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Meldrum's Acid in Organic Synthesis. VI. Synthesis of 2-Substituted Indoles from Acyl Meldrum's Acids and Phenylhydroxylamine *via* [3,3]Sigmatropic Rearrangement

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Phenylhydroxylamine (**13**) oxalate was quite easily acylacetylated by heating with an equimolar amount of acyl Meldrum's acid (**4**) in acetonitrile to give an *N*-acylacetylphenylhydroxylamine (**14**) in high yield. When **14** was treated with another equimolar amount of the same **4** in refluxing toluene, a series of reactions, *O*-acylacetylation, 1-aza-1′-oxa[3,3]sigmatropic rearrangement, decarboxylation, dehydrative cyclization, and deacylation, occurred consecutively to give a 2-substituted indole (**16**) in fair yield, though sometimes accompanied by the formation of a 5-substituted 4-isoxazolin-3-one (**17**).

N-Benzoyl, *N*-acetyl, and *N*-benzyloxycarbonyl derivatives of phenylhydroxylamine (**18**) were treated with phenylacetyl Meldrum's acid (**4i**) in refluxing benzene containing copper powder to give readily rearranged *ortho* alkylation products (**19**), which were converted to the corresponding *N*-acyl-2-benzylindoles (**20**) by treatment with hydrochloric acid in boiling ethanol or with anhydrous *p*-toluenesulfonic acid in benzene at room temperature.

Keywords——acyl Meldrum's acid; phenylhydroxylamine; *N*-acylacetylphenylhydroxylamine; 2-substituted indole; 1-aza-1′-oxa[3,3]sigmatropic rearrangement; acid-catalyzed cyclization

In the preceding paper[1,2] we reported a versatile one-pot synthesis of indolepropionic esters (**2**) from Meldrum's acid (**1**: 2,2-dimethyl-1,3-dioxane-4,6-dione)[3] by simultaneous condensation of three different carbon components as a significant example of the synthetic utility of **1**. As distinct from usual acyclic malonic esters, **1** has high acidity comparable to that of acetic acid,[4] because of its cyclic system. Therefore, the active methylene group in **1** readily reacts with various electrophiles even in the absence of a strong base. The above synthesis of **2**[1] is a remarkable example of such reactivity of **1**, and acylation with various acyl chlorides (**3**) in the presence of pyridine to form 5-acyl Meldrum's acids (**4**), which are easily converted to arbitrary β-keto esters (**5**),[5] provides another example. In the present paper, we report a synthesis of 2-substituted indoles from **4** as a third synthetic application of **1**.

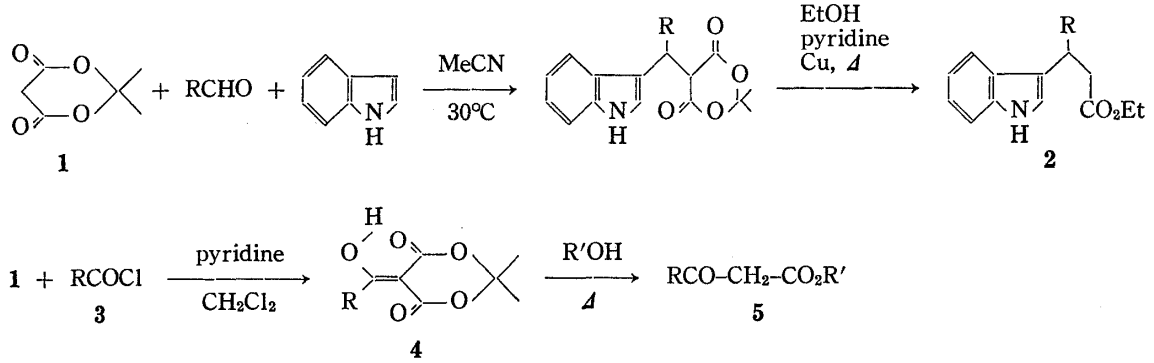

Chart 1

Although there are many efficient and convenient synthetic methods for 3-substituted indoles, few generally useful methods for the synthesis of 2-substituted indoles are so far

available.[6] Recently, Le Corre *et al.* reported a new synthesis of 2-substituted indoles based on the intramolecular Witting reaction of *o*-acylaminobenzyltriphenylphosphonium salts.[7] This method could be useful when the starting phosphonium salts having alkali-resistant acyl groups are easily available.

As part of their extensive studies of ketene, in 1976, Kato *et al.* reported that when a chloroform solution of a phenylhydroxylamine (**6**) and diketene (**7**) was heated under reflux, a complex mixture containing a 2-methylindole (**8**: 5—21%) and an *N*-acetoacetylphenylhydroxylamine (**9**: 37—65%) was obtained, while at 0°C **9** was isolated in good yield.[8] Coates *et al.* subsequently reported a new *ortho* alkylation method involving a decarboxylative 1-aza-1′-oxa-[3, 3]sigmatropic rearrangement of an *N*-acyl-*O*-acylacetylarylhydroxylamine (**11**), prepared from *N*-acetyl or *N*-benzoylphenylhydroxylamine (**10**) by condensation with **7** or benzoylacetic acid, to an *o*-(*N*-acylamino)aryl ketone (**12**).[9] Since an acid-catalyzed dehydrative cyclization of **12** took place easily, this *ortho* alkylation method seems promising for the synthesis of 2-substituted indoles, which are, however, usually limited to 2-methyl- and 2-phenylindoles, because arbitrary acylacetylation agents for **10**, other than **7** and benzoylacetic acid, are not readily available. The present synthesis of **16** from acyl Meldrum's acids (**4**) may provide a new synthetic method for various 2-substituted indoles.[10]

