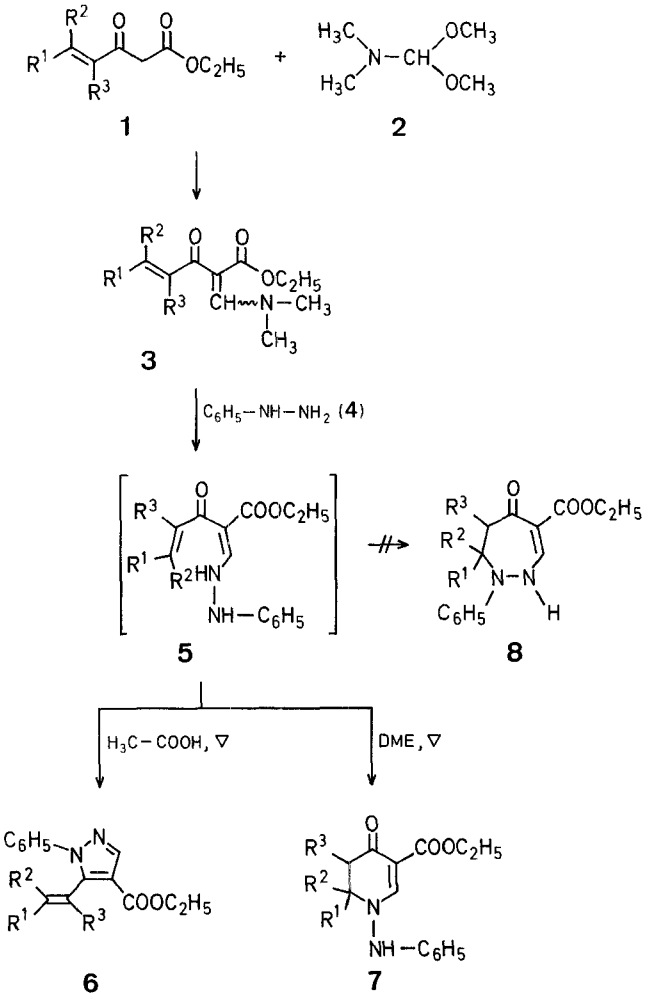

Synthesis of Some 5-Alkenyl-4-ethoxycarbonyl-1-phenylpyrazoles and Ethyl 1-Anilino-4-oxo-1,4,5,6-tetrahydro-3-pyridinecarboxylates

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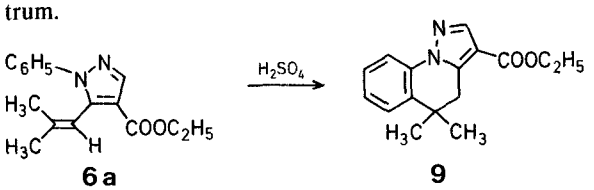
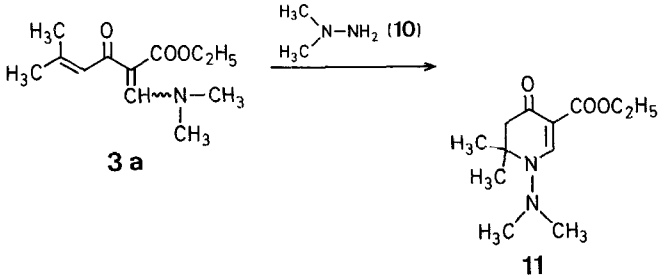
N,N-Dimethylamino derivatives of ketones and β-keto esters are useful intermediates in the synthesis of heterocyclic compounds[1-4]. We report here the reaction of *N,N*-dimethylaminomethylene derivatives **(3)** of β-keto esters **1** bearing an alkenyl substituent with phenyl hydrazine **(4)** to give alkenylpyrazoles **6** or 4-oxo-1,4,5,6-tetrahydropyridines **7** according to the reaction conditions employed.

Condensation of the γ,δ-unsaturated β-keto ester **1** with dimethylformamide dimethylacetal **(2)** affords, in almost quantitative yield, the crude enamine derivative **3**, which in turn, is submitted to the reaction of phenylhydrazine **(4)**. The formation of three products could be expected by ring closure of the initially formed intermediate **5** followed by the attack of the hydrazino moiety at the carbonyl function or at the double bond. The former reaction will give the alkenylpyrazoles **6** as the product while the latter can yield either the 4-oxo-1,4,5,6-tetrahydropyridines **7** or the 5-oxo-2,5,6,7-tetrahydro-1*H*-1,2-diazepines **8**.

