New Antihypertensive Cannabinoids

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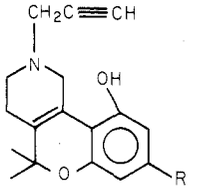
A number of azacannabinoids containing hydroxyacyl and aminoacetyl substituents on the nitrogen atom were synthesized. The hydroxyacetyl and γ-hydroxybutyryl derivatives (**4a** and **7b**, respectively) were potent antihypertensive agents (minimum effective dose, 3–5 mg/kg, orally) of the same order of activity as the highly CNS-active *N*-propargyl derivatives Ia and Ib. Furthermore, **4a** showed weak stimulant properties at hypotensive dose levels, in contrast to the strongly CNS-depressant action characteristic of the *N*-propargyl analogues (Ia,b).

Previous attempts to separate the well-known[1] hypotensive action of the cannabinoid molecule from its behavioral effects have met with only partial success.[2] Of an extensive series of nitrogen analogues tested for CNS activity,[2e,f,3] compounds of type I were among the most



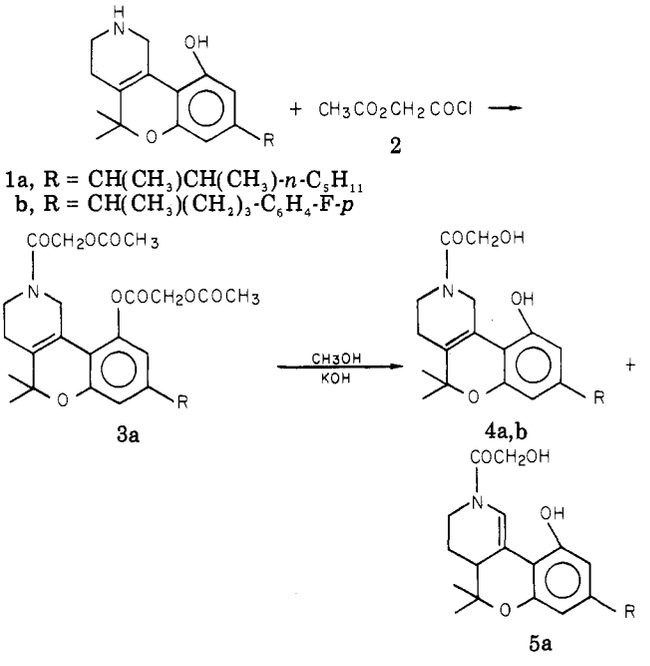
Ia, R = $CH(CH_3)CH(CH_3)$-*n*-C_5H_{11}
b, R = $CH(CH_3)(CH_2)_3$-C_6H_4F-*p*

potent. In these compounds the nitrogen atom is at least moderately basic (pK_a of propargyldimethylamine = 7.05[4]). The corresponding neutral amides of this series (replacement of propargyl by acyl) possessed less than 1% of the potency of Ia.[3] Although both Ia and Ib were strongly hypotensive in spontaneously hypertensive (SH) rats, the minimum effective doses (MED, 1–5 mg/kg orally) were similar to or above those producing undesirable behavioral side effects.[2e,f]

In this paper are presented results showing that when the propargyl group in I is replaced by certain hydroxylated acyl groups, hypotensive action is retained, while CNS activity is greatly reduced.

Chemistry. The hydroxyacetyl derivatives **4a,b** were best prepared according to Scheme I. Treatment of **1a**[3] and **1b**[2f] with acetoxyacetyl chloride gave the diacylated intermediate **3a,b**, readily saponifiable to **4a,b**. Only intermediate **3a** was isolated (67% yield). Better overall yields (79 and 88%) of **4a,b** were obtainable without isolation of **3**. Chromatography of the recrystallization residues from **4a** led to a 3% yield of the isomer **5a**, which showed the presence of a vinyl proton at 7.97 ppm ($CDCl_3$) in its ^1H NMR spectrum. Although this peak appeared as a doublet at room temperature, it coalesced to a singlet at elevated temperatures (~140 °C) sufficient to override the barrier to rotation around the amide C–N bond.

