Friedel–Crafts Reactions with Methyl m-*Tolyl Ether.*

By J. F. Miquel, Ng. Ph. Buu-Hoï, and René Royer.

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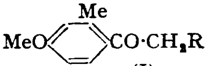
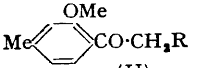
Friedel–Crafts acylation of methyl *m*-tolyl ether has been investigated in detail; it usually gives mixtures of the expected two isomeric ketones, in proportions which vary with the nature of the acylating agent and the experimental conditions. Friedel–Crafts benzylation affords two monobenzyl and one dibenzyl derivative.

Friedel–Crafts acylations have often been performed with methyl *m*-tolyl ether and various acid chlorides (Klages, *Ber.*, 1904, **37**, 3993; von Auwers, Bundesmann, and Wieners, *Annalen*, 1926, **447**, 178; Blau, *ibid.*, 1928, **460**, 93; De Clercq and Buu-Hoï, *Compt. rend.*, 1948, **227**, 1251), but little attention has been paid to the possible formation of isomeric ketones in these reactions. In view of the *ortho*- and *para*-orienting influence of both the methyl and the methoxy-group, such acylations should theoretically lead to mixtures of 4-acyl-3- (I) and 2-acyl-5-methylanisole (II). Buu-Hoï, Royer, and Eckert recently (*J. Org. Chem.*, 1952, **17**, 1463) found that the reaction with benzoyl chloride in the presence of aluminium chloride yielded both possible ketones. A detailed investigation has now been undertaken of acetylation, propionylation, butyrylation, and phenylacetylation of methyl *m*-tolyl ether, under various experimental conditions. The method for separating the *o*-methoxy-ketones from their *para*-isomers consisted of demethylation to the hydroxy-ketones by pyridine hydrochloride (cf. Buu-Hoï, *Rec. Trav. chim.*, 1949, **68**, 759), and then separation of the *o*- from the *p*-hydroxy-ketones by taking advantage of the lower solubility of the sodium derivatives of the former in concentrated aqueous sodium hydroxide (cf. Coulthard, Marshall, and Pyman, *J.*, 1930, 280).



(I)



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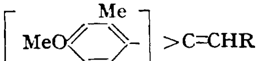

(III)

The results summarized in the Table show that acetylation and butyrylation, with either the acid chloride or the acid anhydride, yielded none or very little of the *o*-methoxy-ketone (II), whereas propionylation, and particularly phenylacetylation, afforded these ketones in considerable amounts. Benzoyl chloride and benzoic anhydride gave the same proportions of *o*- and *p*-ketone. The formation of 1 : 1-di-(4-methoxy-2-methylphenyl)-ethylenes (III) in Friedel–Crafts acylations at high temperature by means of acid chlorides (Xuong and Buu-Hoï, *J.*, 1952, 3741; cf. Gattermann, *Ber.*, 1889, **22**, 1130; Skraup and Nieten, *Ber.*, 1924, **57**, 1300; Mentzer and Xuong, *Compt. rend.*, 1946, **222**, 1004) was observed with acetyl, propionyl, and butyryl chloride. No diarylethylenes were formed when acid anhydrides were used.

Reaction of methyl *m*-tolyl ether with benzyl chloride in the presence of zinc chloride has been shown (Buu-Hoï, Eckert, and Demerseman, *J. Org. Chem.*, 1954, **19**, 726) to be more suitable than the ordinary aluminium chloride-catalyzed Friedel–Crafts reaction for comparing experimental results with the theoretical free-valency indices of the substitution sites. Under the experimental conditions used in the present work, benzylation of methyl *m*-tolyl ether gave 32% of 4-benzyl-3- and 18% of 2-benzyl-5-methylanisole and 29% of 2 : 4-dibenzyl-5-methylanisole. Similar benzylation of *m*-cresol gave 41% of 4-benzyl-3- and 9% of 2-benzyl-5-methylphenol and 25% of 2 : 4-dibenzyl-5-methylphenol. The constitution of the various monobenzyl derivatives was determined by identification with the reduction products of the ketones from Friedel–Crafts benzoylation; that of 2 : 4-dibenzyl-5-methylanisole was determined by its identity with the methylation product of 2 : 4-dibenzyl-3-methylphenol (cf. Huston and Houk, *J. Amer. Chem. Soc.*, 1932, **54**, 1506). From these experiments, it seems that the *para*-position in methyl *m*-tolyl ether is more reactive than the *ortho*-position, a superiority which is less apparent in *m*-cresol itself.

