Reaction of 4-Methylene-5(4*H*)-oxazolones With Diazomethane

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The reaction of diazomethane with some (*E*) and (*Z*)-2-substituted-4-methylene-5(4)-oxazolones (**1a-c**) under two different conditions, has been studied. (*E*) and (*Z*)-1,2-disubstituted-7-oxo-6-oxa-4-azaspiro[2.4]-hept-4-enes (**3a-c, 4a-c**) were mainly obtained, together with multiple addition compounds. The reaction showed to be stereoselective only when the substituents were aromatic. Acid hydrolysis of compounds **3a** and **4a** produced a mixture of (*E*) and (*Z*)-3,5-disubstituted-tetrahydrofuran-2-ones (**8a, 9a**). Smooth methanolysis of the ring led to (*E*) and (*Z*)-1-benzamido-cyclopropanecarboxylic esters (**10a-c, 11a-c**), which, on acid hydrolysis, gave (*E*) and (*Z*)-1-amino-2-phenylcyclopropanecarboxylic acids **12a** and **13a**. The pmr spectra have been analyzed by an iterative computer method, and the computed best values obtained have been used to deduce the stereochemistry of the spiroderivatives.

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We have reported (1-3) that addition of diazomethane to 4-arylidene-5(4*H*)thiazolones gave either cyclopropanation or multiple addition compounds involving enlargement of the thiazolone moiety, depending on the conditions under which the reaction is carried out and also on the substitution. This behavior had not been previously observed in analogous oxazolones, which were known (4-8) to give cyclopropane derivatives. However, Jones and Witty (9) did find recently a similar expansion reaction on 2-benzyloxy-4-benzylidene-5(4*H*)-oxazolone. It was therefore of interest to carefully examine the behavior of some other 2-substituted-4-methylene-5(4H)-oxazolones on treatment with diazomethane, considering also stereoisomeric changes which could lead to useful intermediates towards the synthesis of (*E*) and (*Z*)-cyclopropylogs of α-aminoacids (5-8).

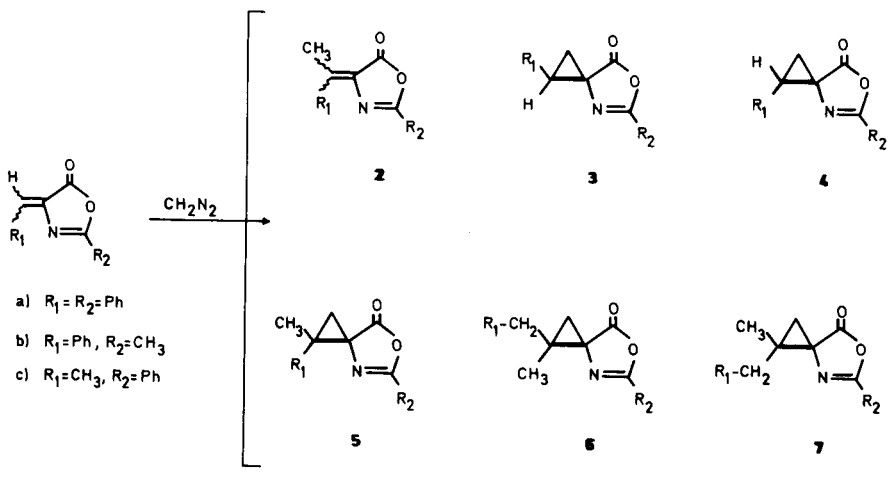
Results and Discussion.

The starting 4-methylene oxazolones (**1**) were prepared by known procedures (10,11) and, as we have described in the case of thiazolones (1-3), their reaction with diazomethane was allowed to proceed in each compound under two different conditions, as follows: A) Adding the appropriate oxazolone on a large excess of ethereal diazomethane at 0° and B) dropping a benzene solution of diazomethane into a benzene solution of the corresponding oxazolone at 45°. The results are summarized in Scheme I and Table I.

The isolated products were mainly the corresponding spiroderivatives **3** and **4**, the addition reaction being stereoselective when R_1 = Ph and R_2 = Ph or other aromatic substituents (1). In these cases, stereospecific homologation-cyclopropanation was also observed (compounds **6** and **7**). There was a lack of selectivity in the reaction with compounds **1b** and **1c**. In neither case were enlargement products of the oxazolone ring detected. There is an interesting contrast with thiazolones and also with the oxazolone studied by Jones (9). Again, substitution at C − 2 and C − 4 seems to be a leading factor which controls the course and stereochemistry of the reaction.

Smooth opening of the oxazolone moiety with methanol-sodium methoxide was accomplished in compounds **3** and

SCHEME I



4 for stereochemical studies (see below).

