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SYNTHESIS OF *E* AND *Z* 1-AMINO-2-ARYL(ALKYL)-CYCLOPROPANECARBOXYLIC ACIDS *via* MELDRUM DERIVATIVES

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Abstract—The reaction of 5-arylidene(alkylidene)-2,2-dimethyl-1,3-dioxane-4,6-diones (**1**) (Meldrum's acid derivatives) with dimethylsulfoxonium methylide gave 1-aryl(alkyl) - 6,6 - dimethyl - 4,8 - dioxo - 5,7 - dioxaspiro [2.5] octanes (**2**) which, on treatment with sodium methoxide or ammonium hydroxide, gave exclusively *E*-1-methoxy-carboyl-2-aryl-cyclopropanecarboxylic acids (**4**) or *Z*-1-carbamoyl-2-aryl(alkyl)-cyclopropanecarboxylic acids (**7**), respectively. Compounds, **4**, under conditions of Curtius-type reactions, yielded *Z*-methyl 1-isocyanate-2-aryl-cyclopropanecarboxylates (**5**), while derivatives **7** were treated with hypobromite, leading to *E*-1-methoxy-carbonylamino-2-aryl(alkyl)-cyclopropanecarboxylic acids (**8**).

Reaction of compounds **5** and **8** with hydrochloric acid produced the corresponding *Z* and *E* 1-amino-2-aryl(alkyl)-cyclopropanecarboxylic acids hydrochlorides (**6**). The ^{1}H-NMR spectral data were analyzed to deduce the stereochemistry of the compounds obtained.

During the last years, increased attention has been paid to the synthesis and study of 1-aminocyclopropane-carboxylic acids.[1-11] Some ten of these aminoacids containing a cyclopropane ring have been isolated from several microorganisms and higher plants,[1c,12,13] 1-aminocyclopropanecarboxylic acid itself being an intermediate in the biosynthesis of ethylene, a phytohormone that initiates fruit ripening and regulates many aspects of plant growth and development.[13] Also *E*-1-amino-2-ethylcyclopropane-carboxylic acid (coronamic acid) is a main constituent of coronatine, a toxin produced by *Ps. coronofaciens.*[1c] However, the biological role of most of these compounds is still unknown.

We have reported the synthesis of *Z*-1-amino-2-arylcyclopropanecarboxylic acids and some of their capabilities as enzyme inhibitors.[3,14,15] A more general method to prepare both *E* and *Z* compounds for further studies was still needed. Here we report a general and inexpensive synthetic procedure for both series of stereoisomers.

RESULTS AND DISCUSSION

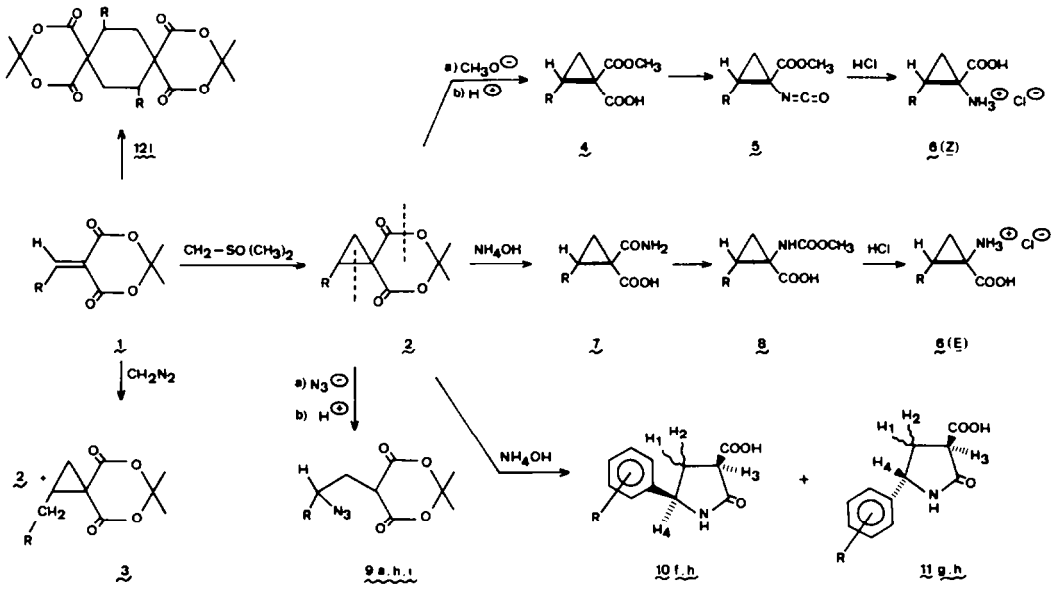
Methylene derivatives **1** were prepared according to Polansky *et al.*[16] The reaction of some compounds **1** with diazomethane has been reported to depend upon the temperature. Thus, spiroderivatives **2** were obtained at −70°, while at room temperature homologs **3** were the main product. In our hands the reaction always yielded mixtures of spiroderivatives **2** and **3**, the ratio varying not only with the temperature, but also with the solvent and especially with the nature of the substituents bonded to the phenyl group. Thus, compounds **1** bearing electron-donor substituents gave little or none of the corresponding spiroderivatives **2**, even at −70°, while electron-acceptor substituents led to better yields of derivatives **2** (Tables 1 and 2).

