SYNTHESIS OF IODINATED DERIVATIVES OF 3-AMINOBENZYLAMINE AND 3,5-DIAMINOBENZYLAMINE FOR X-RAY DIAGNOSTICS

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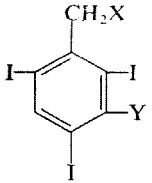
Received January 6th, 1976

Triiodo and tetraiodo derivatives of 3-amino and 3,5-diaminobenzylamine *XXII*—*LXII* were prepared by condensation of substituted benzyl chlorides *I*—*XV* and *XVI*—*XXI* with 2-hydroxyethylaminoethanol, 3-amino-1,2-propanediol, 3-(2,3-dihydroxypropylamino)-1,2-propanediol, 2,3-isopropylidenedioxypropylamine, bis-(2,3-isopropylidenedioxypropyl)amine, 2-amino-2-methyl-1,3-propanediol, 2-methylaminoethanol, 2-ethylaminoethanol and N-methylglucamine.

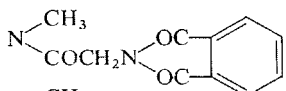
It followed from earlier work in this laboratory[1] that rapid transport of an orally administered X-ray contrast agent from the gastrointestinal tract to the bile system is enhanced by the presence of hydrophilic substituents in their molecule, *e.g.* of hydroxyalkyl, amino and amido groups. Of these derivatives, it was particularly N-[2,4,6-triiodo-3-(acetyl-β,γ-dihydroxy propylamino)benzyl]diethanolamine hydrochloride, with the generic designation Triiodamine[2], that in clinical tests on more than 300 patients receiving 3-g doses *per os* was able after 2—4 h to fill the gall bladder in such a manner that a good image of the gall bladder could be obtained. Higher doses of 6 g *per os* made possible after 30—60 min a primary examination of the bile ducts (the common bile duct, the cystic duct and the choledoch duct): the visualization of the gall bladder was then optimal 2 h after oral administration. The rate of absorption and excretion through the biliary passages was similar with Triiodamine, as with the previously known injection preparations. The compound was highly satisfactory as to its toxicity, tolerance and rate of absorption but in tests on rats and rabbits in high doses it was found to interfere with the fetal development as manifested by the high incidence of dead fetuses.

For these reasons, the synthesis and testing of Triiodamine-type compounds went on, using both triiodo and tetraiodo derivatives, it being known that the development of iodinated X-ray contrast agents proceeded from the diiodo to the triiodo derivatives whereby the toxicity was decreased, and tolerance and contrast effects were increased. The Triiodamine molecule was modified at both nitrogen atoms.

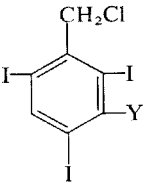
The synthesis of compounds derived from 3-aminobenzylamine *XXII*—*XLVI* of general formula *1* was achieved by condensation of substituted benzyl halogenides *I*—*XV*, mainly of chlorides, of general formula *2*, with 2-hydroxyethylaminoethanol,



1

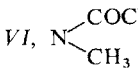
	X	Y
XXII,	$N(CH_2CHCH_2OH)_2$ (OH)	NH_2
XXIII,	$N(CH_2CHCH_2OH)_2$ (OH)	$NHCOCH_3$
XXIV,	$N(CH_2CHCH_2OH)_2$ (OH)	I
XXV,	$N(CH_2CHCH_2OH)_2$ (OH)	$N{=}CH{-}N(CH_3)_2$
XXVI,	$NHCH_2CHCH_2OH$ (OH)	NH_2
XXVII,	$NHCH_2CHCH_2OH$ (OH)	$NHCH_3$
XXVIII,	$NHCH_2CHCH_2OH$ (OH)	OCH_3
XXIX,	$N(CH_2CH_2OH)_2$	$NHCH_3$
XXX,	$N(CH_2CH_2OH)_2$	$NHCOCH_2OH$
XXXI,	$N(CH_2CH_2OH)_2$	$N(COCH_2OH)(CH_2CH_2OH)$
XXXII,	$N(CH_2CH_2OH)_2$	
XXXIII,	$N(CH_2CH_2OH)_2$	$N(CH_3)(COCH_2NH_2)$
XXXIV,	$N(CH_2CH_2OH)_2$	OCH_2CHCH_2OH (OH)
XXXV,	$NH{-}C(CH_2OH)_2(CH_3)$	$NHCH_3$
XXXVI,	$NH{-}C(CH_2OH)_2(CH_3)$	$NHCOCH_2OH$
XXXVII,	$NH{-}C(CH_2OH)_2(CH_3)$	$N(CH_3)(COCH_2OH)$
XXXVIII,	$NH{-}C(CH_2OH)_2(CH_3)$	OCH_3
XXXIX,	$NH{-}C(CH_2OH)_2(CH_3)$	NH_2
XL,	$N(CH_3)(CH_2CH_2OH)$	$NHCOCH_2OH$
XLI,	$N(CH_3)(CH_2CH_2OH)$	OCH_3
XLII,	$N(C_2H_5)(CH_2CH_2OH)$	$NHCOCH_3$
XLIII,	$N(C_2H_5)(CH_2CH_2OH)$	$NHCOCH_2OH$
XLIV,	$N(C_2H_5)(CH_2CH_2OH)$	OCH_2CHCH_2OH (OH)
XLV,	$N(CH_3)(CH_2(CHOH)_4CH_2OH)$	$NHCH_3$
XLVI,	$N(CH_3)(CH_2(CHOH)_4CH_2OH)$	OCH_3

