Preparation and Reactions of Some *o*-Dialkylaminoarylmethylene-substituted Azlactones (Oxazol-5-ones)

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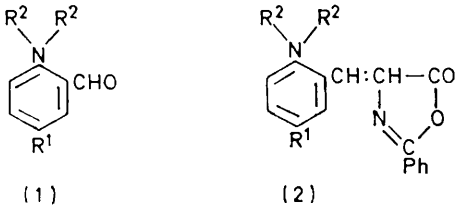
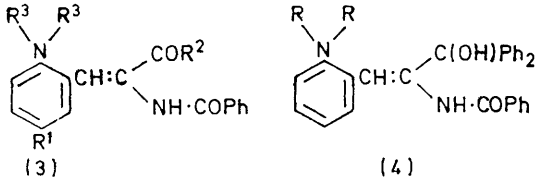
Various azlactones derived from *o*-dialkylaminobenzaldehydes were treated with nucleophiles (aqueous ethanolic sodium hydroxide, amines, and Grignard reagents). The carbinols obtained by reaction with a Grignard reagent were cyclised to give the corresponding indenes (5).

INTEREST in azlactones [oxazol-5-ones; *e.g.* (2)] is due to their importance as versatile synthetic intermediates as well as to some pharmacological activity; accordingly a variety of aryl- and heteroaryl-substituted azlactones have been reported.[1] In connection with our studies concerned with the ' t-amino-effect ' [2] we have elaborated a convenient synthesis of *o*-dialkylaminobenzaldehydes (1; $R^1 = H$) and now describe their conversion into the corresponding *o*-dialkylaminobenzylidene azlactones (2) and some preparative applications of the latter.

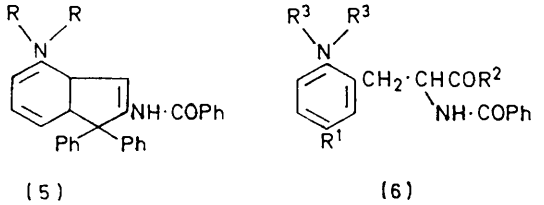


(1) (2)

R^1 = H or NO_2
a; $R^2R^2 = [CH_2]_4$
b; $R^2R^2 = [CH_2]_5$
c; $R^2R^2 = [CH_2]_6$
d; $R^2R^2 = [CH_2]_2 \cdot O[CH_2]_2$



(3) (4)



(5) (6)

The *o*-dialkylaminobenzaldehydes were conveniently prepared by nucleophilic displacement of the activated fluorine in 2-fluorobenzaldehyde with the required dialkylamine in hot dimethylformamide (Table 1). The activation of fluorine towards nucleophiles by an *ortho*-carbonyl group has previously been demonstrated in *o*- and *p*-fluoroaryl alkyl ketones.[3] Use of *o*-chlorobenzaldehyde in these reactions led only to 2-chloro-αα-bisdialkylaminotoluenes,[4] but the *p*-nitro-derivatives (1; $R^1 = NO_2$) were prepared from the corresponding chlorobenzaldehyde and the appropriate secondary amine.[4]

Condensation of the aldehydes (1; $R^1 = H$ or NO_2) with hippuric acid (*N*-benzoylglycine) in acetic anhydride–sodium acetate gave the corresponding unsaturated azlactones (2) (Table 2), characterised by their i.r. spectra [bands at *ca.* 1 800 (C:O), 1 660 (C:N), and 875 cm^{-1} (CH:CH)].

[1] E. Baltazzi, *Quart. Rev.*, 1955, **9**, 150; J. Lykkeberg, N. A. Klitgaard, *Acta Chem. Scand.*, 1972, **26**(1), 266.
[2] O. Meth-Cohn and H. Suschitzky, *Adv. Heterocyclic Chem.*, 1972, **14**, 211.
[3] H. Bader, A. R. Hansen, and F. J. McCarthy, *J. Org. Chem.*, 1966, **31**, 2319.
[4] G. V. Garner, D. B. Mobbs, H. Suschitzky, and J. S. Millership, *J. Chem. Soc.* (*C*), 1971, 3693.

