Potentially Chemotherapeutic Dibenzofurans

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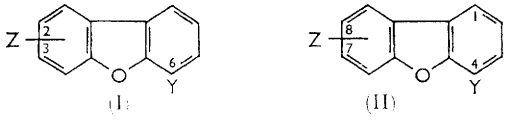
A number of new, mainly 2,6- and 3,6-disubstituted, dibenzofurans have been prepared for evaluation of their chemotherapy, and for use in further syntheses.

ANTIBACTERIAL [1,2] and other useful activity [3] has been associated with the dibenzofuran nucleus. Notwithstanding considerable work by Gilman [4] and others,[5] comparatively few derivatives of this ring system are known, as there are 16 possible disubstituted isomers of the type $C_{12}H_6OY_2$ and 28 of the type $C_{12}H_6OYZ$. Starting from the known methyl 2- and 3-nitrodibenzofuran-6-carboxylates,[6] we have prepared the new compounds (I) in the Table.



(I) (II)

Compounds (I)

Y		Z (2- and 3-)	
$CO{\cdot}NH{\cdot}NH_2$	NH_2	NHAc	NO_2
$CO{\cdot}NH{\cdot}NH_2$	NH_2	OMe	NH_2
OH	OMe	NHAc	NO_2
OAc	NHAc	OMe	NHAc
		Z (3- only)	
Cl	$CO{\cdot}NH_2$		NO_2
$CO{\cdot}N_3$	$NH{\cdot}CO_2Me$		NO_2
NH_2	CO_2H		NHAc

The nitro-esters reacted readily with hydrazine, giving the nitro-acid hydrazines. The isomer (I; Y = $CO{\cdot}NH{\cdot}NH_2$, Z = 3-NO_2) was converted into the azide, which was stable and not satisfactory for the preparation of the isocyanate. However, it reacted with methanol, giving the urethane, but this was not hydrolysed smoothly to the amine. Starting with the nitroacids, the Schmidt reaction gave the amines (I; Y = NH_2, Z = 2- and 3-NO_2) in good yield. The amide (I; Y = $CO{\cdot}NH_2$, Z = 3-NO_2), prepared to explore the Hofmann reaction, was therefore not investigated as a route to the nitro-amine. The nitro-amines, by standard reactions, gave access to the other compounds listed in the Table.

Our 3,6-diamine (m. p. 221°) did not correspond to a diamine (m. p. 154—155°) suggested [7] to have that

[1] S. Shibata *et al.*, *Pharm. Bull., Japan*, 1954, **2**, 45.
[2] N. M. Phatak and C. D. Leake, *J. Pharmacol.*, 1936, **58**, 155.
[3] N. B. Eddy, *J. Pharmacol.*, 1936, **58**, 159.
[4] H. Gilman *et al.*, *J. Amer. Chem. Soc.*, 1954, **76**, 5787, and preceding Papers.
[5] See "Heterocyclic Compounds," Wiley, New York, 1951, vol. II, p. 123.
[6] H. Gilman *et al.*, *J. Amer. Chem. Soc.*, 1939, **61**, 643.
[7] H. Gilman and S. Avakian, *J. Amer. Chem. Soc.*, 1945, **67**, 349.

orientation, prepared from 4,6-di-iododibenzofuran, which seems to be the 3,7-isomer [8] (m. p. 150—152°), produced by two benzyne reactions, as we were able to show that no rearrangement took place during our Schmidt reaction.

Compounds (I; Y = OMe, Z = 2- and 3-NO_2) were acetylated by the Friedel–Crafts reaction, giving ketones (II; X = Ac, Y = OMe, Z = 7- and 8-NO_2). These, after reduction to the amine, diazotisation, and elimination, give the known 1-acetyl-4-methoxydibenzofuran.[9] This confirmed the orientation of the methoxyl group, and thus the 4-amine from which it was derived, in turn obtained from a carboxyl group by the Schmidt reaction.

