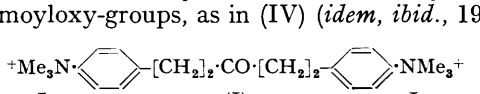
620. *Diacid Bases. Part I. Compounds related to* 1 : 5-*Diphenylpentane*-pp′-*bis*(*trialkylammonium*) *Salts as Anti-cholinesterases.*

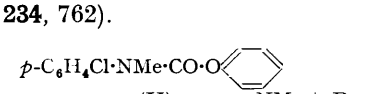
By F. C. Copp.

The discovery that 3-oxo-1 : 5-diphenylpentane-*pp*-bis(trimethylammonium) di-iodide was a selective inhibitor of true cholinesterase led to the preparation, by routine methods, of a number of related mono- and bis-quaternary compounds derived from 1 : 5-diphenyl-pentane, -pentan-3-one, and -pentan-3-ol.

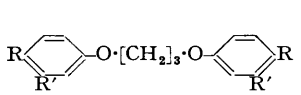
3-Oxo-1 : 5-diphenylpentane-*pp*′-bis(trimethylammonium) di-iodide (I), prepared in these laboratories by Dr. J. R. Catch and the present author, was found to possess marked anti-cholinesterase properties (Fulton and Mogey, personal communication), being much more effective against true than against pseudo-cholinesterase (for differentiation of true and pseudo-cholinesterases see Augustinsson, *Acta Physiol. Scand.*, 1948, **15**, Suppl. 52, p. 21). Further work was therefore undertaken on the relation of structure to activity in this series. Chemically, (I) differs from earlier selective inhibitors of true cholinesterase, *e.g.*, caffeine (Zeller and Bissegger, *Helv. Chim. Acta*, 1943, **26**, 1619), di-2-chloroethylmethylamine (Adams and Thompson, *Biochem. J.*, 1948, **42**, 170), and " Nu-1250 " (II) (Hawkins and Mendel, *ibid.*, 1949, **44**, 260). Whilst this work was in progress the related compounds (III*a* and *b*) were reported by Funke and Depierre (*Compt. rend.*, 1950, **230**, 245) and by Funke, Krucker, and Depierre (*ibid.*, 1950, **231**, 498) to possess high anti-cholinesterase activity, much increased by the introduction of one or two dimethylcarbamoyloxy-groups, as in (IV) (*idem, ibid.*, 1952, **234**, 762).



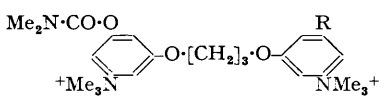
I⁻ (I) I⁻



(II)



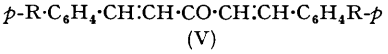
(III*a*; R = NMe_3^+, R = H)
(III*b*; R = H, R′ = NMe_3^+)



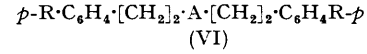
(IV; R = H or O·CO·NMe_2)

The starting material for (I) was 1 : 5-bis-*p*-dimethylaminophenylpentadien-3-one (V; R = NMe_2) (Sachs and Lewis, *Ber.*, 1902, **35**, 3576) which had been previously catalytically reduced to 1 : 5-bis-*p*-dimethylaminophenylpentan-3-one (VI; R = NMe_2, A = CO) (Rupe, Collin, and Schmiderer, *Helv. Chim. Acta*, 1931, **14**, 1340). In our hands, hydrogenation of (V; R = NMe_2) over freshly prepared Raney nickel (Pavlic and Adkins, *J. Amer. Chem. Soc.*, 1946, **68**, 1471) gave solely 1 : 5-bis-*p*-dimethylaminophenylpentan-3-ol (VI; R = NMe_2, A = CH·OH), though use of Raney nickel which had been kept for 2—4 months led to (VI; R = NMe_2, A = CO); use of palladium–charcoal led to a mixture of the alcohol and ketone. With phenyl- or ethyl-magnesium bromide the ketone gave the alcohols (VI; R = NMe_2, A = CPh·OH) (Rupe, Collin, and Schmiderer, *loc. cit.*) and (VI; R = NMe_2, A = CEt·OH). Reduction of the ketone by Clemmensen's method was very slow but eventually gave (VI; R = NMe_2, A = CH_2). These bases were easily converted into the corresponding bisquaternary salts (Table 1, p. 3118) whilst a few mono-quaternary salts were also prepared by similar methods (see Table 2).

