770. *Cyclisation of Acid Chlorides by Friedel–Crafts Reactions.*

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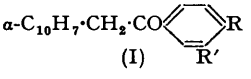
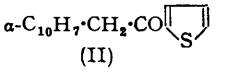
The Friedel–Crafts reaction of aluminium chloride upon various acid chlorides capable of undergoing cyclisation in the presence of molecules of various degrees of reactivity has been examined. The ease of formation of some five- and six-membered-ring ketones could thus be estimated from the extent of competitive formation of open-chain ketones; the results agreed with similar instances already recorded in the literature.

This work originated in an attempt to improve the preparation of acenaphthenone from 1-naphthylacetyl chloride (Friedlander, 1910/1912, **10**, 199; Buu-Hoï and Cagniant, *Compt. rend.*, 1942, **214**, 315) by replacing nitrobenzene and carbon disulphide by various aliphatic and aromatic compounds (including benzene) as solvents. Benzene had been found to be an effective solvent for the cyclisation, by the aid of aluminium chloride, of β-phenylpropionyl and γ-phenylbutyryl chlorides to indan-1-one and 1-tetralone (Amagat, *Bull. Soc. chim.*, 1927, **41**, 940); the same solvent had also been preferred for the cyclisation of γ-3-pyrenylbutyryl chloride (Vollmann, Becker, Corell, and Streeck, *Annalen*, 1937, **531**, 1). We have now found, however, that cyclisation of 1-naphthylacetyl chloride by means of aluminium chloride in benzene gave acenaphthen-1-one in very moderate yield, ω-1-naphthylacetophenone (I; R = R′ = H) being concurrently formed in large amount. When chlorobenzene was used as solvent, 4-chloro-ω-1′-naphthylacetophenone (I; R = Cl, R′ = H) was obtained in similar proportion. When the solvent was toluene, the main reaction product was 4-methyl-ω-1′-naphthylacetophenone (I; R = Me, R′ = H), and when the reaction was performed in carbon disulphide in the presence of thiophen, of anisole, and of veratrole, no acenaphthen-1-one was obtained, but only 2-1′-naphthylacetylthiophen (II), *p*-1′-naphthylacetylanisole (I; R = OMe, R′ = H), and 4-1′-naphthylacetylveratrole (I; R = R′ = OMe), respectively.



(I)



(II)

For the sake of comparison, this investigation was extended to β-phenylpropionyl chloride and its *p*-methyl and *p*-chloro-derivatives, and to γ-phenylbutyryl chloride. With β-phenylpropionyl chloride, our results were in agreement with Rothstein's observation (*J.*, 1951, 1459) that no open-chain ketone is obtained in benzene, whereas, in the presence of anisole, no indan-1-one is formed; we found that thiophen behaved like anisole, and 2-β-phenylpropionyl-

Table I.

Acid chloride	Aromatic or thiophen compound	Yield, %, of: cyclised product	Yield, %, of: open-chain ketone
β-Phenylpropionyl	Benzene	90	0
	Ethylbenzene	50	40
	Anisole	0	90
	Thiophen	0	80
	2 : 5-Dimethylthiophen	20	40
β-*p*-Tolylpropionyl	Benzene	95	0
	Ethylbenzene	50	40
	Diphenyl	90	0
	Chlorobenzene	70	0
	Anisole	0	90
	Thiophen	0	90
	2 : 5-Dimethylthiophen	15	40
β-*p*-Chlorophenylpropionyl	Benzene	0	70
	Ethylbenzene	0	80
	Diphenyl	0	80
	Anisole	0	90
	Thiophen	0	90
	2 : 5-Dimethylthiophen	0	60
γ-Phenylbutyryl	Benzene	95	0
	Ethylbenzene	70	20
	Chlorobenzene	80	0
	Anisole	0	80
	Thiophen	10	60
	2 : 5-Dimethylthiophen	20	30
1-Naphthylacetyl	Benzene	40	30
	Chlorobenzene	40	20
	Ethylbenzene	20	30
	Anisole	10	50
	o-Tolyl methyl ether	10	50
	Veratrole	10	60
	Thiophen	0	60
	2 : 5-Dimethylthiophen	0	50

