Diacid Bases. Part II. Curarising Agents. Derivatives of Diphenyl Ether.*

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Some diacyldiphenyl ethers have been prepared and, with certain exceptions, converted into the di-(α-aminoalkylphenyl) ethers by (*a*) oximation and reduction, or (*b*) reduction to the dialcohol, followed by bromination and subsequent reaction with the appropriate amine. Aminative reduction was not generally applicable and methods (*a*) and (*b*) also failed in some instances. These diamines were converted into the bisquaternary compounds which had curarising properties (Copp and Mogey, *Nature*, 1950, **165**, 601). Evidence is adduced that the purified bisquaternary salts and the intermediate diamines consisted each of only one stereoisomer.

In the search for synthetic curarising agents, a large number of bisquaternary compounds, simulating the bisquaternary alkaloid, *dextro*tubocurarine, have already been prepared (see Paton, *J. Pharm. Pharmacol.*, 1949, **1**, 273; Barber, *Annual Rep. Appl. Chem.*, 1949, **34**, 350; Copp, *ibid.*, 1950, **35**, 352; Taylor, *J.*, 1951, 1150; 1952, 142, 1309). Following similar lines of reasoning, we have prepared a number of bisquaternary compounds (III), (VI), and (IX) derived from diphenyl ether. Their relation to *dextro*tubocurarine, methods of synthesis, and curarising properties of these compounds have already been briefly described (Copp and Mogey, *Nature*, 1950, **165**, 601; see also B.P. 654,433, 654,445) and further chemical details are now reported. The only related known compounds were 4 : 4'-bisaminomethyldiphenyl ether (II; $R^1 = R^2 = R^3 = H$) (Albert, *J.*, 1947, 1452) and 4 : 4'-bis(triethylammonium-methyl)diphenyl ether di-iodide (III; $R^1 = H$, $R^2 = R^3 = R^4 = Et$, $X = I$) (Funke and Engeler, *Bull. Soc. chim.*, 1950, 340) (cf. Funke and Favre, *ibid.*, 1951, 832).

The starting materials for our salts (III), (VI), and (IX) were the diketones (I), (IV),

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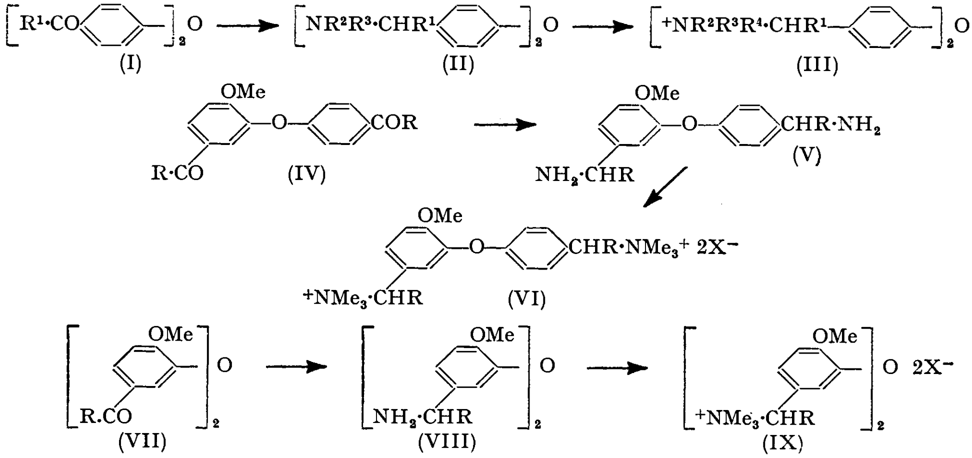
* Part I, *J.*, 1953, 3116.

and (VII) respectively. Diketones of this type previously prepared and orientated include (I; R = Me and Ph) (Dilthey, Bach, Grütering, and Hausdörfer, *J. pr. Chem.*, 1927, **117**, 337), (I; R = CH_2Cl) (G.P. 492,321; von Schickh, *Ber.*, 1936, **69**, 242), (IV; R = Me, CH_2Cl), and (VII; R = CH_2Cl) (Tomita, *J. Pharm. Soc. Japan*, 1934, **54**, 167; *ibid.*, 1936, **56**, 99; 1937, **57**, 151; von Schickh, *loc. cit.*) and we have used similar methods for

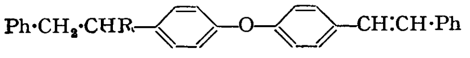


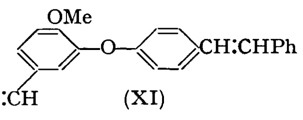
the preparation of a number of analogues of these compounds. The intermediate amines (II), (V), and (VIII) were then obtained by one of the following methods (*a*), (*b*), and (*c*).

(*a*) With the exception of 4 : 4′-di-*o*-toluoyldiphenyl ether, which did not react with hydroxylamine, all the diketones examined in this respect formed well-defined dioximes which were then readily reduced to the diamines (II; $R^2 = R^3 = H$), (V), and (VIII).