3-amino-1,2-propanediol, 3-(2,3-dihydroxypropylamino)-1,2-propanediol, 2,3-isopropylidenedioxypropylamine, bis-(2,3-isopropylidenedioxypropyl)amine, 2-amino-2-methyl-1,3-propanediol, 2-methylaminoethanol, 2-ethylaminoethanol and N-methylglucamine.

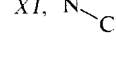


2

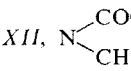
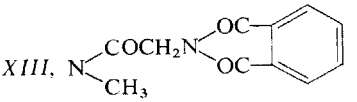
Y

I, NH_2
II, $NHCOCH_3$
III, $NHCOCH_2CH_2CH_3$
IV, I
V, $N{=}CH{-}N(CH_3)_2$
VI, 

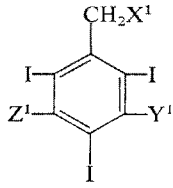
Y

VII, OCH_3
VIII, $NHCH_3$
IX, $NHCOCH_2OCOCH_3$
X, $NHCOCH_2OH$
XI, 

Y

XII, 
XIII, 
XIV, OCH_2CH_2OH
XV, OCH_2CHCH_2OH (OH)

Compounds *I*–*VII* were prepared in this laboratory before[1,3]. The preparation of *I* was now modified so that the reaction of 2,4,6-triiodo-3-amino benzyl alcohol with thionyl chloride is carried out in chloroform or dichloroethane with an addition of pyridine whereby the yields were substantially increased. Chloride *VIII* was prepared by methylation of *I* with formaldehyde in concentrated sulfuric acid[4]. For the preparation of 3-hydroxyacetylamino derivative *X*, freshly prepared acetoxyacetyl chloride was always used, the reaction being conducted in dimethylformamide and the masking group of *IX* being removed by heating with 90% sulfuric acid to 50°C. Analogously, the reaction of *VIII* with acetoxyacetyl chloride in dimethylformamide led to 3-methylacetoxyacetylamino derivative *XI* while saponification of the masking group was done with 75% sulfuric acid which resulted in chloride *XII*. In the preparation of the 3-methylglycyl derivative *XXXIII*, the masking group used was the phthaloyl group, the required 2,4,6-triiodo-3-(methylphthaloylglycyl)aminobenzyl chloride *XIII* being obtained in a reaction of 2,4,6-triiodo-3-methylaminobenzyl chloride *VIII* with phthaloylglycyl chloride in dimethylformamide at 50°C. The cleavage of the masking phthaloyl group was done with hydrazine only after condensation of *XIII* with the appropriate amine. 2,4,6-Triiodo-3-(2-hydroxyethoxy)-benzyl chloride *XIV* and 2,4,6-triiodo-3-(2,3-dihydroxypropoxy)benzyl chloride *XV*

