Intramolecular Cyclocondensation of 4- and 5-Oxocarboxylic Acids to Five- and Six-Membered Ring Systems

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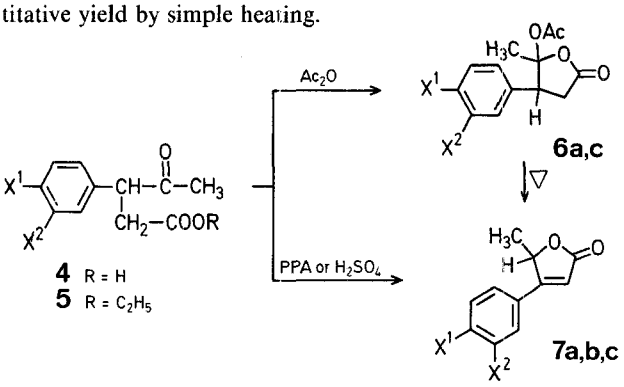
In connection with earlier studies[1,2] concerning the preparation of reactive intermediates for the synthesis of octahydroindole alkaloids, we investigated the cyclization of the dicarboxylic acids **2** and their monoamides **3**.

Compounds **2**and **3** were prepared from *N,N*-dimethyl-3-acetyl-3-aryl-6-nitrilohexanamides (**1**) by alkaline or acidic hydrolysis, respectively. Compounds **1** were in turn obtained by cyanoethylation of the previously described[3] *N,N*-dimethyl-3-aryl-4-oxopentanamides (3-aryllevulinamides).

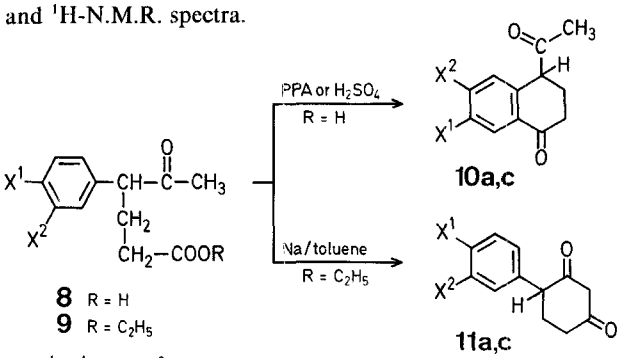
Compounds **2** may be expected to undergo the following types of cyclization reactions in which they react as 4- or 5-oxoalkanoic acids:

(a) Enol lactonization of the free acids or their reactive derivatives (anhydrides, acid chlorides);
(b) Intramolecular acylation of the *C*-methyl group under the conditions of a Dieckmann condensation;
(c) Intramolecular Friedel-Crafts acylation.

We studied the cyclization behaviour of the acids **2** using 3-aryl-4-oxopentanoic acids (**4**), 4-aryl-5-oxohexanoic acids (**8**), and the ethyl esters thereof (**5, 9**) as model compounds. It was found that the reactions of acids **4** or their ethyl esters **5** with polyphosphoric acid or sulfuric acid afford exclusively the lactones **7**. The 2,3 position of the double bond was unambiguously assigned on the basis of the ^{1}H-N.M.R. spectra (homoallylic coupling). As expected[4], the reaction of **4** with acetic anhydride leads to the acetoxylactones **6** which may be converted into **7** in practically quantitative yield by simple heating.



The formation of other possible cyclization products from **4** or **5** such as cyclopentanediones or indanones was not observed. On the other hand, the homologous acids **8** undergo exclusive cyclocondensation to 4-acetyl-1-tetralones (**10**) under the same conditions. With acetic anhydride, however, cyclization does not occur, the only isolable product being the anhydride of **8c**. Contrary to **5**, the ethyl esters **9** may be cyclized to the 4-phenyl-1,3-cyclohexanediones **11** the structure of which was assigned on the basis of the I.R.- and ^{1}H-N.M.R. spectra.



