REACTION OF 6-HYDROXY-7,7-DICYCLOPROPYL-5-OXA-SPIRO[2,4]HEPTAN-4-ONE AND (1-FORMYLCYCLOBUTYL)-ACETIC ACID WITH AMINES

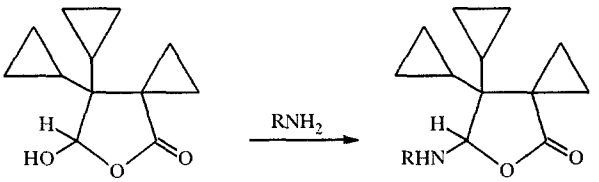
A. G. Bessmertnykh, T. I. Voevodskaya, N. A. Donskaya, and T. V. Zinevich

The reaction of 6-hydroxy-7,7-dicyclopropyl-5-oxaspiro[2,4]heptan-4-one and (1-formylcyclobutyl)acetic acid with amines may serve as a convenient method for the preparation of 5-(arylamino)tetrahydrofuran-2-ones. Treatment with diethylamine gave open-chain or cyclic compounds, depending upon the structure of the starting materials.

The presence of two reactive centers and the possibility of ring-chain tautomers in the β-aldehydroacids leads to multiple products in reaction with nucleophiles [1], but this study mainly dealt with 2-ketobenzoic acids. Other β-aldehydroacids have been only infrequently studied in reactions with nucleophiles [2]. There are other unexplained influences of various factors on the direction of the reaction, thus impeding their use in synthesis.

In the present work we studied some synthetic possibilities for the reaction of β-aldehydoacids with amines. As the objects of study we selected 6-hydroxy-7,7-dicyclopropyl-5-oxaspiro[2,4]-heptan-4-one (I), existing in its cyclic tautomeric forms [3], and (1-formylcyclobutyl)acetic acid (II), containing varying amounts of cyclic and linear tautomeric forms [3]. We showed earlier that upon treatment with methanol compounds I and II gave substitution of the hydroxyl group by the methoxyl group with the formation of cyclic products [3].

It has been shown that reaction of compound I with aniline gives a single reaction product III in quantitative yield.



I III, IV

III R=Ph; IV R=*p*-$MeOC_6H_4$

The IR spectrum of this compound shows absorption bands for the carbonyl group of the lactone at 1755 cm^{-1} and also the characteristic absorption bands for the NH bond at 3320 cm^{-1}. In the ^{13}C NMR spectrum, four signals of the nuclear carbons of the tetrahydrofuran ring are observed, in addition to signals for the carbons in the three-membered rings. In this case the chemical shift of the nuclear carbons $C_{(3)}$, $C_{(4)}$, and $C_{(7)}$ of the starting lactone I [4] and the product III are not significantly different. The chemical shift of the nuclear carbon $C_{(6)}$ at 89.6 ppm agrees with its hemiaminal character in the proposed structure. At lower field the ^1H NMR spectrum shows a broad signal for the protons connected to the nitrogen atom (5.2 ppm) and also the 6-H protons (5.5 ppm). No signals were observed in the 8-13 ppm region. These spectral data indicate that the compounds prepared have structure III and exist only in the cyclic tautomeric forms.

The reaction of compound I with anisidine gave the analogous reaction product in good yield. As with compound III, compound IV exists in the solid phase and in chloroform and benzene solution as the cyclic tautomeric form.

(1-Formylcyclobutyl)acetic acid (II) also easily reacts with aniline and anisidine, giving the cyclic products V and VI in high yield (see below).

The ^1H NMR, ^{13}C NMR, and IR spectra of these compounds in characteristic regions is largely similar to the spectra of compounds III and IV, and we assigned them structures V and VI. However, in the ^{13}C NMR spectra broad lines were observed, most visible for the signals of the $C_{(1)}$, $C_{(3)}$, and $C_{(5)}$ nuclei. Thus, the $C_{(1)}$ and $C_{(3)}$ nuclei were registered in the form of one