(*b*) Reduction by the Meerwein–Ponndorf method was used to convert some of the diketones into the corresponding dialcohols, which were converted into the corresponding dibromides by reaction with hydrogen bromide at —5° (Campbell and Chattaway, *Proc. Roy. Soc.*, 1942, *B*, **130**, 441) and thence into the desired diamines. Usually only these end-products were purified.

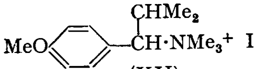
The diketone (I; R = *o*-tolyl) was again unchanged on attempted reduction, which confirms the unreactive nature of its keto-groups. This series of reactions was also apparently unsuitable for the preparation of the amines (II; R = CH_2Ph) and (V; R = CH_2Ph). Thus when (I; R = CH_2Ph) was reduced and the product was brominated and finally treated with alcoholic dimethylamine, a mixture was obtained from which were separated (1) a neutral crystalline product, probably 4-(1-hydroxyphenethyl)-4′-styryldiphenyl ether (X; R = OH), and (2) a crystalline base, probably 4-(1-dimethylaminophenethyl)-4′-styryldiphenyl ether (X; R = NMe_2), characterised as its methiodide and (3) a resinous basic product which contained 4 : 4′-di-(1-dimethylaminophenethyl)diphenyl ether (II; $R^1 = CH_2Ph$, $R^2 = R^3 = Me$) since with methyl iodide it afforded (III; $R^1 = CH_2Ph$, $R^2 = R^3 = R^4 = Me$, X = I) (see also below). The same series of reactions converted 2-methoxy-4′ : 5-bisphenylacetyldiphenyl ether (IV; R = CH_2Ph) into a single neutral crystalline product, probably 2-methoxy-4′ : 5-distyryldiphenyl ether (XI). Analogous observations have recently been made by Goodson and Christopher (*J. Amer. Chem. Soc.*, 1950, **72**, 358) and Kaye and Parris (*ibid.*, 1952, **74**, 1566) who obtained stilbene as the principal product from 1 : 2-diphenylethyl bromide and piperidine or from 1 : 2-diphenylethyl chloride and 2-aminopyridine and *NN*-dimethyl-*N*′-2-pyridylethylenediamine respectively.


(X)


(XI)

(*c*) Reductive amination (Emerson, "Org. Reactions," Wiley & Sons, 1948, Vol. IV, p. 174) appeared to be of preparative value only for the diamines (II; $R = CH_2Ph$); the other diketones examined (II; R = Me, Et, and Ph) gave only negligible yields of basic products when reduced in presence of ammonia or a primary or secondary amine. Some instances have been recorded (Emerson, *op. cit.*) where aliphatic aromatic ketones which carry electron-donating groups on the aromatic nucleus, *e.g.*, 4-hydroxypropiophenone, give only low yields of amines under the usual conditions though the isomeric 4-hydroxybenzyl methyl ketone gives an excellent yield of *p*-2-aminopropylphenol when reduced in presence of ammonia.

The diamines (II; $R^2 = R^3 = H$), (V), and (VIII) were most easily converted into the corresponding bistrimethylammonium salts by exhaustive methylation with methyl iodide in presence of sodium carbonate whilst other quaternary salts (III) were prepared as indicated in Table 4 (p. 878). The alternative methylation of (II; $R^1 = Me$, $R^2 = R^3 = H$) by use of formaldehyde and formic acid (Clarke, Gillespie, and Weisshaus, *J. Amer. Chem. Soc.*, 1933, **55**, 4571) led to impure (II; $R^1 = R^2 = R^3 = Me$), which could only be purified as its dipicrate, and it is probable that this methylation was accompanied by decomposition of the type described by Norcross and Openshaw (*J.*, 1949, 1174) and Raison (*ibid.*, p. 2070). The former authors observed that 4-methoxyaralkyltrimethylammonium iodides, *e.g.*, (XII), eliminated trimethylamine hydriodide when heated, and similar fission occurred on attempted methylation of the parent benzylamines with formic acid and formaldehyde. These decompositions appeared to result from spontaneous separation of the charged nitrogen atom under the influence of electron-donation from the methoxyl group and were assisted still further by increased electron-donation (+*I* effect) resulting from lengthening of the side chain. In the present series of compounds, analogous fission presumably results from electron-donation from the (phenyl) ether linkage. Compared with the above methylation of (II; $R^1 = Me$, $R^2 = R^3 = H$), the analogous methylation of (V; R = Me) and (II; $R^1 = Et$, $R^2 = R^3 = H$) gave lower yields of very impure products, evidently the result of enhanced electron-release from the methoxyl group and the lengthened side chain respectively. However, methylation of (II; $R^1 = C_6H_{13}$, $R^2 = R^3 = H$) gave the pure tertiary amine (II; $R^1 = C_6H_{13}$, $R^2 = R^3 = Me$) directly and it is likely that, in this instance, the much longer chain now sterically hindered the nitrogen from escaping; Norcross and Openshaw (*loc. cit.*) observed that 2-*p*-methoxyphenyl-1 : 1-dimethylpiperidinium iodide, in which the quaternary nitrogen is again prevented from escaping, is also stable.


