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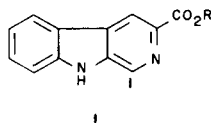
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The 1,3-dipolar cycloaddition reaction between mesoionic oxazolines, formed from either 1,3-dihydro-2-substituted-2*H*-isoindole-1-carboxylic acids or 1,3-dihydro-1-oxo- α -substituted-2*H*-isoindole-2-acetic acids, and dimethylacetylene dicarboxylate has led to the synthesis of several 5*H*-pyrrolo[2,1-*a*]isoindole derivatives **9a-d**.

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1,3-Dipolar cycloaddition reactions between mesoionic heterocycles and a variety of dipolarophilic substituted ethylenes or acetylenes can yield an assortment of heterocyclic systems [1-3]. The facile nature of these cycloadditions offers an appealing alternative to the often more complicated classical heterocyclic ring annelation processes, providing the structure of the target compound can be accommodated within the framework of 1,3-dipolar cycloaddition methodology.

We have applied the reaction of polycyclic mesoionic oxazolones (generated *in situ*) with dimethylacetylene dicarboxylate (DMAD) to provide a new route to the 5*H*-pyrrolo[2,1-*a*]isoindole ring system. Our interest in this ring system stems from its structural coincidence with the unsaturated β -carboline structure **1**. This compound has received renewed attention in recent years due to a spectrum of biological effects found in its derivatives which range from proconvulsant to anticonvulsant activity, as well as anxiogenic or potentially anxiolytic pharmacological effects [4]. The specificity of the β -carbolines biological action is observed to be remarkably sensitive to the



nature of the esterifying group R or substitution at the one position [5,6]. These curious structure-activity relationships have sparked an interest in other heterocyclic systems such as the 6*H*-indolo[2,3-*b*][1,8]naphthyridines, 11*H*-indolo[3,2-*c*][1,8]naphthyridines, isoquinoline and imidazopyridine derivatives, which may share pharmacology similar to the β -carbolines [7,8]. Biological evaluation of these compounds has examined their binding affinity *in vitro* at brain benzodiazepine receptors, through which agents such as diazepam express their anxiolytic activity.

A superimposition of target compound **9a** ($R^2 = H$) and structure **1**, optimized by a least squares fit involving their respective surface areas, is depicted in Figure 1 [9]. The high degree of structural congruence in these nearly planar systems also accommodates a close placement of one

of the carbomethoxy functions in **9a**, with the corresponding biologically-relevant moiety in **1** ($R = CH_3$). The structural similarity shared by these two systems suggests the 5*H*-pyrrolo[2,1-*a*]isoindole nucleus may serve as a potent ligand at the same receptor which interacts with both the β -carbolines and benzodiazepines. The biological activity of the dimethyl-3-substituted-5*H*-pyrrolo[2,1-*a*]isoindole-1,2-dicarboxylate target compounds has not previously been investigated in this context.

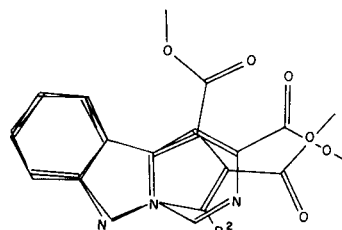


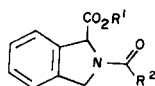
Figure 1

Results and Discussion.

The *N*-acylamino acids used to generate the mesoionic oxazolines by cyclodehydration were synthesized by two different approaches. Reaction of methyl 2-bromomethyl- α -bromophenylacetate (**2**) with benzylamine yields 2-benzyl-1-carbomethoxyisoindoline (**3a**), which through standard catalytic hydrogenation conditions, is debenzylated to **3b** (Scheme 1, method A) [10]. Acylation of **3b** with benzoyl chloride or phenylacetyl chloride generated intermediates **4a** and **4b**, which are converted to their 1,3-dihydro-2-substituted-2*H*-isoindole-1-carboxylic acid derivatives **5c** and **5d** by treatment with base. Base hydrolysis of **3b** yields **3c** which upon reaction with formyl-acetic anhydride or acetic anhydride, leads to the synthesis of **5a** and **5b**, respectively.