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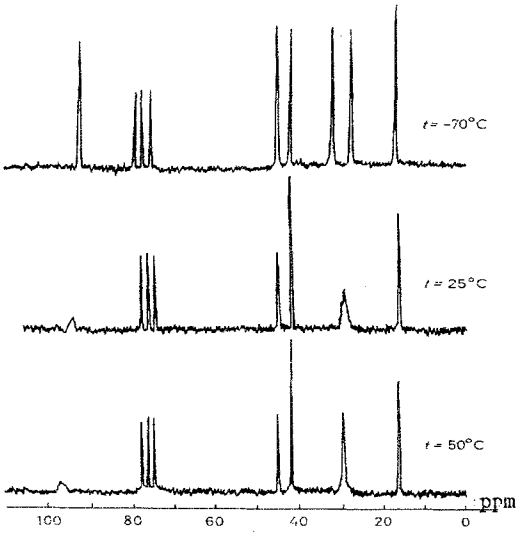


Fig. 1. Portion of the ^{13}C NMR spectrum of compound III.

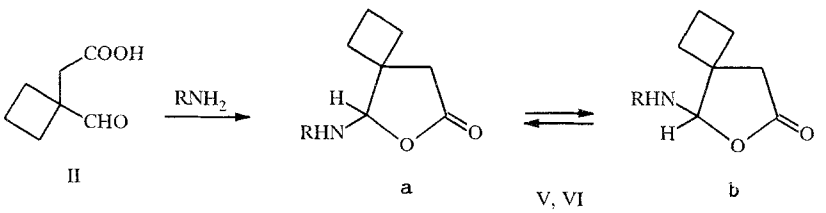
TABLE 1. Yields and Physical-Chemical Properties of Compounds III-VIII

Compound	Name	Empirical formula	mp, °C	IR spectrum, cm^{-1}	Yield, %
III	6-phenylamino-7,7-dicyclopropyl-5-oxaspiro[2,4]heptan-4-one	$C_{18}H_{21}O_2N$	127...128	890, 910, 1610 (Ar), 1760 (C=O), 3420 (N-H)	91
IV	6-(p-Methoxyphenyl-amino-7,7-docyclopropyl-5-oxaspiro-[2,4]heptan-4-one	$C_{19}H_{23}O_3N$	151...152	890, 910, 1615 (Ar), 1760 (C=O), 3425 (N-H)	78
V	5-Phenylamino-6-oxaspiro[3,4]octan-7-one	$C_{13}H_{15}O_2N$	131...132	895, 1610 (Ar), 1765 (C=O), 3380 (N-H)	65*
VI	5-(p-Methoxyphenylamino)-6-oxaspiro[3,4]octan-7-one	$C_{14}H_{17}O_3N$	222...223	890, 1620 (Ar), 1760 (C=O), 3370 (N-H)	68*
VII	6-(Diethylamino-oxido)-7,7-dicyclopropyl-5-oxaspiro-[2,4]heptan-4-one	$C_{16}H_{27}O_3N$	Oil‡	1780 (C=O)†, 2600...3600 (N-H	89
VIII	Diethylammonium (1-formylcyclobutyl)acetate	$C_{11}H_{21}O_3N$	Oil‡	1720, 1780 (C=O), 2200...3600 (N-H)	72

*Yields based on amount of 1,1-dichlorospiro[3.3]heptan-2-one introduced into the reaction [7].

†Asymmetric peak with inflection at 1710 cm^{-1}.

‡Distilled with decomposition. Crystallization unsuccessful.



II a V, VI b

V R=Ph; VI R=*p*-$MeOC_6H_4$

TABLE 2. ^{1}H NMR Parameters for Compounds III-VIII*

Compound	Chemical shift, δ, ppm					
	R††	-(CH$_2$)-	cyclo-C$_3$H$_5$	CH$_2$	6-H	N-H
III	6,98...7,10 m (3H); 7,28...7,46 m (2H)	1,18...1,35 m (2H); 1,44...1,58 m (2H)	0,28...0,38 m (1H); 0,55...0,62 m (2H); 0,64...0,72 m (2H); 0,74...0,82 m (2H); 0,88...0,98 m (1H); 1,18...1,35 m (1H); 1,18...1,35 m (1H)	—	5,55 d J = 10 Hz	5,4 br.d J = 10 Hz
IV	3,9 s (3H); 6,9 br.s (4H)	1,0...1,8 m (6H)	1,0...1,8 m (6H); 0,45...0,96 m (8H)	—	5,4 br.s	5,2 br.s
V	7,0...7,1 m (3H); 7,3...7,5 m (2H)	2,0...2,3 m (4H); 2,4...2,6 m (2H)	—	3,9 br.s	4,6 br.s	6,9 br.s
VI	7,0...7,1 m (3H); 7,3...7,5 m (2H)	2,0...2,3 m (4H); 2,4...2,6 m (2H)	—	2,7 br.s	5,9 s	6,0 br.s
VII	1,2 t (J = 8 Hz) (6H); 2,9 bq,T (J = 8 Hz) (4H)	1,0 br.s 6H)	1,0 (6H); 0,4 (8H)	-	6,9	(2H)
VIII	1,2 t (J = 8 Hz) (6H); 2,8 q (J = 8 Hz) (4H)	1,5...2,1 m (6H)	—	2,6 (2H)	—	9,8 br.s (2H)

