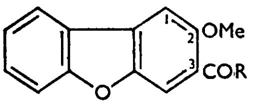
822. *Oxygen Heterocycles. Part VI.* Orientation in the Substitution of 2-Methoxydibenzofuran.*

By Cl. Routier, Ng. Ph. Buu-Hoï, and R. Royer.

2-Methoxydibenzofuran undergoes Friedel–Crafts reactions with aliphatic acid chlorides and succinic anhydride at the 3-position, and with benzoyl chloride and phthalic anhydride at another position; formylation with dimethylformamide occurs at the 3-position. Many new dibenzofuran derivatives have been prepared.

The orientation in reactions with 2-methoxybenzofuran is of interest in view of the many possible sites for substitution. Gilman and Van Ess [1] found that bromination gave predominantly 3-bromo-2-methoxydibenzofuran, with traces of the 1-bromo-derivative, and Schimmelschmidt [2] found that nitration likewise occurs at the 3-position. No studies had yet been made of orientation in its Friedel–Crafts reactions.

Reaction of acetyl chloride with 2-methoxydibenzofuran in the presence of aluminium chloride in nitrobenzene yielded the 3-acetyl derivative (I; R = Me), whose structure was proved by conversion with sodium hypobromite into the known 3-carboxy-2-methoxydibenzofuran. Similarly, propionylation and butyrylation gave the 3-acyl compounds. Succinoylation with succinic anhydride afforded γ-(2-methoxy-3-dibenzofuryl)-γ-oxobutyric acid, whose constitution was established by decarboxylation to 2-methoxy-3-propionyldibenzofuran. The orientation was different in acylation with benzoyl chloride, even under the same experimental conditions, and an *x*-benzoyl-2-methoxydibenzofuran was obtained, which differed from the 3-benzoyl derivative (I; R = Ph) prepared by Friedel–Crafts reaction of the chloride of 2-methoxydibenzofuryl-3-carboxylic acid with benzene. Phthaloylation with phthalic anhydride gave a keto-acid which was decarboxylated to a ketone identical with the product of direct benzoylation of 2-methoxydibenzofuran. The dissimilar behaviour of aliphatic and aromatic acid chlorides and anhydrides is reminiscent of the acylation of 2-methoxynaphthalene.[3]



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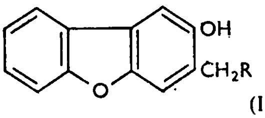

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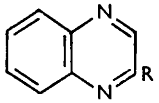

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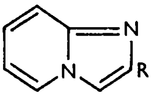

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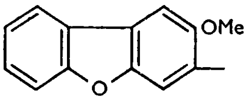

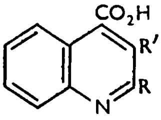

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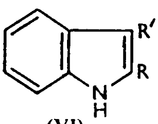

(VI)

2-Methoxydibenzofuran with dimethylformamide in the presence of phosphorus oxychloride gave 3-formyl-2-methoxydibenzofuran (I; R = H); its oxime was dehydrated

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* Part V, Lescot, Buu-Hoï, and Xuong, *J.*, 1956, 2408.

[1] Gilman and van Ess, *J. Amer. Chem. Soc.*, 1939, **61**, 1365.

[2] Schimmelschmidt, *Annalen*, 1950, **566**, 184.

[3] Cf. Fierz-David and Jaccard, *Helv. Chim. Acta*, 1928, **11**, 1042; Haworth and Sheldrick, *J.*, 1934, 864.

with acetic anhydride to a nitrile identical with that prepared [4] by a Sandmeyer reaction from 3-amino-3-methoxydibenzofuran.