In order to avoid these inconveniences we allowed methylene derivatives **1** to react with dimethyl sulfoxonium methylide as described previously for related methylene compounds,[18] adding the proper derivative **1** onto a solution of the ylide in DMF, but we obtained only small amounts of spiroderivatives **2**. However, when the ylide was added onto a stirred solution of the corresponding derivative **1** in dry DMF, the reaction proceeded smoothly, giving good yields of spirocompounds **2**. Care must be taken in order to avoid adding excess of the reagent, since in those cases considerable lowering of the yields were observed. Compounds **2h, j, k**, which could not be obtained with CH_2N_2, were prepared in this way. Compound **1l** did not give **2l**, but dimer **12** (Experimental).

Compounds **2** on treatment with $NaCH_3O$ gave monoesters **4** (Table 3), while reaction with NaN_3 yielded azidoderivatives **9**. On the other hand, hydrolysis of compounds **2** with NH_4OH led in most of the cases to carbamoyl-cyclopropanecarboxylic acids (**7**). However, compound **2h** did not give the expected **7h**, but a mixture of derivatives **10h** and **11h** instead. Similarly, **2f** and **2g** gave a mixture of **7f**, **11f** and **7g**, **10g**, **11g**, respectively.

A possible qualitative explanation of this behavior can be laid in terms of Klopman[19] and Pearson[20] theories on chemical reactivity. As the reaction with hard nucleophiles, such as CH_3O^- or OH^-, is charge-controlled, it should take place on the hard electrophilic carbonylic carbon, leading exclusively to monoesters **4** or diacids, respectively, through C—O cleavage, while attack by softer nucleophiles, such as N_3^- is frontier-controlled, and it should occur at the soft cyclopropane C-1, giving compounds **9**, by C—C cleavage. The behavior of NH_3 depends on the substitution in the aromatic ring. Thus, with compounds **2** bearing electron-acceptor or neutral substituents, it behaves like a hard nucleophile, yielding amides **7**, while with compounds **2h**, possessing an electron-donor substituent, it seems reasonable to think that the strong electrophilic character of the C=O center decreases to a situation in which the reaction is frontier-controlled, yielding compounds **10h** and **11h**. With compounds **2f** and **2g** there is an in between situation, hence products arising from both C—O and C—C cleavages are obtained.

A Curtius-type treatment[21] on compounds **4** yielded isocyanates **5** (Table 3) which were hydrolyzed to



R	R	R
a) C_6H_5	e) 4-FC_6H_4	i) 4-NO_2—C_6H_4
b) 2-ClC_6H_4	f) 2-CH_3—C_6H_4	j) $(CH_3)_2CH$—
c) 3-ClC_6H_4	g) 4-CH_3—C_6H_4	k) 3-(N-acetyl-indolyl)
d) 4-ClC_6H_4	h) 4-CH_3O—C_6H_4	l) 3-(N-methyl-indolyl)

Scheme 1.

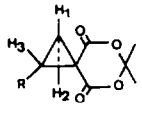
the corresponding *Z*-1-amino-2-aryl-cyclopropanecarboxylic acids **6**-*Z*.

Attempts to convert carbamoyl derivatives **7** into the respective methoxycarbonylamino compounds **8** with lead tetraacetate as oxidizing agent were unsuccessful. Oxidation with hypobromite gave erratic yields of **8**, but finally we obtained good results using a non-aqueous modification of the procedure.[22] Hydrolysis of carbamates **8** lead to the respective *E*-1-amino-2-aryl(alkyl)-cyclopropanecarboxylic acids **6**-*E*.

Stereochemical aspects

^{1}H-NMR spectral data of derivatives **4**, **5** and related compounds are given in Table 3. OMe signals appear at

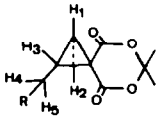
Table 1. 1-Aryl(alkyl)-6,6-dimethyl-4,8-dioxo-5,7-dioxaspiro [2.5] octanes (**2**).



Compound	Method (%)[a] A	B	m.p. (°)[b]	ν_1	ν_2	ν_3	J_{12}	J_{13}	J_{23}	$\nu^c_{CH_3}$
2a	26	43	133–4[c]	2.51	2.65	3.42	−4.7	9.5	9.3	1.71
2b	76	85	125–6	2.47	2.56	3.71	−4.4	9.4	9.4	1.75
2c	55	80	161–3	2.51	2.61	3.39	−4.6	9.6	9.3	1.75
2d	58	78	160–1	2.51	2.60	3.38	−4.9	9.5	9.0	[f]
2e	38	47	160–1	2.53	2.61	3.41	−4.9	9.3	9.1	1.70
2f	15	65	108–9	2.47	2.58	3.56	−4.2	9.5	9.5	1.74
2g	19	70	154–6	2.51	2.64	3.40	−4.7	9.7	9.5	1.70
2h	Traces	40	113–5	2.50	2.62	3.40	−4.8	9.5	9.4	1.69
2i	67	—	181–3[d]	2.59	2.68	3.53	−4.9	9.4	9.2	1.75
2j	Traces	66	47–8	2.18	1.94	2.12	−3.4	9.1	8.7	[g]
2k	Traces	19	Dec.	2.51	2.63	3.52	−4.7	9.5	9.2	[h]

