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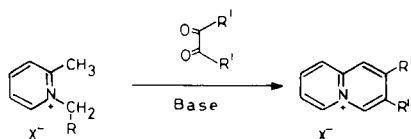
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Condensation of 2-methylpyridinium salts with 1,2-dicarbonyls in the presence of base, yielded 2,3-disubstituted quinolizinium compounds. Results obtained with different pyridinium substrates are discussed.

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The Westphal condensation [1,2] (Figure 1) is an application of the use in synthesis of 2-methylpyridinium salts and their ability to generate carbanions on two points of the molecule namely, *N*-methylene and 2-methyl groups. Reaction of a picolinium salt under basic medium with a 1,2-dicarbonyl would produce a quinolizinium salt.



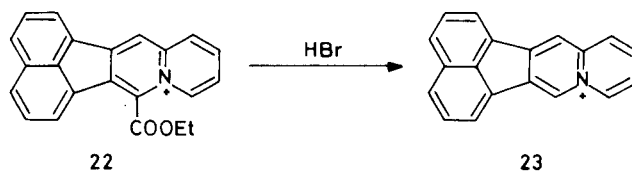
Although not deeply studied, the method seems to be the simplest one to produce a quinolizinium cation, a poorly studied nitrogen bridgehead heterocycle [3-5]. Present paper describes the use of an optimized Westphal condensation [6] using 2-methylpyridinium salts (Table 1) with different stabilising groups.

Results of the condensation with compound **1** (I, R = CH₃CH₂OCO-, Figure 1) are summarized in Table 2. As it can be seen, the ester group is cleaved by hydrolysis from the final product. The use of diacyls **8-10** produced yields apparently related with the ability of each diketone to form a cyclic monoenol stabilised by an H-bond [11]. The lack of reactivity of 1,2-cyclohexanedione is justified as a cyclic monoenol predominates in 99% when dissolved in chloroform and equilibrium in acetone should be similar.

Reaction with benzyls (compounds **11-20**) produced quinolizinium salts but reaction time and yield were markedly affected by the electronic character of the substituents. Thus, electron attracting groups (**16, 17**) produced high yields in ½ hour and by contrast electron donating groups retarded or even prevented the process (**18, 19, 20**). We could not reproduce the condensation with an anisyl group described by Westphal [1].

O-Quinones **21,22** produced similar results, but unexpectedly, 1,2-acenaphthoquinone produced a quinolizinium salt in which the ester group was retained. Conversion

of **22** to **23** was produced by hydrolysis in concentrated hydrobromic acid (Figure 2).



Ketone stabilised substrate **2** produced also a Westphal condensation with cleavage of the benzoyl moiety, but quinolizinium formation competes with Tschitschibabin indolizine synthesis [7,13] (Table 3). The reaction produced mixtures of different composition partially depending of the reactivity of the diketone. Products were easily separated by solubility differences.

Nitrile and amide stabilised substrates **3** and **4** produced the condensation (Table 4) retaining the functional group. Compound **4** produced the lowest yields. Substrates **5-7** did not produce any quinolizinium derivate being recovered unchanged in more than 80% after every reaction.

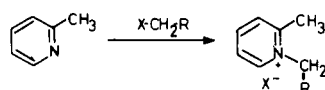
Very important was the choice of the base in every process; sodium acetate produced the best yields with **1**, sodium formate with **3** and triethylamine with **4**. Di-*n*-butylamine produced with **2**, the highest yields of quinolizinium salt.

Microanalytical and spectroscopic data of the products isolated are presented in Table 5.

EXPERIMENTAL

The melting points were determined in open capillary tubes and are uncorrected. Spectra were recorded with a Perkin Elmer 577 grating ir spectrophotometer and with a Perkin Elmer R 24B (60 MHz) and a Brüker EM 390 (300 MHz) ¹H nmr spectrometers. The 1,2-dicarbonyls were either from commercial sources (as diacetyl and benzyl) or prepared from methods previously described such as 4,5-octanedione [14], 1,2-cyclohexanedione [15], 3,3'-dimethylbenzyl [16], 4,4'-dimethylbenzyl [16], 3,3'-dichlorobenzyl [16], 4,4'-dichlorobenzyl [17], 3,3'-dinitrobenzyl [18], 4,4'-dinitrobenzyl [19], 3,3'-dimethoxybenzyl [20], 4,4'-dimethoxybenzyl [21], 3,3',4,4'-tetramethoxybenzyl [22], 9,10-phenanthrenequinone [23] and 1,2-acenaphthoquinone [24].