Wolff–Kishner–Huang-Minlon reduction [5] of 3-acetyl- and 3-propionyl-2-methoxydibenzofuran readily afforded the 3-ethyl- and the 3-*n*-propyl-compound, whose demethylation with pyridine hydrochloride yielded 3-ethyl-2-hydroxy- (II; R = Me) and 2-hydroxy-3-*n*-propyl-dibenzofuran (II; R = Et). γ-(2-Methoxy-3-dibenzofuryl)-γ-oxobutyric acid was also reduced to γ-3-(2-methoxydibenzofuryl)butyric acid, but reduction of 3-butyryl-2-methoxydibenzofuran under the same conditions was accompanied by complete demethylation, to 3-*n*-butyl-2-hydroxydibenzofuran (II; R = Pr^n).

The preferential homonuclear 3-substitution in 2-methoxybenzofuran brought to light is in line with recent observations on similar nuclei such as carbazole or dibenzoselenophen.[6] 3-Acetyl-2-methoxydibenzofuran was brominated in the side chain, as shown by the formation of a quaternary picolinium salt;[7] further, 3-bromoacetyl-2-methoxydibenzofuran with *o*-phenylenediamine [8] gave the quinoxaline (III), and with 2-aminopyridine [9] the hydrobromide of the glyoxalinopyridine (IV).

The use of 3-acyl-2-methoxydibenzofurans for the preparation of various nitrogen-containing heterocycles was investigated. Pfitzinger reactions with isatin gave an interesting example of steric hindrance,[10] 3-acetyl-2-methoxydibenzofuran affording a 40% yield of the corresponding cinchoninic acid (V; R′ = H) after 75 hours' heating, whereas the higher homologue (I; R = Et) gave only 10% of the acid (V; R′ = Me) after 100 hours' heating, and the next higher homologue (I; R = Pr) gave no trace of the cinchoninic acid even after 150 hours. In the indole series, 2-(2-methoxy-3-dibenzofuryl)indole (VI; R′ = H) and the 3-ethyl homologue (VI; R′ = Et) were obtained by Fischer cyclisation of phenylhydrazones of the appropriate ketones; demethylation with pyridine hydrochloride gave the corresponding phenolic indoles.

EXPERIMENTAL

3-*Acetyl*-2-*methoxydibenzofuran* (I; R = Me).—To an ice-cooled, stirred solution of 2-methoxydibenzofuran (45 g.; prepared by methylation of the hydroxy-compound with aqueous sodium hydroxide and dimethyl sulphate) and acetyl chloride (20 g.) in dry nitrobenzene (150 c.c.), finely powdered aluminium chloride (35 g.) was added in small portions; after 14 hr. at room temperature, the mixture was poured into water, and the nitrobenzene removed in steam. Benzene was added, the benzene solution washed with aqueous sodium hydroxide, then with water, and dried (Na_2SO_4), the solvent removed, and the residue distilled *in vacuo*. The *ketone* (42 g.) formed colourless prisms, m. p. 125°, from *cyclo*hexane, giving a yellow halochromy in sulphuric acid (Found: C, 74·9; H, 5·1. $C_{15}H_{12}O_3$ requires C, 75·0; H, 5·0%).

2-*Methoxydibenzofuran*-3-*carboxylic Acid*.—A solution of the foregoing ketone (20 g.) in dioxan (200 c.c.) was shaken for 4 hr. at room temperature with aqueous sodium hypobromite prepared from bromine (12 c.c.) and sodium hydroxide (25 g. in 100 c.c. of water). The aqueous layer was decanted off, treated with aqueous sodium hydrogen sulphite, concentrated *in vacuo*, filtered, and acidified with hydrochloric acid. The precipitated acid (10 g.) formed colourless needles, m. p. 207°, from benzene (Found: C, 69·5; H 4·0. Calc. for $C_{14}H_{10}O_4$: C, 69·4; H, 4·1%). Gilman and van Ess [1] gave m. p. 206—207° for the acid prepared by a Grignard reaction with 3-bromo-2-methoxydibenzofuran and carbon dioxide.

