728. *Alkyl–Oxygen Fission in Carboxylic Esters. Part XII.** 1-o-*Methoxyphenylethyl and α-Naphthylphenylmethyl Compounds. The Relative Effects of the Introduction of* o- *and of* p-*Methoxyl Groups into Phenylmethyl Compounds.*

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1-*o*-Methoxyphenylethyl alcohol has been resolved *via* its hydrogen phthalate, and the tendency of this ester and of α-naphthylphenylmethyl hydrogen phthalate to undergo alkyl–oxygen fission has been investigated. It is shown that an *o*-methoxyl group is somewhat less effective than a *p*-methoxyl group in promoting alkyl–oxygen fission in 1-phenylethyl hydrogen phthalate, and in diphenylmethyl and α-naphthylphenylmethyl compounds. This is ascribed to the super-position upon the powerful, activating, electron-repelling, mesomeric effect of the methoxyl group ($+M$, $\mathrm{CH_3{-}\overset{\curvearrowright}{\ddot{O}}{-}}$), of a weaker, deactivating, electron-attracting, inductive effect ($-I$, $\mathrm{CH_3{-}O{\longleftarrow}}$) which becomes attentuated on relay through the carbon–carbon bonds of the benzene ring.

1-*o*-METHOXYPHENYLETHYL ALCOHOL has been resolved by fractional crystallisation of the brucine salt of its hydrogen phthalate, and the tendency of this ester to undergo alkyl–oxygen fission has been investigated. 1-*o*-Methoxyphenylethyl hydrogen phthalate undergoes unimolecular alkyl–oxygen fission reactions according to the equation:

$$\mathrm{R\overset{\curvearrowright}{-}O\cdot CO\cdot C_6H_4\cdot CO_2H \xrightleftharpoons{\text{Slow}} C_6H_4(CO_2H)_2 + R^+ \xrightarrow[\text{Y}]{\text{Fast}} RY}$$

(where $\mathrm{R} = o\text{-}\mathrm{MeO{\cdot}C_6H_4{\cdot}CHMe}$; $\mathrm{Y} = \mathrm{HO^-}$, AcOH, etc., $p\text{-}\mathrm{Me{\cdot}C_6H_4{\cdot}SO_2^-}$, MeOH, and $\mathrm{RO_2C{\cdot}C_6H_4{\cdot}CO_2^-}$) more readily than 1-phenylethyl hydrogen phthalate (Part II, *J.*, 1942, 605, and Part III, *J.*, 1946, 797), but less readily than 1-*p*-methoxyphenylethyl hydrogen

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* Part XI, *J.*, 1952, 4964.

phthalate. A parallel difference exists between the diphenylmethyl (Parts II and III, *locc. cit.*) and *o*- and *p*-methoxydiphenylmethyl compounds.

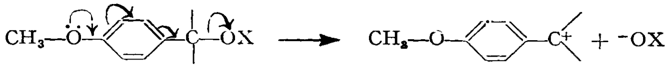
Attempts to resolve α-naphthylphenylmethanol *via* the alkaloidal salts of its hydrogen phthalate and hydrogen succinate were unsuccessful. The tendency of this alcohol and its hydrogen phthalate to undergo typical alkyl–oxygen fission reactions (formation of bis-ether, and of chloride, from the alcohol; formation of *p*-tolyl sulphone, ethyl ether, and neutral phthalate, from the hydrogen phthalate) has been investigated, and again it is shown that the reactivity of related structures by such a mechanism follows the sequence : α-naphthylphenylmethyl < *o*-methoxyphenyl-α-naphthylmethyl < *p*-methoxyphenyl-α-naphthylmethyl compounds.

These differences between the compounds carrying *o*- and *p*-methoxyl substituents, are summarised in the Table.