*The spectra of compounds III and IV were recorded with a VXR-400 instrument and the remaining compounds with a Tesla BS-467.
†R = R (III, V); R = p-MeOC$_6$H$_4$ (IV, VI), R = Et (VII, VIII).

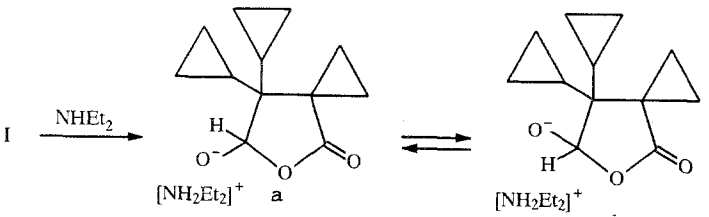
TABLE 3. ^{13}C NMR Parameters for Compounds III-VIII

Compound	Chemical shift, δ, ppm								
	C$_{(1)}$	C$_{(2)}$	C$_{(3)}$	C$_{(4)}$	C$_{(6)}$	C$_{(7)}$	C$_{(8)}$	cyclo-C$_3$H$_5$	N—R
III	9,19	12,85	31,58	177,69	89,57	42,89	—	-0,72; 0,08; 0,58; 1,21; 9,95; 14,09	114,97 (2C); 120,30; 129,28 (2C); 143,96
IV	9,59	12,76	31,46	178,01	91,13	42,60	—	-1,02; -0,14; 0,37; 1,02; 7,84; 13,83	114,76 (2C); 116,66 (2C); 137,60; 154,02; 55,53 (OCH$_3$)
V	29,5 br	15,80	29,5 br	45,52 br	94,0 b	174,39	42,3 br	—	115,38 (2C); 120,86; 129,25 (2C); 114,43
VI	29,10	15,59	29,10	45,02 br	91,5 b	174,51	42,2 br	—	55,42 (OCH$_3$); 115,38 (2C); 120,86; 129,25 (2C); 144,43
VII	11,82		28,77	179,89 br	103,3 b	45,06	—	-0,84; -0,72; 10,03	10,03; 42,20
VIII	26,51	14,49	26,51	49,33	196,96	176,19	43,39	—	10,71; 41,60

*The spectra of compounds III and V were determined with a VXR-400 instrument and the rest with an FT-80A.

wide signal. The shapes of the signals in the ^{13}C NMR spectra were not affected by change in the solution concentration or solvent composition (chloroform, methylene chloride, acetone, pyridine). However, variation of the temperature from 20 to —70°C and from 20 to 55°C led to a diminution of the broad signals (Fig. 1). Transition to temperatures below zero produced the appearance of nonequivalence of the $C_{(1)}$ and $C_{(3)}$ nuclei of the cyclobutane fragment. Analysis of literature data on rotation around the N—Ph and C—N bonds [5], inversion of nitrogen [6] and lactone—lactam tautomers [7], and comparison of these data with the results of our experiments allows the conclusion that none of these processes can possibly serve as a cause of the observed dynamic effect. It is possible that broadening of the signals in the ^{13}C NMR is connected with the existence of an equilibrium, rapid in the NMR time scale, between the isomers of identical structures Va and Vb, which is brought about through the opening of the tautomeric forms (Schiff bases) or through the corresponding zwitterion. The concentration of the open intermediate structures in solution is apparently extremely small, since they were not detected by IR spectroscopy.

