Tetrahedron Vol. 49, No. 21, pp. 4741-4758, 1993

Synthesis of [a]Annulated Carbazoles from Indol-2,3-dione§

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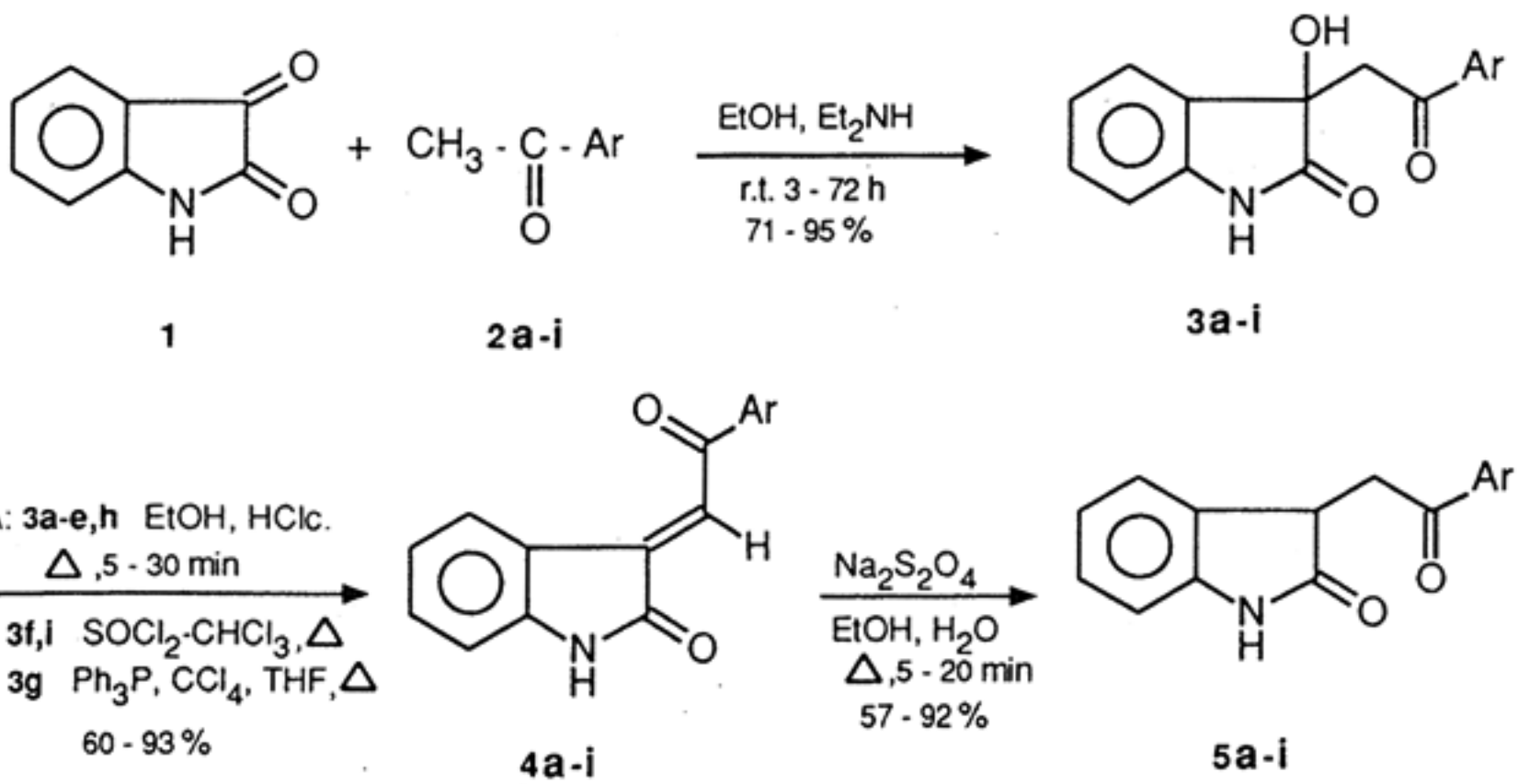
(*Received in UK* 8 *March* 1993)

Abstract: Reaction of ethyl chloroformate with 3-aroylmethylindol-2(3H)-ones **5** affords the ethyl 3-[(2-aryl-2-ethoxycarbonyloxy)ethenyl]-2-(ethoxycarbonyloxy)indole-1-carboxylates **6** from which the corresponding [a]annulated carbazoles **10** are obtained via 6π-electrocyclization.

We have recently reported a synthesis of [a]annulated carbazoles starting from indol-2(3*H*)-one and ethyl arylacetates[1]. The so obtained carbazoles are hydroxy substituted at the position 4. We report here a new and easy entry to [a]annulated carbazoles, hydroxy substituted at the position 3, starting from indol-2,3-dione **1** and arylmethylketones **2**. The starting material of our synthesis are condensed, dehydrated and reduced following in part the reported methods[2] for the

Scheme 1

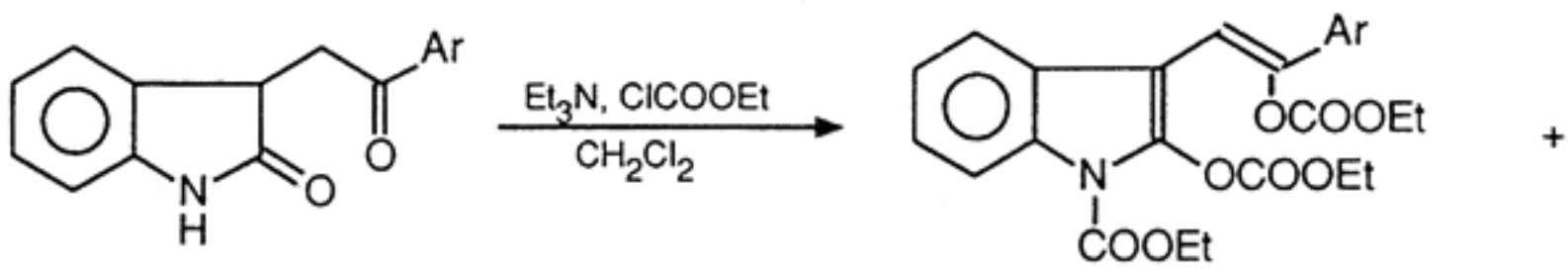


1 **2a-i** **3a-i** **4a-i** **5a-i**

synthesis of 3-(benzoylmethylidene)indol-2(3*H*)-one **5a** (Scheme 1). The result of the diethylamine catalysed condensation between indol-2,3-dione **1** and arylmethylketones **2a-i**, to

give the 3-hydroxy-3(aroylmethyl)indol-2(3*H*)-ones **3a-i**, are reported in Table 1. The 2-acetyl-1-carbethoxyindole **2h** is used because the 2-acetylindole doesn't react with indol-2,3-dione **1**. Dehydration to derivatives **4a-i** is carried out with 36 % HCl in EtOH (Method A)[2], with $SOCl_2$ in CH_2Cl_2 (method B) or with Ph_3P-CCl_4 in THF (method C). The results are reported in Table 2. The reported E stereochemistry for compounds **4a-i** is assigned on the basis of literature data[3]. Double bond reduction in compounds **4a-i** to derivatives **5a-i** is carried out as described[2] with sodium hydrosulfite (Table 3). When compounds **5a-h** are treated with excess of ethyl chloroformate and triethylamine, in CH_2Cl_2 solution at 0 °C, the corresponding ethyl 3-[(2-aryl-2-ethoxycarbonyl- oxy) ethenyl]-2-(ethoxycarbonyloxy) indole-1-carboxylates **6a-h** are formed. In the case of **5b** and **5h**, besides **6b** and **6h**, also derivatives **7b**, **7h** and **8h** are obtained (Scheme 2, Table 4).

