COMMUNICATIONS

Reactions of Arylacetones with Chloroacetamides

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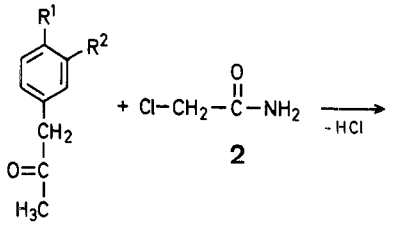
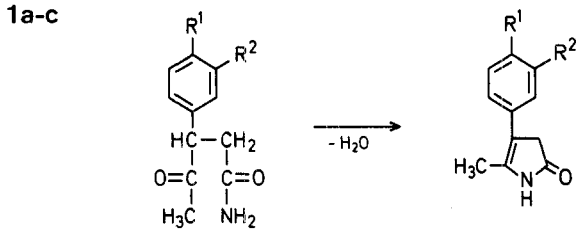
In continuation of studies[1,2] on the synthesis of octahydroindole alkaloids, we expected to prepare the 3-aryllevulinoamides (**3a–c**) from the reactions of arylacetones (**1a–c**) with chloroacetamide (**2**).



1a-c **2**

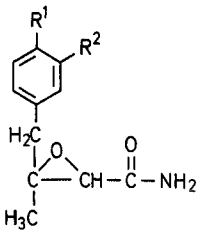


3a-c **4a-c**

	R^1	R^2
a	H	H
b	$-OCH_2O-$	
c	OCH_3	OCH_3

3-Aryllevulinonitrile was previously prepared[3] in low yield from a similar reaction of **1c** with chloroacetonitrile. However, the reactions of **1** with **2** gave different products in low yields depending on the solvent and the reaction conditions.

The products from the reactions of **1a–c** with **2** and an alcoholate in ethanol or isopropyl alcohol were not the expected ketoamides **3a–c** but, as shown by I.R. and N.M.R. spectra, the isomeric glycidamides (**5a–c**). The ^{1}H-N.M.R. spectrum (60 MHz) of **5a** shows singlets at $\delta = 1.20$, 2.90, and 3.36 ppm for the methyl, methylene, and methin protons, respectively. In the 90 MHz ^{1}H-N.M.R. spectrum, the signals for the methyl, methylene, and methin groups are doubled, indicative of a *cis/trans* isomerism of the substituents relative to the oxirane ring. Similarly the ^{13}C-N.M.R. spectrum of **5a** contains 15 signals for the 11 carbon atoms resulting from duplication of all signals except those of the aromatic C-2, C-6, C-3, C-5, and C-4 atoms. The *cis/trans* ratio is estimated to be 1:3 from both ^{1}H- and ^{13}C-spectra.

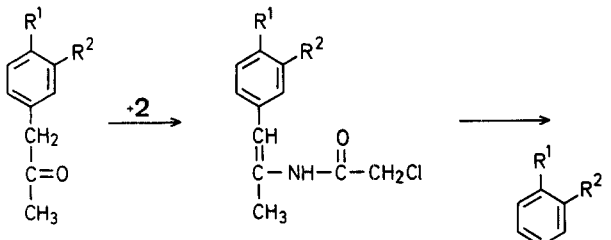


5a-c

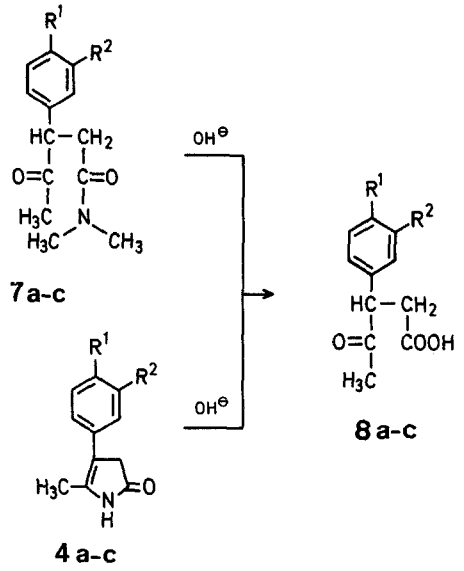
These results are in contrast to previous observations on glycid ester synthesis where pure *trans* esters are obtained using sodium ethoxide in ethanol[4].

