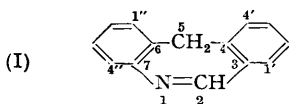


**220. Heterocyclic Derivatives of 1:2:5:6-Dibenzocyclohepta-1:3:5-triene. Part I. 2:3-6:7-Dibenz-1-oxa-4-azacyclohepta-2:4:6-trienes.**

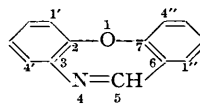
By C. I. BRODRICK, (Miss) M. L. DONALDSON, J. S. NICHOLSON, W. F. SHORT, and D. G. WIBBERLEY.

Methods have been developed for the synthesis of the heterocyclic compounds indicated in the title. Examples of the fission of the seven-membered ring by methyl sulphate and by alcoholic sodium ethoxide are recorded.

*Note on Nomenclature.*—The complex substances described in the memoirs comprising this series have, after consultation with the Editor, been named as illustrated for (I)—(IV).

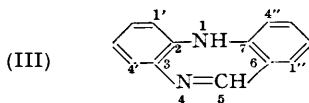


3:4-6:7-Dibenz-1-azacyclohepta-1:3:6-triene.

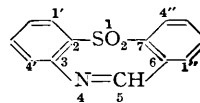


(II)

2:3-6:7-Dibenz-1-oxa-4-azacyclohepta-2:4:6-triene



2:3-6:7-Dibenzo-1:4-diazacyclohepta-2:4:6-triene

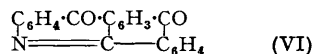
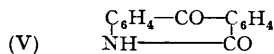


(IV)

2:3-6:7-Dibenzo-1-thia-4-azacyclohepta-2:4:6-triene 1:1-dioxide

INTENSIFICATION of the interest in homocyclic seven-membered rings owing to their presence in a number of natural products suggested the desirability of preparing heterocyclic analogues. For several reasons, including the therapeutic importance of various phenanthridine derivatives, it was decided in the first instance to prepare compounds containing ring systems in which an additional atom or group X (O, NR, S, SO<sub>2</sub>, CH<sub>2</sub>, etc.) was inserted between the benzene rings of phenanthridine. When X is an atom with a lone pair of electrons, the seven-membered ring might display quasi-aromatic properties since it would be relatively free from strain and may be derived by inserting the unsaturated unit ·CH:N· into a five-membered heterocyclic nucleus of the furan, thiophen, or pyrrole type (X = O, S, NR). The extent of the coherence of these units, with consequent production of an aromatic system, cannot be precisely foreseen, and is no doubt limited, *inter alia*, by the fact that it interferes with the independent conjugation of at least one of the benzene rings. The experimental results show that some of the systems exemplify the phenomenon of limited conjugation and the instability of the central ring then gives rise to some novel transformations.

An examination of the literature shows that the above heterocyclic systems are represented by only two compounds, both derived from (I). Beckmann and Liesche (*Ber.*, 1923, **56**, 17) showed that anthraquinone monoxime is converted by phosphorus pentachloride into 2:5-dioxo-3:4-6:7-dibenz-1-azacyclohepta-3:6-diene (V), which was

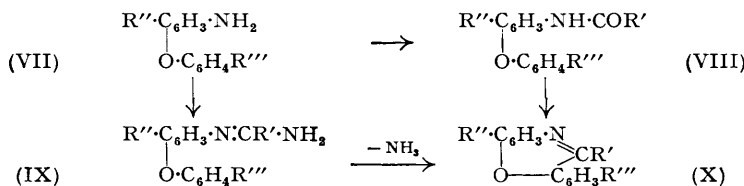


designated 10-hydroxymorphanthrid-9-one by Scholl and Müller (*Ber.*, 1931, **64**, 640), who coined the name "morphanthridine" for (I), because this heterocyclic system is contained in Knorr's now obsolete formula for morphine. Scholl and Müller assigned the structure (VI) to the dehydration product of 1-benzoylanthraquinone 9-monoxime.

Three methods for the preparation of 2:3-6:7-dibenz-1-oxa-4-azacyclohepta-2:4:6-trienes (type II) have now been devised and the compounds prepared are enumerated in the Table.

*Method I.* The Bischler-Napieralski type of ring closure can be applied to 2-acylamino-

diphenyl ethers (VIII), phosphoryl chloride usually being employed as condensing agent but better results being obtained in one case (No. 6) by using phosphorus pentachloride.



*Method II.* The benzenesulphonate of a 2-aminodiphenyl ether (VII) was fused with a nitrile R''·CN giving the amidine (IX) (Oxley and Short, *J.*, 1946, 147) which on being boiled with phosphoryl chloride and nitrobenzene afforded the cyclic compound (X). Similar syntheses of phenanthridines and of dihydroisoquinolines from amidines have already been described (Cymerman and Short, *J.*, 1949, 703; Brodrick and Short, *J.*, 1951, 1343).