4-9	X^1	X^2
a	H	H
b	-O-CH$_2$-O-	
c	-OCH$_3$	-OCH$_3$

Application of the acid-catalyzed cyclization to the dicarboxylic acids **2** and **19** yields analogous results. The cyclization of **2c** using sulfuric acid affords the 1-tetralone **13** whereas the analogous treatment of **2c** with polyphosphoric acid leads to a not yet identified product the microanalysis and mass spectrum of which indicate loss of 1 mol water as compared to **13**. Basic hydrolysis of the unknown product affords **13**; this fact suggests linkage of the side chains via lactonization. Compound **2a** is cyclized in sulfuric acid to give the cyclohexanedione **18a**; a similar reaction, i.e., cyclization of **19a** to the homologous **20a**, has already been reported[5]. Treatment of **2a** with polyphosphoric acid directly affords the unsaturated lactone **12a**; however, when the amount of polyphosphoric acid used is not sufficient to bring about complete cyclization[6] of **2a**, the monocyclic compound **18a** is obtained. Compounds **12** and **21** may be obtained from **18** and **20**, respectively, using acetic anhydride[7] or thionyl chloride.

Compound **18** may also be prepared from **16** or **17** by hydrolysis under mild conditions. Further, compounds **16** and **17** are obtained by cyclocondensation of **14** and **15**, respectively, using sodium in toluene. A possible cyclopentane-

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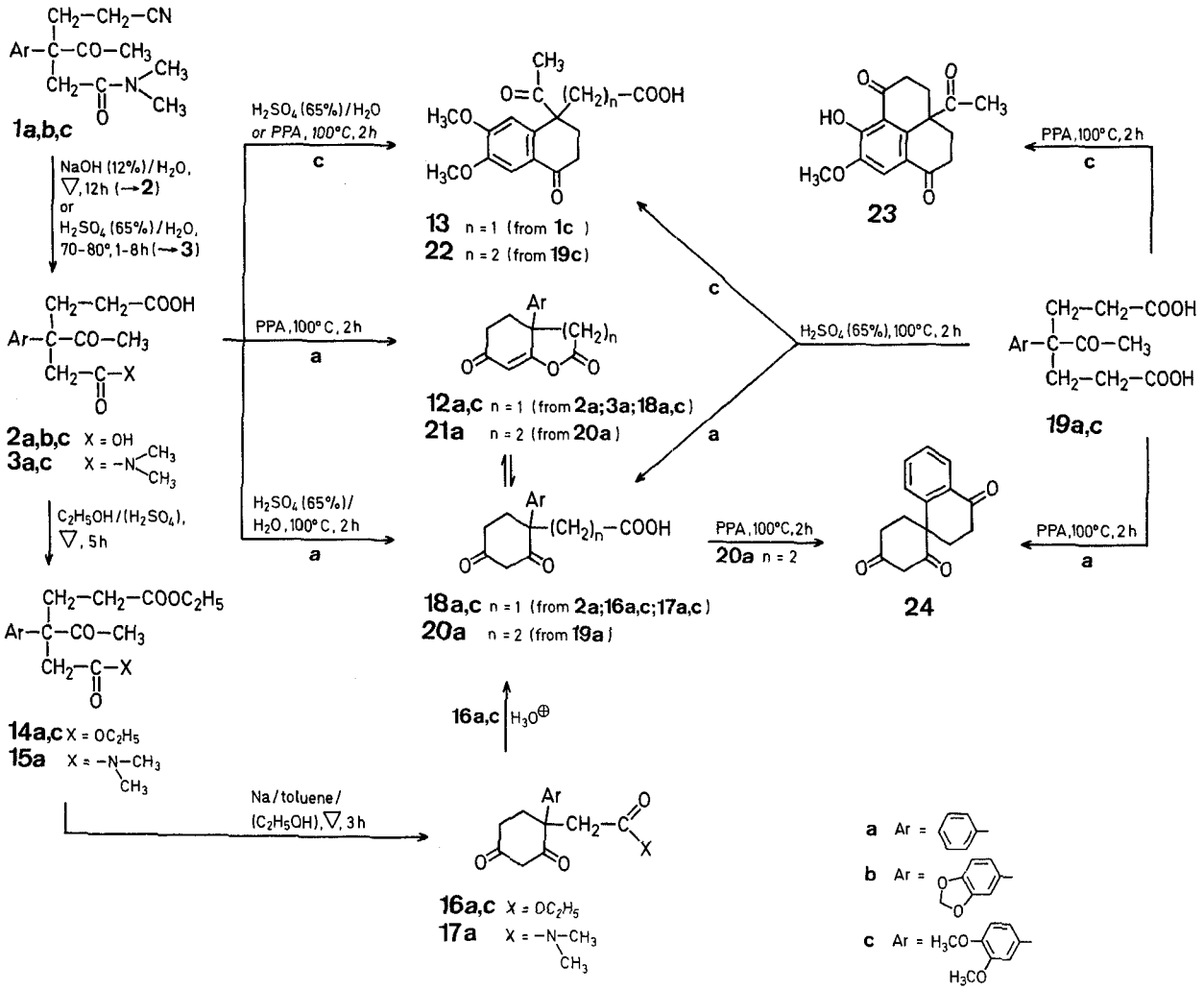