Reaction of **1** with **2** in dimethyl sulfoxide in the presence of potassium *t*-butoxide leads directly to the products **4a–c**. The structures are confirmed by I.R. (NH band) and N.M.R. spectra (homoallylic coupling). The presence of a quartet for methylene and a triplet for methyl protons eliminates the structures of Δ^1-respectively Δ^3-pyrrolinones and structures with an exocyclic double bond as postulated[5] for similar structures.

The possible sequence **1**→**6**→**4**, of which the first step has been described previously for similar ketones[6] is unlikely because this reaction was carried out using acidic dehydration catalysts whereas, in the present work, **1a–c** undergo base-catalysed reaction independent of solvent with *N,N*-dimethylchloroacetamide to the ketoamides **7a–c**. In contrast to literature reports[7,8], the corresponding *N,N*-dimethylglycidamides cannot be detected using isopropyl alcohol/sodium ethoxide nor when using dimethyl sulfoxide/potassium *t*-butoxide as base.

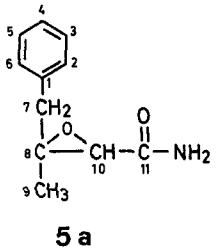


1a-c **6a-c** **4a-c**



The ketoacids **8a–c** are obtained by alkaline hydrolysis of **7a–c** and also of **4a–c**, thus giving further proof for the structures **4** and **7**.

Table 1. ^{13}C-N.M.R-spectrum of **5a** (22.63 MHz)



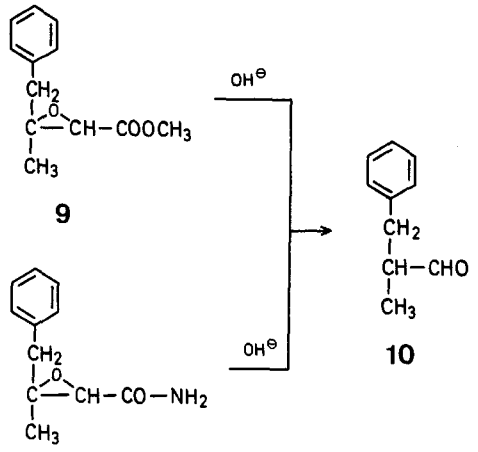
Carbon atom	δ ppm ($CDCl_3$)[a]	Multiplicity ($CDCl_3$)[b]	δ(ppm) (DMSO-d_6)[a]	Multiplicity (DMSO-d_6)[b]
9	16.85	(d)	15.94	q
	22.08	(d)	21.28	q
7	39.02	t		
	43.95	t		
10	60.31	d	59.55	d
	62.00	d	60.78	d
8	63.41	s	61.76	s
	63.85	s	62.15	s
2,3,4,5,6	127.27	d	126.70	d
	128.60	d	128.33	d
	129.93	d	129.63	d
1	135.88	s	136.79	s
	136.59	s	137.31	s
11	170.73	s	170.07	s
			170.15	s

[a] Broad band decoupled.
[b] Off resonance.

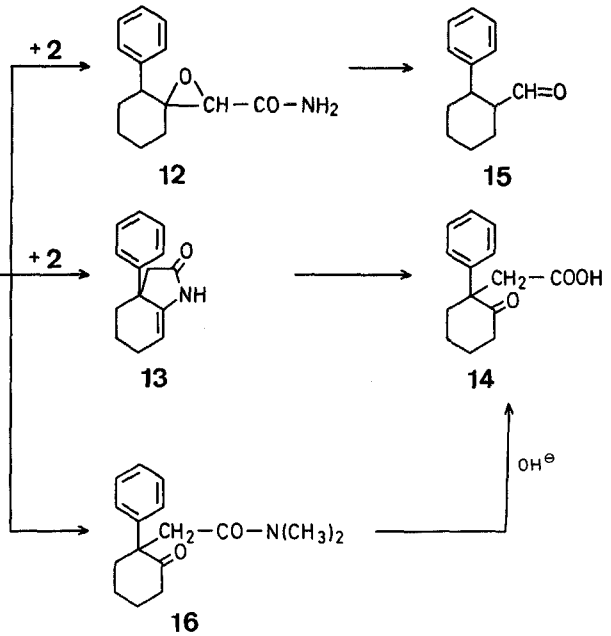
The aldehyde **10** is obtained by alkaline hydrolysis and subsequent decarboxylation of both the amide **5a** and the ester **9**.