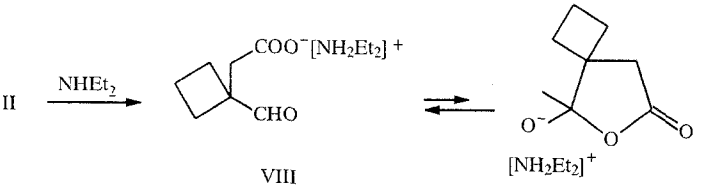
Thus, the reaction of aromatic amines with β-aldehydoacids containing different amounts of open tautomeric forms leads to amino-substituted lactones.



The reaction of lactone I with diethylamine proceeded easily, and the product was formed in quantitative yield. Intense, broad absorption bands in the 3300-2700 cm^{-1} region of the IR spectrum indicated the product to be a salt. At the same time, the presence of the lactone carbonyl group absorption at 1780 cm^{-1}, and also data from the ^{13}C and ^{1}H NMR spectra (according to the above criteria) indicated the product to have structure VII. In this structure all carbon nuclei of the cyclopropyl substituents and the three-membered spiro-ring are magnetically nonequivalent and should be registered as eight signals. However, the spectrum of compound VII shows only three signals for the cyclopropyl substituents and one for the spiro-fragment, since each of the signals had doubled intensities.

This fact compares well with the other spectral data in studying the temperature dependence of the spectra. It was shown that decreasing the temperature at which the spectrum was recorded to —60°C gives a gradual broadening of the signals (particularly the $C_{(4)}$ signal). Here the signal for the methylene groups of the cyclopropane substituents gradually combines to one broad signal. The character of the spectrum did not change upon measuring the concentration dependence or upon substitution of chloroform for methylene chloride. We relate the observed dynamic effect to the presence of rapid isomerization of VIIa ⇄ VIIb, analogous to that proposed for structures V and VI. Since the rupture of the tetrahydrofuran ring in the anionic compound VII is facilitated in comparison with the neutral molecules V and VI, the rate of isomerization is greater, and shows a time-average spectrum even at room temperature. The concentration of the intermediate open form of VII is also small in this case, although the signal of the carbonyl group in the IR spectrum is asymmetric and has an inflection at 1710 cm^{-1}.

Reaction of II with diethyl amine forms a salt which exists in solutions chiefly as the open form VIII. Even though the IR spectrum of VIII shows two absorption bands for the carbonyl group at 1720 and 1780 cm^{-1} (low intensity), the ^{1}H and ^{13}C NMR spectra do not contain clear confirmation of the existence of the cyclic product. A rapid tautomeric equilibrium, strongly displaced to the side of structure VIII, may possibly take place in this case



The change in direction of reaction probably is connected with the increase in basicity of the reagent. In contrast to aromatic amines, diethyl amine protonates under conditions of the reaction and this hinders further substitution of the hydroxyl group.

EXPERIMENTAL

The ^1H NMR spectra were recorded on Tesla BS-467 (60 MHz) and VXR-400 (400 MHz) instruments in $CDCl_3$, with chloroform as internal standard. The ^{13}C NMR spectra were obtained with FT-80A (20 MHz) and VXR-400 (400 MHz) instruments in $CDCl_3$. The IR spectra were recorded on a UR-20 spectrometer.

6-Hydroxy-7,7-dicyclopropyl-5-oxospiro[2.4]heptan-4-one (I) [4] and (1-formylcyclobutyl)acetic acid (II) [8] were synthesized by literature procedures from the corresponding dichlorocyclobutanones.

Reaction of Compounds I and II with Aromatic Amines (General Method). To a solution of 3 mmoles of compound I or compound II* in 25 ml of methylene chloride was added 3 mmoles of the corresponding aromatic amines and the mixture was kept for 10 h. The solvent was removed under vacuum, and the residue was recrystallized from a 1:1 mixture of hexane and chloroform.

Preparation of Compounds VII and VIII (General Method). To a solution of 3 mmoles of compounds I or II* in acetone† was added 3 mmoles of diethylamine and the mixture was kept for 10 h. The solvent was removed under vacuum, and the residue was recrystallized from a 1:1 mixture of hexane and carbon tetrachloride.

The yields and physicochemical characteristics of compounds III-VIII are presented in Table 1. The ^{13}C NMR and ^1H NMR spectral data for compounds III-VIII are given in Tables 2 and 3.

The elemental analyses data corresponded with the calculated values.

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*Compound II was introduced into the reaction without further purification.

†The use of methylene chloride gave the desired product contaminated by insoluble diethylamine hydrochloride.