Scheme 2



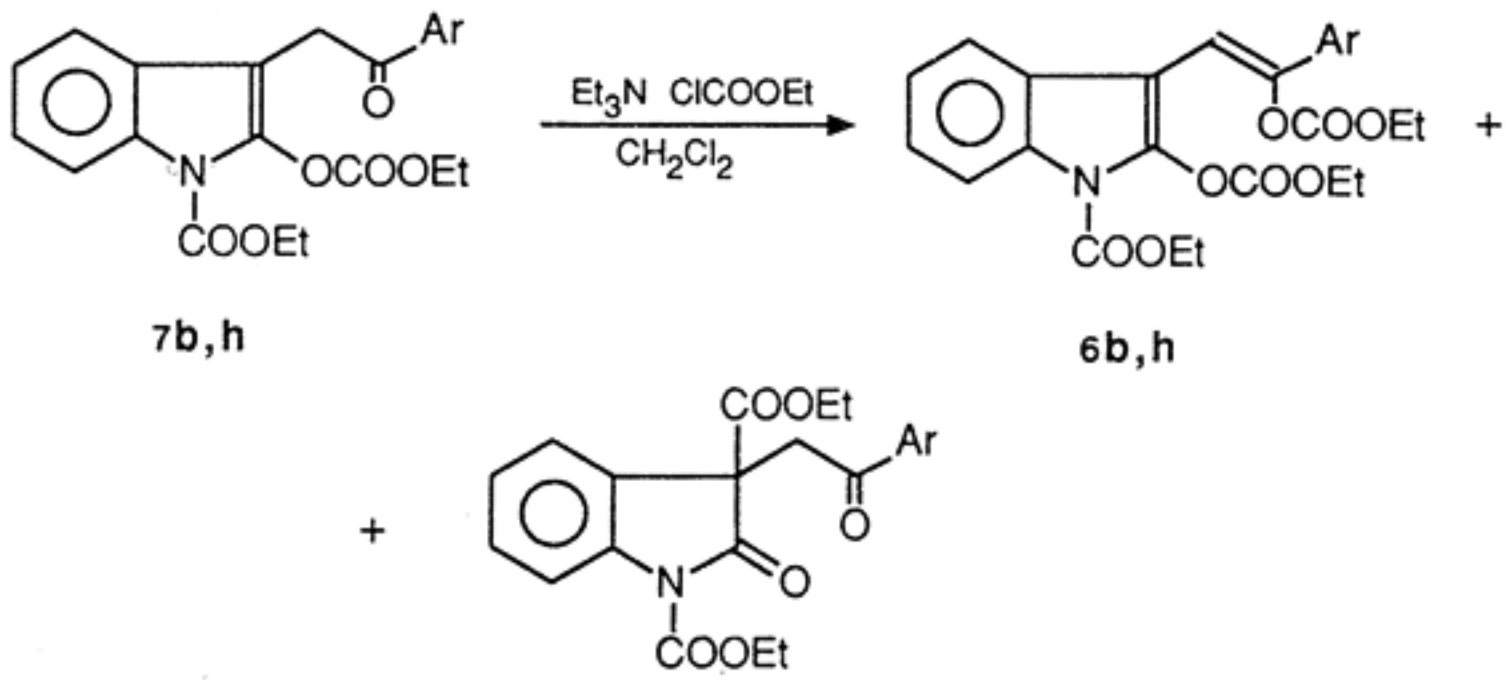
5a-h **6a-h**

7b,h **8a,b,h**

2-5	Ar	2-5	Ar	2-5	Ar
a	Ph	**d**	2-furyl	**g**	2-pyridyl
b	2-thienyl	**e**	2-benzofuryl	**h**	1-carbethoxy-2-indolyl
c	3-thienyl	**f**	3-pyridyl	**i**	4-pyridyl

If the acylation reaction is carried out by heating to reflux after the ethyl chloroformate addition, **5a** affords exclusively **8a** and in the case of **5b**, besides **6b**, compound **8b** is formed in 60 % yield (Table 4). The treatment of **7b** and **7h** with ethyl chloroformate and triethylamine results respectively in the formation of **6b** and a mixture of **6h** and **8h** (Scheme 3, Table 4). Heating a CH_2Cl_2 solution of compounds **7b,h** in the presence of a catalytic amount of 4-dimethylaminopyridine affords derivatives **8b,h** in quantitative yield by O-C migration (Scheme 4). An analogous 4-dimethylaminopyridine catalysed migration has been observed for benzofuran-2(3*H*)-ones derivatives[4].

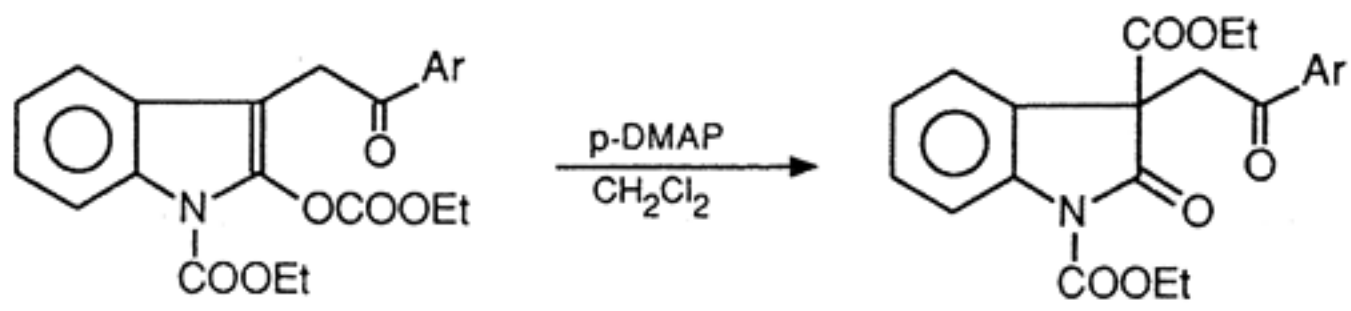
Scheme 3



7b,h **6b,h**

8h

Scheme 4

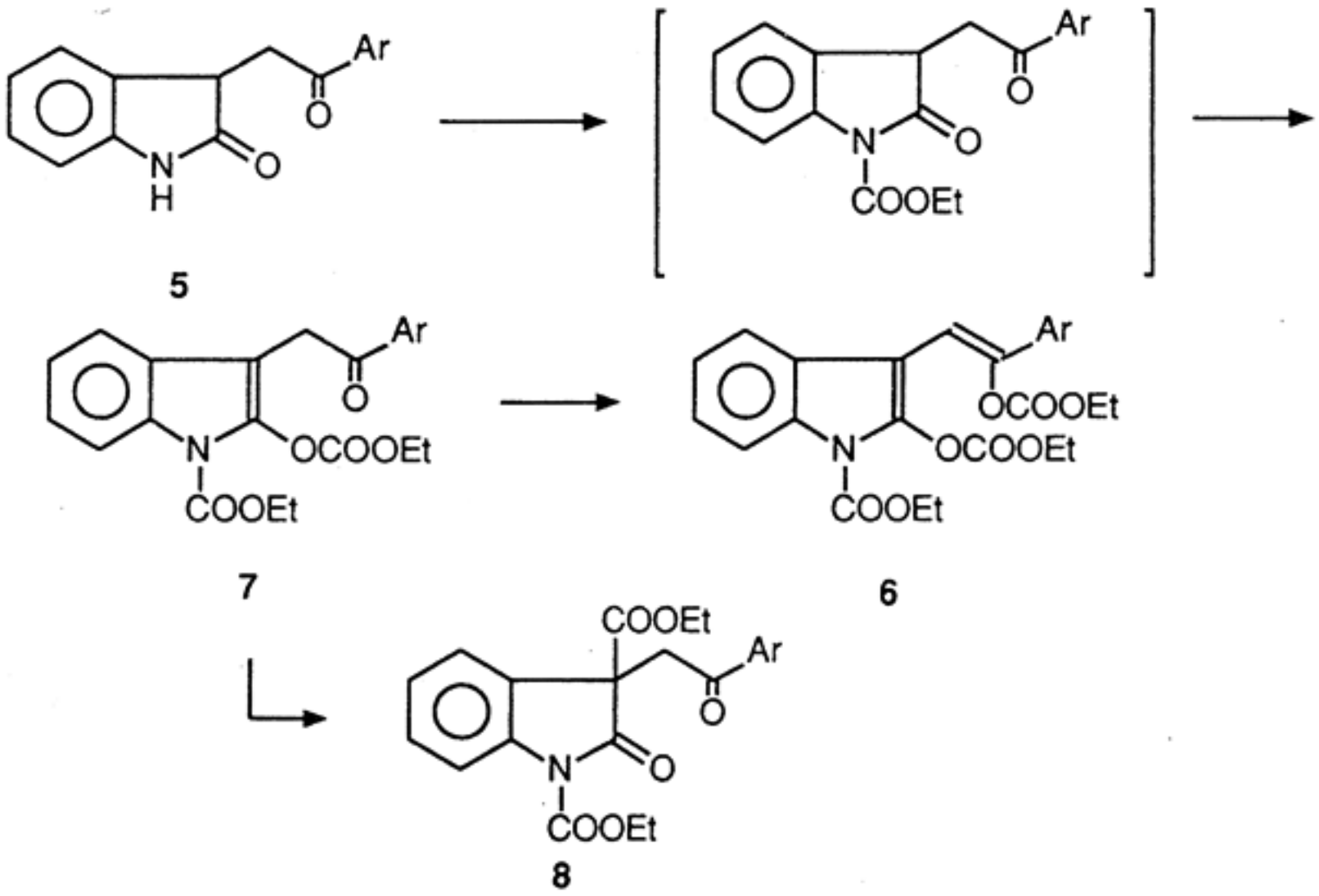


7b,h **8b,h**

The reported structures for compounds **6**, **7** and **8** are based on analytical and spectroscopic data (Table 7) as well as chemical behaviour. Moreover, the structure of compound **6d** has been confirmed by X-ray diffraction analysis[5], and the Figure shows the molecular shape and the numbering scheme. The same Z stereochemistry has been assigned to all compounds **6** on the basis of their ^{1}H-NMR spectra and by comparison with the ^{1}H-NMR spectra of the corresponding E isomers (see later). The above results may be razionalized as follows: ethyl chloroformate attacks the nitrogen atom as the first reaction step and then the oxygen at C-2. Attack at the side chain carbonyl oxygen gives the final compounds **6**. Compounds **8** arise from a competing O-C acyl migration (Scheme 5).