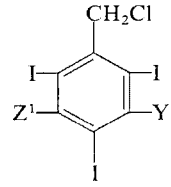


3

	X^1	Y^1	Z^1
XLVII,	$N(CH_2CH_2OH)_2$	$NHCOCH_3$	NH_2
XLVIII,	$N(CH_2CH_2OH)_2$	$NHCOCH_3$	$NHCOCH_3$
IL,	$N(CH_2CH_2OH)_2$	$N(COCH_3)_2$	$N(COCH_3)_2$
L,	$N(CH_2CH_2OH)_2$	$N(COCH_3)CH_2CH_2OH$	NH_2
LI,	$N(CH_2CH_2OH)_2$	$N(COCH_3)CH_2CH(OH)CH_2OH$	NH_2
LII,	$N(CH_2CH_2OH)_2$	$NHCOCH_3$	I
LIII,	$N(CH_2CH_2OH)_2$	$N(COCH_3)_2$	I
LIV,	$N(CH_2CH_2OH)_2$	$N(COCH_3)CH_3$	I
LV,	$N(CH_2CH_2OH)_2$	$N(COCH_3)CH_2CH_2OH$	I
LVI,	$N(CH_2CH_2OH)_2$	$N(COCH_3)CH_2CH(OH)CH_2OH$	I
LVII,	$N(CH_2CH_2OH)_2$	$NHCOCH_3$	OCH_3
LVIII,	$N(CH_2CH_2OH)_2$	$N(COCH_3)CH_2CH_2OH$	$N(COCH_3)CH_2CH_2OH$
LIX,	$N(CH_2CH(OH)CH_2OH)_2$	$NHCOCH_3$	I
LX,	$N(CH_2CH(OH)CH_2OH)_2$	NH_2	I
LXI,	$N(CH_2CH(OH)CH_2OH)_2$	$NHCOCH_3$	OCH_3
LXII,	$N(CH_2CH(OH)CH_2OH)_2$	$NHCOCH_3$	NH_2

were prepared by diazotization of *I* with nitrosylsulfuric acid in glacial acetic acid and by subsequent boiling of the diazonium salt with ethylene glycol or with glycerol.

To prepare compounds derived from 3,5-diaminobenzylamine *XLVII – LXII* of general formula *3*, substituted benzyl chlorides *XVI – XXI* of general formula *4* were used, as prepared earlier in this laboratory[5]. They were condensed with 2-hydroxyethylaminoethanol or with 3-(2,3-dihydroxypropylamino)-1,2-propanediol or with bis-(2,3-isopropylidenedioxypropyl)amine.



4

	Y^1	Z^1		Y^1	Z^1
XVI,	$NHCOCH_3$	NH_2	*XIX*,	$NHCOCH_3$	I
XVII,	$NHCOCH_3$	$NHCOCH_3$	*XX*,	$N(COCH_3)_2$	I
XVIII,	$N(COCH_3)_2$	$N(COCH_3)_2$	*XXI*,	$NHCOCH_3$	OCH_3

Condensation of benzyl chlorides of general formulas *2* and *4* with the appropriate amines giving rise to compounds of general formulas *1* and *3* was done in absolute ethanol in the presence of alkaline metal carbonate or hydrogen carbonate, this being followed by alkylation, hydroxyalkylation or dihydroxalkylation with methyl iodide, 2-chloro-1-ethanol or 3-chloro-1,2-propanediol in aqueous ethanol in the presence of potassium hydroxide or in ethanol in the presence of sodium ethoxide. This led to compounds *XXII – XLVI* of general formula *1* and to compounds *XLVII – LXII* of general formula *3*.

3-Amino-1,2-propanediol and 3-(2,3-dihydroxypropylamino)-1,2-propanediol were prepared in this laboratory according to ref.[6] by a reaction of 2,3-isopropylidenedioxypropyl chloride with ammonia wherein a mono- and a di-substituted amine are formed simultaneously, After isolation of these intermediates the masking group is saponified. It was found to be suitable to use these unsaponified intermediates for condensation with benzyl chlorides and to carry out the saponification subsequently with 0·5M hydrochloric acid at 70°C.

EXPERIMENTAL

Unless stated otherwise, the melting points were determined in Kofler's block and are not corrected. Analytical samples were dried at 100°C/0·1 Torr (or at 50°C/0·1 Torr for m.p. lower than 100°C) for 10 h.

3-Amino-2,4,6-triiodobenzyl Chloride (*I*)

A solution of 42 ml thionyl chloride in 120 ml chloroform was added under stirring at room temperature to a mixture of 60·1 g (0·12 mol) 3-amino-2,4,6-triiodobenzyl alcohol, 480 ml chloroform (anhydrous, alcohol-free) and 12 ml pyridine (dried with NaOH). The mixture was heated to 45°C, kept for 1 h at that temperature whereupon the temperature was raised to 65°C (gentle refluxing) and kept there for 3 h. The mixture was then cooled with water with simultaneously adding 60 ml 96% ethanol. The precipitated product was filtered, washed with some 100 ml chloroform and dried. The yield was 58·3 g (93·8%) *I*, m. p. 171–173°C (decomposition), the compound being sufficiently pure for further reactions.