Other experiments included the reaction of phenylmagnesium bromide on 2-methoxy-4-methyl-1-phenacetylbenzene and dehydration of the tertiary alcohol formed, to yield 1-(2-methoxy-4-methylphenyl)-1 : 2-diphenylethylene, and Fischer cyclisation of the phenylhydrazones of the ketones to 2-(2-methoxy-4-methylphenyl)-3-phenylindole. The demethylation of 4-methoxy-2-methylpropiophenone by pyridine hydrochloride and hydrobromic acid is shown in the Table.

Yields (%) *on demethylation of* 4-*hydroxy*-2-*methylpropiophenone by pyridine hydrochloride and hydrobromic acid* (*d* 1·25; 10 *c.c. per g.*).

Time (min.)	30	45	55	60	75	90	120	180
C_5H_5N,HCl	30	54	—	64	72	68	63	48
HBr	36	61	69	67	49	26	11	5

4-Methoxy-2- and 2-methoxy-4-methyldibenzyl, prepared by Wolff–Kishner reduction of the corresponding phenylacetophenones, were not cyclized to phenanthrene derivatives by aluminium chloride (Ruzicka and Hösli, *Helv. Chim. Acta*, 1934, **17**, 470; Buu-Hoï and Hoán, *J. Org. Chem.*, 1949, **14**, 1023); only 4-hydroxy-2- and 2-hydroxy-4-methyldibenzyl were formed.

EXPERIMENTAL

Acylations of Methyl m-*Tolyl Ether with* 1 *Mol. of Acid Chloride* (*Method A*).—(*a*) An ice-cooled solution of methyl *m*-tolyl ether (12 g.) and propionyl chloride (9·3 g.) in carbon disulphide (100 c.c.) was treated with aluminium chloride (13·5 g.) with stirring, and the mixture left for 24 hr. at room temperature. After decomposition with ice, the organic layer was collected, washed with 10% aqueous sodium hydroxide (to remove hydroxy-ketones, which were then methylated with methyl sulphate and added to the main portion), then with water, and dried (Na_2SO_4), the solvent was removed, and the residue distilled *in vacuo*. The oil obtained, b. p. 147—158°/15 mm., was kept several days in the refrigerator, and gave crystals (9·2 g.), m. p. 43°, of 4-methoxy-2-methylpropiophenone [*semicarbazone*, prisms, m. p. 209° (from ethanol) (Found : N, 17·8. $C_{12}H_{17}O_2N_3$ requires N, 17·7%)]. The liquid portion was boiled for 40 min. with pyridine hydrochloride (13 g.); after addition of water, the product was taken up in ether, and treated with concentrated aqueous sodium hydroxide. The alkaline solution gave on acidification an oil, which was remethylated with methyl sulphate, to give pure 2-methoxy-4-methylpropiophenone (4·8 g.), b. p. 142—144°/15 mm., n_{D}^{18} 1·5502 (Mauthner, *J. prakt. Chem.*, 1921, **103**, 395) [*semicarbazone*, m. p. 214° (from ethanol) (Found : N, 17·9%)].

