid **2b** (1.85 g: 65%) were obtained; mp 124-125°C. Found, %: C 66.32; H 6.89; N 5.14. $C_{16}H_{21}NO_4$. Calculated, %: C 65.97; H 7.21; N 4.81. 2,5-Xylidine (0.23 g) was isolated from the benzene extract.

B. A mixture of anhydride **1** (1.7 g, 0.01 mol,) and 2,5-xylidine (1.21 g, 0.01 mol) in dioxan (40 ml) was boiled for 4 h. After removing dioxan, the residue was treated as in the previous experiment. Fractional crystallization from aqueous alcohol gave acid **3b** (1.7 g, 60%); mp 170-172°C. Found, %: C 65.64; H 6.78; N 4.57. $C_{16}H_{21}NO_4$. Calculated, %: C 65.97; H 7.21; N 4.81. Acid **2b** (0.3 g) was isolated from the mother liquor after removal of acid **3b**.

REFERENCES

1. Weygand-Hilgetag, *Experimental Methods in Organic Chemistry*, [Russian translation], Khimiya, Moscow (1968), p. 450.
2. A. N. Kost (editor), *Handbook of Organic Chemistry* [in Russian], Mir, Moscow (1966), p. 392.
3. F. E. King and D. A. A. Kidd, *J. Chem. Soc.*, 3315 (1951).
4. J. C. Roberts, and K. Selby, *J. Chem. Soc.*, 2335 (1951).
5. J. C. Roberts and B. Shaw, *J. Chem. Soc.*, 2842 (1950).
6. R. L. Jacobs and G. G. Ecke, *J. Org. Chem.*, **28**, 3036 (1963).