[a] A: CH_2N_2; B: CH_2=$SO(CH_3)_2$.
[b] All were recrystallized from EtOAc, with the exception of **2j** (hexane).
[c] Lit.[17b] m.p. = 134–6°.
[d] Lit.[17c] m.p. = 183–5°.
[e] Both CH_3 appeared as a singlet, unless otherwise stated.
[f] Two singlets: 1.70; 1.72.
[g] Two doublets (J_{CH_3-H} = 6.7): 1.00; 1.12.
[h] Two singlets: 1.57; 1.67.

Table 2. 6,6-Dimethyl-4,8-dioxo-5,7-dioxaspiro [2.5] octanes (**3**)



Comp.	Yield (%)	m.p. (°)[a]	ν_1	ν_2	ν_3	ν_4	ν_5	J_{12}	J_{13}	J_{23}	J_{34}	J_{35}	J_{45}	ν_{CH_3}
3a	26	87–8[b]	2.25	2.09	2.58	2.92	3.20	−3.9	9.2	8.3	9.1	6.1	−14.5	1.20; 1.68
3e	44	104–5	2.25	2.07	2.54	2.92	3.16	−3.7	9.0	8.9	8.8	6.1	−14.6	1.25; 1.68
3f	28	77–8	2.25	2.09	2.56	2.97	3.13	−3.9	9.4	8.8	7.4	6.6	−14.6	1.36; 1.70
3g	37	82–3	2.24	2.07	2.55	2.88	3.13	−3.8	8.8	8.7	9.0	6.3	−14.7	1.23; 1.67
3h	45	68–9	2.25	2.08	2.55	2.87	3.13	−3.7	9.1	8.6	9.0	6.0	−14.8	1.25; 1.67
3k	78	169–70	2.29	2.11	2.71	3.09	3.23	−3.8	8.8	8.5	8.0	6.5	−15.3	1.26; 1.67
3l	15	111–2	2.25	2.10	2.70	3.07	3.28	−3.8	8.8	8.6	8.7	5.9	−15.0	1.07; 1.63

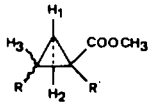
[a] All compounds were recrystallized from EtOAc with the exception of **3h** and **3l** (EtOAc : hexane).
[b] Lit.[17b] 86°.

δ = 3.7–3.9 ppm, which is consistent with a configuration *anti* with respect to the aromatic ring[9,10,23] as shown by values of corresponding monoesters **4a**-*Z* (δ = 3.78), **4a**-*E* (δ = 3.25) and diester **4'a** (δ = 3.33 and 3.77) and also by those of isocyanates **5a**-*Z* (δ = 3.85) and **5a**-*E* (δ = 3.31).

Compound **8a**-*E* was esterified (CH_2N_2) and compared with its corresponding stereoisomer, obtained by treatment of **5a** with MeOH (Experimental). In each isomer, both OMe groups behave in the way observed in derivatives **4** and **5**, —COOMe giving values 3.3 when affected by the anisotropy of the aromatic ring (*E*-compounds) and 3.7 when not (*Z*-derivatives). NH—COOMe groups, less affected, still show values of 3.7 and 3.5, respectively.

On the other hand, for analogous methyl 1-acylamino-2-aryl-cyclopropanecarboxylates we have deduced[10,23] that protons with *syn* configuration to the —NHCO— group appear upfield to protons with *anti* configuration, which also holds for compounds **8**,

Table 3. 1-Methoxycarbonyl-2-aryl-cyclopropanecarboxylic acids (**4**), methyl 1-isocyanate-2-arylcyclopropanecarboxylates (**5**) and related compounds



