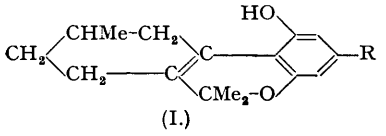
204. *Tetrahydrodibenzopyran Derivatives Isomeric with Tetrahydrocannabinols.*

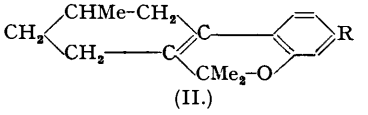
By A. W. D. Avison, A. L. Morrison, and M. W. Parkes.

A new series of tetrahydrodibenzopyran derivatives is described isomeric with that corresponding to synthetic tetrahydrocannabinol. Members of the new series are derived from 4- instead of 5-alkylresorcinols and are thus, in general, easier of access. Hashish activity, as measured by the Gayer test, is still present, but there is less pronounced change of potency with variation in the alkyl substituent. Attempts to prepare *sec.*-alkylresorcinols by direct alkylation of resorcinol are described.

The tetrahydrocannabinol (I; R = n-C_5H_{11}) was first synthesised by Ghosh, Todd, and Wilkinson (*J.*, 1940, 1121) and by Adams and Baker (*J. Amer. Chem. Soc.*, 1940, **62**, 2405). Homologues were also prepared (Russell, Todd, Wilkinson, MacDonald, and Woolfe, *J.*, 1941, 826; Adams, Loewe, Jelinek, and Wolff, *J. Amer. Chem. Soc.*, 1941, **63**, 1971), some of which showed greater pharmacological activity. In particular, the compound (I; R = n-C_6H_{13}), known as " Synhexyl " or " Parahexyl ", had the greatest activity as measured by dog-ataxia or rabbit corneal-areflexia (Gayer test) in the series where R is a straight carbon chain. Homologues where R contains branching alkyl groups vicinal to the aromatic ring were prepared by Adams and his group (*ibid.*, 1948, **70**, 662, 664; 1945, **67**, 1534) and found to exhibit extraordinarily high potencies (many times greater than those obtainable from natural sources) in the dog-ataxia test. Numerous attempts (Todd *et al.*, *J.*, 1941, 169, 826; Adams *et al.*, *J. Amer. Chem. Soc.*, 1941, **63**, 1973, 1977; 1942, **64**, 694, 2653) to vary the *cyclo*hexene or the pyran ring of the tetrahydrocannabinol structure resulted only in compounds having greatly



(I.)



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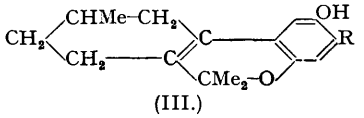

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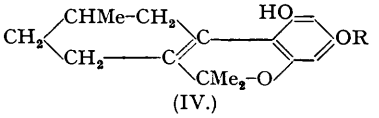


(IV.)

reduced activity, except in the case of hexahydrocannabinol. The only variations tried involving the aromatic ring were as in (II), (III), and (IV) derived from *m*-amylphenol, amylquinol, and phloroglucinol, respectively (Alles, Icke, and Feigen, *ibid.*, 1942, **64**, 2031; Russell, Todd, Wilkinson, MacDonald, and Woolfe, *J.*, 1941, 169; Bergel, Morrison, Rinderknecht, Todd, Macdonald, and Woolfe, *J.*, 1943, 286), no greater success in finding active compounds being achieved. Thus it appeared that only tetrahydrodibenzopyrans of the structure (I), their dihydro-compounds, and natural hemp drugs where the double bond is shifted, were capable of exhibiting hashish activity. However, those synthesised are all obtained only by a long route.

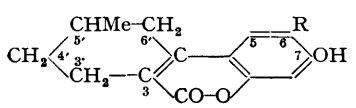
As " Synhexyl " has lately become of interest owing to its reported effect in depressive mental states (Tayleur-Stockings, *Brit. Med. J.*, 1947, 918), the search for active analogues, more easily prepared, is of some importance. The present paper reports some progress in this direction and shows that the specific arrangement of substituents in the tetrahydrocannabinol series is of less pharmacological significance than seemed likely hitherto.