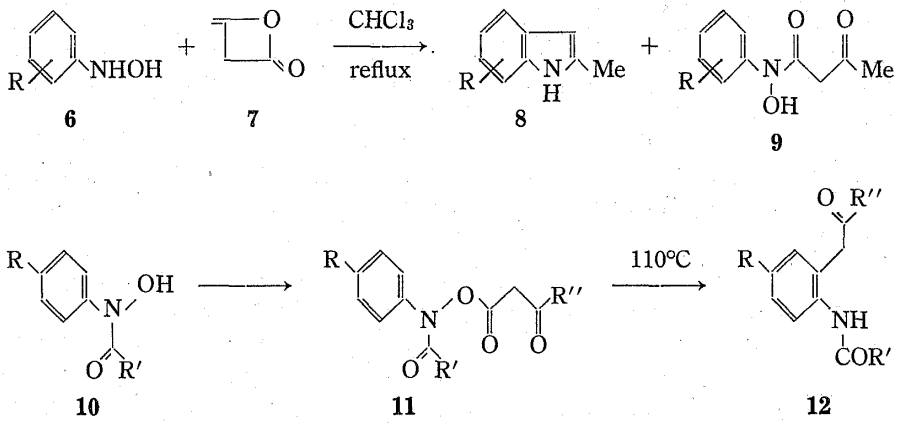

Chart 2

Results and Discussion

Various acyl Meldrum's acids (**4**) were easily prepared from Meldrum's acid (**1**)[3] and the corresponding carboxylic acids or their chlorides (**3**).[5] They have a high reactivity toward nucleophiles, which attack one of the ester-carbonyl groups rather than the keto group.[11] Actually the treatment of **4** with alcohols gave various β-keto esters (**5**).[5] This reaction can be explained in terms of an acylacetylation of alcohols with **4**, which is, therefore, an efficient and convenient synthetic equivalent for an acylacetyl cation (**15a**) or a mixed diketene (**15b**).

When an equimolar solution of acetyl Meldrum's acid (**4a**: R=Me) and phenylhydroxylamine (**13**) oxalate in acetonitrile was refluxed for 30 min, acetoacetylation with simultaneous loss of acetone and carbon dioxide occurred quite easily at the amino group, not at the hydroxyl group, in **13** to give **14a** (R=Me), which has been prepared from **13** and **7**,[8,12] in high yield. This simple method was applied to the synthesis of various *N*-acylacetylphenylhydroxylamines (**14b—i**) having alkyl, phenyl, benzyl, ether and ester groups from acyl Meldrum's acids (**4b—i**). The results are summarized in Table I. The infrared (IR) spectra of **14** clearly indicate that **14** are not *O*-acylacetylated compounds, because an anilide band at 1670—1685 cm^{-1} and a

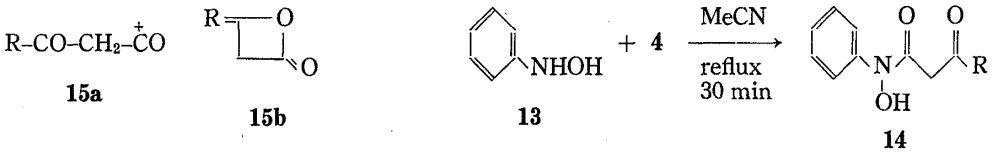

Chart 3

Table I. Preparation of *N*-Acylacetylphenylhydroxylamines (**14**) from Phenylhydroxylamine (**13**) and Acyl Meldrum's Acids (**4**)

Compd.	R	Yield, %	mp °C[a]	IR ν_{max}^{Nujol} cm^{-1}
14a	CH_3	84	124—126 (benzene-hexane)	3275, 1670, 1595
14b	CH_3CH_2	95	135—136 (benzene)	3275, 1670, 1595
14c	$(CH_3)_2CH$	60	94—95 (benzene)	3250, 1670, 1595
14d	$CH_3CH_2CO(CH_2)_2$	76	87—88 (benzene)	3225, 1670, 1590
14e	$CH_3CO_2(CH_2)_2$	74	115—116 (EtOAc)	3250, 1735, 1675, 1595
14f	$CH_3O_2C(CH_2)_2$	91	87—88 (benzene)	3225, 1725, 1670, 1595
14g	$CH_3O_2C(CH_2)_3$	51	92—94 (ether)	3240, 1725, 1675, 1595
14h	C_6H_5	93	136—137 (benzene)	3050, 1685, 1630, 1590
14i	$C_6H_5CH_2$	90	132—134 (benzene)	3250, 1670, 1590

a) Recrystallization solvents are given in parentheses.

hydroxyl band at 3050—3275 cm^{-1} were seen in each case.[13] Nuclear magnetic resonance (NMR) and mass spectra of **14** are also consistent with the above structural assignment.