TABLE 1

o-Dialkylaminobenzaldehydes (1; R^1 = H) from *o*-fluorobenzaldehyde and a secondary amine in hot dimethylformamide

NR^2_2	Yield (%)	B.p. (°C) [mmHg]	Found (%) C	H	N	Formula	Required (%) C	H	N
Pyrrolidin-1-yl	74	153 [1.0]	75.5	7.3	7.9	$C_{11}H_{13}NO$	75.4	7.4	8.0
Piperidino [a]	91	143 [1.0]				$C_{12}H_{15}NO$			
Perhydroazepin-1-yl	61	148 [0.8]	77.0	8.4	7.0	$C_{13}H_{17}NO$	76.9	8.4	6.9
Morpholino	93	162 [12.0]	69.3	6.8	7.2	$C_{11}H_{13}NO_2$	69.1	6.8	7.3

[a] Ref. 4.

TABLE 2

Azlactones (2) from dialkylaminobenzaldehydes (1) and hippuric acid

Azlactone (2) R^2R^2	R^1	M.p. (°C)	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N
$[CH_2]_4$	NO_2	230	70	65.7	4.8	11.5	$C_{20}H_{17}N_3O_4$	66.1	4.7	11.6
$[CH_2]_5$	NO_2	214	69	66.8	5.2	11.0	$C_{21}H_{19}N_3O_4$	66.8	5.1	11.1
$[CH_2]_6$	NO_2	164	75	67.6	5.8	11.0	$C_{22}H_{21}N_3O_4$	67.5	5.4	10.7
$[CH_2]_2{\cdot}O{\cdot}[CH_2]_2$	NO_2	200	67.5	53.0	4.4	10.8	$C_{20}H_{17}N_3O_5$	63.3	4.5	11.1
$[CH_2]_4$	H	111	82	75.0	5.8	8.7	$C_{20}H_{18}N_2O_2$	75.5	5.7	8.8
$[CH_2]_5$	H	144	85	75.8	6.1	8.1	$C_{21}H_{20}N_2O_2$	75.9	6.1	8.4
$[CH_2]_6$	H	118	92	76.0	6.4	7.8	$C_{22}H_{22}N_2O_2$	76.3	6.4	8.1
$[CH_2]_2{\cdot}O{\cdot}[CH_2]_2$	H	165	78	71.8	5.4	8.4	$C_{20}H_{18}N_2O_3$	71.8	5.4	8.4

TABLE 3

o-Dialkylamino-α-benzamidocinnamic acids (3; R^2 = OH)

R^3R^3	R^1	M.p. (°C)	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N
$[CH_2]_4$	NO_2	221	100	62.5	5.1	10.7	$C_{20}H_{19}N_3O_5$	63.0	5.0	11.0
$[CH_2]_5$	NO_2	232	98	63.7	5.5	10.4	$C_{21}H_{21}N_3O_5$	63.8	5.35	10.6
$[CH_2]_6$	NO_2	219	98	63.9	6.0	9.8	$C_{22}H_{23}N_3O_5$	64.5	5.7	10.2
$[CH_2]_2{\cdot}O{\cdot}[CH_2]_2$	NO_2	240	55	60.3	5.1	10.6	$C_{20}H_{19}N_3O_6$	60.4	4.8	10.5
$[CH_2]_4$	H	178	90	70.9	6.3	7.8	$C_{20}H_{20}N_2O_3$	71.3	6.0	8.3
$[CH_2]_5$	H	160	87	68.9	6.2	7.3	$C_{21}H_{22}N_2O_3,H_2O$	68.4	6.6	7.5

TABLE 4

Methyl *o*-dialkylamino-α-benzamidocinnamates (3; R^2 = OMe)