We then tried to obtain the biologically interesting 2-phenyl-1-aminocyclopropanecarboxylic acids **12a** and **13a**. Although early workers (5,6) have not apparently observed difficulties during hydrolysis of the oxazolone moiety in analogous compounds, other (7,8,12) have reported serious drawbacks in the removing of the benzoyl group. In our hands, the attempted hydrolysis under usual basic conditions in both **3a** and **4a** led only to the corresponding benzoyl aminoacids. When more vigorous procedures were tested (e.g. barium hydroxide in sealed tube at 120-130°), considerable destruction of the starting compound was observed, but by no means were amino acids **12a** and **13a** detected in the residual mixtures. Further attempts to liberate the amino group with sodium peroxide (13) failed. Acidic hydrolysis caused cleavage of the cyclopropane moiety, giving a mixture of 3-benzamido-5-phenyl-tetrahydrofuran-2-ones **8a** and **9a** (Scheme II). Prolonged heating in 6N HCl gave a mixture of the free lactones (8).

Stammer *et al* (7) have reported that hydrolysis of **4a** with 6 *N* hydrochloric acid gave not the aminoacid **12a**, but a small yield of styrylglycine. This could arise either by a competitive reaction in the step **4a** → **8a** + **9a** or

SCHEME II

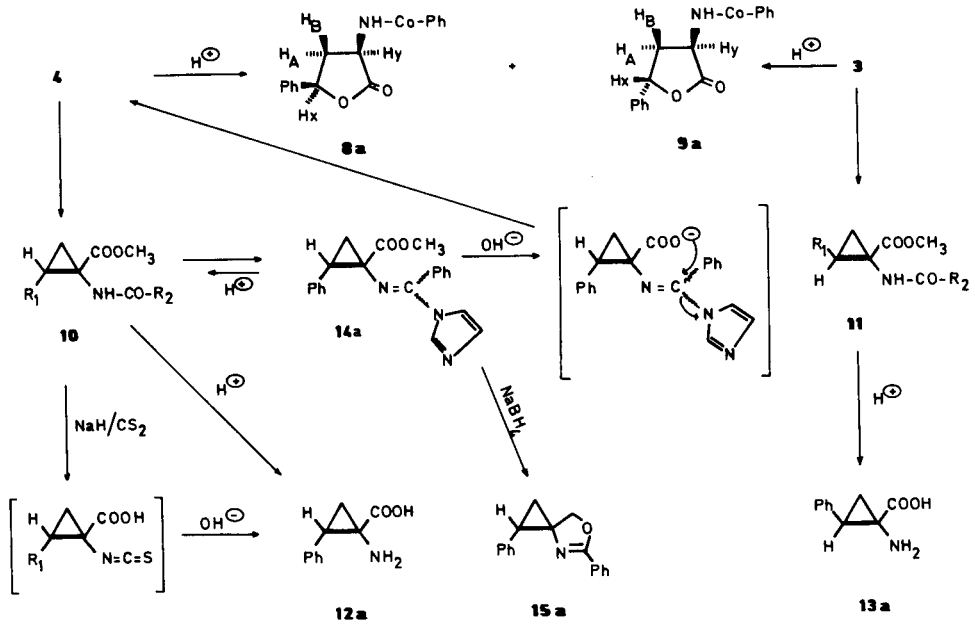


Table I

Compounds Obtained in the Reaction of Diazomethane With Substituted 5(4*H*)-Oxazolones (**1**)

Compound	(*E*)-**a**		Method (%) (a)		(*Z*)-**a**		Method (%) (a)		(*Z*)-**b**		Method (%) (a)		(*Z*)-**c**		Method (%) (a)	
	Rf(b)	mp (°C)	A	B	Rf(b)	mp (°C)	A	B	Rf(b)	mp (°C)	A	B	Rf(c)	mp (°C)	A	B
(*E*)-**2**	0.42	110-111 (d)	10	——												
(*Z*)-**2**	0.45	103-104 (e)	10	——	0.45	103-104	10	——	0.20	120-121	30	40				
3	0.22	111-112	50	55	0.22	111-112	15	15	0.09	92-93	20	20	0.50	49-50	30	30
4	0.35	141-142 (f)	15	15	0.35	141-142	50	60	0.14	67-68	20	20	0.56	59-60	30	30
5	0.25	98-99	——	8	0.25	98-99	——	8					0.65	56-57	30	30
6	0.38	84-85	——	15												
7					0.39	70-71	8	8								

(a) Yields are not optimized. (b) Benzene as eluent. (c) Benzene-ethyl acetate (17:3) as eluent. (d) Lit (16) mp 110°. (e) Lit (16) mp 104.1°. (f) Lit (4) mp 142-143°.

Table II

Spectral Parameters of Compounds **3**, **4**, **10**, **11**.