(XII)

Both the final bisquaternary salts and the intermediate diamines may exist in more than one optically inactive form. Since most of these substances were themselves crystalline or gave crystalline derivatives, it seemed probable that only one form of each was present or finally isolated. Further, when the amines (II; $R^1 = CH_2Ph$, $R^2 = R^3 = H$), and ($R^1 = CH_2Ph$, $R^2 = Me$, $R^3 = H$) [which had been prepared by methods (*a*) and (*c*) respectively, see Table 3, p. 877] were exhaustively methylated with methyl iodide, the resulting di-iodides were apparently identical and the same as that prepared from the impure (II; $R^1 = CH_2Ph$, $R^2 = R^3 = Me$) resulting from method (*b*) (see above). This supports the above conclusions since these three di-iodides are unlikely to be identical mixtures of stereoisomers.

EXPERIMENTAL

The physical properties and analytical data of the various intermediate and final products are summarised in Tables 1—4; the preparative methods are generalised or exemplified in the following text.

Diketones (I) (Table 1).—These were prepared by the method of Dilthey *et al.* (*loc. cit.*). Powdered aluminium chloride (108 g.) was covered with carbon disulphide, and the suspension cooled and stirred whilst diphenyl ether (34 g.) was added, followed slowly by propionyl chloride (46 g.). Cooling was continued for 1 hr. and the mixture then heated under reflux for 30 min. after which the supernatant carbon disulphide was decanted and the residue decomposed with ice and hydrochloric acid. The resulting product was dissolved in chloroform, the solution dried and evaporated, and the residue distilled, to give 4 : *4′-dipropionyldiphenyl ether* (I;

R = Et), b. p. 180—190°/0·1 mm., which rapidly solidified and was recrystallised from methanol.

Diketones (IV) *and* (VII) (Table 1).—These diketones were prepared by using considerably less aluminium chloride, according to Tomita's procedure (*loc. cit.*). A solution of 2 : 2′-dimethoxydiphenyl ether (2·3 g.) and phenylacetyl chloride (3·5 g.) in carbon disulphide (20 ml.) was stirred at 0° whilst powdered aluminium chloride (3·3 g.) was slowly added. The resulting mixture was kept at 0° for 3 hr. and then overnight at room temperature. The product, 2 : 2′-*dimethoxy*-5 : 5′-*bisphenylacetyldiphenyl ether* (VII; R = CH_2Ph), was isolated as in the preceding preparation and distilled (b. p. 240—260°/10^{-5} mm.). The resinous distillate crystallised from ethanol.

TABLE 1. *Diketones* (I), (IV), *and* (VII).

R	B. p.	M. p.	Cryst. from	Yield (%)	Formula	Found (%)		Required (%)	
						C	H	C	H
4 : 4′-*Diacyldiphenyl ethers* (I).									
Et	180—190°/0·1 mm.	96—97·5°	MeOH	85	$C_{18}H_{18}O_3$	76·65	6·5	76·6	6·4
Pr^n	—	102—103	,,	85	$C_{20}H_{22}O_3$	77·5	6·7	77·4	7·1
Bu^n	—	98—99	EtOH	85	$C_{22}H_{26}O_3$	78·2	7·5	78·1	7·7
n-C_5H_{11}	—	104—105·5	,,	71	$C_{24}H_{30}O_3$	78·6	7·9	78·6	8·2
n-C_6H_{13}	—	102—103	,,	85	$C_{26}H_{34}O_3$	79·2	8·6	79·15	8·7
n-C_7H_{15}	—	103	Pr^{i}OH	63	$C_{28}H_{38}O_3$	79·55	8·9	79·6	9·1
p-C_6H_4Me	—	201—202	BuOH	92	$C_{28}H_{22}O_3$	82·75	5·5	82·7	5·5
o-C_6H_4Me	—	81·4—82·5	MeOH	62	$C_{28}H_{22}O_3$	82·55	5·3	82·7	5·5
Ph·CH_2	—	161—163	AcOH	51	$C_{28}H_{22}O_3$	82·5	5·6	82·7	5·5
2-*Methoxy*-4′ : 5-*bisphenylacetyldiphenyl ether* (IV).									
Ph·CH_2	280—300/0·1	134—137	Pr^{i}OH	40	$C_{29}H_{24}O_4$	79·8 (OMe, 6·9)	5·7	79·8 (OMe, 7·1)	5·5
5 : 5′-*Diacyl*-2 : 2′-*dimethoxydiphenyl ethers* (VII).									
Me	202—210/0·1	126—128	MeOH	28	$C_{18}H_{18}O_5$	68·8	5·7	68·8	5·8
Ph·CH_2	250—260/10^{-5}	106—107·5	,,	46	$C_{30}H_{26}O_5$	77·6	6·0	77·2	5·6

Dioximes (Table 2).—A suspension of the diketone, 100% excess of hydroxylamine hydrochloride, and powdered anhydrous sodium carbonate in the appropriate solvent (see Table 2) was heated under reflux for 8 hr. and then poured into water. The resulting dioximes were filtered off and recrystallised.