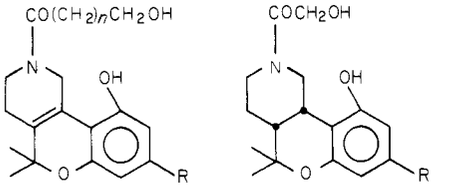
Scheme I



1a, R = $CH(CH_3)CH(CH_3)$-*n*-C_5H_{11}
b, R = $CH(CH_3)(CH_2)_3$-C_6H_4-F-*p*

3a; 4a,b; 5a

The homologue, (**6a**) of **4a** was prepared by treatment



6a, *n* = 1
7a,b, *n* = 2

8a

of **1a** with β-propiolactone at room temperature in ether solution. As expected, the main product was the isomeric β-amino acid, so that **6a** was obtained in only a 7.7% yield. Compounds **7a,b** could be made in somewhat better yield (20–40%) by heating **1a,b** with neat γ-butyrolactone. The *cis*-dihydro derivative (**8a**) of **4a** was prepared in 75% overall yield from the *cis*-dihydro derivative of **1a**[3] in the same way **4a** itself was made from **1a**.

The α-aminoacetyl analogues **9–11** were prepared similarly, except that **1a** was acylated with bromoacetyl bromide. The crude intermediate was treated with an excess of morpholine or piperidine in DMF solution at room temperature. Saponification, again without isolation,

(1) W. D. M. Paton and R. G. Pertwee in "Marijuana: Chemistry, Pharmacology, Metabolism, and Clinical Effects", R. Mechoulam, Ed., Academic Press, New York, 1973, pp 231 and 322.
(2) (a) H. F. Hardman, E. F. Domino, and M. H. Seevers, *Pharmacol. Rev.*, **23**, 295 (1971); (b) F. R. Sidell, J. E. Pless, H. Neitlich, P. Sussman, H. W. Copelan, and V. M. Sim, *Proc. Soc. Exp. Biol. Med.*, **142**, 867 (1973); (c) L. Lemberger, R. McMahon, R. Archer, K. Matsumoto, and H. Rowe, *Clin. Pharmacol. Ther.*, **15**, 380 (1974); (d) J. T. Earnhardt, B. R. Martin, and M. D. Adams, *Fed. Proc., Fed. Am. Soc. Exp. Biol.* 3413 (1975); (e) R. K. Razdan, B. Z. Terris, H. G. Pars, N. P. Plotnikoff, P. W. Dodge, A. T. Dren, J. Kyncl, and P. Somani, *J. Med. Chem.*, **19**, 454 (1976); (f) M. Winn, D. Arendsen, P. Dodge, A. Dren, D. Dunnigan, R. Hallas, K. Hwang, J. Kyncl, Y.-H. Lee, N. Plotnikoff, P. Young, H. Zaugg, H. Dalzell, and R. Razdan, *ibid.*, **19**, 461 (1976); (g) C. Lee, R. Michaels, H. Zaugg, A. Dren, N. Plotnikoff, and P. Young, *ibid.*, **20**, 1508 (1977).
(3) H. G. Pars, F. E. Granchelli, R. K. Razdan, J. K. Keller, D. G. Teiger, F. J. Rosenberg, and L. S. Harris, *J. Med. Chem.*, **19**, 445 (1976).
(4) H. K. Hall, Jr., *J. Am. Chem. Soc.*, **79**, 5441 (1957).

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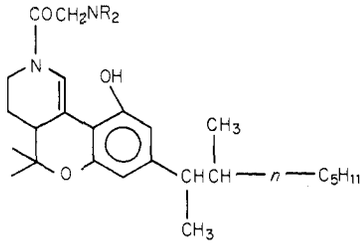
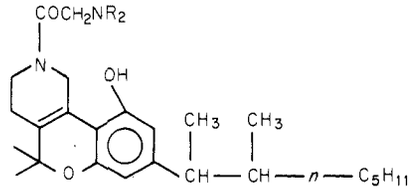


9, NR_2 = c-$N(CH_2CH_2)_2O$
11, NR_2 = c-NC_5H_{10}
12, NR_2 = NH_2



10, NR_2 = c-$N(CH_2CH_2)_2O$
13, NR_2 = NH_2

led to a mixture of isomers from which the exo-forms **9** and **11** could be isolated by crystallization (29 and 24% yields, respectively). The isomer **10** was obtained in 24% yield by chromatography of residues from the recrystallization of **9**.

