Amino acid **1m** was prepared in a similar manner in 85% yield.

Method D. Reduction of 3-Pyrazolidinone Ketone (1e). Sodium borohydride (0.760 g, 20 mmol) was added portionwise to a solution of ketopyrazolidinone **1e** (4.2 g, 11.8 mmol) in EtOH (50 ml) at 0°. After an additional 0.5 h at 0°, the mixture was added to H_2O (100 ml) and extracted thoroughly with Et_2O. The combined Et_2O extracts were dried and evaporated to give an oil that contained two components, as determined by TLC. Chromatography over silica gel (30:1) with $CHCl_3$–MeOH (98:2) gave 2.87 g (68%) of 2-[4-(*p*-fluorophenyl)-4-hydroxybutyl]-1-(*m*-methoxyphenyl)-3-pyrazolidinone (**1h**) as a yellow oil pure by TLC. Distillation [205–207° (0.1 mm)] provided an analytical sample.

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Diester Derivatives as Apomorphine Prodrugs

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A series of diesters of apomorphine was synthesized to serve as prodrugs. They were converted in vivo to free apomorphine, which could be detected in the brain. Stereotyped gnawing behavior and unilateral rotation similar to that produced by apomorphine were induced by all of the diesters but the time course of action of the latter was prolonged. The duration of action generally increased with the size of the ester substituent and appeared to correlate inversely with the rate of hydrolysis of the esters by liver extracts. It is concluded that the diesters serve as prodrugs of apomorphine and their prolonged duration is partly explained by a decreasing rate of hydrolysis attributable to increased steric hindrance at the acyl carbon atoms.

Literature reports have suggested the potential utility of apomorphine (**1**), a putative agonist of dopamine receptors, as an effective agent in the treatment of Parkinson's disease[1-7] and as an antagonist of prolactin release.[8] However, the inherent disadvantages of its short-lived neuropharmacologic effects and poor oral bioavailability have severely limited its therapeutic usefulness.

In previous communications from these laboratories[9,10] we have described the novel preparation of *O,O'*-diacetylapomorphine (**2**) and compared its behavioral effects to apomorphine in the rat. These drugs produced identical stereotyped gnawing behavior and provoked turning toward the contralateral side in rats previously lesioned electrothermally in the left nigrostriatal tract.[10] The dose–response relationship and time course of these effects were similar for the two drugs at the lower dose levels but the diester had a somewhat longer lasting effect at higher doses. Apomorphine, but not its diester, stimulated the

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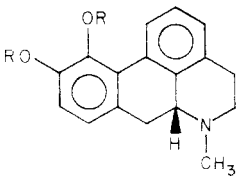
Table I. Product, Yields, Melting Points, and Elemental Analyses of Apomorphine Diesters

Product	Yield, %	Mp, °C (solvent)	Analyses
2	70	124[a]	
3·HCl	71	152-156 (ethanol-ether)	C, H, N
4	82	105-107 (ether)	C, H, N
4·HCl	63	230-232 dec (ethanol-ether)	
5	85	176-178 (ethanol-ether-pentane)	
5·HCl	75	209-212 dec (acetonitrile-ether)	C, H, N
6	82	158[b]	

[a] Previously reported mp 129°.[15] [b] Previously reported mp 156-158°.[16]

production of cAMP when incubated with homogenates of rat corpus striatum. From these results, we suggested that *O,O'*-diacetylapomorphine may serve as a prodrug of apomorphine and must be hydrolyzed (chemically or enzymatically) in vivo to apomorphine, providing the catechol group which seems to be necessary for stimulation of dopamine receptors. As an extension of this work we considered it advantageous to synthesize a series of prodrug *O,O'*-diesters of apomorphine in an attempt to favorably alter the physicochemical properties and time course of action of apomorphine, particularly seeking protracted neuropharmacologic activity. The initial diesters chosen for study and reported herein include the dipropionyl (3), diisobutyryl (4), dipivaloyl (5), and dibenzoyl (6) esters of apomorphine.