The anti-cholinesterase properties of all these compounds were examined in the Biological Division of these laboratories by Mrs. Muriel Fulton and Dr. Mogey. High activity against true cholinesterase only, considered on a molar basis, was not found unless two quaternary groups were present, and (VI; A = CO, R = $\overset{+}{N}Me_2Pr$) was the most active of these bisquaternary compounds. Since this compound was also amongst the least active



(V)



(VI)

against pseudo-cholinesterase, it was decidedly superior to the original compound (I) as a

selective inhibitor of true cholinesterase. The selective effects of (VI; A = CO, R = $\overset{+}{N}Me_2 \cdot CH_2 \cdot CH{:}CH_2$) (" 284C51 ") have been further examined by Austin and Berry (*Biochem. J.*, 1953, **53**, ix).

Experimental

1 : 5-*Bis*-p-*dimethylaminophenylpentadien*-3-*one*.—This compound was prepared by the method of Sachs and Lewis (*loc. cit.*) from *p*-dimethylaminobenzaldehyde and acetone. 1 : 5-*Bis*-p-*diethylaminophenylpentadien*-3-*one*, prepared by analogous means in 12% yield, crystallised from ethanol in bright orange plates, m. p. 168—169° (Found: C, 79·9; H, 8·7; N, 7·5. $C_{25}H_{32}ON_2$ requires C, 79·7; H, 8·6; N, 7·4%). 1-*p*-Dimethylaminophenyl-5-phenylpentadien-3-one was prepared by Borsche's method (*Annalen*, 1910, **375**, 177), and 1-*p*-dimethylaminophenyl-5-*p*-methoxyphenylpentadien-3-one by that of Pfeiffer, Angern, Baches, Fitz, Prahl, Rheinholdt, and Stoll (*ibid.*, 1925, **441**, 258).

Reduction of 1 : 5-*Bis*-p-*dimethylaminophenylpentadien*-3-*one*.—A suspension of 1 : 5-bis-*p*-dimethylaminophenylpentadien-3-one (10 g.) in ethanol or ethyl acetate (100 ml.) was reduced under hydrogen at 10 atm. with 5 g. of catalyst (see below) until absorption became very slow. The catalyst and solvent were removed and the residue treated with 10% excess of semicarbazide acetate in methanol (20 ml.) for 1 hr. The resulting semicarbazone, recrystallised from ethanol, had m. p. 151—152°; the regenerated ketone crystallised in plates (from methanol), m. p. 82—83°. Rupe, Collin, and Schmiderer (*loc. cit.*) found m. p. 86—87°. Its *dihydrobromide*, crystallised from ethanol, had m. p. 186—187° (Found: C, 51·5; H, 6·5; N, 5·7. $C_{21}H_{30}ON_2Br_2$ requires C, 51·7; H, 6·2; N, 5·8%).

The methanolic filtrate from the crude semicarbazone was evaporated and water added to the residue. The resulting 1 : 5-*bis*-p-*dimethylaminophenylpentan*-3-*ol* crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 75—76° (Found: C, 77·2; H, 9·1; N, 8·5. $C_{21}H_{30}ON_2$ requires C, 77·25; H, 9·3; N, 8·6%). Its *dihydrobromide* had m. p. 205—206° (from ethanol) (Found: C, 51·7; H, 6·6; N, 5·85. $C_{21}H_{32}ON_2Br_2$ requires C, 51·6; H, 6·6; N, 5·7%). Its O-*acetate* was an oil, b. p. 206—210°/1·5 × 10^{-4} mm. (Found: C, 74·45; H, 8·55. $C_{23}H_{32}O_2N_2$ requires C, 75·0; H, 8·7%); the *O*-benzoate was a gum which decomposed on attempted distillation though it was satisfactorily characterised as its dimethiodide (see Table 1).

When palladium–charcoal was used for the hydrogenation the ketone and alcohol were obtained in approximately equal quantities. Raney nickel which had been kept for 3—5 months gave little or none of the alcohol whilst Raney nickel used within one month of preparation gave no ketone. The total yield in each case was *ca.* 75%.

