6-chloro-2,4-diphenyl-quinazoline through the reaction with dimethylsulphate in alkaline medium, followed by treatment with chloroacetyl chloride. The acylated product is cyclised with ammonia to diazepam.

Chlordiazepoxide, 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine-4-oxide is official in I.P. as an anxiolytic in divided doses of 10–100 mg per day.

Properties: It is a white to light yellow, crystalline odourless powder; insoluble in water, slightly soluble in ether. Its m.p. is 236–237°C. Its identification tests and assay method by non-aqueous titration are given in I.P.

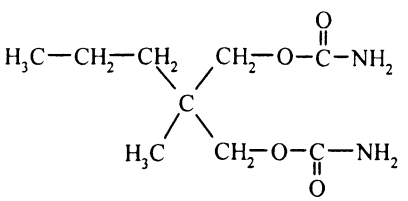
It can lead to addiction and is abused as such.

Its hydrochloride is official in B.P. Both of these products have tablets and capsules as their respective preparations in I.P. and B.P.

Diazepam, 7-chloro-1,3-dihydro-1-methyl-5-phenyl-1,4-benzodiazepine-2-one, as such, and as capsules, tablets and injections are official in I.P. and B.P. and are indicated as anxiolytic, sedative and anticonvulsant. The dose differs in anxiety, insomnia and other indications. The identification tests, standards and assay method based on non-aqueous titration are given in I.P.

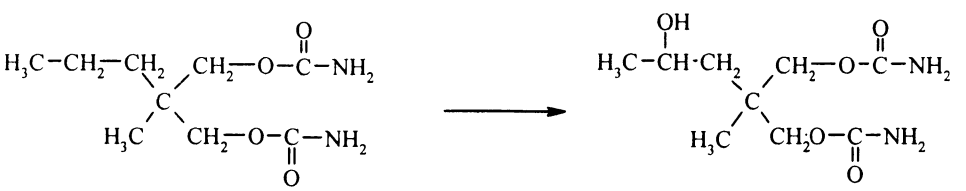
PROPANEDIOL DERIVATIVES

Meprobamate (2-methyl-2-propyl-1,3-propandiol-dicarbamate), as an acyclic hypnotic, is perhaps the first tranquilliser, which was introduced in the therapy in 1954. This substance which had from the beginning made its impression can be said to have shown its effect between the barbiturates and 1,4-benzodiazepines. Its central muscle relaxant action is proportionately much more pronounced and its duration of action is about eight times longer than **mephenesin**, (3-(2-methyl-phenoxy)-1,2-propanediol), a centrally acting muscle relaxant.



Meprobamate
(Cyrpon®, Miltaun®, Equanil®)

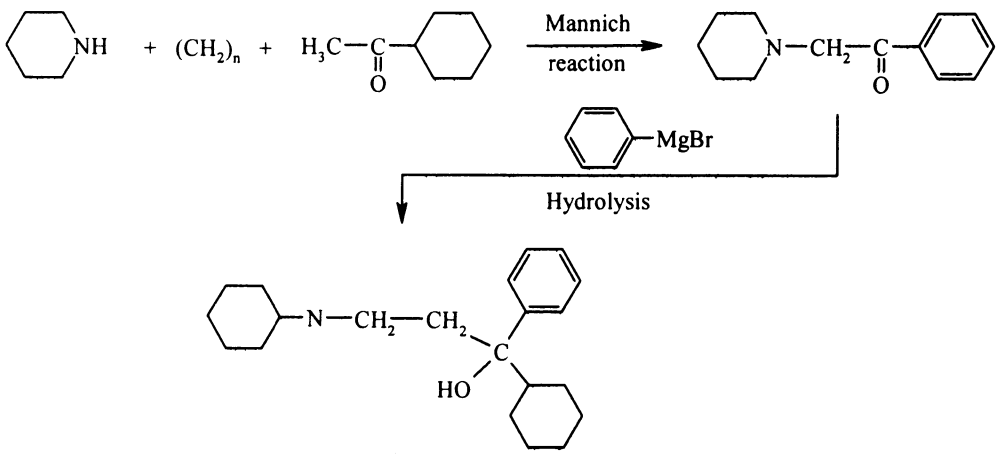
Biotransformation: *Meprobamate* is partly excreted as such and partly as N-glucuronide. Through the hydroxylation there results 2-hydroxypropyl-compound which as such in the free form or in a glucuronide form is eliminated. Metabolically the urethane group behaves inert, as shown below.



Benzhexol/Trihexyphenidyl as HCl is official in I.P. and its tablets containing 2 mg and 5 mg are used orally. One starts with 1 mg and can have a maintenance dose of 5 to 15 mg daily in 3 to 4 divided doses.

It is a white or creamy white crystalline powder, odourless, which is soluble in ethanol and chloroform but only slightly soluble in water. It is identified as per I.P. methods and is assayed by non-aqueous titration (method B) as per I.P.

Synthesis: Trihexyphenidyl and Biperidine show a common 1-phenyl-3-piperidino-propanol structure. The synthesis in both the cases takes place via 2-(1-piperidino) propiophenone, which is prepared through the Mannich-reaction from acetophenone, paraformaldehyde and piperidine. The carbinol is obtained through the Grignard's reaction of Mannich base. For the formation of trihexyphenidyl, the base is reacted with cyclohexyl magnesium bromide, while for the formation of biperidine the corresponding norbornen-compound is required for reaction.



