STUDIES IN THE ISOQUINOLINE SERIES.

PART VII. CYCLOHEXYL-METHYL ISOQUINOLINES.

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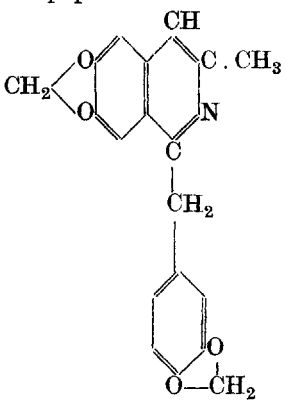
(*Read January 2, 1940.*)

Papaverine has been largely used as an antispasmodic. Owing to the restrictions placed by the state on the manufacture of morphine, it appeared at one time that the amount of papaverine available from natural sources for meeting clinical demands would be inadequate. Accordingly various synthetic products have been placed on the market for clinical use which have a close resemblance to papaverine in constitution and pharmacological action.

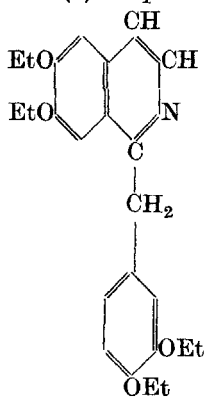
The following are some of the most important antispasmodics which have been placed on the market.—

(1) Eupapaverine.



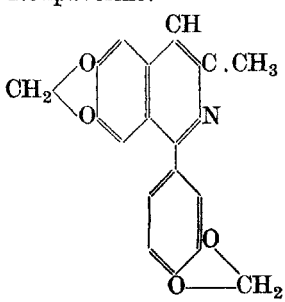
British Patent, 348956.
Chem. Zentr., 102, II, 1196 (1931).

(2) Perparin.



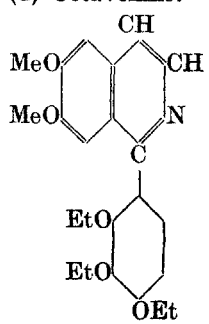
French Patent, 719638.
Chem. Zentr., 103, II, 740 (1932).

(3) Neupaverine.



German Patent, 613005.

(4) Octavenine.

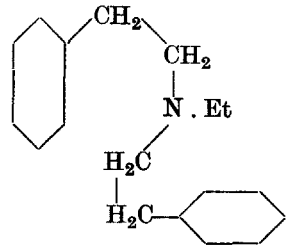


French Patent, 760825.

(5) 3,keto-4, benzoyl-3,4-dihydrobenzoxazine-1 : 4. British Patent, 370350. (*British Chem. Abstracts*, B., 1932, 786.)

(6) Syntropan. The tropic acid ester of 3-diethylamino-2,2-dimethyl propanol-1. Fromherz, *Arch. Exptl. Path. Pharmakol.*, 1933, *173*, 86.

(7) Ethyldi-β-phenyl-ethylamine. U.S. Patent, 2006114.



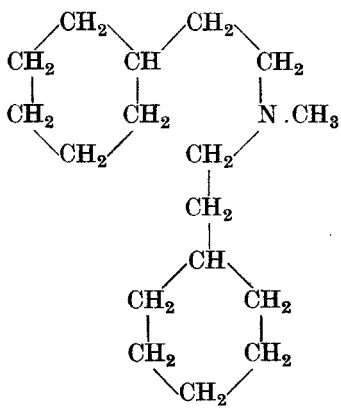
(8) Octin—the acid tartrate or hydrochloride of N, 1,5,trimethyl hexenyl-4,amine. German Patent, 617536.

(9) Transentin—diphenyl acetic acid ester of β-diethylamino-ethanol. Meier, *Klin. Wochschr.*, 1936, *15*, 1403.

(10) Jwendal—tributyl acetamide. (*Arch. Exptl. Pathol. Pharmakol.*, 1937, *186*, 552.)

(11) Sestron—the hydrochloride of ethyldi-γ-phenyl-propylamine. Kulz and Rosenmund, *Klin. Wochschr.*, 1938, *17*, 345.