(*b*) With acetyl chloride (7·8 g.), only 4-methoxy-2-methylacetophenone (12·8 g.), b. p. 145—146°/18 mm., n_{D}^{17} 1·5498 (semicarbazone, m. p. 194°, in agreement with Auwers *et al.*, *loc. cit.*), was obtained.

(*c*) With *n*-butyryl chloride (10·6 g.), the oil obtained (14·6 g.), b. p. 158—170°/16 mm., was demethylated to a portion (0·3 g.), whose sodium derivative was insoluble in concentrated aqueous sodium hydroxide; it gave 2-methoxy-4-methyl-*n*-butyrophenone semicarbazone, m. p. 192°. The soluble product was 4-hydroxy-2-methyl-*n*-butyrophenone, m. p. 98° (from ethanol–water). Remethylation of this ketone gave pure 4-methoxy-2-methyl-*n*-butyrophenone, b. p. 161—163°/15 mm., n_{D}^{21} 1·5376 [*semicarbazone*, prisms, m. p. 182°, from ethanol (Found : N, 16·7. $C_{13}H_{19}O_2N_3$ requires N, 16·7%)].

(*d*) With phenylacetyl chloride (15·5 g.), an oil, b. p. 234—236°/15 mm., was obtained, which was diluted with light petroleum and kept for several days in the refrigerator. 4-Methoxy-2-methyl-1-phenylacetylbenzene (9·4 g.) formed prisms, m. p. 73°, from ethanol (cf. Blau, *Monatsh.*, 1905, **26**, 1149) [*semicarbazone*, prisms, m. p. 165° (from ethanol–water) (Found : C, 65·7; H, 6·5; N, 14·2. $C_{17}H_{19}O_2N_3$ requires C, 65·6; H, 6·4; N, 14·1%)]. The liquid portion, purified *via* its demethylation product, gave 2-*methoxy*-4-*methyl*-1-*phenylacetylbenzene* (8·7 g.), a pale yellow oil, b. p. 221—222°/15 mm., n_{D}^{21} 1·5870 (Found : C, 80·3; H, 6·2. $C_{16}H_{16}O_2$ requires C, 80·0; H, 6·1%) [*semicarbazone*, prisms, m. p. 198° (from ethanol–water) (Found : N, 14·1%)]. In this and the preceding cases only traces of diarylethylene were detected.

(*e*) Benzoyl chloride (14·2 g.) gave a ketone mixture (17·4 g.), which was converted into 4-methoxy-2-methylbenzophenone (Buu-Hoï, Royer, and Eckert, *loc. cit.*), and 2-*methoxy*-4-*methylbenzophenone*, a pale yellow oil, b. p. 204—205°/16 mm., n_{D}^{19} 1·6105 (Found : C, 79·5; H, 6·3. $C_{15}H_{14}O_2$ requires C, 79·6; H, 6·2%) [*semicarbazone*, prisms, m. p. 182° (from ethanol–water) (Found : N, 14·8. $C_{16}H_{17}O_2N_3$ requires N, 14·8%)].

Acylation of Methyl m-*Tolyl Ether with* 0·5 *Mol. of Acid Chloride* (*Method B*).—To a solution of methyl *m*-tolyl ether (2 mol.) and the acid chloride (1 mol.), aluminium chloride (1·5 mol.) was added in small portions with stirring. The mixture was kept for 1 hr. at 70°, then for 24 hr. at room temperature. After treatment with ice, the product was dissolved in ether and worked up as above; the *o*-methoxy-ketone was obtained in the lower-boiling portion, and the higher-boiling residue consisted mainly of the 1 : 1-diarylethylene. 1 : 1-*Di*-(4-*methoxy*-2-*methylphenyl*)*ethylene*, b. p. 205—210°/17 mm., crystallized as leaflets, m. p. 133°, from ethanol (Found: C, 81·6; H, 7·4. $C_{18}H_{20}O_2$ requires C, 81·3; H, 7·2%), and 1 : 1-*di*-(4-*methoxy*-2-*methylphenyl*)*butene*, b. p. 162—165°/1 mm., as leaflets, m. p. 82°, from methanol (Found: C, 78·3; H, 7·7. $C_{20}H_{24}O_2$ requires C, 78·1; H, 7·8%). Both compounds gave a red halochromy with sulphuric acid.