Comp.	R'	Isom	Yield	m.p. (°)[a]	ν_1	ν_2	ν_3	J_{12}	J_{13}	J_{23}	ν_{OCH_3}
4a	COOH	*E*	80	73–5	2.01	2.35	3.29	−5.0	9.4	8.6	3.78
4a	COOH	*Z*	—	sp	2.40	2.31	3.41	−4.7	8.8	9.5	3.25
4'a	COOMe	—	—	sp	1.72	2.18	3.22	−5.2	9.2	8.2	3.33; 3.37
4b	COOH	*E*	85	133–4	2.28	2.52	3.33	−4.8	9.4	9.2	3.90
4c	COOH	*E*	85	sp	2.06	2.36	3.25	−4.8	9.5	8.7	3.82
4d	COOH	*E*	75	87–8	2.05	2.32	3.25	−5.1	9.4	8.5	3.80
4e	COOH	*E*	97	sp	2.15	2.42	3.28	−4.9	9.7	8.8	3.71
4f	COOH	*E*	65	79–80	2.08	2.43	3.19	−4.7	9.4	8.8	3.82
4g	COOH	*E*	80	87–8	2.17	2.47	3.29	−4.8	9.5	8.9	3.85
4h	COOH	*E*	80	73–5	2.02	2.33	3.23	−4.9	9.5	8.5	3.74[c]
4i	COOH	*E*	78	128–30	2.19	2.43	3.37	−5.1	9.5	8.7	3.68
5a	NCO	*Z*	58	sp	1.96	1.60	2.94	−5.7	9.9	8.3	3.85
5a	NCO	*E*[b]	—	sp	2.28	1.70	2.94	−5.3	8.2	9.4	3.31
5b	NCO	*Z*	55	sp	2.00	1.60	3.02	−5.6	9.8	8.4	3.89
5c	NCO	*Z*	70	sp	1.97	1.58	2.89	−5.8	10.1	8.3	3.85
5d	NCO	*Z*	75	90–1	1.95	1.54	2.87	−5.7	10.0	8.2	3.82
5e	NCO	*Z*	78	sp	1.98	1.57	2.91	−5.8	10.1	8.3	3.83
5f	NCO	*Z*	45	sp	1.97	1.63	2.85	−5.8	10.0	8.3	3.86
5g	NCO	*Z*	60	sp	1.93	1.57	2.89	−5.6	9.9	8.3	3.82
5h	NCO	*Z*	55	sp	1.92	1.53	2.87	−5.7	10.1	8.2	3.79[c]
R = Ph	NH—COOMe	*E*	—	sp	2.19	1.61	2.88	−5.5	8.5	9.6	3.32[d]
R = Ph	NH—COOMe	*Z*	—	sp	2.10	1.71	2.93	−5.8	9.7	8.2	3.73[e]

[a] All solid compounds were recrystallized from MeOH–H_2O, with the exception of **5d** (cyclohexane).
[b] Obtained from **4a**-(*Z*).
[c] Interchangeable with peak at 3.80 (s, CH_3O—Ph).
[d] Additional peak at 3.73 (s, NH—COO$\underline{CH_3}$).
[e] Additional peak at 3.56 (s, NH—COO$\underline{CH_3}$).
sp = syrup.

coupling constants being in agreement with this deduction.

In both series of aminoacids **6**, J values are also in agreement with the proposed configurations.

Concerning the 5-substituted-2-oxopyrrolidine-3-carboxylic acids (**10**, **11**), it is well known the difficulty in assigning configurations in 5-membered rings on the basis of their coupling constants. However, other considerations being equal, protons H_3 and H_4 (Scheme 1) seem to be "seen" by protons H_1 and H_2 in an opposite way in compounds **11** (e.g. in **11g**: $J_{13} = 9.1$, $J_{23} = 6.2$ and $J_{14} = 6.1$, $J_{24} = 9.9$) and more similarly in compounds **10** (cf. in **10g**: $J_{13} = 10.4$, $J_{23} = 9.0$ and $J_{14} = 8.5$, $J_{24} = 7.2$). This suggests an array of protons H_3 and H_4 in an *anti* configuration in compounds **11** and a *syn* configuration in derivatives **10**, which have been tentatively assigned as depicted in Scheme 1.

EXPERIMENTAL

The m.ps were determined on a Kofler Thermopan Reichert apparatus and are uncorrected. IR were performed on a Perkin–Elmer 681 spectrometer in KBr pellets. ^{1}H-NMR spectra were recorded for solns in Cl_3CD or DMSO-d_6 on a Varian EM-390 (90 MHz). ^{13}C-NMR were recorded on a Brucker WP 80 SY (20 MHz).

All the chemical shifts are expressed in δ values from Me_4Si as internal standard. Silica gel GF_{254} (E. Merck) was used for TLC experiments. All compounds gave satisfactory microanalyses ($\pm 0.4\%$ for C, H and N, when present).

5 - Arylidene(alkylidene) - 2,2 - dimethyl - 1,3 - dioxane - 4,6 - diones (**1**)

Compounds **1a–l** were prepared according to Polansky *et al.*[16]

1 - Aryl(alkyl) - 6,6 - dimethyl - 4,8 - dioxo - 5,7 - dioxaspiro [2.5] *octanes* (**2**, **3**)

General procedure A[17]. A stirred soln of the appropriate compound **1** (0.03 mol) in ether–MeOH (60:40) was cooled (−70°) and excess of ethereal diazomethane was added portionwise, keeping the temp below −60°. After addition, stirring was maintained for 1 hr and then a few drops of HAc were added. Any solid material deposited was filtered and the soln was evaporated *in vacuo*, the residual oil being either crystallized or chromatographed on silica gel. In most of the cases, mixtures of spiroderivatives **2** and **3** were obtained. Compounds **1h, k, l** gave only derivatives **3h, k, l**, while **1j** led to a complex mixture of products not further investigated, and **1i** gave only the derivative **2i**.

When other solvents were used instead of ether–MeOH (e.g. ether–CH_2Cl_2, ether–acetone, etc.), erratic results in the ratio of compounds **2**:**3** were obtained, and no significant improvement of the yields were achieved, except for derivative **3k**, which was only obtained in CH_2Cl_2.