2,4,6-Triiodo-3-methylaminobenzyl Chloride (*VIII*)

38% aqueous formaldehyde (247 ml) was added dropwise over a period of 30 min to a solution of 130 g (0·25 mol) *I* in 500 ml concentrated sulfuric acid, maintained at 50–55°C and the mixture was stirred at that temperature for 7 h. Then it was left to cool and stand overnight. It was then poured on 8 kg crushed ice, the product was filtered and recrystallized from 260 ml chloroform (charcoal). The yield after processing the mother liquors was 81·5 g (61%) *VIII*, m.p. 111–112°C. For $C_8H_7ClI_3N$ (533·4) calculated: 18·01% C, 1·32% H, 6·65% Cl, 71·39% I, 2·63% N; found: 18·11% C, 1·32% H, 6·98% Cl, 71·17% I, 2·31% N.

3-Acetoxyacetylamino-2,4,6-triiodobenzyl Chloride (*IX*)

129·8 g (0·25 mol) *I* was suspended in 600 ml dimethylformamide and then 68 g freshly prepared acetoxyacetyl chloride[6] (b.p. 58°C/15 Torr) was added dropwise under cooling with water and stirring over a period of 30 min. The mixture was stirred for 18 h at room temperature, poured under stirring into 2 liters water and the crystalline product was filtered. The yield of crude *IX* was 140·8 g (98·2%), m.p. 250–253°C (chlorobenzene). For $C_{11}H_9ClI_3NO_3$ (619·5) calculated: 21·33% C, 1·46% H, 5·73% Cl, 61·47% I, 2·26% N; found: 21·52% C, 1·39% H, 5·59% Cl, 61·62% I, 2·18% N.

3-Hydroxyacetylamino-2,4,6-triiodobenzyl Chloride (*X*)

Crude *IX* (123·9 g, 0·2 mol) was added at room temperature under stirring to 1 200 ml 90% sulfuric acid, it was heated to 50°C and stirred for 2 h at this temperature. Then it was cooled and poured over ice, the precipitated product was filtered and recrystallized from 5 500 ml ethanol. The yield was 94·3 g (82%), m.p. 224–227°C. For $C_9H_7ClI_3NO_2$ (577·4) calculated: 18·72% C, 1·22% H, 6·14% Cl, 65·95% I, 2·43% N; found: 19·09% C, 1·28% H, 6·10% Cl, 65·74% I, 2·34% N.

3-N-Methyl-N-acetoxyacetylamino-2,4,6-triiodobenzyl Chloride (*XI*)

26·7 g (0·05 mol) *VII* was suspended in 90 ml dimethylformamide and 13·5 ml acetoxyacetyl chloride was added dropwise under stirring and cooling with water. The solution was stirred for 10 h at room temperature, poured into 500 ml water, alkalified with 2M-NaOH (to pH 8) and heated in a boiling-water bath. The solid fraction was filtered. The yield was 28·5 g (96%), m.p. 148–149°C (ethanol). For $C_{12}H_{11}ClI_3NO_3$ (633·4) calculated: 22 75% C, 1·75% H, 5·60% Cl, 60·11% I, 2·21% N; found: 22·73% C, 1·84% H, 5·44% Cl, 60·04% I, 2·37% N.

3-N-Methyl-N-hydroxyacetylamino-2,4,6-triiodobenzyl Chloride (*XII*)

Crude product *XI* (28·5 g) was introduced into 300 ml 75% sulfuric acid and stirred for 2 h at 45—50°C. The mixture was poured onto ice and the crystalline product was filtered and recrystallized from 600 ml ethanol. The yield was 23·8 g (80%), referred to *VIII*, m.p. 178—180°C (ethanol). For $C_{10}H_9ClI_3NO_2$ (591·4) calculated: 20·31% C, 1·53% H, 6·00% Cl, 64·38% I, 2·37% N; found: 20·56% C, 1·53% H, 5·55% Cl, 64·33% I, 2·34% N.

3-N-Methyl-N-phthaloylglycylamino-2,4,6-triiodobenzyl Chloride (*XIII*)

10·7 g (0·02 mol) *VIII*, 8·95 g phthaloylglycyl chloride and 40 ml dimethylformamide was heated under stirring to 50°C for 20 h and left to stand overnight in the refrigerator. The product was then filtered, the mother liquors were processed and a further fraction isolated, a total of 13·0 g, m.p. 251—252°C (ethanol). For $C_{18}H_{12}ClI_3N_2O_3$ (720·5) calculated: 30·00% C, 1·68% H, 4·92% Cl, 52·84% I, 4·17% N; found: 30·25% C, 1·69% H, 5·38% Cl, 52·79% I, 4·17% N.