3-*Ethyl*-2-*methoxydibenzofuran*.—A mixture of 3-acetyl-2-methoxydibenzofuran (10 g.), 98% hydrazine hydrate (3 g.), and diethylene glycol (200 c.c.) was heated for 10 min., and after addition of potassium hydroxide (3 g.), refluxed for 2 hr. with removal of water. After cooling and dilution with water, the product was taken up in ether and purified by distillation *in vacuo*, to give a *product* (7 g.), b. p. 197—200°/12 mm., forming colourless leaflets, m. p. 48°, from aqueous ethanol (Found: C, 79·6; H, 6·3. $C_{15}H_{14}O_2$ requires C, 79·6; H, 6·2%).

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[4] Moualin and Venkataraman, *J. Sci. Ind. Res., India*, 1945, **3**, 447.

[5] Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **67**, 2478.

[6] Sawicki, *J. Amer. Chem. Soc.*, 1954, **76**, 664; *J. Org. Chem.*, 1954, **19**, 608.

[7] Tschitschibabin, *Ber.*, 1927, **60**, 1607.

[8] Hinsberg, *Annalen*, 1896, **292**, 246; Buu-Hoï and Khôi, *Bull. Soc. chim. France*, 1950, **17**, 753; Buu-Hoï, Lavit, and Xuong, *J. Org. Chem.*, 1954, **19**, 1617.

[9] Tschitschibabin *et al.*, *Ber.*, 1925, **58**, 1704; 1926, **59**, 2048; 1931, **64**, 2842.

[10] Buu-Hoï, Royer, Xuong, and Jacquignon, *J. Org. Chem.*, 1953, **18**, 1209; Buu-Hoï and Cagniant, *Bull. Soc. chim. France*, 1946, **13**, 123.

3-*Ethyl*-2-*hydroxydibenzofuran* (II; R = Me).—A mixture of the foregoing ether (6 g.) and pyridine hydrochloride (6 g.) was gently refluxed for 30 min., and water added after cooling; the precipitate (5 g.) formed long, colourless needles, m. p. 109—110°, from aqueous ethanol (Found: C, 79·3; H, 5·6. $C_{14}H_{12}O_2$ requires C, 79·2; H, 5·7%).

2-*Methoxy*-3-*propionyldibenzofuran* (I; R = Et).—This *ketone* (21·5 g.), prepared from 2-methoxydibenzofuran (20 g.), propionyl chloride (11 g.), and aluminium chloride (16 g.) as for the lower homologue, crystallised as prisms, b. p. 238°/12 mm., m. p. 123°, from *cyclo*hexane (Found: C, 75·5; H, 5·4. $C_{16}H_{14}O_3$ requires C, 75·6; H, 5·6%). Reduction of this ketone (10 g.) with hydrazine hydrate afforded 2-*methoxy*-3-n-*propyldibenzofuran* (7·5 g.), b. p. 220—222°/12 mm., forming plates, m. p. 44°, from light petroleum (b. p. 35—45°) (Found: C, 80·3; H, 6·5. $C_{16}H_{16}O_2$ requires C, 80·0; H, 6·7%); demethylation of this ether (4 g.) with pyridine hydrochloride (4 g.) gave 2-*hydroxy*-3-n-*propyldibenzofuran* (3·5 g.), crystallising as needles, m. p. 103—104°, from aqueous ethanol (Found: C, 79·9; H, 6·2. $C_{15}H_{14}O_2$ requires C, 79·6; H, 6·2%).

3-n-*Butyryl*-2-*methoxydibenzofuran* (I; R = Pr^n).—This *ketone* (11·5 g.), prepared from 2-methoxydibenzofuran (10 g.), *n*-butyryl chloride (7 g.), and aluminium chloride (8 g.), formed needles, m. p. 123°, b. p. 245—247°/12 mm., from *cyclo*hexane (Found: C, 76·3; H, 6·0. $C_{17}H_{16}O_3$ requires C, 76·1; H, 6·0%). Its reduction was accompanied by demethylation and gave 3-n-*butyl*-2-*hydroxydibenzofuran* (II; R = Pr), prisms, m. p. 101° (from aqueous ethanol) (Found: C, 80·2; H, 6·6. $C_{16}H_{16}O_2$ requires C, 80·0; H, 6·7%).

