A Facile and General Synthesis of 2,5,6-Trisubstituted-6,7-dihydro-1,3,4-oxadiazepines

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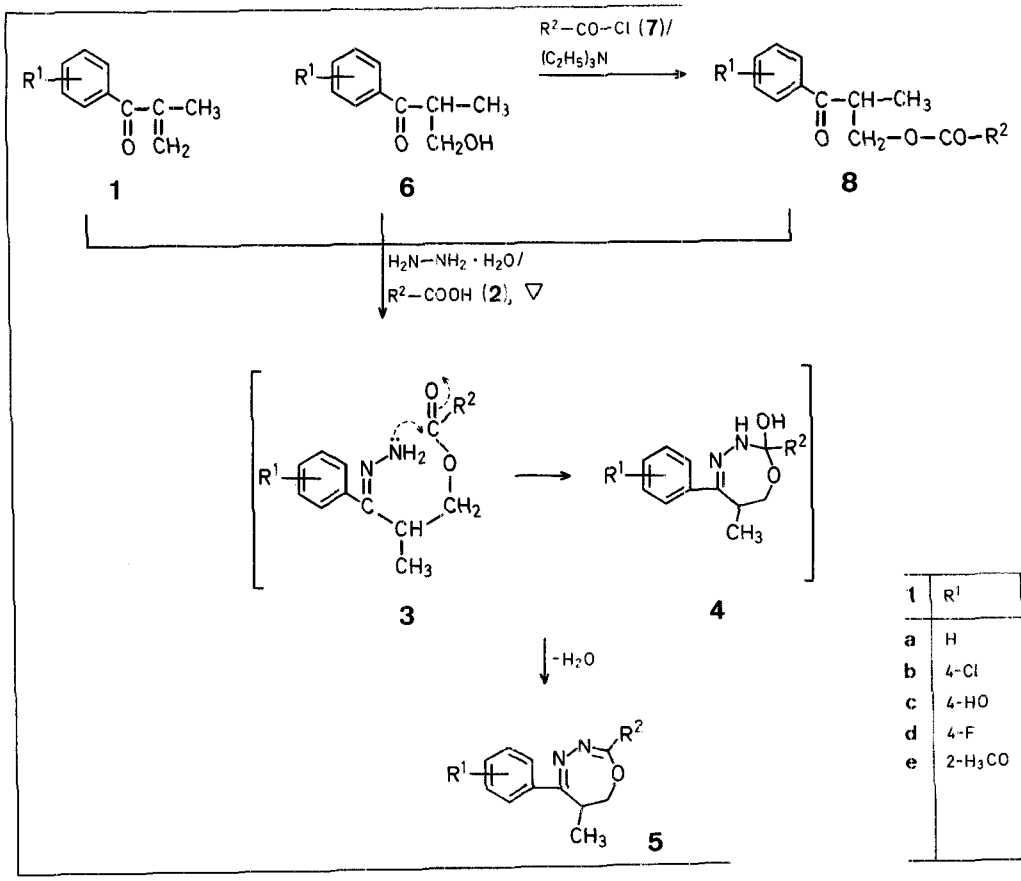
We wish to report a facile and general synthesis of 2,5,6-trisubstituted-6,7-dihydro-1,3,4-oxadiazepines **5**, a heterocyclic system practically unknown in the literature. To our knowledge, in fact, 1,3,4-oxadiazepines are only represented by a few 2,3-disubstituted 5,7,7-trimethyl-2,3,6,7-tetrahydro derivatives, recently obtained by condensing diacetone alcohol with aldehydes[1].

During attempts to obtain 4,5-dihydropyrazoles from 1-aryl-2-methyl-2-propen-1-ones **1** and hydrazines, the 1-phenyl derivative **1a**[2,3] was allowed to react with hydrazine hydrate in refluxing acetic acid (**2**, $R^2 = CH_3$) for 2 h. Work-up of the reaction mixture gave a product in 52% yield, identified as 2,6-dimethyl-5-phenyl-6,7-dihydro-1,3,4-oxadiazepine (**5aa**) by its physical and spectral properties as well as on the basis of further experimental evidence. Thus **5aa** could also be obtained using 3-hydroxy-2-methyl-1-phenyl-1-propanone (**6a**)[2,4] or the acetate **8aa** in the place of **1a** in 58% and 70%, respectively. Though only in minor amounts, **5aa** was also formed from the acetate **8aa** and hydrazine hydrate in refluxing toluene.