Alternatively, the *N*-acylamino acids can be configured in the form of 1,3-dihydro-1-oxo- α -substituted-2*H*-isoindole-2-acetic acid derivatives **7a-d**. The amination of methyl 2-bromomethylbenzoate **6** with a variety of α -aminoester derivatives affords the corresponding *N*-substituted-isoindoles **7a-d** (Scheme 1, method B) in acceptable yields

Table 1

1,3-Dihydro-2-substitued-2*H*-isoindole-1-carboxylic Ester Derivatives **4a-b**

	R ¹	R ²	Mp °C	Yield (%)	Formula	Recrystalliza- tion Solvent	C	Calcd. H	Analysis %			
									N	C	H	N
4a	CH ₃	C ₆ H ₅	124-132	87.6	C ₁₇ H ₁₅ NO ₃	EtOAc	72.58	5.37	4.97	72.27	5.38	4.81
4b	CH ₃	C ₇ H ₇	116-117	78.2	C ₁₈ H ₁₇ NO ₃	EtOAc	73.20	5.80	4.74	73.08	5.83	4.60

1,3-Dihydro-2-substitued-2*H*-isoindole-1-carboxylic Acid Derivatives **5a-d**

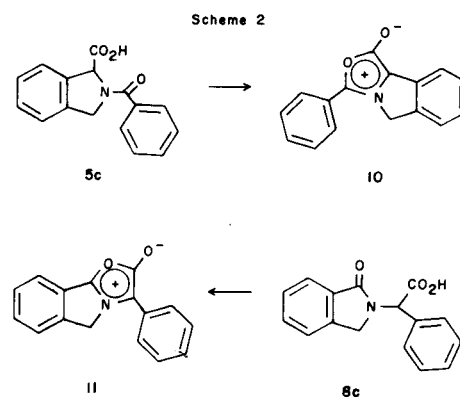
5a	H	H	203-206	47.8	C ₁₀ H ₉ NO ₃	H ₂ O	62.82	4.75	7.33	62.75	4.77	7.52
5b	H	CH ₃	182-183	65.2	C ₁₁ H ₁₁ NO ₃	CH ₃ CN	64.38	5.40	6.82	64.69	5.41	7.09
5c	H	C ₆ H ₅	194-201	80.0	C ₁₆ H ₁₃ NO ₃	EtOAc	71.90	4.90	5.24	71.63	4.90	5.14
5d	H	C ₇ H ₇	161.5-163.5	84.6	C ₁₇ H ₁₅ NO ₃	H ₂ O	72.58	5.37	4.97	72.40	5.39	4.88

[11]. The base hydrolysis of these intermediates supplies the carboxylic acids **8a-d**, which in a manner analogous to compounds **5a-d**, can both serve as precursors in the subsequent 1,3-dipolar cycloaddition reactions to yield identical products represented by **9a-d**.

A significant difference was observed in the scope of the reactivity in the 1,3-dipolar cycloaddition step for intermediates derived from method A or B. Consistently good yields of **9a-d** were available from the reaction of **5a-d** with DMAD, while only **8c** in method B presented any comparable reactivity. Thorough investigations of the factors which affect munchnone (1,3-oxazolium-5-olate) reactivity indicate both steric and electronic parameters can control the reaction course [12]. The contrast observed in the yields of **9a-d**, dependent on whether their synthesis is derived from method A or B (Table 7), suggests the non-equivalence in the reactivity of **8** vs. **5** is associated with one of these factors. Inspection of the Drieding models representing the mesoionic oxazolones derived from the cyclodehydration reactions of either **8a-d** or **5a-d**, did not reveal any untoward steric interactions which would impede the formation of these intermediates. The discrepancy in the yields for products derived from **8** vs. **5** is not caused by the nature of the dipolarophile since this is constant in each series and is not, itself, sterically encumbered.

The reactivity of **5** is unaffected by modifications in the R² group since the yields are fairly uniform throughout this series. Compound **8c** generates a yield of **9c** roughly equivalent to that obtained with **5c** upon reaction with DMAD. The similar nature of the substitution pattern in the mesoionic oxazolones obtained from each of these intermediates is illustrated by compounds **10** and **11** in Scheme 2. The poor yield obtained from **8b**, or the lack of reactivity observed with **8a** or **8d**, emphasizes the impor-

tance of the phenyl substituent at the carbon atom present in the number four position of the general mesoionic structure **12** (Figure 2); a condition which is satisfied in every intermediate derived from **5** by the presence of the fused phenyl ring.



The potential role of the phenyl group at this position in facilitating conversion of the intermediate oxazolones to their corresponding mesoionic tautomers, or in the stabilization of the latter, cannot be disregarded. Previous work indicates isolation of **12** (R¹ = R³ = C₆H₅, R² = H) is possible when the mesoionic ring supports a phenyl group at the number four carbon (R¹ = C₆H₅). However, when R¹ = H, the intermediate munchnone products were too unstable for isolation, and the mesoionic oxazolones underwent electrophilic substitution at this position [13,14].