O-Acylacetylation of **14** with another acyl Meldrum's acid (**4**) followed by thermal decarboxylative 1-aza-1′-oxa[3,3]sigmatropic rearrangement was expected to give *ortho* alkylation products by analogy with **10**→**11**→**12**, and hence an equimolar solution of **14i** (R=$PhCH_2$) and **4f** (R=$MeO_2CCH_2CH_2$) in toluene was heated under reflux for 2 h. Preparative thin-layer chromatography (TLC) on silica gel was applied to the separation of the reaction mixture and two 2-substituted indoles, **16f** and **16i**, and a 5-substituted isoxazolin-3-one (**17i**) were isolated in 22, 5, and 28% yields, respectively. Neither the expected *ortho* alkylation product nor an *O*-acylacetylation product corresponding to **12** and **11**, respectively, was isolated, and further reactions took place to afford the final indoles (**16f**, **i**). Under milder conditions, such as heating in refluxing benzene, **14** was recovered unchanged. The following mechanism may account well for the formation of the main indole (**16f**), though the yield was very poor. A series of reactions, *O*-acylacetylation of **14i** with **4f**, [3,3]sigmatropic rearrangement *via* an enolate (**ii**), decarboxylation, dehydrative cyclization to **iv**, and deacylation, occurred consecutively to afford **16f**. The unexpected minor indole (**16i**) was probably formed by a new thermal reaction of **14i** itself.[14] An acid-catalyzed dehydration of **14i** with acidic **4f** probably gave the side reaction product (**17i**), and this simple reaction has been extended to a new synthesis of various 5-substituted isoxazolin-3-ones (**17**) from **14** with *p*-toluenesulfonic acid.[15]

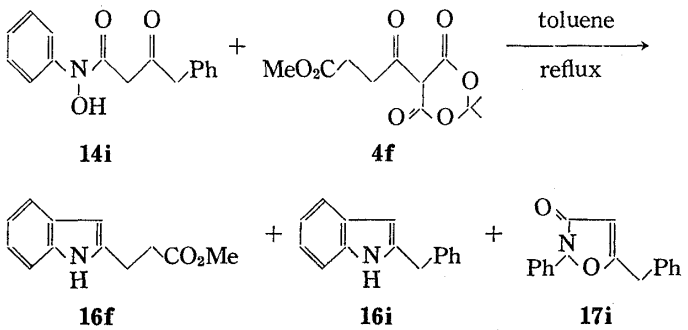

Chart 4

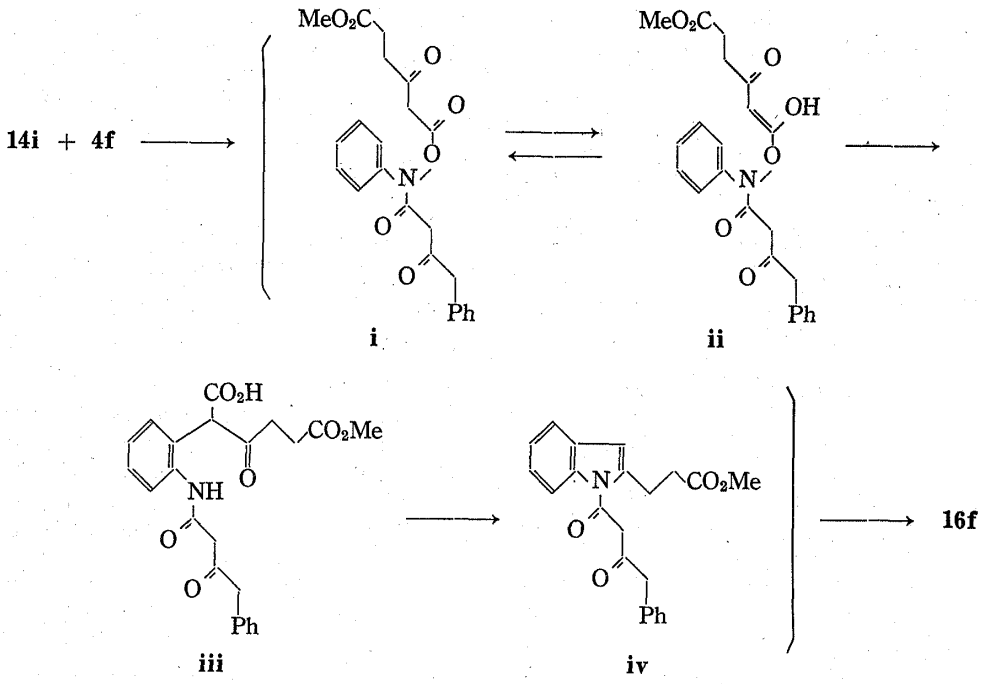

Chart 5

When **14** was heated with the corresponding acyl Meldrum's acid (**4**) having the same R group, only one indole (**16**) was expected to be formed. The expected indole was indeed isolated after chromatographic purification, but the yield was still unsatisfactory, because the concomitant formation of a fair amount of **17** sometimes occurred. Some results are shown in Table II.