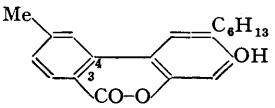
When 4-*n*-hexylresorcinol was treated with ethyl 1-methyl*cyclo*hexan-3-one-4-carboxylate and sulphuric acid, a *cyclo*hexenocoumarin was obtained. The structure of this compound was indicated, by its strong blue fluorescence in alkaline solution and failure to give a colour in the Gibbs test (*J. Biol. Chem.*, 1927, **72**, 649), to be the 7-*hydroxycoumarin* (V; R = n-C_6H_{13}).* This was confirmed by dehydrogenation with palladised charcoal to the *benzocoumarin* (VI), m. p. 220—222°, which was also synthesised from 2-bromo-4-methylbenzoic acid and 4-*n*-hexylresorcinol according to the method of Adams, Pease, Clark, and Baker (*J. Amer. Chem. Soc.*, 1940, **62**, 2197) (with 4-amylresorcinol it had been shown conclusively that condensation takes place in the 6-position; cf. Adams, Baker, *et al.*, *ibid.*, pp. 2201, 2204, 2208).

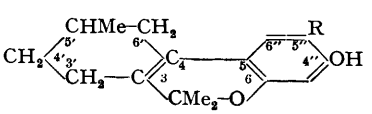
The coumarin (V; R = n-C_6H_{13}) was readily converted by the action of excess of methyl-

* The numbering of (V)—(VII) is that used in earlier papers by Todd and his co-workers.—Ed.

magnesium iodide in the usual way into the corresponding 4″-*hydroxy*-2 : 2 : 5′-*trimethyl*-5″-n-*hexyl*-3′ : 4′ : 5′ : 6′-*tetrahydrodibenzopyran* (VII; R = *n*-C_6H_{13}). The coumarins from 4-*n*-heptyl- and 4-*n*-octyl-resorcinol were prepared by using sulphuric acid or phosphorus oxychloride and ethyl 1-methyl*cyclo*hexan-3-one-4-carboxylate. These were converted without any difficulty into the *tetrahydrodibenzopyrans* (VII; R = *n*-C_7H_{15}) and (VII; R = *n*-C_8H_{17}), respectively. Besides these three *n*-alkyl compounds, we prepared (VII; R = *cyclo*hexyl) from 4-*cyclo*hexylresorcinol. The latter is of interest since there is a secondary carbon atom next to the aromatic nucleus, a factor which seems greatly to enhance activity in the isomeric series, as mentioned above. Compounds of the formula (I; R = *cyclo*alkyl) have not so far been reported, probably owing to the difficulty of synthesising the requisite resorcinols.


(V.)


(VI.)


(VII.)

In efforts to prepare 4-*sec.*-alkylresorcinols by direct alkylation of resorcinol, a variety of conditions was tried. No more than a trace of simple alkylation could be achieved with *n*-octyl alcohol by use of sulphuric acid (cf. Meyer and Bernhauer, *Monatsh.*, 1929, **53/54**, 721), anhydrous hydrogen fluoride (cf. Calcott, Tinker, and Weinmayr, *J. Amer. Chem. Soc.*, 1939, **61**, 1010), or boron fluoride alone (cf. Sowa, Hennion, and Nieuwland, *ibid.*, 1935, **57**, 709) or with the addition of phosphoric oxide (cf. Toussaint and Hennion, *ibid.*, 1940, **62**, 1145). Evidently, for the primary alcohol to effect nuclear alkylation, conditions are required which cause complex decomposition and polymerisation of the resorcinol. *sec.*-Octyl alcohol with anhydrous aluminium chloride and oct-1-ene with fluoboric acid both gave *ca.* 30—40% yields of octylresorcinol. Oct-1-ene with aluminium chloride failed to alkylate resorcinol, apparently becoming itself polymerised. The octylresorcinols from *sec.*-octyl alcohol and oct-1-ene gave rise to the same crystalline *cyclo*hexenocoumarin on treatment with ethyl 1-methyl*cyclo*hexan-3-one-4-carboxylate and phosphorus oxychloride, in rather small yield in both cases. The coumarin isolated seems to be a *sec.*-octyl compound, and is probably the 1-*methylheptyl* compound since it was obtained from oct-1-ene which ought to yield exclusively this isomer (cf. Thomas, " Anhydrous Aluminium Chloride in Organic Chemistry," New York, 1941, pp. 461, 466). Treatment with methylmagnesium iodide in the usual manner gave the *tetrahydrodibenzopyran* of probable structure (VII; R = *n*-C_6H_{13}·CHMe).