The primary α-amino amides **12** and **13** were made by treating **1a** with (*tert*-butyloxycarbonyl)glycine in the presence of dicyclohexylcarbodiimide, followed by removal of the protecting group. In this case, isolation of both isomers required chromatography. Although **12** was obtainable in pure crystalline form (48% yield), **13** (26% yield) could be isolated only as an amorphous powder.

The tendency for these amide derivatives to isomerize from endo to exo forms very likely stems from the energetically favorable conjugative overlap with the π-orbital system of the amide group.[5] It is further tempting to speculate that the seemingly enhanced tendency of the amino amides to isomerize may result from an intramolecular base catalysis of the prototropic shift involving a six-membered cyclic transition state.

Pharmacology and Structure–Activity Relationships. The antihypertensive test results are given in Table I. For comparison, data for "dimethylheptylpyran" (DMHP)[7] and Ib, both redetermined for the present study, as well as values for Δ^9-THC and Ia taken from previous work[2f] are included.

Of prime interest is a comparison of the activities of the two pairs of analogues, **4a,b** and **7a,b**. In the hydroxyacetyl series, **4**, the compound (**4a**) with the completely aliphatic side chain has an MED of about 3 mg/kg, while its analogue, **4b**, with the arylaliphatic side chain is inactive at 100 mg/kg. In the γ-hydroxybutyryl series, **7**, the relationship is reversed. Compound **7a**, with the aliphatic side chain, is inactive at 100 mg/kg, but its arylaliphatic analogue, **7b** (MED ~5 mg/kg), is nearly as potent as **4a**. No such inversion of CNS activity was ever encountered[2f] in a number of pairs of analogues (e.g., Ia,b) differing only in the hydrophobic side chain (e.g., **a,b**). Furthermore, the

Table I. Antihypertensive Activity in Spontaneously Hypertensive Rats

compd	dose,[a] mg/kg po	% decrease[b] in systolic blood pressure (heart rate) after 1 h	4 h	6 h	24 h
Δ^9-THC[c]	25		39		21
	10		6		8
DMHP[d]	10	9 (0)	58 (29)		29 (38)
	3	3 (0)	44 (26)	38 (30)	23 (29)
	1	−6 (−14)	20 (10)	33 (12)	−7 (6)
	0.3	3 (−10)	10 (−5)	2 (−2)	0 (−6)
Ia[c]	10		23		27
	3		7		4
Ib	30	33 (5)	23 (16)	26 (36)	43
	10	34 (−3)	30 (−2)	20 (1)	20 (−6)
	3	8 (−7)	27 (10)	9 (−7)	11 (−14)
	1	1 (−9)	17 (3)	5 (5)	9 (−18)
	0.3	−5 (−29)	−7 (−10)	−5 (−12)	−3 (−5)
3a	30		10 (10)		
4a	30		26 (25)	24 (6)	16 (−1)
	10	20 (12)	34 (25)	19 (7)	4 (11)
	3	9 (−3)	15 (−1)	3 (−12)	3 (6)
	1	0 (−18)	0 (−18)	−5 (−22)	−5 (−18)
4b	100		8 (19)		
	30		10 (30)		
5a	100		49 (27)		
	30	2 (6)	−1 (11)	1 (10)	−1 (18)
6a	100		6 (−1)		
7a	100		0 (19)		
7b	100		32 (20)		
	30	11 (2)	26 (23)	12 (9)	22 (15)
	10[e]	11 (3)	28 (18)	19 (16)	17 (6)
	3	−6 (−17)	5 (0)	9 (5)	−8 (−24)
8a	100		0 (2)		
9	300		26 (9)		
	100[f]		23 (5)		
	30	−8 (−16)	−5 (6)	−1 (0)	−6 (14)
10	100		40 (37)		
	30	10 (−2)	18 (16)	27 (20)	10 (0)
	10	4 (−21)	8 (7)	3 (11)	2 (8)
11	100		10 (−8)		
12	100		12 (7)		
13	30	12 (9)	10 (−5)	8 (13)	2 (10)

