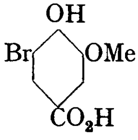
255. *Synthesis of Diphenyl Ethers containing Methoxy- and Ethoxy-groups.*

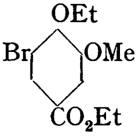
By Harold King.

Alkoxydiphenyl ethers may be useful reference substances in degradation experiments on certain bisbenzyl*iso*quinoline alkaloids. The synthesis of 2 : 2'-*diethoxydiphenyl ether* and three isomeric *methoxyethoxydiphenyl ethers* is herein described.

In connection with experiments on the degradation of *O*-ethylbebeerine (preceding paper), diphenyl ethers containing methoxy- and ethoxy-groups were required as reference substances. 2-Methoxy- and 2 : 2'-dimethoxy-diphenyl ethers were described by Ullmann and Stein (*Ber.*, 1906, **39**, 622) and an improved form of their method has been utilised for synthesising and isolating 2 : 2'-*diethoxy*- and 2-*methoxy*-2'-*ethoxy-diphenyl ethers.* The former was made from guaiethol and *o*-bromophenetole and the latter from guaiethol and *o*-bromoanisole. For the preparation, however, of 3-*methoxy*-2-*ethoxy*-(I) and 2-*methoxy*-3-*ethoxy-diphenyl ethers* a circuitous route had to be followed. For the former the starting material was *O*-acetylvanillin, which was oxidised in 86% yield to *O*-acetylvanillic acid. The latter acid was quantitatively hydrolysed to vanillic acid, which was brominated by Robertson's method (J., 1908, **93**, 792) to 5-bromovanillic acid (II). On ethylation with ethyl sulphate, *ethyl* 5-*bromo*-3-*methoxy*-4-*ethoxybenzoate* (III) was obtained and on condensation with potassium phenoxide in presence of copper powder this gave *O*-ethylvanillic acid (IV) and 5-*carboxy*-3-*methoxy*-2-*ethoxydiphenyl ether* (V). The formation of *O*-ethylvanillic acid is clearly due to catalytic dehalogenation by the copper, a process to which attention has previously been drawn by Lesslie and Turner (J., 1932, 281). Several other similar cases are mentioned in the preceding paper. On decarboxylation of 5-carboxy-3-methoxy-2-ethoxydiphenyl ether (V) by boiling with quinoline and copper, 3-methoxy-2-ethoxydiphenyl ether (I) was obtained in good yield.



(II.)



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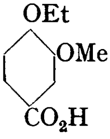

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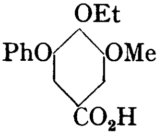

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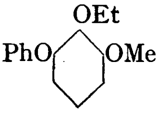

(I.)

In a similar way, by starting from 4-hydroxy-3-ethoxybenzaldehyde ("vanbeenol"), 5-*bromo*-4-*methoxy*-3-*ethoxybenzoic acid* and its *methyl* ester were obtained. The latter with potassium phenoxide and copper powder gave 5-*phenoxy*-4-*methoxy*-3-*ethoxybenzoic acid* and 4-*methoxy*-3-*ethoxybenzoic acid.* The former of these acids on decarboxylation furnished 2-methoxy-3-ethoxydiphenyl ether in good yield.

It is fortunate that these dialkoxydiphenyl ethers are all crystalline substances, since this facilitates comparison. For convenience of reference the melting points are recorded below :

2 : 2'-Dimethoxydiphenyl ether	79—80° *	3-Methoxy-2-ethoxydiphenyl ether	33—34°
2 : 2'-Diethoxydiphenyl ether	53	2-Methoxy-3-ethoxydiphenyl ether	23
2-Methoxy-2'-ethoxydiphenyl ether	91—92		

* King, J., 1936, 1279.

Experimental.

2 : 2'-*Diethoxydiphenyl Ether.*—Guaiethol (8·2 g.; 1·5 mols.), *o*-bromophenetole (7·9 g.; 1·0 mol.), potassium hydroxide (3·3 g.; 1·5 mols.), and copper bronze (0·3 g.) were heated at 190—200° for 30 minutes. An ethereal extract of the reaction mixture was washed with 2N-sodium hydroxide until the alkaline washings were colourless. The residue from the ethereal solution gave on distillation a small fraction, b. p. below 100°/15 mm., and a main fraction of 2 : 2'-*diethoxydiphenyl ether* (2·6 g.), b. p. 140—145°/0·5 mm. This solidified readily and separated from absolute alcohol in large columnar crystals, m. p. 53° (Found : C, 74·0, 74·2; H, 7·0, 7·1. $C_{16}H_{18}O_3$ requires C, 74·4; H, 7·0%).