The disclosed pathways to **5aa** outline a general approach to oxadiazepines **5**, suitable intermediates **1** or **6** and carboxylic acids (**2**) providing the ring substituents at positions 5,6, and 2. Considering the heterocyclic structure of **5** as worthy of a



1	R^1	6	R^1	2, 7	R^2
a	H	a	H	a	CH_3
b	4-Cl	b	4-Cl	b	C_2H_5
c	4-HO	c	4-HO	c	
d	4-F			d	
e	2-H_3CO	f	4-H_3C		
		g	4-H_3CO		

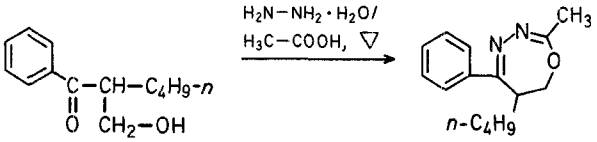
pharmacological investigation, we planned the synthesis of several derivatives of **5**, taking advantage of a convenient procedure reported[2] in the preceding paper for obtaining **1** and **6** from propiophenones, formaldehyde, and sodium hydroxide.

Accordingly, 2-ethyl-5-phenyl-6-methyl- **(5ab)** and 2,5-diphenyl-6-methyl-6,7-dihydro-1,3,4-oxadiazepine **(5ac)** were obtained in satisfactory yield by condensing **6a** with hydrazine hydrate in propanoic acid (at reflux) and in benzoic acid (in melt), respectively (Table 1). Alternatively, the reaction could be performed in the respective acid as the solvent, starting from the propanoate **8ab** and the benzoate **8ac**, easily prepared from **1a** and the appropriate acid chloride **7**. However, if acetic acid was used as the solvent, both **8ab** and **8ac** were transformed into **5aa** thus evidencing that a transesterification occurred before cyclisation.

Following the methods employed for **5aa**, **5ab**, and **5ac** a series of 5-aryl-6-methyl oxadiazepines **5** having alkyl or aryl substituents at the 2-position were synthesised (Table 1) from suitable **1** and **6**. The latter were prepared by adapting the literature procedure[2], except for the *p*-fluoro derivative **1d**, which was obtained by acylation of fluorobenzene with methacryloyl chloride[5].

The experiments reported here all account for the formation of **5** by the mechanism depicted. Compounds **1** and **6** condense with hydrazine hydrate and the appropriate carboxylic acid **2** to give the hydrazone **3** which is converted into the cyclic derivative **4** by intramolecular attack of the amino group to the ester carbonyl. Acid-catalysed loss of water from the unstable **4** eventually affords **5**. Though we were unable to isolate **3** from the reaction products, its formation, at least as a transient intermediate, seems sufficiently proved by the isolation of **5** on heating esters **8** with hydrazine hydrate.

In conclusion, the synthesis of 6,7-dihydro-1,3,4-oxadiazepines **5** has been achieved by a one-flask general procedure which could interchangeably employ, as the starting compound, **6** (as such or as the esters **8**) and **1**. However, when their behavior was examined comparatively, **8** appeared to be the most suitable intermediate.