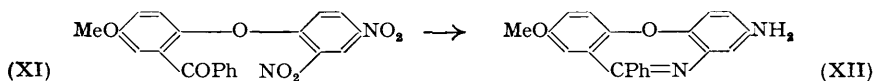
2 : 3-6 : 7-Dibenz-1-oxa-4-azacyclohepta-2 : 4 : 6-trienes.

No.	Substituents	Method	Yield, %	M. p.	Formula	Found, C	H	% N	Required, C	H	% N
(1)	5-Phenyl- .....	I	80	81°	C <sub>19</sub> H <sub>13</sub> ON	82.9	4.8	5.1	84.1	4.8	5.2
		II	78								
(2)	2''-Bromo-5-phenyl- .....	I	33	141—142	C <sub>19</sub> H <sub>12</sub> ONBr	65.5	3.5	4.1	65.1	3.4	4.0
			56								
(3)	3'-Bromo-5-phenyl- .....	I	37	120.5—121.5	C <sub>19</sub> H <sub>12</sub> ONBr	64.7	3.5	4.5	65.1	3.4	4.0
(4)	2''-Methoxy-5-phenyl- ...	I	54	138—139.5	C <sub>20</sub> H <sub>15</sub> O <sub>2</sub> N	79.5	5.1	4.8	79.7	5.0	4.65
(5)	2'' : 3'-Dibromo-5-phenyl- .....	I	58	204—205	C <sub>19</sub> H <sub>11</sub> ONBr <sub>2</sub>	53.2	2.4	3.4	53.15	2.6	3.3
			74								
(6)	2'' : 3'-Dicyano-5-phenyl- .....	I	60	265—267	C <sub>21</sub> H <sub>11</sub> ON <sub>3</sub>	79.05	3.9	—	78.5	3.4	—
			23								
(7)	3'-Amino-2''-methoxy-5-phenyl- .....	III	47	141.5—143	C <sub>20</sub> H <sub>16</sub> O <sub>2</sub> N <sub>2</sub>	76.4	4.8	—	75.95	5.1	—
(8)	3'-Nitro-5-p-nitrophenyl- .....	I	55	264	C <sub>19</sub> H <sub>11</sub> O <sub>5</sub> N <sub>3</sub>	63.0	3.0	11.7	63.2	3.05	11.6
(9)	2''-Methoxy-5-p-nitrophenyl- .....	I	83	182—184	C <sub>20</sub> H <sub>14</sub> O <sub>4</sub> N <sub>2</sub>	69.5	3.95	8.4	69.4	4.0	8.1
(10)	2''-Bromo-5-p-cyano-phenyl- .....	I	66	216—217	C <sub>20</sub> H <sub>11</sub> ON <sub>2</sub> Br	—	—	7.6	—	—	7.5
(11)	3'-Bromo-5-p-cyano-phenyl- .....	I	45	208—209	C <sub>20</sub> H <sub>11</sub> ON <sub>2</sub> Br	—	—	7.8	—	—	7.5
(12)	5-p-Cyanophenyl-2''-methoxy- .....	I	85	180—182	C <sub>21</sub> H <sub>14</sub> O <sub>2</sub> N <sub>2</sub>	77.6	4.4	8.8	77.3	4.3	8.6
(13)	2''-Methoxy-5-p-methylsulphonylphenyl- .....	II	30	150—152	C <sub>21</sub> H <sub>17</sub> O <sub>4</sub> NS	—	—	3.8	—	—	3.7
(14)	2''-Methoxy-5-2-pyridyl- .....	I	62	127—129.5	C <sub>19</sub> H <sub>14</sub> O <sub>2</sub> N <sub>2</sub>	75.8	4.7	9.6	75.5	4.65	9.3

(1) The *picrate* crystallised from alcohol in yellow needles, m. p. 149—150° (Found : N, 11.3, 11.4. C<sub>25</sub>H<sub>16</sub>O<sub>8</sub>N<sub>4</sub> requires N, 11.2%). The *hydrochloride*, prepared in dry ether, had m. p. 135—136° (Found : N, 4.3. C<sub>19</sub>H<sub>11</sub>ONCl requires N, 4.55%). (2) and (5) The higher yields were obtained by a modified procedure designated the "direct method" in the Experimental section. (6) The higher and lower yields were obtained with phosphorus pentachloride and phosphoryl chloride respectively. The dicyanide was also prepared from the corresponding dibromo-compound as described in the Experimental section. (7) The *picrate* crystallised from alcohol in clustered yellow needles, m. p. 175° (decomp.) after softening at 150° (Found : N, 12.7. C<sub>26</sub>H<sub>19</sub>O<sub>9</sub>N<sub>5</sub> requires N, 12.8%). (9) The nitro-compound (1 g.), suspended in ethyl acetate (50 c.c.), was reduced for 15 hours under atmospheric conditions in presence of Raney nickel (0.6 g.), giving yellow prisms of 5-p-aminophenyl-2''-methoxy-2 : 3-6 : 7-dibenz-1-oxa-4-azacyclohepta-2 : 4 : 6-triene (79%), m. p. 177—179° (Found : N, 9.0. C<sub>20</sub>H<sub>16</sub>O<sub>2</sub>N<sub>2</sub> requires N, 8.9%).

