The number of animals alive at the end of 48 h was recorded and the LD_{50} value estimated according to the method of Litchfield and Wilcoxon.[9] If none were dead after 48 h at 300 mg/kg, the LD_{50} value was estimated to be greater than 300 mg/kg and no further dosing was required. If numerous deaths occurred at 300 mg/kg, the compound was dosed at 100 mg/kg and the LD_{50} value estimated from the number of deaths at that dose.

Dose–Response SHR Assay. The procedures for the dose–response SHR assay were identical to the primary level procedure, except rats were dosed at 100, 30, 10, and 3 mg/kg. Five rats were used for each dose, and heart rate and blood pressure were recorded.

References and Notes

(1) M. L. Cannon, R. P. Tannenbaum, and M. LaFranco, *Am. Pharm.*, **NS18**, 250 (1978).
(2) U.S. Veterans Administration, Cooperative Study Group on Antihypertensive Agents, *J. Am. Med. Assoc.*, **213**, 1143 (1970).
(3) T. R. Dober, A. Kagen, and W. B. Kunnel, "Habits and Coronary Heart Disease", The Framingham Heart Study, U.S. Department of Health, Education, and Welfare, Public Health Service, National Heart Institute, 1966.
(4) E. D. Freis, *Physiol. Rev.*, **40**, 27 (1960).
(5) E. D. Frohlich, R. O. Tarazi, and H. P. Dustan, *Am. J. Med. Sci.*, **257**, 9 (1969).
(6) J. Koch-Weser, *Am. J. Cardiol.*, **32**, 499 (1973).
(7) J. Koch-Weser, *N. Engl. J. Med.*, **295**, 320 (1976).
(8) J. Koch-Weser, *Am. Heart J.*, **95**, 1 (1978).
(9) J. T. Litchfield, Jr., and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).
(10) W. W. Paudler, and T. K. Chen, *J. Heterocycl. Chem.*, **7**, 767 (1970).
(11) N. Rabjohn, *Org. React.*, **5**, 331 (1949).
(12) J. Wagner, J. W. Faigle, P. Imhof, and G. Liehr, *Arzneim.-Forsch.*, **27** (II), 2388 (1977).
(13) C. Hansch, J. E. Quinlan, and G. L. Lawrence, *J. Org. Chem.*, **33**, 347 (1968).
(14) C. Hansch, E. J. Lien, and F. Helmer, *Arch. Biochem. Biophys.*, **128**, 319 (1968).
(15) L. P. Hammett, "Physical Organic Chemistry", McGraw-Hill, New York, 1940, Chapter 7.
(16) C. K. Hancock and C. P. Falls, *J. Am. Chem. Soc.*, **83**, 4214 (1961).

Synthesis of 2,3,4,4a,5,9b-Hexahydro-1*H*-pyrido[4,3-*b*]indole Derivatives and Their Central Nervous System Activities

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The synthesis and some pharmacological effects of *cis*- and *trans*-2-substituted 2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole derivatives are described. In these derivatives, the substituents of the 2, 5 and 8 position, together with the relative configuration of the 4a and 9b position, influenced the potency of the central nervous system activities. A *cis*-2-[3-(*p*-fluorobenzoyl)propyl] analogue (**5k**) of carbidine (1) possessed not only thymoleptic-like biological activity but had more potent neuroleptic activity than the parent drug.

It has been reported that carbidine (*cis*-2,8-dimethyl-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole dihydrochloride, 1) is an effective antipsychotic agent with thymoleptic properties.[1,2] In animal studies, 1 not only depresses the central nervous system (CNS) but also enhances the stereotyped behavior induced by methamphetamine,[1-3] a property which is characteristic of thymoleptics.[2,4] However, the CNS-depressing activities of 1 were found to be extremely weak when tested on the basis of criteria for the typical neuroleptics, as will be shown. So, an attempt was made to prepare novel hexahydro-1*H*-pyrido[4,3-*b*]indole derivatives which were as potent as the existing neuroleptics in CNS-depressing activities but which, like 1, still possessed the ability to potentiate the methamphetamine-induced stereotypy. It was found that *cis*-2-[3-(*p*-fluorobenzoyl)propyl]-8-methyl-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole (**5k**) possessed such pharmaceutical properties.

Chemistry. Hydrogenolysis of 2-benzyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indoles **2** on palladium/carbon gave the debenzylated compounds **3**, which were catalytically hydrogenated in dilute hydrochloric acid on platinum dioxide to afford (4a,9b-*cis*)-2,3,4,4a,5,9b-hexahydro derivatives **4** (Scheme I). The alkylation of **4** afforded the 2-substituted products **5**. The alkylation or acylation of the butyrophenone derivative **5k** gave the 5-substituted derivatives **6**.