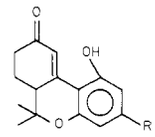
[a] Unless otherwise indicated, four rats were tested at each dose level, and the results were averaged. [b] The analysis of variance of the test procedure revealed that all changes in the blood pressure and heart rate greater than 15% are significant at the level $p \leq 0.05$. Negative values represent increases. [c] Values taken from ref 2f. [d] Dimethylheptylpyran: the synthetic cannabinoid prepared by Adams and co-workers[7] and extensively studied pharmacologically and clinically.[2a-c] [e] $n = 15$. [f] $n = 8$.

Table II. Effect on Spontaneous Motor Activity in Rats

compd	dose, mg/kg, po	% decrease or increase in motor act. at 1 h	2 h	cumulative
DMHP	30	−88	−94	−89
	10	−46	−98	−55
	3	−20	−17	−20
	1	−32	+87	−22
	0.3	−21	+28	−17
	0.1	−3	+10	−2
4a	300	−46	−42	−45
	100	+29	+32	+30
	30	+67	+23	+60
	10	+38	+116	+50

[a] Values less than 25% are considered inactive.

(5) These amides represent an intermediate position between compounds of type 1 (where little, if any, tendency toward exo isomerism is observed) and those of type



in which exoisomerization is essentially complete.[6]

(6) R. Archer, W. Blanchard, W. Day, D. Johnson, E. Lavagnino, C. Ryan, and J. Baldwin, *J. Org. Chem.*, **42**, 2277 (1977).
(7) R Adams, M. Harfenist, and S. Loewe, *J. Am. Chem. Soc.*, **71**, 1624 (1949).

potencies of **4a** and **7b** are similar to their more basic counterparts, Ia (MED ~5 mg/kg) and Ib (MED ~1 mg/kg), respectively, and **4a** is approximately one-fifth as potent as DMHP (MED ~0.5 mg/kg).

Other structural changes are clearly counterproductive. The exo isomer, **5a**, is much less potent than the endo form, **4a**, and both the intermediate homologue, **6a**, and the *cis*-dihydro derivative, **8a**, are inactive. Although the morpholino amides **9** and **10** are significantly active at higher dose levels (30–100 mg/kg), the other examples of this series (**11–13**) show only borderline activity at best.

In order to compare the CNS activities of the new antihypertensive cannabinoids with their more traditional analogues, we ran **4a** and DMHP side by side in the rat motor activity test. Results are given in Table II. The MED of DMHP needed to produce significant depression of motor activity is about 5 mg/kg as compared to 0.5 mg/kg for antihypertensive action (ratio = 10). Comparable values for **4a** are 300 and 3 mg/kg, respectively, giving a ratio of about 100. Furthermore, at lower dose levels (10–100 mg/kg), **4a** is weakly, but significantly, stimulative. In addition, it was found that oral doses of **4a** up to 100 mg/kg produced no "hyperexcitability" in rats. It is known[2g] that the four reference substances, Δ^9-THC, DMHP, Ia, and Ib, cause intense hyperexcitability in rats at oral doses in the range 1–5 mg/kg. (See ref 8 for a description of rat hyperexcitability.)

Studies involving chronic administration of **4a** in rats and dogs revealed the development of tachyphylaxis toward its antihypertensive action within 2 to 3 weeks; so work with this compound was terminated.

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were conducted on a Perkin-Elmer Model 240 and were within 0.4% of calculated values. Infrared spectra were recorded on a Perkin-Elmer 283B or 521 spectrophotometer. Proton magnetic resonance spectra were recorded either on a Varian T-60 spectrometer or a Varian HA-100 instrument with tetramethylsilane as the internal standard. Deuterium exchanges were performed on all compounds possessing labile hydrogens. ^{13}C NMR spectra were obtained with a JEOL Model FX-90 Q spectrometer. The mass spectrum was recorded with an AEI Model MS 902 spectrometer. Thin-layer chromatograms were carried out on Silic AR-7GF to a distance of 15 cm. Spots were detected by visual examination under UV light or by development with ceric sulfate spray. All IR and NMR spectra of isolated intermediates and target compounds were consistent with the assigned structures.