The intermediate 2-aminodiphenyl ethers (VII) were obtained from the corresponding nitro-compounds which were usually prepared by the Ullmann method and only one point calls for comment. Bogert and Evans (*Ind. Eng. Chem.*, 1926, **18**, 300) state that reduction of 2 : 4-dinitrodiphenyl ether with stannous chloride affords 4-amino-2-nitrodiphenyl ether, whereas Brewster and Strain (*J. Amer. Chem. Soc.*, 1934, **56**, 117) regard the product as 2-amino-4-nitrodiphenyl ether. The synthesis of 3'-nitro-5-*p*-nitrophenyl-2 : 3-6 : 7-dibenz-1-oxa-4-azacyclohepta-2 : 4 : 6-triene (No. 8) from this amine shows that the amino-group is in the 2-position.

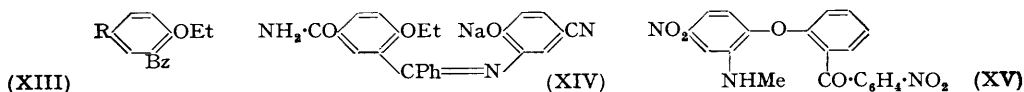
*Method III.* This method is exemplified by the preparation of 3'-amino-2''-methoxy-5-phenyl-2 : 3-6 : 7-dibenz-1-oxa-4-azacyclohepta-2 : 4 : 6-triene (No. 7). 2-Hydroxy-5-methoxybenzophenone and 1-chloro-2 : 4-dinitrobenzene gave 2-(2 : 4-dinitrophenoxy)-5-methoxybenzophenone (XI), which afforded the cyclic compound (XII) on catalytic reduction in presence of Raney nickel.



The bromo-compounds numbered (5), (10), and (11) in the Table were converted into the corresponding dicyanides (by the action of cuprous cyanide in boiling quinoline), and the first two then into the diamidines by the Pinner method.

Attempts to reduce 2'' : 3'-dicyano-5-phenyl-2 : 3-6 : 7-dibenz-1-oxa-4-azacyclohepta-2 : 4 : 6-triene with sodium and ethanol resulted in the fission of the ether linkage by sodium ethoxide, the nature of the products obtained depending on the method of isolation adopted. When water was introduced into the cooled reaction mixture, 5-cyano-2-ethoxybenzophenone (XIII; R = CN) was obtained, but when water was added before removal of alcohol the products isolated were the sodium salt (XIV) of 5-carbamyl-2-ethoxybenzophenone 5-cyano-2-hydroxyphenylimine, 5-carbamyl-2-ethoxybenzophenone (XIII; R = CO·NH<sub>2</sub>), and 5-carboxy-2-ethoxybenzophenone (XIII; R = CO<sub>2</sub>H). The structures of these compounds follow from their interrelation and the identity of the acid (XIII; R = CO<sub>2</sub>H) with a specimen obtained by oxidising 2-ethoxy-5-methylbenzophenone (XIII; R = Me) (Auwers, *Ber.*, 1903, **36**, 3892) with potassium permanganate. The first step in the fission of the ether presumably involves attraction of the ethoxide ion to position 7 and, in view of the relatively small attraction of electrons by the cyano-group (cf. Hargreaves and McGookin, *J. Soc. Chem. Ind.*, 1950, **69**, 186), the electromeric effect of the nitrogen atom in position 4 probably plays a more important part than the cyano-group in withdrawing electrons from C<sub>(7)</sub>.

Dr. A. E. S. Fairfull investigated the methylation of 3'-nitro-5-*p*-nitrophenyl-2 : 3-6 : 7-dibenz-1-oxa-4-azacyclohepta-2 : 4 : 6-triene (No. 8) and found that fission of the heterocyclic nucleus readily occurs. The heterocyclic compound and methyl sulphate afford a gum, probably the methomethylsulphate, which gives orange-red prisms, m. p. 152—153°, on crystallisation from methanol, the change being facilitated by the addition of a little water. This compound behaves as an amino-ketone, giving a 2 : 4-dinitrophenylhydrazone and colourless, readily hydrolysed salts with mineral acids, and is formulated as 2-(2-methylamino-4-nitrophenoxy)-4'-nitrobenzophenone (XV), being produced by hydrolysis of the methomethylsulphate, followed by isomerisation of the methohydroxide successively to the alcohol and the amino-ketone :  $\cdot\text{CPh}\cdot\overset{+}{\text{N}}\text{Me}\cdot\} \text{Me}\bar{\text{S}}\text{O}_4 \longrightarrow \text{HO}\cdot\overset{+}{\text{C}}\text{Ph}\cdot\text{NHMe} \longrightarrow \text{(XV)}$ .