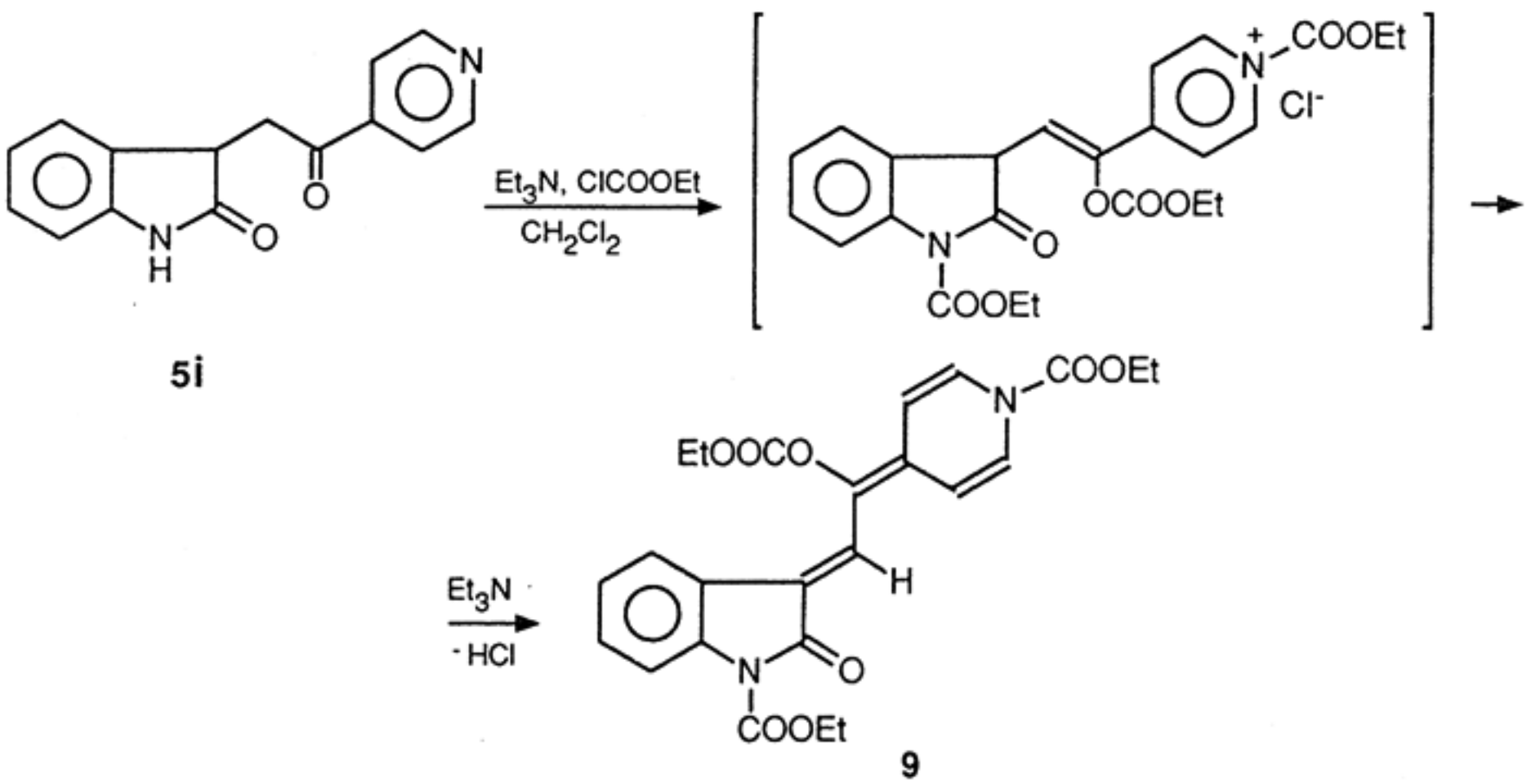
This scheme, supported by the results obtained in the case of **b** and **h** series, appears to be likely also for the compounds **a, c-e**. For the derivatives **f, g, i,** the presence of the electron-attracting pyridine ring, and the likely formation of an acyl pyridinium chloride, may increase the acidity of the hydrogen atoms at C-8 and, in the acylation scheme, the second reaction step may be the attack at the carbonyl oxygen at C-9. Indeed the acylation of **5i** takes a completely different course: only the deep violet derivative **9** is obtained in moderate yield (Scheme 6, Table 4). The structure of compound **9** follows from analytical and spectroscopic data. For the formation of compound **9** we suggest the pathway reported in Scheme 6.

Scheme 5



When compounds **6** are irradiated (in CH_2Cl_2 or in CH_3CN solution) with an internal light-source (HPK-125 W high pressure Hg-lamp), the corresponding [a]annulated carbazoles **10** are

Scheme 6

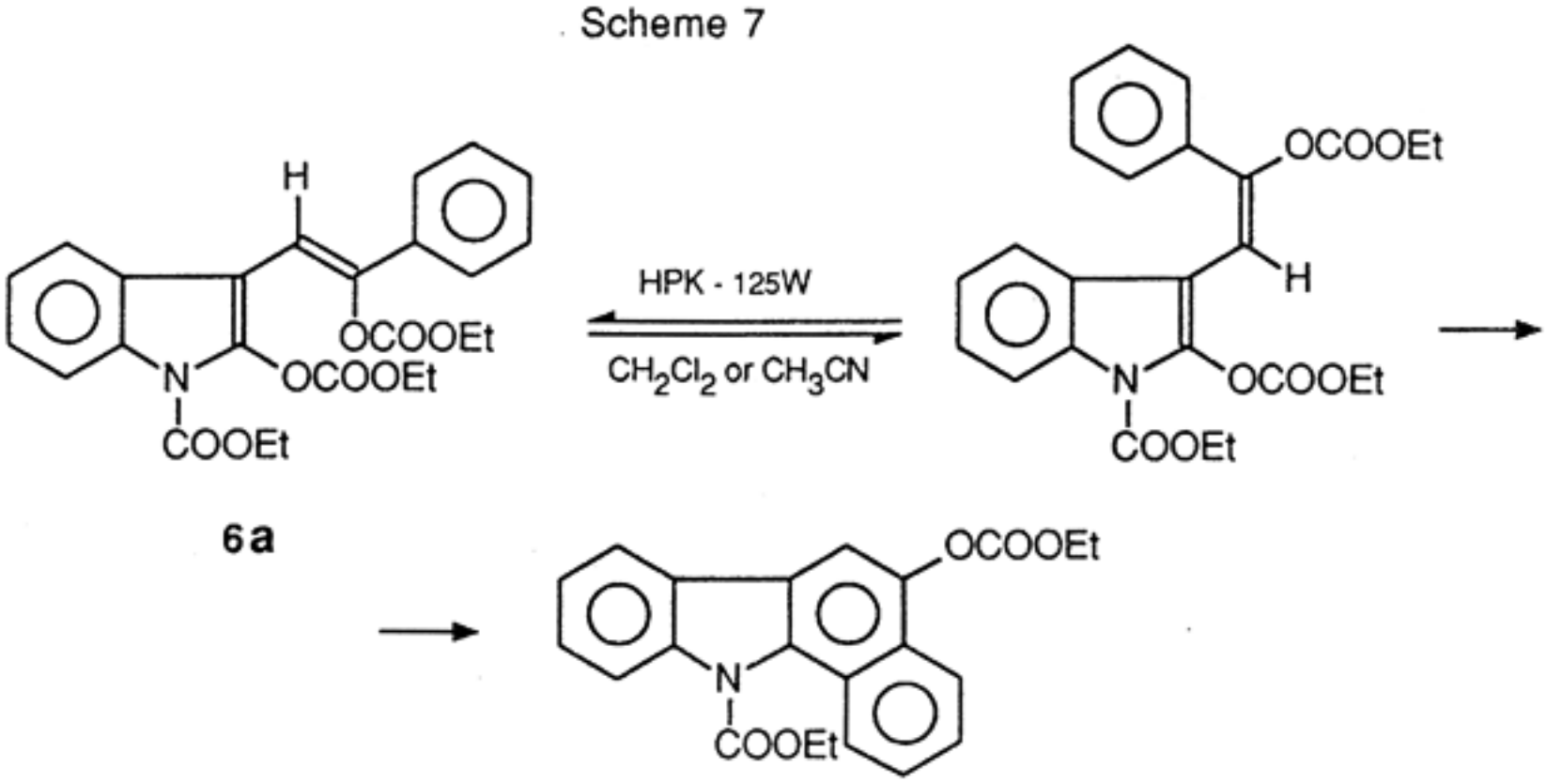


formed via 6π-electrocyclization followed by aromatization with ethanol and carbon dioxide elimination (Scheme 7, Table 5). By this route, benzo[a]- **10a**, thieno[3,2-a]- **10b**, thieno[2,3-a]- **10c**, furo[3,2-a]- **10d**, benzofuro[3,2-a]- **10e**, pyrido[2,3-a]- **10fa**, pyrido[4,3-a]- **10fb**, pyrido[3,2-a]- **10g** and indolo[2,3-a]carbazole **10h** have been obtained (Scheme 7). The reported yields for

compounds **10** (Table 5) are based on reacted starting material **6**, after irradiation for the reported time.