R^3R^3	R^1	M.p. (°C)	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N
$[CH_2]_4$	NO_2	208	85	64.0	5.5	10.6	$C_{21}H_{21}N_3O_5$	63.8	5.4	10.6
$[CH_2]_5$	NO_2	204	90	64.2	5.6	10.1	$C_{22}H_{23}N_3O_5$	64.5	5.7	10.3
$[CH_2]_6$	NO_2	195	72	65.4	6.0	10.0	$C_{23}H_{25}N_3O_5$	65.2	6.0	9.9
$[CH_2]_2{\cdot}O{\cdot}[CH_2]_2$	NO_2	174	70	59.6	5.2	10.3	$C_{21}H_{21}N_3O_6$	61.3	5.1	10.2
$[CH_2]_4$	H	172	85	72.0	6.3	8.0	$C_{21}H_{22}N_2O_3$	72.0	6.3	8.0
$[CH_2]_5$	H	177	82	72.1	6.7	7.4	$C_{22}H_{24}N_2O_3$	72.5	6.6	7.7

TABLE 5

Hydrazides and amides of *o*-dialkylaminocinnamic acids (3; R^2 = NR_2 or $NH{\cdot}NR_2$)

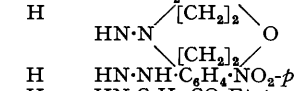
R^3R^3	R^1	R^2	M.p. (°C)	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N
$[CH_2]_4$	NO_2	$HN{\cdot}NC_5H_{10}$	134	80	66.6	6.4	14.5	$C_{27}H_{31}N_5O_4$	66.25	6.4	14.3
$[CH_2]_5$	NO_2	$HN{\cdot}NH_2$	156	78	61.3	5.2	16.8	$C_{21}H_{23}N_5O_4$	61.6	5.7	17.1
$[CH_2]_4$	H	$HN{\cdot}NH_2$	158	52	68.2	6.3	15.6	$C_{20}H_{22}N_4O_2$	68.5	6.3	15.9
$[CH_2]_6$	H	$HN{\cdot}NH_2$	96	75	69.7	7.4	14.7	$C_{22}H_{26}N_4O_2$	69.8	6.9	14.8
$[CH_2]_2{\cdot}O{\cdot}[CH_2]_2$	H		167	62	68.6	6.8	12.8	$C_{24}H_{28}N_4O_3$	68.5	6.7	13.3
$[CH_2]_5$	H	$HN{\cdot}NH{\cdot}C_6H_4{\cdot}NO_2$-*p*	188	68	66.8	5.5	14.6	$C_{27}H_{27}N_5O_4$	66.8	5.6	14.4
$[CH_2]_5$	H	$HN{\cdot}C_6H_4{\cdot}CO_2Et$-*p*	145	85	72.3	6.7	8.0	$C_{30}H_{31}N_3O_4$	72.4	6.3	8.4
$[CH_2]_5$	H	NC_4H_8	154	89	74.0	7.1	9.9	$C_{25}H_{29}N_3O_2$	74.4	7.2	10.4

TABLE 6

Cinnamyl alcohols (4)

RR	M.p. (°C)	Yield (%)	Found (%) C	H	N	Formula	Required (%) C	H	N
$[CH_2]_4$	163	82	81.3	6.2	5.8	$C_{32}H_{30}N_2O_2$	81.0	6.4	5.9
$[CH_2]_5$	148	76	81.6	6.7	5.6	$C_{33}H_{32}N_2O_2$	81.1	6.6	5.2
$[CH_2]_6$	157	65	81.6	6.7	5.3	$C_{34}H_{34}N_2O_2$	81.2	6.8	5.6

TABLE 7

2-Benzamido-3-*o*-(dialkylamino)propionic acids and esters (6; R^2 = OH or OMe)

