rate of hydrolysis due to increased steric hindrance about the acyl carbon atoms. This view is in concert with a report[13] that the rate of enzymatic hydrolysis by serum esterases of a series of diesters of the catecholamine analogue, terbutaline, is decreased by increasing steric bulk about the acyl carbons. Moreover, we have found that the apparent rate of hydrolysis of the larger esters in the presence of rat liver extract is slower than that of smaller esters, as indicated by the rate of production of ethyl acetate–extractable apomorphine fluorescence (excitation–emission maxima, 276–380 nm).[14] Thus, for example at 60 min of incubation, diisobutyrylapomorphine (4) was 55% hydrolyzed to apomorphine, while the hydrolysis of dibenzoylapomorphine (6) was only about 9% complete, starting from an initial concentration of these nonfluorescent esters at 0.4 mM. When these two esters were administered to the mouse intraperitoneally, apomorphine fluorescence was also recovered from homogenates of whole mouse brain, using the methods described by Von-Voightlander et al.[14]

Based on the above data, we conclude that the diesters serve as prodrugs of apomorphine and exhibit extented half-lives (depot activity). The active product of the esters is probably apomorphine, which can be produced in vivo, presumably to exert agonistic effects on striatal or other dopamine receptors in the central nervous system. The prolonged activity of the larger esters can be partly explained by a decreasing rate of hydrolysis due to increased steric hindrance at the site of hydrolysis.

Experimental Section

Melting points were determined in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Elemental analyses were performed by Gailbraith Laboratories, Knoxville, Tenn., where results for those elements were within ±0.4% of the theoretical value. Ir absorption spectra were recorded on a Beckmann Model 18A spectrophotometer. The NMR spectra were recorded on a Varian T-60 spectrometer using Me_4Si or DSS as internal standards.

Apomorphine Diesters. General Procedure. Apomorphine·HCl·0.5H_2O (1 g, 3.2 mmol; S. B. Penick) was dissolved in CF_3COOH (10 ml) and treated with an excess of the appropriate acid chloride (32 mmol). The mixture was warmed on a steam bath for 1 h and the volatiles were then removed under reduced pressure. The residue was partitioned between saturated $NaHCO_3$ solution and Et_2O. The Et_2O was removed and the residue either isolated and recrystallized or converted to an HCl salt and then recrystallized.

Spectral analyses (ir and NMR) were completed for compounds **2**, **3**·HCl, **4**, **4**·HCl, **5**, **5**·HCl, and **6**. Typical results with compound **5**·HCl were as follows: ir(KBr) ν_{max} 1760 cm^{-1}; NMR ($CDCl_3$) δ 1.28 and 1.37 (2 s, 18 H), 3.02 (NCH_3), 7.17 (m, 4 H), 7.84 ppm (d of d, 1 H).

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Drugs Derived from Cannabinoids. 6.[1] Synthesis of Cyclic Analogues of Dimethylheptylpyran