Compound	R_1	R_2	Stereo-isomer	ν (δ)	J (Hz)	Other significant parameters	Compound	ν (δ)	J (Hz)	Other significant parameters	$\Delta \delta_{ox}$-δ_{ext}
3a	Ph	Ph	*E*	ν_1 = 2.38	J_{12} = -5.5		**11a**	ν_1 = 1.71	J_{12} = -5.6	3.34 (s, 3H,	0.67
				ν_2 = 2.36	J_{13} = 9.6			ν_2 = 2.31	J_{13} = 9.6	CH_3O)	0.05
				ν_3 = 3.52	J_{23} = 9.2			ν_3 = 2.96	J_{23} = 8.6		0.56
4a	Ph	Ph	*Z*	ν_1 = 2.33	J_{12} = -5.3		**10a**	ν_1 = 1.86	J_{12} = -6.0	3.70 (s, 3H,	0.47
				ν_2 = 2.24	J_{13} = 8.7			ν_2 = 2.29	J_{13} = 8.0	CH_3O)	-0.05
				ν_3 = 3.20	J_{23} = 9.7			ν_3 = 3.05	J_{23} = 9.5		0.15
3b	Ph	CH_3	*E*	ν_1 = 2.26	J_{12} = -5.5	2.21 (s, 3H,	**11b**	ν_1 = 1.61	J_{12} = -5.5	2.04 (s, 3H,	0.65
				ν_2 = 2.22	J_{13} = 9.6	CH_3)		ν_2 = 2.25	J_{13} = 9.7	CH_3O), 3.31	-0.03
				ν_3 = 3.40	J_{23} = 9.2			ν_3 = 2.83	J_{23} = 8.4	(s, 3H, CH_3O)	0.57
4b	Ph	CH_3	*Z*	ν_1 = 2.22	J_{12} = -5.2	2.18 (s, 3H,	**10b**	ν_1 = 1.74	J_{12} = -6.2	1.83 (s, 3H,	0.48
				ν_2 = 2.10	J_{13} = 7.8	CH_3)		ν_2 = 2.22	J_{13} = 8.2	CH_3), 3.74	-0.12
				ν_3 = 3.09	J_{23} = 9.6			ν_3 = 2.95	J_{23} = 9.3	(s, 3H, CH_3O)	0.14
3c	CH_3	Ph	*E*	ν_1 = 2.04	J_{12} = -4.7	1.40 (d, 3H,	**11c**	ν_1 = 1.36	J_{12} = -5.6	1.26 (d, 3H,	0.68
				ν_2 = 1.58	J_{13} = 9.1	CH_3, J = 6.2)		ν_2 = 1.58	J_{13} = 9.5	CH_3, J = 6.3)	0.00
				ν_3 = 2.26	J_{23} = 8.6			ν_3 = 1.64	J_{23} = 7.6	3.67 (s, 3H,	0.62
										CH_3O)	
4c (a)	CH_3	Ph	*Z*			1.41 (d, 3H,	**10c**	ν_1 = 0.94	J_{12} = -5.0	1.20 (d, 3H,	
						CH_3, J = 6.2)		ν_2 = 1.73	J_{13} = 7.6	CH_3, J = 6.3)	
				ν_3 = *ca.* 2.0				ν_3 = 1.90	J_{23} = 9.4	3.68 (s, 3H,	*ca* 0.10
										CH_3O)	

(a) This compound could not be analyzed.

through cleavage of these lactones, followed by dehydration. In any case, we have not been able to detect any styrylglycine.

On the basis of a reported reaction of amides (14), compound **10a** was treated with *N,N'*-thionyldiimidazole to give compound **14a**, in which the reduction of the C=N bond was attempted, with the intention of removing the blocking group by subsequent hydrolysis. Instead, cyclization-reduction took place on the carbonyl group, furnishing the spirooxazole **15a**. Since basic hydrolysis of **14a** gave the spirooxazolone **4a**, probably by the mechanism outlined in the Scheme II, compound **15a** could be produced through a similar pathway. Treatment of **10a** with $NaH-CS_2$ (15) led to the isothiocycanate (N=C=S, 2100 cm^{-1}), which was hydrolyzed *in situ* to the aminoacid **12a**, although in low yield. Similar treatment on **11a** was unfruitful.

However, when both **10a** and **11a** were refluxed with hydrochloric acid-acetic acid, the corresponding aminoacids **12a** and **13a** were obtained in 60% and 85% yield, respectively. Hydrolysis of **10a** also produced compounds **8a** and **9a**, and required much more refluxing time, probably for steric reasons.

Stereochemical Aspects.

The spirooxazolone **4a** was described by Awak *et al.* (4), without comments on its stereochemistry. Similar reactions to that used by Awad have been reported (5-7) but, on the basis of present knowledge, all the additions have been carried out on (*Z*)-oxazolones, and only one stereoisomer out of the two theoretically possible spirocyclopropanes have been described. Burger (6) obtained both stereoisomers of 1-(4-methoxyphenyl)-5-phenyl-7-oxo-6-oxa-4-azaspiro[2.4]hept-4-ene (**3** and **4**: R_1 = *p*-methoxyphenyl, R_2 = phenyl), but the (*E*)-isomer was prepared through an independent pathway.