1, R = H
2, R = CH_3CO
3, R = CH_3CH_2CO
4, R = $(CH_3)_2CHCO$
5, R = $(CH_3)_3CCO$
6, R = C_6H_5CO

Chemistry. The novel procedure developed for the preparation of *O,O'*-diacetylapomorphine[9] was conveniently extended to the preparation of the diesters in this study. This procedure utilizing an appropriate acyl halide in trifluoroacetic acid eliminates the problems of oxidation of apomorphine and scission of the hydropyridine ring which is characteristic of aporphines in general when treated with an acyl halide[11] or ethyl chloroformate and base.[12] A more complete discussion with a mechanistic interpretation for the avoidance of the untoward ring-opening reaction has been reported previously.[9] The physical constants of the diesters prepared are listed in Table I, and representative spectral data are included in the Experimental Section, where the general method for the preparation of the diesters is also given.

Pharmacological Preparations. These drugs were dissolved in acidic, nitrogen-gassed, antioxidant-treated isotonic saline as described previously[10] or in a vehicle containing (by volumes) ethanol (30%), polyethylene glycol 400 (U.S.P. grade, J. T. Baker, 40%), and distilled water (30%), prepared by first dissolving the drugs in warm ethanol. The drugs were administered intraperitoneally in volumes less than 1.0 ml. Doses up to 300 mg/kg were well tolerated by rats. None of the compounds had appreciable or consistent behavioral effects when given by gastric tube. In preliminary experiments, no differences in stereotyped behavior were observed with the drugs dissolved in the saline or the polyethylene glycol–ethanol–water solvent system and the results with both vehicles were pooled. Thereafter, at doses of drugs above 30 μmol/kg the polyethylene glycol–ethanol–water system was used routinely. All drug solutions were used immediately after preparation to avoid oxidation of the aporphines.

Table II. Duration of Stereotyped Behavior in the Rat (Hours ± SEM) (*N*)

Compd (mol wt)[a]	Dose, μmol/kg ip 50	100	200
Apomorphine·HCl·0.5H_2O (312)	1.6 ± 0.2 (20)	1.9 ± 0.3 (4)	2.6 ± 0.4 (12)
2 (351)	2.1 ± 0.1 (20)	2.3 ± 0.1 (7)	2.7 ± 0.1 (9)
3·HCl (415)	1.6 ± 0.1 (4)	1.9 ± 0.1 (4)	2.9 ± 0.2 (4)
4·HCl (443)	2.5 ± 0.1 (4)[b]	3.3 ± 0.1 (7)[b]	4.9 ± 0.2 (7)[b]
5·HCl (471)	3.1 ± 0.1 (12)[b]	5.1 ± 0.2 (7)[b]	7.8 ± 0.3 (7)[b]
6 (475)	3.8 ± 0.1 (4)[b]	6.3 ± 0.2 (7)[b]	10.8 ± 0.5 (7)[b]

[a] Note that the esters, unlike apomorphine, are not hydrated. [b] $p < 0.01$ (compared with apomorphine) by Student's *t* test.

Results and Discussion

Stereotyped movements and unilateral rotation were evaluated, respectively, by a rating scale method and by direct inspection as previously described.[10] After intraperitoneal administration all of the diesters elicited stereotyped gnawing behavior similar to that produced by apomorphine, but the time course of the behavioral action of the diesters was decidedly different from the parent compound. The increase in duration of action was small for the diacetyl ester 2 and negligible for the dipropionyl ester 3, but the diisobutyryl 4, dipivaloyl 5, and dibenzoyl 6 esters produced dose-dependent and prolonged stereotyped gnawing, particularly at higher doses above 50 μmol/kg ip (Table II). For example, at a dose of 200 μmol/kg, dibenzoylapomorphine had a duration of action more than three times that of apomorphine. The duration of action generally increased with the size of the ester substituent and the amount of drug administered. Another difference between apomorphine and its esters was the latency to a peak score of stereotyped behavior: 26 ± 4 (mean ± SEM), 41 ± 4, and 83 ± 13 min for apomorphine (1), dipropionylapomorphine (3), and dibenzoylapomorphine (6), respectively. Very similar results were obtained in the case of turning behavior. As observed previously for diacetylapomorphine (2),[10] all of the new esters were inactive (10–100 μM) in increasing the production of cAMP in striatal homogenates containing adenylate cyclase activity sensitive to apomorphine and dopamine (not shown). In contrast, when diisobutyrylapomorphine (4) was preincubated with slices of rat liver, cAMP synthesis from ATP in striatal homogenates was stimulated by samples of the medium exposed to liver, presumably reflecting the hydrolysis of the ester to produce free apomorphine.

It seems likely that the increased duration of action of the diesters reflects not only a probable increase in the lipophilic character of the larger esters but also a decreased

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