Recently, Blicke and Monroe (*J. Amer. Chem. Soc.*, 1939, *61*, 91) have synthesized methyldi-β-cyclohexyl-ethylamines which have proved to be strong antispasmodics. They may be formulated thus:

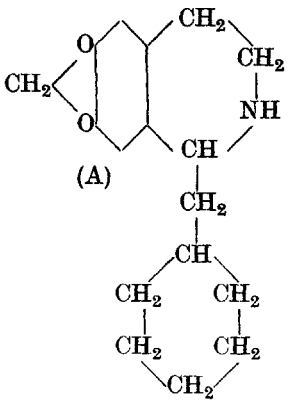


Although these compounds are obviously different from papaverine, they still bear an interesting relation to the completely hydrogenated papaverine molecule with the isoquinoline ring ruptured. Blicke and Zienty (*ibid.*, p. 93) have synthesized methyldi-α-cyclohexyl-ethylamine,

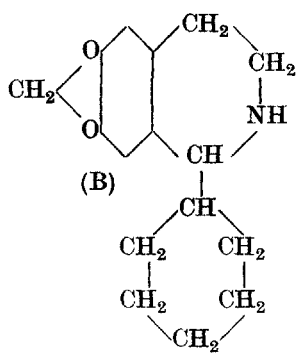
$$CH_3 . CH(C_6H_{11}) . N(CH_3) — CH(C_6H_{11}) . CH_3,$$

which also shows equally strong antispasmodic properties.

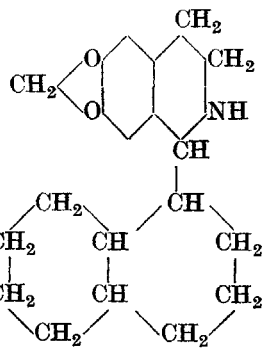
In the light of these experiments, it was hoped that polymethylene compounds substituted in position 1 of the 1,2,3,4-tetrahydro-isoquinolines should prove to be strong antispasmodics. Accordingly, syntheses of the types of compounds A, B, and C, shown below, were undertaken :



(A)



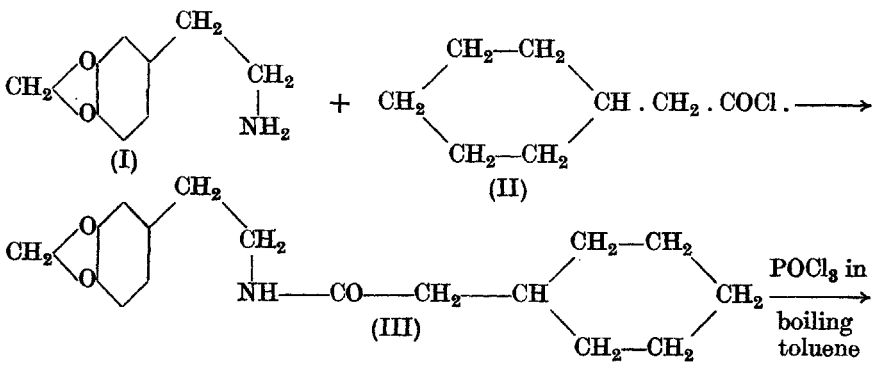
(B)

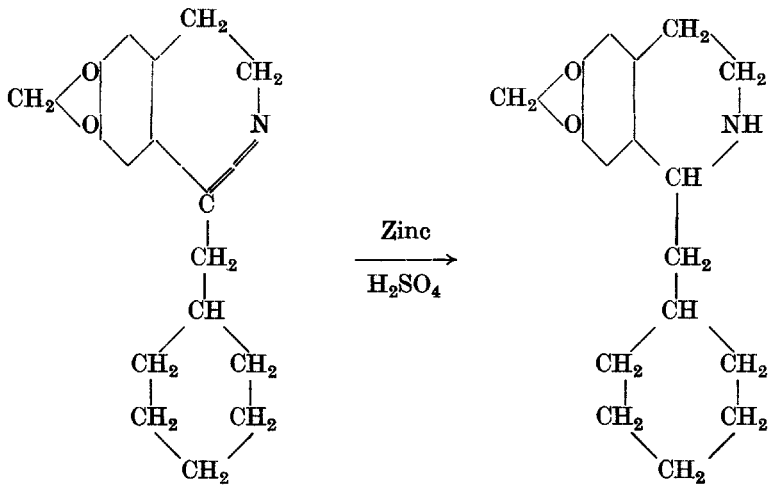


(C)

1-Cyclohexyl isoquinoline.

The scheme outlined below represents the various steps in the synthesis of 1-cyclohexyl isoquinoline :





Cyclohexyl malonic acid was prepared by the reduction and hydrolysis of ethyl cyclohexylidene cyano-acetate obtained by the condensation of cyclohexanone and ethyl cyano-acetate. (Harding, Haworth, and Perkin, *J. Chem. Soc.*, 1909, *93*, 1943; Vogel, *J. Chem. Soc.*, 1928, 2023.)