thiophen was produced exclusively. Toluene in Rothstein's experiments took an intermediary position, as did ethylbenzene in ours. β-*p*-Tolylpropionyl chloride behaved substantially like its lower homologue, whereas β-*p*-chlorophenylpropionyl chloride was remarkably resistant to cyclisation, and yielded open-chain ketones exclusively, with benzene, ethylbenzene, diphenyl, thiophen, and anisole. A similar deactivating effect of nuclear chlorine atoms was observed by Kalinowski and Kalinowski (*J. Amer. Chem. Soc.*, 1948, **70**, 1970) in the cyclisation of *p*-chloro- and 2 : 4-dichloro-phenoxyacetic acid to the corresponding coumaranones. The outstanding susceptibility of γ-phenylbutyryl chloride towards cyclisation is demonstrated by the formation of 1-tetralone even in the presence of thiophen.

Table I, which gives the ratio of cyclised product to open-chain ketone (under our experimental conditions), not only expresses the ease of formation of cyclic ketones, but gives also a scale of the reactivity of various compounds in Friedel–Crafts ketone syntheses, which is similar to earlier results obtained by other methods.

The new ketones were characterised by Pfitzinger reactions with isatin, and by formation, from their phenylhydrazones, of generally well-crystallised 2 : 3-disubstituted indoles (cf. Buu-Hoï, *J.*, 1949, 2882).

Experimental.

Preparation of Intermediates.—1-Naphthylacetic acid free from its 2-isomer was best prepared from 1-methylnaphthalene by side-chain bromination with *N*-bromosuccinimide (Buu-Hoï, *Annalen*, 1944, **556**, 1), condensation with sodium cyanide, and hydrolysis of the nitrile obtained. The β-arylpropionic acids were prepared by standard malonate syntheses from the appropriate benzyl chlorides; γ-phenylbutyric acid was obtained from β-benzoylpropionic acid by means of a Kishner–Wolff reduction (Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **67**, 2487). All the acid chlorides were prepared by the thionyl chloride procedure, and purified by vacuum-distillation.

Friedel–Crafts Reactions.—The aluminium chloride used was a pure product (Merck); the thiophen (Eastman Kodak), 2 : 5-dimethylthiophen (prepared from acetonylacetone and phosphorus trisulphide), benzene, ethylbenzene, and the phenyl ethers were redistilled and carefully dried.

(a) *With no extra solvent.* An ice-cooled solution of the appropriate acid chloride (1 part) in dry benzene, toluene, or chlorobenzene (5 parts) was treated with aluminium chloride in slight excess (1·2 mols. per mol. of acid chloride); the mixture was kept overnight at room temperature, and worked up in the usual way.

(b) *With an extra solvent.* The procedure was the same, except that the aromatic compound studied (1 part) was diluted in all instances with dry carbon disulphide (4 parts); the reaction mixture from thiophen and 2 : 5-dimethylthiophen, however, was kept at room temperature for only 2 hours.

Characterisation of Cyclisation Products.—Acenaphthen-1-one (b. p. 190—200°/16 mm.) was recrystallised from methanol and characterised by m. p. (120—121°) and mixed m. p., and by its oxime, m. p. 183°. Indan-1-one (b. p. 128—130°/12 mm.) was characterised by its m. p. (42°) and its semicarbazone, m. p. 236—238°. 6-Methylindan-1-one (b. p. 157—160°/18 mm.), recrystallised from methanol, had m. p. 62—63° (cf. Miller and Rohde, *Ber.*, 1890, **23**, 1898), and gave a *semicarbazone* crystallising from methanol in colourless needles, m. p. 256° (Found: C, 64·7; H, 6·2. $C_{11}H_{13}ON_3$ requires C, 65·0; H, 6·4%), and a *thiosemicarbazone*, forming from ethanol fine prisms, m. p. 220° (Found: C, 60·1; H, 6·0. $C_{11}H_{13}N_3S$ requires C, 60·3; H, 5·9%). 1-Tetralone was characterised by its semicarbazone, m. p. 223—225°.

In every instance, separation of the cyclic ketone from the far-higher-boiling open-chain ketone was satisfactorily achieved by vacuum-fractionation.