EXPERIMENTAL

2- *and* 3-*Nitrodibenzofuran*-6-*carbohydrazide*.—The nitro-esters [6] (8 g.), suspended in methanol (600 ml.), were refluxed for 2 hr. with hydrazine hydrate (2 ml.; 99%). The concentrated solutions, on cooling, deposited the *hydrazides* (6·2 g., 78%), m. p. 255 and 222—223°, respectively (Found: C, 57·8; H, 3·3; N, 15·3%. C, 57·9; H, 3·6; N, 15·3%. $C_{13}H_9N_3O_4$ requires C, 57·6; H, 3·3; N, 15·5%).

Dibenzofuran-4-*carbohydrazide*.—Methyl dibenzofuran-4-carboxylate (1 g.) [6] was refluxed for 1 hr. in ethanol (10 ml.) with hydrazine hydrate (1 equiv.). The concentrated solution, on cooling, deposited the *hydrazide* (0·8 g., 80%), m. p. 174°, needed as a model compound (Found: C, 69·0; H, 4·4; N, 12·4. $C_{13}H_{10}N_2O_2$ requires C, 69·0; H, 4·4; N, 12·4%).

2- *and* 3-*Aminodibenzofuran*-6-*carbohydrazide*.— The amino-esters [6] on treatment with hydrazine as above, gave the *amino-carbohydrazides* (75%), m. p. 245 and 210°, respectively (Found: C, 64·6; H, 4·6; N, 17·4%. C, 64·7; H, 4·8; N, 17·0%. $C_{13}H_{11}N_3O_2$ requires C, 64·7; H, 4·6; N, 17·4%).

3-*Nitrodibenzofuran*-6-*carbonyl Azide*.—The above hydrazide (5·4 g.), as a suspension in acetic–hydrochloric acids at 0°, was treated with a solution of sodium nitrite (2 g.) during ½ hr., with stirring. After a further ½ hr., the product was collected and dried, then refluxed in chloroform for 1 hr. Concentration gave the *azide*, m. p. 240° (decomp.) (Found: C, 55·3; H, 2·4. $C_{13}H_6N_4O_4$ requires C, 55·3; H, 2·1%). When it was refluxed for 1 hr. in methanol, it gave the *methyl urethane*, m. p. 197° (Found: C, 58·7; H, 3·6; N, 9·8. $C_{14}H_{10}N_2O_5$ requires C, 58·7; H, 3·5; N, 10·0%). This was hydrolysed very slowly by hydrochloric acid in ethanol, and in acetic acid the acetamide was produced. This amide was not readily hydrolysed to the amine which was, therefore, not easily accessible by this route.

2- *and* 3-*Nitro*-6-*aminodibenzofuran*.—The nitro-acids [6] gave the corresponding *nitro-amines* (80%), m. p. 204 and 188° (from benzene), by a modified Schmidt reaction [10] (Found: C, 63·3; H, 3·6; N, 12·2%. C, 63·1; H, 3·5; N, 12·2%. $C_{12}H_8N_2O_3$ requires C, 63·2; H, 3·5; N, 12·3%). Acetylation gave 2- and 3-*nitro*-6-*acetamidodibenzofuran*, m. p. 268 and 259°, respectively (from acetic acid–methanol) (Found: C, 62·5; H, 3·8; N, 10·4%. C, 61·8; H, 3·8; N, 10·2; O, 23·8%. $C_{14}H_{10}N_2O_4$ requires C, 62·2; H, 3·7; N, 10·4; O, 23·7%). The 2,6-isomer was brominated in acetic acid, to give 4-*acetamido*-1-*bromo*-8-*nitrodibenzofuran*, m. p. 298° (Found: Br, 22·5. $C_{14}H_9BrN_2O_4$ requires Br, 22·9%).

3-*Nitrodibenzofuran*-6-*carboxyamide*.—The acid was refluxed with thionyl chloride in benzene; evaporation and treatment with ammonia gave the *amide* which was recrystallised from acetic acid then ethanol, m. p. 295° (Found: C, 60·6; H, 3·1; N, 11·1. $C_{13}H_8N_2O_4$ requires C, 60·9; H, 3·2; N, 11·0%).