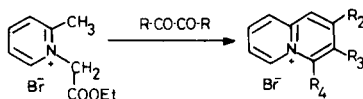
Table 1
1-Substituted-2-methylpyridinium Salts



Compound	R	X ⁻	Reaction Time, (hours)	Yield (%) [a]	Mp (°C) [b]	Lit Mp (°C)
1	CH ₃ CH ₂ OCO	Br	1/2	86	128	128 [c]
2	C ₆ H ₅ CO	Br	1/2	83	214-215	214 [d]
3	NC	Cl	72	70	205	204-206 [e]
4	H ₂ NCO	Cl	14	70	212-213	—
5	C ₆ H ₅	Cl	8	51	98	98 [f]
6	<i>p</i> -O ₂ NC ₆ H ₄	Br	3/4	42	215	211 [g]
7	<i>o</i> -O ₂ NC ₆ H ₄	Br	3/4	40	176	—

[a] In isolated pure product. [b] Crystallized from ethanol-ether. [c] From [1]. [d] From [7]. [e] From [8]. [f] From [9]. [g] From [10].

Table 2
Quinolizinium Salts from 1



Compound	R ₂	R ₃	R ₄	Reaction Time (hours)	Yield (%) [a]	Mp (°C, dec)	Lit Mp (°C)
8	CH ₃	CH ₃	H	2	88	235-236	233 [b]
9	CH ₃ (CH ₂) ₂	CH ₃ (CH ₂) ₂	H	2	41	177-178	—
10	(CH ₂) ₄	(CH ₂) ₄	—	No reaction after 72 hours [c]			—
11	C ₆ H ₅	C ₆ H ₅	H	2	79	286	284-285 [d]
12	<i>m</i> -CH ₃ C ₆ H ₄	<i>m</i> -CH ₃ C ₆ H ₄	H	4	85	258-259	—
13	<i>p</i> -CH ₃ C ₆ H ₄	<i>p</i> -CH ₃ C ₆ H ₄	H	5	54	299	—
14	<i>m</i> -ClC ₆ H ₄	<i>m</i> -ClC ₆ H ₄	H	3	75	282-283	—
15	<i>p</i> -ClC ₆ H ₄	<i>p</i> -ClC ₆ H ₄	H	4	72	313-314	—
16	<i>m</i> -O ₂ C ₆ H ₄	<i>m</i> -O ₂ C ₆ H ₄	H	1/2	91	276-278	—
17	<i>p</i> -O ₂ C ₆ H ₄	<i>p</i> -O ₂ C ₆ H ₄	H	1/2	89	329-330	—
18	<i>m</i> -CH ₃ OC ₆ H ₄	<i>m</i> -CH ₃ OC ₆ H ₄	H	5	59	230	—
19	<i>p</i> -CH ₃ OC ₆ H ₄	<i>p</i> -CH ₃ OC ₆ H ₄	—	No reaction after 72 hours [c]			—
20	<i>m,p</i> -CH ₃ OC ₆ H ₃	<i>m,p</i> -CH ₃ OC ₆ H ₃	—	No reaction after 72 hours [c]			—
21	diphenyl- <i>o,o'</i> -di-yl [e]		H	2	75	338	332 [b]
22	naphth-1,8-di-yl [f]		COOEt	2	73	129-130	—

[a] In isolated pure product. [b] From [1]. [c] Dicarbonyl compound was recovered unchanged in more than 85% yield. [d] From [12]. [e] Produces acenaphthylene ring. [f] Produces phenanthrene ring.

General Procedure for Preparation of 1-Substituted-2-methylpyridinium Salts (Table 1, Compounds 1, 2, 4-7).

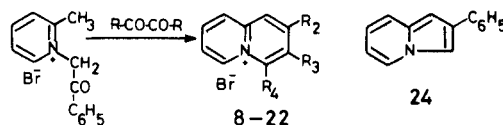
2-Picoline (0.22 mole), the halide (0.2 mole) and acetone (50 ml) were heated under reflux for the time described in Table 1. The salt was filtered off as a white powder which was crystallised from ethanol-ether.