Pfitzinger Reactions.—A positive Pfitzinger reaction with isatin was observed with all the open-chain ketones obtained in the course of this work, except for 2 : 5-dimethyl-3-γ-phenylbutyryl-thiophen, this failure being probably due to steric hindrance (cf. Buu-Hoï, *J.*, 1946, 795; 1948, 106) exerted by the methyl group in the *ortho*-position; some cinchoninic acids thus obtained, and their derivatives, are reported below. Except where other-wise stated the solvent for crystallisation was acetic acid.

3-1′-*Naphthyl*-2-*phenylcinchoninic Acid.*—A mixture of 1-naphthylacetylbenzene (2 g.), isatin (1·6 g.), and potassium hydroxide (1·8 g.) in ethanol (20 c.c.) was refluxed for 48 hours; after dilution with water and removal of the neutral impurities by ether-extraction, acidification with acetic acid yielded the *acid* as a yellow precipitate (0·8 g.) which formed from ethanol small crystals, m. p. 297° (decomp. above 270°) (Found: C, 83·0; H, 4·2. $C_{26}H_{17}O_2N$ requires C, 83·2; H, 4·5%).

3-*Benzyl*-2-p-*ethylphenylcinchoninic acid* formed colourless prisms, m. p. 296° (Found: C, 81·4; H, 5·9. $C_{25}H_{21}O_2N$ requires C, 81·7; H, 5·7%); its decarboxylation yielded 3-benzyl-2-*p*-ethylphenylquinoline, characterised by its *picrate*, forming from ethanol yellow needles, m. p. 217° (Found: N, 10·2. $C_{30}H_{24}O_7N_4$ requires N, 10·1%). 3-*Benzyl*-2-p-*methoxyphenylcinchoninic acid* formed colourless prisms, m. p. 271° (Found: C, 77·8; H, 5·2. $C_{24}H_{19}O_3N$ requires C, 78·0; H, 5·1%); 3-*benzyl*-2-p-*methoxyphenylquinoline picrate* formed from ethanol shiny yellow needles, m. p. 203° (Found: N, 9·8. $C_{25}H_{22}O_8N_4$ requires N, 10·1%).

2-p-*Methoxyphenyl*-3-p-*methylbenzylcinchoninic acid* crystallised in colourless prism, m. p. 276° (Found: C, 78·0; H, 5·4. $C_{25}H_{21}O_3N$ requires C, 78·3; H, 5·5%). 2-p-*Methoxyphenyl*-3-2′-*phenylethylcinchoninic acid* formed fine colourless needles, m. p. 278° (Found: C, 78·2; H, 5·2. $C_{25}H_{21}O_3N$ requires C, 78·3; H, 5·5%), and was decarboxylated to 2-4′-methoxyphenyl-3-2″-phenylethylquinoline whose *picrate* (from ethanol) had m. p. 206° (Found: N, 9·5. $C_{30}H_{24}O_8N_4$ requires

N, 9·8%). 3-p-*Chlorobenzyl*-2-*phenylcinchoninic acid* had m. p. 306° (Found: C, 73·6; H, 4·5. $C_{23}H_{16}O_2NCl$ requires C, 73·9; H, 4·3%); 3-p-*chlorobenzyl*-2-*phenylquinoline picrate* formed from ethanol shiny yellow prisms, m. p. 226° (Found: N, 9·8. $C_{28}H_{19}O_7N_4Cl$ requires N, 10·0%). 3-p-*Chlorobenzyl*-2-p-*ethylphenylcinchoninic acid* formed fine colourless needles, m. p. 261° (Found: C, 74·5; H, 5·0. $C_{25}H_{20}O_2NCl$ requires C, 74·7; H, 4·9%); 3-p-*chlorobenzyl*-2-p-*ethylphenylquinoline picrate* formed from benzene fine yellow prisms, m. p. 197° (Found: N, 9·2. $C_{30}H_{23}O_7N_4Cl$ requires N, 9·5%). 3-p-*Chlorobenzyl*-2-p-*methoxyphenylcinchoninic acid* formed fine colourless needles, m. p. 259° (Found: C, 71·0; H, 4·5. $C_{24}H_{18}O_3NCl$ requires C, 71·3; H, 4·4%). 3-p-*Chlorobenzyl*-2-p-*diphenylylcinchoninic acid* formed colourless prisms, m. p. 299° (Found: C, 77·2; H, 4·6. $C_{29}H_{20}O_2NCl$ requires C, 77·4; H, 4·4%); the picrate of its decarboxylation product had m. p. 204°. 3-2′-*Phenylethyl*-2-2″-*thienylcinchoninic acid* formed from methanol shiny colourless prisms, m. p. 242—243° (Found: C, 73·2; H, 4·5. $C_{22}H_{17}O_2NS$ requires C, 73·5; H, 4·7%); 3-2′-*phenylethyl*-2-2″-*thienylquinoline* crystallised from methanol in fine needles, m. p. 82° (Found: C, 79·8; H, 5·5. $C_{21}H_{17}NS$ requires C, 80·0; H, 5·4%).