General procedure B. To a stirred soln of the corresponding compound **1** (0.01 mol) in dry DMF (20 ml), cooled at 5–10° (water-bath), a soln of dimethyl sulfoxonium methylide[18] (from 12.5 mmol of NaH and 13.5 mmol of trimethylsulfonium iodide) was added dropwise. The mixture was stirred for 15 min and then poured with stirring onto cooled water–benzene (60:40). The aqueous layer was further extracted with benzene (3 × 25 ml), the combined benzene fractions were washed (H_2O; 3 × 25 ml), dried ($MgSO_4$) and the solvent removed *in vacuo* to give the corresponding derivatives **2** (Table 1).

Compound **1l** did not give derivative **2l** but 3,3,12,12 - tetramethyl - 8,16 - di[3 - (N - methylindolyl)] - 1,5,10,14 - tetraoxo - 2,4,11,13 - tetraoxadispiro [5.2.5.2] hexadecane as white needles (25%) m.p. = 258–60° dec. ($CHCl_3$–MeOH). (Found: C, 67.92; H, 5.70; N, 4.72. Calc for $C_{34}H_{34}N_2O_8$: C, 68.22; H, 5.72; N, 4.68%.) IR (cm^{-1}): 1767, 1740 (C=O); ^{1}H-NMR (Cl_3CD): 0.79 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 2.24 (dd, $1H_A$, gem., $J_{AM} = 13.7$ Hz; $J_{AX} = 2.4$ Hz), 3.72 (s, 3H, CH_3N), 3.77 (t, $1H_M$, gem., $J_{AM} \simeq J_{MX} = 13.7$ Hz), 5.10 (dd, $1H_X$), 6.91 (s, $1H_2$, indole), *ca* 7.2 (m, 3H, indole), *ca* 7.7 (m, 1H, indole); ^{13}C-NMR (Cl_3CD): 27.77 ($\underline{C}H_3$), 29.87 ($\underline{C}H_3$), 32.87 (CH_3N), 35.37 ($\underline{C}H_2$), 36.25 ($\underline{C}H$), 54.73 (CO—$\underline{C}$—CO), 105.07 (O—$\underline{C}$—O), 108.94, 111.84, 119.97, 122.26, 127.27, 128.21, 128.37, 136.35 (8$\underline{C}$-indole), 170.19 ($\underline{C}$=O), 171.33 ($\underline{C}$—O); *m/e*: 598 (M^+, 19), 394 (18), 157 (76.5), 144 (27.5), 58 (25.5), 43 (100%).

E - 1 - Methoxycarbonyl - 2 - aryl(alkyl) - cyclopropanecarboxylic acids (**4**)

General procedure. The appropriate derivative **3** (0.01 mol) was stirred with a soln of KOH (0.56 g, 0.01 mol) in abs MeOH (100 ml) for 2–3 hr. The solvent was then removed *in vacuo* and the resulting salt was dissolved in H_2O (20 ml) and acidified (HCl) to give the above compounds. Similar results were obtained when the reaction was carried out with equimolecular amounts of $NaCH_3O$ instead of KOH.

Product **2j** gave a mixture of *E* and *Z* derivatives; ^{1}H-NMR (Cl_3CD): 3.64 (s, CH_3O) and 3.66 (s, CH_3O).

Z - 1 - Methoxycarbonyl - 2 - phenyl - cyclopropanecarboxylic acid (**4a-Z**)

Monoester **4a-*E*** (200 mg) was treated with excess of CH_2N_2 to give syrupy diester **4'a** (Table 3). The diester (164 mg) was refluxed with KOH (390 mg) in H_2O–MeOH 1:1 (6 ml) for 1 hr. The solvent was removed *in vacuo* and the residual solid was dissolved in H_2O and acidified (HCl) to give **4a-*Z***, m.p. = 117–8° (ether–hexane) (Table 3).

Z - 1 - Carbamoyl - 2 - aryl(alkyl) - cyclopropanecarboxylic acids (**7**)

General procedure. To a stirred soln of the corresponding compound **2** (4 mmol) in dioxane (25 ml), 30 ml of conc NH_4OH were added in portions through a period of 1 hr. Stirring was continued for 2–3 hr and the solvent was removed *in vacuo*. The residual salt was dissolved (H_2O) and acidified (HCl) to pH ≃ 2 to give **7**.

Derivative **2f** gave a mixture of **7f** and **11f**, which was treated with conc $HNaCO_3$. Part of the mixture got into soln. Filtration and acidification of the soln yielded **7f**. The insoluble portion was treated with HCl to give *trans*-**11f** (62%), m.p. = 130–3° (EtOH). (Found: C, 60.65; H, 6.40; N, 5.72. Calc for $C_{12}H_{13}NO_3 \cdot H_2O$: C, 60.76; H, 6.33; N, 5.91%.) IR (cm^{-1}): 3380–3250 (COOH + NH), 1715, 1600 (C=O acid + lactam). ^{1}H-NMR (DMSO-d_6): 1.94 (m, $1H_1$ gem., $J_{12} = -13.1$, $J_{13} = 9.3$, $J_{14} = 4.9$ Hz), 2.31 (s, 3H, CH_3), 2.76 (m, $1H_2$ gem., $J_{23} = 6.6$, $J_{24} = 8.1$ Hz), 3.29 (dd, $1H_3$, $\underline{H}C$—C=O), 4.96 (dd, $1H_4$, $\underline{H}C$—N), 7.23 (s, 4H arom.), *ca* 8.4 (broad, 1NH).