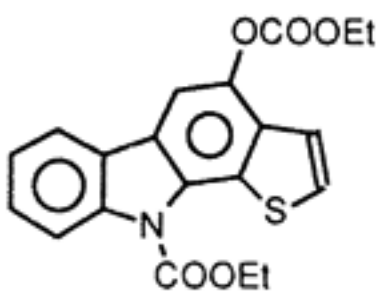
Besides **10**, unreacted **6**, as an inseparable E/Z mixture, was also isolated. By comparison of the ^{1}H-NMR spectra of the starting compounds **6** (which are pure Z isomers) with those of the E/Z mixture, the assignment of the chemical shift of the more significative protons of the E isomers is

Scheme 7

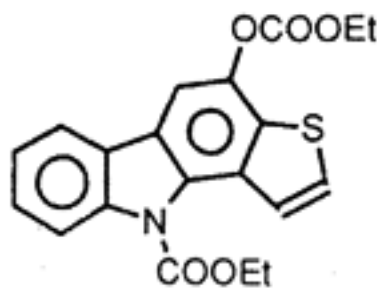


6a

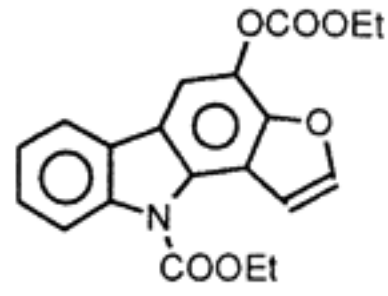
10a



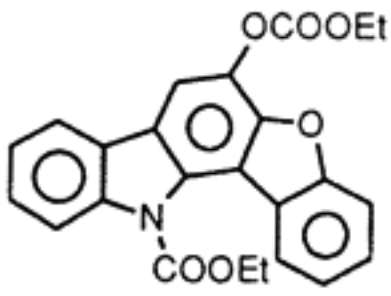
10b



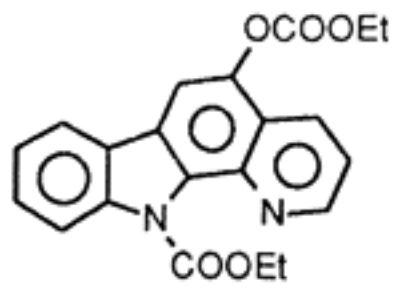
10c



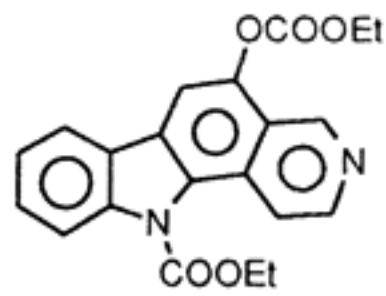
10d



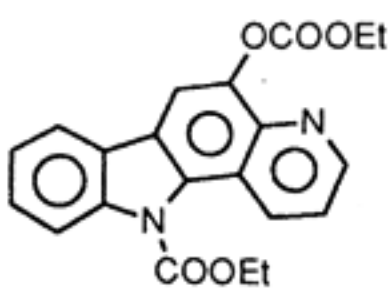
10e



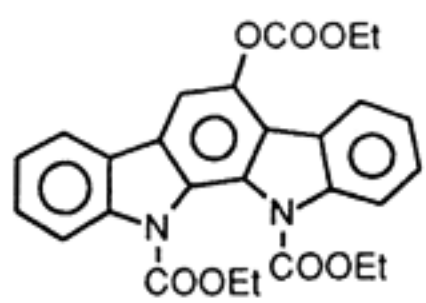
10fa



10fb



10g



10h

possible (Table 6). The chemical shift of the olefinic H-9 proton in the Z isomers of compounds **6** is in the range δ= 6.54-7.36, whereas in the E isomers this signal is consistently shifted upfield of

0.12-0.37 ppm, since in the former case the deshielding effect of the aryl group is operative. The chemical shift of the H-4 in the E isomers is also shifted upfield of 0.49-0.77 ppm with respect to the H-4 in the Z isomers, owing to the shielding effect of the neighbouring aryl group.

The described synthetic path is versatile and allows also the preparation of pyrido carbazoles with the only exclusion of pyrido[3,4-a]carbazoles.

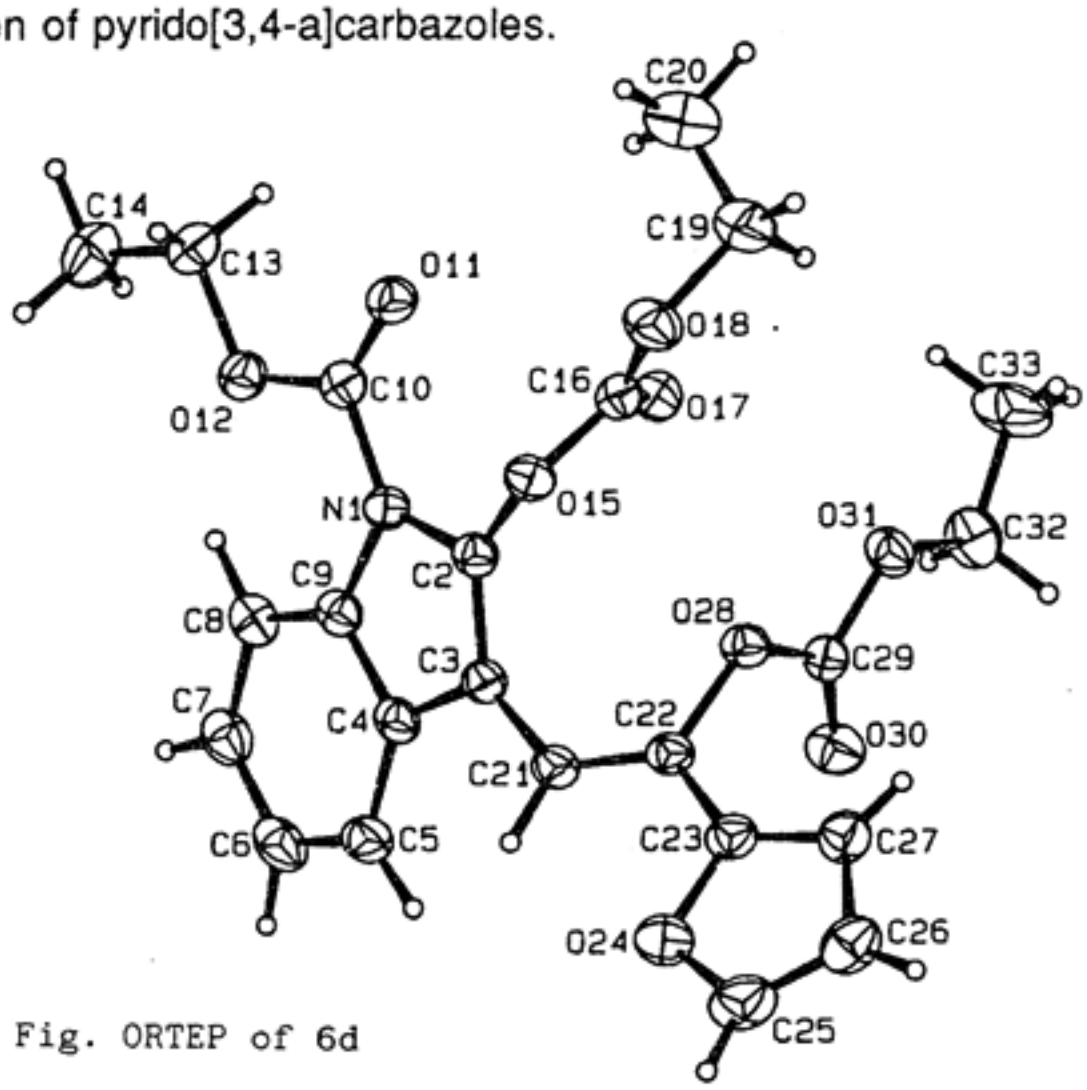


Fig. ORTEP of 6d

EXPERIMENTAL

Melting points are determined on a Buchi apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 298 instrument, in nujol mull for solids and as liquid film for oils. ^{1}H-NMR were recorded on a Bruker AC 300 spectrometer in $CDCl_3$ solution. Column chromatography was performed on Merck Kieselgel 60, 0.063 - 0.2 mm and on Florisil 0.150 - 0.250 mm. Evaporation was carried out under vacuum in a rotary evaporator. Irradiation were carried out with a HPK-125 W Philips, high-pressure mercury vapor lamp in a preparative photochemical reactor equipped with a pyrex double-walled immersion well for H_2O cooling of lamp.