## EXPERIMENTAL

### Preparation of intermediates.

*2-Benzamidodiphenyl Ether.*—2-Nitrodiphenyl ether (Brewster and Groening, *Org. Synth.*, 1934, **14**, 66) was reduced as described by Ullmann (*Ber.*, 1896, **29**, 1881) and the crude amine was benzoylated directly, giving 2-benzamidodiphenyl ether (61%), m. p. 76.5—77° (Found : C, 78.85; H, 5.6; N, 5.1. C<sub>19</sub>H<sub>15</sub>O<sub>2</sub>N requires C, 78.9; H, 5.2; N, 4.8%).

*2-Benzamido-4'-bromodiphenyl Ether.*—4'-Bromo-2-nitrodiphenyl ether (98 g.), prepared by Henley's method (*J.*, 1930, 1223), reduced iron powder (88 g.), water (98 c.c.), and hydrated ferric chloride (0.9 g.) were stirred and heated on the steam-bath for an hour, and the amine was collected in ether. The amine hydrochloride (75.5%), m. p. 183—185°, was precipitated by the addition of concentrated hydrochloric acid, and acetylation gave 2-acetamido-4'-bromodiphenyl ether, m. p. 105—106° in agreement with McCombie, Macmillan, and Scarborough (*J.*, 1930, 1206). Benzoylation in 10% aqueous sodium hydroxide at room temperature afforded 2-benz-

*amido-4'-bromodiphenyl ether* (53%), m. p. 98—99° (Found: N, 3.9.  $C_{18}H_{14}O_2NBr$  requires N, 3.8%).

*2-Benzamido-4-bromodiphenyl Ether*.—4-Bromo-2-nitrodiphenyl ether, prepared in 85% yield by Henley's method (*loc. cit.*), gave 2-amino-4-bromodiphenyl ether (37%), m. p. 53—54°, when reduced with iron and aqueous ferric chloride as described above. McCombie, Macmillan, and Scarborough (*loc. cit.*) record m. p. 54°. The amine was benzoylated in nitrobenzene, and the solution of the benzamido-compound was treated with phosphoryl chloride (see below).

*2-Benzamido-4'-methoxydiphenyl Ether*.—2-Amino-4'-methoxydiphenyl ether hydrochloride (2.5 g.; Mole and Turner, *J.*, 1939, 1720), ether (10 c.c.), benzoyl chloride (1.5 g.), and *n*-sodium hydroxide (40 c.c.) were shaken for 5 minutes, and the resulting solid was recrystallised from alcohol, giving *2-benzamido-4'-methoxydiphenyl ether* (88%), m. p. 135.5—136.5° (Found: N, 4.75.  $C_{20}H_{17}O_3N$  requires N, 4.4%). *4-Nitro-2-p-nitrobenzamidodiphenyl ether*, prepared from 2-amino-4-nitrodiphenyl ether (Bogert and Evans, *loc. cit.*), crystallised from alcohol in colourless needles, m. p. 173° (Found: N, 11.1.  $C_{19}H_{13}O_6N_3$  requires N, 11.1%).

*4'-Methoxy-2-p-nitrobenzamidodiphenyl ether* (82%), prepared similarly to the benzamido-compound, separated from alcohol in yellow blades, m. p. 132—133° (Found: N, 7.8.  $C_{20}H_{16}O_5N_2$  requires N, 7.7%). *p*-Cyanobenzoyl chloride (83%), m. p. 65—66°, was obtained by the method of Ashley, Barber, Ewins, Newbery, and Self (*J.*, 1942, 115), but the residue obtained by removing excess of thionyl chloride was crystallised directly from benzene-light petroleum (1:2). *2-p-Cyanobenzamido-4'-methoxydiphenyl ether* (74%), prepared from this chloride, had m. p. 119—121° (Found: N, 8.0.  $C_{21}H_{16}O_3N_2$  requires N, 8.1%). Nicotinoyl chloride hydrochloride, prepared from nicotinic acid (5.7 g.) and thionyl chloride (20 c.c.) (Späth and Spitzer, *Ber.*, 1926, 59, 1477), slowly dissolved in boiling chlorobenzene (63 c.c.), and the resulting solution was boiled for 5 minutes with a solution of 2-amino-4'-methoxydiphenyl ether (10 g.) in warm chlorobenzene (16 c.c.). The product was extracted into 5*N*-hydrochloric acid, liberated by ammonia, and crystallised from a large volume of light petroleum, giving rods (43%) of *4'-methoxy-2-nicotinamidodiphenyl ether*, m. p. 93—94° (Found: N, 8.9.  $C_{19}H_{16}O_3N_2$  requires N, 8.75%).