Reaction of 2-benzyl-8-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (**2c**) with BH_3–THF, followed by acid hydrolysis and subsequent neutralization, gave the *trans*-2,3,4,4a,5,9b-hexahydro derivative **7b**. The same treatment of the 8-fluoro derivative **2b**, however, gave the mixture of trans (**7a**) and cis compounds. This mixture was treated with acetic anhydride for separation to give the 5-acetyl derivatives **8b** and **8a** in a ratio of 6:1. Compound **8b** was hydrolyzed to **7a**, while **8a** gave **4b** by the same hydrolysis followed by catalytic hydrogenolysis. Hydrogenolysis of **7** gave the debenzylated compounds **9**, which were converted into the 2-substituted derivatives **10a–e** and the 2,5-disubstituted ketones **11** in similar procedures mentioned above.

Compounds **4c** and **9b** were benzoylated and then treated with formaline, followed by catalytic hydrogenation, to give the 2-benzoyl-5-methyl derivatives **13**, which were quarternized with methyl iodide to give the 5,5-dimethyl derivatives **14a** and **14b**, respectively (Scheme II). In the NMR spectra, the difference in chemical shifts of the methyl group owing to the anisotropic shielding of the benzene ring[5] is 10 Hz for **14a** and 40 Hz for **14b**, which suggest the former to be the cis form and the latter to be the trans form, as was expected from the reduction procedures.[6]

Pharmacological Results and Discussion. The CNS-depressing property of hexahydropyrido[4,3-*b*]indole derivatives obtained in this study was examined by their effect on locomotor, muscle relaxating, and cataleptic activities in mice; the results are shown in Table I. It seems that the CNS-depressing property of these derivatives is affected by the substituent in the 2, 5, and 8 positions. Among the cis compounds (**5a–h** and **5k**) with a methyl group in the 8 position similar to 1, the compounds (**5g**, **5h**, and **5k**) with the bulky substituent group, such as 3-(2-chlorophenothiazin-10-yl)propyl, 4,4-bis(*p*-fluorophenyl)butyl, and 3-(*p*-fluorobenzoyl)propyl, in the

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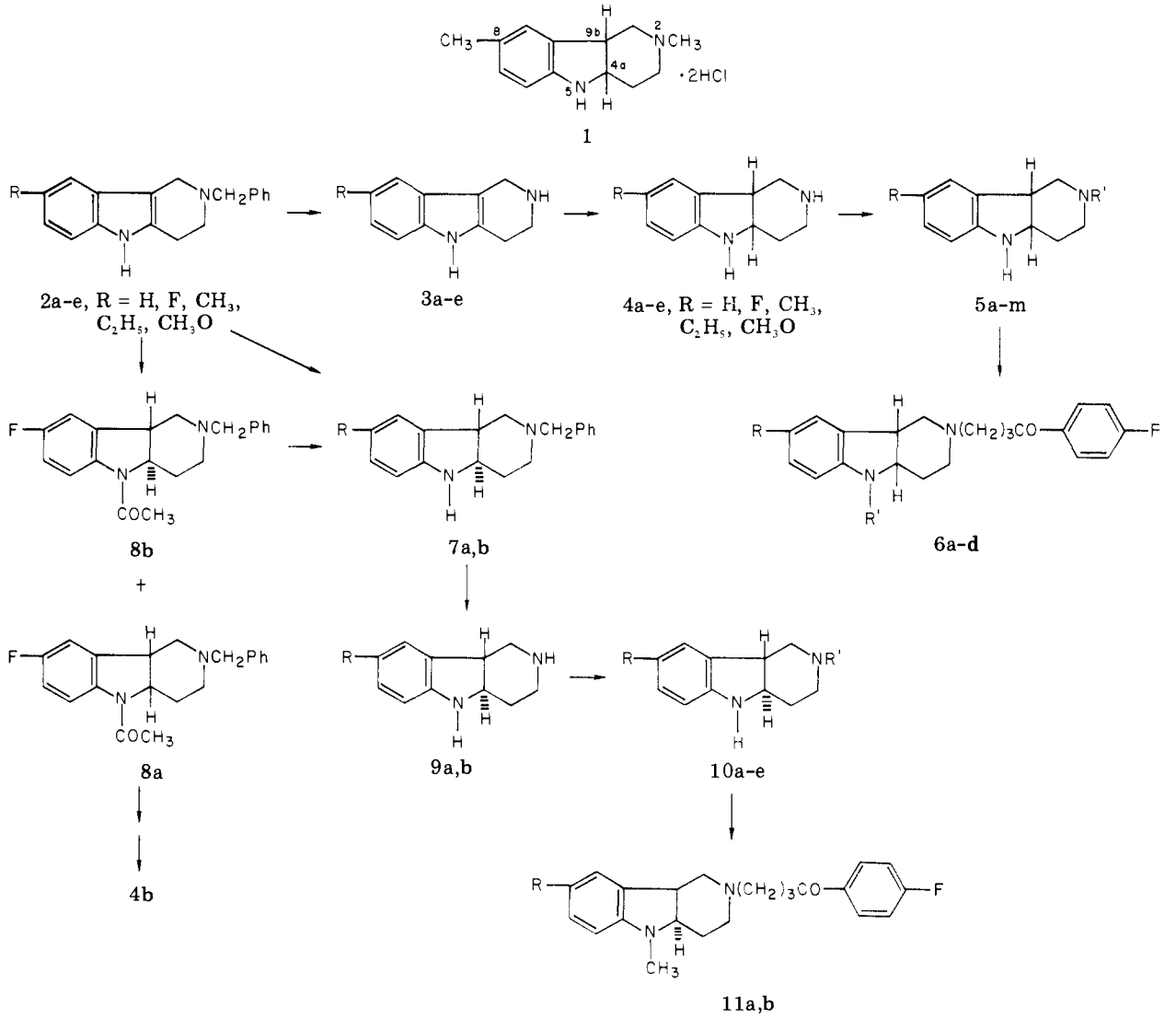
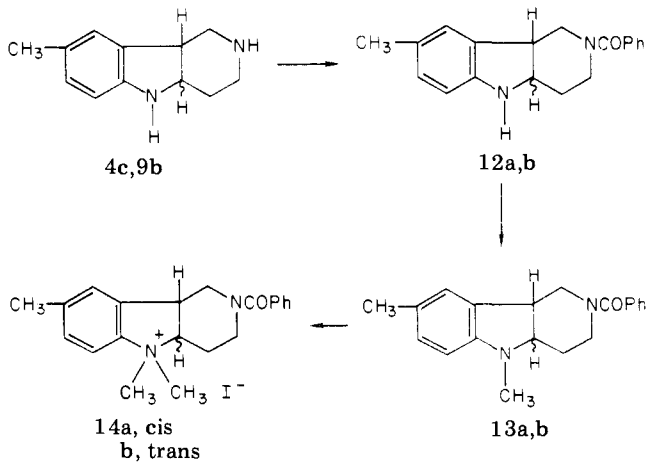
Scheme I