We have found that the 5-alkenyl-4-ethoxycarbonyl-1-phenylpyrazoles **6** are formed when the reaction is carried out in acetic acid as solvent. The structure of the alkenylpyrazoles **6** is in good agreement with the microanalytical and spectral data (Table 1). The position of the 1-phenyl group in compounds **6b-e** is deduced from the observed singlet resonance in the ^{1}H-N.M.R. spectra, characteristic of an α-substituent[5]. Confirmation of the position of the phenyl group in compound **6a** is supported by its electrophilic intramolecular cyclization to 5,5-dimethyl-3-ethoxycarbonyl-4,5-dihydropyrazolo[1,5-*a*]quinoline **(9)** as evidenced by the ^{1}H-N.M.R. spectrum.



When the reaction is carried out in anhydrous 1,2-dimethoxyethane as solvent, ethyl 1-anilino-4-oxo-1,4,5,6-tetrahydro-3-pyridinecarboxylates **(7)** are formed. This ring system is very



stable; no rearrangement is observed by refluxing in acetic acid for 12 h or on standing at room temperature in trifluoroacetic acid. This lack of reactivity is in marked contrast to that observed for a 5-oxo-2,5,6,7-tetrahydro-1*H*-1,2-diazepine structure[6]. In order to support the tetrahydropyridine structure for compounds **7**, we synthesized ethyl 6,6-dimethyl-1-dimethylamino-4-oxo-1,4,5,6-tetrahydro-3-pyridinecarboxylate **(11)** by reacting *N,N*-dimethylhydrazine **(10)** with the enamine derivative **3a** ($R^1=R^2=CH_3$, $R^3=H$).

The microanalytical, ^{1}H-N.M.R., I.R., and U.V. data for compounds **7** (see Table 2) and compound **11** are entirely consistent with the assignment of a tetrahydropyridine structure. This is also well confirmed by comparison of the ^{13}C-N.M.R. chemical shifts for compounds **7a** and **11** (see Table 2). Moreover those chemical shifts for compound **7a** are different from those reported for a 7,7-dimethyl-5-oxo-2-phenyl-2,5,6,7-tetrahydro-1*H*-1,2-diazepine structure [$\delta=194.0$ (C-4); 57.5 (C-5); 68.5 ppm (C-6)][6].

Although a few syntheses of alkenylpyrazoles have been reported in the literature[7], we found no examples of 1-anilino- or 1-amino-4-oxo-1,4,5,6-tetrahydro-3-pyridinecarboxylic acid derivatives.

γ,δ-Unsaturated β-Keto Esters 1:

These are prepared as described in the literature; ethyl 5-methyl-3-oxo-4-hexenoate (**1**; $R^1=R^2=CH_3$, $R^3=H$)[8]; ethyl (*E*)-4-methyl-3-oxo-4-hexenoate (**1**; $R^1=R^3=CH_3$, $R^2=H$)[9]; ethyl (*E*)-3-oxo-4-hexenoate (**1**; $R^1=CH_3$, $R^2=R^3=H$)[10]; ethyl 4-methyl-3-oxo-4-pentenoate (**1**, $R^1=R^2=H$, $R^3=CH_3$)[10]; ethyl (*E,E*)-3-oxo-4,6-octadienoate (**1**, $R^1=CH_3$—CH=CH—; $R^2=R^3=H$)[11].

5-Alkenyl-4-ethoxycarbonyl-1-phenylpyrazoles (6a–e); General Procedure:

A solution of dimethylformamide dimethylacetal (**2**; 1.91 g, 16 mmol) in benzene (10 ml) is added in one portion to a solution of the γ,δ-unsaturated β-keto ester **1** (10 mmol) in benzene (10 ml). The mixture is refluxed for 1 h. Evaporation of the solvent under reduced pressure affords the crude enamine derivatives **3**.

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): $\delta=2.91$–3.01 ppm [s, 6H, $N(CH_3)$].

The enamine **3** obtained is dissolved in acetic acid (50 ml), phenylhydrazine (**4**; 1.08 g, 10 mmol) is added and the mixture is refluxed overnight. The reaction mixture is poured into water (250 ml) and extracted with chloroform (3 × 50 ml). The combined organic phase is washed with 5% sodium hydrogen carbonate (2 × 50 ml), water (50 ml), and then dried with sodium sulfate. The chloroform is evaporated and the residue is chromatographed through a column (22 mm × 35 cm) of silica gel (50 g) using hexane/ethyl acetate (1 : 1) as eluent. The range of fraction collected for each product is given below.