The five new tetrahydrodibenzopyrans of series (VII) were investigated pharmacologically together with tetrahydrocannabinol, its acetate, and some of its homologues previously described. The Gayer test (cf. Marx and Eckhardt, *Arch. Exp. Path. Pharm.*, 1933, **170**, 395) for corneal areflexia was performed on rabbits, the substances being injected intravenously in solution in propylene glycol. Concentrations were such that the dose to be given per kg. of body weight was always contained in 0·1 ml. Two animals were used for each dose level and the " score " or number of blinks in response to twenty applications of the horse hair to the cornea was determined for each rabbit at intervals after injection. The minimum scores obtained were plotted against the logarithm of the dose in mg. per kg. of body weight, and the relation found to be linear over most of the range. In the results summarised in the table, the activities of the compounds are expressed by the dose reducing the response to the test to 50%, as read from the dosage–response curve. Acute toxicities were determined in mice, also by intravenous injection in propylene glycol solution. A method similar to that described by Davies, Raventos, and Walpole (*Brit. J. Pharmacol.*, 1946, **1**, 255), who reported low activity with cannabis resin extract, was used to investigate analgesic properties. It was found that similar activity is possessed by synthetic tetrahydrocannabinol, higher members of this series, and the only compound (VII; R = *n*-C_6H_{13}) so far tested in the new series. The substances were injected into groups of young rats by subcutaneous route in propylene glycol solution and tested in comparison with parallel groups of rats receiving pethidine hydrochloride, 7·5 mg. per kg. of body weight in aqueous solution. The results given in the table are obtained from the dosage–response curves, which are parallel to that obtained for pethidine hydrochloride.

Reviewing the results in the table, it can be seen that, in spite of differences of structure, the same order of hashish activity in rabbits, analgesic activity in rats, and toxicity in mice exists in the new series (VII) as in the tetrahydrocannabinol series (I). However, it is interesting to observe that the variation of activity with variations in structure of the side

	R =	Gayer test, ED_{50}, mg./kg.	Mice, LD_{50}, mg./kg.	Dose having standard analgesic effect, mg./kg.
Series (I) :	*n*-C_5H_{11} (acetate)	0·3	non-lethal at 200	60·0 (free phenol)
	n-C_6H_{13} (" Synhexyl ")	0·03	140	100·0
	iso-C_6H_{13}	0·3	—	—
	n-C_7H_{15}	0·03	—	—
	sec.-C_8H_{17}	0·0025	390	160·0
Series (VII) :	*n*-C_6H_{13}	0·125	490	50·0
	n-C_7H_{15}	0·06	188	—
	n-C_8H_{17}	0·04	ca. 400	—
	*cyclo*Hexyl	0·04	60	—
	sec.-C_8H_{17}	0·07	ca. 400	—

chain R differs markedly in the two series. We have not yet obtained any new compound with the exceptionally high activity we report for the *sec.*-octyl homologue of (I), which confirms the result published by Adams and Loewe (*loc. cit.*) for this and similar compounds using the dog-ataxia test. It should be pointed out that the tests using rabbits and dogs measure only two aspects of the pharmacology of these substances. So far there is no evidence that the most interesting action of *Cannabis Indica* and its synthetic analogues, its powerful euphoriant effect in man, has any relationship to the ataxia or corneal anæsthesia produced in animals.

