STUDIES IN THE ISOQUINOLINE SERIES

Part I. Synthesis of 1-Benzyl Isoquinoline Derivatives

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THE remarkable ease of oxidation of 1-benzyl-3 : 4-dihydroisoquinolines was first observed by Buck, Haworth and Perkin,[1] who carried out a study of the oxidation of compounds of this type bearing alkoxy groups in the benzyl portion of the molecule. However 3 : 4-dihydro-1-(2′-nitrobenzyl)-isoquinoline derivatives, several of which have been prepared in connection with aporphine syntheses, are remarkably stable as first observed by Gulland and Haworth.[2] In connection with a study of the mechanism of oxidation of 1-benzyl-3 : 4-dihydroisoquinoline derivatives, we had occasion to synthesise a number of compounds belonging to this class, with varying substituents in the benzyl portion of the molecule. The dihydroisoquinolines were made by cyclisation of arylacetyl derivatives of homovera-trylamine by the classical Bischler-Napieralski method, with phosphorus oxychloride in boiling toluene or phosphorus pentachloride in cold chloroform. The last reagent invariably gave higher yields of cleaner products. The dihydroisoquinolines were also reduced to the corresponding tetrahydroisoquinolines for purposes of pharmacological examination. We record here the data on the compounds prepared in the course of this study. A study of the oxidation of these dihydroisoquinolines will be reported in another paper.

EXPERIMENTAL PROCEDURE

Phenylacetic acids

The phenylacetic acids employed in this study were prepared by procedures already described in literature.

N-β-(3′ : 4′-Dimethoxyphenethyl)-phenylacetamides

The amides were made by the procedure of Gulland and Haworth.[2] The amides are listed in Table I and the yields reported are those obtained by this method. The amides could also be made by the following alternative procedure, illustrated in the case of N-2-Bromo-β-(3′ : 4′-dimethoxyphenethyl)-phenyl-acetamide.

TABLE I

N-β-(3′ : 4′-Dimethoxyphenethyl)-Acetamides

Substituted phenylacetamides	Mol. Formula	M.P. °C.	Yield %	% Nitrogen	
				Found	Required
Nil	$C_{18}H_{21}O_3N$	108	65	4·70	4·68
2–Br	$C_{18}H_{20}O_3NBr$	128	84	4·14	3·70
3-Br	$C_{18}H_{20}O_3NBr$	105–6	76	3·79	3·70
4-Br	$C_{18}H_{20}O_3NBr$	129	81	4·12	3·70
2-Me	$C_{19}H_{23}O_3N$	123–24	94	4·57	4·47
3-Me	$C_{19}H_{23}O_3N$	92–93	85	4·81	4·47
4-Me	$C_{19}H_{23}O_3N$	121	84	4·82	4·47
2-OMe	$C_{19}H_{23}O_4N$	119–20	81	4·47	4·26
3-OMe[3]	$C_{19}H_{23}O_4N$	114	82	4·54	4·26
4-OMe[4]	$C_{19}H_{23}O_4N$	124–25	94	4·46	4·26
2-Nitro[2]	$C_{18}H_{20}O_5N_2$	110–11	86	8·45	8·14
3-Nitro	$C_{18}H_{20}O_5N_2$	132–33	78	8·40	8·14
4-Nitro[5]	$C_{18}H_{20}O_5N_2$	119–20	86	8·00	8·14
4-Cyano	$C_{19}H_{20}O_3N_2$	131–32	61	8·75	8·64

A mixture of 2-bromophenylacetic acid (5·5 g.) and homoveratrylamine (5 g.) was heated at 180–200° in an oil-bath for one hour. After cooling, the solid was broken up, ground successively with dilute hydrochloric acid (2N) and dilute sodium hydroxide solution (2N), filtering after each operation and finally washed with water. The residue after drying in a desiccator weighed 8 g. and melted at 128°.