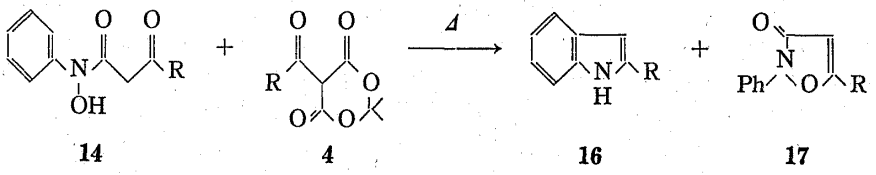

Chart 6

TABLE II. Thermal Reaction of **14** and the Corresponding **4**

Compd.	Yield, %	mp °C[a)]	IR ν_{max}^{Nujol} cm^{-1}	Compd.	Yield, %
16b	21	45—46.5 (pet. ether)		**17b**	46
16e	40	76—77 (hexane)	3300, 1700	**17e**	—
16f	58	97—98 (hexane)	3350, 1715	**17f**	3
16g	38	64—66 (hexane)	3350, 1720	**17g**	—
16i	50	85—86 (hexane)[16)]		**17i**	20

a) Recrystallization solvents are given in parentheses.

Next, in order to avoid the side reaction and to reduce the required amount of **4** to half, an acylphenylhydroxylamine (**18**) was used in the place of **13** itself as a starting material. An equimolar solution of *N*-benzoylphenylhydroxylamine (**18a**)[17)] and **4i** in toluene was refluxed to give a rearranged *ortho* alkylation product (**19a**) in 30—67% yield and a small amount of *N*-benzoyl-2-benzylindole (**20a**). There was no detectable amount of an expected intermediary *O*-acylacetylated compound (**21a**: R=$PhCH_2$) in the reaction mixture. The former product (**19a**) was gradually converted to the latter (**20a**) upon further heating in xylene, but the overall yield was unsatisfactory. Similarly, when the *N*-acetyl (**18b**)[18)] and *N*-benzyl-

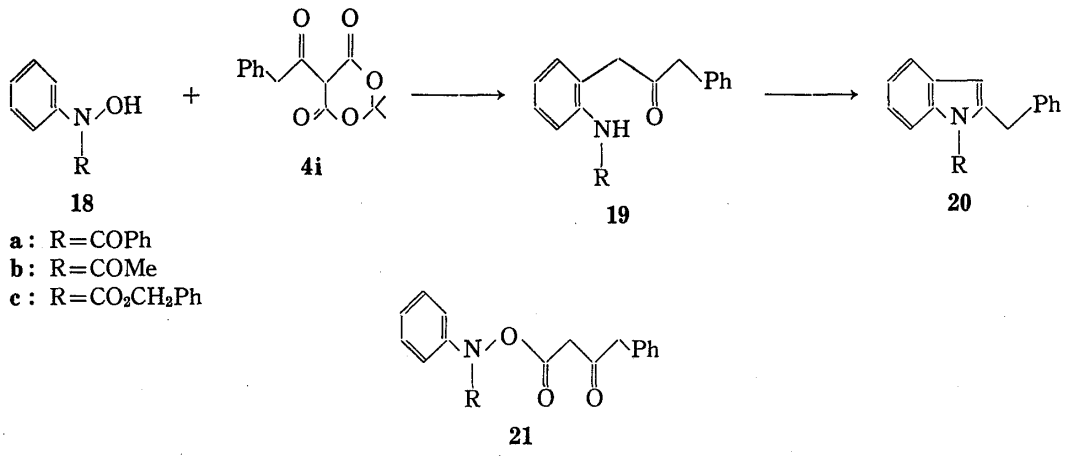

Chart 7

oxycarbonyl (**18c**) derivatives were heated with **4i** in toluene or xylene, the corresponding mixtures of **19** and **20** were obtained, though also in poor yields.

The following conditions were milder and rather efficient. When a benzene solution of **18a** and **4i** in the presence of copper powder was refluxed for 1 h, the *O*-acylacetylation and the decarboxylative [3,3]sigmatropic rearrangement occurred smoothly to give **19a** in good yield. Similarly, **18b** and **18c** gave **19b** and **19c**, respectively. The results are shown in Table III. A dehydrative cyclization of **19a** to **20a** was achieved by heating of **19a** in 10% hydrochloric acid–ethanol (0.6: 1) under reflux for 20 min to give **20a** in 79% yield, but the following procedure gave an excellent result. When anhydrous *p*-toluenesulfonic acid (0.8—1 eq) was added to a benzene solution of **19a**, colorless crystals of *p*-toluenesulfonic acid hydrate were precipitated almost immediately and **20a** was isolated quantitatively after removal of *p*-toluenesulfonic acid by filtration followed by passage of the filtrate through a short alumina column. Similarly, **19b** was treated with anhydrous *p*-toluenesulfonic acid, but because **20b** was less stable to the acid, a mixture of **20b** and 2-benzylindole (**16i**) was obtained, and hence the mixture was treated with sodium carbonate in aqueous methanol to give **16i** in 90% yield.