*2-Benzamido-4:4'-dibromodiphenyl Ether*.—The corresponding nitro-compound, prepared in 71% yield by Henley's method (*loc. cit.*), gave an 83% yield of 2-amino-4:4'-dibromodiphenyl ether hydrochloride, m. p. 176—177°, on reduction with iron and aqueous ferric chloride, the technique described above being used. The amine had m. p. 68—69° (McCombie, Macmillan, and Scarborough, *loc. cit.*, p. 1207, record m. p. 70°) and benzoylation in 10% aqueous sodium hydroxide gave *2-benzamido-4:4'-dibromodiphenyl ether*, m. p. 132—133° (Found: N, 3.2.  $C_{19}H_{13}O_2NBr_2$  requires N, 3.1%).

*2-Benzamido-4:4'-dicyanodiphenyl Ether*.—The corresponding amine (6.4 g.; Berg and Newbery, *J.*, 1949, 645), benzoyl chloride (10 g.), and pyridine (50 c.c.) were boiled for 30 minutes, and the product was isolated and recrystallised from ethyl acetate, giving prisms (73%) of *2-benzamido-4:4'-dicyanodiphenyl ether*, m. p. 177° (Found: N, 12.4.  $C_{21}H_{13}O_2N_3$  requires N, 12.4%).

*2-(2:4-Dinitrophenoxy)-5-methoxybenzophenone*.—2-Hydroxy-5-methoxybenzophenone (5 g.; Bogert and Howells, *J. Amer. Chem. Soc.*, 1930, 52, 840), 1-chloro-2:4-dinitrobenzene (4.5 g.), and alcoholic sodium ethoxide (from 0.51 g. of sodium and 25 c.c. of absolute alcohol) were boiled for an hour, then cooled, and the resulting solid washed successively with 95% alcohol, water, and 95% alcohol, leaving the crude product (61%). Crystallisation from alcohol gave colourless prisms of *2-(2:4-dinitrophenoxy)-5-methoxybenzophenone*, m. p. 126.5—128.5° (Found: N, 7.1.  $C_{20}H_{14}O_7N_2$  requires N, 7.1%).

#### 2:3-6:7-Dibenz-1-oxa-4-azacyclo-2:4:6-trienes.

*Method I*.—The mixture of amide (0.7—30 g.), phosphoryl chloride (1—1.4 c.c. per g. of amide) and nitrobenzene (0—4 c.c. per g. of amide) was heated in an oil-bath at 170—190°, or when no nitrobenzene was used (Nos. 4, 9, and 12) so that the mixture boiled gently. Evolution of hydrogen chloride was complete in 3—7 hours except in example 14 where the mixture was heated for 20 hours. Somewhat different proportions of reactants were used in the preparation of compound no. 6 and the method is described below in detail, together with the alternative method using phosphorus pentachloride and stannic chloride. Compound no. 3 was prepared by the direct method (described below) in which the aminodiphenyl ether was benzoylated and the amide treated directly with phosphoryl chloride, and this method was also used in alternative preparations of compounds nos. 2 and 5. The methods employed for the isolation of the oxaza-compounds are sufficiently illustrated by the detailed examples given below.

2'' : 3'-Dicyano-5-phenyl-2 : 3-6 : 7-dibenz-1-oxa-4-azacyclohepta-2 : 4 : 6-triene (no. 6). (1) A low yield (23%) of this compound was obtained by heating 2-benzamido-4 : 4'-dicyanodiphenyl ether (0.7 g.), phosphoryl chloride (2 c.c., 10.5 mols.), and nitrobenzene (6 c.c.) at 180° for 6 hours. (2) Phosphorus pentachloride (0.9 g., 2.1 mols.) in hot nitrobenzene (10 c.c.) was added to a solution of 2-benzamido-4 : 4'-dicyanodiphenyl ether (0.7 g.) in nitrobenzene (20 c.c.) at 130°, the temperature was then raised to 210°, stannic chloride (2 drops) was added, and the mixture was boiled for 2 hours. The dark residue obtained when nitrobenzene had been removed at 100° under reduced pressure afforded the crude oxa-aza-compound (0.4 g., 60%), and recrystallisation from alcohol gave colourless plates of the pure compound, m. p. 265—267°, which gave the analytical results recorded in the Table. (3) 2'' : 3'-Dibromo-5-phenyl-2 : 3-6 : 7-dibenz-1-oxa-4-azacyclohepta-2 : 4 : 6-triene (no. 5) (4.4 g.) and cuprous cyanide (5.0 g., 5.4 mols.) were added during 15 minutes to boiling quinoline (20 c.c.) and, after the mixture had been boiled for another 30 minutes, it was cooled to 100° and poured into excess of 3*N*-hydrochloric acid. The solid was washed with dilute acid and recrystallised from 2-ethoxyethanol, giving the crude cyanide, m. p. 260—263° (1.15 g., 36%). Vacuum-sublimation and a further crystallisation raised the m. p. to 265—267°, undepressed on admixture with a specimen prepared by the first method (Found : C, 77.8; H, 3.5; N, 13.2. Calc. for C<sub>21</sub>H<sub>11</sub>ON<sub>3</sub> : C, 78.5; H, 3.4; N, 13.1%). The use of less cuprous cyanide resulted in the survival of unchanged bromo-compound and the product was then very difficult to purify.