Compound **2g** led to a mixture of compounds which was treated as above, giving **7g** and *cis*-**10g** (35%), m.p. = 160–1° (EtOH). (Found: C, 65.61; H, 5.83; N, 6.35. Calc for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39%.) IR (cm^{-1}): 3480–3250 (COOH + NH), 1725, 1670 (C=O acid + lactam). ^{1}H-NMR (DMSO-d_6): 2.01 (m, $1H_1$ gem., $J_{12} = -12.5$, $J_{13} = 10.4$, $J_{14} = 8.5$ Hz), 2.30 (s, 3H, CH_3), 2.66 (m, $1H_2$ gem., $J_{23} = 9.0$, $J_{24} \simeq 7.2$ Hz), 3.41 (m, $1H_3$, $\underline{H}C$—C=O), 4.58 (m, $1H_4$, $\underline{H}C$—N), 7.20 (s, 4H arom.), *ca* 8.3 (broad, 1NH).

From the mother liquors of the isolation of **10g**, an additional solid was further obtained. ^{1}H-NMR shown to be a mixture of **10g** and a second derivative whose spectrum was analyzed by subtraction of that of **10g**. A structure **11g** was tentatively assigned to this compound, which refused to be isolated. ^{1}H-NMR (DMSO-d_6): 2.03 (m, $1H_1$ gem., $J_{12} = -14.9$, $J_{13} = 9.1$, $J_{14} = 6.1$ Hz), 2.30 (s, 3H, CH_3), 2.70 (m, $1H_2$ gem., $J_{23} = 6.2$, $J_{24} = 9.9$ Hz), 3.32 (m, $1H_3$, $\underline{H}C$—C=O), 4.58 (m, $1H_4$, $\underline{H}C$—N), 7.17 (s, 4H arom.), *ca*. 8.4 (broad, 1NH).

Compound **2h** did not give derivative **7h**, but derivative **10h**, m.p. = 155–6° (EtOH) (90%). (Found: C, 61.08; H, 5.51; N, 5.61. Calc for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.53; N, 5.95%.) IR (cm^{-1}): 3600–3100 (COOH + NH), 1730, 1690 (C=O acid

+lactam). ^{1}H-NMR (DMSO-d_6): 2.02 (m, $1H_1$ gem., J_{12} = −12.7, J_{13} = 10.4, J_{14} = 8.5 Hz), 2.65 (m, $1H_2$ gem., J_{23} = 8.9, J_{24} = 6.9 Hz), 3.41 (m, $1H_3$, HC—C=O), 3.78 (s, 3H, CH_3O), 4.57 (m, $1H_4$, HC—N), *ca* 7.0 (m, 2H arom.), *ca* 7.3 (m, 2H arom.), *ca* 8.3 (broad, 1NH). From the mother liquors a small amount of an additional compound was further isolated. As above it was shown to be a mixture of **10b** and **11b** and the spectrum of the latter was analyzed by subtraction of the former. ^{1}H-NMR (DMSO-d_6): 2.03 (m, $1H_1$ gem., J_{12} = −13.1, J_{13} = 9.4, J_{14} = 5.7 Hz), 2.66 (m, $1H_2$ gem., J_{23} = 5.4, J_{24} = 7.8 Hz), 3.34 (m, $1H_3$, HC—C=O), 3.78 (s, 3H, CH_3O), 4.73 (m, $1H_4$, HC—N), *ca* 7.0 (m, 2H arom.), *ca* 7.3 (m, 2H arom.), *ca* 8.4 (broad, 1NH).

5-(2-Azido-2-arylethyl)-2,2-dimethyl-1,3-dioxane-4,6-diones (**9**)

General procedure. On a cooled soln of NaN_3 (0.33 g, 5 mmol) in H_2O (5 ml), a soln of the appropriate compound **2** (5 mmol) in dioxane (10–15 ml) was added dropwise with stirring. The reaction was allowed to proceed for 45–60 min and the solvent was then eliminated *in vacuo*. The residual salt was dissolved in H_2O and acidified (1 N HCl) with cooling to pH ≃ 2. The following azides were obtained:

5-(2-Azido-2-phenylethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (**9a**): White needles (87%) m.p. = 70–2° (dioxane). (Found: C, 58.42; H, 5.35; N, 14.76. Calc for $C_{14}H_{15}N_3O_4$: C, 58.12; H, 5.22; N, 14.52%.) IR (cm^{-1}): 2108 (N_3), 1795+1746 (C=O). ^{1}H-NMR (Cl_3CD): 1.78 (s, 3H, CH_3), 1.81 (s, 3H, CH_3), 2.30 (m, $1H_1$ gem., J_{12} = −14.1, J_{13} = 7.7, J_{14} = 5.3 Hz), 2.62 (m, $1H_2$, J_{23} = 3.9, J_{24} = 10.6 Hz), 3.70 (m, $1H_3$), 5.06 (m, $1H_4$), 7.42 (s, 5H arom.).