9 **10**

Table 1. Compounds **5** prepared

Compound No.	R^1	R^2	Reaction Conditions: Method	Reaction Conditions: Keto educt	Yield [%]	b.p. [°C]/torr[a] or m.p. [°C] (solvent)	Molecular formula[b]	^{1}H-N.M.R. ($CDCl_3$/TMS)[c] δ [ppm]
5aa	H	CH_3	A	**1a**	52	150°/0.5	$C_{12}H_{14}N_2O$ (202.3)	1.3 (d, 3H, J = 6 Hz); 2.4 (s, 3H); 3.5–4.3 (m, 3H); 7.4–8.0 (m, 5H)
			A	**6a**	58			
			A	**8aa**	70			
5ab	H	C_2H_5	A	**6a**	50	70–74° (ether)	$C_{13}H_{16}N_2O$ (216.3)	1.05–1.35 (dt, 6H); 2.65 (q, 2H); 3.2–4.0 (m, 3H); 6.9–7.8 (m, 5H)
			A	**8ab**	60	115°/0.05		
5ac	H	C_6H_5	B	**6a**	40	80–82°	$C_{17}H_{16}N_2O$ (246.3)	1.4 (d, 3H, J = 6 Hz); 3.6–4.4 (m, 3H); 7.35–8.15 (m, 10H)
			B	**8ac**	58	(ethanol)		
5ba	4-Cl	CH_3	A	**1b**	31	87–90°	$C_{12}H_{13}ClN_2O$ (236.7)	1.3 (d, 3H, J = 6 Hz); 2.45 (s, 3H); 3.55–4.2 (m, 3H); 7.3–7.95 (app.q, 4H)
			A	**8ba**	41	(ether)		
5ca	4-HO	CH_3	A	**1c**	46	220–222°	$C_{12}H_{14}N_2O$ (218.3)	1.2 (d, 3H); 2.20 (s, 3H); 3.3 (br., s, 1H); 3.6–3.9 (m, 3H); 6.8 (d, 2H, J = 9 Hz); 7.5 (d, 2H, J = 9 Hz)
			A	**6c**	52	(ethanol)		
			A	**8ca**	72			
5cb	4-HO	C_2H_5	A	**8cb**	51	171–173° (ethanol)	$C_{13}H_{16}N_2O_2$ (232.3)	1.2–1.4 (td, 6H); 2.8 (q, 2H); 3.6–4.3 (m, 3H); 6.8 (d, 2H, J = 9 Hz); 7.6 (d, 2H, J = 9 Hz); 8.0 (s, 1H)
5da	4-F	CH_3	A	**1d**	62	103–105° (ether)	$C_{12}H_{13}FN_2O$ (220.4)	1.25 (d, 3H, J = 6 Hz); 2.45 (s, 3H); 3.55–4.15 (m, 3H); 7.0–7.9 (m, 4H)
5ea	2-H_3CO	CH_3	A	**1e**	58	170°/0.7	$C_{13}H_{16}N_2O_2$ (232.3)	1.15 (d, 3H, J = 6 Hz); 2.4 (s, 3H); 3.8 (s, 3H); 3.6–4.2 (m, 3H); 6.9–7.9 (m, 4H)
5fa	4-H_3C	CH_3	A	**8fa**	41	101° (ether)	$C_{13}H_{16}N_2O$ (216.3)	1.3 (d, 3H, J = 6 Hz); 2.4 (s, 6H); 3.55–4.15 (m, 3H); 7.2 (d, 2H, J = 9 Hz); 7.65 (d, 2H, J = 9 Hz)
5ga	4-H_3CO	CH_3	A	**8ga**	41	80–83° (ether)	$C_{13}H_{16}N_2O_2$ (232.3)	1.2 (d, 3H, J = 6 Hz); 2.3 (s, 3H); 3.8 (s, 3H); 3.6–4.1 (m, 3H); 6.9 (d, 2H, J = 9 Hz); 7.7 (d, 2H, J = 9 Hz)
5gc	4-H_3CO	C_6H_5	B	**8gc**	63	111–114° (ethanol)	$C_{18}H_{18}N_2O_2$ (294.4)	1.3 (d, 3H, J = 6 Hz); 3.8 (s, 3H); 3.6–4.2 (m, 3H); 6.7–8.0 (m, 9H)
5gd	4-H_3CO	4-Cl—C_6H_4	B	**8gd**	30	133–134° (ethanol)	$C_{18}H_{17}ClN_2O_2$ (328.8)	1.35 (d, 3H, J = 6 Hz); 3.8 (s, 3H); 3.8–4.3 (m, 3H); 6.7–8.0 (m, 8H)

[a] Kugelrohr distillation, bath temperature given.
[b] Satisfactory microanalyses obtained: C ± 0.30, H ± 0.26, N ± 0.24, F − 0.05, Cl + 0.2.
[c] Recorded on Hitachi-Perkin Elmer R 600 FT Spectrometer at 60 MHz.