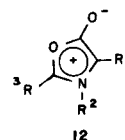


Figure 2

Table 2

IR, ¹H-NMR and ¹³C-NMR Spectral Data of Compounds **4a-b**

	IR, cm ⁻¹ (potassium bromide)	¹ H-NMR (deuteriochloroform), δ (ppm)	¹³ C-NMR (deuteriochloroform), δ (ppm)
4a	2950, 1755, 1635, 1410, 1200, 1175, 750	Major Rotamer = 3.76 (3H, s), 4.66 (1H, d, J = 13.8 Hz), 4.96 (1H, d, J = 13.8 Hz), 5.92 (1H, s), 7.37 (9H, m); Minor Rotamer = 3.49 (3H, s), 5.05 (2H, s), 5.57 (1H, s), 7.37 (9H, m)	52.51 (q), 54.66 (t), 65.13 (d), 122.77 (d), 123.17 (d), 126.98 (d), 128.06 (d), 128.48 (d), 128.85 (d), 130.23 (d), 134.48 (s), 136.00 (s), 137.10 (s), 170.05 (s), 170.15 (s)
4b	2950, 1750, 1660, 1645, 1635, 1425, 1200, 750, 710	Major Rotamer = 3.70 (3H, s), 3.79 (2H, s), 4.82 (2H, m), 5.68 (1H, s), 7.30 (9H, m) [a]	41.58 (t), 52.39 (q), 52.59 (t), 65.24 (d), 122.95 (d), 123.03 (d), 126.98 (d), 128.09 (d), 128.64 (d), 128.83 (d), 129.04 (d), 134.06 (s), 134.59 (s), 136.90 (s), 169.92 (s), 170.05 (s)

[a] Minor rotamer is obscured by the major rotamer.

The failure to form the mesoionic oxazolones due to incomplete cyclodehydration of **8a**, **8b**, and **8d** cannot be discounted, since a complete examination of the very polar

reaction side products obtained in their attempted dipolar cycloadditions was not implemented. The dramatic difference in yields obtained in these two synthetic approaches to the 5*H*-pyrrolo[2,1-*a*]isoindole ring indicates additional mechanistic studies are warranted in this area. No significant biological activity was observed for compounds **9a-d**. This is quite possibly due to the lack of a basic nitrogen atom in the 5*H*-pyrrolo[2,1-*a*]isoindole nucleus to correspond to the basic pyridine ring nitrogen of the β-carbolines.

EXPERIMENTAL

All ir spectra were recorded on a Nicolet MX-1 FT-IR spectrometer. The ¹H-nmr spectra were recorded on a Perkin-Elmer R-32 spectrometer, and the ¹³C-nmr spectra were recorded on a Varian FT-80 spectrometer in 5 mm o.d. sample tubes in either deuteriochloroform, using 2% (v/v) tetramethylsilane as the internal reference, or perdeuteriodimethylsulfoxide. Melting points were determined using a Thomas-Hoover capillary apparatus and are uncorrected.

1,3-Dihydro-2*H*-isoindole-1-carboxylic Acid (**3c**).