Compound 3 was prepared as described in [8].

General Procedure for the Preparation of Quinolizinium Salts Derived from 1 (Table 2, Compounds 8-22).

N-Ethoxycarbonylmethyl-2-methylpyridinium bromide (2.6 g, 10 mmoles), the corresponding dicarbonyl compound (11.5 mmoles) and 0.83 g of dry sodium acetate (10 mmoles) were suspended in acetone (20 ml) and refluxed as indicated in Table 2. The mixture was allowed to cool

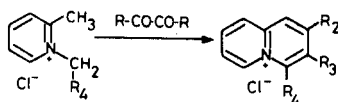
Table 3
Quinolizinium Salts from 2



Compound	R ₂	R ₃	R ₄	Reaction Time (hours)	Yield (%) [a]	24 Yield (%) [a,b]
8	CH ₃	CH ₃	H	2	59	11
9	CH ₃ (CH ₂) ₃	CH ₃ (CH ₂) ₃	H	2	5	60
11	C ₆ H ₅	C ₆ H ₅	H	2	67	4
12	<i>m</i> -CH ₃ C ₆ H ₄	<i>m</i> -CH ₃ C ₆ H ₄	H	4	5	6
13	<i>p</i> -CH ₃ C ₆ H ₄	<i>p</i> -CH ₃ C ₆ H ₄	H	5	9	49
14	<i>m</i> -ClC ₆ H ₄	<i>m</i> -ClC ₆ H ₄	H	2	12	52
15	<i>p</i> -ClC ₆ H ₄	<i>p</i> -ClC ₆ H ₄	H	2	11	43
16	<i>m</i> -O ₂ NC ₆ H ₄	<i>m</i> -O ₂ NC ₆ H ₄	H	2	57	9
21	diphenyl- <i>o,o'</i> -di-yl [c]		H	2	6	70
23	naphth-1,8-di-yl		H	2	8	42

[a] In isolated pure product. [b] Mp 215° as described in [7]. [c] Produces acenaphthylene ring. [d] Produces phenanthrene ring.

Table 4
Quinolizinium Salts from 3 and 4



Compound	R ₂	R ₃	R ₄	Reaction Time (hours)	Yield ϕ [a]	Mp (°C, dec)
25	CH ₃	CH ₃	NC	2	78 [b]	318 [c]
26	<i>m</i> -O ₂ NC ₆ H ₄	<i>m</i> -O ₂ NC ₆ H ₄	NC	½	65 [b]	276 [c]
27	diphenyl- <i>o,o'</i> -di-yl [f]		NC	½	83 [b]	207-308 [c]
28	naphth-1,8-di-yl [g]		NC	2	89 [b]	350 [c]
28	CH ₃	CH ₃	H ₂ NCO	2	13 [d]	235-236 [e]
29	C ₆ H ₅	C ₆ H ₅	H ₂ NCO	2	11 [d]	202 [e]
30	C ₆ H ₅	C ₆ H ₅	H ₂ NCO	2	11 [d]	202 [e]
31	<i>p</i> -ClC ₆ H ₄	<i>p</i> -ClC ₆ H ₄	H ₂ NCO	2	11 [d]	289-290 [e]

[a] In isolated pure product. [b] Sodium formiate was used as base. [c] From ethanol. [d] Triethylamine was used as base. [e] From ethanol-ether. [f] Produces acenaphthylene ring. [g] Produces phenanthrene ring.

and neutralized with hydrobromic acid. The mixture was concentrated to dryness and the residue triturated with 2 ml of acetone to dissolve the excess of dicarbonyl compound. The residue was dissolved in the minimum quantity of boiling ethanol and acetone was added until turbidity appeared, then the mixture was cooled and the sodium bromide which precipitated was filtered off. The remaining solution was concentrated to dryness and the solid crystallised from ethanol. Yields are presented in Table 2.

Synthesis of Acenaphtho[1,2-*b*]quinolizinium Bromide.

Compound 22 (2 g, 4.9 mmoles) was dissolved in hydrobromic acid (30 ml) and the solution was heated under reflux for 6 hours. A yellow precipitate was formed and the suspension was concentrated to dryness. The residue was crystallised from ethanol-water producing 0.8 g (yield, 48%) of 23 as yellow needles of mp 257-259°.

