Acylation and Alkylation Reactions. Part IV.¹ The Cyclisation of Alkylsubstituted Phenoxyacetyl Chlorides to Benzofuran-3(2H)-ones

By M. H. Palmer • and N. M. Scollick, Department of Chemistry, University of Edinburgh, West Mains Rd., Edinburgh 9

The interaction of 14 alkyl-substituted phenoxyacetyl chlorides with aluminium chloride in benzene gives the cyclic ketones as the dominant products. In the reactions of the 4-chloro-3-methyl and 3,4-dimethyl compounds the major cyclic product is the 5,6-disubstituted benzofuranone; the reactions with the 3,4-polymethylene derivatives give largely the linear isomer in the case of the tri, penta,- and hexa-methylene compounds and largely the angular isomer in the case of the tetramethylene compound.

INTERACTION of aluminium chloride with various phenoxyacetyl chlorides in benzene leads to (a) intramolecular or intermolecular acylation or (b) decarbonylation followed by alkylation of the solvent and rearrangement of the resulting benzyl ether to the phenol and diphenylmethane or to the benzylphenol (in which the ortho-isomer predominates).^{2,3} In carbon disulphide and other inert solvents the aryl chloromethyl ether results from the decarbonylation process.⁴ The proportions of these products vary with the substituents in the aryloxyacetyl chloride (1). We have extended these reactions to a number of methyl- and polymethylene-substituted compounds (1) in order to determine the proportions of cyclic ketones formed from unsymmetrically substituted acid chlorides where cyclisation can occur in more than one direction.

RESULTS

The reactions of the acid chlorides (1c-h) and (1j) (Table 1) with aluminium chloride in benzene at 5° gave, after hydrolysis with aqueous acid, crude neutral products, the i.r. and ¹H n.m.r. spectra of which were similar to those of the pure cyclic ketones (2); those were in fact readily seprated by crystallisation. In these reactions the pro-

¹ Part III, M. H. Palmer and G. J. McVie, J. Chem. Soc. (B), 1968, 856.

- M. H. Palmer and G. J. McVie, J. Chem. Soc. (B), 1968, 742.
 M. H. Palmer and G. J. McVie, J. Chem. Soc. (B), 1968, 745.

portions of intermolecular ketone and decarbonylation products were small, as shown by the low intensity (or absence in some instances) of absorptions at $\tau 4.0 \pm 0.2$ (4), 5.0 ± 0.2 (3), and 6.1 ± 0.2 [(6) and (7)]. The cyclic products exist almost entirely in the 3-(2H)-one form $[\nu_{max}]$ 1700 ± 10 cm.⁻¹ (C=O) and ¹H n.m.r. spectra in Table 1], in agreement with earlier evidence based upon u.v. spectra and reactivity,⁵ although they dissolve in strong alkali.



The proportions of the 4- and 6-methylbenzofuranones and various 4,5- and 5,6-disubstituted benzofuranones obtained by cyclisation are shown in Table 2; other products ⁴ M. H. Palmer and G. J. McVie, Tetrahedron Letters, 1966,

6405. ⁵ K. V. Auwers and E. Auffenberg, Ber., 1919, 52, 92; Mme. Ramart-Lucas and M. van Cowenbergh, Bull. Soc. chim. France, 1935, 1381.

identified are shown in the footnotes. Measurement of the i.r. absorption at the frequencies given in Table 3 was the principal method of analysis; most of the samples were separated by chromatography and/or fractional crystallisation; calibration curves of absorbance against concentration were obtained for mixtures of known composition.

n = 6) could be accounted for in terms of a mixture of (10; n = 6) and (11; n = 6) in which the former predominated.

Attempts were made to synthesise the benzofuranone (2; R = 4-Me) and some of the other 4,5-disubstituted benzofuranones by variations of the cyclisation reaction; a

	TABLE 1	
Yields and	physical constants of benzofuran-3(2H)-ones (2)