TABLE III. *ortho*-Alkylation Products (**19**) and *N*-Acyl-2-benzylindoles (**20**) from *N*-Acylphenylhydroxylamines (**18**) and Phenylacetyl Meldrum's Acid (**4i**)

Product	Yield, %	mp °C[e]	IR ν_{max}^{Nujol} cm^{-1}
19a	67[a]	116—118 (benzene-hexane)	3300, 1705, 1645, 1600, 1580
19b	54[a]	109—110 (benzene)	3270, 1705, 1650, 1580
19c	56[a]	100—102 (benzene)	3260, 1705, 1690, 1585
20a	52[b], 79[c]	88—89 (ether)	3300, 1685, 1595
20b	46[b,d]		
20c	47[b]	68—70 (ether-hexane)	3300, 1735, 1600

a) Yields after recrystallization.
b) Overall yields from **18** using HCl–EtOH in the second step.
c) Overall yields from **18** using TsOH in the second step.
d) Yields after hydrolysis to 2-benzylindole (**16i**).
e) Recrystallization solvents are given in parentheses.

Practically, **20** was obtained from **18** and **4i** without isolation of the intermediary **19**. Thus, after removal of the copper powder and the solvent from the reaction mixture of **18** and **4i**, the residue was treated with hydrochloric acid in refluxing ethanol for 20 min or with anhydrous *p*-toluenesulfonic acid in benzene at room temperature for 5 min to obtain **20**.

The benzoyl group of **20a** was easily removed by treatment with sodium carbonate in aqueous methanol at room temperature for 1 h to give 2-benzylindole (**16i**) quantitatively.

Experimental

***N*-Acylacetylphenylhydroxylamines (14)**——An MeCN (5 ml) solution of an acyl Meldrum's acid (5-acyl-2,2-dimethyl-1,3-dioxane-4,6-dione) (**4**; 1 mmol) and phenylhydroxylamine (**13**) oxalate (199 mg, 1 mmol) was refluxed for 30 min. After evaporation of the solvent *in vacuo*, the residue was taken up in CH_2Cl_2 (20—30 ml), and the CH_2Cl_2 solution was washed with H_2O then dried over Na_2SO_4. Evaporation of the solvent *in vacuo* left almost pure crystals of **14**. When crude **14** was an oil, it was crystallized from a small amount of benzene and collected by filtration. The results are summarized in Tables I, IV, and V.

Table IV. *N*-Acylacetylphenylhydroxylamines (**14**)

Compd.	R	Appearance	Formula	Analysis (%) Calcd (Found) C	H	N
14b	CH_3CH_2	Prisms	$C_{11}H_{13}NO_3$	63.75 (63.87	6.32 6.35	6.76 6.78)
14c	$(CH_3)_2CH$	Leaflets	$C_{12}H_{15}NO_3$	65.14 (65.00	6.83 6.72	6.33 6.17)
14d	$CH_3CH_2O(CH_2)_2$	Prisms	$C_{13}H_{17}NO_4$	62.14 (61.86	6.82 6.76	5.57 5.58)
14e	$CH_3CO_2(CH_2)_2$	Prisms	$C_{13}H_{15}NO_5$	58.86 (58.78	5.70 5.71	5.28 5.29)
14f	$CH_3O_2C(CH_2)_2$	Needles	$C_{13}H_{15}NO_5$	58.86 (58.91	5.70 5.80	5.28 5.07)
14g	$CH_3O_2C(CH_2)_3$	Prisms	$C_{14}H_{17}NO_5$	60.20 (60.16	6.14 6.14	5.02 5.06)
14h	C_6H_5	Prisms	$C_{15}H_{13}NO_3$	70.58 (70.79	5.13 5.05	5.49 5.77)
14i	$C_6H_5CH_2$	Prisms	$C_{16}H_{15}NO_3$	71.36 (71.33	5.61 5.56	5.20 5.26)

Table V. MS and NMR Spectral Data for **14**

Compd.	MS *m/e*, (%)[a]	NMR ($CDCl_3$), δ[b]
14b	207 (M^+, 17), 109 (100), 57 (58)	10.8 (3H, t, 7), 1.96 (2H, q, 7), 2.79 (1H, d, 17), 3.05 (1H, d, 17), 7.10—7.82 (5H, m)
14c	221 (M^+, 20), 113 (68), 109 (100)	1.07 (3H, d, 7), 1.11 (3H, d, 7), 2.17 (1H, sept, 7), 2.73 (1H, d, 17), 3.07 (1H, d, 17), 7.13—7.68 (5H, m)
14d	251 (M^+, 13), 143 (100), 109 (41), 101 (85), 59 (90)	1.26 (3H, t, 7), 2.05—2.15 (1H, m), 2.30—2.45 (1H, m), 2.92 (1H, d, 17), 3.02 (1H, d, 17), 3.61 (2H, q, 7), 3.67 (1H, m), 4.00—4.12 (1H, m), 5.92 (1H, s), 7.14—7.71 (5H, m)
14e	265 (M^+, 5), 157 (26), 115 (89), 109 (100)	2.07 (3H, s), 2.29 (2H, t, 6), 2.84 (1H, d, 17), 3.14 (1H, d, 17), 4.26—4.48 (2H, m), 4.85 (1H, s), 7.13—7.66 (5H, m)
14f	265 (M^+, 6), 157 (71), 115 (100), 109 (51)	2.28 (2H, t, 7), 2.56—2.67 (2H, m), 2.85 (1H, d, 17), 3.03 (1H, d, 17), 3.72 (3H, s), 5.53 (1H, s), 7.04—7.69 (5H, m)
14g	279 (M^+, 3), 171 (93), 139 (62), 129 (100), 109 (68), 101 (70)	1.73—1.98 (4H, m), 2.45 (2H, t, 6), 2.80 (1H, d, 17), 3.07 (1H, d, 17), 3.69 (3H, s), 4.86 (1H, s), 7.12—7.73 (5H, m)
14h	255 (M^+, 7), 147 (82), 109 (26), 105 (100), 77 (63)	3.15 (1H, d, 17), 3.29 (1H, d, 17), 7.13—7.76 (10H, m)
14i	269 (M^+, 16), 161 (89), 109 (63), 91 (100)	2.82 (1H, d, 17), 3.13 (1H, d, 17), 3.21 (1H, d, 14), 3.32 (1H, d, 14), 3.68 (1H, s), 7.11—7.68 (10H, m)