These reactions could be transferred to 2-phenylcyclohexanone (**11**) to give the amide **12** and the hexahydroindolone **13**, thus providing a simple route to 3a-aryloctahydroindolones.

The structure of **12** was proved by alkaline hydrolysis with subsequent decarboxylation to give the aldehyde **15**. The properties of **13** correspond well to those previously



reported[9]. The ketoamide **16** is formed by reaction of **11** with *N*,*N*-dimethylchloroacetamide; both **16** and **13** can be hydrolysed to the known[9] ketoacid **14**.



Preparation of 3-Aryl-2-methyl-2-pyrroline-5-ones 4a–c and 3a-Phenyl-2-oxo-1,2,3,3a,4,5,6-hexahydroindole (13); General Procedure:

To a solution of potassium *t*-butoxide (0.25 mol) in dimethyl sulfoxide (150 ml) was slowly added ketone **1** or **11** (0.225 mol) and, after cooling to room temperature, chloroacetamide **2** (0.25 mol) was portionwise added. The reaction mixture was heated at 80° for 2 h and after cooling, poured into ice/water (500 ml). After being allowed to stand overnight, the suspension was extracted with chloroform. The extract was washed with water and the solvent removed *in vacuo*. After removal of unreacted ketone in vacuo the residue was crystallised for isopropyl alcohol.

Preparation of 3-Benzyl-3-methylglycidamides 5a–c and 4-Phenyl-1-oxaspiro-[2.5]-octane-2-carboxamide (12); General Procedure:

To a solution of sodium (1 mol) in isopropyl alcohol (1200 ml) was added dropwise ketone **1** or **11** (1 mol) under stirring. 30 min after the last addition chloroacetamide **2** (1 mol) was added portionwise, and the reaction mixture heated 1 h under reflux. After cooling to room temperature a second addition of sodium (0.1 mol) followed by chloroacetamide (0.1 mol) was made and the reaction mixture heated 8 h under reflux. The solution was filtered to remove sodium chloride, evaporated *in vacuo* and extracted with chloroform. After removal of solvent and unreacted ketone in vacuo, the residue was crystallised from isopropyl alcohol.

Table 2. Reaction Products from Ketones **1** or **11** with **2**

Product	M.p.	Yield[a] (%)	Ketone recovered (%)	Analysis					I.R. (KBr) (cm^{-1})	^{1}H-N.M.R. δ (ppm)	Other data
4a	162–165°	35	33	$C_{11}H_{11}NO$ (173.2)	calc.	C 75.93	H 6.37	N 8.05	3210, 1705, 1665	60 MHz[b]: 2.16(t, 3H, CH_3, ^5J = 2.3 Hz) 3.39(q, 2H, CH_2; ^5J = 2.3 Hz 9.70(bs, 1H, NH)	Mass spectrum: m/e = 173.1 ($M^{\oplus}$, 87.5%), 144(100%)
					found	75.71	6.42	8.00			
4b	213–214°	28	29	$C_{12}H_{11}NO_3$ (217.2)	calc.	C 66.36	H 5.11	N 6.45	3170 1687, 1645	60 MHz[b]: 2.00(t, 3H, CH_3, ^5J = 2.7 Hz) 3.30(q, 2H, CH_2, ^5J = 2.7 Hz) 6.01(s, 2H, OCH_2) 9.61(bs, 1H, NH)	—
					found	66.22	5.12	6.14			
4c	165°	25	22	$C_{13}H_{15}NO_3$ (233.3)	calc.	C 66.93	H 6.48	N 6.00	3170 1690, 1640	60 MHz[c]: 2.14(t, 3H, CH_3, ^5J = 2.5 Hz) 3.35(q, 2H, CH_2, ^5J = 2.5 Hz) 3.83(s, 6H, OCH_3) 8.84(bs, 1H, NH)	—
					found	67.13	6.58	5.76			
13	183°	22	48	$C_{14}H_{15}NO$ (213.3)	calc.	C 78.84	H 7.09	N 6.57	3190, 3060 1710(w), 1678(s)	—	reference[9]
					found	78.99	6.96	6.46			
5a	162–163°	23	51	$C_{11}H_{13}NO_2$ (191.2)	calc.	C 68.81	H 6.82	N 7.30	3390, 3205 1664	90 MHz[c]: 1.28, 1.34(s, 3H, CH_3) 1.91, 2.94(s, 2H, CH_2) 3.28, 3.39(s, 1H, CH) 6.32(2H, NH_2)	Mass spectrum: m/e = 191 ($M^{\oplus}$, 5%), 147 (100%), 91 (98%)
					found	69.01	6.84	7.31			
5b	163–164°	16	44	$C_{12}H_{13}NO_4$ (235.2)	calc.	C 61.28	H 5.57	N 5.96	3430, 3190 1662	60 MHz[b]: 1.19(s, 3H, CH_3) 2.80(s, 2H, CH_2) 3.33(s, 1H, CH) 6.03(s, 2H, OCH_2O) 7.34(2H, NH_2)	—
					found	61.41	5.64	6.11			
5c	130°	16	42	$C_{13}H_{17}NO_4$ (251.3)	calc.	C 62.13	H 6.82	N 5.57	3360, 3175 1664	90 MHz[c]: 1.28, 1.34(s, 3H, CH_3) 1.85, 2.87(s, 2H, CH_2), 3.29, 3.39(s, 1H, CH) 3.86, 3.88(s, 6H, OCH_3) 6.31(2H, NH_2)	—
					found	62.24	6.89	5.41			
12	183–184°	9	48	$C_{24}H_{17}NO_2$ (231.3)	calc.	C 72.70	H 7.41	N 6.05	3395, 3190 1635	60 MHz[b]: 1.72(bs, 8H, CH_2) 3.31(m, 1H, CH) 3.36(s, 1H, CH—CO)	—
					found	72.47	7.52	6.15			