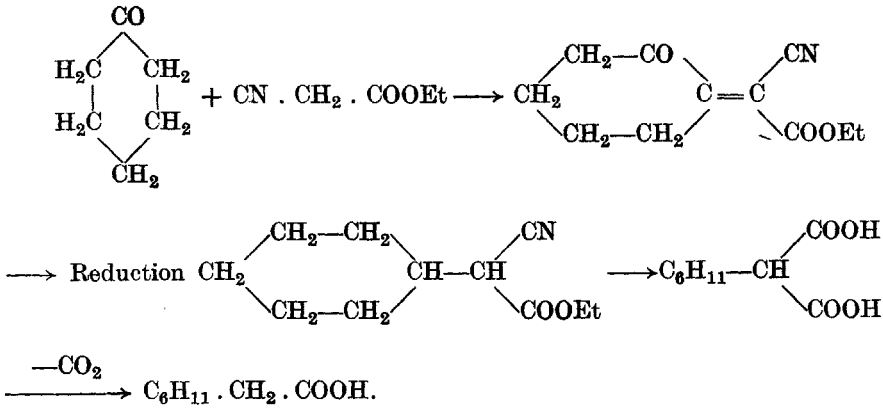
The malonic acid was heated under reduced pressure in an oil bath when decarboxylation took place and the cyclohexyl acetic acid distilled over. This was converted by treatment with thionyl chloride into cyclohexyl-acetyl chloride which, in presence of aqueous alkali, reacted with homopiperonyl amine to give cyclohexyl-acetyl-β-3 : 4,methylenedioxy-phenyl ethyl amide (M.P. 128°).

The amide, in presence of phosphoryl chloride in boiling toluene, gave 1, cyclohexyl-methyl-6 : 7,methylenedioxy-3 : 4,dihydroisoquinoline. M.P. 100°. The hydrochloride in a dilute solution exhibits a strong blue fluorescence. Reduction of the base with zinc spangles and sulphuric acid gave the tetrahydro base which could not be crystallized successfully, probably owing to its low melting point. The tetrahydro base gave a sparingly soluble hydrochloride which showed only a very feeble fluorescence in a large volume of water. The reduced base gave a sticky benzoyl derivative which could not be crystallized. The *p*-nitro-benzoyl derivative, however, was prepared in a pure crystalline condition.

Experiments are in progress with cyclohexane carboxylic and dekalin carboxylic acids.

Experimental.

Cyclohexyl acetic acid was prepared from cyclohexanone according to the scheme outlined below :—



Preparation of cyclohexylidene cyano-acetate.

(Harding, Haworth and Perkin, *Journ. Chem. Soc.*, 1908, *93*, 1943.)

Equimolecular proportions of cyclohexanone (9·8 g.) and ethyl cyano-acetate (11·3 g.) were mixed with a few drops of piperidine and allowed to stand for a few minutes. Condensation takes place readily with the separation of water.

The product was heated on the water bath for two hours, diluted with water, and extracted with ether. The ether extract was washed with dilute hydrochloric acid, dried over anhydrous calcium chloride and the solvent removed. The pale yellow oil was distilled under reduced pressure (165°–67°/15 mm.).

151°/12 mm. $n_D^{18°} = 1{\cdot}4974$ (Vogel, *Journ. Chem. Soc.*, 1928, 2023).

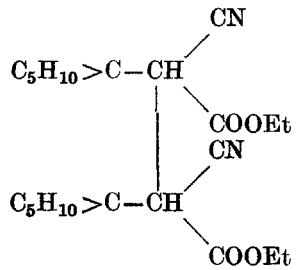
160°–63°/15 mm. (Lapworth and MacRae., *Journ. Chem. Soc.*, 1922, *121*, 2754).

151°/10 mm. $n_D^{19·5°} = 1{\cdot}49670$ (Birch, Kon and Norris, *Journ. Chem. Soc.*, 1923, *123*, 1373).

Ethyl r-cyclohexyl cyano-acetate.

(Vogel, *ibid.*, 2023.)

The unsaturated ester (10·0 g.) was reduced with moist aluminium amalgam (15·0 g.); there was a period of induction of about three hours and the reaction was complete after nine hours, when the product was worked up in the usual fashion and distilled. Ethyl-*r*-cyclohexyl cyano-acetate (8·5 g.) passed over at 144–46/14 mm. The viscid residue was dissolved in methyl alcohol and the solvent evaporated in vacuum over concentrated sulphuric acid and traces of impurities removed by extracting with boiling light petroleum, when it melted at 87°. It was the bimolecular product,



The liquid reduction product, on redistillation, boiled at 145°/14 mm. and had $n_D^{18.5°} = 1.4612$.

Cyclohexyl malonic acid.