TABLE 2. *Dioximes.**

R	M. p.	Cryst. from †	Formula	Found, %	Required, %
				N	N
From (I).					
Et	155—156°	MeOH	$C_{18}H_{20}O_3N_2$	9·1	9·0
Pr^n	122—124	Et_2O–Pet	$C_{20}H_{24}O_3N_2$	8·1	8·2
Bu^n	116—117	,,	$C_{22}H_{28}O_3N_2$	7·5	7·6
n-C_5H_{11}	Two forms, 87—88, 103—104·5	Et_2O–*c*H	$C_{24}H_{32}O_3N_2$	7·2	7·1
n-C_6H_{13}	95—96	Et_2O–Pet	$C_{26}H_{36}O_3N_2$	6·5	6·6
n-C_7H_{15}	76	,,	$C_{28}H_{40}O_3N_2$	6·1	6·2
p-C_6H_4Me	167—169	BuOH	$C_{28}H_{24}O_3N_2$	6·4	6·4
Ph·CH_2	162	EtOH	$C_{28}H_{24}O_3N_2$	6·4	6·4
From (IV).					
Me	166—167·5	Pr^{i}OH	$C_{17}H_{18}O_4N_2$	8·8	8·9
Ph·CH_2	155—156	MeOH	$C_{29}H_{26}O_4N_2$	5·7	6·0
From (VII).					
Me	209—210	Pr^{i}OH	$C_{18}H_{20}O_5N_2$	8·1	8·1
Ph·CH_2	183—184	MeOH–EtOH	$C_{30}H_{28}O_5N_2$	5·5	5·6

* All prepared in Pr^{i}OH, except nos. 5—7 which were prepared in BuOH.
† Pet = light petroleum (b. p. 40—60°), *c*H = *cyclo*hexane.

Diamines (II), (V), *and* (VIII) (Table 3).—(a) *Reduction of dioximes.* 4 : 4′-Diacetyldiphenyl ether dioxime (Dilthey *et al.*, *loc. cit.*) (21·5 g.) was reduced in a saturated solution of ammonia in ethanol (200 ml.) over Raney nickel (2 g.) under hydrogen at 90°/50 atm. (about 3 hr.). The

TABLE 3. *Intermediate diamines* (II), (V), *and* (VIII).

