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Some tryptamine derivatives: 1-aryloxy-3-[(2-indol-3′-ylethyl)amino]propan-2-ols

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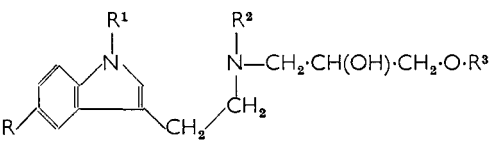
The preparation of some 1-aryloxy-3-[(2-indol-3′-ylethyl)amino]propan-2-ols is described. Their biological activity was insignificant.

BECAUSE many effective psycholytic drugs are substituted indoles related to 5-hydroxytryptamine (5-HT) we have prepared a series of substituted tryptamines of type (I) containing a 3-aryloxy-2-hydroxypropyl

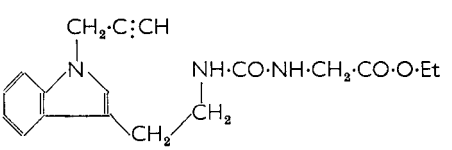


(I)

moiety, in the hope that these might possess useful central nervous system (CNS) activity possibly of the tranquilliser type (compare Beasley, Petrow & Stephenson, 1958).

5-Substituted tryptamines required in this work were prepared by the general method of Abramovitch & Shapiro (1955, 1956) and Abramovitch (1956), with slight variations of these methods as described by Pelchowicz & Bergmann (1959, 1960).

1-Alkyltryptamines were obtained as described by Potts & Saxton (1954) using sodamide in liquid ammonia as the alkylating medium. 1-Prop-2′-ynyltryptamine, prepared by this latter route, was characterised by the preparation of its *N*′-acetyl derivative and by reaction with ethyl isocyanatoacetate to yield the substituted hydantoate (II).



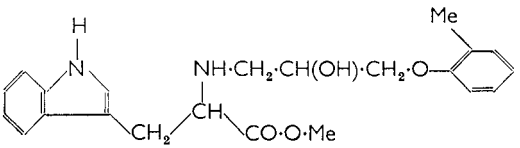
(II)

The required 1-aryloxy-3-[2-indol-3′ylethylamino]propan-2-ols (I) were obtained in moderate yield by reaction of a tryptamine with the appropriate 1-aryloxy-2,3-epoxypropane in refluxing alcoholic solution.

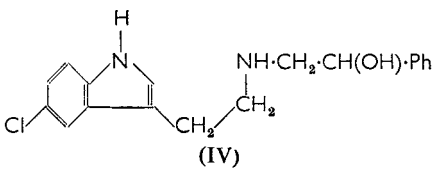
In preliminary experiments we had found that the methyl ester of tryptophan reacted with 1,2-epoxy-3-*o*-tolyloxypropane in methanolic solution to give the product (III), whilst reaction between 5-chlorotryptamine and styrene oxide yielded the required product (IV).

From the British Drug Houses Ltd., Graham Street, London, N.1.

Finally, the β-carboline derivative (V) was prepared for direct comparison with the open-chain analogue (I; R = MeO, $R^1 = R^2 = H$, R^3 = *o*-tolyl). It was obtained readily by reaction of 1,2,3,4-tetrahydro-6-methoxy-β-carboline (Abramovitch & Shapiro, 1956) with 1,2-epoxy-3-*o*-tolyloxypropane.



(III)



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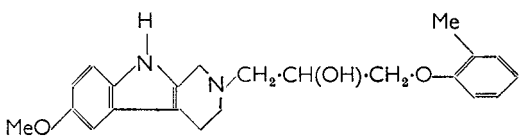


(V)

BIOLOGICAL STUDY

Biological study of the above products by Dr. D. K. Vallance and Mr. D. I. Barron (Biological Department, Godalming, Surrey) showed that only 1-{[2-(5-methoxy-1-prop-2′-ynylindol-3-yl)ethyl]amino}-3-*o*-tolyloxypropan-2-ol (I; R = MeO, $R^1 = R^2 = H$, R^3 = *o*-tolyl) possessed a moderate degree of CNS depressant activity. Thus, compared with chlorpromazine hydrochloride as standard, its activity was 1/9 in antagonising the toxicity of amphetamine in aggregated mice, 1/13 in preventing footshock-induced fighting in mice, 1/19 in anti-tremorine activity in mice and 1/24 in preventing head twitches induced in mice by the intraperitoneal injection of 5-hydroxytryptophan. Additionally, the compound had 1/26 of the activity of diphenylhydantoin in the maximal leptazol seizure test. The compound was not considered worthy of more detailed biological study.