1-Aryl-2-methyl-2-propen-1-ones 1a–e, 2-Alkyl-1-aryl-3-hydroxy-1-propanones 6a–e, f, g and 2-Hydroxymethyl-1-phenyl-1-hexanone (9):

With the exception of **1c, d** and **6a**, all compounds are prepared by the method reported in the preceding paper[2] involving the reaction of the appropriate aryl alkyl ketone, 37% formaldehyde and 0.5 normal sodium hydroxide solution in the given molar ratio at room temperature for 15 h. The crude reaction product is chromatographed on silica gel eluting with cyclohexane/ethyl acetate (from 98 : 2 to 70 : 30) collecting in the order **1**, starting ketone, and **6**. Physical and spectral data of compounds not reported in the literature are given below:

1-(p-Chlorophenyl)-2-methyl-2-propen-1-one **(1b)**: A 1 : 1.1 : 1.1 molar ratio of ketone, 37% formaledehyde, and 0.5 normal sodium hydroxide is used; yield: 50%; purified by column chromatography (see above; Ref.[6], b.p. 87.5–88 °C/3 torr).

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 2.0 (s, 3H); 5.6 (s, 1H); 5.9 (s, 1H); 7.4–7.8 ppm (m, 4H).

1-(o-Methoxyphenyl)-2-methyl-2-propen-1-one **(1e)**: A 1 : 1.1 : 2.2 molar ratio of ketone, 37% formaldehyde, and 0.5 normal sodium hydroxide is used; yield: 31%; purified by column chromatography (see above; Ref.[7], oil).

3-Hydroxy-2-methyl-1-(p-chlorophenyl)-1-propanone **(6b)**: Same molar ratio of starting materials as for **1b** is used; yield: 17%; b.p. 190 °C/22 torr.

$C_{10}H_{11}ClO_2$ (198.4)	calc.	C 60.46	H 5.58	Cl 17.85
	found	60.16	5.30	17.50

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.3 (d, 3H, J = 6 Hz); 2.9 (br.s, 1H); 3.3–4.0 (m, 3H); 7.4 (d, 2H, J = 9 Hz); 8.0 ppm (d, 2H, J = 9 Hz).

2-Hydroxymethyl-1-phenyl-1-hexanone **(9)**: Same molar ratio of starting materials as for **1b** is used; yield: 34%; b.p. 120 °C/0.5 torr (Kugelrohr distillation).

$C_{13}H_{18}O_2$ (206.3)	calc.	C 75.70	H 8.79
	found	75.69	8.96

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 0.8–1.7 (m, 9H); 2.3 (s, 1H); 3.6–4.0 (m, 3H); 7.3–8.2 ppm (m, 5H).

Compounds **1c**[2], **1d**[5], and **6a**[4] are prepared according to literature procedures.

1-(p-Fluorophenyl)-2-methyl-2-propen-1-one **(1d)**: yield: 50%; purified by column chromatography (see above; Ref.[5], b.p. 40–42 °C/0.1 torr).

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 2.1 (s, 3H); 5.6 (s, 1H); 5.9 (s, 1H); 7.8–8.0 (m, 4H).

3-Hydroxy-2-methyl-1-phenyl-1-propanone **(6a)**: yield: 64%; b.p. 130–132 °C/2 torr (Ref.[4], b.p. 116–117 °C/1.5 torr).