[a] Yields referred to reacted ketone.
[b] Solvent DMSO-d_6.
[c] Solvent $CDCl_3$.

Preparation of 3-Aryllevulinic Acid *N,N*-Dimethylamides 7a–c and 2-(*N,N*-Dimethylcarboxamidomethyl)-2-phenylcyclohexane-1-one (16); General Procedure:

To a solution of potassium *t*-butoxide (0.25 mol) in dimethyl sulfoxide (150 ml) was slowly added ketone **1** or **11** (0.25 mol) under stirring. *N,N*-Dimethylchloroacetamide (0.25 mol) was added dropwise at room temperature and the reaction mixture heated to 100° for 2 h. The mixture was poured into water (2500 ml), extracted with chloroform, and washed with water. After removal of solvent and unreacted ketone, the residue was distilled in vacuo and if possible crystallised from ethyl acetate or isopropyl ether.

Preparation of 3-Aryllevulinic Acids 8a–c and 2-Carboxymethyl-2-phenylcyclohexane-1-one (14); General Procedure:

Lactams **4** or **13** or amides **7** or **16** (0.05 mol) are heated in a mixture of 10% sodium hydroxide solution (40 ml) and dioxan (10 ml) for 6 h. The reaction solution is diluted with water (100 ml) and extracted with chloroform. The alkaline water phase is acidified with hydrochloric acid and extracted with chloroform. After removal of solvent in vacuo, the residue is crystallised from isopropyl alcohol, isopropyl ether, or ethyl acetate.

3-Benzyl-3-methylglycid Acid Methyl Ester (9):

Synthesis according to preparation of glycidamides (general procedure); yield: 35%; b.p. 91–94°/0.06 torr; yellowish liquid.

3-Phenyl-2-methylpropionaldehyde (10):

Method A: from **9**:

A solution of **9** (29 mmol) in 10% sodium hydroxide solution (30 ml) was refluxed for 2 h, diluted with water (50 ml), and extracted with chloroform (10 ml). The alkaline water phase was acidified with hydrochloric acid to pH 4 and extracted with chloroform. After removal of solvent in vacuo **10** was obtained as yellow

Table 3. Reaction Products from **1** or **11** with *N,N*-Dimethylchloroacetamide. Products of Hydrolysis of Lactams **4** and **13** or of Amides **7** or **16**