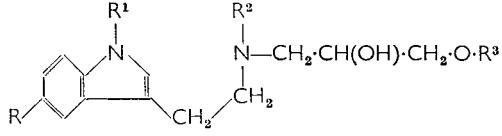
Experimental

Melting-points are uncorrected.

Some of the examples illustrate the preparative methods for the compounds listed in Table 1 which contains relevant analytical data.

Methyl ester of N-(2-*hydroxy*-3-*o*-*tolyloxypropyl*) *tryptophan.* A solution of the methyl ester of DL-tryptophan (4·4 g) and 1,2-epoxy-3-*o*-tolyloxypropane (3·3 g) in methanol (25 ml) was heated under reflux for 2 hr and the solvent then distilled off at reduced pressure. The residual

TABLE 1.



R	R¹	R²	R³	m.p. °C	Formula	Found C	Found H	Found Cl	Found N	Required C	Required H	Required Cl	Required N
MeO	H	H	Ph	109–111	$C_{20}H_{24}N_2O_3$	70·5	7·1		8·0	70·6	7·1		8·2
H	H	H	*o*-Me·C_6H_4	113–115	$C_{20}H_{24}N_2O_2$	73·5	7·2		9·1	74·0	7·5		8·6
MeO	H	H	*o*-Me·C_6H_4	128–130	$C_{21}H_{26}N_2O_3$	70·6	7·4		8·4	71·15	7·4		7·9
MeO	H	H	*o*-Me·C_6H_4	155–157†	$C_{21}H_{27}ClN_2O_3$†	64·3	6·9	9·6	7·5	64·5	7·0	9·1	7·2
Me	H	H	*o*-Me·C_6H_4	130–132	$C_{21}H_{26}N_2O_2$	74·8	7·6		8·1	74·5	7·7		8·3
Cl	H	H	*o*-Me·C_6H_4	148–150	$C_{20}H_{25}ClN_2O_3$	67·1	6·6	10·0	8·0	66·9	6·5	9·9	7·8
F	H	H	*o*-Me·C_6H_4	118–120	$C_{20}H_{23}FN_2O_2$	69·9	6·5	5·4*	8·3	70·2	6·8	5·6*	8·2
H	CH_2·C:CH	H	*o*-Me·C_6H_4	94–96	$C_{23}H_{26}N_2O_3$	76·0	7·4		7·6	76·2	7·2		7·7
H	Ph·CH_2	H	*o*-Me·C_6H_4	78–80	$C_{27}H_{30}N_2O_2$	78·0	7·4		6·6	78·2	7·3		6·8
H	H	Et	*o*-Me·C_6H_4	162–164†	$C_{22}H_{29}ClN_2O_2$†	67·5	7·7	9·0	7·2	67·9	7·5	9·1	7·2
EtO	H	H	*o*-Me·C_6H_4	121–122	$C_{23}H_{28}N_2O_3$	71·4	7·5		7·3	71·7	7·7		7·6
MeO	CH_2·C:CH	H	*o*-Me·C_6H_4	94–96	$C_{24}H_{28}N_2O_3$	73·2	7·2		7·3	73·4	7·2		7·1
Cl	H	CH_2·C:CH	*o*-Me·C_6H_4	186–188†	$C_{23}H_{26}Cl_2N_2O_2$†	63·6	6·0	16·7	6·7	63·7	6·1	16·4	6·5
MeO	H	Ph·CH_2	*o*-Me·C_6H_4	118–120	$C_{28}H_{32}N_2O_3$	75·1	7·2		6·7	75·6	7·3		6·3
MeO	H	H	*m*-Me·C_6H_4	116–118	$C_{21}H_{26}N_2O_3$	70·8	7·7		7·8	71·15	7·4		7·9
H	H	H	*o*-MeO·C_6H_4	124–126	$C_{20}H_{24}N_2O_3$	70·2	7·1		8·1	70·6	7·1		8·2
MeO	H	H	*o*-MeO·C_6H_4	125–127	$C_{21}H_{26}N_2O_4$	67·6	7·1		7·8	68·1	7·1		7·6
MeO	H	H	*p*-MeO·C_6H_4	102–104	$C_{21}H_{26}N_2O_4$	68·4	7·3		7·1	68·1	7·1		7·6
MeO	H	H	*o*-Cl·C_6H_4	133–135	$C_{20}H_{23}ClN_2O_3$	64·4	6·3	9·1	7·4	64·1	6·2	9·5	7·5
MeO	H	H	*p*-Cl·C_6H_4	120–122	$C_{20}H_{23}ClN_2O_3$	64·0	6·1	9·1	7·2	64·1	6·2	9·5	7·5
H	Et	H	*p*-Cl·C_6H_4	110–112	$C_{21}H_{25}ClN_2O_2$	67·7	7·0	9·5	7·3	67·6	6·8	9·5	7·5
MeO	H	H	2,4-Cl_2·C_6H_4	117–119	$C_{20}H_{22}Cl_2N_2O_3$	58·9	5·6	16·9	6·8	58·7	5·4	17·3	6·8
MeO	H	H	*o*-C_6H_5·C_6H_4	122–124	$C_{26}H_{28}N_2O_3$	74·9	6·6		6·8	74·9	6·8		6·7