Since we have isolated both stereoisomers out of each reaction, we have studied the pmr spectra of all the stereoisomers, a pair of which (**3a** and **4a**) was submitted to X-ray crystal analysis (17). Spectral parameters are

given in Table II. Geminal protons of the cyclopropane ring appear as the AB part of an ABX system and show very little chemical shift difference. We have deduced (1) that protons with *syn* configuration with respect to the N=C group appear downfield to protons with *anti* configuration when R_1 is an aromatic substituent. Cleavage of the oxazolone moiety by methanolysis (compounds **10** and **11**) induces an upfield shifting (by 0.5-0.7 ppm) of protons *syn* to the N=C group, and the situation is reversed. In addition, when R_1 is an aromatic substituent the methyl group of methyl esters shows upfield when *syn* to the substituent. Compound **4c** could not be analyzed, but the corresponding ester **10c** gave parameters in accordance with its predicted configuration, opposite to that of **11c**. We have also tentatively assigned tetrasubstituted spirocyclopropanes (1) (compounds **5-7**) by comparison with analogous derivatives found in the literature (18).

Concerning tetrahydrofuranones, the configurations have been tentatively made mainly on the basis of the three large coupling constants exhibited by H_A in compound **8a** and also in the low value of J_{BX} in compound **9a**.

EXPERIMENTAL

Melting points were determined on a Kofler Thermopan Reichert apparatus and are uncorrected. The infrared spectra were preformed on a Perkin Elmer 137 E spectrometer in potassium bromide pellets. Date are reported in cm^{-1}. Routine pmr and cmr spectra were recorded for solutions in deuteriochloroform on a Perkin Elmer R-12 60 MHz and a Varian XL-100 spectrometer provided with a Nicolet 1180 data system. Chemical shifts are expressed in δ values from TMS as internal standard and coupling constants are reported in Hz. Silica Gel GF_{254} (E. Merck) was used for both tlc and plc experiments.

4-Methylene-5(4H)-oxazolones (**1**).

The starting compounds (*Z*)-**1a-c** were prepared from the corresponding aldehydes and hippuric acid or acetyl-glycine, by previously reported methods (10,11). (*Z*)-2-Phenyl-4-benzylidene-5(4*H*)-oxazolone (**1a**) was converted into the (*E*)-stereoisomer by the hydrobromic acid-benzene procedure (11).

Reaction of Diazomethane With Compounds **1**. General Procedures.

Method A.

Twenty mmoles of the appropriate oxazolone were added portionwise on ice-cooled ethereal diazomethane (100 ml, *ca.* 70 mmoles). The mixture was kept in the cool for 10 hours, treated with a few drops of acetic acid and filtered. The solvent was removed *in vacuo*. Compounds **3** or **4** usually crystallized at this stage. The solid was collected by filtration and recrystallized. The mother liquors were evaporated *in vacuo* and submitted to plc (*ca.* 100 mg /20 × 20 × 0.15 cm plates, with benzene or benzene-ethyl acetate 17:3, as shown in Table I). Fractions were rechromatographed when necessary.

Method B.

A benzene solution of diazomethane (100 ml, *ca.* 50 mmoles) was dropped into a solution of the proper oxazolone (**1**) (20 mmoles) in benzene (50 ml) at 45°. Rapid evolution of nitrogen took place. The solution was then allowed to stand at room temperature for 10-12 hours. A few drops of acetic acid were added and the solvent was evaporated *in vacuo* to a yellow syrup. A little ether was added, from which compounds **3** and **4** usually crystallized on cooling. The solid was filtered and purified. The solution was worked up as above.

The following compounds were obtained by either methods A and/or B (see Table I and Scheme I). In each case, substitution is given in parenthesis.

(*E*)-2-Phenyl-4-(1-methylbenzylidene)-5(4*H*)-oxazolone (*E*-**2a**).

This compound was obtained as tiny pale yellow needles (from ethanol); ir: 1800 + 1785 (C=O); pmr: 2.66 (s, 3H, CH_3), 7.48 (s, 5H, Ph), *ca.* 7.6 (m, 3H, arom), *ca.* 8.1 (m, 2H, arom).

Anal. Calcd. for $C_{17}H_{13}NO_2$: C, 77.54; H, 4.97; N, 5.32. Found: C, 77.65; H, 5.15; N, 5.30.

(*Z*)-2-Substituted-4-(1-methylbenzylidene)-5(4*H*)-oxazolones (**2**).

Compound (*Z*)-**2a** (2-phenyl).

This compound was obtained as yellowish needles (from ethanol); ir: 1780 + 1760 (C=O); pmr: 2.78 (s, 3H, CH_3), **ca.** 7.5 (m, 6H, arom), *ca.* 8.0 (m, 4H, arom).

Anal. Calcd. for $C_{17}H_{13}NO_2$: C, 77.54; H, 4.97; N, 5.32. Found: C, 77.73; H, 5.13; N, 5.20.