1-Benzyl-3 : 4-dihydro-6 : 7-dimethoxyisoquinolines

The amides were cyclised to the 3 : 4-dihydroisoquinolines by either of the following procedures:

(*a*) *Cyclisation with phosphorus oxychloride.*—A suspension of the amide (1 g.) in dry toluene (10 c.c.) was refluxed for two hours with phosphorus oxychloride (3 c.c.). The solution was then poured on to crushed ice and

after decomposition of the excess phosphorus oxychloride, the aqueous layer was separated and extracted with ether for removal of non-basic impurities. The aqueous layer was then cooled well, and made basic with sodium hydroxide solution in an atmosphere of hydrogen. The liberated base was rapidly extracted with ether and the ether extract was dried over potassium hydroxide. The dry ether extract was saturated with dry hydrogen chloride gas and the precipitated hydrochloride was filtered, washed with ether and recrystallised from an alcohol-ether mixture.

In the case of N-(3′ : 4′-dimethoxyphenethyl)-2-nitrophenyl-acetamide, the cyclisation was effected by leaving the amide in toluene solution with

TABLE

1-*Benzyl*-6 : 7-*dimethoxy*-

Substituent	Hydrochloride					
	Mol. Formula	M.P. °C.	Yield %		% Nitrogen	
			$POCl_3$	PCl_5	Found	Required
Nil	$C_{18}H_{20}O_2NCl$	182	70	84	4·40	4·40
2–Br	$C_{18}H_{19}O_2NClBr$	197 (decomp.)	73	91	3·66	3·53
3–Br	$C_{18}H_{19}O_2NClBr$	190	69	78	3·70	3·53
4–Br	$C_{18}H_{19}O_2NClBr$	175	73	91	3·19	3·53
2–Me	$C_{19}H_{22}O_2NCl$	186	71	90	4·33	4·22
3–Me	$C_{19}H_{22}O_2NCl$	111–12	68	85	4·29	4·22
4–Me	$C_{19}H_{22}O_2NCl$	196–97 (decomp.)	66	88	4·55	4·22
2–OMe	$C_{19}H_{22}O_3NCl$	169–70	75	80	3·98	4·03
3–OMe	$C_{19}H_{22}O_3NCl$	183	76	76	4·40	4·03
4–OMe	$C_{19}H_{22}O_3NCl$[4]	165	71	90	4·24	4·03
2–Nitro	$C_{18}H_{19}O_4N_2Cl$[2]	218 (decomp.)	82	95	7·52	7·73
3–Nitro	$C_{18}H_{19}O_4N_2Cl$	190	76	88	7·64	7·73
4–Nitro	$C_{18}H_{19}O_4N_2Cl$	180–81	85	99	7·66	7·73
4–Cyano	$C_{19}H_{19}O_2N_2Cl$	209–11	76	79	8·04	8·18

phosphorus oxychloride at room temperature, the product being worked up as described earlier.

(*b*) *Cyclisation with phosphorus pentachloride.*—A solution of the amide (1 g.) in dry chloroform (10 c.c.) was treated cautiously with phosphorus pentachloride (1·3 g.) and left for 48 hours protected from moisture. The chloroform was removed *in vacuo* and the residue treated with crushed ice. The acid solution was worked up as earlier to yield the base hydrochloride.

The data relating to the yields of the dihydroisoquinolines and the physical constants of the hydrochlorides and the picrates are recorded in Table II.

II

3 : 4-*dihydroisoquinolines*

Mol. Formula	M.P. °C.	Picrate	
		% Nitrogen	
		Found	Required
$C_{24}H_{22}O_9N_4$	176	10·70	11·00
$C_{24}H_{21}O_9N_4Br$	183	9·60	9·51
$C_{24}H_{21}O_9N_4Br$	183–84 (decomp.)	9·90	9·51
$C_{24}H_{21}O_9N_4Br$	197–98 (decomp.)	9·97	9·51
$C_{25}H_{24}O_9N_4$	192	10·84	10·69
$C_{25}H_{24}O_9N_4$	193–94 (decomp.)	10·77	10·69
$C_{25}H_{24}O_9N_4$	182–83 (decomp.)	11·04	10·69
$C_{25}H_{24}O_{10}N_4$	164–66	10·53	10·37
$C_{25}H_{24}O_{10}N_4$	156–57	10·74	10·37
$C_{25}H_{24}O_{10}N_4$[4]	168–69 (decomp.)	10·10	10·37
$C_{24}H_{21}O_{11}N_5$	195–97 (decomp.)	13·00	12·61
$C_{24}H_{21}O_{11}N_5$	197–98 (decomp.)	12·88	12·61
$C_{24}H_{21}O_{11}N_5$	193–94	12·97	12·61
$C_{25}H_{21}O_9N_5$	200–2 (decomp.)	12·75	13·08