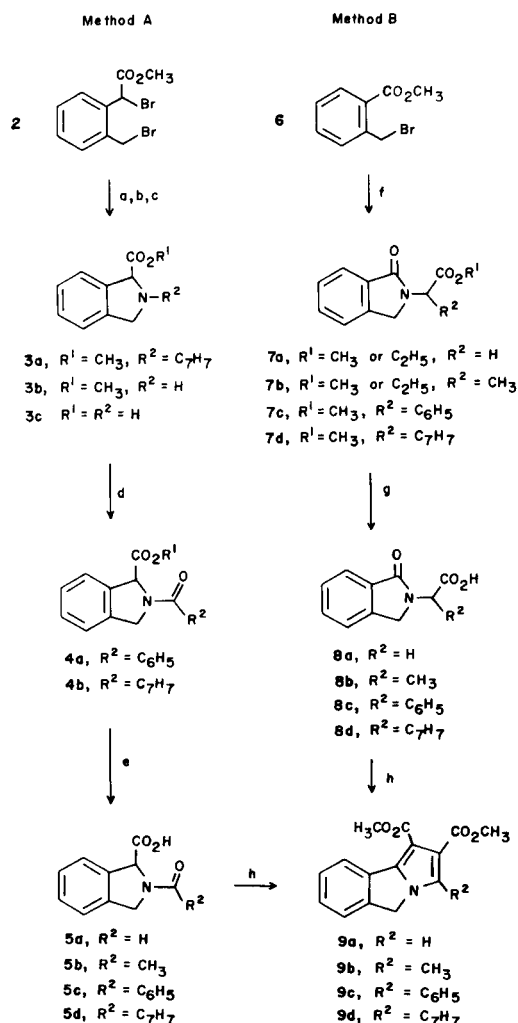
A solution of 3.0 g (0.014 moles) of methyl 1,3-dihydro-2*H*-isoindole-1-carboxylate hydrochloride **3b** in water (20 ml) was mixed with a solution of 1.4 g (0.036 moles) of sodium hydroxide and heated on a steam cone until hydrolysis was complete (30 minutes). The cooled solution was filtered, acidified slowly with concentrated hydrochloric acid, and the solvent was removed on a rotary evaporator. The resulting solid was triturated with ethanol (2 × 50 ml), and the combined triturations were filtered, reduced in volume, and treated with an equal volume of ethyl ether leading to the crystallization of 2.7 g (93%) of the white hydrochloride salt, **3c**, mp 214-218°; ir (potassium bromide): 3430, 2900, 1735, 1395, 1200, 765, 750 cm⁻¹; nmr (perdeuteriodimethylsulfoxide): δ 4.59 (2H, m), 5.58 (1H, s), 7.44 (4H, m), 9.60 (3H, br s); cmr (perdeuteriodimethylsulfoxide): δ 49.83 (t), 63.49 (d), 123.19 (d), 128.44 (d), 129.25 (d), 133.19 (s), 134.79 (s), 168.10 (s).

Anal. Calcd. for C₉H₉NO₂·HCl·0.66H₂O: C, 51.07; H, 5.40; N, 6.62; H₂O: 5.67. Found: C, 51.15; H, 5.35; N, 6.57; H₂O: 4.87.

General Procedure for the Preparation of 1,3-Dihydro-2-substituted-2*H*-isoindole-1-carboxylic Ester Derivatives **4a-b**.

A mixture of 4.0 g (0.02 mole) of 1-carbomethoxyisoindole **3b** and 4.7 g (0.04 mole) of triethylamine in methylene chloride (65 ml) was treated dropwise with a solution of 3.8 g (0.03 mole) of benzoyl chloride in 20 ml of methylene chloride at room temperature. The mixture was refluxed 12 hours, cooled, and washed with water (2 × 100 ml). The organic phase was isolated, dried (sodium sulfate), filtered, and the solvent removed on

Scheme 1



Reagents: a. H₂N-C₇H₇, MeOH Δ; b. H₂-50 psi, 10% Pd/C, EtOH Δ; c. NaOH, H₂O Δ; d. benzoyl chloride or phenacetyl chloride, Et₃N, CH₂Cl₂; e. NaOH, H₂O Δ; f. methyl-α-substituted-glycinate derivative; g. NaOH, H₂O Δ; h. DMAD, (Ac)₂O, Δ.