By similar methods were prepared: 1 : 5-*bis*-p-*diethylaminophenylpentan*-3-*one*, b. p. 210°/0·05 mm. (Found: C, 79·3; H, 9·6. $C_{25}H_{36}ON_2$ requires C, 78·9; H, 9·5%) [*semicarbazone*, m. p. 129° (from methanol) (Found: C, 71·3; H, 8·7; N, 16·3. $C_{26}H_{39}ON_5$ requires C, 71·4; H, 8·9; N, 16·0%); *dihydrobromide*, m. p. 160—161° (from ethanol–ethyl acetate) (Found: C, 55·6; H, 7·1; N, 5·25. $C_{25}H_{38}ON_2Br_2$ requires C, 55·3; H, 7·1; N, 5·2%)]; 1-p-*dimethylaminophenyl*-5-*phenylpentan*-3-*one*, m. p. 75° (from methanol) (Found: C, 81·1; H, 8·1. $C_{19}H_{23}ON$ requires C, 81·1; H, 8·2%) [*semicarbazone*, m. p. 140° (from ethanol) (Found: N, 16·3. $C_{20}H_{26}ON_4$ requires N, 16·6%)]; 1-p-*dimethylaminophenyl*-5-p-*methoxyphenylpentan*-3-*one*, b. p. 180—185°/0·03 mm., m. p. 39—41° (Found: N, 4·6. $C_{20}H_{25}O_2N$ requires N, 4·5%) [*semicarbazone*, m. p. 156° (from ethanol) (Found: N, 15·0. $C_{21}H_{28}O_2N_4$ requires N, 15·2%)]; 1 : 5-*bis*-p-*diethylaminophenylpentan*-3-*ol*, b. p. 224—228°/0·1 mm., m. p. 50—51° (Found: C, 78·85; H, 9·9; N, 7·2. $C_{25}H_{38}ON_2$ requires C, 78·5; H, 9·9; N, 7·3%) [*dihydrobromide*, m. p. 174·5—175·5° (from ethanol–ethyl acetate) (Found: C, 54·85; H, 7·3; N, 5·2. $C_{25}H_{40}ON_2Br_2$ requires C, 55·1; H, 7·4; N, 5·1%)]; 1-p-*dimethylaminophenyl*-5-p-*methoxyphenylpentan*-3-*ol*, b. p. 220°/0·03 mm., m. p. 60° (Found: C, 76·25; H, 8·4; N, 4·5. $C_{20}H_{27}O_2N$ requires C, 76·6; H, 8·7; N, 4·5%).

1 : 5-*Bis*-p-*dimethylaminophenylpentane*.—1 : 5-Bis-*p*-dimethylaminophenylpentan-3-one (5 g.) was reduced with amalgamated zinc (125 g.), hydrochloric acid (250 ml., diluted with 200 ml. of water), and acetic acid (25 ml.) for 60 hr., a further 125 g. of zinc being added after 30 hr. and hydrochloric acid (20 ml.) every 6 hr. The resulting thick suspension was decanted from the undissolved zinc and made just alkaline with concentrated sodium hydroxide solution. The thick precipitate was filtered, washed with water, and repeatedly extracted with boiling ethanol. The combined extracts were evaporated and the residual gum (3·5 g.) was treated with excess of semicarbazide acetate in boiling methanol (10 ml.) for 2 hr. The resulting mixture was cooled, filtered, and evaporated. The residue was distributed between water (20 ml.) and ether (50 ml.) and kept at 0° for 72 hr. The mixed liquids were decanted from a

small amount of semicarbazone, and the ethereal layer dried and evaporated. The residue, 1 : 5-*bis*-p-*dimethylaminophenylpentane* was a viscous liquid (2·0 g.), b. p. 208—210°/0·2 mm. (Found: C, 80·6; H, 9·5; N, 8·9. $C_{21}H_{30}N_2$ requires C, 81·2; H, 9·7; N, 9·0%). The *dihydrobromide* crystallised from *iso*propanol–ethyl acetate as needles, m. p. 186—187° (Found: C, 53·1; H, 6·8; N, 5·65. $C_{21}H_{32}N_2Br_2$ requires C, 53·4; H, 6·8; N, 5·9%).

TABLE 1. *Bisquaternary salts of* (VI).