R^1	NR^2R^3	Compound	B. p./mm. or m. p.	Cryst. from	Formula	Found (%)				Required (%)			
						C	H	N	Cl	C	H	N	Cl
4 : 4′-*Di*-(1-*dialkylaminoalkyl*)*diphenyl ethers* (II).													
Me	NH_2	Base ^{a}	152—154°/0·02		$C_{16}H_{20}ON_2$	75·0	7·8	—	—	75·0	7·8	—	—
			39—41°										
		2HCl	266	EtOH–Et_2O	$C_{16}H_{22}ON_2Cl_2$	—	—	8·25	21·3	—	—	8·5	21·6
,,	NMe_2	Base *	154/0·01		$C_{20}H_{28}ON_2$	76·7	8·7	9·2	—	76·9	9·0	9·0	—
		2HCl	248	EtOH–$COMe_2$	$C_{20}H_{30}ON_2Cl_2$	—	—	7·5	18·7	—	—	7·3	18·4
,,	$N<[CH_2]_4>O$	Base ^{b}	215—220/0·01		$C_{24}H_{32}O_3N_2$	72·8	7·8	7·2	—	72·7	8·1	7·1	—
		$2H_2C_2O_4$ ‡	138—139	MeOH	$C_{28}H_{36}O_{11}N_2$	58·2	6·2	—	—	58·3	6·3	—	—
,,	$N<[CH_2]_4>CH_2$	Base ^{b}	211/0·01		$C_{26}H_{36}ON_2$	79·4	8·5	7·1	—	79·6	9·2	7·1	—
		$2H_2C_2O_4$ ‡	136—137	EtOH	$C_{30}H_{40}O_9N_2$	62·5	7·0	4·8	—	62·9	7·0	4·9	—
Et	NH_2	Base ^{a}	176—178/0·07		$C_{18}H_{24}ON_2$	76·35	8·4	9·8	—	76·0	8·5	9·8	—
		2HCl	263	EtOH–EtOAc	$C_{18}H_{26}ON_2Cl_2$	—	—	—	19·8	—	—	—	19·8
Pr^n	,,	Base ^{a}	173—178/0·05		$C_{20}H_{28}ON_2$	76·7	8·8	9·3	—	76·9	9·0	9·0	—
Bu^n	,,	Base ^{a}	178—182/0·05		$C_{22}H_{32}ON_2$	—	—	8·1	—	—	—	8·2	—
n-C_5H_{11}	,,	Base ^{a}	198—200/0·05		$C_{24}H_{36}ON_2$	—	—	7·5	—	—	—	7·6	—
		2HCl	269	MeOH–Et_2O	$C_{24}H_{38}ON_2Cl_2$	—	—	6·45	16·1	—	—	6·35	16·0
,,	$N<[CH_2]_4>CH_2$	Base ^{b}	235—240/0·05		$C_{34}H_{52}ON_2$	—	—	5·5	—	—	—	5·55	—
n-C_6H_{13}	NH_2	Base ^{a}	212—218/0·02		$C_{26}H_{40}ON_2$	78·6	9·9	—	—	78·7	10·1	—	—
		2HCl	264—266	Dil. HCl	$C_{26}H_{42}ON_2Cl_2$	—	—	6·0	15·35	—	—	6·0	15·1
,,	NMe_2	Base *	214—216/0·04		$C_{30}H_{48}ON_2$	—	—	6·0	—	—	—	6·2	—
		2HCl	272	EtOH	$C_{30}H_{50}ON_2Cl_2$	—	—	5·2	13·5	—	—	5·3	13·5
n-C_7H_{15}	NH_2	Base ^{a}	220—230/0·02		$C_{28}H_{44}ON_2$	79·2	10·0	6·7	—	79·2	10·4	6·6	—
		2HCl	261	Dil. HCl	$C_{28}H_{46}ON_2Cl_2$	—	—	—	14·5	—	—	—	14·3
Ph	,,	Base ^{a}	220—230/0·05		$C_{26}H_{24}ON_2$	—	—	7·05	—	—	—	7·4	—
p-C_6H_4·Me	,,	Base ^{a}	230—240/0·07		$C_{28}H_{28}ON_2$	—	—	7·0	—	—	—	6·9	—
Ph·CH_2	,,	Base ^{a}	250—256/0·05		$C_{28}H_{28}ON_2$	82·3	6·9	7·1	—	82·3	6·9	6·9	—
		2Et·SO_3H	255	MeOH–EtOAc	$C_{32}H_{40}O_7N_2S_2$	—	—	4·45	—	—	—	4·4	—
,,	NHMe	Base ^{c}	266—270/0·05		$C_{30}H_{32}ON_2$	—	—	6·4	—	—	—	6·4	—
4′ : 5-*Bis*-1-*aminoalkyl*-2-*methoxydiphenyl ethers* (V).													
Me	—	Base ^{a}	174/0·05		$C_{17}H_{22}O_2N_2$	—	—	9·8	—	—	—	9·8	—
			33—35										
		2HCl	196	Pr^iOH–Et_2O	$C_{17}H_{24}O_2N_2Cl_2$	—	—	—	19·5	—	—	—	19·7
Ph·CH_2	—	Base ^{a}	275—280/10^{-5}		$C_{29}H_{30}O_2N_2$	79·7	6·4	6·2	—	79·4	6·9	6·4	—
5 : 5′-*Bis*-1-*aminoalkyl*-2 : 2′-*dimethoxydiphenyl ethers* (VIII).													
Me	—	Base ^{a}	190—194/0·05		$C_{18}H_{24}O_3N_2$	68·6	7·6	9·2	—	68·3	7·6	8·85	—
Ph·CH_2	—	Base ^{a}	†		—	—	—	—	—	—	—	—	—
		$2H_2C_2O_4$ ‡	165	MeOH	$C_{34}H_{36}O_{11}N_2$	63·5	5·35	4·5	—	63·0	5·6	4·3	—

$^{a, b, c}$ Prepd. by methods (*a*), (*b*), (*c*) respectively.

* See text for prep. † Decomposed on attempted distillation and not purified. ‡ Di(hydrogen oxalate).

TABLE 4. *Bisquaternary salts* (III), (VI), *and* (IX).

M. p.s accompanied by varying degrees of decomp. All salts were dried at 100° *in vacuo* before analysis; the loss on drying is given where a definite hydrate was apparently present.