	Reacting molecule	
Reaction	o-MeO·C_6H_4·CHMe·O·CO·C_6H_4·CO_2H	p-Isomer *
Hydrolysis	Optical purity of alcohol produced.	
(i) In 8% aq. NaOH	99%	90%
(ii) In 4% aq. NaOH	95%	Much racemisation
Racemisation	Half-life of racemisation at room temp.	
(i) In acetic acid	63 hr.	9 hr.
(ii) In 2N-formic acid in acetic acid	55 hr.	7 hr.
(iii) In 5N-formic acid in acetic acid	43 hr.	2·5 hr.
(iv) In 2·5N-HCl in acetone	50 min.	Approx. 1·5 min.
Reaction with sodium toluene-*p*-sulphinate in 0·3N-NaOH	Almost quant. yield of sulphone after 1 month.	Quant. yield of sulphone after 5 days.
Reaction with MeOH.	No reaction with anhyd. MeOH. (−)-Ester gives (±)-methyl ether after 5 hr. in 90% aqueous MeOH at b. p.	(−)-Ester gives (±)-methyl ether after 12 hr. in anhydrous MeOH at room temp.
Formation of neutral ester	Neutral ester obtained from 0·1N-NaOH after 5 days.	Neutral ester obtained from 0·3N-NaOH after 2 days.
	o-MeO·C_6H_4·CHPhX †	p-Isomer †
Reaction with MeOH (X = OH).	No reaction on distillation with MeOH during 6 hr.	Methyl ether formed.
Reaction with sodium toluene-*p*-sulphinate in 0·3N-NaOH (X = o-HO_2C·C_6H_4·CO_2^-).	Pptn. of sulphone starts after 3 hr.; complete after 6 days.	Quant. yield of sulphone after 20 min.
	o-MeO·C_6H_4·CH($C_{10}H_7$-1)·O·CO·C_6H_4·CO_2H ‡	p-Isomer ‡
Formation of neutral ester from 0·3N-NaOH.	Good yield after 4 days.	Good yield after 2 days.

* Part IV, *J.*, 1946, 803; K. A. Nandi, Thesis, London, 1940.
† Part II (*loc. cit.*); R. Poplett, Thesis, London, 1944.
‡ Part III (*loc. cit.*); A. A. Evans, Thesis, London, 1944.

Thus the introduction of an *o*- or *p*-methoxyl group into the benzene ring of such 1-phenylmethyl compounds increases their tendency to react by a unimolecular alkyl–oxygen fission mechanism, and this effect is greater when the methoxyl group is located in the *para*- than when it is in the *ortho*-position. This overall accelerating effect, which has also been observed in di-*p*-methoxyphenylmethanol (Part X, *J.*, 1951, 386; Balfe, Kenyon, and Thain, *J.*, 1952, 790) and in 2 : 4 : 6-trimethoxyphenylmethyl compounds (Part XI, *J.*, 1952, 4964), may be ascribed to the powerful, mesomeric, electron release (+*M* effect) of the methoxyl group operating in conjugation with the alkyl–oxygen bond, *e.g.* :



Some further factor must account for the reduced effectiveness of the methoxyl group when located in the *ortho*-position. Steric inhibition of resonance by the methoxyl group in the 1-*o*-methoxyphenylethyl cation cannot be of major importance in this respect since molecular models show that the ion can assume a strainless planar configuration. More probably the effect is a result of the superposition of the inductive electron attraction ($-I$ effect, CH_3—O◄—) of the methoxyl group upon its more powerful mesomeric electron release; this inductive effect rapidly becomes attenuated on relay through carbon–carbon bonds, and thus will operate more effectively from the *ortho-* than from the *para*-position in decreasing the electron releasing power of the " alkyl " carbon atom, and hence in reducing its tendency to undergo alkyl–oxygen fission.

EXPERIMENTAL

(±)-1-o-*Methoxyphenylethyl Alcohol.*—The alcohol, prepared from methylmagnesium iodide and *o*-methoxybenzaldehyde in 86% yield, had b. p. 84—86°/0·6 mm., n_{D}^{25} 1·5372. Klages (*Ber.*, 1903, **36**, 3588) reports $n_{\mathrm{D}}^{14·7}$ 1·5379. The phenylurethane had m. p. 105—106°; Klages (*loc. cit.*) reports 106°. *Di*-(1-o-*methoxyphenylethyl*) *ether* was formed (1%) when the alcohol was distilled at 124—126°/17 mm., or, very slowly, when the pure alcohol was kept at room temperature; it separates from methanol as needles, m. p. 117—118° (Found: C, 75·3; H, 7·6. $C_{18}H_{22}O_3$ requires C, 75·5; H, 7·7%).

(±)-1-o-*Methoxyphenylethyl Hydrogen Phthalate.*—A solution of the alcohol (52 g.) and phthalic anhydride (53 g.) in pyridine (28 g.) was kept at 60° for 2 hr. and, next day, decomposed with ice and dilute hydrochloric acid. The resulting *ester* separated slowly from carbon disulphide–ligroin in large rectangular prisms, m. p. 93—94° (90%) (Found, by titration: equiv., 297. $C_{17}H_{16}O_5$ requires equiv., 300).