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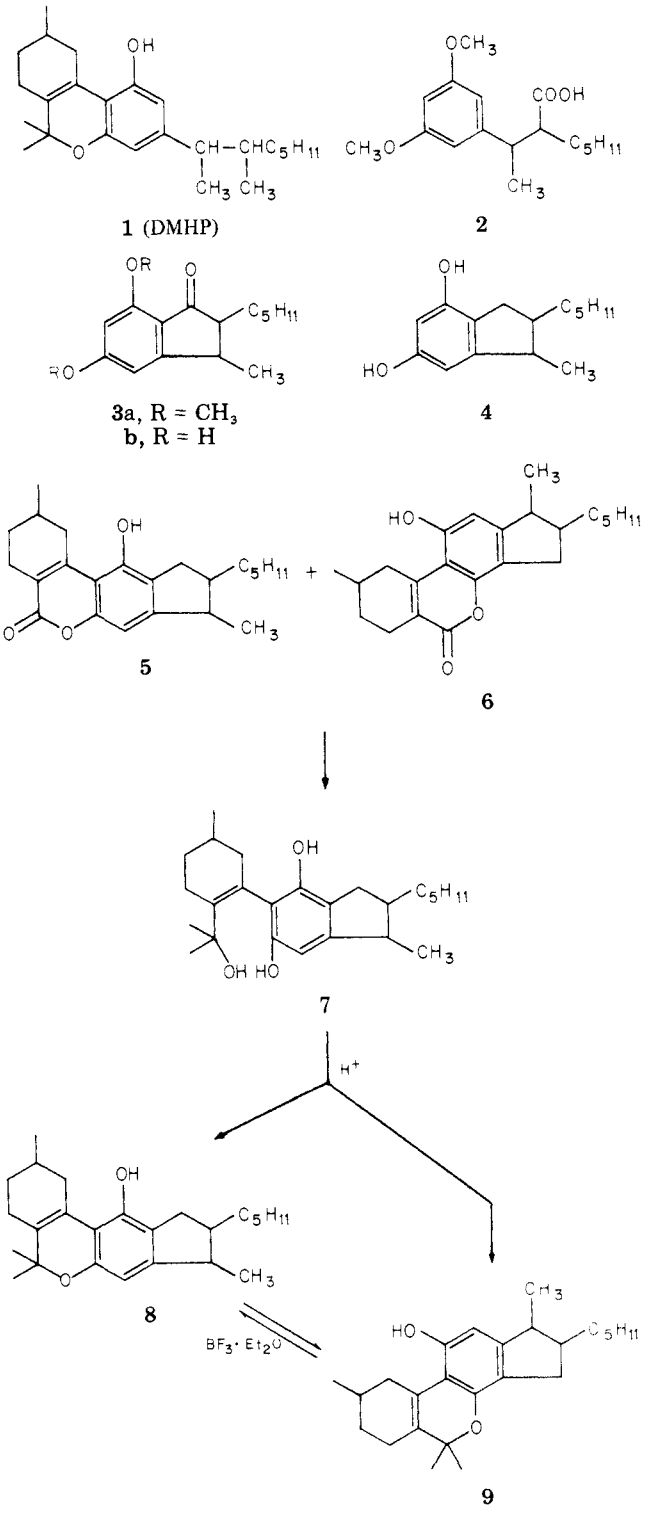
Two cyclic analogues 8 and 9 of dimethylheptylpyran (DMHP, 1) were synthesized by the Pechmann condensation of the resorcinol 4 with ethyl 4-methyl-2-cyclohexanone-1-carboxylate followed by Grignard addition with MeMgI. In selected pharmacological tests both analogues 8 and 9 were considered inactive compared to DMHP as CNS and cardiovascular agents.

During the early work on the structure elucidation of the active constituent of marihuana, Adams[2] and Todd[3] and their co-workers discovered the physiologically active $\Delta^{6a,10a}$-tetrahydrocannannabinols. After extensive structure–activity study of this synthetic series, Adams found the 1,2-dimethylheptyl analogue (DMHP, 1) to be the most potent as shown by the dog ataxia test.[2] Extensive pharmacological studies have since been reported for DMHP[4] and in more recent years clinical studies[4c,e] have shown it to have powerful blood pressure lowering properties. These findings in man have confirmed the reported antihypertensive activity of DMHP in laboratory

animals.[4b] As a part of our ongoing program of structure–activity modification of DMHP, we prepared the cyclic analogues **8** and **9** to study their effect on the CNS and antihypertensive activity. In this paper, we report the synthesis of cyclic analogues **8** and **9** and the effect of this structure modification on the antihypertensive and CNS activity of DMHP.

Polyphosphoric acid cyclization of the acid **2**[5] gave the indanone **3a** which, on demethylation (HI–CH_3COOH) followed by Clemmensen reduction, furnished the indandiol **4**. Pechmann condensation ($POCl_3$–C_6H_6) of **4** with ethyl 4-methyl-2-cyclohexanone-1-carboxylate gave a mixture of pyrones **5** and **6** (55:45 by GLC). On Grignard addition with excess MeMgI, the mixture of pyrones was converted to the triol **7** which on acid catalysis ring closed to a mixture (50:50) of the two isomeric pyrans **8** and **9**. They were separated by chromatography and it was found that both compounds could be interconverted on treatment with BF_3·Et_2O in CH_2Cl_2 at 25 °C. The structural assignments of **8** and **9** were based on the position of the aromatic proton in the NMR[6] which is shielded in **9** (δ 6.0) compared to **8** (δ 6.2). The indan substituents CH_3 and C_5H_{11} in both **8** and **9** are expected to be trans to each other. This point could not be unambiguously established by NMR; GLC analysis, however, showed each compound to consist of a single component.