Compound (*Z*)-**2b** (2-methyl).

This compound was obtained as white crystals (from ethyl acetate); ir: 1790 + 1760 (C=O); pmr: 2.26 (s, 3H, $CH_3-C=N$), 2.70 (s, 3H, CH_3), *ca.* 7.5 (m, 3H, arom), *ca.* 7.8 (m, 2H, arom).

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.83; H, 5.34; N, 6.92.

(*E*)-(1,5-Disubstituted)-7-oxo-6-oxa-4-azaspiro[2.4]hept-4-enes (**3**).

Compound **3a** (1,5-diphenyl).

This compound was obtained as white crystals (ethyl acetate; ir: 1800 (C=O); pmr: (see Table II).

Anal. Calcd. for $C_{17}H_{13}NO_2$: C, 77.54; H, 4.97; N, 5.32. Found: C, 77.38; H, 4.94; N, 5.27.

Compound **3b** (1-phenyl-5-methyl).

This compound was obtained as a white solid (ethyl acetate containing a few drops of anhydrous acetate to avoid cleavage); ir: 1795 (C=O); pmr: (see Table II).

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.42; H, 5.49; N, 7.05.

Compound **3c** (5-phenyl-1-methyl).

This compound was obtained as flocculent white needles (ethanol); ir: 1795 (C=O); pmr: The spectrum could not be thoroughly analyzed (see Table II).

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.36; H, 5.55; N, 6.78.

(*Z*)-(1,5-Disubstituted)-7-oxo-6-oxa-4-azaspiro[2.4]hept-4-enes (**4**).

Compound **4a** (1,5-diphenyl).

This compound was obtained as white needles (ethyl acetate-ethanol); ir: 1800 (C=O); pmr: (see Table II).

Anal. Calcd. for $C_{17}H_{13}NO_2$: C, 77.54; H, 4.97; N, 5.32. Found: C, 77.71; H, 5.12; N, 5.26.

Compound **4b** (1-phenyl-5-methyl).

This compound was obtained as small white crystals (ethyl acetate containing a few drops of anhydrous acetate to avoid ring cleavage); ir: 1795 (C=O); pmr: (see Table II).

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.40; H, 5.63; N, 7.09.

Compound **4c** (5-phenyl-1-methyl).

This compound was obtained as small white crystals (ethanol); ir: 1810 (C=O); pmr: (see Table II).

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.62; H, 5.73; N, 7.02.

(*Z*)-1-Methyl-1,5-diphenyl-7-oxo-6-oxa-4-azaspiro[2.4]hept-4-ene (**5a**).

This compound was obtained as flocculent white needles (from ethanol); ir: 1810 (C=O); pmr: 1.78 (s, 3H, CH_3), 2.15 (d, 1H, gem, J = 4.7), 2.35 (d, 1H, gem), 7.32 (s, 5H, Ph), *ca.* 7.5 (m, 3H, arom), *ca.* 8.1 (m, 2H, arom).

Anal. Calcd. for $C_{18}H_{15}NO_2$: C, 77.95; H, 5.45; N, 5.05. Found: C, 77.71; H, 5.63; N, 5.13.

1,1-Dimethyl-5-phenyl-7-oxo-6-oxa-4-azapiro[2.4]hept-4-ene (**5c**).

This compound was obtained as flocculent white microneedles (from ethanol-water); ir: 1790 (C=O); pmr: 1.46 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.75 (d, 1H, gem, J = 4.8), 1.86 (d, 1H, gem), *ca.* 7.5 (m, 3H, arom), *ca.* 8.0 (m, 2H, arom).

Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.53; H, 6.08; N, 6.50. Found: C, 72.69; H, 6.03; N, 6.28.

1-Methyl-1-benzyl-5-phenyl-7-oxo-6-oxa-4-azaspiro[2.4]hept-4-enes (**6a**, **7a**).

Compound **6a**.

This compound was obtained as a white solid (from 2-propanol); ir: 1790 (C=O); pmr: 1.38 (s, 3H, CH_3), 1.91 (d, 1H, gem, J = 4.5), 1.99 (d, 1H, gem), 3.01 (d, C*H*H − Ph, J = 14), 3.23 (d, CH*H* − Ph), *ca.* 7.2 (m, 5H, CH_2 − Ph), *ca.* 7.4 (m, 3H, arom), *ca.* 8.0 (m, 2H, arom).

Anal. Calcd. for $C_{19}H_{17}NO_2$: C, 78.32; H, 5.88; N, 4.80. Found: C, 77.87; H, 6.07; N, 4.64.

Compound **7a**.

This compound was obtained as white crystals (from ethanol); ir: 1790 (C=O); pmr: 1.35 (s, 3H, CH_3), 1.81 (d, 1H, gem, J = 5.5), 2.12 (d, 1H, gem), 3.14, (s, 2H, CH_2 − Ph), 7.26 (s, 5H, Ph), *ca.* 7.5 (m, 3H, arom), *ca.* 8.15 (m, 2H, arom).