3-Hydroxy-3-(Aroylmethyl)-indol-2(3H)-ones ***3****; General Procedure:*

To a warm solution of indol-2,3-dione **1** (7.36 g, 50 mmol) in EtOH (150 mL), arylmethylketone **2** (50 mmol) in EtOH (30 mL) and Et_2NH (0.5 mL) were added. After the reported time (Table 1) at r.t. the crystallized product was filtered and washed with cold EtOH (20mL) and Et_2O (25 mL).

3-(Aroylmethylidene)-indol-2(3H)-ones ***4****;*

Method A. A suspension of compound **3** (10 mmol) in EtOH (40 mL) and HCl conc. (40 mL) was heated to boiling. The insoluble reactant **3** rapidly dissolved and a quick precipitation of the deep red product **4** occured. The mixture was heated to reflux for the indicated time (Table 2),

then concentrated under vacuum, diluted with H_2O (60 mL) and cooled. The precipitate was filtered , washed with H_2O (100 mL) and cold EtOH (20 mL).

Method B:. A mixture of compound **3** (10 mmol), CH_2Cl_2 (50 mL) and $SOCl_2$ (30 mmol) was heated under reflux for the reported time (Table 2). After the solvent evaporation, the residue was diluted with H_2O (50 mL), extracted with CH_2Cl_2 (2 x 40 mL), dried (Na_2SO_4), filtered and evaporated. The crude product was purified by crystallization.

Method C. To a solution of **3g** (5.36 g, 20 mmol) in anhydrous THF (60 mL), Ph_3P (7.86 g, 30 mmol) and CCl_4 (5 mL) were added. After heating to reflux for 6h, the mixture was evaporated, diluted with H_2O (50 mL), extracted with CH_2Cl_2 (2 x 40 mL), dried, filtered and evaporated. The residue obtained after evaporation was chromatographed on silica gel with a gradient elution (100% CH_2Cl_2 to 10% Et_2O - 90% CH_2Cl_2) and crystallized to give pure **4g** (Table 2).

*3-Aroylmethylindol-2(3H)-ones **5**; General Procedure:*

To a suspension of compound **4** (20 mmol) in EtOH (100 mL), $Na_2S_2O_4$ (5.22 g, 30 mmol) in H_2O (25 mL) was added. After heating at 55-60 °C for the reported time (Table 3), the color changes from red to pale yellow. The solvent was then evaporated, the residue diluted with H_2O (40 mL), extracted with CH_2Cl_2 (2 x 30 mL), dried (Na_2SO_4), filtered and evaporated. The residue was purified by crystallization.

*Reaction of compounds **5** with ethyl chloroformate and triethylamine. Compounds **6, 7 ,8** and **9** Prepared:*

Compound **5** (10 mmol) was dissolved in CH_2Cl_2 (70 mL) and then Et_3N (6.96 mL, 50 mmol) was added. The reaction mixture was cooled at 0-5 °C and ethyl chloroformate (3.85 mL, 40 mmol) in CH_2Cl_2 (10 mL) was added under stirring. After being warmed to room temperature overnight, the reaction mixture was washed with H_2O (2 x 50 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated. The products were separed by silica gel column chromatography and crystallized (Table 4).

*[a]Annulated Carbazoles **10**; General Procedure:*

Compound **6** (1.5 g) was dissolved in the appropriate solvent (Table 5) (100 mL), the solution placed in the photochemical reactor and N_2 bubbled through the solution for 5 min before irradiation. After irradiation for the reported time, the solution was evaporated and the residue separated by silica gel column chromatography.

*Reaction of compounds **7b,h** with ethyl chloroformate and triethylamine. Compounds **6b** and **6h, 8h** Prepared:*

Starting from compounds **7b,h** (2 mmol), Et_3N (1.1 mL, 8 mmol) and ethyl chloroformate (0.58 mL, 6 mmol) in CH_2Cl_2 (30 mL) and working as reported for compounds **5**, pure compounds **6b** and **6h, 8h** were obtained (Table 4).

*Compounds **8b,h** from **7b,h**.*

To a solution of compound **7** (1 mmol) in CH_2Cl_2 (40 mL) was added 4-dimethylamino

pyridine (30 mg). After 2h the solution was washed successively with 5% HCl (20 mL), water (20 mL) and dried (Na_2SO_4). The mixture was filtered, evaporated and the residue crystallized to pure compound **8.**

X-ray structure determination of ***6d.***

Monoclinic, space group $P2_1/c$, a=17.066(2), b=10.109, c=14.435(2) Å, β=111.79 (°), V=2312.4(7) $Å^{-3}$, Z= 4, D_X=1.314 $g.cm^{-3}$. Single crystal X-ray measurements were performed on a *Nonius CAD-4* diffractometer, using graphite-monochromated Mo-kα radiation (λ=0.71073 Å). 4045 reflections were collected in the range $0 < \vartheta < 25$; of these, 2419 with $I > \sigma(I)$ were considered observed. Data were corrected for Loretz and polarization coefficients (Lp). The structures was solved by direct methods (MULTAN[6]). The refinement was carried on by minimizing the function $\Sigma w(F_o - k|F_c|)^2$, with weights $w=1/\sigma^2(F_o)$, where $\sigma^2(F_o) = [\sigma^2(I)+0.00091^2]/(2F_oLp)^2$. Scattering factors were taken from Ref. 7. Figure shows an ORTEP view of the molecule with the atomic numbering scheme of heavy atoms: ellipsoids are drawn at 20% of probability level. C, N, and O atoms were refined anisotropically, H atoms isotropically; H atoms of ethyls groups were introduced in structure factors calculations, but not refined. The ethyl group bonded to O31 is disordered: the terminal methyl carbon atom is present both in *trans* and *gauche* configuration with polutation factors 0.5; For clarity Figure shows only the first configuration. Final difference Fourier maps showed a residue of 0.36 $eÅ^{-3}$ at 1.26 Å from C19: this probably indicates that also this ethyl group is affected by disorder, but with population factor very different for the two conformations.The full-matrix least-squares refinement gave final R and R_w values of 0.043 and 0.048, respectively. Bond distances and angles are in the normal range. Furane ring is strictly planar, while the indole system shows little distorsion due to the repulsion among the group bonded at N1, C2 and C3.

Table 1. 3-Hydroxy-3(aroylmethyl)indol-2(3*H*)-ones **3.**

Product	Reaction time (h)	Yield (%)	mp (°C) (solvent)
3a	48	71	165-166[a] (EtOH)
3b	48	80	166-167 ($MeOH-Et_2O$)
3c	48	93	177-179 (EtOH)
3d	24	86	190-191 ($MeOH-Et_2O$)
3e	48	95	184-186 (EtOH)
3f	48	76	132-135 dec. ($CH_3COCH_3-CH_2Cl_2$)
3g	48	87	156-157 (EtOH)
3h	72	75	210-212 dec. (EtOH)
3i	3	76	156-158 ($CH_3COCH_3-CH_2Cl_2$)

[a] in Ref. 2 reported 169-172 °C.

Table 2. 3-(Aroylmethylidene)-indol-2(3*H*)-ones **4**.

Product	Method	Reaction time (min)	Yield (%)	mp (°C) (solvent)
4 a	A	30	90	192-194[a] (EtOH)
4 b	A	15	67	181-183 (CH_2Cl_2-Et_2O)
4 c	A	5	88	173-174 (CH_2Cl_2-Et_2O)
4 d	A	10	78	201-202 (EtOH-Et_2O)
4 e	A	10	87	230-232 (CH_2Cl_2-Et_2O)
4 f	B	480	60	220-221 (MeOH)
4 g	C	360	74	190-191 (CH_2Cl_2-Et_2O)
4 h	A	30	90	239-241 (CH_2Cl_2-Et_2O)
4 i	B	360	93	186-188 (CH_2Cl_2-Et_2O)

[a] In ref. 2 reported 193-194 °C.