γ-(2-*Methoxy*-3-*dibenzofuryl*)-γ-*oxobutyric Acid*.—Into an ice-cooled suspension of 2-methoxydibenzofuran (21 g.) and succinic anhydride (13 g.) in nitrobenzene (150 c.c.), aluminium chloride (17 g.) was stirred in small portions; after 12 hr. at room temperature, followed by 15 min. at 50—60°, the mixture was poured on ice, the nitrobenzene removed in steam, and the *keto-acid* purified *via* its sodium salt. After recrystallisation, first from aqueous acetic acid, then from benzene, it formed prisms (20 g.), m. p. 195—196° (Found: C, 68·3; H, 4·4. $C_{17}H_{14}O_5$ requires C, 68·5; H, 4·7%). Reduction of this acid (13·5 g.) with hydrazine hydrate (9 g.) and potassium hydroxide (9 g.) in diethylene glycol (200 c.c.) afforded γ-(2-*methoxy*-3-*dibenzofuryl*)*butyric acid* (7 g.), m. p. 59—60° (from light petroleum) (Found: C, 71·6; H, 5·5. $C_{17}H_{16}O_4$ requires C, 71·8; H, 5·7%).

3-*Benzoyl*-2-*methoxydibenzofuran* (I; R = Ph).—2-Methoxydibenzofuran-3-carboxylic acid (7 g.; prepared by dimethylation of commercial 2-hydroxy-acid with aqueous sodium hydroxide and dimethyl sulphate, and subsequent saponification of methyl 2-methoxydibenzofuran-3-carboxylate) was converted by thionyl chloride into its solid chloride; a solution of this in dry benzene (200 c.c.) was treated with aluminium chloride (5 g.), and the mixture kept for 12 hr. at room temperature, refluxed for 1 hr., then worked up in the usual way. The *ketone* (3 g.) formed colourless prisms, m. p. 133—134°, from *cyclo*hexane (Found: C, 79·2; H, 4·4. $C_{20}H_{14}O_3$ requires C, 79·5; H, 4·7%).

x-*Benzoyl*-2-*methoxydibenzofuran*.—To a water-cooled solution of 2-methoxydibenzofuran (8 g.) and benzoyl chloride (6 g.) in dry nitrobenzene (100 c.c.), aluminium chloride (5 g.) was added in small portions with stirring, and the mixture left for 14 hr. at room temperature, then worked up in the usual way. The *ketone* (7 g.) obtained, b. p. 270—275°/12 mm., crystallised from *cyclo*hexane, as needles, m. p. 124°, whose solutions in sulphuric acid were yellow (Found: C, 79·4; H, 4·8%). The m. p. was strongly depressed on admixture with 3-benzoyl-2-methoxydibenzofuran. The most probable positions entered by the benzoyl substituent are positions 1 or 8.

x-o-*Carboxybenzoyl*-2-*methoxydibenzofuran*.—This *compound* (11 g.), prepared from phthalic anhydride (9 g.), 2-methoxydibenzofuran (10 g.), and aluminium chloride (9 g.) in nitrobenzene (150 c.c.) as for the succinoylation, crystallised as colourless, sublimable needles, m. p. 236° (Found: C, 72·5; H, 3·9. $C_{21}H_{14}O_5$ requires C, 72·8; H, 4·1%). Heating of a mixture of it with lime gave a ketone, which melted at 124°, alone or mixed with the foregoing *x*-benzoyl-2-methoxydibenzofuran.