2-*Methoxy*-2'-*ethoxydiphenyl ether* was prepared in a similar way from *o*-bromoanisole (9·3 g.)

and obtained as an oil which solidified (3·6 g.), b. p. 150°/0·6 mm. It crystallised from alcohol in clusters of stout rods, m. p. 91—92° (Found : C, 73·0, 72·9; H, 6·4, 6·2. $C_{15}H_{16}O_3$ requires C, 73·7; H, 6·6%).

Vanillic Acid.—*O*-Acetylvanillin (Pisovschi, *Ber.*, 1910, **43**, 2139) (38·8 g.) was dissolved in stabilised acetone (250 c.c.) and water (200 c.c.), and the mechanically stirred solution treated with finely powdered permanganate (46 g.) until the pink colour persisted. The solution was warmed and filtered, the manganese oxides extracted twice with hot water, and the combined solutions concentrated and acidified, giving an 86% yield of *O*-acetylvanillic acid, m. p. 144°. The acid (34·7 g.) was dissolved in 2N-sodium hydroxide (3 mols.) at room temperature and, after the slight exothermic action was over, the solution was acidified; the yield of vanillic acid was practically quantitative.

5-*Bromo*-3-*methoxy*-4-*ethoxybenzoic Acid.*—5-Bromovanillic acid * (49·4 g.), prepared by Robertson's method (J., 1908, **93**, 792), in 2N-sodium hydroxide (150 c.c.) was heated at 90° and ethyl sulphate (92·4 g.) and 2N-sodium hydroxide (200 c.c.) were run simultaneously into the mechanically stirred solution during 25 minutes. The *ethyl* ester (III) was extracted from the alkaline solution with ether and distilled; yield 33·6 g., m. p. 25—26°, b. p. 197°/15 mm. (Found : C, 47·8, 47·7; H, 5·3, 5·2. $C_{12}H_{15}O_4Br$ requires C, 47·5; H, 5·0%). The main alkaline solution on acidification gave 5-*bromo*-3-*methoxy*-4-*ethoxybenzoic acid* (24·1 g.), which crystallised from 40% aqueous ethyl alcohol in needles, m. p. 141—142° (Found : C, 44·0, 43·8; H, 4·3, 4·1; Br, 28·6, 28·7. $C_{10}H_{11}O_4Br$ requires C, 43·6; H, 4·0; Br, 29·1%).

Syntheses of 5-*Carboxy*-3-*methoxy*-2-*ethoxydiphenyl Ether* (V).—Potassium (1·95 g.; 1·5 mols.) was dissolved in absolute alcohol (25 c.c.), phenol (4·7 g.; 1·5 mols.) added, and the solution evaporated to dryness. Copper powder (0·4 g.) and ethyl 5-bromo-3-methoxy-4-ethoxybenzoate (10·1 g.; 1·0 mol.) were then added, and the mixture heated in an oil bath at 180—190° for 6 hours; it solidified as soon as this temperature was reached, but gradually liquefied on continued heating. The product, after cooling, was boiled with 10% methyl-alcoholic potassium hydroxide for 1 hour, the alcohol removed, and water added. The solution was saturated with carbon dioxide, extracted with ether to remove phenolic substances (2·8 g.), and acidified; the voluminous precipitate obtained, owing to its sparing solubility in ether, was collected partly by filtration, giving solid (A), and the remainder by ether extraction. The solid (A) (2·35 g.), m. p. 196°, proved to be *O*-ethylvanillic acid (IV) (Found : C, 61·2, 61·4; H, 6·0, 6·0. Calc. : C, 61·2; H, 6·2%). Its identity was confirmed by direct comparison with an authentic specimen. The ethereal extract gave a mixture of acids (6·45 g.), which on titration with N-sodium hydroxide required 21·7 c.c. for neutralisation. Eight successive portions of N-hydrochloric acid (each 3 c.c.) were now added, followed by ether extraction after each addition. Of the eight fractions thus obtained, the first five were mainly composed of an acid melting just above 100°, and the last three were mainly crude *O*-ethylvanillic acid. The first five fractions were combined (4·65 g.), and on extraction with low-boiling petroleum (Soxhlet) gave 5-*carboxy*-3-*methoxy*-2-*ethoxydiphenyl ether* (3·0 g.), which was sparingly soluble in petrol or ligroin, but crystallised from 80% alcohol, in which it was readily soluble, in small needles, m. p. 116—117° (Found : C, 67·0, 67·1; H, 5·6, 5·7. $C_{16}H_{16}O_5$ requires C, 66·6; H, 5·6%).