Both compounds **8** and **9** are considered inactive as CNS agents[7] compared to DMHP (**1**). They showed little or no activity in the mouse fighting (10 mg/kg po), mouse audiogenic seizure (up to 30 mg/kg po), and the rat motor activity tests (5 mg/kg po). Compound **8** was also inactive in cardiovascular studies in hypertensive rats whereas compound **9** showed only marginal decrease in blood pressure, 6% at 10 mg/kg po at 3 h. In the same test, DMHP (**1**) reduced blood pressure 38–40% at 10 mg/kg po for 24 h and its antihypertensive activity could be detected at as low a dose as 0.1 mg/kg po (8%). It is thus seen that the cyclization of the aromatic side chain in DMHP dramatically reduces its CNS and cardiovascular activities.



Experimental Section

Melting points are uncorrected and were determined on a Thomas-Hoover capillary melting point apparatus. Elemental analyses were carried out by Spang Microanalytical Laboratories, Ann Arbor, Mich. NMR spectra were determined on a Varian T-60 instrument. Ir and NMR spectra of all compounds were consistent with the assigned structures. For GLC analysis a Varian Model 1440 instrument was used (column packing, 2% OV-17).

2-*n*-Amyl-3-methyl-5,7-dimethoxyindanone (3a). To 3.5 g (0.012 mol) of α-*n*-amyl-β-methyl-3,5-dimethoxyhydrocinnamic acid[5] (**2**), 40 ml of commercial polyphosphoric acid was added and the mixture was heated at 90–93°. After 16 h it was decomposed by pouring on excess crushed ice and extracted with ether. The etheral extract was washed with dilute $NaHCO_3$ followed by water. After drying, the solvent was evaporated to leave a gum, 3.15 g (95%). It showed a single spot on TLC (1:4 ethyl acetate–hexane).

2-*n*-Amyl-3-methyl-5,7-dihydroxyindanone (3b). A mixture of 3.1 g (0.0109 mol) of **3a**, 10 ml of HI, and 7 ml of acetic anhydride (the acetic anhydride is added very carefully in small portions as there is a violent reaction) was heated in a 100-ml round-bottom flask fitted with a distillation setup in an oil bath at 160°. During this reaction nitrogen was allowed to flow continuously. When the thermometer at the distillation head registered 115°, the heating was stopped. Water was added to the mixture and under vacuum most of the HI was distilled off. This was repeated and after cooling CH_2Cl_2 was added. After separation of the organic phase the residue was again extracted and the combined CH_2Cl_2 extracts were washed with water until neutral. After drying the solvent was evaporated to leave a reddish brown viscous liquid which was pure by TLC (1:4 ethyl acetate–hexane).

2-*n*-Amyl-1-methylindan-4,6-diol (4). A solution of 4 g of $HgCl_2$ in 80 ml of water was added to 40 g of granulated zinc and allowed to stand for 1 h. The water was decanted and the wet zinc amalgam was added to a 500-ml round-bottom flask containing 10 g (0.04 mol) of **3b**. The mixture was heated under reflux after the addition of 300 ml of 33% HCl and an additional 30 ml of concentrated HCl was added in small portions while heating. An oil separated toward the end of the reaction. After cooling, the mixture was poured in excess water and extracted with ether. The ether extract was washed with 5% sodium bicarbonate solution followed by water until neutral. After drying the solvent was evaporated to leave a solid which was crystallized from ether–petroleum ether (bp 30–40°) to yield 8.2 g (88%) of colorless crystals: mp 133–134°; the ir spectrum showed no carbonyl absorption but a very strong OH band. Anal. ($C_{15}H_{22}O_2$) C, H.

2,8-Dimethyl-11-hydroxy-1,2,3,4,5,8,9,10-octahydro-5-oxo-9-*n*-pentylbenz[*d*]indeno[5,6-*b*]pyran (5) and 3,10-Dimethyl-1-hydroxy-3,4,5,7,7,8,9,10-octahydro-7-oxo-4-*n*-pentylbenz[*d*]indeno[4,5-*b*]pyran (6). Pechmann condensation of 4.68 g (0.02 mol) of **4** and 3.68 g (0.02 mol) of ethyl 4-methyl-2-cyclohexanone-1-carboxylate according to the procedure of Adams[8] after 1.5 h gave a creamy solid: 4 g (57%); mp 183–186° (ethyl acetate–petroleum ether). The material showed a single spot on TLC (1:4 ethyl acetate–hexane) but the NMR and GLC showed it to be a mixture of **5** and **6** (55:45 by GLC). Anal. ($C_{22}H_{30}O_3$) C, H.