Acylation of Methyl m-*Tolyl Ether with Acid Anhydride* (*Method C*).—The technique used was that of Noller and Adams (*J. Amer. Chem. Soc.*, 1924, **46**, 1892). The yields recorded in the Table were reproduced to within 2% in at least two experiments for each case.

Yields (%) *of ketones and* 1 : 1-*diarylethylenes in Friedel–Crafts acylation of methyl* m-*tolyl ether.*

		Method A	Method B	Method C
Acetylation	*o*-Methoxy-ketone	Nil	Nil	Nil
	p-Methoxy-ketone	78	66	82
	Diarylethylene	Trace	22	Nil
Propionylation	*o*-Methoxy-ketone	27	Nil	32
	p-Methoxy-ketone	52	58	52
	Diarylethylene	Trace	25	Nil
Butyrylation	*o*-Methoxy-ketone	Trace	Nil	5
	p-Methoxy-ketone	70	52	78
	Diarylethylene	Nil	19	Nil
Phenacetylation	*o*-Methoxy-ketone	39	Nil	—
	p-Methoxy-ketone	36	39	—
	Diarylethylene	3	34	—
Benzoylation	*o*-Methoxy-ketone	18	Nil	21
	p-Methoxy-ketone	59	72	62

4-*Methoxy*-2-*methyldibenzyl*.—A solution of 4-methoxy-2-methyl-1-phenylacetylbenzene (22·6 g.) and 90% hydrazine hydrate (8 g.) in diethylene glycol (200 c.c.) was heated for 15 min.; potassium hydroxide (9 g.) was added, and the mixture was refluxed with removal of water for 3 hr. After cooling, dilute hydrochloric acid was added, and the product taken up in benzene. The benzene layer was washed with 10% aqueous sodium hydroxide (solution A), then with water, and dried (Na_2SO_4). The residue from evaporation of benzene gave on fractionation *in vacuo*, pure 4-*methoxy*-2-*methyldibenzyl* (18 g.), b. p. 214—216°/16 mm., needles, m. p. 71° (from methanol) (Found: C, 84·7; H, 7·9. $C_{16}H_{18}O$ requires C, 84·9; H, 7·9%). The substance described by Hill and Short (*J.*, 1935, 1123) as an oil, b. p. 180—190°/10 mm., was probably a mixture of isomers. Acidification of the alkaline solution afforded 4-*hydroxy*-2-*methyldibenzyl* (1·3 g.), prisms, m. p. 137—138° (from methanol) (Found: C, 84·7; H, 7·5. $C_{15}H_{16}O$ requires C, 84·9; H, 7·5%).

2-*Methoxy*-4-*methyldibenzyl*.—Prepared as above from 2-methoxy-4-methyl-1-phenylacetylbenzene, this *compound* (9 g.) was a colourless oil, b. p. 187—189°/16 mm., n_D^{19} 1·5770 (Found: C, 85·1; H, 7·9%). 2-*Hydroxy*-4-*methyldibenzyl* (0·6 g.) was an oil, b. p. 226—230°/16 mm., n_D^{22} 1·5842 (Found: C, 85·1; H, 7·4%).

1-(2-*Methoxy*-4-*methylphenyl*)-1 : 2-*diphenylethylene*.—2-Methoxy-4-methyl-1-phenylacetylbenzene similarly gave 1-(2-*methoxy*-4-*methylphenyl*)-1 : 2-*diphenylethan*-1-ol (4·4 g.), prisms, m. p. 140° (from methanol) (Found: C, 82·9; H, 6·8. $C_{22}H_{21}O_2$ requires C, 83·2; H, 6·6%); dehydration with formic acid yielded the *ethylene*, b. p. 245°/17 mm., prisms, m. p. 77° (from methanol) (Found: C, 87·8; H, 6·1%).