Product	Fraction Collected	Yield [g]
6a	90 to 180 ml	2.11
6b	90 to 180 ml	2.11
6c	85 to 175 ml	1.90
6d	85 to 165 ml	1.88
6e	85 to 175 ml	2.09

Ethyl 4-Oxo-1,4,5,6-tetrahydro-3-pyridinecarboxylates (7a–d); General Procedure:

The crude enamine **3** obtained as described above for the preparation of pyrazoles **6** is dissolved in anhydrous 1,2-dimethoxyethane (50 ml) and refluxed with phenylhydrazine (**4**; 1.08 g, 10 mmol) overnight. For the isolation of **7a–c**, the solvent is evaporated and the residue is

Table 1. 5-Alkenyl-4-ethoxycarbonyl-1-phenylpyrazoles **6a–e**

Product No.	R^1	R^2	R^3	Yield [%]	m.p. [°C]	Molecular formula[a]	I.R. ($CHCl_3$) ν [cm^{-1}]	U.V. (C_2H_5OH) λ [nm] (ε)	^{1}H-N.M.R. ($CDCl_3$/TMS_{int}) δ [ppm]
6a	CH_3	CH_3	H	78	oil	$C_{16}H_{18}N_2O_2$ (270.3)	1710, 1605, 965	251 (14200)	1.36 (t, 3H, $J=7$ Hz); 1.42 (s, 3H); 1.88 (s, 3H); 4.31 (q, 2H, $J=7$ Hz); 6.05–6.25 (m, 1H); 7.2–7.6 (m, 5H); 8.10 (s, 1H)
6b	CH_3	H	CH_3	78	75°[b]	$C_{16}H_{18}N_2O_2$ (270.3)	1715, 1605, 965	246 (14000)	1.36 (t, 3H, $J=7$ Hz); 1.70 (apparent doublet, 3H, $J=7$ Hz); 1.8–1.9 (m, 3H); 4.33 (q, 2H, $J=7$ Hz); 5.4–5.8 (m, 1H); 7.46 (s, 5H); 8.10 (s, 1H)
6c	CH_3	H	H	74	oil	$C_{15}H_{16}N_2O_2$ (256.3)	1710, 1605, 965	257 (14000)	1.39 (t, 3H, $J=7$ Hz); 1.83 (d, 3H, $J=5.5$ Hz); 4.35 (q, 2H, $J=7$ Hz); 6.1–6.8 (m, 2H); 7.50 (s, 5H); 8.10 (s, 1H)
6d	H	H	CH_3	73	78°[b]	$C_{15}H_{16}N_2O_2$ (256.3)	1710, 1600, 965, 910	244 (12400)	1.36 (t, 3H, $J=7$ Hz); 2.0–2.1 (m, 3H); 4.35 (q, 2H, $J=7$ Hz); 5.10 (s, 1H); 5.4–5.5 (m, 1H); 7.50 (s, 5H); 8.11 (s, 1H)
6e[c]	H_3C—CH=CH—	H	H	74	oil	$C_{17}H_{18}N_2O_2$ (282.3)	1710, 1600, 990, 955	296 (17900)	1.34 (t, 3H, $J=7$ Hz); 1.79 (d, 3H, $J=5.5$ Hz); 4.38 (q, 2H, $J=7$ Hz); 5.3–7.2 (m, 4H); 7.51 (s, 5H); 8.14 (s, 1H)

[a] The microanalyses were in satisfactory agreement with the calculated values: C ±0.17, H ±0.14, N ±0.30.
[b] Recrystallized from hexane.
[c] (*E,E*)-Isomer.

Table 2. Ethyl 4-Oxo-1,4,5,6-tetrahydro-3-pyridinecarboxylates **7a–d**

Product No.	R^1	R^2	R^3	Yield [%]	m.p. [°C]	Molecular formula[a]	I.R. ($CHCl_3$) ν [cm^{-1}]	U.V. (C_2H_5OH) λ [nm] (ε)	^{1}H-N.M.R. ($CDCl_3/TMS_{int}$) δ [ppm]
7a	CH_3	CH_3	H	72	203°	$C_{16}H_{20}N_2O_3$ (288.3)	3290, 1730, 1675, 1605, 1580	237 (16500), 306 (15900)	1.28 (t, 3H, J=7 Hz); 1.36 (s, 6H); 2.69 (s, 2H); 4.24 (q, 2H, J=7 Hz); 6.8–7.5 (m, 6H, 1H exchangeable with D_2O); 8.26 (s, 1H)[c]
7b[b]	CH_3	H	CH_3	52	183°	$C_{16}H_{20}N_2O_3$ (288.3)	3280, 1730, 1670, 1610, 1585	238 (17300), 308 (15200)	1.1–1.5 (m, 9H); 2.2–3.2 (m, 1H); 3.3–4.4 (m, 3H, with a quadruplet at 4.21); 6.8–7.5 (m, 6H, 1H exchangeable); 8.29, 8.33 (2s, 1H)
7c	CH_3	H	H	56	170°	$C_{15}H_{18}N_2O_3$ (274.3)	3280, 1730, 1670, 1605, 1585	238 (16700), 307 (15100)	1.28 (t, 3H, J=7 Hz); 1.33 (d, 3H, J=7 Hz); 2.44 (dd, 1H, J=15 and 6 Hz); 2.65 (dd, 1H, J=15 and 6 Hz); 3.9–4.4 (m, 3H with a quadruplet at 4.19); 6.8–7.5 (m, 6H, 1H exchangeable); 8.35 (s, 1H)
7d	H	H	CH_3	63	138°	$C_{15}H_{18}N_2O_3$ (274.3)	3270, 1730, 1675, 1615, 1590	237 (15800), 306 (15600)	1.18 (d, 3H, J=7 Hz); 1.29 (t, 3H, J=7 Hz); 2.5–3.0 (m, 1H); 3.3–3.9 (m, 2H); 4.23 (q, 2H, J=7 Hz); 6.8–7.5 (m, 6H, 1H exchangeable); 8.44 (s, 1H)