(+)-1-o-*Methoxyphenylethyl Hydrogen Phthalate.*—From a solution of the (±)-ester (36 g.) and brucine (54 g.) in acetone (250 c.c.), the brucine salt of the (+)-ester rapidly separated. After four recrystallisations from acetone–chloroform (1 : 1), it (needles, m. p. 193—194°; 35 g.) was suspended in acetone and decomposed by dilute hydrochloric acid, and the liberated ester extracted with ether. The (+)-hydrogen *ester*, a clear viscous oil, had equiv. 299 (by titration) and $[\alpha]_{\mathrm{D}}^{19}$ +19·30° (*l*, 2; *c*, 2·081 in $CHCl_3$).

(−)-1-o-*Methoxyphenylethyl Hydrogen Phthalate.*—The mother-liquor from the first crop of brucine salt was concentrated and set aside; the brucine salt of the (−)-ester (35 g.) slowly separated. This salt, after eight recrystallisations from acetone, was obtained as needles, m. p. 112—114° (18 g.), which, after decomposition with dilute hydrochloric acid yielded the (−)-hydrogen ester as an oil, $[\alpha]_{\mathrm{D}}^{18}$ −19·2° (*l*, 2; *c*, 1·545 in $CHCl_3$).

(−)-1-o-*Methoxyphenylethyl Alcohol.*—The (+)-hydrogen phthalate (3 g.) in a solution of sodium (1 g.) in 96% ethanol (20 c.c.) was heated on the steam-bath for some minutes until a thick precipitate was produced. The mixture, diluted with water and extracted with ether, yielded the (−)-alcohol (1·2 g.), b. p. 83—85°/0·5 mm., n_{D}^{25} 1·5310, d_4^{25} 1·0780, $[\alpha]_{\mathrm{D}}^{20}$ −50·1° (homogeneous, l, 0·25) [Klages, *loc. cit.*, gives $d_4^{14·7}$ 1·0862 for the (±)-alcohol]. This (−)-alcohol was reconverted into the hydrogen phthalate, $[\alpha]_{\mathrm{D}}^{21}$ +19·15° (*l*, 2; *c*, 1·931 in $CHCl_3$).

(±)-, (+)-, *and* (−)-1-o-*Methoxyphenylethyl Benzoate.*—From the (±)-alcohol (1·5 g.), benzoyl chloride (1·4 g.), and pyridine (1·0 g.), the (±)-*benzoate* was obtained as needles (from ethanol), m. p. 34—36° (Found: C, 75·5; H, 6·2. $C_{16}H_{16}O_3$ requires C, 75·4; H, 6·2%). By a similar procedure the (−)-alcohol yielded the (+)-benzoate, m. p. 45—46°, $[\alpha]_{\mathrm{D}}^{19}$ +81·2° (*l*, 1; *c*, 1·405 in $CHCl_3$), and the (+)-alcohol yielded the (−)-benzoate, m. p. 45—46°, $[\alpha]_{\mathrm{D}}^{20}$ −80·6° (l, 1; *c*, 1·402 in $CHCl_3$).

Reactions of 1-o-*Methoxyphenylethyl Hydrogen Phthalate.*—(i) *Hydrolysis with dilute aqueous sodium hydroxide.* The optical purity of the alcohol produced by hydrolysis with 8% and with 4% aqueous sodium hydroxide is reported in the Table.

(ii) *Racemisation in acid solution.* The half-life of the racemisation of the hydrogen phthalate under acid conditions at room temperature, is given in the Table. From an acetic acid solution of the (+)-hydrogen phthalate, the (±)-acetate was isolated: the rotatory power of a solution of the (+)-hydrogen phthalate (1·0 g.) in glacial acetic acid (20 c.c.) at room temperature fell to 50% of the original value after 63 hr. and to 10% after 3 weeks. The mixture yielded, on decomposition, the (±)-acetate (0·4 g.), b. p. 118—120°/17 mm., n_{D}^{25} 1·5267.