2- *and* 3-*Nitro*-6-*hydroxydibenzofuran*.—The nitro-amines (1 g.) were diazotised using a method for weak amines,[11] and the diazo-solution was added during 1 hr. to a refluxing 50% solution of copper sulphate (300 ml.). After a further 2 hr. the cooled solution was filtered and the *nitro-phenols* recrystallised from aqueous alcohol; yield 75%, m. p. 231 and 200°, respectively (Found: C, 63·1; H, 3·4; N, 6·0%. C, 62·7; H, 3·2; N, 5·9%. $C_{12}H_7NO_4$ requires C, 62·9; H, 3·1; N, 6·1%).

The above phenols, on methylation, gave 2- and 3-*nitro*-6-*methoxydibenzofuran*, m. p. 199 and 175°, respectively (Found: C, 64·1; H, 3·6; N, 5·8%. C, 64·5; H, 3·7; N, 5·8%. $C_{13}H_9NO_4$ requires C, 64·2; H, 3·7; N, 5·8%).

The 2,6-nitro-ether was brominated in acetic acid, to give 1-*bromo*-4-*methoxy*-8-*nitrodibenzofuran*, m. p. 233° (Found: Br, 24·5. $C_{13}H_8BrNO_4$ requires Br, 24·7%).

6-*Chloro*-3-*nitrodibenzofuran*.—When hydrochloric acid was used for diazotisation, no phenol was obtained. The product was the *chloro-compound*, m. p. 150° (from aqueous ethanol) (Found: C, 58·1; H, 2·3; Cl, 13·4; N, 5·6. $C_{12}H_6ClNO_3$ requires C, 58·2; H, 2·4; Cl, 14·3; N, 5·6%).

2- *and* 3-*Amino*-6-*methoxydibenzofuran*.—The nitro-ethers, above, were catalytically reduced over palladium–charcoal in ethanol, giving the *amines*, m. p. 145 and 130°, respectively [from light petroleum (b. p. 60—80°)] (Found: C, 72·9; H, 5·4; N, 6·7%. C, 72·8; H, 5·3; N, 6·5%. $C_{13}H_{11}NO_2$ requires C, 73·2; H, 5·2; N, 6·6%).

The amines were characterised as the *acetyl derivatives*, m. p. 227 and 184°, respectively (from benzene) (Found: C, 70·4; H, 5·3; N, 5·5%. C, 70·6; H, 5·5; N, 5·5%. $C_{15}H_{13}NO_3$ requires C, 70·6; H, 5·1; N, 5·5%).

2,6- *and* 3,6-*Diaminodibenzofuran*.—The nitro-amines gave the corresponding *diamines* on catalytic reduction, m. p. 156 and 221°, respectively (from ethanol) (Found: C, 72·3; H, 5·2; N, 14·0%. C, 72·8; H, 5·1; N, 13·9%. $C_{12}H_{10}N_2O$ requires C, 72·7; H, 5·1; N, 14·1%). The amines were characteristised as their *diacetyl derivatives*, m. p. 299 and 303°, respectively (from acetic acid–methanol) (Found: C, 68·4; H, 5·0; N, 9·7%. C, 67·8; H, 5·1; N, 10·2%. $C_{16}H_{14}N_2O_3$ requires C, 68·1; H, 5·0; N, 9·9%).

2- *and* 3-*Acetamido*-6-*acetoxydibenzofuran*.—The nitro-phenols were reduced with hydrogen and palladium–charcoal in ethanol. The amino-phenols were taken up in benzene after removal of the catalyst and ethanol. As they were air-sensitive, acetic anhydride was added, and, after evaporation, the residual oils were recrystallised from methanol. The *diacetates* had m. p. 239 and 230°, respectively, for the 2,6- and 3,6-isomers (Found: C, 67·8; H, 4·8; N, 4·9%. C, 67·5; H, 5·2; N, 4·6%. $C_{16}H_{13}NO_4$ requires C, 67·8; H, 4·6; N, 5·0%).

[6] Bayer & Co., D.R.P. 48,709/1889; *Frdl.*, 1905, **2**, 410.
[8] H. Gilman *et al.*, *J. Amer. Chem. Soc.*, 1939, **61**, 2836.
[10] L. H. Briggs and J. W. Lyttleton, *J. Chem. Soc.*, 1943, 421.
[11] K. Tatematsu and B. Kubora, *Bull. Chem. Soc. Japan*, 1934, **9**, 448.