dione structure of **16** and **17** can be excluded on the basis of the I.R. and ^{1}H-N.M.R. spectra as well as from the conversion of **16** and **17** to **12**.

As expected, tetralones are the main products obtained from the cyclocondensation of the diacids **19**; compound **22** is thus formed from **19c** in the presence of sulfuric acid whereas the tricyclic compound **23** is formed with demethylation of one methoxy group when polyphosphoric acid is used as the condensing agent. Treatment of **19a** with polyphosphoric acid affords the spiro triketone **24** the structural assignment of which is based on ^{1}H-N.M.R.-spectral data and on its alternative formation from **20a** in the presence of polyphosphoric acid.

Table. Cyclization Products

Product	from Educt	Conditions	Yield [%]	m.p. [°C]	Molecular formula[a]	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. (CDCl$_3$/TMS) δ [ppm]	Other Data
6c	**4c**	Ac_2O	57	146–147°	$C_{15}H_{18}O_6$ (294.4)	1796; 1730	1.46 (s, 3H, CH_3); 2.13 (s, 3H, CO—CH_3); 4.04 (dd, 1H, CH, $^3J_1$ = 2.64 Hz, $^3J_2$ = 9.1 Hz)	
7a	**4a**	PPA	94	55–56°	$C_{11}H_{10}O_2$ (174.2)	1755; 1618	1.55 (d, 3H, CH_3, J = 6.4 Hz); 5.58 (dq, 1H, CH, ^4J = 1.2 Hz, ^3J = 6.4 Hz); 6.27 (d, 1H, =CH, ^4J = 1.2 HZ)	frequence-sweep decoupling δ = 1.55 ppm: 5.58 (s, 1H, CH); 6.27 (s, 1H, =CH)
	4a	H_2SO_4	70					
	5a	PPA	83					
	6a (crude)	▽	98					
7b	**4b**	PPA	24	143–144°	$C_{12}H_{10}O_4$ (218.4)	1715; 1600		
7c	**4c**	PPA	79	121–122°	$C_{13}H_{14}O_4$ (2343)	1715; 1600		
	4c	H_2SO_4	35					
	6c	▽	96					
10a	**8a**	PPA	37	oil[b]		1715; 1688	2.25 (s, 3H, CO—CH_3); 4.00 (t, 1H, CH, J = 4.8 Hz)	
	8a	H_2SO_4	15					
10c	**8c**	PPA	70	95°	$C_{14}H_{16}O_4$ (248.3)	1710; 1675	6.53; 7.29 (s, 2H$_{arom}$)	
	8c	H_2SO_4	46					