Table 3. 3-Aroylmethylindol-2(3*H*)-ones **5**.

Product	Reaction time (min)	Yield (%)	mp (°C) (CH_2Cl_2-Hx)[a]
5 a	20	92	176-177 [b]
5 b	10	57	143-144
5 c	10	62	144-146
5 d	5	63	165-166
5 e	5	64	191-192
5 f	10	60	144-145
5 g	5	73	143-145
5 h	20	68	166-167
5 i	10	76	159-160

[a] Hx: hexane

[b] In ref. 2 reported 177 °C.

Table 4. Reaction with Ethyl chloroformate of Compounds **5** and **7**.

Starting material	Products	Yield (%)	Eluent	mp (°C) (solvent)
5a	**6a**	80	Hx-CH_2Cl_2 (1:1)	97-99 (Hx-Et_2O)
5a[a]	**8a**	81	CH_2Cl_2	106-108 (Et_2O)
5b	**6b**	69	Hx-CH_2Cl_2 (1:1)	77-79 (HX-Et_2O)
	7b	8		81-83 (Hx-Et_2O)
5b[a]	**6b**	38	CH_2Cl_2	
	8b	60		85-87 (Hx-Et_2O)
7b	**6b**	75		
7b[b]	**8b**	95		
5c	**6c**	58	Hx-CH_2Cl_2 (1:1)	99-101 (Hx-Et_2O)
5d	**6d**	74	Hx-CH_2Cl_2 (1:1)	91-92 (Hx-Et_2O)
5e	**6e**	88	CH_2Cl_2	110-112 (Hx-Et_2O)
5f	**6f**	50	Hx-AcOEt (4:1)	109-110 (Et_2O)
5g	**6g**	85	$CHCl_3$-Et_2O (20:1)	104-106 (Hx-Et_2O)
5h	**6h**	30	Hx-CH_2Cl_2 (1:1)	73-80 (Hx-Et_2O)
	7h	8		141-144 (Et_2O)
	8h	50		107-109 (Hx-Et_2O)
7h	**6h**	62	CH_2Cl_2	
	8h	36		
7h[b]	**8h**	93		
5i	**9**	46	CH_2Cl_2-Et_2O (20:1)	171-173 (CH_2Cl_2-Et_2O)

[a] Reaction carried by heating to reflux for 10 min after the ethyl chloroformate addition.

[b] 4-dimethylaminopyridine catalyzed rearrangement.

Table 5. [a]Annulated Carbazoles **10** Prepared.

Product	Yield (%)	mp (°C) (solvent)	Eluent	Unreacted Material % (E/Z ratio)	Irradiation Time (h)/solvent
10a	76	112-113 ($Hx\text{-}Et_2O$)	$Hx\text{-}CH_2Cl_2$ (1:1)	20 (1.3)	6 CH_3CN
10b	83	132-134 (Et_2O)	$Hx\text{-}CH_2Cl_2$ (1:1)	10 (3.7)	5 CH_3CN
10c	38	138-140 ($CH_2Cl_2\text{-}Et_2O$)	$Hx\text{-}CH_2Cl_2$ (1:1)	38 (2.5)	7 CH_3CN
10d	74	106-108 ($Hx\text{-}Et_2O$)	$Hx\text{-}CH_2Cl_2$ (1:1)	53 (2.5)	4 CH_3CN
10e	83	136-138 (Et_2O)	$Hx\text{-}CH_2Cl_2$ (2:1)	17 (2.0)	3 CH_3CN
10fa	30	110-111 ($Hx\text{-}Et_2O$)	$CH_2Cl_2\text{-}Et_2O$ (20:1)	5 (2.1)	4 CH_2Cl_2
10fb	53	156-158 ($CH_2Cl_2\text{-}Et_2O$)			
10g	44	131-133 (Et_2O)	$Hx\text{-}CH_2Cl_2$ (1:1)	10 (2.5)	4 CH_2Cl_2
10h	30	161-163 (Hx)	$Hx\text{-}Et_2O$ (2:1)	60 (2.1)	7 CH_3CN

Table 6. H-4 and H-9 Chemical Shift in (Z)- and (E)-**6** Derivatives.

(Z)-**6**	H-9	H-4	(E)-**6**	H-9	H-4
6 a	6.57	7.65	**6 a**	6.40	6.88
6 b	6.56	7.68	**6 b**	6.29	_[a]
6 c	6.54	7.66	**6 c**	6.30	6.96
6 d	6.69	7.70	**6 d**	6.30	_[a]
6 e	6.80	7.77	**6 e**	6.45	_[a]
6 f	6.63	7.65	**6 f**	6.51	7.06
6 g	7.36	7.49	**6 g**	6.59	6.89
6 h	6.60	7.67	**6 h**	6.48	7.18

[a] The signal is in the aromatic envelope (δ = 7.00-7.34).

Table 7. Spectral Data of New Compounds.

Product	IR (Nujol or film) ν cm^{-1}	^{1}H-NMR δ, J (Hz)
3 b	3370, 3330, 1732, 1650	DMSO: 3.50 (1H, d, 16.7), 3.93 (1H, d, 16.7), 6.08 (1H, s)[a], 6.80 (2H, m), 7.19 (3H, m), 7.96 (2H, m), 10.22 (1H, s)[a]
3 c	3300, 3260, 1710, 1668, 1618	DMSO: 3.47 (1H, d, 17.1), 3.90 (1H, d, 17.1), 6.03 (1H, s)[a], 6.77 (1H, d, 7.7), 6.83 (1H, t, 7.5),7.13 (1H, t, 7.6), 7.26 (1H, d, 7.3), 7.33 (1H, d, 5.0), 7.51 (1H, m), 8.46 (1H, m), 10.21 (1H, s)[a]
3 d	3340, 3300, 1725, 1715sh, 1660	DMSO: 3.30 (1H, d, 16.2), 3.75 (1H, d, 16.2), 6.10 (1H, s)[a], 6.60-6.88 (3H, m), 7.13 (1H, t, 7.3), 7.24 (1H, d, 7.3), 7.44 (1H, d, 3.6), 7.92 (1H, bs), 10.20 (1H, s)[a]
3 e	3390, 3230, 1710, 1685, 1632	DMSO: 3.27 (1H, d, 16.3), 3.57 (1H, d, 16.3), 5.61 (1H, s)[a], 6.59 (2H, m), 6.88 (1H, t, 7.7), 6.92 (2H, m), 7.21 (3H, m), 7.42 (1H, d, 7.9)
3 f	3350, 1737, 1705, 1629, 1600	3.62 (1H, d, 17.2), 3.87 (1H, d, 17.2), 5.00 (1H, s)[a], 6.85 (1H, d, 7.8), 6.98 (1H, t, 7.5), 7.20 (1H, t, 7.8), 7.34 (2H, m), 8.12 (1H, dt, 1.9, 8.0), 8.53 (1H, s)[a], 8.55 (1H, dd, 4.8, 1.6), 9.03 (1H, d, 2.2)
3 g	3160-3480, 1725, 1705, 1628	3.52 (1H, d, 15.2), 3.87 (1H, d, 15.2), 6.73 (1H, bs)[a], 6.85 (1H, d, 7.8), 7.00 (1H, t, 7.5), 7.23 (2H, m), 7.54 (1H, m), 7.89 (1H, dt, 1.7, 7.8), 8.08 (1H, d, 7.8), 7.94 (1H, bs)[a], 8.68 (1H, d, 4.7)
3 h	3300, 3130, 1760, 1713, 1689, 1646, 1629	DMSO: 1.46 (3H, t, 7.1), 3.46 (1H, d, 16.5), 4.00 (1H, d, 16.5), 4.52 (2H, q, 7.1), 6.04 (1H, s)[a], 6.78 (1H, d, 7.7), 6.84 (1H, t, 7.5), 7.13 (1H, t, 7.5), 7.24-7.39 (3H, m), 8.02 (1H, d, 7.7), 8.10 (1H, d, 8.3), 8.69 (1H, s), 10.23 (1H, s)[a]