5-[2-Azido-2(4-methoxyphenyl)-ethyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (**9h**): White needles (78%) m.p. = 91–2° (cyclohexane). (Found: C, 56.63; H, 5.36; N, 12.90. Calc for $C_{15}H_{17}N_3O_5$: C, 56.43; H, 5.33; N, 13.17%.) IR (cm^{-1}): 2106 (N_3), 1803+1753 (C=O). ^{1}H-NMR (Cl_3CD): 1.77 (s, 3H, CH_3), 1.79 (s, 3H, CH_3), 2.30 (m, $1H_1$, J_{12} = −14.7, J_{13} = 7.4, J_{14} = 5.1 Hz), 2.62 (s, $1H_2$, J_{23} = 4.4, J_{24} = 9.4 Hz), 3.68 (m, $1H_3$), 3.81 (s, 3H, CH_3O), 5.00 (m, $1H_4$), *ca* 6.9 (2H arom.) *ca* 7.3 (2H arom.).

5-[2-Azido-2-(4-nitrophenyl)-ethyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (**9i**): White needles (80%) m.p. = 115–7° (EtOH). (Found: C, 50.38; H, 4.33; N, 16.93. Calc for $C_{14}H_{14}N_4O_6$: C, 50.30; H, 4.19; N, 16.77%.) IR (cm^{-1}): 2110 (N_3), 1802+1753 (C=O). ^{1}H-NMR (Cl_3CD): 1.78 (s, 3H, CH_3), 1.85 (s, 3H, CH_3), 2.31 (m, $1H_1$, J_{12} = −14.2, J_{13} = 8.4, J_{14} = 4.7 Hz), 2.61 (m, $1H_2$, J_{23} = 3.2, J_{24} = 10.8 Hz), 3.81 (m, $1H_3$), 5.09 (m, $1H_4$), *ca* 7.6 (2H arom.), *ca* 8.3 (2H arom.).

Z-Methyl 1-isocyanate-2-arylcyclopropanecarboxylates (**5**)

General procedure. The proper compound **4** (12 mmol) was suspended in acetone (45 ml) and H_2O (3.5 ml). The mixture was cooled (ice bath) and Et_3N (1.3 g, 13 mmol) was added. Ethyl chloroformate (1.6 g, 15 mmol) in acetone (5 ml) was then added dropwise with stirring. After 30 min, a soln of NaN_3 (1.2 g, 18 mmol) in H_2O (4 ml) was added dropwise. The soln was then stirred for 1 hr, poured into ice water (150 ml) and extracted with ether (4 × 40 ml). The ethereal soln was dried ($MgSO_4$) and the solvent removed *in vacuo* to give an oil (acyl azide), which was dissolved in dry toluene (25 ml) and heated on a steam bath for 2–3 hr (N_2 evolved), and the solvent removed *in vacuo* to give the corresponding isocyanate **5** (Table 3), which was used in the following steps without any further purification.

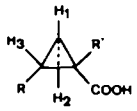
E-1-Methoxycarbonylamino-2-aryl(alkyl)-cyclopropanecarboxylic acids (**8**)

The corresponding derivative **7** (5 mmol) and Br_2 (1.2 g, 7.5 mmol) in MeOH (20 ml) were stirred for 30–45 min. A soln of NaMeO (from 0.6 g of Na and 20 ml of MeOH) was then added. After 1 hr of stirring, the soln was refluxed for 14 hr, the solvent was removed *in vacuo*, the residual solid treated with H_2O (10 ml) and acidified (1M HCl) with cooling to give the corresponding compound **8** (Table 4). All attempts to convert **7b** and **7i** into the respective **8b** and **8i** were unfruitful, the starting material being recovered unchanged.

Methyl 1-methoxycarbonylamino-2-phenyl-cyclopropanecarboxylates

E-Stereoisomer. It was obtained by reaction of **8a** (100 mg) with ethereal CH_2N_2.

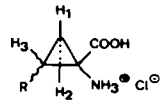
Table 4. Cyclopropanecarboxylic acids **7** and **8**.