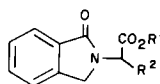
Table 3

IR, ¹H-NMR and ¹³C-NMR Spectral Data of Compounds **5a-d**

	IR, cm ⁻¹ (potassium bromide)	¹ H-NMR (perdeuteriodimethylsulfoxide), δ (ppm)	¹³ C-NMR (perdeuteriodimethylsulfoxide), δ (ppm)
5a	3480, 2920, 2500, 1735, 1640, 1590, 1430, 1380, 1225, 1210, 745	Rotamer A = 4.65 (2H, m), 5.46 (1H, s), 7.38 (4H, m), 8.34 (1H, s), 13.00 (1H, br s); Rotamer B = 4.94 (2H, m), 5.80 (1H, s), 7.38 (4H, m), 8.42 (1H, s), 13.00 (1H, br s) [a]	Rotamer A = 49.36 (t), 62.72 (d), 122.84 (d), 123.29 (d), 127.66 (d), 128.58 (d), 134.79 (s), 136.03 (s), 161.41 (d), 170.46 (s); Rotamer B = 50.83 (t), 63.79 (d), 123.29 (d), 123.53 (d), 127.85 (d), 128.58 (d), 134.84 (s), 136.50 (s), 162.46 (d), 171.56 (s) [b]
5b	3460, 2570, 1730, 1610, 1585, 1460, 1415, 1260, 1205, 760, 735	Major Rotamer = 2.06 (3H, s), 4.87 (2H, s), 5.40 (1H, s), 7.35 (4H, m), 11.80 (1H, br s); Minor Rotamer = 2.00 (3H, s), 4.68 (2H, m), 5.73 (1H, s), 7.35 (4H, s), 11.80 (1H, br s)	Major Rotamer = 21.72 (q), 52.55 (t), 64.58 (d), 122.58 (d), 123.13 (d), 127.75 (d), 128.51 (d), 135.17 (s), 137.45 (s), 168.73 (s), 170.96 (s); Minor Rotamer = 21.57 (q), 51.65 (t), 65.35 (d), 122.98 (d), 127.60 (d), 135.87 (s), 136.60 (s), 168.93 (s), 171.55 (s)
5c	2920, 1750, 1735, 1620, 1605, 1590, 1570, 1450, 1435, 1190, 755	4.80 (2H, m), 5.71 (1H, s), 7.44 (9H, m), 11.95 (1H, br s)	54.12 (t), 65.13 (d), 122.64 (d), 123.10 (d), 126.84 (d), 127.79 (d), 128.42 (d), 130.04 (d), 134.66 (s), 136.03 (s), 137.29 (s), 168.89 (s), 179.91 (s)
5d	2920, 2600, 1725, 1715, 1620, 1605, 1585, 1580, 1460, 1450, 1255, 720	Major Rotamer = 3.81 (2H, s), 4.92 (2H, s), 5.47 (1H, s), 7.31 (9H, m), 11.30 (1H, br s); Minor Rotamer = 3.65 (2H, m), 4.72 (2H, m), 5.85 (1H, s), 7.31 (9H, m), 11.30 (1H, br s)	40.33 (t), 52.15 (t), 64.93 (d), 122.53 (d), 123.10 (d), 126.38 (d), 127.76 (d), 128.07 (d), 128.17 (d), 128.51 (s), 129.26 (d), 134.98 (s), 137.24 (s), 169.23 (s), 170.87 (s)

[a] 50:50 Mixture of rotamers. [b] Signals at 123.29 and 128.58 ppm represent two absorbances at each chemical shift.

Table 4

1,3-Dihydro-1-oxo-α-substituted-2H-isoindole-2-acetic Ester Derivatives **7a-d**

	R ¹	R ²	Mp °C	Yield (%)	Formula	Recrystallization Solvent	Analysis %					
							Calcd.			Found		
							C	H	N	C	H	N
7a	CH ₃ , Et [a]	H	symp	59.5	C ₁₁ H ₁₁ NO ₃ , C ₁₂ H ₁₃ NO ₃	—	—	—	—	—	—	—
7b	CH ₃ , Et [a]	CH ₃	symp	54.8	C ₁₂ H ₁₃ NO ₃ , C ₁₃ H ₁₅ NO ₃	—	—	—	—	—	—	—
7c	CH ₃	C ₆ H ₅	80-81	69.5	C ₁₇ H ₁₅ NO ₃	EtOAc-Skelly B (1:1)	72.58	5.37	4.97	72.27	5.26	4.86
7d	CH ₃	C ₇ H ₇	69-75	46.2	C ₁₈ H ₁₇ NO ₃	Et ₂ O	73.20	5.80	4.74	73.10	5.87	4.97

1,3-Dihydro-1-oxo-α-substituted-2H-isoindole-2-acetic Acid Derivatives **8a-d**

8a	H	H	208-211 [b]	89.3	C ₁₀ H ₉ NO ₃	H ₂ O	62.82	4.74	7.32	61.84	4.61	6.90 [c]
8b	H	CH ₃	205-208	86.4	C ₁₁ H ₁₁ NO ₃	MeOH-H ₂ O (1:1)	64.38	5.40	6.82	64.38	5.33	6.64
8c	H	C ₆ H ₅	181-182	95.2	C ₁₆ H ₁₃ NO ₃	MeOH-H ₂ O (1:1)	71.90	4.90	5.24	71.61	4.85	5.13
8d	H	C ₇ H ₇	206-208.5	88.2	C ₁₇ H ₁₅ NO ₃	MeOH-H ₂ O (1:1)	72.58	5.37	4.97	72.26	5.40	4.84

[a] A mixture of methyl and ethyl esters is obtained when the amination is attempted with ethyl-α-substituted-glycinate derivatives in methanol as the solvent. The purification of this ester mixture was not pursued. [b] Reported mp 212°, ref [15]. [c] Karl Fischer analysis indicates 0.88% water present.

a rotary evaporator. The resulting syrup was crystallized from ethyl acetate (50 ml) affording 5.7 g (88%) of white product **4a**.