3-(2,3-Dihydroxypropoxy)-2,4,6-triiodobenzyl Chloride (*XV*)

Crystalline nitrosylsulfuric acid (20 g) was added over a period of 90 min under stirring to a suspension of 77·9 g (0·15 mol) *I* in 380 ml glacial acetic acid and the mixture was further stirred for 4 h. The precipitated yellow diazonium salt was filtered, introduced into 1 000 ml glycerol and heated for 30 min at 90°C, when all of it dissolved. After cooling, 1 000 ml water was added. The precipitated *XV* was recrystallized from 550 ml ethanol. The yield was 55·8 g (62·6%) m.p. 150—151°C (ethanol). For $C_{10}H_{10}ClI_3O_3$ (594·4) calculated: 20·21% C, 1·70% H, 5·96% Cl, 64·06% I; found: 20·72% C, 1·71% H, 5·97% Cl, 63·84% I.

3-(2-Hydroxyethoxy)-2,4-6-triiodobenzyl Chloride (*XIV*)

This was prepared in analogy with *XV*. The yield of ethanol-crystallized product was 64%, m.p. 133—135°C. For $C_9H_8ClI_3O_2$ (564·4) calculated: 19·15% C, 1·43% H, 6·28% Cl, 67·47% I; found: 19·11% C, 1·42% H, 6·13% Cl, 67·72% I.

N-(3-Acetylamino-5-amino-2,4,6-triiodobenzyl)-diethanolamine Hydrochloride (*XLVII*) (Method *A*)

A mixture of 40·35 g (0·07 mol) *XVI*, 22·0 g (0·21 mol) 2-hydroxyethylaminoethanol, 5·9 g (0·07 mol) sodium hydrogen carbonate and 520 ml ethanol was refluxed for 8 h under stirring using a moisture trap on the condenser. The inorganic salts were then filtered and ethanol was evaporated *in vacuo*. The residue was combined with 150 ml water, the product was transferred to a dish and washed several times with water an dissolved in 150 ml 40°C ethanol, the solution was acidified with ethanolic hydrochloric acid to pH 4 and left to crystallize in a refrigerator. The product was filtered and recrystallized from 150 ml 20% aqueous ethanol (activated charcoal). After processing of the mother liquors a total of 35·5 g (75%) *XLVII* was obtained; m.p. 184—185°C (decomposition). The analysis is shown in Table I. Compounds *XLVIII*, *IL*, *LII* and *LIII* were prepared analogously.

TABLE I

Properties and Analyses of *XXII—LXII*

Compound	Procedure yield, %	M.p., °C solvent	Formula (mol.wt.)	Calculated/Found % C	% H	% Cl	% I	% N
XXII[a]	*C* 69	152—156 ethanol	$C_{13}H_{19}I_3N_2O$ (648·0)	24·09 24·19	2·96 3·00	— —	58·75 58·71	4·32 3·41
XXII[b]		203—205 ethanol	$C_{13}H_{20}ClI_3N_2O$ (684·5)	22·81 23·06	2·95 2·87	5·18 5·11	55·62 55·46	4·09 4·03
XXIII[a]	*C* 80	132—136 20% aqueous ethanol	$C_{15}H_{21}I_3N_2O_5$ (690·1)	26·11 26·03	3·07 3·05	— —	55·17 55·41	4·06 3·98
XXIII[b]		199—205 reprecipitated	$C_{15}H_{22}ClI_3N_2O_5$ (726·5)	24·80 24·84	3·05 3·12	4·88 5·05	52·40 52·22	3·86 3·92
XXIV[a]	*C* 47	180—188 (decomp.) water	$C_{13}H_{17}I_4NO_4 . H_2O$ (776·9)	20·08 20·01	2·46 2·27	— —	65·33 65·19	1·80 1·73
XXV[b]	*C* 91	213—219 (decomp.) methanol	$C_{16}H_{26}Cl_2I_3N_3O_4$ (776·1)	24·76 24·26	3·38 3·35	9·14 8·91	49·06 48·35	5·41 5·11
XXVI[a]	*C*	145—147 ethanol	$C_{10}H_{13}I_3N_2O_2$ (574·0)	20·92 21·20	2·28 2·28	— —	66·34 66·42	4·88 4·83
XXVI[b]	64	180—186 (decomp.) water	$C_{10}H_{14}ClI_3N_2O_2$ (610·5)	19·67 19·66	2·31 2·41	5·81 5·75	62·37 62·45	4·59 4·38
XXVII[a]	*C* 76	113—114 ethanol	$C_{11}H_{15}I_3N_2O_2$ (588·0)	22·47 22·57	2·57 2·40	— —	64·75 64·52	4·76 4·55
XXVII[b]		163—164[c] (decomp.) ethanol	$C_{11}H_{16}ClI_3N_2O_2$ (624·5)	21·16 21·22	2·58 2·45	5·68 5·89	60·97 60·72	4·49 4·32
XXVIII[b]	*C* 35	161—162[c] (decomp.) ethanol	$C_{11}H_{15}ClI_3NO_3$ (589·0)	21·12 21·31	2·42 2·36	5·67 5·92	60·88 60·03	2·24 2·37
XXIX[b]	*A* 78	171—172 (decomp.) ethanol)	$C_{12}H_{18}ClI_3N_2O_2$ (638·5)	22·57 22·42	2·84 2·84	5·55 5·43	59·63 59·90	4·39 4·40
XXX[b]	*A* 70	193—197 methanol	$C_{13}H_{18}ClI_3N_2O_4$ (682·5)	22·88 22·60	2·65 2·43	5·19 5·27	55·79 55·28	4·11 3·98
XXXI[b]	*B* 77	105—110 ethanol	$C_{15}H_{22}ClI_3N_2O_5$ (726·5)	24·80 24·63	3·05 2·96	4·88 4·94	52·40 52·76	3·86 3·46