-		Found (%)				Calc. (%)			τ Values (CS ₂)						
Re-	TZ-+ (0)	Yield	M. m. (nolwork)	\overline{c}				\overline{c}	 	<u> </u>	CH	4 11	= = LI	6 IJ	7 11
actant	$\frac{1}{2}$	(%)	m.p. (sorvent)	C	п	CI		C	п	CI	Cn_2	4-11	9-H	0-H	1-п
(1)	R														
(la)	6-Me	83 4	85° (EtOH) ^ø	73.2	$5 \cdot 8$			73.0	5.4		5.58	2.62	2.62	7.59	3.18
(1b)	4,5-Me₂)		68 [light petroleum (b.p.	74.0	6.5		7				5.65	$7 \cdot 6$	7.83	2.74	3.32
	- }	98 .	4060°)]												
(1b)	5,6-Me,		112 (EtOH)	73.7	$6 \cdot 2$						5.65	2.76	7.78	7.71	3.19
(1c)	4,6-Me,	96	62 [light petroleum (b.p.	73.7	5.9		l	74.1	6.9		5.66	7.59	3.44	7.70	3.50
• •			$40-60^{\circ}$				ſ	14.1	0.7						
(1d)	4.7-Me.	92	93 (EtOH)	74.4	5.8						5.60	7.55	3.36	$3 \cdot 28$	7.80
(le)	5.7-Me.	92	79 (EtOH) •	73.9	6.1						5.63	2.93	7.75	2.93	7.81
àť	6.7-Me.	91	82 (EtOH)	73.9	$5 \cdot 9$		J				5.61	2.86	3.24	7.70	7.87
(1g)	4.5.6-Me.	88	78 (C_eH_e)	74.5	6.9		ì	7 50	00		5.70	7.60	7.95	7.74	3.40
(1h)	4.6.7-Me.	85	92 (MeOH) /	74.5	6.6		5	79.0	0.9		5.70	7.65	3.55	7.79	7.93
(lii)	5-Cl. 4-Me	40.4	104 (EtOH)	59.1	3.7	18.4	1	50.0	9.0	10 5	5.50	7.53		2.58	3.14
ίιi	5-Cl. 6-Me	40 🖉	122 (EtOH)	59.1	3.9	19.6	ſ	99·2	3.8	18.9	5.50	2.52		7.55	3.04
λiń	5-Cl. 4.6-Me.	98	138 (EtOH) »	60.5	4.7	18.0		61 .0	4 ∙6	18.1	5.55	7.44		7.59	3.23
$(\mathbf{i}\mathbf{k})$	5.6-[CH.].	94	107 (EtOH)	75.7	5.7			75.8	5.8		5.60	2.76			3.17
- lin'	4.5-[CH.].	0.0	105 (EtOH)	76.3	$6 \cdot 2$		٦	F 0.0			5.70			2.91	3.32
λīń	5.6-[CH.].	98	98 (EtOH)	75.6	6.3		}	76.0	6.4		5.65	2.85			3.33
$(\overline{1m})$	4 5-[CH.].		90 (EtOH)	77.5	6.9		٦		= 0		5.62			$2 \cdot 80$	3.30
(1m)	5 6-[CH.].	95	88 (EtOH)	77.5	6.9		ĵ	77.1	7.0		5.64	2.81		- 00	3.25
(ln)	5,6-[CH ₂] ₆	40	89 (EtOH)	75 7	7.1			77.8	7.5		5.60	2.72			3.19

^a Total yield of 4- and 6-methylbenzofuran-3(2H)-ones. ^b J. A. Elvidge and R. G. Foster (*J. Chem. Soc.*, 1964, 981), give m.p. 85-86°. ^c Total yield of 4,5- and 5,6-dimethylbenzofuran-3(2H)-ones. ^d K. von Auwers (*Ber.*, 1916, **49**, 809) gives m.p. 75-76°. ^e K. Fries and G. Fink (*Ber.*, 1908, **41**, 4271), give m.p. 75°. ^f L. I. Smith and G. A. Boyack (*J. Amer. Chem. Soc.*, 1948, **70**, 2687) give m.p. 89-91°. ^g Total yield of (2; R = 5-Cl, 4-Me-) and (2; R = 5-Cl, 6-Me). ^h J. P. Brown and E. B. McCall (*J. Chem. Soc.*, 1957, 3875) give m.p. 137-140°.

TABLE 2

~				<i>c</i>				
~	rolio Irotono	#0 t1 0 0	obtomod	trom	tha	11 norrm motrico	0.010	chlomdog
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		100000	OD COMPOCE					

Reactant (1; $R =$):	3-Me	$3,4-Me_2$	4-Cl, 3-Me	3,4-[CH ₂] ₃	3,4-[CH ₂] ₄	3,4-[CH ₂] ₅
4-Substituted ketone (2)	30 a, b	26 c, d	37 0,0	5 °	63 ¢	9 0
6-Substituted ketone (2)	70	74	63	95	37	91
^a By n.m.r. analysis of CH ₂ absorp	tions; accura	acy $\pm 10\%$.	Also formed in re	eaction: (3; I	R = 3-Me) and (7)	(3 and 13% c

total product respectively). ^e By i.r. analysis (absorptions in Table 3); accuracy $\pm 5\%$. ^d Also formed in reaction: (7) (5%). ^e (3; R = 4-Cl, 3-Me) and (7) also isolated.