Table 1 summarizes the physical data and Table 2 the spectral data of these compounds.

General Procedure for the Preparation of 1,3-Dihydro-2-substituted-2H-isoindole-1-carboxylic Acid Derivatives **5c-d**.

A suspension of 5.3 g (0.02 mole) of methyl 1,3-dihydro-2-benzoyl-2H-isoindole-1-carboxylate (**4a**) in water (75 ml) was mixed with a solution of 1.5 g (0.04 mole) of sodium hydroxide in 6 ml of water and the resulting solution was heated on a steam cone until the starting material dissolved (25 minutes). The cooled solution was filtered and slowly acidified with concentrated hydrochloric acid resulting in the formation of a precipitate which was collected by filtration. The collected solid was recrystalliz-

Table 5

IR, ¹H-NMR and ¹³C-NMR Spectral Data of Compounds **7c-d**

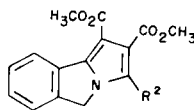
	IR, cm ⁻¹ (potassium bromide)	¹ H-NMR (deuteriochloroform), δ (ppm)	¹³ C-NMR (deuteriochloroform), δ (ppm)
7c	2950, 1745, 1690, 1470, 1450, 1205, 740, 705	3.77 (s, 3H), 3.92 (d, 1H, J = 16.5 Hz), 4.76 (d, 1H, J = 16.5 Hz), 6.32 (s, 1H), 7.34 (m, 8H), 7.85 (m, 1H)	47.59 (t), 52.34 (q), 57.82 (d), 122.87 (d), 123.84 (d), 127.87 (d), 128.63 (d), 128.74 (d), 129.09 (d), 131.64 (d), 131.77 (s), 134.53 (s), 142.06 (s), 168.48 (s), 170.71 (s)
7d	1730, 1690, 1470, 1455, 1285, 1260, 1210, 1180, 800, 760, 700	3.17 (dd, 1H, J = 10.0, 14.4 Hz), 3.52 (dd, 1H, J = 6.0, 14.4 Hz), 3.68 (s, 3H), 4.27 (d, 1H, J = 16.1 Hz), 4.55 (d, 1H, J = 16.1 Hz), 5.41 (dd, 1H, J = 6.0, 10.0 Hz), 7.20 (m, 5H), 7.40 (m, 3H), 7.79 (m, 1H)	35.8 (t), 47.6 (t), 52.2 (q), 54.8 (d), 122.9 (d), 123.7 (d), 126.9 (d), 127.8 (d), 128.5 (d), 128.6 (d), 131.5 (d), 131.9 (s), 136.5 (s), 141.7 (s), 168.7 (s), 171.1 (s)

Table 6

IR, ¹H-NMR and ¹³C-NMR Spectral Data of Compounds **8a-d**

	IR, cm ⁻¹ (potassium bromide)	¹ H-NMR (perdeuteriodimethylsulfoxide), δ (ppm)	¹³ C-NMR (perdeuteriodimethylsulfoxide), δ (ppm)
8a	2930, 2600, 1725, 1650, 1615, 1480, 1455, 1230, 1200, 740	4.28 (2H, s), 4.50 (2H, s), 7.59 (4H, m), 12.80 (1H, br s)	43.50 (t), 50.24 (t), 122.91 (d), 123.35 (d), 127.82 (d), 131.53 (d), 131.71 (s), 142.09 (s), 167.85 (s), 170.56 (s)
8b	2920, 2580, 1730, 1685, 1650, 1615, 1470, 1450, 1245, 735	1.51 (3H, d, J = 7.5 Hz), 4.50 (2H, s), 4.85 (1H, q, J = 7.5 Hz), 7.59 (4H, m), 12.85 (1H, br s)	15.31 (q), 46.82 (t), 49.15 (d), 122.83 (d), 123.43 (d), 127.84 (d), 131.48 (d), 131.96 (s), 142.10 (s), 167.58 (s)
8c	2920, 1735, 1680, 1630, 1470, 1445, 1220, 1210, 1195, 735, 700	3.91 (1H, d, J = 17.0 Hz), 4.65 (1H, d, J = 17.0 Hz), 6.00 (1H, s), 7.42 (8H, m), 7.71 (1H, m), 13.20 (1H, br s)	47.65 (t), 58.03 (d), 123.01 (d), 123.53 (d), 127.92 (d), 128.44 (d), 128.82 (d), 128.93 (d), 131.47 (s), 131.66 (d), 134.77 (s), 142.07 (s), 167.62 (s), 171.31 (s)
8d	2940, 2580, 1730, 1635, 1470, 1440, 1205, 1195, 735, 695	3.30 (2H, m), 4.38 (2H, s), 5.13 (1H, dd, J = 5.2 and 10.8 Hz), 7.15 (5H, m), 7.48 (4H, m)	34.73 (t), 47.34 (t), 54.79 (d), 122.87 (d), 123.35 (d), 126.43 (d), 127.80 (d), 128.31 (d), 128.46 (d), 131.51 (d), 131.57 (s), 137.44 (s), 141.85 (s), 167.85 (s), 171.89 (s)