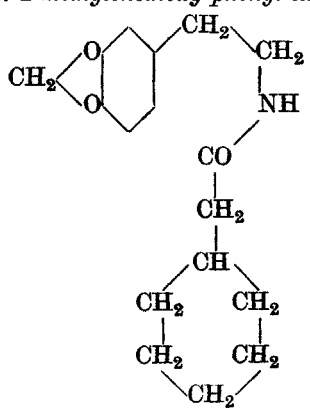
(Vogel, *Journ. Chem. Soc.*, 1928, 2023.)

A solution of ethyl cyclohexyl cyano-acetate (20 g.) in rectified spirit (40 g.) and a solution of potassium hydroxide (30 g.) in water (60 c.c.) was refluxed for 18 hours and evaporated to dryness. An aqueous solution of the residue was shaken with ether to remove unchanged substance, acidified and the precipitated acid filtered. The acid mother liquor, on extraction with ether, yielded some more of the acid. M.P. 178°. The yield was nearly quantitative. The acid was purified by dissolving in $NaHCO_3$ solution and precipitating with HCl.

Cyclohexyl acetic acid.

Cyclohexyl malonic acid (6 g.) was distilled under reduced pressure from an oil-bath, when decarboxylation took place. The acetic acid distilled at 117°/5 mm. Yield, 2 g. A considerable amount of a non-acidic material was left behind in the flask, which was not investigated. (Cf. Hope and Perkin, *Journ. Chem. Soc.*, *95*, 1364; they report the preparation of the acid in good yields by keeping the malonic acid at 180°, but do not record the formation of the non-acidic substance.)

Cyclohexyl-acetyl-β-3 : 4-methylenedioxy-phenyl ethylamide.



Cyclohexyl acetic acid (2·65 g.) was carefully mixed with thionyl chloride (1·86 c.c.) when a vigorous reaction set in with copious evolution of hydrogen chloride. The reaction was completed by heating the mixture on the steam-bath for half an hour. The syrupy liquid was added in small portions to an ice cold emulsion of homopiperonylamine (3·0 g.), in a solution of 10 per cent potassium hydroxide (20 c.c.) with vigorous shaking after each addition. After the addition was complete, the product was allowed to stand in an ice-bath for 10 minutes and filtered. The residue was thoroughly washed with petroleum ether and dried in vacuum desiccator. The dried amide crystallized from alcohol (charcoal) in fine, long needles melting at 128°. Yield, 4·9 g.

16·36 mg. of the amide (dried in vacuum) gave 0·760 c.c. 'N_2' at 32° and 763 mm. pressure.

Found : N, 5·23 per cent.

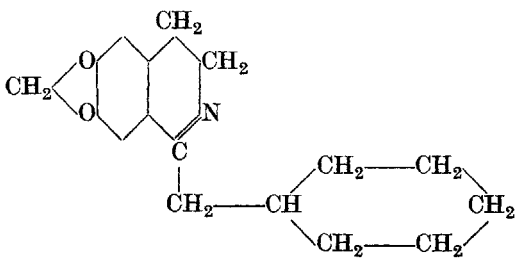
$C_{17}H_{23}O_3N$ requires N, 4·85 per cent.

17·10 mg. gave 44·44 mg. of CO_2 and 12·73 mg. of H_2O.

Found : C, 70·87; H, 8·27 per cent.

$C_{17}H_{23}O_3N$ requires C, 70·55; H, 8·02 per cent.

1-*Cyclohexyl-6 : 7-methylenedioxy-3 : 4-dihydroisoquinoline.*



The above amide (2·0 g.) was suspended in dry toluene (15 c.c.) and phosphorus oxychloride (10 c.c.) added. The mixture became warm and was then refluxed for 2½ hours at 120°–130°. The fluorescent toluene solution was cooled and petroleum ether added till there was no more separation of a crystalline precipitate. The precipitate was collected at the pump, washed well with petroleum ether and treated with 15 c.c. hot water containing 2·5 c.c. concentrated hydrochloric acid. The hot solution was filtered, cooled and ether extracted. The acid layer was freed from ether by warming on a water-bath, cooled to 0°C., and basified with liquor ammonia. The base separated as an amorphous powder on standing. When the base was crystallized slowly from dilute alcohol, it separated in long silky needles. Yield, 1·5 g. M.P. 100°.

The base dissolves easily in alcohol and moderately in benzene and ether. When shaken with water, it exhibits a bright blue fluorescence.

18·37 mg. (dried in vacuum) gave 0·87 c.c. of nitrogen at 31·5°C. and 759·4 mm. pressure ; 22·98 mg. gave 63·12 mg. of CO_2 and 16·56 mg. of H_2O.