Acetoxyacetyl Chloride (2). To 100 g (1.32 mol) of glycolic acid was added dropwise, with stirring, 150 mL (>0.2 mol) of acetyl chloride at a rate to keep the temperature below 30 °C, using a cold water bath for cooling. While the solution stirred overnight at room temperature, product crystallized and was collected on a sintered glass filter, washed well with pentane, suspended in 500 mL of hexane, stirred for 30 min at room temperature, and collected once more at the filter. Drying gave 134 g (88%) of acetoxyacetic acid, mp 55–60 °C (lit.[9] mp 66 °C). A solution of 176 g (1.49 mol) of this acid in 110 mL of acetyl chloride and 225 mL of thionyl chloride was heated under reflux for 1.3 h. The mixture was concentrated under reduced pressure at a bath temperature below 50 °C, and the residue was distilled at reduced pressure through a 12-cm column packed with glass beads. There was obtained 158 g (77.5%) of **2**: bp 43–44 °C (7 mm) [lit.[9] bp 55 °C (10 mm)]; n^{21}_D 1.4268.

10-(Acetoxyacetoxy)-2-(acetoxyacetyl)-5,5-dimethyl-8-(1,2-dimethylheptyl)-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[4,3-*c*]pyridine (3a). A cold, stirred solution of **1a**[3] (8.94 g, 0.025 mol) in methylene chloride (100 mL) was treated dropwise with acetoxyacetyl chloride (**2**; 10.24 g, 0.075 mol) while maintaining the temperature below 5 °C. This was followed by the addition of triethylamine (9.5 g) at 15 °C or below. The stirred mixture was heated under reflux for 1.25 h, cooled, and treated with excess dilute hydrochloric acid. The separated organic layer was washed successively with 5% aqueous sodium bicarbonate and water and dried over anhydrous magnesium sulfate. Concentration of the filtered solution gave 15.6 g of a brown gum that crystallized on trituration and stirring (1 h) with 120 mL of hexane. The material was collected at the filter and dried to give 9.43 g (67%) of **3a**, mp 94–96 °C. Pure **3a** [mp 102–104 °C; R_f (EtOAc), 0.50] was obtained by two recrystallizations from ether–hexane. Anal. ($C_{31}H_{43}NO_8$) C, H, N.

5,5-Dimethyl-8-(1,2-dimethylheptyl)-10-hydroxy-2-(hydroxyacetyl)-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[4,3-*c*]pyridine (4a). A solution of 5.6 g (0.01 mol) of **3a** in 55 mL of methanol containing 5 mL of 45% aqueous potassium hydroxide was stirred at room temperature for 2 h. To this was added 6 N hydrochloric acid to a pH of 6, and the solution was concentrated to near dryness on a rotary evaporator. The residue was taken up in water and ether, separated, washed with water (2 × 50 mL), and dried over anhydrous magnesium sulfate. Filtration and concentration to dryness gave 4.1 g (98% yield) of crystalline **4a**, mp 124–126 °C. Recrystalliation from acetonitrile raised the melting point by only 1 °C: R_f (10% CH_3OH in $CHCl_3$) 0.48. Anal. ($C_{25}H_{37}NO_4$) C, H, N.

Compound **4a** could be prepared in 79% overall yield (0.25 mol batch size) from **1a** without purifying **3a** before hydrolysis. Also **4a** was obtained in one step (but in only 12% yield) by heating **1a** with excess ethyl glycolate at 90–100 °C for 22 h.