Table. Cyclization Products

Product	from Educt	Conditions	Yield [%]	m.p. [°C]	Molecular formula[a]	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]	Other Data
11a	**9a**	Na	63	113°	$C_{12}H_{12}O_2$ (188.2)	1605; 1598	5.65 [s, 1H (75%), =CH]; 9.83 [s, 1H (75%), —OH] (75% enolization)	
11c	**9c**	Na	58	125–12°		1608; 1595	5.56 [s, 1H (75%), =CH]	
13	**2c**	PPA (+hydrolysis)	24	198°	$C_{16}H_{18}O_6$ (306.3)	1705; 1670	($CDCl_3$/DMSO-d_6/TMS): 2.15 (s, 3H, $COCH_3$); 7.33, 7.49 (s, $2H_{arom}$)	
	2c	H_2SO_4	51					
22	**19c**	H_2SO_4	19	126°	$C_{17}H_{20}O_6$ (320.3)	1710; 1676	2.08 (s, 3H, CO—CH_3); 6.60, 7.63 (s, $2H_{arom}$)	
12a	**2a**	PPA	47	92–93°	$C_{14}H_{12}O_3$ (228.2)	1830; 1660	3.04 (s, 2H, CH_2—CO)	M.S.: m/e = 228.1 (M^+, 100%)
	18a	$SOCl_2$	28				6.00 (s, 1H, =CH)	
	18a	Ac_2O	49					
12c	**18c**	Ac_2O	80	134°	$C_{16}H_{16}O_5$ (288.3)	1818; 1675		
	18c	$SOCl_2$	48					
21a	**20a**	Ac_2O	33	112–113° (110–111°)[7]		1768; 1675; 1631		M.S.: m/e = 242.1 (M^+, 10%); 57 (100)
16a	**14a**	Na	73	148°	$C_{16}H_{18}O_4$ (274.3)	1738	5.53 (s, 1H, =CH)	
17a	**15a**	Na	40	140–141°	$C_{16}H_{19}NO_3$ (273.3)	1640; 1610	.79, 3.14 (s, 6H, N—CH_3); 5.70 (s, 1H, =CH)	M.S.: m/e = 273.1 (M^+)
18a	**2a**	H_2SO_4	52	170–171°	$C_{14}H_{14}O_4$ (246.3)	3408; 1690	(DMSO-d_6/TMS): 2.69 (ABq, 2H, CH_2—CO, δ_A = 2.62, δ_B = 2.75, J = 16.4 Hz)	M.S.: m/e = 246.1 (M^+)
	2a	PPA (1/2 amount)	75					
	16a	hydrolysis	85					
	17a	hydrolysis	54					
18c	**16c**	hydrolysis of crude material	31	200–201°	$C_{16}H_{18}O_6$ (306.3)	1700	(DMSO-d_6/TMS): 2.69 (ABq, 2H, CH_2); 5.33 (s, 1H, =CH)	
	12c	hydrolysis	87					
23	**19c**	PPA	42	169–170°	$C_{16}H_{16}O_5$ (288.3)	1710; 1674; 1648	2.21 (s, 3H, CO—CH_3); 3.93 (s, 3H, O—CH_3); 13.56 (s, 1H, —OH)	strong intramolecular hydrogen bond (ν_{OH} band absent), forms colored Fe chelates
24	**19a**	PPA	28	197°	$C_{15}H_{14}O_3$ (242.3)	1690; 1618; 1598	5.48 (s, 1H, =CH)	
	20a	PPA	16					

[a] The microanalyses were in good agreement with the calculated values: C, ±0.31; H, ±0.19; N, −0.18.
[b] Purified by column chromatography on silica gel using benzene/ethyl acetate (3/1) as eluent.