Anal. Calcd. for $C_{19}H_{17}NO_2$: C, 78.32; H, 5.88; N, 4.80. Found: C, 78.06; H, 5.88; N, 4.54.

Methyl 1-Acylamino-2-substituted-cyclopropanecarboxylates (**10**, **11**).

General Procedure.

One tenth to one g of the corresponding spiro derivative was dissolved in absolute methanol containing sodium methoxide (*ca.* 10 mg), heating when necessary. Cooling of the clear solution furnished the title compounds. The following cyclopropanecarboxylates were obtained (2-substitution and acyl group are given in each case).

Compound **10a** (1-benzamido-2-phenyl).

This compound was obtained as flocculent white microneedles, mp = 164-165° (from methanol); ir: 3295 (NH), 1725 (C=O), 1660 (amide); pmr: (see Table II).

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.02; H, 5.62; N, 4.58.

Compound **11a** (1-benzamido-2-phenyl).

This compound was obtained as flocculent white needles, mp = 195-196° (from methanol); ir: 3320 (NH), 1740 (C=O), 1640 (amide); pmr: (see Table II).

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.45; H, 5.73; N, 4.58.

Compound **10b** (1-acetamido-2-phenyl).

This compound was obtained as white crystals, mp = 132-133° (from methanol; ir: 3320 (NH), 1730 (C=O), 1655 (amide); pmr: (see Table II).

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.95; H, 6.44; N, 6.01. Found: C, 67.05; H, 6.65; N, 6.12.

Compound **11b** (1-acetamido-2-phenyl).

This compound was obtained as white crystals (from methanol); ir: 3280 (NH), 1735 (C=O), 1670 (amide); pmr: (see Table II).

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.95; H, 6.44; N, 6.01. Found: C, 66.70; H, 6.53; N, 5.98.

Compound **10c** (1-benzamido-2-methyl).

This compound was obtained as white crystals, mp 158-159° (from methanol); ir: 3300 (NH), 1728 (C=O), 1648 (amide); pmr: (see Table II).

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.00. Found: C, 66.90; H, 6.61; N, 6.15.

Compound **11c** (1-benzamido-2-methyl).

This compound was obtained as white crystals, mp = 154-155° (from methanol); ir: 3290 (NH), 1735 + 1720 (C=O), 1645 (amide), pmr: (see Table II).

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.00. Found: C, 67.04; H, 6.61; N, 6.13.

Alkaline Hydrolysis of Compounds **3a**, **4a** and Derivatives. General Procedures.

A) The corresponding spirooxazolone (0.03 mole) was refluxed with ethanol sodium hydroxide (4) to give, respectively (*E*) and (*Z*)-1-benzamido-2-phenylcyclopropanecarboxylic acids. The (*E*)-isomer had mp 188-189°. The (*Z*)-isomer had mp 242° (lit mp (4) 242°).

B) The corresponding cyclopropanecarboxylic acids (0.02 mole) obtained as above were refluxed with 2*N* aqueous sodium hydroxide for 5 days. Acidification of the cold solution furnished the starting compounds. No amino acids were detected in the mother liquors.

C) The corresponding acids (0.02 mole) obtained in A), were treated with a 2*N* aqueous solution of barium hydroxide in a sealed tube at 120-130° for 2 hours. A brown intractable powder deposited from the reaction. Acidification of the clear filtered solution gave a mixture of benzoic acid and starting material. No signs of the amino acid appeared in the mother liquors.

Attempted Reaction of Compounds **10a** and **11a** With Sodium Peroxide (13).

One g (3.4 mmoles) of compound **10a** was suspended in 10 ml of water-methanol (8:2) at 80-90° and 0.53 g (6.8 mmoles) of sodium peroxide was added portionwise. The mixture was stirred for 6 hours. The solution was then cooled at 0°. On acidification (hydrochloric acid), (*Z*)-1-benzamido-2-phenylcyclopropanecarboxylic acid was obtained in 90% yield. Again, no amino acid was detected in the aqueous solution.

The (*E*)-isomer (**11a**), on similar treatment, behaved in an analogous manner.

Acidic Hydrolysis of Compounds **3a** and **4a**. General Method.

Four mmoles of the corresponding spiro derivative was stirred at room temperature for 1.5 hours with a mixture of acetic acid (15 ml) and 12*N* hydrochloric acid (15 ml). The solution was diluted with water and extracted with benzene (3 x 20 ml). The benzene solution was washed with aqueous sodium hydroxide and water, dried with sodium sulfate and evaporated *in vacuo* to give 0.4 g (40%) of a white solid which was chromatographed on plc (*ca.* 100 mg/20 × 20 × 0.15 cm plates and chloroform as eluent × 6 developments). The following compounds were isolated.

Hydrolysis of **3a**.