Comp.	R'	m.p. (°)	Yield (%)	Recryst. solv.	ν_1[a]	ν_2	ν_3	J_{12}	J_{13}	J_{23}	ν_{OCH_3}
7a	$CONH_2$	191–2	72	H_2O	1.75	2.04	2.98	−4.4	9.1	8.1	—
7b	$CONH_2$	193–4	58	H_2O	1.90	2.16	3.00	−4.4	9.2	8.3	—
7c	$CONH_2$	182–3	83	H_2O	1.74	2.04	3.00	−4.5	9.1	8.0	-
7d	$CONH_2$	206–8	73	EtOH–H_2O	1.78	2.05	2.99	−4.5	9.0	8.2	—
7e	$CONH_2$	196–7	95	EtOH–H_2O	1.79	2.05	3.00	−4.5	9.2	8.1	—
7f	$CONH_2$	195–6	27	H_2O	1.81	2.15	2.91	−4.2	9.2	8.1	—
7g	$CONH_2$	198–9	46	EtOH–H_2O	1.74	2.01	2.92	−4.2	9.2	8.1	—
7i	$CONH_2$	166–8	91	EtOH	1.81	2.13	3.14	−4.7	9.2	8.1	—
7j	$CONH_2$	176–7	89	H_2O	[b]						
8a	NH—COOMe	179–80	62	H_2O	1.40	1.99	2.72	−5.3	9.6	8.5	3.58
8c	NH—COOMe	150–2	78	H_2O	1.44	2.00	2.72	−5.2	9.5	8.5	3.58
8d	NH—COOMe	230–2	67	H_2O	1.44	1.98	2.70	−5.1	9.6	8.6	3.58
8e	NH—COOMe	184–6	58	MeOH–H_2O	1.42	1.98	2.70	−5.2	9.7	8.4	3.58
8f	NH—COOMe	177–9	32	H_2O	1.40	2.04	2.62	−5.1	9.6	8.4	3.60
8g	NH—COOMe	201–3	67	MeOH–H_2O	1.36	1.96	2.66	−5.2	9.6	8.5	3.55
8j	NH—COOMe	144–5	50	H_2O	[b]						3.53

[a] All compounds were registered in DMSO-d_6.
[b] The spectrum could not be analyzed.

Table 5. 1-Amino-cyclopropanecarboxylic acids hydrochlorides (**6**).



Comp.	Conf.	m.p. (d) (°)[a]	Yield (%)	ν_1[b]	ν_2	ν_3	J_{12}	J_{13}	J_{23}
6a	*Z*	204–5	66	2.09	1.95	3.34	−7.1	10.1	8.2
6a	*E*	211–3	47	2.20	1.95	3.18	−6.9	8.5	10.3
6b	*Z*	207–8	73	2.17	1.96	3.21	−7.1	10.0	8.7
6c	*Z*	188–90	70	2.09	1.93	3.27	−7.1	10.0	8.3
6c	*E*	219–21	41	2.20	1.98	3.16	−7.2	8.7	10.7
6d	*Z*	205–7	54	2.07	1.89	3.25	−6.8	9.6	8.3
6d	*E*	230–2	67	2.19	1.96	3.15	−7.1	8.8	10.5
6e	*Z*	215–6	76	2.10	1.94	3.27	−7.0	9.7	8.6
6e	*E*	214–6	49	2.16	1.93	3.12	−7.0	8.7	10.4
6f	*Z*	200–1	64	2.18	2.05	3.11	−7.2	10.6	8.4
6f	*E*	227–8	51	2.20	1.95	3.04	−6.9	8.8	10.3
6g	*Z*	200–2	56	2.05	1.91	3.23	−7.0	10.0	8.3
6h	*Z*	197–9	57	2.06	1.90	3.22	−7.0	10.0	8.4
6j	*E*	228–30	67						

[a] All the aminoacids were recrystallized from absol. EtOH–Et_2O.
[b] Spectra registered for solution in D_2O (DDS as standard). Compound **6j** could not be analyzed.

Z-Steroisomer. Part of the acyl azide (200 mg) obtained from **4a** was dissolved in absol. MeOH instead of toluene, and was heated on a steam bath for 2 hr. The solvent was then removed *in vacuo* to syrupy title compound (Table 3).

Z - 1 - Amino - 2 - aryl - cyclopropanecarboxylic acids hydrochlorides (**6-Z**)

General procedure A. The appropriate compound **8** (3 mmol) in NaOH–EtOH (0.75 g in 40 ml) was refluxed for 24 hr, the solvent removed *in vacuo* and the residual salt dissolved in H_2O (10 ml), acidified (1M HCl) and evaporated *in vacuo* to dryness. The solid was extracted with boiling absol EtOH (4 × 10 ml), and the EtOH removed *in vacuo* to the corresponding hydrochloride, which was recrystallized from absol EtOH–Et_2O.

General procedure B. The corresponding derivative **8** (3 mmol) was refluxed for 48 hr with conc HCl (15 ml) and HOAc (10 ml). The solvent was then removed *in vacuo*, and the hydrochloride recrystallized as above.

E - 1 - Amino - 2 - aryl(alkyl) - cyclopropanecarboxylic acids hydrochlorides (**6-E**)

General procedure. The appropriate isocyanate **5** (3 mmol) was refluxed for 8–9 hr in 6 M HCl (15 ml). The soln was filtered and evaporated *in vacuo* to give the corresponding hydrochloride, recrystallized as above.

The compounds obtained by any of these procedures are shown in Table 5.

Compound **6j-E** gave ^{13}C-NMR (DMSO-d_6): 17.78 ($\underline{C}H_2$), 21.65 and 21.95 (2 $\underline{C}H_3$), 25.82 ($\underline{C}H$), 34.23 ($\underline{C}H$), 37.59 (), 169.85 ($\underline{C}OOH$).

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