a) Relative intensities in %.
b) Proton numbers, splitting patterns, and coupling constants in Hz are given in parentheses.

***N*-Benzoylphenylhydroxylamine (18a)**——Benzoyl chloride (4.22 g, 30 mmol) was added dropwise to a stirred mixture of phenylhydroxylamine (**13**) oxalate (4.98 g, 25 mmol) and $NaHCO_3$ (6.72 g, 80 mmol) in benzene (100 ml) and H_2O (10 ml). The mixture was stirred for 40 min, then the benzene layer was separated, washed with 2 N HCl and H_2O, and dried over Na_2SO_4. Evaporation of the solvent left almost colorless crystals, which were recrystallized from petroleum ether to give colorless prisms of **18a** (5.22 g, 98%), mp 118—120°C (lit.[15] mp 120—121°C). IR ν_{max}^{Nujol} cm^{-1}: 3150, 1620, 1590, 1575. MS *m/e*: 213 (M^+), 197, 109, 105 (base). *Anal.* Calcd for $C_{13}H_{11}NO_2$: C, 73.22; H, 5.20; N, 6.57. Found: C, 73.31; H, 5.20; N, 6.44.

***N*-Acetylphenylhydroxylamine (18b)**——Similarly, **18b** was synthesized in 72.8% yield, mp 64—66°C (ligroin) (lit.[16] 66.5°C). IR ν_{max}^{Nujol} cm^{-1}: 3125, 1590. MS *m/e* relative intensity (%): 151 (M^+, 45), 135 (9), 109 (100). NMR ($CDCl_3$) δ: 2.20 (3H, s), 7.46 (5H, s).

***N*-Benzyloxycarbonylphenylhydroxylamine (18c)**——Similarly, **18c** was synthesized from **13** oxalate (995 mg, 5 mmol) in 99.1% (1.204 g) yield, colorless leaflets, mp 78—80°C (ether–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3220, 1660, 1590, 1580. MS *m/e* relative intensity (%): 243 (M^+, 1.3), 227 (4), 91 (100). NMR ($CDCl_3$) δ: 1.62 (1H, s), 5.26 (2H, s), 7.23—7.45 (10H, m). *Anal.* Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.73. Found: C, 69.16; H, 5.37; N, 5.86.

Reaction of 3-Methoxycarbonylpropionyl Meldrum's Acid (4f) and *N*-(Phenylacetoacetyl)phenylhydroxylamine (14i)——A toluene (3 ml) solution of **4f** (72 mg, 0.28 mmol) and **14i** (75 mg, 0.28 mmol) was refluxed for 2 h. After evaporation of the solvent *in vacuo*, the residue was subjected to preparative TLC on silica gel (ether–hexane=1: 1) to give the following three products.

2-[2-(Methoxycarbonyl)ethyl]indole (**16f**): Yield 13 mg (22%), mp 97—98°C (hexane). IR ν_{max}^{Nujol} cm^{-1}: 3350, 1715. MS *m/e* relative intensity (%): 203 (M^+, 70), 144 (74), 130 (100). NMR ($CDCl_3$) δ: 2.72 (2H, t, J=7 Hz), 3.06 (2H, t, J=7 Hz), 3.70 (3H, s), 6.22 (1H, s), 7.00—7.14 (2H, m), 7.29 (1H, d, J=7 Hz), 7.50 (1H, d, J=7 Hz), 8.46 (1H, s). *Anal.* Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.83; H, 6.44; N, 6.95.

2-Benzylindole (**16i**): Yield 3 mg (5%), mp 85—86°C (petroleum ether) (lit.[15] 86°C). IR ν_{max}^{Nujol} cm^{-1}: 3350, 1595. UV λ_{max}^{EtOH} nm: 221, 273, 290. MS *m/e* relative intensity (%): 207 (M^+, 96), 130 (100).

5-Benzyl-2-phenyl-4-isoxazolin-3-one (**17i**): Yield 20 mg (28%), mp 117—118°C (benzene–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3100, 1665, 1640, 1595. MS *m/e* relative intensity (%): 251 (M^+, 41), 104 (48), 91 (100). NMR ($CDCl_3$) δ: 3.90 (2H, s), 5.55 (1H, s), 7.10—7.80 (10H, m). *Anal.* Calcd for $C_{16}H_{13}NO_2$: C, 76.47; H, 5.22; N, 5.57. Found: C, 76.33; H, 5.31; N, 5.41.