[a] The microanalyses were in satisfactory agreement with the calculated values: C ±0.16, H ±0.14, N ±0.08.
[b] Mixture of *cis/trans* isomers.
[c] ^{13}C-N.M.R. ($CDCl_3/TMS_{int}$): δ=51.5 (C-5); 63.1 (C-6); 187.8 ppm (C-4).

treated with ethyl acetate (10 ml). The crystals formed are collected by filtration. Compound **7d** is obtained by chromatography of the residue on a column (22 mm × 35 cm) of silica gel (50 g) using ethyl acetate as eluent from the fraction 150–350 ml; yield: 1.75 g (63%). Analytical samples of **7** are prepared by recrystallization from acetonitrile.

5,5-Dimethyl-3-ethoxycarbonyl-4,5-dihydropyrazolo[1,5-*a*]quinoline (9): A mixture of the alkenylpyrazole **6a** (1.35 g, 5 mmol) and concentrated sulfuric acid (13.5 ml) is stirred overnight at room temperature. The resulting mixture is diluted with crushed ice and extracted with chloroform (3 × 50 ml). The extracts are washed with water (2 × 50 ml) and dried with sodium sulfate. The chloroform is evaporated and the residue is chromatographed through a column (22 mm × 35 cm) of silica gel (50 g) using hexane/ethyl acetate (1:1) as eluent. The compound **9** is collected in the fraction 80–140 ml, oil; yield: 1.00 g (74%).

$C_{16}H_{18}N_2O_2$	calc.	C 71.09	H 6.71	N 10.36
(270.3)	found	71.14	6.73	10.31

I.R. ($CHCl_3$): ν=1710 cm^{-1} (C=O).

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ=1.33 (s, 6H); 1.39 (t, 3H, J=7 Hz); 3.24 (s, 2H); 4.36 (q, 2H, J=7 Hz); 7.1–7.6 (m, 3H); 7.9–8.2 ppm (m, 2H, with a singlet at 8.09).

Ethyl 6,6-Dimethyl-1-dimethylamino-4-oxo-1,4,5,6-tetrahydro-3-pyridinecarboxylate (11):
A solution of dimethylformamide dimethylacetal (**2**; 1.91 g, 16 mmol) in benzene (10 ml) is added to a solution of **1a** (1.7 g, 10 mmol) in benzene. The mixture is refluxed for 1 h and the solvent is evaporated under reduced pressure to afford the crude enamine **3**. The enamine **3** is dissolved in anhydrous dimethoxymethane (50 ml) and refluxed with *N,N*-dimethylhydrazine (**10**; 0.6 g, 10 mmol) overnight. After evaporation of the solvent, the residue is triturated with hexane (20 ml) and the crystalline solid obtained is filtered under suction; yield: 2.09 g (87%). An analytical sample is obtained by recrystallization from hexane/ethyl acetate (4:1); m.p. 106 °C.

$C_{12}H_{20}N_2O_3$	calc.	C 59.98	H 8.39	N 11.66
(240.3)	found	59.72	8.58	11.56

I.R. ($CHCl_3$): ν=1725, 1665, 1575 cm^{-1}.

U.V. (C_2H_5OH): λ_{max}=240 (11000); 309 nm (14800).

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): δ=1.34 (t, 3H, J=7 Hz); 1.38 (s, 6H); 2.51 (s, 2H); 2.73 (s, 6H); 4.28 (q, 2H, J=7 Hz); 8.39 ppm (s, 1H).

^{13}C-N.M.R. ($CDCl_3/TMS_{int}$): δ=52.0 (C-5); 63.1 (C-6); 186.6 (C-4) ppm.

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