Cyclization Reactions in Polyphosphoric Acid or Sulfuric Acid; General Procedure:
A stirred suspension of the carboxylic acid (0.1 mol) in polyphosphoric acid (PPA; 35 g per 1 carboxy group) or 65% sulfuric acid (160 ml per 1 carboxy group) is heated at 100 °C for 2 h. When PPA is used the mixture is decomposed by the addition of water (100 ml for 35 g PPA); when sulfuric acid is used the mixture is poured into water (800 ml). Crystallization occurs spontaneously. The product is isolated by suction and recrystallized. Alternatively, the product is extracted from the aqueous-organic two-phase mixture using chloroform (3 × 50 ml), the extract is washed with saturated sodium hydrogen carbonate solution (30 ml) and then water (50 ml), and the solvent is evaporated; the residue is recrystallized from an appropriate solvent (isopropanol, ethanol, ethyl acetate, diisopropyl ether).

Cyclization Reactions in Acetic Anhydride or Thionyl Chloride; General Procedure:
The carboxylic acid is dissolved in excess acetic anhydride or thionyl chloride and the solution refluxed for 2 h. The solvent is then evaporated and the residue recrystallized from appropriate solvents.

Cyclization of Carboxylic Esters using Sodium in Toluene; General Procedure:
A solution of the ester (0.1 mol) in dry toluene (50 ml) is added to a suspension of sodium (2.3 g, 0.1 mol) in toluene (80 ml) containing absolute ethanol (0.5 ml). The mixture is refluxed for 3 h and the solid sodium salt is filtered off. The salt is dissolved in water (50 ml), the solution acidified with mineral acid to pH 2, and extracted with chloroform (3 × 20 ml). The solvent is evaporated and the residual product is recrystallized from isopropanol or ethanol.

***N,N*-Dimethyl-3-acetyl-3-aryl-6-nitrilohexanamides (1a, b, c); General Procedure:**

To a stirred solution of the 3-aryllevulinic acid dimethylamide (*N,N*-dimethyl-3-aryl-4-oxopentanamide; 1.0 mol) in *t*-butanol (60 ml) is added a 40% solution (10 ml) of tetramethylammonium hydroxide in methanol, followed by the dropwise addition of acrylonitrile (53.1 g, ~1.0 mol) at room temperature. The mixture is heated at 50 °C for 2 h and is then diluted with chloroform (250 ml). The solution is washed with dilute hydrochloric acid (50 ml), dried with sodium sulfate, and evaporated in vacuo. The residual product is recrystallized from isopropanol.

Amide **1a**; yield: 73%; m.p. 125–126 °C.

$C_{16}H_{20}N_2O_2$	calc.	C 70.60	H 7.40	N 10.29
(272.3)	found	70.59	7.39	10.31

I.R. (KBr): ν = 2242; 1710; 1640 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 2.0 (s, 3H, CO—CH_3); 2.25 (m, 4H, CH_2); 2.97, 3.08 (s, 6H, N—CH_3); 3.24 ppm (s, 2H, CH_2—CO).

Amide **1b**; yield: 90%; m.p. 154–155 °C.

$C_{17}H_{20}N_2O_4$	calc.	C 64.54	H 6.32	N 8.86
(316.4)	found	63.88	6.29	8.83

Amide **1c**; yield: 79%; m.p. 124–125 °C.

$C_{18}H_{24}N_2O_4$	calc.	C 65.04	H 7.28	N 8.43
(332.4)	found	65.35	7.29	8.40

3-Acetyl-3-arylhexanedioic Acids (2a, b, c); General Procedure:

A suspension of the *N,N*-dimethyl-3-acetyl-3-aryl-6-nitrilohexanamide (**1a, b, c**; 0.55 mol) in 12% aqueous sodium hydroxide (500 ml) is refluxed for 12 h, then acidified with hydrochloric acid, and extracted with chloroform (3 × 100 ml). The extract is evaporated and the residual product is recrystallized from isopropanol or ethyl acetate.

Diacid **2a**; yield: 79%; m.p. 127–129 °C.