TABLE I
(*Continued*)

Compound	Procedure yield, %	M.p., °C solvent	Formula (mol.wt.)	Calculated/Found % C	% H	% Cl	% I	% N
XXXII[b]	*A* 82	210—212 ethanol	$C_{22}H_{23}ClI_3N_3O$ (825·6)	32·00 31·55	2·80 2·83	4·29 4·25	46·12 45·39	5·09 4·84
XXXIII[b]	— 61	200—205 reprecipitated	$C_{14}H_{22}Cl_2I_3N_3O_3$ (732·0)	22·97 22·80	3·03 2·99	9·69 9·28	52·01 52·09	5·74 5·67
XXXIV[a]	*A* 45	152[c] ethanol	$C_{14}H_{20}I_3NO_3$ (663·1)	25·36 25·54	3·04 3·10	— —	57·42 57·26	2·11 2·09
XXXV[a]	*A* 78	140—141 ethanol	$C_{12}H_{17}I_3N_2O_2$ (602·0)	23·94 24·01	2·85 2·64	— —	63·24 63·32	4·65 4·44
XXXV[b]		164—169 reprecipitated	$C_{12}H_{18}ClI_3N_2O_2$ (638·5)	22·57 22·48	2·84 2·90	5·55 6·68	59·63 59·34	4·39 4·19
XXXVI[a]	— 81	168—171 10% aqueous methanol	$C_{13}H_{17}I_3N_2O_4$ (646·0)	24·16 24·22	2·65 2·65	— —	58·94 58·93	4·34 4·47
XXXVI[b]		228—231[c] (decomp.) ethanol	$C_{13}H_{18}ClI_3N_2O_4$ (682·5)	22·88 22·94	2·66 2·57	5·19 5·39	55·79 55·75	4·10 4·23
XXXVII[b]	*A* 64	244—247 (decomp.) methanol	$C_{14}H_{20}ClI_3N_2O_4$ (696·5)	24·14 24·36	2·90 2·91	5·09 5·42	54·66 54·36	4·02 4·06
XXXVIII[b]	*A* 64	176—180[c] ethanol	$C_{12}H_{17}ClI_3NO_3$ (638·6)	22·54 22·51	2·68 2·67	5·55 5·19	59·54 59·36	2·19 2·20
XXXIX[a]	*A* 72	76—77 methanol	$C_{10}H_{13}I_3N_2O$ (558·0)	21·52 21·65	2·35 2·41	— —	68·24 68·11	5·02 4·85
XXXIX[b]		190—197[c] water	$C_{10}H_{14}ClI_3N_2O$ (594·5)	20·20 20·11	2·37 2·47	5·97 6·23	64·05 63·39	4·71 4·54
XL[a]	*A* 76	128—129 ethanol	$C_{12}H_{15}I_3N_2O_3$ (616·0)	23·40 23·45	2·45 2·39	— —	61·81 61·76	4·55 4·63
XLI[b]	*A* 54	98—106 water	$C_{11}H_{15}ClI_3NO_2$ (609·5)	21·68 21·82	2·48 2·34	5·82 5·63	62·47 61·74	2·30 2·35
XLII[a]	*A* 80	148—153 ethanol	$C_{13}H_{18}ClI_3N_2O_2 . C_2H_5OH$ (696·6)	25·86 25·99	3·47 3·56	5·09 5·33	54·67 54·44	4·04 4·03
XLII[b]		170—173 water	$C_{13}H_{18}ClI_3N_2O_2$ (650·5)	24·00 23·82	2·79 2·75	5·45 5·73	58·53 58·22	4·31 4·21

TABLE I
(*Continued*)