R^3R^3	R^1	R^2	M.p. (°C)	Yield (%)	Found (%) C	H	N	Formula	Required C	H	N
$[CH_2]_5$	H	OMe	126	85	71.9	7.1	7.5	$C_{22}H_{26}N_2O_2$	72.1	7.15	7.6
$[CH_2]_4$	NH_2	OMe	110	89	56.4	6.5	8.8	$C_{21}H_{26}ClN_3O_3,2.5H_2O$	56.3	6.95	9.35
$[CH_2]_5$	NH_2	OMe	181	92	57.8	6.9	8.9	$C_{22}H_{28}ClN_3O_3,2H_2O$	58.2	7.1	9.25
$[CH_2]_2$·O·$[CH_2]_2$	NH_2	OMe	140	90	60.0	6.5	9.5	$C_{21}H_{26}ClN_3O_4$	60.1	6.2	10.0
$[CH_2]_4$	NH_2	OH	141	70	54.6	6.5	8.9	$C_{20}H_{24}ClN_3O_3,2H_2O$	54.1	6.8	9.5
$[CH_2]_6$	NH_2	OH	178	94	56.1	6.8	8.7	$C_{22}H_{28}ClN_3O_3,3H_2O$	56.2	6·8	8.9
$[CH_2]_2$·O·$[CH_2]_2$	NH_2	OH	172	82	52.0	6.2	9.1	$C_{20}H_{24}ClN_3O_4,3H_2O$	52.2	6.6	9.1
$[CH_2]_5$	·NHCOPh	H	174	83	66.3	6.4	7.5	$C_{28}H_{29}N_3O_4,2H$ O	66.3	6.7	8.3

Unsaturated azlactones behave for the most part like acid anhydrides towards nucleophilic reagents, which attack usually at the electrophilic carbonyl carbon atom with ring opening.

Our arylmethyleneoxazolones (2) were not hydrolysed by boiling water but were easily cleaved by treatment with aqueous ethanolic sodium hydroxide to give the corresponding benzoylaminocinnamic acids (3; R^2 = OH) (Table 3). Methanolysis with sodium acetate as catalyst [5] gave the cinnamic esters (3; R^2 = OMe) (Table 4). Reaction with various hydrazines as well as amines also proceeded smoothly to give the expected hydrazides and amides respectively (3; R^1 = H or NO_2, R^2 = HN·NR_2 or HNR_2) (Table 5). Only in the case of the weakly basic ethyl *p*-aminobenzoate was it necessary to use triethylamine as catalyst.

It was recently shown [6] that the carbinols produced by treatment of azlactones derived from pyridinecarbaldehydes with Grignard reagents can be cyclised to pyrindines. By an analogous procedure we prepared the dialkylamino-substituted carbinols (4a—c) (Table 6) and cyclised them in acetic–hydrochloric acid or polyphosphoric acid to the corresponding indenes (5a and b).

Catalytic reduction of the cinnamic acid derivatives (3; R^1 = H or NO_2, R^2 = OH or OMe) over palladium–charcoal gave high yields of the novel 2-benzamido-3-dialkylaminophenylpropionic acid derivatives (6; R^1 = H or NH_2, R^2 = OH or OMe) (Table 7).

EXPERIMENTAL

o-Dialkylaminobenzaldehydes.—(a) *Unsubstituted* (1; R^1 = H). To a solution of freshly distilled *o*-fluorobenzaldehyde [7] (0.15 mol) in dimethylformamide (60 ml) and anhydrous potassium carbonate (0.175 mol) was added the appropriate secondary amine (0.175 mol) and the mixture was refluxed for 5 h. It was then cooled, poured into water, and extracted with chloroform. The extract was washed with water to remove dimethylformamide, dried ($MgSO_4$), and evaporated *in vacuo* to leave the *aldehyde*, which was purified by distillation (Table 1). 2-Dimethylaminobenzaldehyde was prepared by a pressure reaction at 100 °C for 12 h between 2-fluorobenzaldehyde (0.1 mol) in ethanol (80 ml) and dimethylamine (0.22 mol). After completion of the reaction the solvent was driven off and the aldehyde obtained as an oil, b.p. 103° at 3 mmHg (12.7 g) (lit.,[7b] b.p. 120° at 1 mmHg).