$C_{14}H_{16}O_5$	calc.	C 63.63	H 6.10
(264.3)	found	63.95	6.25

I.R. (KBr): ν = 1705; 1690 cm^{E-1}.

Diacid **2b**; yield: 63%; m.p. 170–171 °C.

$C_{15}H_{16}O_7$	calc.	C 58.44	H 5.23
(308.3)	found	58.47	5.68

Diacid **2c**; yield: 82%; m.p. 189–190 °C.

$C_{16}H_{20}O_7$	calc.	C 59.26	H 6.21
(324.3)	found	59.20	6.35

^{1}H-N.M.R. (DMSO-d_6): δ = 1.90 (s, 3H, CO—CH_3); 3.09 ppm (ABq, 2H, CH_2—CO, δ_A = 2.92, δ_B = 3.26, J = 16, 13 Hz).

***N,N*-Dimethyl-3-acetyl-3-phenyl- (3a) and *N,N*-Dimethyl-3-acetyl-3-(3,4-dimethoxyphenyl)-hexanedioic Acid 1-Amide (3c):**

The *N,N*-dimethyl-3-acetyl-3-aryl-6-nitrilohexanamide (**1a, c**; 0.29 mol) is added to 65% sulfuric acid (200 ml). The stirred mixture is heated at 80 °C for 1 h, and then poured into water (500 ml). The monoamide which crystallizes from the mixture is isolated by suction and recrystallized from isopropanol.

Monoamide **3a**; yield: 73%; m.p. 212–213 °C.

$C_{16}H_{21}NO_4$	calc.	C 66.04	H 7.07	N 4.81
(291.3)	found	65.91	7.33	4.75

I.R. (KBr): ν = 1720; 1612 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): δ = 1.92 (s, 3H, CO—CH_3); 2.85, 3.10 (s, 6H, N—CH_3); 3.27 ppm (s, 2H, CH_2—CO).

Monoamide **3c**; yield: 38%; m.p. 157–158 °C. The product is contaminated by 10% **2c** as determined by ^{1}H-N.M.R. analysis.

I.R. (KBr): ν = 1705; 1624 cm^{-1}.

Diethyl 3-Acetyl-3-phenylhexanedioate (14a), Diethyl 3-Acetyl-3-(3,4-dimethoxyphenyl)-hexanedioate (14c), 3-Acetyl-3-phenylhexanedioic Acid 1-Dimethylamide 6-Ethyl Ester (15a); General Procedure:

The hexanedioic acid derivative **2a, c** or **3a** (62 mmol) is refluxed for 5 h in ethanol (50 ml) containing conc. sulfuric acid (2 ml). The solution is concentrated in vacuo and the residue redissolved in chloroform (50 ml). The solution is washed with saturated sodium hydrogen carbonate solution (20 ml), and evaporated in vacuo. The residual product is recrystallized from isopropanol or distilled in vacuo.

Diester **14a**; yield: 73%; b.p. 148–150 °C/0.03 torr.

$C_{18}H_{24}O_5$	calc.	C 67.48	H 7.55
(320.4)	found	67.80	7.66

I.R. (film): ν = 1720 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 2.0 (s, 3H, CO—CH_3); 3.05 ppm (ABq, 2H, CH_2—CO—, δ_A = 2.99, δ_B = 3.12; J = 14, 4 Hz).

Diester **14c**; yield: 61%; m.p. 84–85 °C.

$C_{20}H_{28}O_7$	calc.	C 63.15	H 7.41
(380.4)	found	62.98	7.45

I.R. (KBr): ν = 1730 cm^{-1}.

Amide Ester **15a**; yield: 74%; m.p. 105 °C.

$C_{18}H_{25}NO_4$	calc.	C 67.69	H 7.89	N 4.39
(319.4)	found	67.81	8.04	4.34

I.R. (KBr): ν = 1725; 1705; 1640 cm^{-1}.

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