Fraction 1 consisted of 0.27 g (25%) of (*Z*)-3-benzamido-5-phenyltetrahydrofuran-2-one (**8a**), Rf = 0.18, tiny white needles, mp = 176-177° (from ethanol); ir: 3380 (NH), 1760 (C=O), 1660 (amide); pmr: (see Scheme II) 2.29 (m, H_A, J_{AB} = -12.5, J_{AX} = 11.2, J_{AY} = 12.2), 3.23 (m, H_B, J_{BX} = 5.3, J_{BY} = 8.1), 5.02 (m, H_Y, $J_{Y\text{-}NH}$ = 6.26), 5.46 (m, H_X), 7.08 (d, broad, 1H, NH), *ca.* 7.3 (m, 8H, arom), *ca.* 7.7 (m, 2H, arom).

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.97. Found: C, 72.85; H, 5.46; N, 4.99.

Fraction 2 consisted of 0.16 g (15%) of (*E*)-3-benzamido-5-phenyltetrahydrofuran-2-one (**9a**), Rf = 0.22, white needles, mp = 171-172° (from ethanol); ir: 3340 (NH), 1780 (C=O), 1645 (amide); pmr: (see Scheme II) 2.74 (m, H_A, J_{AB} = −12.9, J_{AX} = 8.7, J_{AY} = 10.2), 2.95 (m, H_B, J_{BX} = 2.5, J_{BY} = 9.1), 4.74 (m, H_Y, $J_{Y\text{-}NH}$ = 6.0), 5.8 (m, H_X, $J_{X\text{-}NH}$ = −0.3), 6.95 (d, broad, 1H, NH), *ca.* 7.4 (m, 8H, arom), *ca.* 7.7 (m, 2H, arom).

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.97. Found: C, 72.72; H, 5.60; N, 5.12.

Hydrolysis of **4a** under the same conditions gave identical compounds, **8a** and **9a**, in similar yields.

Reaction of **10a** With Sodium Hydride and Carbon Disulfide [Based on Shahak (15)].

Two g (6.8 mmoles) of **10a** were refluxed for 6 hours in 40 ml of dry benzene with 0.34 g (6.8 mmoles) of sodium hydride (50% in paraffin) under anhydrous conditions. The resulting suspension was stirred at 0° and 0.8 g (10.5 mmoles) of carbon disulfide was added dropwise. The mixture was stirred for 15 hours, filtered and the solvent removed *in vacuo*. The residual red solid (containing isothiocyanate, ir: 2100 cm^{-1}) was stirred for 3 days with 20 ml of 10% aqueous potassium hydroxide. The solution was acidified with 12*N* hydrochloric acid, the solid filtered off and the clear solution treated with active charcoal. The solvent was removed *in vacuo* to give a white solid which was extracted twice with 20 ml of boiling absolute ethanol. The ethanol was removed *in vacuo* and the residual hydrochloride of **12a** was recrystallized from absolute ethanol-ether to give 150 mg (11%) of (*Z*)-1-amino-2-phenylcyclopropanecarboxylic acid hydrochloride, mp = 208-209°, lit (3a) = 207-208°; ir: 3200-2500 (COOH + NH_3^+), 1730 (C=O); pmr (deuteriodimethylsulfoxide, TMS): 1.85 (m, H_A, J_{AB} = -6.0, J_{AX} = 10.2), 1.95 (m, H_B, J_{BX} = 8.1), 2.96 (m, H_X), *ca.* 7.4 (m, 5H, arom).

Anal. Calcd. for $C_{10}H_{12}ClNO_2$: C, 56.22; H, 5.66; N, 6.55; Cl, 16.59. Found: C, 55.96; H, 5.95; N, 6.42; Cl, 16.90.

Attempted Reaction of **11a** With Sodium Hydride-carbon Disulfide.

One g (3.4 mmoles) of compound **11a** was treated as above. However, the corresponding amino acid **13a** was not detected in the final mixture. The solid obtained after acidification showed identical properties as (*E*)-1-benzamido-2-phenylcyclopropanecarboxylic acid. Additional attempts under different conditions and solvents (dioxane, dimethylacetamide, etc) failed.

Methyl (*Z*)-1-[1-(*N*-Imidazolyl)benzylideneamino]-2-phenylcyclopropanecarboxylate (**14a**) (Based on (14)).

One g (3.4 mmoles) of compound **10a** in 15 ml of dichloromethane was added on 3.4 mmoles freshly prepared *N,N'*-thionyldiimidazole (19) in dry tetrahydrofuran. The mixture was stirred at 35° for 4 hours and then at room temperature overnight. After filtration, the solvent was removed *in vacuo* to give a syrup which was chromatographed on silica gel (eluent: benzene-ethyl acetate 17:3). 0.59 g (52%) of compound **14a** was obtained as a syrup; ir: 1725 (C=O); pmr: 1.36 (m, $1H_A$, gem., J_{AB} = -5.4, J_{AX} = 7.1), 1.94 (m, $1H_B$, J_{BX} = 10.3), 3.62 (s, 3H, CH_3O), *ca.* 7.4 (m, 13H, arom + imidazole); cmr: 22.88 (CH_2 cyclopropane), 34.62 (CH cyclopropane), 48.02 (C cyclopropane), 51.95 (CH_3O), 117.23-136.75 (C arom + imidazole), 156.75 (C=N), 171.07 (C=O).