3i	3480, 3220, 1705, 1690, 1620	DMSO: 3.59 (1H, d, 17.1), 3.81 (1H, d, 17.1), 5.94 (1H, s)[a], 6.83 (2H, m), 7.10 (1H, t, 7.7), 7.18 (1H, d, 7.1), 7.58 (2H, m), 8.64 (2H, m), 9.92 (1H, s)[a]
4b	3280, 1720, 1652	6.84 (1H, d, 7.8), 7.04 (1H, t, 7.7), 7.20 (1H, m), 7.33 (1H, t, 7.7), 7.71 (1H, bs)[a], 7.75 (2H, m), 7.94 (1H, d, 3.8), 8.52 (1H, d, 7.8)
4c	3180, 3100, 1712, 1680, 1650	6.85 (1H, d, 7.8), 7.03 (1H, t, 7.7), 7.32 (1H, t, 7.7), 7.38 (1H, dd, 2.8, 5.1), 7.70 (1H, dd, 1.2, 5.1), 7.74 (1H, s), 7.93 (1H, bs)[a], 8.28 (1H, dd, 1.2, 2.8), 8.49 (1H, d, 7.8)
4d	3200, 1711, 1658, 1622	6.62 (1H, dd, 1.6, 3.6), 6.84 (1H, d, 7.8), 7.05 (1H, t, 7.7), 7.34 (1H, t, 7.7), 7.43 (1H, d, 3.6), 7.69 (1H, d, 1.6), 7.74 (1H, s), 7.83 (1H, bs)[a], 8.71 (1H, d, 7.8)
4e	3170, 1718, 1663	6.85 (1H, d, 7.8), 7.08 (1H, t, 7.8), 7.35 (2H, m), 7.52 (1H, t, 7.4), 7.53 (1H, bs)[a], 7.63 (1H, d, 7.6), 7.75 (1H, d, 8.5), 7.76 (1H, s), 7.88 (1H, s), 8.77 (1H, d, 7.8)
4f	3150, 1712, 1661, 1600	6.83 (1H, d, 7.8), 6.94 (1H, t, 7.8), 7.27 (1H, t, 7.7), 7.44 (1H, dd, 4.8, 8.0), 7.74 (1H, s), 8.34 (2H, m), 8.78 (1H, dd, 1.7, 4.8), 9.27 (1H, d, 2.2), 9.27 (1H, bs)[a]
4g	3200, 1721, 1677, 1611	6.86 (1H, d, 7.8), 7.05 (1H, t, 7.7), 7.33 (1H, t, 7.7), 7.50 (1H, dd, 4.8, 7.5), 7.89 (1H, dt, 1.6, 7.7), 7.99 (1H, bs)[a], 8.19 (1H, d, 7.8), 8.65 (1H, d, 7.8), 8.76 (1H, d, 4.6)
4h	3160, 1754, 1712, 1650	DMSO: 1.45 (3H, t, 7.1), 4.52 (2H, q, 7.1), 6.88 (1H, d, 7.7), 7.00 (1H, t, 7.6), 7.46 (2H, m), 7.67 (1H, s), 8.17 (1H, d, 7.8), 7.40 (2H, m), 8.70 (1H, s), 10.78 (1H, s)[a]
4i	3190, 1718, 1665	6.86 (1H, d, 7.8), 7.05 (1H, t, 7.8), 7.37 (1H, t, 7.6), 7.78 (1H, s), 7.87 (2H, m), 7.97 (1H, bs)[a], 8.51 (1H, d, 7.8), 8.87 (2H, m)
5b	3180, 1702, 1661, 1623	3.38 (1H, dd, 8.9, 17.8), 3.75 (1H, dd, 3.3, 17.8), 4.06 (1H, dd, 3.3, 8.9), 6.88 (1H, d, 7.7), 6.96 (1H, t, 7.5), 7.12 (1H, t, 4.3), 7.20 (2H, m), 7.65(1H, d, 4.8), 7.73 (1H, d, 3.8), 8.10 (1H, bs)[a]
5c	3220, 1711, 1677, 1613	3.27 (1H, dd, 9.0, 18.0), 3.65 (1H, dd, 3.2, 18.0), 3.97 (1H, dd, 3.2, 9.0), 6.86 (2H, m), 7.12 (2H, m), 7.27 (1H, dd, 2.9, 5.1), 7.51 (1H, dd, 0.9, 5.1), 8.03 (1H, dd, 0.9, 2.9), 8.94 (1H, bs)[a]
5d	3170, 1693, 1664, 1620	3.30 (1H, dd, 8.9, 18.0), 3.66 (1H, dd, 3.5, 18.0), 4.05 (1H, dd, 3.5, 8.9), 6.53 (1H, dd, 1.7, 3.6), 6.87 (1H, d, 7.7), 6.95 (1H, t, 7.4), 7.20 (3H, m), 7.58 (1H, d, 1.4), 8.17 (1H, bs)[a]
5e	3200, 1708, 1685, 1630	3.44 (1H, dd, 8.9, 18.1), 3.81 (1H, dd, 3.5, 18.1), 4.10 (1H, dd, 3.5, 8.9), 7.21 (2H, m), 7.30 (1H, t, 7.4), 7.45-7.57 (3H, m), 7.69 (1H, d, 7.9), 7.71 (1H, bs)[a]
5f	3180, 1697, 1684, 1618	3.47 (1H, dd, 8.5, 18.4), 3.82 (1H, dd, 3.3, 18.4), 4.08 (1H, dd, 3.3, 8.5), 6.90 (1H, d, 8.0), 6.96 (1H, t, 7.5), 7.19 (2H, m), 7.41 (1H, dd, 4.8, 8.0), 8.23 (1H, dt, 1.9, 8.0), 8.58 (1H, bs)[a], 8.78 (1H, dd, 3.3, 4.8), 9.18 (1H, d, 1.9)
5g	3190, 1693, 1619	3.80 (1H, dd, 6.8, 17.8), 4.05-4.15 (3H, m), 6.87 (1H, d, 7.9), 6.94 (1H, t, 7.4), 7.17 (2H, m), 7.47 (1H, m), 7.82 (1H, dt, 1.7, 7.7), 8.02 (1H, d, 7.8), 8.10 (1H, bs)[a], 8.65 (1H, d, 4.7)