Found : C, 74·91 ; H, 8·01 ; N, 5·30 per cent.

$C_{17}H_{21}O_2N$ requires C, 75·23 ; H, 7·81 ; N, 5·16 per cent.

The platinichloride.

The base (0·5 g.) was dissolved in 3 c.c. hydrochloric acid (1 : 1) and treated with a solution of 5 per cent chloroplatinic acid till there was no more precipitate formed. The light yellow amorphous solid was collected at the pump, washed well with water, and then with a little dilute alcohol. After drying in the steam oven it melted at 204° (decomp.).

44·3 mg. of the platinum salt (dried in vacuum at 100°) gave 9·287 mg. of platinum.

Found : Pt, 20·96 per cent.

$(C_{17}H_{21}O_2N)_2 . H_2PtCl_6$ requires Pt, 20·49 per cent.

The hydrochloride.

The base (0·1 g.) was rubbed with concentrated hydrochloric acid (1 c.c.) and kept overnight in vacuum. The solid was crystallized from hot absolute alcohol which deposited glistening plates melting at 188°-189°. The salt is very hygroscopic and becomes sticky on exposure to air for a few minutes. Its solution in water exhibits a mild blue fluorescence.

38·44 mg. (dried in vacuum) required 5·4 c.c. of 1·108 N/50 NaOH.

Found : Cl, 11·04 per cent.

$C_{17}H_{21}O_2N . HCl$ requires Cl, 11·5 per cent.

The picrate.

The base (0·1 g.) was dissolved in dilute hydrochloric acid (3 c.c.) and a concentrated solution of picric acid was added. The picrate was collected at the pump and crystallized from acetone. Short, stout needles melting at 162°.

16·92 mg. gave 1·64 c.c. of nitrogen at 763 mm. pressure and 32°C.

Found : N, 11·15 per cent.

$C_{17}H_{21}O_2N . C_6H_3O_7N_3$ requires N, 11·10 per cent.

1,Cyclohexyl-6 : 7,methylenedioxy-1 : 2 : 3 : 4,tetrahydro-isoquinoline.

The dihydro base (1 g.), zinc spangles (3 g.) and copper sulphate (0·05 g.) were taken in water (35 c.c.) and concentrated sulphuric acid (3 c.c.) added in the course of an hour to the mixture heated on a water-bath. Heating was continued for another hour after addition and the product filtered hot. The residue was treated with boiling water thrice (10 c.c. each time) and filtered. The combined filtrate was cooled and basified with excess of ammonia. The sticky precipitate was extracted with ether, the extract dried over anhydrous potassium carbonate and the solvent removed. The residue that was left was also sticky and could not be crystallized successfully. It was therefore

converted into the pure hydrochloride by dissolving in dilute hydrochloric acid, evaporating the solution to dryness on a water-bath and crystallizing from dilute alcohol. It separated in plates, melting at 214°.

The *hydrochloride* is sparingly soluble in cold but dissolves readily in hot water, the solution exhibiting a blue fluorescence.

39·21 mg. (dried at 100°) requires 5·7 c.c. of 1·108 N/50 NaOH.

10·12 mg. gave 0·514 c.c. of nitrogen at 759·9 mm. and 33°C.

Found : Cl, 11·43; N, 4·50 per cent.

$C_{17}H_{24}O_2NCl$ requires Cl, 11·47; N, 4·52 per cent.

The *p-nitrobenzoyl derivative* was prepared by suspending the reduced base (0·1 g.) in 10 per cent potassium hydroxide solution (5 c.c.), adding *p*-nitrobenzoyl chloride (0·5 g.) in small quantities and shaking vigorously.

The separating solid was collected, washed well with dilute alkali and then with water, dried, and the solid triturated successively with small amounts of petroleum ether and dry ether. The residue crystallized from boiling alcohol in glistening plates, melting at 164°.

20·84 mg. (dried in vacuum) gave 1·245 c.c. of nitrogen at 759·7 mm. and 32°C.

Found : N, 6·69 per cent.

$C_{24}H_{26}O_5N_2$ requires N, 6·63 per cent.

The *picrate*, prepared in the usual manner, crystallized from dilute alcohol in felted leaflets, melting at 178°.

15·00 mg. gave 1·443 c.c. of nitrogen at 761·3 mm. and 31°C.

Found : N, 11·08 per cent.

$C_{17}H_{23}O_2N \cdot C_6H_3O_7N_3$ requires N, 11·15 per cent.

PRESIDENCY COLLEGE,
MADRAS,
30th November, 1939.