Hydrolysis of Compound **14a**.

Treatment of **14a** with 10% aqueous potassium hydroxide for 20 hours gave, upon acidification, (*Z*)-1,5-diphenyl-7-oxo-6-oxa-4-azaspiro[2.4]-hept-4-ene (**4a**). Compound **14a** (0.26 g, 0.75 mmoles) in 10 ml of dioxane was stirred with 4 ml of 6*N* hydrochloric acid for 30 minutes. The white solid deposited (150 mg) was filtered and recrystallized from ethanol. It showed identical properties that **10a**.

Reduction of Compound **14a** With Sodium Borohydride.

To a stirred of 0.5 g (1.4 mmoles) of compound **14a** in 7 ml of absolute ethanol at 50°, 0.26 g (7.0 mmoles) of sodium borohydride was added portionwise. The mixture was left overnight. A white solid crystallized, which was filtered and extracted with chloroform. The solvent was removed *in vacuo* to give (*Z*)-1,5-diphenyl-6-oxa-4-azaspiro[2.4]hept-4-ene (**15a**) as a white solid, mp = 119-120° (from ethyl acetate); ir: no significant signal at 1650-1800 region; pmr: 1.38 (m, $1H_A$, J_{AM} = -5.9, J_{AX} = 9.5), 1.70 (m, $1H_M$, J_{MX} = 7.2), 2.19 (m, $1H_X$), 4.45 (s, 2H, CH_2), *ca.* 7.3 (m, 3H, arom), *ca.* 7.8 (m, 2H, arom); cmr: 21.18 (CH_2 cyclopropane), 31.28 (CH cyclopropane, 55.90 (C cyclopropane), 74.03 (CH_2), 125.65-130.81 (C arom), 164.54 (C=N).

Anal. Calcd. for $C_{17}H_{15}NO$: C, 81.92; H, 6.38; N, 5.54. Found: C, 81.89; H, 6.06; N, 5.61.

1-Amino-2-phenylcyclopropanecarboxylic Acids (**12a**, **13a**). General Procedure.

One g (3.4 mmoles) of the corresponding isomer (compound **10a** and **11a**) dissolved in 25 ml of acetic acid and 25 ml of 12*N* hydrochloric acid was refluxed for 3-8 hours. The solvent was then removed *in vacuo* and the solid was extracted several times with boiling benzene to remove benzoic acid. The residual white solid was recrystallized from absolute ethanol. The following aminoacid hydrochlorides were obtained:

Hydrochloride of **12a**.

The reaction took 8 hours to complete, yield, 60%. The product appeared mixed with compounds produced by the opening of the cyclopropane ring. Several recrystallizations gave the pure compound, mp = 208-209° (See above).

Hydrochloride of **13a**.

The reaction was accomplished in 3 hours, yield 85%, white needles, mp = 218-220 dec; ir: 3500-2500 (COOH + NH_3^+), 1730 (C=O); pmr (deuteriodimethylsufoxide): 1.94 (m, H_A, J_{AB} = -6.2, J_{AX} = 10.4), 1.99 (m, H_B, J_{BX} = 8.4), 3.08 (m, H_X), 7.33 (s, 5H, arom).

Anal. Calcd. for $C_{10}H_{12}ClNO_2$: C, 56.22; H, 5.66; N, 6.55; Cl, 16.59. Found: C, 55.88; H, 5.81; N, 6.58: Cl, 16.81.

PMR Spectral Data.

The spectra of compounds **3, 4, 8a, 9a, 10, 11** were recorded for solutions in deuteriochloroform with TMS as internal standard on a Varian XL-100 spectrometer in the frequency-sweep mode. Spectral widths of 1000 and 250 Hz were used for measurements. Analyses of the systems were performed by a Nicolet 1180 data system using an ITRCAL program. The experimental and calculated spectra from the resulting best values matched satisfactorily.

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Addendum.

After this paper was sent for publication, a different synthesis of *E* and *Z*-1-amino-2-phenylcyclopropanecarboxylic acids, starting with products **3a** and **4a**, has been described (S. W. King, J. M. Riordan, E. M. Holt and C. H. Stammer *J. Org. Chem.*, **47**, 3270 (1982). Their crystallographic studies gave the same conclusions as previous determinations (17) and the spectral data of the *E* and *Z* isomers are in accordance with our own findings (see also I. Arenal, M. Bernabé, E. Fernández Alvarez and R. Hernández Perretta, *An. Quim.*, **77C**, 93 (1981).