Separation of the pure linear ketone (10; n = 4) from the mixture proved impossible, but the compound was synthesised from 3-hydroxynaphthalene-2-carboxylic acid (see following paper). Similarly the angular ketone (11; n = 6) could not be separated, but a small sample of the crude material was obtained from cyclo-octanone and diethyl acetone-1,3-dicarboxylate in an eight-stage synthesis. Most of the strong i.r. absorptions in the mixture from (9;

TABLE 3

Analysis of mixtures-i.r. absorptions

(2: R =)		$\nu(\varepsilon)$	
5-Cl. 4-Me	750 (128)	900 (106)	
5-Cl, 6-Me	700 (170)	820 (306)	
4,5-Me,	1230 (149)	1270 (167)	
5,6-Me.	730 (86)	1200 (136)	1250 (157)
4,5-[CH ₂] ₄	805 (207)	1155 (96)	
5,6-[CH ₂] ₄	850 (104)	1110 (305)	
4,5-[CH ₂] ₅	830 (230)	1050 (198)	
5,6([CH ₂] ₅	840 (101)	900 (85)	
4,5-[CH ₂] ₆	825 ()	1050 ()	1220 (—)
5,6-[CH ₂] ₆	870 ()	1120 ()	1250 (—)

change in isomer ratio was expected. The Fries rearrangement of the aryl chloroacetates (12) to the phenols (13), followed by cyclisation with aqueous sodium acetate was





investigated. The chloroacetate (12; R = 3-Me) with aluminium chloride at 150° for 6 hrs. gave a mixture of at least three compounds (τ 7.55, 7.65, and 7.75) from which

$$\operatorname{RC}_{6}H_{4} \cdot \operatorname{O} \cdot \operatorname{CH}_{2} \cdot \operatorname{COCl} \longrightarrow \operatorname{RC}_{6}H_{3}(\operatorname{OH}) \cdot \operatorname{CO} \cdot \operatorname{CH}_{2}\operatorname{Cl} \longrightarrow (2)$$
(12)
(13)

only (13; R = 5-Me) was isolated. The ¹H n.m.r. spectrum of the product from (12; $R = 3,4-Me_2$) showed the presence of two components (four methyl and two methylene resonances), only one of which contained a hydroxy-group; only the phenol (13; R = 4,5-Me₂) was isolated, but the second component was clearly the ketone (2; R = 5.6-Me₂). The mixture from (12; R = 4-Cl, 3-Me) probably contained three components (singlets at τ 7.47, 7.6, and 7.66); the phenol (13; R = 5-Cl, 6-Me) and the ketone (2; R = 5-Cl, 6-Me) were isolated and the third component, contaminated with the other materials, had spectra as expected for the ketone (2; R = 5-Cl, 4-Me).

DISCUSSION

The high rates of cyclisation relative to decarbonylation and intermolecular acylation for the alkyl substituted phenoxyacetyl chlorides (1) are in agreement with those found previously for (1; R = 2- or 4-Me) (Part II).³ Except for the case of the naphthalene derivative (9; n = 4), in all of the reactions where two cyclic ketones may be formed the dominant product is the



5,6-disubstituted benzofuranone. The anomalous reactivity in the 1-position of 5,6,7,8-tetrahydro-2-naphthol derivatives, relative to 3,4-dimethylphenol and indan-5-ol (Mills-Nixon effect 6) is confirmed here and extended to the 7- and 8-membered rings. No substitution reactions of the benzocyclo-octene (14; n = 6) have been reported previously, while the nitration (by nitric acid) ⁷ and chloromethylation ⁸ of (14; n = 5) are both claimed to give 8-substituted products. These conclusions are probably correct, but the latter reaction lacks proof and the former is based on the nitration of (14; n = 4) with dinitrogen tetroxide, an unfortunate analogy, since most electrophilic substitutions on (14; n = 4) occur at the 1-position.6