11-Hydroxy-1,2,3,4,5,8,9,10-octahydro-9-*n*-pentyl-2,5,5,8-tetramethylbenz[*d*]indeno[5,6-*b*]pyran (8) and 1-Hydroxy-3,4,5,7,7,8,9,10-octahydro-4-*n*-pentyl-3,7,7,10-tetramethylbenz[*d*]indeno[4,5-*b*]pyran (9). Grignard addition with CH_3MgI was carried out according to the procedure described by us earlier.[9] It gave a purple gum which by TLC in 10% ether–petroleum ether showed the presence of two spots. The material was chromatographed on 150 g of Florisil in petroleum ether and eluted with graded ether (0.5–2%)–petroleum ether mixtures. Compound **8** was less polar and came off the column first. It was recrystallized from petroleum ether as colorless crystals, mp 101–103°, which on keeping become a semisolid. Anal. ($C_{25}H_{36}O_2$) C, H.

The later fractions from the chromatography column furnished **9** as colorless crystals (C_2H_5OH–H_2O), mp 104–106°. Anal. ($C_{25}H_{36}O_2$) C, H.

Both compounds **8** and **9** on treatment with BF_3·Et_2O in CH_2Cl_2 at room temperature gave a mixture containing **8** and **9** (1:1 by GLC).

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Preparation of 16α-Alkoxy and 16α-Acyloxy Derivatives of 21-Chloro-17-acyloxy Corticosteroids and Determination of Their Vasoconstrictor Activities in Humans

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A number of 16α-alkoxy and 16α-acyloxy derivatives of 21-chloro-17-acyloxy corticosteroids have been prepared. The synthetic routes used were (a) reaction of the 16α,17-disubstituted 21-mesylate with lithium chloride and (b) reaction of the 16α-substituted 17,21-cyclic ortho ester with triphenylmethyl chloride. The vasoconstrictor activities in humans exhibited by these compounds were significantly lower than that of a 16β-methyl analogue.

Replacement of the 21-hydroxyl group of certain corticosteroids with a Cl atom had led to the synthesis of clinically useful, topical antiinflammatory agents, for example, 21-chloro-9-fluoro-11β-hydroxy-16β-methyl-17-(propanoyloxy)pregna-1,4-diene-3,20-dione (1, clobetasol propionate)[1] and 21-chloro-9-fluoro-11β-hydroxy-2',2'-dimethylpregn-4-eno[16α,17-*d*][1,3]dioxolane-3,20-dione (2, halcinonide).[2] In order to explore further the relationship between structure and topical antiinflammatory activity, we undertook to prepare 16α-acyloxy and 16α-alkoxy derivatives of 21-chloro-17-acyloxy corticoids. This note describes the preparation of such derivatives and the determination of their vasoconstrictor[3] activity in humans.

Chemistry. Hydrolysis of ortho ester **3a** (prepared from the known 16α-methoxy-17,21-diol[4] by the standard procedure[5]) to the 17-ester **4a** was complicated by the formation of by-products (21-ester and 17,21-diol). After chromatography and recrystallization, **4a** was obtained in 31.6% yield. Conversion of **4a** to the 21-chloro derivative **5a** was accomplished via the 21-mesylate.

Hydrolysis of ortho ester **3b** gave a mixture containing large amounts of the corresponding 17,21-diol 21-acetate (TLC analysis) and was not preparatively useful. Vitali and Gardi[5] noted a similar disparity between orthopentanoate and orthoacetate hydrolysis, but the effect here seems more pronounced.

Rather than explore alternate procedures[6] for hydrolysis, we chose to apply the elegant conversion of ortho esters to esters of chlorohydrins utilized by Newman and Chen.[7] Reaction of the 16-unsubstituted ortho ester **6a** with triphenylmethyl chloride in refluxing dichloromethane gave the 21-chloro-17-pentanoate **7a** in 27% yield. This material was identical with a sample prepared via the 21-mesylate.[8]

Application of this method to the ortho esters listed in Table I gave the desired 21-chloro 17-esters in the indicated yields (of analytically pure, TLC homogeneous material). Hydrolysis of **9d** with potassium carbonate in methanol at 0° gave the parent 21-chloro-11β,16α,17-triol, thus establishing unambiguously the assigned structure.