† = Hydrochloride
* = Fluorine

gum solidified on trituration with ether to yield the ester (2·4 g). m.p 125–127° (from methanol). Found: C, 69·5; H, 6·8; N, 7·0. $C_{22}H_{26}N_2O_4$ requires: C, 69·1; H, 6·9; N, 7·3%. The *hydrochloride* had m.p. 157–160° (decomp.) (from methanol-ether). Found: C, 63·2; H, 6·4; Cl, 8·7; N, 6·7. $C_{22}H_{27}ClN_2O_4$ requires: C, 63·1; H, 6·5; Cl, 8·5; N, 6·7%. The *phosphate* obtained when a solution of the base (3·5 g) in pyridine (20 ml) was treated with phosphoryl chloride (1·7 ml), and the mixture allowed to stand at room-temperature for 30 min and then poured into water, had m.p. 208–210° (decomp.) (from methanol). Found: C, 55·7; H, 5·7; N, 6·1; P, 7·0. $C_{22}H_{27}N_2O_7P$ requires: C,55·4; H, 5·7; N, 5·9; P, 6·5%.

2-{[2-(5-*Chloroindol*-3-*yl*)*ethyl*]*amino*}-1-*phenylethanol.* A suspension of 5-chlorotryptamine hydrochloride (4·6 g) in hot ethanol (15 ml) was treated with a solution of sodium hydroxide (0·8 g) in ethanol (10 ml). The mixture was filtered to remove sodium chloride, the filtrate treated with styrene oxide (2·3 ml), and the solution heated at reflux temperature for 1 hr. The ethanol was distilled off at reduced pressure to yield the alcohol (1·4 g), m.p. 129–131° [from benzene-light petroleum (b.p. 60–80°)]. Found: C, 68·9; H, 5·8; Cl, 11·4; N, 8·8. $C_{18}H_{19}ClN_2O$ requires: C, 68·7; H, 6·1; Cl, 11·3; N, 8·9%.

1-*Prop*-2′-*ynyltryptamine hydrochloride* (compare Potts & Saxton, 1954). To a solution of sodamide [prepared from sodium (1·7 g) in liquid ammonia (250 ml)], powdered tryptamine (11·7 g) was added in portions during 10 min with stirring at −60°. The mixture was stirred for a further 5 min then prop-2-ynyl bromide (9·2 g) was added dropwise; stirring was continued for 1 hr at −60° after which time the ammonia was allowed to evaporate freely. The residue was decomposed with water and the base isolated with ether; the base (12·1 g) had b.p. 150° at 0·2 mm. The *hydrochloride* had m.p. 191–193° (from ethanol-ether). Found: C, 67·0; H, 6·4; Cl, 14·5; N, 11·6. $C_{13}H_{15}ClN_2$ requires: C, 66·5; H, 6·5; Cl, 15·1; N, 11·9%.

N′-*Acetyl*-1-(*prop*-2-*ynyl*)*tryptamine* was obtained when the foregoing base (1·2 g) was heated with a mixture of acetic acid (3 ml) and acetic anhydride (2 ml) for 1 hr. It had m.p. 128–130° (from methanol). Found: C, 74·7; H, 6·7; N, 12·1. $C_{15}H_{16}N_2O$ requires: C, 75·0; H, 6·6; N, 11·7%.