3-*Methoxy*-2-*ethoxydiphenyl Ether* (I).—The preceding acid (2·0 g.), quinoline (30 c.c.), and copper powder (2·0 g.) were boiled together for 1 hour. An ethereal extract of the product was washed with acid and with alkali and distilled; the oil (1·6 g.) obtained gave 3-*methoxy*-2-*ethoxydiphenyl ether* (1·4 g.), b. p. 155°/2 mm., which solidified at 0° after a few days. It separated from ethyl alcohol, in which it was very readily soluble, in bold crystals, m. p. 33—34° (Found : C, 73·5, 73·3; H, 6·8, 6·6. $C_{15}H_{16}O_3$ requires C, 73·7; H, 6·6%).

4-*Acetoxy*-3-*ethoxybenzaldehyde.*—4-Hydroxy-3-ethoxybenzaldehyde ("vanbeenol", W. J. Bush and Co.) (16·6 g.) was dissolved in N-potassium hydroxide (100 c.c.) and treated with acetic anhydride (11·2 g.). A colourless oil separated on shaking and, after being warmed for a short time in the water-bath, crystallised on cooling; yield 92%. For analysis the *aldehyde* was crystallised from petrol, forming clear tablets, m. p. 48—49° (Found : C, 63·3, 63·3; H, 5·7, 5·8. $C_{11}H_{12}O_4$ requires C, 63·4; H, 5·8%).

4-*Acetoxy*-3-*ethoxybenzoic Acid.*—The preceding aldehyde (20·1 g.) in stabilised acetone (110 c.c.) and water (70 c.c.) was treated at room temperature with finely powdered potassium permanganate (23 g.) until a permanent pink colour was obtained. The solution was filtered and the manganese oxides were extracted twice with boiling water. All filtrates were combined and after concentration were acidified; 4-*acetoxy*-3-*ethoxybenzoic acid* (18·2 g.) then separated.

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* Robertson gives m. p. 221°, but we find m. p. 231°.

For analysis a portion was crystallised from 85 parts of boiling water, forming long slender needles, m. p. 152—153° (Found: C, 58·7, 58·8; H, 5·4, 5·5. $C_{11}H_{12}O_5$ requires C, 58·9; H, 5·4%).

4-Hydroxy-3-ethoxybenzoic Acid.—The corresponding acetoxy-compound (22·4 g.) was dissolved in 2N-sodium hydroxide (150 c.c.) and kept for 1 hour. On acidification *4-hydroxy-3-ethoxybenzoic acid* separated (17·6 g.). It was soluble in 30 vols. of boiling water and separated in feathery crystals, m. p. 164—165° (Found: C, 59·2, 59·0; H, 5·4, 5·5. $C_9H_{10}O_4$ requires C, 59·3; H, 5·5%).

5-Bromo-4-hydroxy-3-ethoxybenzoic Acid.—The above hydroxy-acid (9·1 g.) and anhydrous sodium acetate (4·1 g.) were dissolved in purified glacial acetic acid (84 c.c.) and treated dropwise with a 30% solution of bromine (8 g.) in acetic acid (27 c.c.). On dilution with water to dissolve sodium bromide, the *bromo-acid* (8·75 g.) was left undissolved. On concentration of the mother-liquor a further 3·15 g. were obtained. For analysis the acid was crystallised from 12 vols. of boiling 50% alcohol, forming needles or plates, m. p. 207° (Found for freshly crystallised material: loss at 120°, 17·4. $C_9H_9O_4Br,3H_2O$ requires H_2O, 17·2%. Found for material which had been kept for a few days: C, 34·4, 34·4; H, 4·7, 4·6. $C_9H_9O_4Br,2H_2O$ requires C, 34·3; H, 4·2%). The crude bromo-acid from the mother-liquor contained a substance insoluble in sodium bicarbonate solution; it crystallised readily in clusters of needles from 5 parts of boiling methyl alcohol and proved to be 2 : *4-dibromo-6-ethoxyphenol*, m. p. 110° (Found: C, 32·7, 32·8; H, 2·9, 2·8; Br, 53·4, 53·8. $C_8H_8O_2Br_2$ requires C, 32·4; H, 2·7; Br, 54·0%).