3'-Bromo-5-phenyl-2 : 3-6 : 7-dibenz-1-oxa-4-azacyclohepta-2 : 4 : 6-triene (no. 3). A mixture of 2-amino-4-bromodiphenyl ether (6.6 g.), benzene (12.5 c.c.) and nitrobenzene (37.5 c.c.) was distilled until the internal temperature reached 210° and was then cooled to 185° and kept at this temperature during the slow (20 minutes) addition of benzoyl chloride (3.1 c.c., 1.1 mols.). The temperature was then kept at 212° for 15 minutes, and lowered to 205° before the addition of phosphoryl chloride (2.5 c.c., 1.2 mols.). After the mixture had been boiled for 2 hours, part of the solvent was removed by distillation (15 c.c.), and the residue was cooled, shaken with aqueous sodium hydroxide, and extracted with chloroform. The black brittle solid which remained when the solvents were removed at 100° under reduced pressure was crystallised from 2-ethoxyethanol and gave the crude cyclic compound, m. p. 120—122° (3.2 g., 37%). A sample recrystallised from the same solvent had m. p. 120.5—121.5° and gave the analytical results shown in the Table.

2''-Bromo- (no. 2) and 2'' : 3'-dibromo-5-phenyl-2 : 3-6 : 7-dibenz-1-oxa-4-azacyclohepta-2 : 4 : 6-triene (no. 5) were similarly prepared in 56 and 74% yield respectively.

Method II.—5-Phenyl-2 : 3-6 : 7-dibenz-1-oxa-4-azacyclohepta-2 : 4 : 6-triene (no. 1). *o*-Phenoxypyphenylammonium benzenesulphonate, obtained in 95% yield from the acid and amine in alcohol, separated from alcohol-ether in colourless crystals, m. p. 150—151° (Found : N, 4.4. C<sub>18</sub>H<sub>17</sub>O<sub>4</sub>NS requires N, 4.1%). When this salt (11.4 g.) and phenyl cyanide (3.4 g.) were heated at 200° for 2½ hours, *N*-*o*-phenoxyphenylbenzamidine was obtained in 72% yield and after crystallisation from benzene—light petroleum had m. p. 120—121° (Found : N, 10.1. C<sub>19</sub>H<sub>16</sub>ON<sub>2</sub> requires N, 9.7%). The amidine (2.4 g.), phosphoryl chloride (3.8 c.c., 5 mols.), and nitrobenzene (16 c.c.) were boiled under reflux for 4 hours, the temperature rising from 160° to 175°, and, after the nitrobenzene had been removed by distillation under reduced pressure, the mixture was cooled and triturated with 5*N*-sodium hydroxide. The oxa-aza-compound was collected in ether and converted into its *picrate* (2.7 g., 64%), which after crystallisation from alcohol had m. p. 150°, undepressed on admixture with a sample prepared by method I (Found : N, 11.4. C<sub>25</sub>H<sub>16</sub>O<sub>8</sub>N<sub>4</sub> requires N, 11.2%).

2''-Methoxy-5-*p*-methylsulphonylphenyl-2 : 3-6 : 7-dibenz-1-oxa-4-azacyclohepta-2 : 4 : 6-triene (no. 13). 2-Amino-4'-methoxydiphenyl ether benzenesulphonate (6.7 g.; m. p. 179—181°) and *p*-cyanophenyl methyl sulphone (3.3 g.) were heated at 210° for 2 hours, and then extracted with a large volume of boiling water. The aqueous solution was extracted with chloroform, then made alkaline, and the amidine collected in chloroform. Crystallisation from 95% alcohol afforded colourless needles (0.92 g., 13%) of *N*-(*o*-4-methoxyphenoxyphenyl)-*p*-methylsulphonylbenzamidine, m. p. 146—147° (Found : N, 7.2. C<sub>21</sub>H<sub>20</sub>O<sub>4</sub>N<sub>2</sub>S requires N, 7.1%). When the amidine (0.7 g.) and phosphoryl chloride (2 c.c., 12.5 mols.) were boiled together for 5 hours, the oxa-aza-compound was obtained in 30% yield as a non-basic solid which crystallised from methanol in pale yellow needles, m. p. 150—152°, and gave the analytical results recorded in the Table.