5,5-Dimethyl-8-(1,2-dimethylheptyl)-10-hydroxy-2-(hydroxyacetyl)-2,3,4,4a-tetrahydro-5*H*-[1]benzopyrano[4,3-*c*]pyridine (5a). The recrystallization residues (12.2 g of friable amorphous glass) obtained from the 0.25-mol batch of compound **4a** was chromatographed on a 5 × 100 cm column containing 620 g of silica (Woelm; 32–63 μm particle size). Ethyl acetate at a flow rate of 0.57 mL/min was used for elution. From the combined early fractions was obtained 4.07 g of amorphous material that crystallized from CH_3CN to give 3.20 g (3.1% yield) of pure **5a**: mp 109–110 °C; R_f (10% CH_3OH in $CHCl_3$) 0.55. Anal. ($C_{25}H_{37}NO_4$) C, H, N. The ^1H NMR spectrum of **5a** shows a peak at 7.97 ppm corresponding to the vinyl proton at the 1-position. This peak is absent in the ^1H NMR spectrum of **4a**.

5,5-Dimethyl-8-[5-(4-fluorophenyl)-2-pentyl]-10-(hydroxyacetyl)-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[4,3-*c*]pyridine (4b). Compound **1b**[2f] was treated with acetoxyacetyl chloride according to the above procedure for **1a**, but the intermediate corresponding to **3a** was not isolated. It was saponified directly to give an 88% overall yield of **4b**, mp 146–148 °C (from CH_3CN). Anal. ($C_{27}H_{32}FNO_4$) C, H, N.

5,5-Dimethyl-8-(1,2-dimethylheptyl)-10-hydroxy-2-(3-hydroxypropionyl)-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[4,3-*c*]pyridine (6a). A stirred suspension of 20 g (0.056 mol) of **1a** in 60 mL of dry ether was treated dropwise with a solution of 4.4 g (0.063 mol) of β-propiolactone in 20 mL of dry ether. The reaction temperature was kept at 23–25 °C by means of a cold-water bath. After being stirred at room temperature for 48 h, precipitated byproduct carboxylic acid (18.4 g) was removed by filtration and washed with dry ether. The combined filtrate and washings were washed successively with 2 N potassium bicarbonate solution and water and dried over anhydrous magnesium sulfate. Filtration and concentration to dryness gave a light colored glass (2.8 g) that was purified by chromatography on silica gel 60 with ethyl acetate for elution. There was obtained 1.86 g (7.7%) of **6a**: mp 84–87 °C (from hexane); R_f (10% CH_3OH in $CHCl_3$) 0.50. Anal. ($C_{26}H_{39}NO_4$) C, H, N.

5,5-Dimethyl-8-(1,2-dimethylheptyl)-10-hydroxy-2-(4-hydroxybutyryl)-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[4,3-*c*]pyridine (7a). A stirred suspension of 10 g (0.028 mol) of **1a** in 45 mL of γ-butyrolactone was warmed at 65 °C (under N_2) for 8 h. The excess of lactone was removed with a rotary evaporator at 60 °C bath temperature and under reduced pressure (1.5 mm). The residue was taken up in a mixture of ether and water, separated, washed successively with 1 N hydrochloric acid

(8) C. Lee, H. Zaugg, R. Michaels, A Dren, N. Plotnikoff, P. Young, *J. Med. Chem.*, under Notes in this issue.
(9) W. Walter, M. Steffen, and K. Heyns, *Chem. Ber.*, **99**, 3204 (1966).

and water, and dried over anhydrous magnesium sulfate. Filtration and concentration to dryness gave a light-colored friable foam (11.1 g). Half of this material was chromatographed on a column of 100–200 mesh Florisil (300 g) with ethyl acetate for elution. There was obtained 2.53 g (42%) of **7a** as an amorphous glass, crystallizable from acetonitrile: mp 126–129 °C; R_f (10% CH_3OH in $CHCl_3$) 0.45. Anal. ($C_{27}H_{41}NO_4$) C, H, N.

5,5-Dimethyl-8-[5-(4-fluorophenyl)-2-pentyl]-10-hydroxy-2-(4-hydroxybutyryl)-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[4,3-*c*]pyridine (7b). Compound 1b was treated with butyrolactone as in the foregoing procedure, and the crude product was chromatographed on a column of silica gel 60 with 2% methanol in ethyl acetate for elution. Compound 7b was obtained in 23% yield as a tan glass that could not be crystallized, R_f (15% C_2H_5OH in $C_6H_5CH_3$) 0.36. MS Calcd for $C_{29}H_{36}FNO_4$: *m/e* 481.2628. Found: *m/e* 481.2620.