General Procedure for the Preparation of Quinolizinium Salts Derived from 2 (Table 3, Compounds 8, 9, 11-16, 21, 22).

One g (3.7 mmoles) of *N*-benzoylmethyl-2-methylpyridinium bromide, the corresponding dicarbonyl compound (4.2 mmoles) and 0.48 g (0.63 ml, 3.7 mmoles) of di-*n*-butylamine were suspended in 10 ml of acetone and the mixture was refluxed as indicated in Table 3. Then the solution was concentrated to dryness and the residue was triturated with 3 × 3 ml

Table 5
Analytical and Spectroscopic Data from Compounds 1-31 [a]

Compound	Mp (°C)	Molecular Formulae	Found (%) / Required (%)			$\nu_{\text{C}=\text{N}}$	Others	¹ H NMR Data (δ)
			C	H	N			
1 [g,h]	128 [b]					1625	1745	8.70 (d, 1H, J = 8 Hz), 8.40 (t, 1H), 7.90 (d, 2H, J = 9 Hz), 5.55 (s, 2H), 2.8 (s, 3H), 4.3 (q, 2H), 1.3 (t, 3H)
2 [g,h]	214-215 [c]					1620	1690	8.70 (d, 1H, J = 8 Hz), 8.50 (t, 1H), 8.0 (m, 2H), 7.4-7.9 (m, 5H), 4.7 (s, 2H), 2.75 (s, 3H)
3 [g,h]	205 [d]					1630	2230	8.70 (d, 1H, J = 6 Hz), 8.40 (t, 1H), 7.90 (d, 2H, J = 7 Hz), 4.55 (s, 2H), 3.25 (s, 3H)
4 [g,i]	212-213	C ₆ H ₁₁ ClN ₂ O	51.50 (51.48)	5.72 (5.94)	15.32 (15.01)	1630	1710	9.10 (d, 1H, J = 6 Hz), 8.57 (t, 1H), 8.12 (d, 2H, J = 8 Hz), 5.57 (s, 2H), 2.74 (s, 3H)
5 [g,h]	98 [e]					1640	1350	9.0 (d, 1H, J = 6 Hz), 8.6 (t, 1H), 8.20 (m, 2H), 7.50 (s, 5H), 5.95 (s, 2H), 2.90 (s, 3H)
6 [g,h]	215 [f]					1630	1360	9.20 (d, 1H, J = 6 Hz), 8.85 (t, 1H), 8.40 (m, 2H), 8.30 (d, 2H), 7.85 (d, 2H), 6.30 (s, 2H), 3.0 (s, 3H)
7 [g,h]	176	C ₁₃ H ₁₃ BrN ₂ O ₂	50.24 (50.50)	4.58 (4.24)	9.45 (9.06)	1630	1350	9.0 (d, 1H), 8.65 (t, 1H), 8.30 (m, 2H), 7.90 (d, 1H), 7.50 (d, 1H), 7.20 (m, 2H), 6.25 (d, 2H), 2.95 (d, 3H)
8 [j,i]	235-236 [k]					1640		9.37 (s, 1H), 9.2.7 (d, 1H, J = 6.6 Hz), 8.43 (m, 2H), 8.27 (t, 1H), 8.0 (t, 1H), 2.6 (s, 3H), 2.53 (s, 3H)
9 [g,i]	177-118	C ₁₅ H ₂₀ BrN·H ₂ O	57.88 (57.69)	6.81 (7.10)	4.79 (4.48)	1652		9.43 (s, 1H), 9.40 (d, 1H), 8.50 (s, 1H), 7.9-8.6 (m, 3H), 2.88 (t, 4H, J = 6 Hz), 1.78 (m, 4H), 1.02 (t, 6H, J = 7 Hz)
11 [j,i]	286 [l]					1645		9.72 (s, 1H), 9.58 (d, 1H, J = 6.9 Hz), 8.83 (s, 1H), 8.73 (d, 1H, J = 6 Hz), 8.34 (bt, 1H), 8.16 (bt, 1H), 7.4 (s, 10H)