The present paper is a continuation of work started in this field by Bergel, Todd, *et al.* (cf. *Annalen*, 1930, **482**, 55; 1932, **493**, 250; *Biochem. J.*, 1939, **33**, 123, etc.).

Experimental.

7-Hydroxy-5'-methyl-6-n-hexyl-3 : 4-cyclohexenocoumarin (V; R = *n*-C_6H_{13}).—4-*n*-Hexylresorcinol (22·0 g.), prepared by Clemmensen reduction of 4-*n*-hexoylresorcinol (Dohme, Cox, and Miller, *J. Amer. Chem. Soc.*, 1926, **48**, 1688), was dissolved in ethyl 1-methyl*cyclo*hexan-3-one-4-carboxylate (22·0 g.), and concentrated sulphuric acid (40 ml.) added slowly. After standing at room temperature for 21 hours, the dark, viscous reaction mixture was poured on ice with vigorous stirring. The resulting light-brown solid was collected and crystallised from methanol. The *coumarin* consisted of cream-coloured prisms, m. p. 167—168° (Found : C, 75·8; H, 8·2. $C_{20}H_{26}O_3$ requires C, 76·4; H, 8·3%), and exhibited an intense blue fluorescence in solution in alcoholic potassium hydroxide. No colouration was obtained with 2 : 6-dichloroquinonechloroimide (Gibbs, *J. Biol. Chem.*, 1927, **72**, 649).

7-Hydroxy-5'-methyl-6-n-hexyl-3 : 4-benzocoumarin (VI).—(*A*) The above compound (1·0 g.) was intimately mixed with 5% palladised charcoal (0·5 g.) and heated slowly to 260°, evolution of hydrogen then setting in briskly. The temperature was slowly increased to 300—310° and held there until no more hydrogen was given off. The cooled residue was washed with hot alcohol and filtered whilst hot. On cooling, the *benzocoumarin* crystallised in colourless needles, m. p. 220—222°. Recrystallisation did not increase the m. p. (Found : C, 77·2; H, 7·0. $C_{20}H_{22}O_3$ requires C, 77·4; H, 7·15%).

(*B*) 2-Bromo-4-methylbenzoic acid (1·75 g.) and 4-*n*-hexylresorcinol (1·5 g.) were dissolved in N-aqueous sodium hydroxide (10 ml.). The solution was heated to boiling and 10% copper sulphate solution (0·5 ml.) was added, resulting in formation of a brown precipitate which was collected. This became nearly white on washing with alcohol, and on recrystallisation from the same solvent, colourless needles were obtained, m. p. 220—222°. No depression in melting point was observed when the products from procedures (*A*) and (*B*) were mixed.

4''-Hydroxy-2 : 2 : 5'-trimethyl-5''-n-hexyl-3' : 4' : 5' : 6'-tetrahydrodibenzopyran (VII; R = *n*-C_6H_{13}).—The above-described methyl*cyclo*hexeno-coumarin (10·0 g.), dissolved in dry benzene (150 ml.), was added to the Grignard reagent prepared in the usual way from methyl iodide (47·5 g.) and magnesium (8·0 g.) in dry ether (120 ml.). The mixture was boiled under reflux for 15 hours, cooled, and poured on ice. After treatment with saturated ammonium chloride solution, the ether was separated and washed twice with water. Drying, concentration, and distillation of the residue in a vacuum gave the required *tetrahydrodibenzopyran* as a light-amber resin distilling at 180—185°/0·3 mm. (Found : C, 79·9; H, 9·6. $C_{22}H_{32}O_2$ requires C, 80·5; H, 9·8%).