Preparation of Indoles from Ketones Ar·$[CH_2]_n$·COAr′.—A solution of the crude phenylhydrazones of the ketones in acetic acid saturated with hydrogen chloride (cf. Buu-Hoï, *J.*, 1949, 2882) was brought to the boil, cooled, and poured into water; the indoles formed were taken up in benzene, and purified by vacuum-distillation and subsequent recrystallisation from methanol or ligroin. They all gave dark violet picrates. For these *ketones* and *indoles* see Tables II and III.

TABLE II.

Ketones of general formula Ar·$[CH_2]_n$·CO·Ar′.

Ketone *						Found, %:		Reqd., %:	
Ar	Ar′	*n*	M. p.†	B. p.	Formula	C	H	C	H
α-$C_{10}H_7$	C_6H_5	1	81°	250—255°/18 mm.	$C_{18}H_{14}O$	87·5	5·9	87·8	5·7
α-$C_{10}H_7$	*p*-C_6H_4Me	1	109	260—262/18	$C_{19}H_{16}O$	87·3	6·4	87·7	6·2
α-$C_{10}H_7$	*p*-C_6H_4Cl	1	97	260—265/18	$C_{18}H_{13}OCl$	77·1	4·8	77·0	4·6
α-$C_{10}H_7$	*p*-C_6H_4·OMe	1	124	260—265/18	$C_{19}H_{16}O_2$	82·3	6·1	82·6	5·8
α-$C_{10}H_7$	3 : 4-$C_6H_3(OMe)_2$	1	115	285—287/18	$C_{20}H_{18}O_3$	78·2	5·8	78·4	5·9
α-$C_{10}H_7$	2-C_4H_3S	1	82	260—262/18	$C_{16}H_{12}OS$	76·0	5·0	76·2	4·8
C_6H_5	*p*-C_6H_4Et	2	Liq.	232—235/18	$C_{17}H_{18}O$	85·4	7·7	85·7	7·6
C_6H_5	C_4H_3S	2	33	203—205/15	$C_{13}H_{12}OS$	72·0	5·8	72·2	5·5
C_6H_5	3-C_4HSMe_2- 2: 5	2	Liq.	209—210/15	$C_{15}H_{16}OS$	73·5	6·6	73·8	6·5
p-C_6H_4Me	*p*-C_6H_4Et	2	Liq.	244—246/18	$C_{18}H_{20}O$	85·8	8·1	85·7	7·9
p-C_6H_4Me	*p*-C_6H_4OMe	2	52	238—240/18	$C_{17}H_{18}O_2$	80·1	7·3	80·3	7·1
p-C_6H_4Me	2-C_4H_3S	2	Liq.	225—226/17	$C_{14}H_{14}OS$	73·2	6·0	73·0	6·1
p-C_6H_4Me	3-C_4HSMe_2-2 : 5	2	Liq.	217—219/14	$C_{16}H_{18}OS$	74·2	7·1	74·4	7·0
p-C_6H_4Cl	C_6H_5	2	58	230—232/18	$C_{15}H_{13}OCl$	73·3	5·1	73·6	5·3
p-C_6H_4Cl	*p*-C_6H_4Et	2	48	245/17	$C_{17}H_{17}OCl$	74·6	6·0	74·9	6·2
p-C_6H_4Cl	*p*-C_6H_4·OMe	2	78	258—260/16	$C_{16}H_{15}O_2Cl$	69·8	5·8	69·9	5·5
p-C_6H_4Cl	*p*-C_6H_4Ph	2	143	300—302/16	$C_{21}H_{17}OCl$	78·4	5·1	78·6	5·3
p-C_6H_4Cl	2-C_4H_3S	2	54	232—235/16	$C_{13}H_{11}OClS$	62·1	4·4	62·3	4·4
C_6H_5	*p*-C_6H_4Et	3	Liq.	244—245/18	$C_{18}H_{20}O$	85·6	8·1	85·7	7·9
C_6H_5	*p*-C_6H_4·OMe	3	56	240—242/18	$C_{17}H_{18}O_2$	80·0	7·0	80·3	7·1
C_6H_5	2-C_4H_3S	3	Liq.	205—207/14	$C_{14}H_{14}OS$	72·8	6·4	73·0	6·1
C_6H_5	2-C_4HSMe_2	3	Liq.	216—218/14	$C_{16}H_{18}OS$	74·2	7·2	74·4	7·0
C_6H_5	3 : 4-$C_6H_3(OMe)_2$	3	64	260/18	$C_{18}H_{20}O_3$	75·8	7·3	76·0	7·0