12 [j,i]	258-259	C ₂₃ H ₂₀ BrN·H ₂ O	67.59 (67.65)	4.63 (4.93)	3.40 (3.43)	1650		9.62 (s, 1H), 9.51 (d, 1H), J = 7.2 Hz), 8.80 (s, 1H), 8.70 (d, 1H), 8.43 (t, 1H), 8.15 (t, 1H), 7.24 (d, 4H), 7.23 (s, 2H), 6.9-7.1 (m, 2H), 2.30 (s, 6H)
13 [j,i]	299	C ₂₃ H ₂₀ BrN·½H ₂ O	69.03 (69.17)	5.17 (5.30)	3.29 (3.50)	1650		9.58 (s, 1H), 9.50 (d, 1H, J = 7.5 Hz), 8.72 (s, 1H), 8.66 (d, 1H, J = 7.5 Hz), 8.37 (bt, 1H), 8.12 (bt, 1H), 7.22 (s, 8H), 2.33 (s, 6H)
14 [j,i]	282-283	C ₂₁ H ₁₄ BrCl ₂ N	58.21 (58.49)	2.98 (3.27)	3.02 (3.25)	1650		9.73 (s, 1H), 9.50 (d, 1H, J = 7.5 Hz), 8.87 (s, 1H), 8.67 (d, 1H), 8.47 (t, 1H), 8.20 (t, 1H), 7.15-7.60 (t, 8H)
15 [j,i]	313-314	C ₂₁ H ₁₄ BrCl ₂ N·H ₂ O	55.92 (56.15)	3.20 (3.20)	2.83 (2.83)	1650		9.67 (s, 1H), 9.47 (d, 1H, J = 6.8 Hz), 8.60 (d, 1H, J = 7.5 Hz), 8.37 (bt, 1H), 8.10 (bt, 1H), 7.33 (dd, 8H)
16 [j,i]	276-278	C ₂₁ H ₁₄ BrN ₃ O ₄ ·H ₂ O	53.90 (53.63)	3.24 (3.42)	8.68 (8.93)	1657	1360	9.86 (s, 1H), 9.53 (d, 1H, J = 6.8 Hz), 9.00 (s, 1H), 8.75 (d, 1H, J = 7.2 Hz), 8.53 (bt, 1H), 8.27 (m, 1H), 8.1-8.45 (m, 4H), 7.6-7.8 (m, 4H)
17 [j,i]	329-330	C ₂₁ H ₁₄ BrN ₃ O	55.54 (55.75)	3.30 (3.11)	9.09 (9.29)	1650	1360	9.4 (s, 1H), 9.37 (d, 1H), 8.6 (s, 1H), 8.2-8.6 (m, 3H), 8.35 (d, 4H, J = 8 Hz), 7.65 (d, 4H)
18 [j,i]	230	C ₂₃ H ₁₂ BrNO ₂	65.13 (65.41)	5.02 (4.77)	3.15 (3.32)	1650	1530	9.75 (s, 1H), 9.6 (d, 1H, J = 7.5 Hz), 8.84 (s, 1H), 8.74 (d, 1H, J = 8.1 Hz), 8.43 (t, 1H), 8.15 (t, 1H), 6.95 (s, 2H), 7.2 (t, 2H), 6.86 (dd, 4H), 3.43 (s, 3H)
21 [g,h]	338 [m]					1650		9.60 (s, 1H), 9.00 (d, 1H, J = 6 Hz), 8.60 (s, 1H), 7.8-8.3 (m, 7H), 7.1-7.6 (m, 4H)
22 [g,n]	129-130	C ₂₂ H ₁₇ BrNO ₂	64.78 (64.87)	4.10 (4.20)	3.21 (3.43)	1640		8.94 (d, 1H, J = 6 Hz), 8.41 (bs, 3H), 7.42-8.24 (m, 7H), 4.98 (q, 2H), 1.67 (t, 3H)
23 [g,n]	257-259	C ₁₉ N ₁₂ BrN	68.00 (68.28)	3.60 (3.62)	3.87 (4.19)	1640		9.07 (d, 1H, J = 6 Hz), 7.5-8.4 (m, 11H)
25 [g,n]	318	C ₁₂ H ₁₁ ClN ₂	65.61 (65.90)	5.26 (5.07)	12.96 (12.80)	1650	2230	9.45 (d, 1H, J = 6 Hz), 8.45 (s, 1H), 8.0-8.60 (m, 3H), 2.70 (s, 3H), 2.40 (s, 3H)
26 [g,n]	276	C ₂₂ H ₁₃ ClN ₄ O ₄ ·H ₂ O	58.47 (58.60)	3.16 (3.35)	12.15 (12.42)	1650	1360	9.31 (d, 1H, J = 6 Hz), 8.5-8.75 (m, 2H), 8.20-8.50 (m, 4H), 7.60-7.9 (m, 4H)
27 [g,n]	307-308	C ₂₂ H ₁₃ ClN	77.22 (77.52)	3.64 (3.84)	8.47 (8.21)	1650		9.76 (d, 1H, J = 6 Hz), 9.67 (s, 1H), 9.25 (d, 1H, J = 9 Hz), 8.2-8.8 (m, 7H), 7.6-8.0 (m, 3H)