	R^1	NR^{2}R^{3}R^4	X	M. p.	Cryst. from	Formula	Found (%)			Required (%)		
							N	X	H_2O	N	X	H_2O
(III)	H	NMe_3	I	241—242°	MeOH–$COMe_2$	$C_{20}H_{30}ON_2I_2$	—	45·0	—	—	44·8	—
	Me	,,	,,	218—220	Aq. MeOH	$C_{22}H_{34}ON_2I_2$	4·5	41·8	—	4·7	42·6	—
	,,	NMe_2Et	,,	171—172	Aq. $COMe_2$	$C_{24}H_{38}ON_2I_2$	4·4	40·2	—	4·5	40·7	—
	,,	$MeN<[CH_2]_4>CH_2$	,,	170 (soft. 110)	Aq. PrOH	$C_{28}H_{42}ON_2I_2,5H_2O$	4·3	37·8	11·5	4·1	37·5	11·7
	,,	$MeN<[CH_2]_4>O$	,,	155	Amorphous	$C_{26}H_{38}O_3N_2I_2$	—	36·9	—	—	37·3	—
	,,	$NMe_2\cdot CH_2\cdot Ph$	Br	50—51	Warm H_2O	$C_{34}H_{42}ON_2Br_2$	3·9	25·3	—	4·2	24·3	—
	Et	NMe_3	I	238—240	MeOH	$C_{24}H_{38}ON_2I_2$	4·3	40·8	—	4·5	40·7	—
	Pr^n	,,	,,	241 (soft. 235)	,,	$C_{26}H_{42}ON_2I_2$	4·4	—	—	4·3	—	—
	Bu^n	,,	,,	226 (soft. 222)	EtOH	$C_{28}H_{46}ON_2I_2$	4·4	37·5	—	4·1	37·3	—
	n-C_5H_{11}	,,	,,	Two stages 229—230 248—250	MeOH	$C_{30}H_{50}ON_2I_2$	(C, 50·8; H, 6·8.)			(C, 50·9; H, 7·0.)		
	,,	,,	Br	208—209	EtOH–Et_2O	$C_{30}H_{50}ON_2Br_2,H_2O$	—	26·4	3·0	—	26·0	2·8
	,,	$MeN<[CH_2]_4>CH_2$	I	133	Pr^{i}OH	$C_{36}H_{58}ON_2I_2$	—	31·9	—	—	32·2	—
	,,	,,	Br	69—72 (deliquesc.)	Pr^{i}OH–Et_2O	$C_{36}H_{58}ON_2Br_2,2H_2O$	—	23·4	5·0	—	23·0	4·9
	n-C_6H_{13}	NMe_3	I	Two stages 228—229 247—249	Insol.	$C_{32}H_{54}ON_2I_2$	—	34·7	—	—	34·5	—
	,,	,,	Cl	80—85	Resin	$C_{32}H_{54}ON_2Cl_2$	—	12·9	—	—	12·8	—
	n-C_7H_{15}	,,	I	Two stages 220—221 240—242	EtOH	$C_{34}H_{58}ON_2I_2$	—	33·3	—	—	33·2	—
	,,	,,	Br	211	EtOH–Et_2O	$C_{34}H_{58}ON_2Br_2$	—	23·6	—	—	23·8	—
	Ph	,,	Cl *	166—167	Aq. $COMe_2$	$C_{32}H_{38}ON_2Cl_2,4H_2O$	4·9	13·1	11·5	5·2	13·2	11·8
	p-C_6H_4Me	,,	,, *	135—136	EtOH–Et_2O	$C_{34}H_{42}ON_2Cl_2,4H_2O$	4·7	12·6	10·8	5·0	12·5	11·3
	Ph·CH_2	,,	I	Two stages 210—212 266—267	MeOH	$C_{34}H_{42}ON_2I_2$	—	33·6	—	—	33·9	—
	,,	,,	Br	267—268 (soft. 214—216)	Aq. $COMe_2$	$C_{34}H_{42}ON_2Br_2$	—	24·4	—	—	24·5	—
(VI)	Me	—	I	186—187	,,	$C_{23}H_{36}O_2N_2I_2$	4·3	40·9	—	4·5	40·6	—
	Ph·CH_2	—	Br *	170	Amorphous	$C_{35}H_{44}O_2N_2Br_2,2H_2O$	—	23·3	5·0	—	23·4	5·0
(IX)	Me	—	I	172—173	Aq. $COMe_2$	$C_{24}H_{38}O_3N_2I_2$	4·3	38·8	—	4·3	38·7	—
	Ph·CH_2	—	,,	171—172	Amorphous	$C_{36}H_{46}O_3N_2I_2$	3·3	31·6	—	3·5	31·4	—

* Prepared directly from the crude iodides which were not investigated.

catalyst was then filtered off, the filtrate evaporated under reduced pressure, and the residue distributed between ether and N-hydrochloric acid. The acid layer was made alkaline with concentrated aqueous sodium hydroxide, and the precipitated oil extracted with ethyl acetate since it was immiscible with ether. The solution was dried and evaporated, and the residual 4 : *4′-bis-1″-aminoethyldiphenyl ether* (II; $R^1 = Me$, $R^2 = R^3 = H$), distilled *in vacuo* (b. p. 152—154°/0·02 mm.; 15 g.).