(b) *Nitro-derivatives* (1; R^1 = NO_2). These were prepared as previously described.[4]

Preparation of Azlactones (2).—An equimolar mixture of the aldehyde and finely powdered hippuric acid (0.1 mol) was heated on a steam-bath with addition of sodium acetate (0.05 mol) and acetic anhydride (0.1 mol) for 2 h The mixture was then cooled and, after addition of ethanol (20 ml), kept overnight. The *solid* was filtered off, washed with water (100 ml) followed by ice-cold ethanol (20 ml), and recrystallised from benzene.

o-Dialkylaminocinnamic Acids (3; R^2 = OH).—The azlactone (0.01 mol) was refluxed in ethanol (50 ml) containing sodium hydroxide (0.01 mol) for 2 h. The ethanol was then driven off and the mixture poured into water. Acidification (HCl) precipitated the *cinnamic acid derivative* (3) (Table 3), which was recrystallised from ethanol.

Methyl o-Dialkylaminocinnamates (3; R^2 = OMe).—A suspension consisting of methanol (30 ml), the azlactone (0.01 mol), and sodium acetate (0.05 mol) was kept under reflux for 20 h. After removing the methanol and pouring the mixture into water the *product* was filtered off, washed with water, and recrystallised from ethanol–ethyl acetate (Table 4).

Amides and Hydrazides of o-Dialkylaminocinnamic Acids (3; R^2 = NR_2).—An ethanolic solution (50 ml) of the azlactone (0.01 mol) containing the required amine or hydrazine (0.01 mol) was boiled under reflux for *ca.* 8 h. After cooling the mixture was poured into water and extracted with chloroform. The solution was dried then evaporated *in vacuo* to leave the *product* which was recrystallised from petroleum (Table 5).

Reaction of Azlactones with Phenylmagnesium Bromide.—To an ethereal solution (100 ml) of phenylmagnesium bromide [from magnesium (0.03 mol) and bromobenzene (0.03 mol)] was added a fine suspension of the azlactone (0.01 mol) in ether (50 ml) over 1 h. The mixture was then kept under reflux for 4 h, left overnight, and finally hydrolysed with saturated aqueous ammonium chloride. The ether layer was separated, dried ($MgSO_4$), and evaporated. The *residue* was recrystallised from ethanol (Table 6).

4-Dialkylaminoindenes (5).—A fine suspension of the carbinol (3) (1.0 g) in a mixture of acetic (20 ml) and hydrochloric acid (10 ml) was kept at 80 °C for 1 h. The product was separated by addition of saturated aqueous sodium acetate. It was filtered off and washed with water. Cyclisation was also effected with polyphosphoric acid at 110 °C for 1 h. *2-Benzamido-1,1-diphenyl-4-pyrrolidinoindene* (84%) (5; RR = $[CH_2]_4$) had m.p. 90° (Found: C, 84.0; H, 6.6; N, 6.0. $C_{33}H_{30}N_2O$ requires C, 84.2; H,

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[7] (*a*) V. V. Korshak and G. S. Kolesnikov, *Sintezy org. Soedinenii Sbornik*, 1952, **2**, 140; (*b*) I. Heilbron and H. M. Bunbury, 'Dictionary of Organic Compounds,' Eyre and Spottiswoode, 4th edn., London, 1968.

6.4; N, 5.95%). The *2-piperidinoindene* (5; RR = $C_5H_{10}N$–) (76%) had m.p. 96° (Found: C, 83.9; H, 6.4; N, 5.7. $C_{32}H_{28}N_2O$ requires C, 84.2; H, 6.2; N, 6.1%).

2-Benzamido-3-(o-dialkylaminophenyl)propionic Acids or Esters (6; R^2 = OH *or* OMe).—The ester (3; R^1 = H, R^2 = OMe) (0.01 mol) was hydrogenated at 50 atm as a suspension in ethanol over palladium–charcoal at room temperature. The nitro-compounds (3; $R^1 = NO_2$, R^2 = OH or OMe) were reduced at 80 °C (90 atm) to give the corresponding amines, which were isolated as hydrochlorides or in one case as a benzoyl derivative (Table 7).

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