Table 5, continued

Compound	Mp (°C)	Molecular Formulae	Found (%) / Required (%)			$\nu_{C=N}$	Others	¹ H NMR Data (δ)
			C	H	N			
28 [g,n]	350	C ₂₀ H ₁₁ ClN ₂	76.12 (76.30)	3.80 (3.52)	8.94 (8.89)	1645		9.67 (d, 1H, J = 6 Hz), 9.06 (s, 1H), 8.2-8.8 (m, 7H), 8.12 (d, 1H, J = 6 Hz), 7.85 (d, 1H, J = 6 Hz)
29 [g,i]	235-236	C ₁₂ H ₁₃ ClN ₂ O	60.72 (60.89)	5.75 (5.53)	11.54 (11.83)	1650	1690	7.99-8.93 (m, 7H), 2.62 (s, 3H), 2.48 (s, 3H)
30 [g,i]	202	C ₂₂ H ₁₇ ClN ₂ O·½H ₂ O	70.99 (71.44)	4.65 (4.90)	7.29 (7.57)	1640	1690	9.29 (s, 1H), 9.03 (d, 1H, J = 6.5 Hz), 8.13-8.84 (m, 5H), 7.30 (s, 10H)
31 [g,i]	289-290	C ₂₂ H ₁₅ Cl ₃ N ₂ O·½H ₂ O	59.87 (60.22)	3.36 (3.67)	6.05 (6.38)	1640	1690	9.20 (d, 1H, J = 6 Hz), 8.90 (s, 1H), 7.50-8.80 (m, 3H), 7.45 (s, 8H)

[a] Analysis is described for new compounds. [b] 128° in [1]. [c] 214° in [7]. [d] 204-206 in [8]. 98° in [9]. 211° in [10]. [g] Perkin Elmer R 24 B (60 MHz). [h] ¹H NMR in deuterium oxide, DSS as internal reference. [i]. ¹H NMR in DMSO, TMS as internal reference. [j] Bruker EM 390 (90 MHz). [k] 233° in [1]. [l] 284-285° in [12]. [m] 332° in [1]. [n] ¹H NMR in TFA, TMS as internal reference.

of toluene to yield the quinolizinium salt by crystallisation from ethanol. The 2-phenylindolizine was dissolved in organic extracts and was isolated by chromatography on a 10 cm column of neutral alumina (Brockmann grade 1) with dichloromethane as the eluent followed by crystallisation from ethanol.

General Procedure for the Preparation of the Quinolizinium Salts Derived from **3**.

N-Cyanomethyl-2-methylpyridinium chloride (0.84 g, 5 mmoles), the corresponding dicarbonyl compound (5.75 mmoles) and 0.34 g (5 mmoles) of sodium formate were suspended in acetone (10 ml) and the mixture was refluxed as indicated in Table 4. The suspension was then filtered and the remaining solid was washed with 3 × 3 ml of acetone, diluted in the minimum quantity of water and the solution acidified with 10% hydrochloric acid at 0-5°. Finally the mixture was concentrated to dryness trying not to heat the mixture over 40°. The residue was crystallised from ethanol.

General Procedure for the Preparation of Quinolizinium Salts Derived from **4**.

1-Carbamoylmethyl-2-methylpyridinium chloride (0.93 g, 5 mmoles), the corresponding dicarbonyl compound (5.75 mmoles) and 0.5 g (0.7 ml, 5 mmoles) of triethylamine were suspended in acetone (10 ml) for 2 hours. The mixture was then concentrated to dryness and the residue crystallised from ethanol-ether.

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