3-*Formyl*-2-*methoxydibenzofuran* (I; R = H).—A mixture of 2-methoxydibenzofuran (19·5 g.), dimethylformamide (10 g.), and phosphorus oxychloride (20 g.) was cautiously heated until a reaction set in; the mixture, which became brown, was then heated for a further 6 hr. on a water-bath, and, after addition of saturated aqueous sodium acetate in excess and further refluxing for a few min., the product was taken up in chloroform and fractionated *in vacuo*. The *aldehyde* (5·5 g.), b. p. 237—240°/12 mm., formed needles, m. p. 165°, from *cyclo*hexane, giving an orange halochromy in sulphuric acid (Found: C, 74·6; H, 4·7. $C_{14}H_{10}O_3$ requires C, 74·3; H, 4·5%). The corresponding *aldoxime* crystallised as prisms, m. p. 199—200°, from aqueous ethanol (Found : N, 5·7. $C_{14}H_{11}O_3N$ requires N, 5·8%). A solution of this oxime (2 g.) in acetic anhydride (150 c.c.) was refluxed for 5 hr., and then treated with dilute aqueous sodium hydroxide; the precipitate was collected and crystallised from methanol, giving 3-cyano-2-methoxydibenzofuran, colourless, sublimable needles, m. p. 208° (lit.,[4] m. p. 200°) (Found : N, 6·0. Calc. for $C_{14}H_9O_2N$: N, 6·2%). Hydrolysis of this nitrile with sodium hydroxide in ethanol yielded 2-methoxydibenzofuran-3-carboxylic acid, m. p. 207° alone or mixed with a sample prepared from 2-hydroxydibenzofuran-3-carboxylic acid.

3-*Bromoacetyl*-2-*methoxydibenzofuran*.—To a solution of 3-acetyl-2-methoxydibenzofuran (9 g.) in acetic acid (200 c.c.), bromine (7 g.) was added dropwise with stirring, and the mixture left for 5 hr. until dissolution occurred, then poured into water. The precipitate was collected, washed with water, and crystallised from ethanol, giving cream-coloured needles (7 g.), m. p. 164—165° (Found : C, 56·3; H, 3·5. $C_{15}H_{11}O_3Br$ requires C, 56·4; H, 3·4%). The corresponding quaternary 2-*picolinium bromide*, prepared by refluxing for 2 hr. a solution in ethanol (20 c.c.) of this bromo-ketone (2 g.) and α-picoline (0·6 g.), crystallised as large, colourless prisms, m. p. 256—257° (decomp.), from aqueous ethanol (Found : N, 3·6. $C_{21}H_{18}O_3NBr$ requires N, 3·4%); treatment of a boiling aqueous solution of this salt (1 g.) with sodium hydrogen carbonate (5 g.) yielded 2-(2-*methoxy*-3-*dibenzofuryl*)*pyrrocoline* (0·5 g.), forming yellowish needles, m. p. 134°, from ethanol (Found : N, 4·2. $C_{21}H_{15}O_2N$ requires N, 4·4%).

2-(2-*Methoxy*-3-*dibenzofuryl*)*quinoxaline* (III).—A mixture of the foregoing ω-bromo-ketone (1 g.), *o*-phenylenediamine (0·4 g.), and sodium acetate (0·5 g.) in ethanol (150 c.c.) was refluxed for 5 hr., water was added, and the precipitate collected and recrystallised from ethanol, giving yellowish needles, m. p. 92—93° (Found : N, 8·3. $C_{21}H_{14}O_2N_2$ requires N, 8·6%).

4-(2-*Methoxy*-3-*dibenzofuryl*)*pyridino*(1′ : 2′-1 : 2)*glyoxaline Hydrobromide*.—A mixture of the bromo-ketone (1 g.) and 2-aminopyridine (0·3 g.) in ethanol (15 c.c.) was refluxed for 12 hr. The *salt* precipitated on cooling formed fine, yellowish prisms (0·6 g.), m. p. 310° (decomp.), from ethanol (Found : N, 7·0; Br, 20·0. $C_{20}H_{15}O_2N_2Br$ requires N, 7·1; Br, 20·3%).