***cis*-5,5-Dimethyl-8-(1,2-dimethylheptyl)-10-hydroxy-2-(hydroxyacetyl)-5*H*-[1]benzopyrano[4,3-*c*]piperidine (8a).** A stirred solution of 11.0 g (0.028 mol) of the hydrochloride salt of *cis*-5,5-dimethyl-8-(1,2-dimethylheptyl)-10-hydroxy-5*H*-[1]-benzopyrano[4,3-*c*]piperidine[2] in methylene chloride (85 mL) was cooled in ice and treated (under nitrogen) with acetoxyacetyl chloride (9.18 g, 0.067 mol) and triethylamine in the manner described above for the preparation of **3a**. However, the intermediate (dehydro-3a) was not isolated but saponified directly as described for the preparation of **4a**. Pure **8a**, mp 152–154 °C from CH_3CN), was obtained in a 75% overall yield. Anal. ($C_{25}H_{39}NO_4$) C, H, N.

5,5-Dimethyl-8-(1,2-dimethylheptyl)-10-hydroxy-2-(morpholinoacetyl)-2,3,4,4a-tetrahydro-5*H*-[1]benzopyrano[4,3-*c*]pyridine (9). To an ice-cold, stirred solution of 7.16 g (0.02 mol) of **1a** in methylene chloride (40 mL) was added dropwise a solution of bromoacetyl bromide (9.70 g, 0.048 mol) in methylene chloride (10 mL), followed by triethylamine (4.84 g, 0.048 mol) in methylene chloride (10 mL). The temperature was kept below 8 °C during both additions. The reaction mixture was stirred in the ice bath for 1.5 h and then at room temperature for 4 h. Most of the solvent was removed under a stream of nitrogen in a water bath held at 35–40 °C. The residue was taken up in dry DMF (40 mL), cooled in ice, and treated dropwise with stirring with neat morpholine (8.71 g, 0.10 mol), keeping the temperature below 15 °C. After being stirred overnight at room temperature, the reaction mixture was poured into water, and insoluble material was taken up in methylene chloride, washed with water, and concentrated to dryness. The residue (11.3 g) was taken up in methanol (100 mL), cooled in ice, treated with 45% aqueous potassium hydroxide solution (10 mL), and stirred at room temperature (under nitrogen) for 2 h. The solution was cooled in ice and adjusted to about pH 9, first with 6 N hydrochloric acid and finally with dry ice. The resulting precipitate was collected at the filter and shaken with a mixture of water and methylene chloride until solution was complete. The organic layer was separated, washed with water, and concentrated to dryness. The crystalline residue (5.0 g, mp 205–215 °C) was recrystallized from DME to give 2.76 g (29%) of **9**, mp 218–220 °C. Anal. ($C_{29}H_{44}N_2O_4$) C, H, N. The ^1H NMR spectrum of **9** shows a single proton peak at 8.40 ppm. This peak is absent in the ^1H NMR spectrum of **10**.

5,5-Dimethyl-8-(1,2-dimethylheptyl)-10-hydroxy-2-(morpholinoacetyl)-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[4,3-*c*]pyridine (10). All soluble fractions and recrystallization residues obtained from the isolation of **9** were combined (5.45 g) and chromatographed on a column of silica gel 60 with ethyl acetate for elution. After a further fraction of **9** (1.01 g, 11%), the major component was collected, consisting of the isomer **10** (2.29 g, 24%), mp 104–106 °C (from hexane). Anal. ($C_{29}H_{44}N_2O_4$) C, H, N.

5,5-Dimethyl-8-(1,2-dimethylheptyl)-10-hydroxy-2-(piperidinoacetyl)-2,3,4,4a-tetrahydro-5*H*-[1]benzopyrano[4,3-*c*]pyridine (11). By substituting piperidine for morpholine in the foregoing procedure, we obtained **11** in 24% yield, mp 220–222° (from DME). Anal. ($C_{30}H_{46}N_2O_3$) C, H, N. No attempt was made to isolate the endo isomer of **11**. The ^1H NMR spectrum of **11** displays a peak at 8.38 ppm corresponding to the vinyl proton.