7-Hydroxy-5'-methyl-6-n-heptyl-3 : 4-cyclohexenocoumarin (V; R = *n*-C_7H_{15}).—4-*n*-Heptylresorcinol (14·5 g.) from 4-*n*-heptoylresorcinol (Dohme, Cox, and Miller, *loc. cit.*) and ethyl 1-methyl*cyclo*hexan-3-one-4-carboxylate (12·8 g.) were dissolved in dry benzene (80 ml.). The solution was boiled for 5 minutes and kept at room temperature for 18 hours. When the dark solution was washed with aqueous sodium hydrogen carbonate, crystallisation began. The pink solid was filtered off, washed with water and benzene, and had m. p. 158—160°. When prepared by the sulphuric acid method, the crystals were pale green. Recrystallisation from 90% alcohol gave the *coumarin* as plates, m. p. 160—161° (Found : C, 76·1; H, 8·6. $C_{21}H_{28}O_3$ requires C, 76·8; H, 8·6%).

4''-Hydroxy-2 : 2 : 5'-trimethyl-5''-n-heptyl-3' : 4' : 5' : 6'-tetrahydrodibenzopyran (VII; R = *n*-C_7H_{15}).—The above coumarin was treated with excess of methylmagnesium iodide in ether–benzene in the same manner as for the corresponding hexyl compound. The *dibenzopyran* was an amber resin, b. p. 198—202°/0·2 mm. (Found : C, 80·3; H, 9·6. $C_{23}H_{34}O_2$ requires C, 80·7; H, 10·0%).

7-Hydroxy-5'-methyl-6-n-octyl-3 : 4-cyclohexenocoumarin (V; R = *n*-C_8H_{17}).—4-*n*-Octylresorcinol (Dohme, Cox, and Miller, *loc. cit.*) was treated exactly as the *n*-heptyl compound to give the *coumarin* as pale pink crystals from benzene, m. p. 152—153° (Found : C, 76·7; H, 8·5. $C_{22}H_{30}O_3$ requires C, 77·2; H, 8·6%).

4''-Hydroxy-2 : 2 : 5'-trimethyl-5''-n-octyl-3' : 4' : 5' : 6'-tetrahydrodibenzopyran (VII; R = *n*-C_8H_{17}). —Treatment of the above compound with methylmagnesium iodide in the manner already described gave rise to the desired *dibenzopyran* as an amber resin distilling at 193—196°/*ca.* 0·001 mm. (Found: C, 80·0; H, 10·5. $C_{24}H_{36}O_2$ requires C, 80·9; H, 10·2%).

4-cyclo*Hexylresorcinol*.—The method described by Bartlett and Garland (*J. Amer. Chem. Soc.*, 1927, **49**, 2098) was considerably improved by the use of anhydrous hydrogen fluoride as condensing agent. Anhydrous hydrogen fluoride (*ca.* 100 ml.) was run from a cooled, inverted cylinder into a copper vessel with a lid having a thermometer well, stainless-steel stirrer, and hole for making additions (cf. Calcott, Tinker, and Weinmayr, *loc. cit.*) with efficient ice-cooling. Rubber gloves were worn throughout and a good fume-cupboard was employed. Resorcinol (55 g., "AnalaR" grade) was added rapidly with stirring and then *cyclo*hexanol (50 g.) was run in slowly, the temperature being kept below 8°. The mixture was left overnight and then poured on crushed ice in a Pyrex beaker (1 l.). The resulting gummy mass was dissolved in ether and the ethereal solution separated, and washed three times with water and once with sodium hydrogen carbonate solution. The extract was then dried and concentrated to give a gum which was induced to crystallise by trituration with benzene and light petroleum (b. p. 60—80°). The 4-*cyclo*hexylresorcinol was obtained as colourless crystals, m. p. 123—125°. The analytical specimen (recrystallised from benzene and light petroleum) had m. p. 127—128° (Found: C, 74·7; H, 8·2; active H, 1·9 atoms/mol. Calc. for $C_{12}H_{16}O_2$: C, 75·0; H, 8·4%; active H, 2·0 atoms/mol.).

7-Hydroxy-5'-methyl-6-cyclohexyl-3 : 4-cyclo*hexenocoumarin* (V; R = *cyclo*hexyl) was prepared by the phosphorus oxychloride method from 4-*cyclo*hexylresorcinol. The substance could not be recrystallised owing to its insolubility but became nearly white when washed with methanol. It had m. p. 280—285° (Found: C, 77·2; H, 7·7. $C_{20}H_{24}O_3$ requires C, 76·9; H, 7·75%).