Reaction of an Acyl Meldrum's Acid (4) and the Corresponding Acylacetylphenylhydroxylamine (14)——A toluene (7.5 ml) solution of an acyl Meldrum's acid (**4**; 1.1 mmol) and the corresponding acylacetylphenylhydroxylamine (**14**; 1.1 mmol) was refluxed for 2 h. After evaporation of the solvent, the residue was subjected to preparative TLC to give a 2-substituted indole (**16**) and a 5-substituted 2-phenyl-4-isoxazolin-3-one (**17**). The results are summarized in Tables II and VI.

Table VI. 2-Substituted Indoles (**16**)

Compd.	IR ν_{max}^{Nujol} cm^{-1}	UV λ_{max}^{EtOH} nm	MS *m/e*, (%)[a]	NMR δ($CDCl_3$)[b]	Formula Analysis Calcd (Found) C H N
16b	3370 1585	221 271 289	145(M^+, 56) 130(100)		
16e	3300 1700 1590	272 278 281 289	303(M^+, 25) 143(100) 130(52)	2.09 (3H, s) 3.09 (2H, t, 7) 4.38 (2H, t, 7) 6.30 (1H, s) 7.05—7.50 (4H, m) 8.04 (1H, s)	$C_{12}H_{13}NO_2$ 70.91 6.45 6.89 (70.86 6.46 6.88)
16g	3350 1720	273 279 282 290	217(M^+, 48) 144(49) 130(100)	2.07 (2H, q, 7) 2.40 (2H, t, 7) 2.80 (2H, t, 7) 3.66 (3H, s) 6.24 (1H, s) 7.03—7.56 (4H, m) 8.08 (1H, s)	$C_{13}H_{15}NO_2$ 71.86 6.96 6.45 (71.90 6.96 6.37)

a) Relative intensities in %.
b) Proton numbers, splitting patterns, and coupling constants in Hz are given in parentheses.

***N*-Benzoyl-2-(phenylacetoacetyl)aniline (19a)**——A benzene (8 ml) solution of phenylacetyl Meldrum's acid (**4i**: 262 mg, 1 mmol) and *N*-benzoylphenylhydroxylamine (**18a**: 213 mg, 1 mmol) containing copper powder (50 mg) was refluxed for 1 h. Removal of the copper powder by filtration and evaporation of the solvent left a pale yellow crystalline residue (338 mg), which was washed with ether to decolorize it and then recrystallized from benzene–hexane to give colorless needles of **19a** (219 mg, 66.5%), mp 116—118°C. UV λ_{max}^{EtOH} nm: 207, 253. MS *m/e* relative intensity (%): 329 (M^+, 2), 238 (22), 211 (38), 105 (100), 91 (20), 77 (16). NMR ($CDCl_3$) δ: 3.80 (2H, s), 3.88 (2H, s), 7.06—7.54 (11H, m), 7.96—8.05 (3H, m), 9.36 (1H, s). *Anal.* Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.08; H, 5.71; N, 4.06.

***N*-Acetyl-2-(phenylacetoacetyl)aniline (19b)**——*N*-Acetylphenylhydroxylamine (**18b**: 151 mg, 1 mmol) and **4i** (262 mg, 1 mmol) were treated as described above to give a crystalline product (239 mg), which was recrystallized from benzene to give colorless prisms of **19b** (134 mg, 53.6%), mp 109—110°C. UV λ_{max}^{EtOH} nm: 214. MS *m/e* relative intensity (%): 267 (M^+, 13), 176 (18), 149 (28), 134 (100), 106 (88), 91 (94). NMR ($CDCl_3$) δ: 2.12 (3H, s), 3.74 (2H, s), 3.83 (2H, s), 7.02—7.36 (8H, m), 7.82 (1H, d, J=8 Hz), 8.32 (1H, s). *Anal.* Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 75.85; H, 6.40; N, 5.14.

***N*-Benzyloxycarbonyl-2-(phenylacetoacetyl)aniline (19c)**——*N*-Benzyloxycarbonylphenylhydroxylamine (**18c**: 121.5 mg, 0.5 mmol) and **4i** (131 mg, 0.5 mmol) were treated as described above to give an oil (186 mg), which was chromatographed on an alumina column. Elution with ether–hexane (1: 1) gave a solid product, which was recrystallized from benzene to give colorless needles of **19c** (101 mg, 56%), mp 100—102°C. UV λ_{max}^{EtOH} nm: 211, 230 (sh). MS *m/e* relative intensity (%): 359 (M^+, 1), 268 (1), 91 (100). NMR ($CDCl_3$) δ: 3.71 (2H, s), 3.80 (2H, s), 5.18 (2H, s), 6.94—7.42 (13H, m), 7.68 (1H, s), 7.76 (1H, d, J=8 Hz). *Anal.* Calcd for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89; N, 3.90. Found: C, 77.07; H, 5.95; N, 3.87.