(iii) *Formation of* 1-o-*methoxyphenylethyl* p-*tolyl sulphone.* From a mixture of the (−)-hydrogen phthalate (0·6 g.) in aqueous sodium hydroxide (7·0 c.c. of 0·3N) and sodium toluene-*p*-sulphinate (0·43 g.) in water (3 c.c.), deposition of a white solid began after 2 days and was complete after 1 month. Recrystallisation from ethanol gave (±)-1-o-*methoxyphenylethyl* p-*tolyl sulphone* (0·45 g.) as short rods, m. p. 131—132° (Found : C, 66·0; H, 6·2; S, 10·9. $C_{16}H_{18}O_3S$ requires C, 66·2; H, 6·2; S, 11·0%). At 70° the reaction was complete after 15 min. The same sulphone was obtained by the oxidation of the corresponding sulphide. From a mixture of the (±)-hydrogen phthalate (7·5 g.) in acetone (20 c.c.) and thio-*p*-cresol (3·0 g.) suspended in 98% formic acid (15 c.c.), phthalic acid (3·6 g.) rapidly separated. The filtrate was neutralised with dilute sodium hydroxide solution and extracted with ether, yielding 1-o-*methoxyphenylethyl* p-*tolyl sulphide* (6·0 g.), b. p. 183—185°/17 mm. (Found : C, 74·6; H, 7·1; S, 12·3. $C_{16}H_{18}OS$ requires C, 74·4; H, 7·0; S, 12·4%). Hydrogen peroxide (6·0 c.c. of 90-vol.) was added to a solution of the sulphide (2·0 g.) in glacial acetic acid (20 c.c.); after 2 days the solution was diluted with aqueous sodium hydroxide solution, yielding 1-*o*-methoxyphenylethyl *p*-tolyl sulphone (2·0 g.), m. p. and mixed m. p. 131—133°.

(iv) *Formation of* 1-o-*methoxyphenylethyl methyl ether.* A solution of the (−)-hydrogen phthalate (2·5 g.) and water (2·0 g.) in methanol (25 c.c.) was boiled under reflux for 2 hr., whereafter the solution possessed 4% of its original rotatory power. After a further 3 hr. the optically inactive mixture yielded the (±)-*methyl ether* (1·0 g.), b. p. 90—93°/17 mm., n_D^{25} 1·5973 (Found : C, 72·4; H, 8·6. $C_{10}H_{14}O_2$ requires C, 72·3; H, 8·6%). No reaction occurred when a similar anhydrous reaction mixture was heated under reflux for 6 hr.

(v) *Formation of neutral ester.* After 24 hr., a solution of the (+)-hydrogen phthalate (6 g.) in aqueous sodium hydroxide (200 c.c. of 0·1N) began to deposit the oily *di*-(1-o-*methoxyphenylethyl*) *phthalate.* After 5 days this was removed and heated at 100°/0·4 mm. to remove traces of the alcohol, leaving a residual oil which could not be solidified, $[\alpha]_D^{20}$ +4·5° (*l*, 2; *c*, 4·00 in $CHCl_3$) (Found by hydrolysis : equiv., 420. $C_{26}H_{26}O_6$ requires equiv., 434). Hydrolysis of this neutral ester with alcoholic sodium hydroxide gave (−)-1-*o*-methoxyphenylethyl alcohol, b. p. 83—85°/0·5 mm., $[\alpha]_D^{20}$ −15·4° (*l*, 0·25; homogeneous), n_D^{25} 1·5340. Hydrolysis of the original (+)-hydrogen phthalate under similar conditions yielded the optically pure alcohol.

(−)-1-p-*Methoxyphenylethyl Hydrogen Phthalate.*—This ester was prepared and resolved as described in Part IV (*loc. cit.*). The half-life of racemisation under acid conditions is reported in the Table.

α-*Naphthylphenylmethanol.*—The alcohol, prepared in good yield either by the interaction of α-naphthylmagnesium bromide and benzaldehyde, or by the reduction of α-naphthyl phenyl ketone in ethanol with zinc dust and sodium hydroxide, separates from carbon disulphide in needles, m. p. 86° (Acree, *Ber.*, 1904, **37**, 2727, gives m. p. 85—86°). Its solution in pyridine is readily converted by acetic anhydride or acetyl chloride into the corresponding *acetate*, needles, m. p. 80—80·5° (Found : C, 82·5; H, 5·9. $C_{19}H_{16}O_2$ requires C, 81·9; H, 6·0%). After 35 hr. at 150—155°, the alcohol (3·0 g.) yielded *di*-(α-*naphthylphenylmethyl*) *ether* (0·30 g.) as white glistening needles (from acetone), m. p. 172—173° (Found : C, 90·0; H, 5·7. $C_{34}H_{26}O$ requires C, 90·1; H, 5·8%).