4''-Hydroxy-2 : 2 : 5'-trimethyl-5''-cyclohexyl-3' : 4' : 5' : 6'-tetrahydrodibenzopyran (VII; R = *cyclo*hexyl).—Reaction of the above coumarin with excess of methylmagnesium iodide yielded the *tetrahydrodibenzopyran* as a light yellow, brittle glass, b. p. 185—195°/*ca.* 0·0006 mm. (Found: C, 80·35; H, 9·0. $C_{22}H_{30}O_2$ requires C, 81·0; H, 9·3%).

4-sec.-*Octylresorcinol*.—(*A*) Anhydrous aluminium chloride (66·8 g.) was dissolved in nitrobenzene (130 ml.), and the solution added slowly and with stirring to a mixture of resorcinol (27·5 g.) and *sec.*-octyl alcohol (32·5 g.) dissolved in nitrobenzene (100 ml.), the temperature being kept at 70—80°. Evolution of hydrogen chloride began after about half the aluminium chloride had been added. The mixture was kept at *ca.* 80° for 5 hours and then cooled and poured on ice and hydrochloric acid. Ether was added, and after being separated, the ethereal extract was washed twice with water, dried, and concentrated. The 4-sec.-*octylresorcinol* was obtained as a golden syrup by distillation and collection of the fraction (14·7 g.), b. p. 147—153°/0·1 mm. (Found: C, 75·5; H, 9·9; active H, 2·0 atoms/mol. $C_{14}H_{22}O_2$ requires C, 75·6; H, 10·0; active H, 2 atoms/mol.).

(*B*) Oct-1-ene (25·0 g.), prepared from the action of *n*-amylmagnesium bromide and allyl chloride or bromide according to Kazanskii *et al.*, (*J. Gen. Chem. U.S.S.R.*, 1947, **17**, 1503; *Chem. Abs.*, 1948, **42**, 2225), was mixed with resorcinol (24·6 g.) and fluoboric acid (1·2 g.) (prepared according to Nieuwland and Sowa, *J. Amer. Chem. Soc.*, 1935, **57**, 454) was added. The mixture was well stirred and heated by means of an oil-bath to 140°. The red liquid obtained was kept at this temperature for 3 hours and then cooled to about 80°, and hot water (80 ml.) added. The aqueous layer was removed, and the residue washed twice more with hot water to remove unchanged resorcinol. On distillation, the *sec.*-octylresorcinol (18·7 g.) was collected at 149—155°/0·1 mm.

7-Hydroxy-5'-methyl-6-sec.-octyl-3 : 4-cyclo*hexenocoumarin* (V; R = *sec.*-C_8H_{17}).—4-*sec.*-Octylresorcinol (12·5 g.) and ethyl 1-methyl*cyclo*hexan-3-one-4-carboxylate were dissolved in dry benzene (80 ml.) and treated with phosphorus oxychloride (8·65 g.) in the manner already described. When washed, the benzene solution deposited no crystals and concentration led to a red syrup. This was induced to crystallise on treatment with light petroleum (b. p. 80—100°) to give pale pink crystals (4·4 g.), m. p. 192—195°. Recrystallisation from benzene–light petroleum gave the *coumarin* as almost colourless crystals, m. p. 197° (Found: C, 77·4; H, 8·7. $C_{22}H_{30}O_3$ requires C, 77·2; H, 8·8%). This product was the same whether the octylresorcinol from (*A*) or (*B*) was employed.

4''-Hydroxy-2 : 2 : 5'-trimethyl-5''-sec.-octyl-3' : 4' : 5' : 6'-tetrahydrodibenzopyran (VII; R = *sec.*-C_8H_{17}) was obtained from the above coumarin and methylmagnesium iodide as an amber resin, b. p. *ca.* 163°/0·001 mm. (Found: C, 79·9; H, 9·7. $C_{24}H_{36}O_2$ requires C, 80·9; H, 10·2%).

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