TABLE III

1-Benzyl-1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxyisoquinolines

Substituent	Hydrochloride				Picrate			
	Mol. Formula	M.P. °C.	% Nitrogen		Mol. Formula	M.P. °C.	% Nitrogen	
			Found	Required			Found	Required
2–Br	$C_{18}H_{21}O_2NClBr$	215–16	3·13	3·51	$C_{24}H_{23}O_9N_4Br$	181–82	9·68	9·48
3–Br	$C_{18}H_{21}O_2NClBr$	225–27	3·72	3·51	$C_{24}H_{23}O_9N_4Br$	155	9·19	9·48
4–Br	$C_{18}H_{21}O_2NClBr$	213–14	3·37	3·51	$C_{24}H_{23}O_9N_4Br$	180 (Sintering at 165)	9·70	9·48
2–Me	$C_{19}H_{24}O_2NCl$	196–98	3·84	4·20	$C_{25}H_{26}O_9N_4$	184–85	10·61	10·64
3–Me	$C_{19}H_{24}O_2NCl$	208–10	4·51	4·20	$C_{25}H_{26}O_9N_4$	171–72	10·40	10·64
4–Me	$C_{19}H_{24}O_2NCl$	222–24	3·78	4·20	$C_{25}H_{26}O_9N_4$	173–75	10·60	10·64
2–OMe	$C_{19}H_{24}O_3NCl$	176–78	3·83	4·01	$C_{25}H_{26}O_{10}N_4$	155–56	10·24	10·33
4–OMe	$C_{19}H_{24}O_3NCl$[4]	195–97	4·07	4·01	$C_{25}H_{26}O_{10}N_4$	148–50	10·13	10·33
2–NH_2	$C_{18}H_{24}O_2N_2Cl_2$	220 (decomp.)	7·57	7·55	$C_{30}H_{28}O_{16}N_8$	gum	..	..
3–NH_2	$C_{18}H_{24}O_2N_2Cl_2$	237–39 (decomp.)	7·41	7·55		198 (decomp.)	14·57	14·81
4–NH_2	$C_{18}H_{24}O_2N_2Cl_2$	233 (decomp.)	7·28	7·55	$C_{30}H_{28}O_{16}N_8$	181–82 (decomp.)	14·50	14·81

1-*Benzyl*-1 : 2 : 3 : 4-*Tetrahydro*-6 : 7-*dimethoxyisoquinolines*

The three nitrobenzyl-dihydroisoquinolines could not be reduced successfully by catalytic reduction. In these cases, the dihydroisoquinoline hydrochloride (1 g.) dissolved in concentrated hydrochloric acid (20 c.c.) and water (10 c.c.) was treated with zinc dust (6 g.) at 60–70° with stirring. After two hours, the solution was filtered, cooled strongly, made alkaline and extracted with benzene. The benzene extract after drying over potassium hydroxide, was saturated with dry hydrogen chloride gas. The dihydrochloride was filtered and crystallised from absolute alcohol-ether mixture.

All the other dihydroisoquinoline hydrochlorides were reduced in alcoholic solution with Adams' catalyst at a pressure of 60 lb. per sq. inch. After filtering off the catalyst, the solvent was removed, yielding the tetrahydroisoquinoline hydrochlorides in nearly quantitative yield. Further purification was effected by crystallisation from absolute alcohol.

The tetrahydroisoquinolines are listed in Table III.

SUMMARY

A series of 1-benzyl-3 : 4-dihydro-6 : 7-dimethoxy-, and 1-benzyl-1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxyisoquinolines with varying substituents in the benzyl portion of the molecule, and their derivatives are reported.

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