Compound	Procedure yield, %	M.p., °C solvent	Formula (mol.wt.)	Calculated/Found				
				% C	% H	% Cl	% I	% N
XLIII[a]	*A* 81	144—146 ethanol	$C_{13}H_{17}I_3N_2O_3$ (630·1)	24·78 24·90	2·72 2·75	— —	60·43 60·21	4·45 4·14
XLIV[b]	*A* 76	140 ethanol	$C_{14}H_{20}I_3NO_4$ (647·1)	25·98 26·09	3·11 3·21	— —	58·84 58·83	2·16 2·16
XLV[a]	*A* 78	152—153 ethanol	$C_{15}H_{23}I_3N_2O_5$ (692·1)	26·03 26·10	3·40 3·35	— —	55·01 55·04	4·05 4·03
XLVI[a]	*A* 85	152—154 ethanol	$C_{15}H_{22}I_3NO_6$ (693·1)	25·99 25·89	3·20 3·23	— —	54·94 54·91	2·02 2·18
XLVII[b]	*A* 75	184—185 (decomp.) ethanol–ether	$C_{13}H_{19}ClI_3O_3$ (681·5)	22·92 22·75	2·81 2·93	5·19 5·00	55·88 55·87	6·17 6·33
XLVIII[a]	*A* 85	145—147 5% aqueous ethanol	$C_{15}H_{20}I_3N_3O_4$ (687·1)	26·22 25·89	2·93 3·08	— —	55·41 55·21	6·12 5·88
XLVIII[b]		224—227 (decomp.) water	$C_{15}H_{21}ClI_3N_3O_4$ (723·6)	24·27 24·15	3·13 3·07	4·78 4·76	51·35 51·20	5·67 5·78
IL[b]	*A* 61	203—207 (decomp.) water	$C_{19}H_{25}ClI_3N_3O_6$ (807·6)	28·26 28·40	3·12 3·13	4·39 4·33	47·13 48·01	5·20 5·14
L[a]	*B* 80	69—72 reprecipitated	$C_{15}H_{22}I_3N_3O_4$ (689·1)	26·14 26·25	3·22 3·51	— —	55·25 54·12	6·10 5·86
L[d]		176—181 (decomp.) water	$C_{15}H_{23}ClI_3N_3O_8$ (789·6)	22·81 23·13	2·94 3·05	4·49 4·66	48·22 47·95	5·37 5·18
LI[a]	*B* 54	66—74 reprecipitated	$C_{16}H_{24}I_3N_3O_5$ (719·1)	26·73 26·90	3·36 3·61	— —	52·94 52·14	5·85 5·93
LII[b]	*A* 91	207—208 (decomp.) 90% aqueous ethanol	$C_{13}H_{17}ClI_4N_2O_3$ (792·4)	19·71 19·72	2·16 1·83	4·47 4·04	64·07 64·00	3·54 3·57
LIII[b]	*A* 70	192—194 90% aqueous ethanol	$C_{15}H_{19}ClI_4N_2O_4$ (834·5)	21·58 21·59	2·30 2·35	4·25 4·20	60·83 60·90	3·36 3·53
LIV[a]	*B* 86	69—72 reprecipitated	$C_{14}H_{18}I_4N_2O_3$ (770·0)	21·84 22·01	2·36 2·43	— —	65·94 65·72	3·64 3·86

TABLE I
(*Continued*)

Compound	Procedure yield, %	M.p., °C solvent	Formula (mol.wt.)	Calculated/Found % C	% H	% Cl	% I	% N
LIV[b]		187—189 (decomp.) water	$C_{14}H_{19}ClI_4N_2O_3$ (806·4)	20·24 20·64	2·41 2·42	4·39 4·27	62·95 63·17	3·47 3·39
LV[b]	*B* 50	144—146 85% aqueous ethanol	$C_{15}H_{21}ClI_4N_2O_4$ (836·4)	21·54 21·15	2·53 2·69	4·24 4·03	60·68 59·62	3·35 3·25
LVI[b]	*B* 66	128—134 ethanol–ether	$C_{16}H_{23}ClI_4N_2O_5$ (866·5)	22·18 21·84	2·68 2·69	4·09 4·20	58·59 57·77	3·23 3·91
LVII[b]	*A* 54	164—165 95% aqueous ethanol	$C_{14}H_{20}ClI_3N_2O_4$ (696·5)	24·13 24·00	2·89 3·06	5·09 4·98	54·66 54·83	4·02 4·05
LVIII[a]	*B* 45	40 (reprecipitated)	$C_{19}H_{28}I_3N_3O_6$ (775·2)	29·44 29·44	3·64 3·87	— —	49·11 49·23	5·42 5·29
LIX[b]	*C* 66	218—221 (decomp.) methanol	$C_{15}H_{21}ClI_4N_2O_5$ (852·5)	21·13 20·89	2·48 2·57	4·16 4·10	59·55 58·18	3·28 3·31
LX[b]	C 58	173—185 (decomp.) 95% aqueous ethanol	$C_{13}H_{19}ClI_4N_2O_4$ (810·4)	19·27 19·35	2·36 2·47	4·38 4·21	62·65 62·30	3·46 3·18
LXI[b]	*C* 77	215—219 (decomp.) methanol	$C_{16}H_{24}ClI_3N_2O_6$ (756·6)	25·40 25·55	3·20 3·33	4·69 4·38	50·32 50·59	3·70 3·45
LXII[b]	*C* 48	213—215 (decomp.) ethanol)	$C_{15}H_{23}ClI_3N_2O_5$ (727·6)	24·76 24·68	3·19 3·06	4·87 5·63	52·33 52·05	3·85 4·51