Trihexyphenidyl

Benzhexol is used in the treatment of parkinsonism. The centrally acting anticholinergic effect overcomes the reduced amount of dopamine resulting from the cholinergic effects. There results a balancing effect between dopamine and acetylcholine in favour of dopamine. Besides some side effects, like drying of mouth that occurs with atropine etc. are less pronounced with centrally acting anticholinergics.

Methixene overweighs the tremor-reducing action, while the other anticholinergic anti-parkinsonian agents have mostly rigors reducing properties.

Procyclidine (Kemadrin®) is official in B.P. as hydrochloride and its tablets are prescribed. As a white, slightly bitter powder, it is sparingly soluble in water.

Orphenadrine (Disipal®) is official in B.P. and is used as a hydrochloride or as a citrate, the former being freely soluble in water, while the latter only sparingly. The drug is used as a mild anticholinergic and antihistaminic. Orphenadrine citrate is additionally used to relieve pain due to voluntary muscle spasm (muscle relaxant). Besides, Orphenadrine and **Chlorphenoxamine**

Preparation: In the laboratory it is prepared by following Whole's method, which consists in evaporating a solution of ammonium cyanate to dryness.

$$\underset{\text{Ammonium cyanate}}{NH_4OCN} \rightleftharpoons \underset{\text{Urea}}{CO(NH_2)_2}$$

An improved method of preparation is by using a solution of potassium cyanate and ammonium sulphate in equal proportions. This solution is evaporated to dryness and the residue is extracted with alcohol, which is filtered, concentrated and cooled to crystallise urea.

Description: Urea is a colourless to white crystalline powder, odourless (developing odour of ammonia on long standing) with cooling and saline taste. It is soluble in water (1.5 parts) alcohol (10 parts). Its M.P. is 132° to 134°.

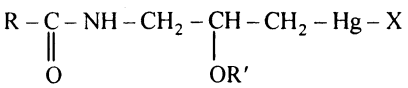
Tests for purity: It is tested for M.P., reaction, alcohol soluble matter and sulphated ash.

Assay: It is assayed by Kjeldahl's nitrogen determination method (see monograph for details).

Dose: 5–10 g.

Mercurial Diuretics

These drugs get themselves attached to the –SH (sulfhydryl) groups of the enzyme responsible for tubular reabsorption. They were the only diuretics used earlier. However, since they have had a number of side effects, they do not have much role to play now. They can be represented with the following general structure.



Of a number of mercurial diuretics the important compounds are given in the Table 22.1.

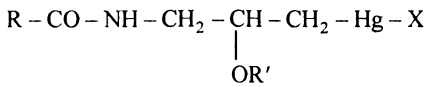
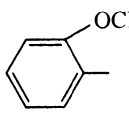
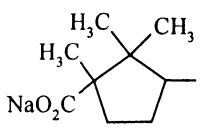


Table 22.1.

*Name**	*R*	*R'*	*X*
Mersalyl acid, I.P., B.P.		$-CH_3$	–OH
Meralluride, U.S.P.	$HOOC-CH_2.CH_2COOH-$	$-CH_3$	Theophylline
Sodium Mercaptomerin, U.S.P.		$-CH_3$	$-S.CH_2.COONa$

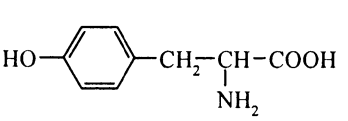
* None of the mercurial diuretics is now official in I.P.

CHAPTER

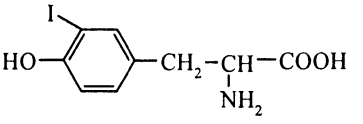
23

Thyroid Hormones

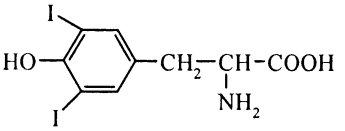
The thyroid gland produces two hormones, thyroxine and the tri-iodothyroxine, which are called the thyroid hormones. Thyroxine, though present in larger quantity, is less active than tri-iodothyroxine. Both the hormones are released in response to the thyroid stimulating hormone from anterior pituitary. The thyroid gland converts the inorganic iodide, present in the blood plasma, to iodine.



Tyrosine

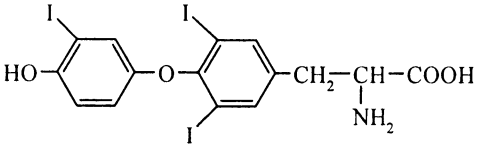


3-Iodotyrosine

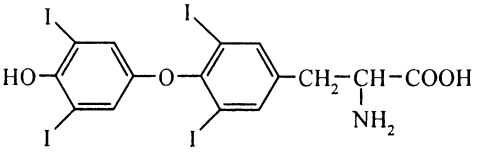


3,5-Di-iodotyrosine

Thyronine



3,5,3'-Tri-iodothyronine



L-Thyroxine

The resulting iodine reacts with tyrosine to give 3-iodo-tyrosine and 3,5-di-iodotyronine which combine together to give thyronine and 3,5,3′-tri-iodothyronine. Thyronine and tri-iodothyronine have been used to treat hypothyroidism characterised by the formation of goitre. L-Thyroxine tablets are available in the market as 100 mcg tablets (Eltroxin - Glaxo).

Structure of Thyroxine

Molecular formula of Thyroxine is $C_{15}H_{11}O_4NI_4$.