* The first six ketones crystallised from ethanol, and the other solid ketones from ligroin in colourless needles. All ketones gave yellow to orange halochromic colours with sulphuric acid.

† "Liq." denotes liquid.

TABLE III.

3- *and* 2 : 3-*Disubstituted indoles.*

	M. p.	Formula	Found, %: C	Found, %: H	Reqd., %: C	Reqd., %: H
3-β-Phenylpropionyl	161°	$C_{17}H_{15}ON$	81·6	6·2	81·9	6·0
2-Methyl-3-β-phenylpropionyl	147	$C_{18}H_{17}ON$	82·0	6·2	82·1	6·5
3-(β-*p*-Chlorophenylpropionyl)	198	$C_{17}H_{14}ONCl$	71·6	5·0	71·9	4·9
2-Methyl-3-(β-*p*-tolylpropionyl)	139	$C_{19}H_{19}ON$	82·2	7·0	82·3	6·8
3-(β-6-Tetralylpropionyl) *	·150	$C_{21}H_{21}ON$	83·0	6·8	83·2	6·9
3-(β-*p*-Chlorophenylpropionyl)-2-methyl	165	$C_{18}H_{16}ONCl$	72·6	5·2	72·6	5·4
2-Methyl-3-γ-phenylbutyryl	158	$C_{19}H_{19}ON$	82·0	6·6	82·3	6·8
3-Benzyl-2-*p*-methoxyphenyl	152	$C_{22}H_{19}ON$	84·2	6·0	84·3	6·1
3-*p*-Chlorobenzyl-2-*p*-methoxyphenyl	166	$C_{22}H_{18}ONCl$	75·6	5·1	76·0	5·2
3-*p*-Chlorobenzyl-2-phenyl	111	$C_{21}H_{16}NCl$	79·2	5·2	79·4	5·0
3-*p*-Chlorobenzyl-2-*p*-ethylphenyl	101	$C_{23}H_{20}NCl$	79·6	5·6	79·9	5·8
3-*p*-Chlorobenzyl-2-*p*-diphenylyl	292	$C_{27}H_{20}NCl$	82·0	4·9	82·3	5·1
2-Methoxyphenyl-3-2′-phenylethyl	110	$C_{23}H_{21}ON$	84·5	6·2	84·4	6·4
3-2′-Phenylethyl-2-2″-thienyl	98	$C_{20}H_{17}NS$	79·0	5·8	79·2	5·6

* The acid was prepared from 6-chloromethyltetralin by the routine malonate synthesis.

Oddo Reactions with the Acid Chlorides (cf. *Gazzetta*, 1910, **40**, [2], 353, and Table III).—To a Grignard reagent made from ethyl bromide and magnesium in ether, indole (or 2-methylindole) was added, and the mixture refluxed for 15 minutes on a water-bath and then cooled in ice; a solution in ether of the appropriate acid chloride was added in small portions, and the reaction mixture refluxed for a further 15 minutes, and decomposed with an aqueous solution of ammonium chloride. After evaporation of ether, the solid ketones obtained were recrystallised from methanol or ligroin, forming shiny, colourless prisms.

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