Method III.—3'-Amino-2''-methoxy-5-phenyl-2 : 3-6 : 7-dibenz-1-oxa-4-azacyclohepta-2 : 4 : 6-triene (no. 7). 2-(2 : 4-Dinitrophenoxy)-5-methoxybenzophenone (0.8 g.) was dissolved in ethyl acetate (50 c.c.) and shaken with Raney nickel (1 g.) in hydrogen. Under atmospheric conditions

the reduction was complete in 16 hours, and the gum obtained after removal of the catalyst and the solvent was dissolved in 5*N*-hydrochloric acid (30 c.c.). The acid solution was extracted with ether, then made alkaline with ammonia, and the product collected in ether. Evaporation of the ethereal solution gave a gum which solidified on trituration with methanol, and crystallisation from the same solvent gave the oxa-aza-compound, m. p. 140—142° (0.3 g., 47%). Further crystallisation raised the m. p. to 141.5—143° and the sample gave the analytical results recorded in the Table.

*Preparation of cyanides and amidines.*

2''- and 3'-Cyano-5-p-cyanophenyl-2 : 3-6 : 7-dibenz-1-oxa-4-azacyclohepta-2 : 4 : 6-triene.—These cyanides were obtained in 62 and 38% yield respectively when the 2''- and 3'-bromo-compounds (35 g.) and cuprous cyanide (18.5 g., 2.2 mols.) were added during 15 minutes to boiling quinoline (150 c.c.), the mixtures being boiled for a further 30 minutes and then poured into 2*N*-hydrochloric acid. The cyanides were purified by crystallisation from 2-ethoxyethanol. 2''-Cyano-5-p-cyanophenyl-2 : 3-6 : 7-dibenz-1-oxa-4-azacyclohepta-2 : 4 : 6-triene had m. p. 243—244° (Found : C, 78.5; H, 3.4; N, 13.4%) and 3'-cyano-5-p-cyanophenyl-2 : 3-6 : 7-dibenz-1-oxa-4-azacyclohepta-2 : 4 : 6-triene had m. p. 233—234° (Found : C, 77.8; H, 3.35; N, 13.3. C<sub>21</sub>H<sub>11</sub>ON<sub>3</sub> requires C, 78.5; H, 3.4; N, 13.1%).

2'' : 3'-Diamidino-5-phenyl-2 : 3-6 : 7-dibenz-1-oxa-4-azacyclohepta-2 : 4 : 6-triene.—The corresponding dicyanide (6.4 g., above) was suspended in a mixture of dry ethanol (7 c.c.) and dry nitrobenzene (20.8 c.c.) and saturated with dry hydrogen chloride at 0°. A homogeneous solution was obtained after 24 hours at room temperature, and after a further 24 hours there was a fine yellow precipitate, and dry ether was added to complete the separation of the ethyl imidate hydrochloride. The solid was shaken with 10% alcoholic ammonia (68 c.c.) and after 3 days the solid was removed, the filtrate was evaporated to dryness under reduced pressure at room temperature, and the residue was dissolved in water (8 c.c.) and acidified with hydrochloric acid. The pale cream-coloured solid (3 g., 32%), m. p. 285—288°, was purified by reprecipitation from alcohol with dry ether and recrystallisation from 2*N*-hydrochloric acid. The amidine dihydrochloride dihydrate had m. p. 290—293° (Found : N, 14.8; Cl', 15.1; H<sub>2</sub>O, 7.5. C<sub>21</sub>H<sub>17</sub>ON<sub>5</sub>·2HCl·2H<sub>2</sub>O requires N, 15.1; Cl', 15.4; H<sub>2</sub>O, 7.8%).

2''-Amidino-5-p-amidinophenyl-2 : 3-6 : 7-dibenz-1-oxa-4-azacyclohepta-2 : 4 : 6-triene.—This amidine was obtained in 25% yield from the corresponding dicyanide by the method used in the case of the isomeric compound. The amidine dihydrochloride hydrate, crystallised from dilute hydrochloric acid, had m. p. 280—283° (Found : loss at 100°/vac., 9.4. Found, on dried material : C, 58.3; H, 4.7; N, 16.3. C<sub>21</sub>H<sub>19</sub>ON<sub>5</sub>Cl<sub>2</sub>·2½H<sub>2</sub>O requires H<sub>2</sub>O, 9.5. C<sub>21</sub>H<sub>19</sub>ON<sub>5</sub>Cl requires C, 58.9; H, 4.4; N, 16.4%).