2-(2-*Methoxy*-3-*dibenzofuryl*)*indole* (VI; R = H).—A mixture of 3-acetyl-2-methoxydibenzofuran (5 g.) and phenylhydrazine (2·5 g.) was heated for 15 min. at 120° with removal of water; finely powdered anhydrous zinc chloride (5 g.) was then added, and heating renewed at 180° for 20 min. After cooling, dilute aqueous acetic acid was added; the product was then taken up in benzene, the benzene solution washed with water and dried (Na_2SO_4), the solvent distilled off, and the solid residue recrystallised from ethanol (charcoal), giving long, colourless needles, m. p. 168° (Found : C, 80·2; H, 5·0; N, 4·6. $C_{21}H_{15}O_2N$ requires C, 80·5; H, 4·8; N, 4·5%). It gave benzene solutions with a strong violet fluorescence, and a brown picrate.

2-(2-*Hydroxy*-3-*dibenzofuryl*)*indole*.—A mixture of the foregoing indole (2 g.) and redistilled pyridine hydrochloride (6 g.) was refluxed for 15 min., and water was added after cooling. The precipitate formed was converted into the sodium salt, which formed yellowish leaflets from hot water. Decomposition of this salt with aqueous acetic acid gave an *indole*, crystallising as yellowish, oxidisable prisms (1 g.), m. p. 234—235° (decomp.) (Found : N, 4·9. $C_{20}H_{13}O_2N$ requires N, 4·7%).

3-*Ethyl*-2-(2-*methoxy*-3-*dibenzofuryl*)*indole* (VI; R = Et).—Prepared from 3-*n*-butyryl-2-methoxydibenzofuran (5 g.), phenylhydrazine (2 g.), and zinc chloride (5 g.) as for the lower homologue, this *indole* (2 g.) formed yellowish prisms, m. p. 150°, from ethanol (Found : C, 80·6; H, 5·4. $C_{23}H_{19}O_2N$ requires C, 80·9; H, 5·6%). 3-*Ethyl*-2-(2-*hydroxy*-3-*dibenzofuryl*)*indole* formed yellowish, oxidisable prisms, m. p. 191° (decomp.), from benzene (Found : N, 4·0. $C_{22}H_{17}O_2N$ requires N, 4·3%).

2-(2-*Methoxy*-3-*dibenzofuryl*)*cinchoninic Acid* (V; R′ = H).—A solution of isatin (2·6 g.), 3-acetyl-2-methoxydibenzofuran (5 g.), and ethanol (50 c.c.) was refluxed with potassium hydroxide (3·5 g.; dissolved in the minimum of water) for 75 hr.; the mixture was diluted with water, the neutral impurities removed by ether-extraction, and the aqueous layer acidified with acetic acid. The precipitate formed fine, yellowish prisms (3·2 g.), subliming above 230°, m. p. 260°, from aqueous acetic acid (Found : C, 74·5; H, 4·0; N, 3·9. $C_{23}H_{15}O_4N$ requires C, 74·8; H, 4·1; N, 3·8%). Thermal decarboxylation of this acid gave 2-(2-*methoxy*-3-*dibenzofuryl*)*quinoline*, forming pale yellow needles, m. p. 175°, from ethanol (Found : N, 4·4. $C_{22}H_{15}O_2N$ requires N, 4·3%).

2-(2-*Methoxy*-3-*dibenzofuryl*)-3-*methylcinchoninic Acid* (V; R′ = Me).—This *acid* (0·3 g.), obtained after 100 hours' refluxing, formed fine, yellowish prisms, m. p. 317—318°, from aqueous acetic acid (Found : C, 75·0; H, 4·5; N, 3·6. $C_{24}H_{17}O_4N$ requires C, 75·2; H, 4·5; N, 3·7%).

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

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