5,5-Dimethyl-8-(1,2-dimethylheptyl)-2-glycyl-10-hydroxy-2,3,4,4a-tetrahydro-5*H*-[1]benzopyrano[4,3-*c*]pyridine (12) **and 5,5-Dimethyl-8-(1,2-dimethylheptyl)-2-glycyl-10-hydroxy-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[4,3-*c*]-pyridine** (13). To a stirred solution of 8.94 g (0.025 mol) of **1a** and 4.82 g (0.0275 mol) of *tert*-butoxycarbonyl)glycine in dry dioxane (40 mL) was added 5.68 g (0.0275 mol) of solid dicyclohexylcarbodiimide. The temperature rose to 38 °C. After being stirred at room temperature for 22 h, the dicyclohexylurea (5.51 g, 89%) was removed by filtration, and the filtrate was concentrated nearly to dryness. The residue, taken up in ether, was washed successively with water, 5% sodium bicarbonate solution, and water and then dried ($MgSO_4$). Filtration and concentration gave a light yellow glass (12.88 g) that could not be crystallized. A 10.8-g sample of this material, dissolved in methylene chloride (30 mL), was cooled in ice and treated with 30 mL of trifluoroacetic acid in one portion. After standing at room temperature for 1.5 h, it was poured into ice and extracted with ether, which was washed and dried as before. A brown glass (8.91 g) comprised of two major components was obtained. Separation was accomplished by chromatography on a column (3.5 × 90 cm) packed with 230 g of silica (Woelm; 36–63 μm particle size) and with the solvent ethyl acetate–ethanol–concentrated ammonium hydroxide (92:8:1) for elution. The component of high R_f proved to be **12** (4.16 g, 48%), which was recrystallized, successively, from ethyl acetate and DME: mp 180–183 °C; R_f 0.42 ($CHCl_3/CH_3OH$/conc NH_4OH, 90:10:2. The ^1H NMR spectrum of **12** shows a peak at 8.30 ppm. This peak is absent in the spectrum of **13**. Anal. ($C_{25}H_{38}N_2O_3$) C, H, N.

The second component, **13**, was obtained as a pale yellow amorphous powder (2.28 g, 26%), R_f 0.32 ($CHCl_3/CH_3OH$/conc NH_4OH, 90:10:2), that could not be obtained analytically pure.

Pharmacology. The spontaneous motor activity[2e,8] and hyperexcitability[2g] tests in rats were carried out according to procedures described previously.

Antihypertensive Activity. Adult genetic hypertensive rats were used. Blood pressure and heart rate measurements were made with a photocell and occluding cuff on the tail. The animals were placed in a constant-temperature box at 33 °C before measurements were made at 1, 4, 6, or 24 h after dosage. Solid drugs were given orally as suspensions in 0.5% methylcellulose; oils (DMHP and Δ^9-THC) were given as suspensions in olive oil and 0.5% methylcellulose.

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Registry No. 1a, 26685-53-0; 1b, 60926-09-2; **2**, 13831-31-7; **3a**, 83732-25-6; **4a**, 81402-29-1; **4b**, 81410-13-1; **5a**, 83732-26-7; **6a**, 81402-28-0; **7a**, 81402-27-9; **7b**, 81402-26-8; **8a**, 83732-28-9; **9**, 81402-30-4; **10**, 81402-31-5; 11, 81402-32-6; **12**, 81402-33-7; **13**, 81402-34-8; glycolic acid, 79-14-1; acetyl chloride, 75-36-5; β-propiolactnoe, 57-57-8; γ-butyrolactone, 96-48-0; 5,5-dimethyl-8-(1,1-dimethylheptyl-10-hydroxy-5*H*-[1]benzopyrano[4,3-*c*]-piperidine hydrochloride, 83732-27-8; bromoacetyl bromide, 598-21-0; 2-(bromoacetyl)-5,5-dimethyl-8-(1,2-dimethylheptyl)-10-hydroxy-5*H*-[1]benzopyrano[4,3-*c*]piperidine, 83732-29-0; (*tert*-butoxycarbonyl)glycine, 4530-20-5.