*Alkaline Fission of 2'' : 3'-Dicyano-5-phenyl-2 : 3-6 : 7-dibenz-1-oxa-4-azacyclohepta-2 : 4 : 6-triene.*—Sodium (4 g., 8.7 atomic proportions) was slowly added to a suspension of the dicyanide (6.4 g.) in boiling absolute alcohol (120 c.c.), the mixture was boiled for another 2 hours, and the resulting red-brown solution was worked up by one of the following methods. (a) The solution was neutralised at 0° with an equivalent of 36% hydrochloric acid, and sodium chloride was then removed; the filtrate, concentrated to 1/3 vol. under reduced pressure, gave 5-cyano-2-ethoxybenzophenone (35.5%), m. p. 101—102.5° or 104—105° after several crystallisations from alcohol (Found : C, 76.2; H, 5.0; N, 5.7. C<sub>16</sub>H<sub>13</sub>O<sub>2</sub>N requires C, 76.5; H, 5.2; N, 5.6%). This cyanide was also obtained from the corresponding amide (0.4 g.) and boiling acetic anhydride (5 c.c.). (b) Water (50 c.c.) was added, the mixture was concentrated to crystallising point, then cooled, and the yellow sodium salt (A) collected and neutralised with 2*N*-hydrochloric acid, giving a solid which was recrystallised from alcohol. The solution deposited a crop of crystals immediately and a second solid separated from the filtrate after several days. The former were recrystallised from ethanol giving colourless needles of 5-carbamyl-2-ethoxybenzophenone 5-cyano-2-hydroxyphenylimine, m. p. 209—210° (Found : C, 72.5; H, 5.0; N, 11.1. C<sub>23</sub>H<sub>19</sub>O<sub>3</sub>N<sub>3</sub> requires C, 71.7; H, 4.9; N, 10.9%). The second solid (above) was 5-carbamyl-2-ethoxybenzophenone, m. p. 157—158° [Found : C, 71.55; H, 5.55; N, 5.2; OEt, 15.95%; *M* (Rast), 279. C<sub>16</sub>H<sub>15</sub>O<sub>3</sub>N requires C, 71.4; H, 5.6; N, 5.2; OEt, 16.7%; *M*, 269]. The yellow sodium salt (A) also gave this amide, m. p. and mixed m. p. 157—158° (33.6%), when it was boiled with dilute hydrochloric acid. The amide afforded a 2 : 4-dinitrophenylhydrazone, m. p. 258—264°, was dehydrated by acetic anhydride to the corresponding cyanide (above), and when it (0.2 g.) was boiled for 5 hours with 5*N*-sodium hydroxide (5 c.c.) it gave 5-carboxy-2-ethoxybenzophenone, m. p. 176—177° (Found : C, 71.15; H, 5.5. C<sub>16</sub>H<sub>14</sub>O<sub>4</sub> requires C, 71.1; H, 5.2%). This acid (18.5%) was also obtained when the filtrate from the yellow sodium salt (A)

was acidified with concentrated hydrochloric acid, and was synthesised from 2-hydroxy-5-methylbenzophenone (Rosenmund and Schnurr, *Annalen*, 1928, **460**, 56). This phenol (11 g.), sodium ethoxide solution [from sodium (1.2 g., 1 atom) and absolute alcohol (50 c.c.)], and ethyl bromide (4.6 c.c., 1.2 mols.) were boiled for 4 hours and afforded 2-ethoxy-5-methylbenzophenone (55%), m. p. 44—45° (Found: C, 79.7; H, 6.5. Calc. for  $C_{16}H_{16}O_2$ : C, 80.0; H, 6.7%). Auwers (*loc. cit.*) records m. p. 68°. When this ether (17 g.), potassium permanganate (30 g., equiv. to 4O), and water (350 c.c.) were stirred and heated on the steam-bath for 5 hours, part (6 g.) was recovered and part oxidised to 5-carboxy-2-ethoxybenzophenone (1.1 g.), m. p. and mixed m. p. 176—177° (Found: C, 71.3; H, 5.1%).

*3'-Nitro-5-p-nitrophenyl-2 : 3-6 : 7-dibenz-1-oxa-4-azacyclohepta-2 : 4 : 6-triene and Methyl Sulphate* [Experiments by Dr. A. E. S. FAIRFULL].—The nitro-compound (1.8 g.) and methyl sulphate (3 c.c., 6.4 mols.) were boiled for 10 minutes, benzene was then added, and the resulting brown gum was triturated with ether and dissolved in hot methanol. On being cooled the solution deposited an orange solid (1.3 g., 66.5%), m. p. 149—151°, which on further crystallisation gave orange-red prisms of 2-(2-methylamino-4-nitrophenoxy)-4'-nitrobenzophenone, m. p. 152—153° (Found: C, 60.9; H, 3.9; N, 10.7.  $C_{20}H_{15}O_6N_3$  requires C, 61.1; H, 3.8; N, 10.7%). Brady's reagent (in sulphuric acid) afforded the 2 : 4-dinitrophenylhydrazone which separated from glacial acetic acid in orange prisms, m. p. 234—235° (Found: N, 17.2.  $C_{26}H_{19}O_9N_7$  requires N, 17.1%). The amino-ketone afforded a white *hydrobromide*, m. p. 200—202° (Found: N, 9.1.  $C_{20}H_{16}O_6N_3Br$  requires N, 8.9%), and a sulphate, m. p. 191—192°; the free base was regenerated from both these salts by warm water.

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