α-*Naphthylphenylmethyl Hydrogen Phthalate.*—A mixture of the alcohol (23·5 g.), phthalic anhydride (14·8 g.), and pyridine (15 c.c.) was kept at 55—60° for 16 hr. and the resulting homogeneous liquid, diluted with an equal volume of acetone, was decomposed with cold hydrochloric acid. The initially pasty *hydrogen phthalate* rapidly hardened (m. p. 153—154°) and separated from methanol in prismatic needles, m. p. 158—158·5° (36·5 g.) (Found, by titration : equiv., 384. $C_{25}H_{18}O_4$ requires equiv., 382).

α-*Naphthylphenylmethyl Hydrogen Succinate.*—A mixture of the alcohol (7 g.), succinic anhydride (3 g.), and pyridine (5 c.c.), after 4 hr. on the steam-bath, yielded the *hydrogen succinate* (9·7 g.) as short needles, m. p. 122—123° (Found : equiv., 338. $C_{21}H_{18}O_4$ requires equiv., 334).

Each of these acid esters was combined with several of the commoner alkaloids but in all cases the salts remained non-crystalline, and no optical resolution could be accomplished.

Formation of α-*Naphthylphenylmethyl Chloride.*—(i) *With thionyl chloride.* Thionyl chloride (7·0 c.c.) was added slowly to a solution of the alcohol (9·0 g.) in benzene (50 c.c.). After being heated under reflux for 1 hr., the mixture was decolorised with animal charcoal, and the solvent removed, yielding α-naphthylphenylmethyl chloride (7·0 g.) as needles (from ether–light petroleum), m. p. 59° (Found : Cl, 13·5. Calc. for $C_{17}H_{13}Cl$: Cl, 14·0%). Norris and Blake (*J. Amer. Chem. Soc.*, 1928, **50**, 1812) give m. p. 64—64·5°.

(ii) *With hydrochloric acid.* A mixture of the alcohol (12·0 g.) in acetone (15 c.c.) and concentrated hydrochloric acid (100 c.c.) was kept for 30 min. at 80°. The resulting oil was dried *in vacuo* (KOH), and extracted with light petroleum, the extract yielding the chloride (from ligroin or carbon disulphide, 9·0 g.), b. p. 230°/17 mm., m. p. and mixed m. p. 59°.

(iii) *With acetyl chloride.* Acetyl chloride (2·0 c.c.) was added to the alcohol (2·0 g.) at room temperature, an orange colour immediately developing. After drying *in vacuo* (KOH), the mixture yielded the chloride (from ligroin, 1·2 g.), b. p. 228°/16 mm., m. p. and mixed m. p. 59°.

Reactions of α-Naphthylphenylethyl Hydrogen Phthalate.—(i) *Formation of α-naphthylphenylmethyl* p-*tolyl sulphone.* A solution of the hydrogen phthalate (4·0 g.) and sodium toluene-*p*-sulphinate (2·25 g.) in 98% formic acid (50 c.c.) was heated on the steam-bath for 8 hr. and diluted with water. The resulting *sulphone* (3·3 g.) separated from ethanol in plates, m. p. 122° (Found: S, 8·3. $C_{24}H_{20}O_2S$ requires S, 8·5%). On the other hand, from an aqueous sodium hydroxide solution of the acid phthalic ester and sodium toluene-*p*-sulphinate, the only product which separated was the alcohol.

(ii) *Formation of ethyl α-naphthylphenylmethyl ether.* A solution of the hydrogen phthalate (5·0 g.) in absolute ethanol (75 c.c.) was heated under reflux for 18 hr. The products consisted of unchanged acid ester (2·2 g.) and the *ethyl ether*, b. p. 202—204°/14 mm., which separated from ether–light petroleum in needles (1·6 g.), m. p. 47° (Found: C, 87·2; H, 7·1. $C_{19}H_{18}O$ requires C, 87·0; H, 6·9%). Replacement of absolute ethanol by 70% ethanol resulted in an improvement of the yield of ethyl ether from 46% to 58% during the same period of heating.

The ethyl ether was also obtained in quantitative yield when α-naphthylphenylmethyl chloride was heated with absolute ethanol under reflux for 3 hr.

(iii) *Non-formation of neutral phthalic or succinic esters.* Solutions of the acid phthalic or succinic esters in equivalent amounts of aqueous sodium hydroxide of different concentrations (N/20—N) deposited—very slowly at room temperature, more rapidly on warming—α-naphthylphenylmethanol quantitatively. There was no trace of a neutral ester. Similarly, a solution of the acid phthalic ester (2·0 g.) in chloroform (20 c.c.) after being heated under reflux for 30 hr. yielded the unchanged acid ester (1·95 g.).

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