It has been suggested ⁹ that the Mills-Nixon effect arises from differences in electron density at the angular (1-) and linear (3-) positions of the phenols (14), and that this can be detected from the chemical shifts of the aromatic protons. We have measured the chemical shifts of (14; n = 3-6) at various concentrations in the 2-4M range in deuteriochloroform; the shifts are little affected by concentration and the order is (14; n = 3): 4-H < 1-H < 3-H; (14; n = 4): 4-H < 3-H < 1-H; (14; n = 5): 4-H < 1-H < 3-H;(14; n = 6): 4-H < 3-H = 1-H. The benzylic protons (α and α')

⁹ G. Eigenmann and Hch. Zollinger, Helv. Chim. Acta, 1965, 48, 1791.

are degenerate for (14; n = 3-6) and there is little difficulty in measuring the resonance centre. The values τ 7.10 (n = 3), 7.23 (n = 4), 7.30 (n = 5), and 7.36 (n = 6) show an upfield trend with increasing ring size. The difference between (15) and (16) for a given n has been interpreted in terms of reduced ring current (or magnetic anisotropy).¹⁰ This does not account for the chemical shifts of (14; n = 3-6) since a reduction in ring current should lead to the same upfield shift for all protons. Further, electron density has been criticised as a criterion for reactivity,¹¹ and explanations based upon localisation energy seem preferable.12

Benzofuran-3(2H)-ones-I.r. Spectra.-All the compounds in Table 1 show strong absorption in the region 1200–1300 (Ar–O stretch) and 1030 ± 20 cm.⁻¹ (CH₂-O stretch). The 4,5-disubstituted compounds all have strong characteristic absorptions at 750 ± 10 and 820 ± 10 cm⁻¹ (C-H deformation) and second absorptions in the C-O ranges mentioned above. The 5,6disubstituted compounds have absorptions at 740 \pm 10, 880 ± 30 , and 1110 cm.⁻¹. In analysis of cyclisation mixtures these or other absorptions were used (Table 3). depending upon the separation of the required line from other absorptions.

EXPERIMENTAL

I.r. spectra were recorded with a Unicam SP 200 spectrophotometer and ¹H n.m.r. spectra with a Perkin-Elmer R10 (60 Mc./sec.) spectrometer.

Cyclisation Reactions .-- Typical reactions between the aryloxyacetyl chlorides and aluminium chloride in benzene are described for $(1; R = 3, 4-Me_2)$ and (1; R = 4-Cl, 3-Me).

4,5- and 5,6-Dimethylbenzofuran-3(2H)-ones.-The aryloxyacetyl chloride (1; R = 3,4-Me₂) (20 g.) in dry benzene (100 ml.) was rapidly added to a stirred suspension of aluminium chloride (15 g.) in benzene (100 ml.) at 5°. After 2 hr. the mixture was treated with ice and 2M-hydrochloric acid. The benzene solution together with ethereal extracts $(3 \times 100 \text{ ml.})$ of the aqueous phase was washed with aqueous sodium carbonate and then sodium hydroxide (10% w/v). The organic phase was dried and evaporated to leave a red crystalline solid (16 g.). Chromatography of a portion of the mixture on alumina with benzene as eluant gave (a) diphenylmethane [$\tau 2.92(s)$ and 6.17(s) (10:2)], identical with an authentic sample; (b) a yellow oil which gave 4,5-dimethylbenzofuran-3(2H)-one, v_{max} . (CS₂) 1270 and 1230 cm.⁻¹; and (c) a yellow solid which gave 5,6-dimethylbenzofuran-3(2H)-one, $\nu_{\rm max.}$ (CS₂) 1250 and 1200 cm.⁻¹.

In another experiment steam distillation of the crude mixture gave the compounds in the same order of volatility.

Reaction of the Aryloxyacetyl Chloride (1; R = 4-Cl, 3-Me) with Aluminium Chloride in Benzene.-Reaction of (1; R = 4-Cl, 3-Me) (20 g.) with aluminium chloride (15 g.) in benzene (total 200 ml.) at 5° for 2 hr. followed by hydrolysis with 2M-hydrochloric acid and extraction of the benzene phase with 2M-sodium hydroxide gave a neutral red oil ¹⁰ H. Meier, Eu. Müller, and H. Suhr, Tetrahedron, 1967, 23,

⁶ G. M. Badger, *Quart. Rev.*, 1951, 5, 152.
⁷ P. A. S. Smith and W. L. Berry, *J. Org. Chem.*, 1961, 26, 27.
⁸ P. Cagniant, *Compt. rend.*, 1948, 226, 1623; R. Granger, Orgenei, and A. Marget-Hulle, 1946, 1962, 1972, 1973.