(b) *Meerwein–Ponndorf reduction, etc.* 4 : 4′-Diacetyldiphenyl ether (I; R = Me) (20 g.) was reduced with aluminium *iso*propoxide (25 g.) in dry *iso*propanol (250 ml.) (Wilds, "Organic Reactions," Wiley & Sons, 1944, Vol. II, p. 199). When reduction was complete the mixture was poured into excess of dilute hydrochloric acid, and the precipitated 4 : *4′-bis-1″-hydroxyethyldiphenyl ether* (see below) was separated at the centrifuge. It was then dissolved in a mixture of ether and toluene, and the solution dried overnight (Na_2SO_4), filtered, and saturated at −5° with hydrogen bromide during 3 hr. The red mixture was poured on ice, and the organic layer separated, washed with aqueous sodium carbonate, dried for 10 min. (Na_2SO_4), and filtered. Morpholine (40 ml.) was added to the filtrate, and the mixture heated on a steam-bath. After 3 hr., the resulting suspension was cooled and filtered, and the filtrate exhaustively extracted with 0·5N-hydrochloric acid. The regenerated base was collected in ether and distilled *in vacuo*, and the fraction, b. p. 220—230°/0·01 mm. (11·5 g.), was added to a solution of oxalic acid (6 g.) in ethanol. Addition of ether gave a gum from which the supernatant liquors were decanted. The residue was stirred with acetone, the acetone decanted, and the residue redissolved in methanol. 4 : *4′-Bis-1″-morpholinoethyldiphenyl ether di(hydrogen oxalate)* slowly crystallised in needles, m. p. 138—139° (14·1 g.). The regenerated *base* had b. p. 216—217°/0·01 mm.

Another preparation of the intermediate, 4 : 4′-bis-1″-hydroxyethyldiphenyl ether slowly solidified and, recrystallised from ether–toluene, had m. p. 86—87° (Found: C, 74·5; H, 7·3. $C_{16}H_{18}O_3$ requires C, 74·4; H, 7·0%). *4′ : 5-Di-(1-hydroxy-2-phenylethyl)-2-methoxydiphenyl ether* (see below), similarly prepared, slowly crystallised from toluene and had m. p. 82—83° (Found: C, 78·6; H, 6·2. $C_{29}H_{28}O_4$ requires C, 79·1; H, 6·4%), but 4 : 4′-bis-1″-hydroxyhexyldiphenyl ether and 4 : 4′-di-(1-hydroxyphenethyl)diphenyl ether (see below) could not be crystallised. They decomposed on attempted distillation.

(c) *Reductive amination.* 4 : 4′-Bisphenylacetyldiphenyl ether (I; $R = CH_2Ph$) (11 g.) was reduced in a saturated solution of methylamine in *n*-butanol (200 ml.) over Raney nickel (3 g.) under hydrogen at 80°/90 atm. The resulting 4 : *4′-di-(1-methylaminophenethyl)diphenyl ether* (II; $R^1 = CH_2{\cdot}Ph$, $R^2 = H$, $R^3 = Me$) was separated from non-basic products as before; it was a viscid liquid (4·2 g.), b. p. 266—270°/0·01 mm.

Bisquaternary Compounds (III), (VI), *and* (IX) (Table 4).—A solution of 4 : 4′-bis-1″-aminoethyldiphenyl ether (4·6 g.) and methyl iodide (20 ml.) in methanol (50 ml.) was heated to reflux with anhydrous sodium carbonate (4·2 g.). After 2 hr., the inorganic material was filtered off and the filtrate cooled, 4 : *4′-di-(1-trimethylammoniumethyl)diphenyl ether di-iodide* (III; $R^1 = R^2 = R^3 = R^4 = Me$, X = I) separating in thick prisms, m. p. 218—219° (decomp.). Alternatively, a small excess of methyl iodide was added to methanolic 4 : 4′-bis-1″-dimethylaminoethyldiphenyl ether (II; $R^1 = R^2 = R^3 = Me$) (see below); there was a vigorous reaction and the desired di-iodide rapidly crystallised, having m. p. 218—219° undepressed on admixture with the di-iodide obtained as above. The quaternisations of other ditertiary amines prepared by method (*b*) were similarly effected.

The di-iodides of the higher members of the series were too insoluble in water for biological testing and were therefore converted into the more soluble dichlorides or dibromides by treatment with the appropriate silver halide in boiling methanol.

4 : *4′-Bis-1″-dimethylaminoethyldiphenyl Ether* (II; $R^1 = R^2 = R^3 = Me$) (Table 3).—4 : 4′-Bis-1″-aminoethyldiphenyl ether (28 g.) was methylated with formic acid (60 ml.) and aqueous formaldehyde (37%; 48 ml.) (see Clarke, Gillespie, and Weisshaus, *loc. cit.*). After 10 hours' heating at 100°, concentrated hydrochloric acid (8 ml.) was added before evaporation *in vacuo*. Excess of concentrated aqueous ammonia was added to the residue, the separated oil taken up into ethyl acetate, and the residual aqueous layer extracted several times with the same solvent. The combined extracts were dried and evaporated, and the residue distilled, but the product (12·3 g.) was impure. It was therefore treated with excess of picric acid in ethanol, and the resulting dipicrate recrystallised from acetic acid from which it separated in yellow prisms, m. p. 200°. This was decomposed by addition to a warm solution of concentrated hydrochloric acid in acetic acid, the solution quickly cooled, and the precipitated picric acid filtered off. The filtrate was poured into water, a further crop of picric acid removed, and the solution

extracted several times with ether. The residual aqueous solution was made strongly alkaline with concentrated aqueous sodium hydroxide and then extracted repeatedly with ethyl acetate. The combined extracts were dried and evaporated; the residual *product* (II; $R^1 = R^2 = R^3 =$ Me) had b. p. 153—158°/0·01 mm.