Table 7

Dimethyl 3-Substituted-5*H*-pyrrolo[2,1-*a*]isoindole-1,2-dicarboxylate Derivatives **9a-b**

R ²	Mp °C	Yield (%) (Method A)	Yield (%) (Method B)	Formula	Recrystalliza- tion Solvent	C	Calcd. H	Analysis %				
								N	C	H	N	
9a	H	127-128	31.8	No Reaction	C ₁₅ H ₁₃ NO ₄	CH ₃ OH	66.41	4.83	5.16	66.24	4.85	5.49
9b	CH ₃	185-187	64.0	4.4	C ₁₆ H ₁₅ NO ₄	CH ₃ OH	67.36	5.29	4.90	67.41	5.34	4.76
9c	C ₆ H ₅	155-158.5	68.3	77.3	C ₂₁ H ₁₇ NO ₄	CH ₃ OH	72.61	4.93	4.03	72.68	4.71	3.97
9d	C ₇ H ₇	148-149	75.1	No Reaction	C ₂₂ H ₁₉ NO ₄	CH ₃ OH	73.11	5.29	3.87	73.04	5.27	3.79

ed from ethyl acetate (40 ml) yielding 4.0 g (80%) of product **5c**.

Table 1 summarizes the physical data and Table 3 the spectral data of these compounds.

General Procedure for the Preparation of 1,3-Dihydro-1-oxo- α -substituted-2*H*-isoindole-2-acetic Ester Derivatives **7a-d**.

A solution of 50 g (0.22 mole) of methyl 2-bromomethyl benzoate (**6**), 96.9 g (0.48 mole) of methyl-*DL*- α -phenylglycinate hydrochloride, and 66.8 g (0.66 mole) of triethylamine was refluxed 36 hours in methanol (500 ml). The reaction mixture was cooled, filtered, and the solvent re-

moved on a rotary evaporator. The collected solid was dissolved in methylene chloride (200 ml) and extracted with 0.1*N* hydrochloric acid (2 × 200 ml). The organic phase was isolated, dried (sodium sulfate), filtered, and the solvent removed on a rotary evaporator yielding an oil. Bulb to bulb distillation (168-180°, 0.3 torr) yielded **7c** which was crystallized from ethyl acetate-Skelly B (1:1) affording 43.0 g (70%) of white solid.

Table 4 summarizes the physical data and Table 5 the spectral data of these compounds.

General Procedure for the Preparation of 1,3-Dihydro-1-oxo- α -substituted-2*H*-isoindole-2-acetic Acid Derivatives **8a-d**.

Table 8

IR, ¹H-NMR and ¹³C-NMR Spectral Data of Compounds **9a-d**

	IR, cm ⁻¹ (potassium bromide)	¹ H-NMR (deuteriochloroform), δ (ppm)	¹³ C-NMR (deuteriochloroform), δ (ppm)
9a	2950, 1740, 1710, 1700, 1450, 1230, 1210, 1165, 1060, 770, 750	3.81 (3H, s), 3.92 (3H, s), 4.85 (2H, s), 7.29 (3H, m), 7.35 (1H, s), 8.11 (1H, m)	50.64 (t), 51.28 (q), 51.36 (q), 106.29 (s), 119.47 (s), 122.64 (d), 122.78 (d), 122.92 (d), 127.43 (s), 128.19 (d), 131.36 (s), 140.91 (s), 143.10 (s), 164.12 (s), 164.51 (s)
9b	2950, 1715, 1700, 1440, 1215, 1175, 1135, 765	2.37 (3H, s), 3.74 (3H, s), 3.81 (3H, s), 4.95 (2H, s), 7.36 (3H, m), 8.01 (1H, m) [a]	10.97 (q), 49.03 (t), 51.01 (q), 105.62 (s), 115.09 (s), 121.91 (d), 123.39 (d), 127.15 (d), 128.00 (d), 131.21 (s), 131.75 (s), 139.40 (s), 141.47 (s), 162.29 (s), 163.81 (s) [a]
9c	2950, 1710, 1690, 1455, 1435, 1200, 1170, 765, 700	3.70 (3H, s), 3.85 (3H, s), 4.96 (2H, s), 7.40 (8H, m), 8.16 (1H, m)	50.56 (t), 51.32 (q), 51.93 (q), 106.47 (s), 118.62 (s), 122.56 (d), 123.10 (d), 127.46 (d), 128.21 (d), 128.34 (d)
9d	2950, 1720, 1705, 1455, 1210, 1125, 750, 705	3.84 (3H, s), 3.90 (3H, s), 4.14 (2H, s), 4.39 (2H, s), 7.19 (8H, m), 8.06 (1H, m)	31.50 (t), 49.19 (t), 51.23 (q), 51.52 (q), 106.04 (s), 116.85 (s), 122.57 (d), 126.67 (d), 127.03 (d), 128.03 (s), 128.50 (d), 128.66 (d), 131.29 (s), 133.26 (s), 136.69 (s), 140.78 (s), 164.71 (s), 165.64 (s)