R	A	Acid radical (X)	M. p.	Solvent for crystn.	Formula	Found (%) N	Found (%) X	Reqd. (%) N	Reqd. (%) X	Loss on drying (%)
NMe_3	CH_2	I	126—127°	EtOH	$C_{23}H_{36}N_2I_2$	4·4	42·4	4·7	42·7	4·1
NMe_3	CO	I	244	MeOH	$C_{23}H_{34}ON_2I_2$	4·7	41·85	4·6	41·9	—
NMe_2Et	CO	I	198	Aq. PriOH	$C_{25}H_{38}ON_2I_2$	—	40·3	—	39·9	2·6
NMe_2Pr	CO	I	178—179	EtOH	$C_{27}H_{42}ON_2I_2$	—	38·5	—	38·2	—
		Br	191—192	,,	$C_{27}H_{42}ON_2Br_2$	—	28·1	—	28·0	—
$NMe_2{\cdot}CH_2{\cdot}CH{:}CH_2$	CO	I	179—180	MeOH–EtOAc	$C_{27}H_{38}ON_2I_2$ [a]	—	38·4	—	38·4	—
		Br	199—200	EtOH	$C_{27}H_{38}ON_2Br_2$	—	28·4	—	28·2	—
$NMe_2{\cdot}CH_2{\cdot}C{:}CH$ ...	CO	I	102—103	,,	$C_{27}H_{34}ON_2I_2$	—	38·8	—	38·7	2·6
		Br	α-form, 161	EtOH–EtOAc	$C_{27}H_{34}ON_2Br_2$	—	28·45	—	28·4	—
			β-form, 89—90	EtOH	,,	—	27·8	—	,,	5·3
$NMeEt_2$	CO	I	88—90	,,	$C_{27}H_{42}ON_2I_2$	—	38·2	—	38·2	8·0
NMe_2Bu	CO	I	206—207	MeOH	$C_{29}H_{46}ON_2I_2$	—	36·6	—	36·7	—
		Br	194—195	EtOH–EtOAc	$C_{29}H_{46}ON_2Br_2$	—	26·8	—	26·7	—
$NMe_2{\cdot}CH_2Ph$	CO	Cl	127—128	BuOH	$C_{35}H_{42}ON_2Cl_2$	—	12·4	—	12·3	4·8
NMe_3	CH·OH	I	205—206	EtOH	$C_{23}H_{36}ON_2I_2$	4·4	41·3	4·6	41·6	—
NMe_2Et	CH·OH	I	178—180	,,	$C_{25}H_{40}ON_2I_2$ [b]	4·5	—	4·4	—	—
$NMeEt_2$	CH·OH	I	112—113	EtOH–PriOH	$C_{27}H_{44}ON_2I_2$	—	38·4	—	38·1	—
NMe_3	CH·OAc	I	127—129	MeOH	$C_{25}H_{38}O_2N_2I_2$ [c]	4·35	—	4·3	—	4·8
NMe_3	CH·OBz	I	137	MeOH–EtOH	$C_{30}H_{40}O_2N_2I_2$	—	35·0	—	35·5	3·1
NMe_3	CEt·OH	I	81—82	EtOH	$C_{25}H_{40}ON_2I_2$	4·5	39·9	4·4	39·8	6·1
NMe_3	CPh·OH	I	151—153	MeOH–Et_2O	$C_{29}H_{40}ON_2I_2$	4·1	36·9	4·1	37·0	—

[a] Found: C, 49·1; H, 5·8. Reqd.: C, 49·1; H, 5·8%. [b] Found: C, 47·1; H, 6·1. Reqd.: C, 47·0; H, 6·3%. [c] Found: C, 46·0; H, 5·8. Reqd.: C, 46·1; H, 5·9%.

TABLE 2. *Monoquaternary salts and miscellaneous bisquaternary salts,* p-$R{\cdot}C_6H_4{\cdot}B{\cdot}A{\cdot}B{\cdot}C_6H_4{\cdot}NMe_3^+$-$p$ X^-.

R	B	A	X	M. p.	Solvent for crystn.	Formula	Found (%) N	Found (%) X	Reqd. (%) N	Reqd. (%) X
H	CH:CH	CO	I	174°	Aq. MeOH	$C_{20}H_{22}ONI$	3·5	—	3·3	—
H	CH:CH	CO	Cl	169—170	EtOH–Et_2O	$C_{20}H_{22}ONCl$	—	10·8	—	10·75
$^+NMe_3\}I^-$	CH:CH	CO	I	195	H_2O	$C_{23}H_{30}ON_2I_2$	4·6	—	4·6	—
H	$[CH_2]_2$	CO	I	183	EtOH	$C_{20}H_{26}ONI$	—	30·2	—	30·0
NMe_2,HI ...	$[CH_2]_2$	CO	I	203	EtOH–MeOH	$C_{22}H_{32}ON_2I_2$	4·5	—	4·7	—
OMe	$[CH_2]_2$	CO	I	173—175	EtOH	$C_{21}H_{28}O_2NI$	3·3	28·0	3·1	28·0
OMe	$[CH_2]_2$	CH·OH	I	131	MeOH–Et_2O	$C_{21}H_{30}O_2NI$	3·3	28·2	3·1	27·9

1 : 5-*Bis*-p-*dimethylaminophenyl*-3-*ethylpentan*-3-*ol*.—1 : 5-Bis-*p*-dimethylaminophenylpentan-3-one (6·0 g.) was treated with ethylmagnesium bromide [from ethyl bromide (7·5 g.) and magnesium (1·5 g.)]. The *product* was a gum, which was sublimed at 155°/0·001 mm., and subsequently crystallised (m. p. 40°) (Found: N, 8·0. $C_{23}H_{34}ON_2$ requires N, 7·9%).

Quaternary Salts.—These *salts* were prepared from the appropriate alkyl halide and tertiary amine in acetone or ethanol (see Tables 1 and 2). M. p.s refer to materials which have been dried for 24 hr. *in vacuo* at room temperature; analyses refer to materials dried at 100° *in vacuo*, further (usually small) losses of uncertain significance occurring which are quoted only when >2%.

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