Product	B.p.	Yield (%)	From compound	Analysis					I.R. (KBr) cm^{-1}	^{1}H-N.M.R ($CDCl_3$) δ (ppm)
7a	124°/0.12 torr	77		$C_{13}H_{17}NO_2$ (219.3)	calc.	C 71.25	H 7.82	N 6.40	1710, 1640 (film)	2.20 (s, 3H, $COCH_3$) 2.57 (d, 1H, CH_2[a]), $^3J_1 = 4$ Hz) 2.94, 3.00 (s, 6H, N—CH_3) 3.33 (double d, 1H, CH_2, $^2J = 16.4$ Hz, $^3J_2 = 10.6$ Hz) 4.37 (double d, 1H, CH, $^3J_1 = 4$ Hz, $^3J_2 = 10.6$ Hz)
					found	71.15	7.91	6.35		
7b	170–72/0.15 torr m.p. 80–81°	63		$C_{14}H_{17}NO_4$ (263.3)	calc.	C 63.87	H 6.51	N 5.32	1705, 1636	
					found	63.89	6.48	5.31		
7c	168/0.04 torr m.p. 81–82°	69		$C_{15}H_{21}NO_4$ (279.3)	calc.	C 64.51	H 7.58	N 5.01	1710, 1638	2.20 (s, 3H, $COCH_3$) 2.40 (doubled, 1H, CH_2, $^3J_1 = 4$ Hz, $^2J = 17$ Hz) 2.93, 3.00 (s, 6H, N—CH_3) 3.28 (double d, 1H, CH_2, $^3J_2 = 10.4$ Hz, $^2J = 17$ Hz) 3.87 (s, 6H, OCH_3) 4.29 (double d, 1H, CH, $^3J_1 = 4$ Hz, $^3J_2 = 10.4$ Hz)
					found	64.64	7.59	4.91		
16	148–53/0.05 torr m.p. 117°	47		$C_{16}H_{21}NO_2$ (259.4)	calc.	C 74.08	H 8.16	N 5.40	1702, 1624	
					found	74.19	8.20	5.22		
8a	m.p. 96.6°	68	**7a**	$C_{11}H_{12}O_3$ (192.2)	[b]				3180 1738, 1685	2.10 (s, 3H, $COCH_3$) 2.54 (double d, 1H, CH_2, $^3J_1 = 5.2$ Hz, $^2J = 17.6$ Hz) 3.27 (double d, 1H, CH_2, $^3J_2 = 9.7$ Hz, $^2J = 17.6$ Hz) 4.15 (double d, 1H, CH, $^3J_1 = 5.2$ Hz, $^3J_2 = 9.7$ Hz) 10.62 (bs, 1H, OH)
	m.p. 95.2°	34	**4a**							
8b	m.p. 127.5°	73	**7b**	$C_{12}H_{12}O_5$ (236.2)	calc.	C 61.02	H 5.12			
	m.p. 127–128°	59	**4b**		found	61.04	5.10		1702	
8c	m.p. 98.5°	79	**7c**	$C_{13}H_{16}O_5$ (252.3)	calc.	C 61.89	H 6.39			
	m.p. 97–98°	63	**4c**		found	61.79	6.30		1708	
14	m.p. 134.2°	69	**13**	$C_{14}H_{16}O_3$ (232.3)	calc.	C 72.39	H 6.94			
	m.p. 133–134°	48	**16**		found	72.49	6.97			

[a] Second d overlapped by N—CH_3 protons; by addition of Eu(DPM)$_3$ shift to 3.12 (double d, 1H, CH_2; $^3J_1 = 4$ Hz, $^2J = 16.4$ Hz).
[b] Equivalent weight 189.4 by potentiometric titration with 0.1 *N* NaOH.

oil; yield of raw material: 95%; b.p. 120–124°/3 torr; 2,4-Dinitrophenylhydrazone: m.p. 117°.
I.R. (Film): $\nu_{C=O}$ 1715 cm^{-1}.

Method B: from **5a**:
Procedure as described for method A; b.p. 120–124°/3 torr.
I.R. (Film): $\nu_{C=O}$ 1715 cm^{-1}.

$C_{16}H_{16}N_4O_4$ (328.3)	calc.	C 58.54	H 4.91	N 17.06
	found	58.51	4.98	17.29

Compound **10** prepared from **9** or **5a** had identical peaks in G.L.C as single and as mixed products (G.L.C conditions: silicone OV 17 5% on Chromosorb G AW-DMCS/steel column 2 m/column temp. 150°).

2-Phenylcyclohexane-1-carbaldehyde (15):
Preparation as described for **10**; yellow liquid; yield: 35%.
I.R. (Film): $\nu_{C=O}$ 1715 cm^{-1}.
Derivative: 2,4-Dinitrophenylhydrazone m.p. 149.9°.

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