H. Orzalesi, and A. Muratelle, *ibid.*, 1961, 252, 1478.

^{3713.} ¹¹ N. M. Atherton and J. N. Murrell, Ann. Reports, 1964, 61,

^{203.} ¹² C. A. Coulson and H. C. Longuet-Higgins, *Trans. Faraday Soc.*, 1946, **42**, 756; J. Vaughan, G. J. Welch, and G. J. Wright, *Tetrahedron*, 1965, **21**, 1665.

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(20 g.) which partly solidified. Two methods of separation of the products were used. (a) Filtration of the solid followed by fractional crystallisation from ethanol gave the *benzofuranone* (2; R = 5-Cl, 6-Me). The first filtrate (oil) when chromatographed on alumina gave diphenylmethane (identical with an authentic specimen) on elution with benzene, and a solid (m.p. $60-62^{\circ}$) on elution with benzeneether. The latter on fractional crystallisation from light petroleum (b.p. $60-80^{\circ}$ gave the *acetophenone* (3; R = 4-Cl, (a) The mixture from (12; R = 3-Me) on fractional crystallisation from light petroleum (b.p. 60-80°) gave the phenol (13; R = 5-Me), m.p. 101-102° (lit.,¹³ 100°).

(b) The mixture from (12; $R = 3,4-Me_2$) on fractional crystallisation from ethanol gave the *phenol* (13; R = 4,5-Me), m.p. 101° (Found: C, 60.9; H, 5.5; Cl, 17.4%. $C_{10}H_{11}ClO_2$ requires C, 60.4; H, 5.5; Cl, 17.8%).

(c) The mixture from (12; R = 4-Cl, 3-Me) gave the benzofuranone (2; R = 5-Cl, 6-Me), m.p. 120—122° (Found

TABLE 4

Properties of the aryl chloromethyl ketones (13)

R		ν _{max.} (C=O) (cm. ⁻¹)	τ Values «							
	M.p.		3-H	4-H	5-H	6-H	CH,	OH		
5-Me	102°	1655	2.45	3.33	(7.65)	3.27	5·50	-1.53		
4-Cl, 5-Me	120 - 122	1660	$2 \cdot 40$		(7.63)	3.15	5.50	-1.41		
4,5-Me ₂	101	1655	2.67	(7·75) °	(7.80) •	3.33	5.53	-1.31		

^a In carbon disulphide. ^b In Nujol. ^c Assignment uncertain; these figures may be interchanged.

3-Me), m.p. 66° (Found: C, 69.2; H, 4.9%. C₁₅H₁₃ClO₂ requires C, 69.0; H, 5.0%). A further fraction from the chromatography on fractional crystallisation from light petroleum and then ethanol gave 5-chloro-4-methylbenzo-furan-3(2H)-one, m.p. 104°.

Fries Rearrangements.—The phenyl chloroacetates (12*a*; R = 3-Me; *b*; R = 3,4-Me₂, and *c*; R = 4-Cl, 3-Me) (10 g.) were heated with aluminium chloride (20 g.) at 150° for 6 hr. Treatment of the mixture with aqueous acid and steam distillation gave volatile fractions, which were treated as follows:

¹³ J. R. Catch, D. F. Elliot, D. H. Hey, and E. R. H. Jones, *J. Chem. Soc.*, 1949, 552. C, 59·1; H, 3·8; Cl, 19·6%), by fractional crystallisation from ethanol, and the *phenol* (13; R = 4-Cl, 5-Me), m.p. 111° (Found: C, 49·0; H, 3·6; Cl, 32·5%). C₉H₈Cl₂O₂ requires C, 49·3; H, 3·6; Cl, 32·4%), by fractional crystallisation of the first filtrate from benzene.

Cyclisation of the Phenols (13) to the Benzofuranones (2).— 2-Chloro-2'-hydroxy-4'-methylacetophenone (13; R = 5-Me) (1 g.) was boiled with ethanol (30 ml.) containing sodium acetate (1 g.) for 1 hr. Evaporation and treatment with water gave a solid which gave the ketone (2; R = 6-Me) (0.6 g.), m.p. 85° (from ethanol). In a similar way the phenol (13; R = 4,5-Me₂) gave the ketone (2; R = 5,6-Me₂).

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