2-(4-*Methoxy*-2-*methylphenyl*)-3-*phenylindole*.—The crude phenylhydrazone of 4-methoxy-2-methyl-1-phenacetylbenzene was cyclized with acetic acid saturated with hydrogen chloride (cf. Buu-Hoï, *J.*, 1949, 2882), to give 2-(4-*methoxy*-2-*methylphenyl*)-3-*phenylindole*, b. p. 305—310°/15 mm., leaflets, m. p. 176° (from ethanol) (Found: C, 84·3; H, 6·1. $C_{22}H_{19}ON$ requires C, 84·3; H, 6·1%). 2-(2-*Methoxy*-4-*methylphenyl*)-3-*phenylindole*, similarly prepared from 2-methoxy-4-methyl-1-phenylacetylbenzene, boiled at 300—302°/15 mm., and crystallized as leaflets, m. p. 138°, from ethanol (Found: C, 83·6; H, 6·2%).

Benzylation of Methyl m-*Tolyl Ether*.—A solution of methyl *m*-tolyl ether (61 g.) and benzyl chloride (70 g.) in dry chloroform (400 c.c.) was refluxed with freshly fused, finely powdered zinc chloride (30 g.) for 15 hr. The chloroform layer which was formed on treatment with water was washed with water, then dried (Na_2SO_4), and the residue on evaporation of the solvent was fractionated *in vacuo*. The fraction of b. p. 175—195°/15 mm. (56 g.) partly solidified after prolonged storage in the refrigerator. The solid gave, on recrystallization from light petroleum, *4-benzyl-3-methylanisole* (32%), prisms, m. p. 43° (Found: C, 85·1; H, 7·4. $C_{15}H_{16}O$ requires C, 84·9; H, 7·5%), identical with the Wolff–Kishner reduction product of 4-methoxy-2-methylbenzophenone; the product described by Stadnikov and Baryscheva (*Ber.*, 1928, **61**, 1999) as an oil, b. p. 181—187°/20 mm., n_D^{18} 1·5767, was probably a mixture. After repeated fractional crystallization, the liquid portion was redistilled, giving *2-benzyl-5-methylanisole* (18%), b. p. 179°/15 mm., n_D^{18} 1·5864 (Found: C, 85·2; H, 7·4%), identical with the Wolff–Kishner reduction product of 2-methoxy-4-methylbenzophenone. The portion of b. p. 240—255°/15 mm. (28·5 g.) was 2 : *4-dibenzyl-5-methylanisole*, which crystallized from light petroleum as prisms, m. p. 70° (Found: C, 87·3; H, 7·1. $C_{22}H_{22}O$ requires C, 87·4; H, 7·3%), and was demethylated by pyridine hydrochloride to 2 : 4-dibenzyl-5-methylphenol, m. p. 106°.

Benzylation of m-*Cresol*.—A solution of *m*-cresol (55 g.) and benzyl chloride (70 g.) in chloroform (400 c.c.) was refluxed for 10 hr. with zinc chloride (30 g.), and the mixture worked up as above. Repeated fractionation *in vacuo* gave a 9% yield of 2-benzyl-5-methylphenol, b. p. 123—127°/1 mm., m. p. 47° (from light petroleum), a 41% yield of 4-benzyl-3-methylphenol, b. p. 147—150°/1 mm., m. p. 93·5° (from ligroin), and a 25% yield of 2 : 4-dibenzyl-5-methylphenol, m. p. 106° (from benzene), in accord with Huston and Houk (*loc. cit.*).

DEPARTMENT OF ORGANIC CHEMISTRY,
THE RADIUM INSTITUTE, UNIVERSITY OF PARIS.

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