[a] Base. [b] Hydrochloride. [c] Determined in a capillary. [d] Perchlorate.

N-[3-(N′-Acetyl-N′-methyl)amino-2,4,5,6-tetraiodobenzyl]diethanolamine Hydrochloride (*LIV*) (Method *B*)

Compound *LII* (27·7 g, 0·035 mol) was dissolved in a mixture of 220 ml ethanol and 65 ml 5M potassium hydroxide and the solution was stirred for 10 min at room temperature. Then it was combined with 19·9 g (0·14 mol) methyl iodide, the reaction vessel was closed and the mixture was stirred for 5 h. The alkalinity of the solution was set to pH 8—9 using hydrochloric acid (1 : 1),

the inorganic salts were filtered and the filtrate was evaporated *in vacuo*. The residue was combined with 70 ml water and the crude base was triturated several times with water until it solidified. The product was filtered, washed with water and dried *in vacuo* at 40–50°C. A total of 23·3 g (86%) base *LIV* was obtained, m.p. 69–72°C. The hydrochloride melted at 180–183°C (decomposition). The analysis is shown in Table I. Compounds *L*, *LI*, *LV*, *LVI* and *LVIII* were prepared analogously.

N-(3-Acetylamino-2,4,5,6-tetraiodobenzyl)bis-2,3-dihydroxypropylamine Hydrochloride (*LIX*) (Method *C*)

44 g (0·064 mol) *XIX*, 15 g (0·141 mol) sodium hydrogen carbonate (anhydrous), 26 g (0·106 mol) bis-(2,3-isopropylidenedioxypropyl)amine and 150 ml ethanol was refluxed under stirring for 15 h. The solid fraction was filtered and the filtrate was evaporated *in vacuo*. The residue was covered with 200 ml 1M hydrochloric acid and heated for 1 h to 65–70°C, cleared with charcoal, the base was precipitated with ammonia and the solid was washed twice with 20 ml water, the water was removed with 1-butanol and the residue dissolved in 250 ml ethanol. The hydrochloride was precipitated with an ethanolic solution of hydrogen chloride, filtered and dried in a desiccator. Processing of the mother liquor yielded another fraction, 36 g (65·8%) in all of *LIX*; m.p. 209 to 214°C (decomposition, methanol). The analysis is shown in Table I. Compounds *LX* and *LXII* were prepared analogously.

N-[3-(N′-Methyl-N′-glycyl)amino-2,4,6-triiodobenzyl]diethalamine Hydrochloride (*XXXIII*)

Hydrochloride of *XXXII* (40 g, 0·048 mol) was suspended in 400 ml ethanol and combined dropwise with 10 ml hydrazine added under stirring. The mixture was stirred for 2·5 h when all the solid dissolved whereupon a solid fraction gradually separated and was filtered. The mother liquor was evaporated *in vacuo*, the residue was combined with 200 ml 2M hydrochloric acid and the mixture was heated under stirring for 10 min at 50°C. The solid was filtered and the mother liquor was concentrated *in vacuo*. The residue was dissolved in 400 ml hot water, the base was precipitated with ammonia, washed with water, dehydrated azeotropically with 2-propanol and the remaining base (after distillation of 2-propanol) was dissolved in 200 ml ethanol. The hydrochloride was precipitated by adding an ethanolic solution of hydrogen chloride. The yield was 21·6 g (61·5)% compound *XXXIII*, melting at 200–205°C.

The analyses were done by Mrs J. Komancová, Mrs V. Šmídová and Mr M. Čech at the analytical department of this institute (under the direction of Dr J. Körbl).

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Translated by A. Kotyk.