N-*Ethoxycarbonylmethyl*-N′-{[2-(1-*prop*-2′-*ynylindol*-3-*yl*)*ethyl*]*amino*} *urea* was obtained when a solution of 1-prop-2′ynyltryptamine (2·0 g) in ether (30 ml) was treated dropwise with a solution of ethyl isocyanatoacetate (1·3 g) in ether (10 ml). It (2·4 g) had m.p. 121° (from benzene). Found: C, 65·8; H, 6·2; N, 12·7. $C_{18}H_{21}N_3O_3$ requires: C, 66·1; H, 6·5; N, 12·8%.

5-*Methoxy*-1-*prop*-2′-*ynyltryptamine hydrochloride* was prepared by alkylation of 5-methoxytryptamine with prop-2-ynyl bromide, using sodamide-liquid ammonia as described for 1-prop-2′-ynyltryptamine. The *base* (64% yield) had b.p. 180–190° at 0·1 mm. The *hydrochloride* had m.p. 200–202° (from ethanol-ether). Found: C, 63·6; H, 6·6; Cl, 13·4; N, 10·2. $C_{14}H_{17}ClN_2O$ requires: C, 63·6; H, 6·5; Cl, 13·4; N, 10·5%.

1-{[2-(5-*Methoxy*-1-*prop*-2'-*ynylindol*-3-*yl*)*ethyl*]*amino*}-3-*o*-*tolyloxypropan*-2-*ol*. A solution of the foregoing hydrochloride (1·6 g) in methanol (10 ml) was treated with a solution of potassium hydroxide (1 equiv.) in methanol (10 ml), followed by 1,2-epoxy-3-*o*-tolyloxypropane (0·9 ml). The mixture was heated under reflux for 2 hr and then filtered to remove potassium chloride. The filtrate was evaporated at reduced pressure to yield the alcohol, m.p. 94–96° [from benzene-light petroleum (b.p. 60–80°)].

1-{N-[2-(5-*Chloroindol*-3-*yl*)*ethyl*]-N-*prop*-2-*ynylamino*}-3-o-*tolyloxypropan*-2-*ol hydrochloride*. A solution of 1-{[2-(5-chloroindol-3-yl)-ethyl]amino}-3-*o*-tolyloxypropan-2-ol (3·6 g) in methanol (30 ml) was treated with prop-2-ynyl bromide (0·6 g). The mixture was heated under reflux for 15 hr. and then concentrated at reduced pressure. The residual gum was triturated with ether and the *hydrobromide* (2·2 g, m.p. 150–153°) of the starting base was then filtered off. The ethereal filtrate was washed with water, dried with anhydrous magnesium sulphate and then treated with dry hydrogen chloride to yield the hydrochloride, m.p. 186–188° (from ethanol).

3-[2-(2-*Hydroxy*-3-o-*tolyloxypropylamino*)*ethyl*]-5-*methoxyindole*-2-*carboxylic acid*. To a suspension of 3-ethyl-5-methoxyindole-2-carboxylic acid (2·4 g) in ethanol (25 ml) was added a solution of sodium hydroxide (0·4 g) in water (5 ml), followed by 1,2-epoxy-3-*o*-tolyloxypropane (1·65 g). The homogeneous mixture was heated under reflux for 3 hr, the ethanol distilled off at reduced pressure and replaced by water, and the solution acidified with acetic acid. The solids were collected, dried and extracted with boiling ethyl acetate, after which a small residue of insoluble starting material remained. The ethyl acetate extract deposited the acid (1·4 g) on cooling. It had m.p. 208–210° (from ethanol). Found: N, 6·8. $C_{22}H_{26}N_2O_5$ requires: N, 7·0%.

1-(1,2,3,4-*Tetrahydro*-6-*methoxy*-β-*carbolin*-3-*yl*)-3-o-*tolyloxypropan*-2-*ol*. To a solution of 1,2,3,4-tetrahydro-6-methoxy-β-carboline (4 g) in ethanol (100 ml) was added 1,2-epoxy-3-*o*-tolyloxypropane (3·3 g) and the mixture heated at reflux temperature for 3 hr. The alcohol (5·8 g) crystallised out on cooling and had m.p. 160–162° (from ethyl acetate). Found: C, 71·6; H, 7·4; N, 7·6. $C_{22}H_{26}N_2O_3$ requires: C, 72·1; H, 7·2; N, 7·6%.

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