5h	3210, 1762, 1751, 1690, 1660	1.50 (3H, t, 7.1), 3.37 (1H, dd, 9.1, 17.5), 3.75 (1H, dd, 3.3, 17.5), 4.13 (1H, dd, 3.3, 9.1), 4.54 (2H, q, 7.1), 6.87 (2H, d, 7.7), 6.96 (1H, t, 7.5), 7.20 (2H, m), 7.38 (2H, m), 7.56 (1H, bs)[a], 8.17 (1H, m), 8.29 (1H, s), 8.37 (1H, m)
5i	3205, 1702, 1685	3.46 (1H, dd, 8.5, 18.5), 3.81 (1H, dd, 3.3, 18.5), 4.07 (1H, dd, 3.3, 8.5), 6.90 (1H, d, 7.8), 6.97 (1H, t, 7.5), 7.19 (2H, m), 7.73 (2H, m), 7.99 (1H, bs)[a], 8.81 (2H, m)
6a	1738, 1762, 1748, 1632	1.20 (3H, t, 7.1), 1.39 (3H, t, 7.1), 1.45 (3H, t, 7.1), 4.15 (2H, q, 7.1), 4.35 (2H, q, 7.1), 4.48 (2H, q, 7.1), 6.57 (1H, s), 7.25-7.42 (5H, m), 7.56-7.63 (3H, m), 8.08 (1H, d, 7.9)
6b	1790, 1771, 1737, 1627	1.20 (3H, t, 7.1), 1.41 (3H, t, 7.1), 1.45 (3H, t, 7.1), 4.16 (2H, q, 7.1), 4.37 (2H, q, 7.1), 4.48 (2H, q, 7.1), 6.56 (1H, s), 7.01 (1H, dd, 3.8, 4.9), 7.21 (1H, d, 3.6), 7.24-7.36 (3H, m), 7.68 (1H, m), 8.08 (1H, m)
6c	1784, 1762, 1735, 1628	1.18 (3H, t, 7.1), 1.40 (3H, t, 7.1), 1.45 (3H, t, 7.1), 4.14 (2H, q, 7.1), 4.36 (2H, q, 7.1), 4.47 (2H, q, 7.1), 6.54 (1H, s), 7.28-7.35 (3H, m), 7.39 (1H, m), 7.66 (1H, dd, 1.7, 7.3), 8.08 (1H, d, 7.7)
6d	1790, 1771, 1746, 1639	1.21 (3H, t, 7.1), 1.41 (3H, t, 7.1), 1.45 (3H, t, 7.1), 4.17 (2H, q, 7.1), 4.37 (2H, q, 7.1), 4.47 (2H, q, 7.1), 6.45 (2H, m), 6.69 (1H, s), 7.31 (2H, m), 7.43 (1H, bs), 7.70 (1H, d, 8.8), 8.08 (1H, d, 8.9)
6e	1790, 1776, 1740, 1627	1.23 (3H, t, 7.1), 1.43 (3H, t, 7.1), 1.46 (3H, t, 7.1), 4.20 (2H, q, 7.1), 4.39 (2H, q, 7.1), 4.43 (2H, q, 7.1), 6.80 (1H, s), 7.01 (1H, s), 7.19-7.38 (4H, m), 7.49 (1H, d, 8.1), 7.55 (1H, d, 7.5), 7.77 (1H, m), 8.10 (1H, m)
6f	1775, 1761, 1735	1.21 (3H, t, 7.1), 1.40 (3H, t, 7.1), 1.45 (3H, t, 7.1), 4.16 (2H, q, 7.1), 4.37 (2H, q, 7.1), 4.48 (2H, q, 7.1), 6.63 (1H, s), 7.30 (3H, m), 7.65 (1H, d, 7.3),7.84 (1H, dt, 1.9, 8.1), 8.09 (1H, d, 7.9), 8.59 (1H, dd, 1.9, 4.9), 8.87 (1H, d, 2.3)
6g	1738, 1761, 1750, 1633	1.22 (3H, t, 7.2), 1.38 (3H, t, 7.2), 1.44 (3H, t, 7.2), 4.18 (2H, q, 7.2), 4.35 (2H, q, 7.2), 4.47 (2H, q, 7.2), 7.20 (1H, m), 7.31 (2H, m), 7.36 (1H, s), 7.49 (1H, d, 8.2), 7.71 (2H, m), 8.08 (1H, d, 7.8), 8.62 (1H, d, 5.0)
6h	1785, 1761, 1734	1.19 (3H, t, 7.1), 1.40 (3H, t, 7.1), 1.46 (3H, t, 7.1), 1.48 (3H, t, 7.1), 4.15 (2H, q, 7.1), 4.37 (2H, q, 7.1), 4.50 (4H, m), 6.60 (1H, s), 7.27-7.41 (3H, m), 7.67 (1H, m), 7.85 (1H, s), 7.86 (1H, d, 7.8), 8.10 (1H, d, 8.1), 8.23 (1H, d, 8.1)
7b	1770, 1735, 1725, 1675, 1665	1.40 (3H, t, 7.1), 1.44 (3H, t, 7.1), 4.17 (2H, s), 4.35 (2H, q, 7.1), 4.46 (2H, q, 7.1), 7.10 (1H, t, 4.4), 7.22-7.33 (2H, m), 7.54 (1H, d, 7.4), 7.61 (1H, d, 4.9), 7.83 (1H, d, 3.7), 8.05 (1H, d, 8.1)
7h	1784, 1753, 1736, 1675, 1648	1.37 (3H, t, 7.1), 1.43 (3H, t, 7.1), 1.51 (3H, t, 7.1), 4.32 (2H, q, 7.1), 4.45 (2H, q, 7.1), 4.53 (2H, q, 7.1), 4.17 (2H, s), 7.22-7.39 (4H, m), 7.56 (1H, d, 8.0), 8.06 (1H, d, 8.0), 8.14 (1H, d, 8.0), 8.35 (1H, m), 8.44 (1H, s)
8a	1780, 1745, 1730,1695	1.13 (3H, t, 7.1), 1.48 (3H, t, 7.1), 4.05 (1H, d, 18.6), 4.14 (2H, dt, 1.3, 7.1), 4.30 (1H, d, 18.6), 4.51 (2H, q, 7.1), 7.09 (1H, t, 7.5), 7.18 (1H, m), 7.31-7.43 (3H, m), 7.54 (1H, t, 7.4), 7.88 (2H, m), 7.99 (1H, d, 8.2)
8b	1780, 1735, 1675	1.11 (3H, t, 7.2), 1.45 (3H, t, 7.2) 3.98 (1H, d, 18.2), 4.12 (2H, q, 7.2), 4.20 (1H, d, 18.2), 4.49 (2H, q, 7.2), 7.05-7.22 (3H, m), 7.33 (1H, t, 8.0),

		7.59 (1H, d, 4.7), 7.73 (1H, d, 3.8), 7.96 (1H, d, 8.0)
8h	1787, 1761, 1751, 1740, 1730, 1675	1.14 (3H, t, 7.1), 1.49 (3H, t, 7.1), 1.52 (3H, t, 7.1), 3.99 (1H, d, 18.0), 4.15 (2H, m), 4.20 (1H, d, 18.0), 4.52 (2H, q, 7.1), 4.56 (2H, q, 7.1), 7.10 (1H, t, 7.5), 7.22-7.36 (4H, m), 8.00 (1H, d, 8.2), 8.12 (2H, m), 8.35 (1H, s)
9	1765, 1752, 1728, 1715, 1663	1.21 (3H, t, 7.1), 1.41 (3H, t, 7.1), 1.44 (3H, t, 7.1), 4.15 (2H, q, 7.1), 4.42 (2H, q, 7.1), 4.46 (2H, q, 7.1), 6.31 (1H, dd, 2.2, 8.1), 6.63 (1H, dd, 2.2, 8.2), 7.10 (1H, t, 7.6), 7.21 (1H, t, 7.9), 7.48 (2H, m), 7.65 (1H, s), 7.93 (2H, m)
10a	1771, 1751	1.46 (3H, t, 7.1), 1.48 (3H, t, 7.1), 4.41 (2H, q, 7.1), 4.59 (2H, q, 7.1), 7.39 (1H, t, 7.5), 7.46-7.61 (3H, m), 7.92 (1H, s), 7.95 (1H, d, 7.6), 8.09 (1H, m), 8.20 (1H, d, 8.2), 8.30 (1H, m)
10b	1770, 1745	1.44 (3H, t, 7.2), 1.55 (3H, t, 7.2), 4.40 (2H, q, 7.2), 4.63 (2H, q, 7.2), 7.33-7.52 (3H, m), 7.87 (1H, s), 7.95 (1H, d, 7.8), 8.16 (2H, m)
10c	1761, 1749	1.44 (3H, t, 7.1), 1.59 (3H, t, 7.1), 4.39 (2H, q, 7.1), 4.70 (2H, q, 7.1), 7.39 (1H, t, 7.3), 7.48 (3H, m), 7.83 (1H, s), 7.96 (1H, d, 7.5), 8.26 (2H, d, 8.3)
10d	1771, 1746	1.47 (3H, t, 7.1), 1.61 (3H, t, 7.1), 4.42 (2H, q, 7.1), 4.67 (2H, q, 7.1), 7.36-7.49 (2H, m), 7.66 (1H, d, 2.2), 7.71 (1H, d, 2.2), 7.79 (1H, s), 7.94 (1H, dd, 7.7, 1.3), 8.24 (1H, d, 8.1)
10e	1773, 1738	1.38 (3H, t, 7.2), 1.46 (3H, t, 7.2), 4.42 (2H, q, 7.2), 4.60 (2H, q, 7.2), 7.39-7.55 (4H, m), 7.66 (1H, d, 8.1), 7.85 (1H, d, 7.6), 7.94 (1H, s), 7.95 (1H, d, 7.5),8.22 (1H, d, 8.2)
10fa	1765, 1745	1.40 (3H, t, 7.2), 1.46 (3H, t, 7.2), 4.41 (2H, q, 7.2), 4.59 (2H, q, 7.2), 7.40 (1H, t, 7.4), 7.47 (1H, dd, 4.2, 8.5), 7.54 (1H, t, 7.4), 8.01 (1H, d, 7.6), 8.02 (1H, s), 8.14 (1H, d, 8.3), 8.39 (1H, dd, 1.6, 8.5), 8.95 (1H, dd, 1.6, 4.2)
10fb	1767, 1742	1.48 (3H, t, 7.1), 1.53 (3H, t, 7.1), 4.33 (2H, q, 7.1), 4.63 (2H, q, 7.1), 7.44 (1H, t, 7.5),7.56 (1H, t, 7.4), 8.00 (1H, d, 7.8), 8.03 (1H, s), 8.21 (2H, m), 8.64 (1H, d, 6.0), 9.52 (1H, s)
10g	1760, 1735	1.45 (3H, t, 7.1), 1.52 (3H, t, 7.1), 4.41 (2H, q, 7.1), 4.61 (2H, q, 7.1), 7.40-7.55 (3H, m), 7.97 (1H, d, 7.2), 8.09 (1H, s), 8.20 (1H, d, 8.3), 8.79 (1H, dd, 1.6, 8.8), 8.93 (1H, dd, 1.6, 4.1)
10h	1771, 1727	1.37 (6H, m), 1.48 (3H, t, 7.1), 4.44 (6H, m), 7.37-7.43 (2H, m), 7.52 (2H, m), 7.91 (1H, s), 7.98 (1H, d, 7.6), 8.14 (1H, d, 7.7), 8.30 (2H, m)

[a] Exchange with D_2O.

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§ We are pleased to dedicate this manuscript to Professor Raffaello Fusco on the occasion of his 82nd birthday.