5-Bromo-4-methoxy-3-ethoxybenzoic Acid and its Methyl Ester.—A solution of the bromohydroxyethoxy-acid (13·0 g.) in 2N-sodium hydroxide (37·5 c.c.) was heated to 90° and vigorously stirred while methyl sulphate (18·9 g.) and 2N-sodium hydroxide (37·5 c.c.) were run in simultaneously during 15 minutes, a further 20 c.c. of 2N-alkali being finally added. The crystalline solid obtained on cooling was taken up in ether and washed with small portions of 2N-alkali and finally with water. On removal of the solvent the residue of *methyl 5-bromo-4-methoxy-3-ethoxybenzoate* crystallised (11·5 g.). For analysis it was crystallised from its own volume of methyl alcohol, forming flattened needles or plates, m. p. 77—78° (Found: C, 45·8, 45·6; H, 4·6, 4·4. $C_{11}H_{13}O_4Br$ requires C, 45·7; H, 4·5%). The aqueous alkaline mother-liquor and washings were combined and acidified and gave *5-bromo-4-methoxy-3-ethoxybenzoic acid* (2·5 g.). It was crystallised first from 7 parts of boiling ethyl acetate and then from 1600 parts of boiling water. From both solvents it separated in fine woolly needles, m. p. 183—184° (Found: C, 44·0, 44·0; H, 4·1, 4·0. $C_{10}H_{11}O_4Br$ requires C, 43·6; H, 4·0%).

From the accumulated acid fractions of several experiments, a small fraction was isolated which was insoluble in sodium bicarbonate solution. This proved to be *methyl 5-bromo-4-hydroxy-3-ethoxybenzoate* and formed pearly elongated leaflets, m. p. 111—112°, from 6 vols. of boiling methyl alcohol (Found: C, 44·0, 44·1; H, 4·1, 4·0. $C_{10}H_{11}O_4Br$ requires C, 43·6; H, 4·0%).

Condensation of Methyl 5-Bromo-4-methoxy-3-ethoxybenzoate with Potassium Phenoxide.—Potassium (2·92 g.; 1·5 mols.) was dissolved in absolute ethyl alcohol (Manske, *J. Amer. Chem. Soc.*, 1931, **53**, 1106), and phenol (7·05 g.; 1·5 mols.) added. The solution was evaporated to dryness in a vacuum with the aid of heat, and the residue was mixed with copper powder (0·5 g.) and the bromomethoxyethoxy-ester (14·45 g.; 1 mol.) and heated (oil-bath) at 180° for 6 hours, the small amounts of alcohol liberated being removed by a current of air. The cooled melt was boiled with methyl-alcoholic potassium hydroxide for 1 hour, and the alcohol removed. The residue was diluted with water, saturated with carbon dioxide, extracted with ether to remove phenolic substances, acidified, and extracted with ether, which left a crystalline residue (11·0 g.) on evaporation. This was exactly neutralised with N-sodium hydroxide (41 c.c.) and then fractionally acidified with nine 5 c.c. portions of N-hydrochloric acid, each addition of acid being followed by ether extraction with 20 c.c. each time. Of the nine fractions of solidified acids thus obtained, the first five showed a similar m. p. among themselves and the last four had a higher m. p. The first five fractions were combined (6·6 g.) and extracted (Soxhlet) with light petroleum (b. p. 60—80°), from which a crystalline acid (5·37 g.) slowly separated in crusts, m. p. 110—113°. It was recrystallised from 80% aqueous alcohol, forming bold plates which had two m. p.'s, 117—118° and 134°. Sometimes the lower m. p. was not observed. This acid proved to be *5-phenoxy-4-methoxy-3-ethoxybenzoic acid* (Found: C, 66·6, 66·8; H, 5·6, 5·8. $C_{16}H_{16}O_5$ requires C, 66·6; H, 5·6%).

The last four fractions from the above separation were combined and crystallised from 133 parts of boiling water; *4-methoxy-3-ethoxybenzoic acid* separated in woolly needles, m. p. 165° (Found: C, 61·2, 61·4; H, 6·3, 6·3. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·2%).

2-Methoxy-3-ethoxydiphenyl Ether.—5-Phenoxy-4-methoxy-3-ethoxybenzoic acid (20 g.) was boiled for 1 hour with synthetic quinoline (30 c.c.) and copper powder (2 g.). An ethereal solution of the reaction mixture was filtered from copper powder and extracted with 3N-acid and with 2N-alkali to remove basic and acidic substances. The oil (1·45 g.) left on removal of the ether was distilled at 0·5 mm. and gave 1·08 g., b. p. 138—141°. On keeping below 0°, *2-methoxy-3-ethoxydiphenyl ether* solidified; crystallised from a very small volume of alcohol, it had m. p. 23° (Found: C, 73·9; H, 6·8. $C_{15}H_{16}O_3$ requires C, 73·7; H, 6·6%).

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