Table 2. Characterization of Esters **8** prepared

Product No.	R^1	R^2	Yield[a] [%]	b.p. [°C]/torr[b] or m.p. [°C] (solvent)	Molecular formula[c]	I.R.[d] ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS)[e] δ [ppm]
8aa	H	CH_3	75	80–85°/0.05	$C_{12}H_{14}O_3$ (206.2)	1740, 1680	1.2 (d, 3H, J = 6 Hz); 1.9 (s, 3H); 3.5–4.3 (m, 3H); 7.3–7.9 (m, 5H)
8ab	H	C_2H_5	80	90–95°/0.05	$C_{13}H_{16}O_3$ (220.3)	1775, 1680	0.9–1.3 (dt, 6H); 2.1 (q, 2H); 3.5–4.3 (m, 3H); 7.3–7.9 (m, 5H)
8ac	H	C_6H_5	65	125°/0.05	$C_{17}H_{16}O_3$ (268.3)	1720, 1680	1.3 (d, 3H, J = 6 Hz); 3.7–4.4 (m, 3H); 7.2–7.9 (m, 10H)
8ba	4-Cl	CH_3	55	–[f]	$C_{12}H_{13}ClO_3$ (240.7)	1750, 1685	1.25 (d, 3H, J = 6 Hz); 2.0 (s, 3H); 3.7–4.5 (m, 3H); 7.5 (d, 2H, J = 9 Hz); 8.0 (d, 2H, J = 9 Hz)
8ca	4-HO	CH_3	75[g]	130–132°[h] (ethanol)	$C_{12}H_{14}O_4$ (222.2)	3300, 1720, 1660	1.1 (d, 3H, J = 6 Hz); 2.1 (s, 3H); 3.5–4.5 (m, 3H); 6.9 (d, 2H, J = 9 Hz); 7.3 (br.s, 1H); 7.9 (d, 2H, J = 9 Hz)
8cb	4-HO	C_2H_5	50[g]	53–56°[h]	$C_{13}H_{16}O_4$ (236.26)	3300, 1720, 1675	1.0–1.3 (dt, 6H); 2.25 (q, 2H, J = 7 Hz); 3.8–4.6 (m, 3H); 6.9 (d, 2H, J = 8 Hz); 7.3 (br.s, 1H); 7.85 (d, 2H, J = 8 Hz)
8fa	4-H_3C	CH_3	54	–[f]	$C_{13}H_{16}O_3$ (220.3)	1740, 1680	1.15 (d, 3H, J = 6 Hz); 1.9 (s, 3H); 2.4 (s, 3H); 3.6–4.4 (m, 3H); 7.25 (d, 2H, J = 9 Hz); 7.85 (d, 2H, J = 9 Hz)
8ga	4-H_3CO	CH_3	57	–[f]	$C_{13}H_{16}O_4$ (236.3)	1740, 1680	1.2 (d, 3H, J = 6 Hz); 2.0 (s, 3H); 3.9 (s, 3H); 3.7–4.4 (m, 3H); 7.0 (d, 2H, J = 9 Hz); 8.0 (d, 2H, J = 9 Hz)
8gc	4-H_3CO	C_6H_5	74	160°/0.05	$C_{18}H_{18}O_4$ (298.3)	1710, 1685	1.3 (d, 3H, J = 6 Hz); 3.9 (s, 3H); 4.0–4.8 (m, 3H); 7.0 (d, 2H, J = 9 Hz); 8.0 (d, 2H, J = 9 Hz)
8gd	4-H_3CO	4-Cl—C_6H_4	76	170°/0.05[i]	$C_{18}H_{17}ClO_4$ (332.8)	1710, 1670	1.3 (d, 3H, J = 6 Hz); 3.8 (s, 3H); 4.0–4.8 (m, 3H); 6.9 (d, 2H, J = 9 Hz); 7.3 (d, 2H, J = 9 Hz); 7.7–8.0 (m, 4H)

[a] Yields not optimized.
[b] Kugelrohr distillation, bath temperature given.
[c] Satisfactory microanalyses obtained: C ±0.25; H ±0.15, Cl ±0.13 (Exceptions: **8cb**, C – 0.39; **8gc**, C – 0.48).
[d] Recorded on a Perkin Elmer 257 spectrometer.
[e] Recorded on Hitachi-Perkin Elmer R 600 FT spectrometer at 60 MHz.
[f] Isolated by silica gel chromatography eluting with cyclohexane/ethyl acetate (9 : 1).
[g] Prepared from **2c** and the appropriate acyl chloride in ether solution.
[h] Isolated by silica gel chromatography using benzene as eluent.
[i] Solidified on cooling; m.p. 52–54 °C (not crystallised).