4 : 4′-*Bis*-1″-*dimethylaminoheptyldiphenyl ether* (II; $R^1 = C_6H_{13}$, $R^2 = R^3 =$ Me) was analogously prepared but purification *via* the dipicrate was unnecessary. It was an oil, b. p. 212—217°/0·04 mm.

Reduction, etc., of 4 : 4′-*Bisphenylacetyldiphenyl Ether* (I; R = CH_2Ph). *Attempted Preparation of* 4 : 4′-*Di*-(1-*dimethylaminophenethyl*)*diphenyl Ether* (II; $R^1 = CH_2Ph$, $R^2 = R^3 =$ Me).—4 : 4′-Bisphenylacetyldiphenyl ether (7·5 g.) was reduced with aluminium *iso*propoxide (12 g.) in *iso*propanol (200 ml.), the resulting dialcohol brominated as previously described, and the resulting dibromide and alcoholic dimethylamine (20%; 100 ml.) caused to react in an autoclave at 90°. After 3 hr. the mixture was cooled, the ethanol evaporated, and water added to the residue. The insoluble material was collected in ether, and the basic products (A) were separated from the neutral products (B) with 0·5N-hydrochloric acid.

Fraction (A) was a resin (3·7 g.), b. p. 230—240°/0·1 mm. Its solution in methanol rapidly deposited crystals of 4-(1-*dimethylaminophenethyl*)-4′-*styryldiphenyl ether* (X; R = NMe_2) (1·9 g.), m. p. 111—112° (from *iso*propanol) (Found: C, 85·6; H, 6·9; N, 3·4. $C_{30}H_{29}ON$ requires C, 85·9; H, 7·0; N, 3·3%). Its *methiodide*, crystallised from aqueous ethanol, had m. p. 158° (Found: N, 2·4; I, 22·5. $C_{31}H_{32}ONI$ requires N, 2·4; I, 22·6%). Evaporation of the original methanolic mother-liquors of this base gave a gum, b. p. 228—235°/0·01 mm. (1·4 g.). With methyl iodide in methanol, it gave a crystalline solid (1·1 g.), m. p. 260—267° after shrinking at 200—205°. This was twice recrystallised from methanol–ethanol, yielding slender prisms of 4 : 4′-di-(2-phenyl-1-trimethylammonium-ethyl)diphenyl ether di-iodide (III; $R^1 = CH_2Ph$, $R^2 = R^3 = R^4 =$ Me, X = I) (Table 4; see below).

Evaporation of the ethereal solution of (B) gave a crystalline residue of 4-(1-*hydroxyphenethyl*)-4′-*styryldiphenyl ether*; crystallised from *iso*propanol, this had m. p. 113—114° (Found: C, 85·6; H, 6·5. $C_{28}H_{24}O_2$ requires C, 85·7; H, 6·2%).

When 2-methoxy-4′ : 5-bisphenylacetyldiphenyl ether (IV; R = CH_2Ph) was subjected to the same series of reactions, only 2-*methoxy*-4′ : 5-*distyryldiphenyl ether* (XI), m. p. 177° (from ethyl acetate), resulted (Found: C, 86·2; H, 5·7. $C_{29}H_{24}O_2$ requires C, 86·1; H, 5·9%).

4 : 4′-*Di*-(2-*phenyl*-1-*trimethylammoniumethyl*)*diphenyl Ether Di-iodide* (III; $R^1 = CH_2Ph$, $R^2 = R^3 = R^4 =$ Me, X = I).—Exhaustive methylation of 4 : 4′-di-(1-aminophenethyl)diphenyl ether (II; $R^1 = CH_2Ph$, $R^2 = R^3 =$ H), prepared by method (*a*) (see Table 3), gave the above *di-iodide*, m. p. 266—267° after sintering at 210—212° (from methanol) (Found: I, 33·6. $C_{34}H_{42}ON_2I_2$ requires I, 33·9%). Similar methylation of 4 : 4′-di-(1-methylaminophenethyl)diphenyl ether, prepared by method (*c*) (see above and Table 3), gave a product, m. p. 265—266°, sintering at 214—215° (Found: N, 3·5; I, 33·5. Calc. for $C_{34}H_{42}ON_2I_2$: N, 3·5; I, 33·9%). The m. p.s of these two products showed no depression on admixture with each other or on admixture with the (same) di-iodide obtained from the impure 4 : 4′-bis-(1-dimethylaminophenethyl)diphenyl ether (II; $R^1 = CH_2{\cdot}Ph$, $R^2 = R^3 =$ Me), prepared by method (*b*) (see above).

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