3-*Aminodibenzofuran*-6-*carboxylic Acid*.—The literature [6] does not give the m. p. of this compound which we found to be 234°. The methyl ester had m. p. 170° and the *acetamido-acid* had m. p. 311° (from acetic acid) (Found: C, 66·5; H, 4·1; N, 5·2. $C_{15}H_{11}NO_4$ requires C, 66·9; H, 4·1; N, 5·2%).

3-*Acetamido*-6-*aminodibenzofuran*.—The acetamido-acid, above, gave, by the Schmidt reaction as described, the *amine*, m. p. 179° (from aqueous ethanol) (Found: C, 70·0; H, 5·2; N, 11·7. $C_{14}H_{12}N_2O_2$ requires C, 70·0; H, 5·0; N, 11·7%). Acetylation gave 3,6-diacetamidodibenzofuran, identical (mixed m. p.) with that prepared from the diamine.

1-*Acetyl*-4-*methoxy*-7- *and* -8-*nitrodibenzofuran*.— The nitro-ethers (3·4 g.), suspended in dry nitrobenzene (30 ml.) at 0°, were treated with a solution of anhydrous aluminium chloride (3 g.) and acetyl chloride (2·2 g.) in nitrobenzene (10 ml.) precooled to 0°. The nitro-ethers dissolved, and, after 1 day at room temperature, concentrated hydrochloric acid was added, the mixtures steam-distilled, and the residues treated with charcoal in acetic acid, giving, on cooling, the *ketones* (70%), m. p. 213 and 241° for the 7- and 8-isomers, respectively (Found: C, 63·1; H, 3·8; N, 4·9%. C, 63·0; H, 3·9; N, 5·0%. $C_{15}H_{11}NO_5$ requires C, 63·2; H, 3·9; N, 4·9%).

The *ketoximes* had m. p. 220 and 230°, respectively (from ethanol) (Found: C, 60·1; H, 4·4; N, 8·9%. C, 60·2; H, 4·2; N, 9·2%. $C_{15}H_{12}N_2O_5$ requires C, 60·0; H, 4·0; N, 9·3%).

The 7-nitro-methoxy-ketone above (1 g.), in water (130 ml.), was refluxed for 6 hr. with sodium hydroxide (2 g.) and potassium permanganate (3 g.). After filtration, the colour was discharged by bisulphite solution. Acidification then gave 1-*carboxy*-4-*methoxy*-7-*nitrodibenzofuran* (20 mg.), m. p. 275—279° (decomp.) (Found: C, 58·6; H, 3·2; N, 4·6. $C_{14}H_9NO_6$ requires C, 58·5; H, 3·2; N, 4·9%).

The Friedel–Crafts reaction of the 3,6-nitro-ether, using methylcarbamoyl chloride, formed by passing dry hydrogen chloride into methyl isocyanate,[12] gave a better yield of the above acid as its *methyl amide*, m. p. 313° (from acetic acid) (Found: C, 59·9; H, 4·0; N, 9·4. $C_{15}H_{12}N_2O_5$ requires C, 60·0; H, 4·0; N, 9·3%).

1-*Acetyl*-7-*amino*-4-*methoxydibenzofuran*.— The corresponding nitro-compound, above, gave, on hydrogenation with palladium–charcoal in ethanol, the *amine*, m. p. 224° (Found: C, 70·7; H, 5·4; N, 5·3. $C_{15}H_{13}NO_3$ requires C, 70·6; H, 5·1; N, 5·5%). To a solution of this amine (0·5 g.) in 48% sulphuric acid (3 ml.) and ethanol (15 ml.), was added, dropwise with stirring, at 80°, a solution of sodium nitrite (1·2 g.) in water (2·5 ml.). After 15 min., the resulting solution was cooled, yielding 1-acetyl-4-methoxydibenzofuran, m. p. after three recrystallisations from ethanol, 134—135° (lit.,[9] 134—134·5°) (Found: C, 75·1; H, 5·0. Calc. for $C_{15}H_{12}O_3$: C, 75·0; H, 5·0%). Reduction and diazotisation of 1-acetyl-4-methoxy-8-nitrodibenzofuran gave, similarly, the identical methoxy-ketone, mixed m. p. undepressed.

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[12] G. Schroeter, *Ber.*, 1909, **42**, 3356.