1-Benzoyl-2-benzylindole (20a)——a) A solution of *N*-benzoyl-2-(phenylacetoacetyl)aniline (**19a**: 165 mg, 0.5 mmol) in 10% HCl (3.6 ml) and EtOH (6 ml) was refluxed for 20 min. After evaporation of the solvent *in vacuo*, the residue was taken up in CH_2Cl_2, washed with saturated $NaHCO_3$ solution and H_2O, dried over Na_2SO_4, and concentrated to give a pale yellow oil (142 mg), which was chromatographed on a short alumina column. Elution with ether–hexane (1: 1) gave a solid, which was recrystallized from ether to give colorless needles of **20a** (122 mg, 78.5%), mp 88—89°C. UV λ_{max}^{EtOH} nm: 208, 258. MS *m/e* relative intensity (%): 311 (M^+, 38), 206 (30), 105 (100). NMR ($CDCl_3$) δ: 4.32 (2H, s), 6.46 (1H, s), 6.80—7.73 (14H, m). *Anal.* Calcd for $C_{22}H_{17}NO$: C, 84.86; H, 5.50; N, 4.50. Found: C, 84.91; H, 5.56; N, 4.52.

b) Anhydrous *p*-toluenesulfonic acid (45—57 mg, 0.26—0.33 mmol) was added to a stirred benzene (6 ml) solution of **19a** (108 mg, 0.33 mmol) at room temperature. After 5 min, precipitated *p*-toluenesulfonic acid hydrate was filtered off and the filtrate was concentrated *in vacuo* to leave a solid (122 mg), which was passed through a short alumina column in ether–hexane (1: 1) to give almost pure **20a** (102 mg, 99%).

c) 2-Benzylindole (**16i**: 10.4 mg, 0.05 mmol) was added to NaH (1.5 mg, 0.06 mmol) in dimethylformamide (DMF) (0.3 ml). After evolution of gas had ceased, benzoyl chloride (8.5 mg, 0.3 mmol) in tetrahydrofuran (THF) (0.2 ml) was added. The mixture was stirred for 1 h at room temperature, then poured into cold NH_4Cl solution, and the whole was extracted with EtOAc. The EtOAc extract was washed with H_2O, dried over Na_2SO_4, and concentrated to leave **20a** (12.6 mg, 81%).

2-Benzyl-1-benzyloxycarbonylindole (20c)——*N*-Benzyloxycarbonylphenylhydroxylamine (**18c**: 243 mg, 1 mmol) and **4i** (262 mg, 1 mmol) were treated as described above to give crude **19c** as an oil, which was heated in 10% HCl (7.2 ml) and EtOH (12 ml) under reflux for 20 min. After evaporation of the solvent *in vacuo*, the residue was chromatographed on an alumina column and recrystallized from ether–hexane to give colorless prisms of **20c** (161 mg, 47%), mp 68—70°C. UV λ_{max}^{EtOH} nm: 210, 228, 258, 281, 292. MS *m/e* relative intensity (%): 341 (M^+, 7), 250 (15), 91 (100). NMR ($CDCl_3$) δ: 4.34 (2H, s), 5.36 (2H, s), 6.19 (1H, d, J=1 Hz), 7.11—7.47 (14H, m). *Anal.* Calcd for $C_{23}H_{19}NO_2$: C, 80.91; H, 5.61; N, 4.10. Found: C, 81.18; H, 5.52; N, 3.93.

2-Benzylindole (16i)——a) Anhydrous *p*-toluenesulfonic acid (20 mg, 0.12 mmol) was added to a benzene (2 ml) solution of *N*-acetyl-2-(phenylacetoacetyl)aniline (**19b**: 32 mg, 0.12 mmol), and the mixture was stirred at room temperature for 5 min. After removal of precipitated *p*-toluenesulfonic acid hydrate by filtration, the filtrate was concentrated *in vacuo* to leave an oil, which was chromatographed on a short silica gel column. Elution with ether–hexane (1: 1) gave a mixture (28 mg) of **16i** and *N*-acetyl-2-benzylindole (**20b**) as an oil. IR ν_{max}^{neat} cm^{-1}: 3375, 1705, 1615, 1600. The product mixture was stirred in a mixture of MeOH (3 ml) and H_2O (0.5 ml) containing Na_2CO_3 (9 mg) at room temperature for 10 min. The MeOH was evaporated off, then H_2O was added and the mixture was extracted with EtOAc. The EtOAc extract was dried over Na_2SO_4 and concentrated to leave almost pure **16i** (22.3 mg, 90%).

b) **18b** (151 mg, 1 mmol) and **4i** (262 mg, 1 mmol) were treated as described above to give crude **19c**, which, without further purification, was heated in 10% HCl and EtOH to give a mixture of **20c** and **16i** as an oil (115 mg). The mixture was treated with Na_2CO_3 in MeOH–H_2O for 10 min to give **16i** (95 mg, 46%).

c) 1-Benzoyl-2-benzylindole (**20a**: 6.3 mg, 0.02 mmol) was dissolved in a mixture of MeOH (1 ml) and H_2O (0.2 ml) containing Na_2CO_3 (3 mg), and the solution was stirred for 1 h at room temperature. After evaporation of MeOH, the residue was taken up in EtOAc, washed with H_2O, and dried over Na_2SO_4. Evaporation of the solvent left **16i** (3.9 mg, 93%).

References and Notes

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