[a] The ¹H-nmr and ¹³C-nmr data were recorded in a mixture of deuteriochloroform and perdeuteriodimethylsulfoxide.

A suspension of 42 g (0.15 mole) of methyl 1,3-dihydro-1-oxo- α -phenyl-2H-isoindole-2-acetate **7c** in water (150 ml) was mixed with a solution of 12 g (0.3 mole) of sodium hydroxide in water (55 ml), and the resulting solution was heated on a steam cone until the starting material dissolved (30 minutes). The cooled solution was filtered, slowly acidified with concentrated hydrochloric acid, and extracted with ethyl acetate (3 \times 150 ml). The organic extracts were combined, dried (sodium sulfate), filtered, and solvent removed on a rotary evaporator affording a white solid. The solid was recrystallized from methanol-water (1:1) yielding 3.8 g (95%) of **8c**.

Table 4 summarizes the physical data and Table 6 the spectral data of these compounds.

General Procedure for the Preparation of Dimethyl 3-Substituted-5H-pyrrolo[2,1-*a*]isoindole-1,2-dicarboxylate Derivatives **9a-d**.

Method A.

A mixture of 3.2 g (0.012 mole) of 2-benzoyl-1,3-dihydro-2H-isoindole-1-carboxylic acid **5c** and 2.0 g (0.014 mole) of dimethyl acetylenedicarboxylate was slowly heated to 120° in acetic anhydride (50 ml). Carbon dioxide evolution began at 75° becoming most intense at 100°. The temperature of the solution was maintained at 120° for 45 minutes, and the solvent was removed on a rotary evaporator yielding a dark syrup which was crystallized from methanol affording 3.7 g (68%) of **9c** as a white solid. The preparation of **9a**, while analogous to **9b-d**, also included flash chromatography in ethyl acetate-Skelly B (30:70) to obtain an analytically pure sample.

Method B.

The stoichiometry and procedure used in method B was identical to that employed in method A except 1,3-dihydro-1-oxo- α -phenyl-2H-isoindole-2-acetic acid (**8c**) was used as the starting material.

1,3-Dihydro-2-formyl-2H-isoindole-1-carboxylic Acid (**5a**).

A solution of 1.3 g (7.9 mmoles) of 1,3-dihydro-2H-isoindole-1-carboxylic acid (**3c**) in 10 ml of formic acid (95-97%) was treated dropwise with 7 ml of acetic anhydride at 5° in an ice bath. The ice bath was removed, the temperature rapidly increased to 30°, and the ice bath was reapplied to maintain this temperature for 3 hours. The solvent was removed on a rotary evaporator affording a white residue which was recrystallized from water (15 ml) yielding 0.8 g (57%) of **5a** as white crystals.

Table 1 summarizes the physical data and Table 3 the spectral data of this compound.

2-Acetyl-1,3-dihydro-2H-isoindole-1-carboxylic Acid (**5b**).

A solution of 2.0 g (12.3 mmoles) of 1,3-dihydro-2H-isoindole-1-carboxylic acid (**3c**) was refluxed 3 hours in acetic anhydride (30 ml) and pyridine (7 ml). The reaction mixture was cooled and the solvent removed on the rotary evaporator. The collected solid was recrystallized from acetonitrile yielding 2.1 g (83%) of **5b** as a white solid.

Table 1 summarizes the physical data and Table 3 the spectral data of this compound.

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