Scheme II



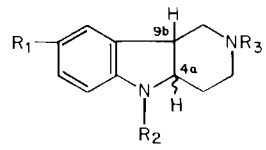
2 position showed a potent activity in the locomotor test and only **5k** was highly effective in all tests. As to the substituent in the 8 position of the *cis*-butyrophenone analogues **5i–m**, the order of increasing potency was Et < H < F ≤ MeO < Me. In the active butyrophenone derivatives **5k**, introduction of substituents in the 5 position decreased the activities and **5k** possessed the most potent activities in the cis series.

The compounds which showed marked activities in the above tests were examined for their effect on the methamphetamine-induced stereotyped behavior in rats. The results are shown in Table II. The 8-alkyl derivatives with a hydrogen or a lower alkyl group in the 5 position and a 3-(*p*-fluorobenzoyl)propyl group in the 2 position potentiated the stereotyped behavior similar to 1, but the 8-unsubstituted, 8-fluoro, and 8-methoxy analogues **5i**, **5j**, and **5m** and the 2-[3-(2-chlorophenothiazin-10-yl)propyl] derivatives **5g** exhibited no effect on this behavior or weakly antagonized it. The 2-[3-(*p*-fluorobenzoyl)-propyl]-8-methyl-2,3,4,5-tetrahydro derivative **15**[7] also showed no effect. Compound **5k** showed a potentiating effect as potent as 1 on the stereotyped behavior at 2–10 mg/kg ip, which was the most potent among the compounds tested.

In addition, **5k** enhanced apomorphine-induced gnawing at 0.03–0.7 mg/kg sc in rats. At higher doses (Table III), however, **5k**, like typical neuroleptics, blocked the methamphetamine-induced hyperactivity in mice and apomorphine-induced gnawing in rats. On the other hand, 1 showed only potentiating effects on the stereotypy induced by both agents.

The neuroleptic activity of **5k** was examined in more detail and the results obtained are shown in Table III. Compound **5k** exhibited an inhibition of locomotion, conditioned avoidance response, and self-stimulation and

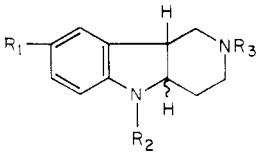
Table I. Chemical and Pharmacological Data on 2-Substituted 2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole Derivatives



no.	R_1	R_2	R_3	4a, 9b rel config	proced	mp, °C	recrystn solvent	yield, %	formula[a]	locomot inhibn,[h] %	musc relaxatn[i]	catalepsy[i]
5a	CH_3	H	C_2H_5	cis	A	200–203	dil EtOH	43	$C_{14}H_{20}N_2 \cdot 2HCl \cdot 0.25H_2O$	54.7	1/5[b]	0/5[b]
5b	CH_3	H	CH_2CH_2OH	cis	A	183–185	dil EtOH	37	$C_{14}H_{20}N_2O \cdot 2HCl$	30.7	0/5	0/5
5c	CH_3	H	$CH_2CH_2COCH_3$	cis	C	106–107	*i*-PrOH	38	$C_{16}H_{22}N_2O \cdot C_4H_4O_4$[c]	38.8	0/5	0/5
5d	CH_3	H	$(CH_2)_3N(CH_3)_2$	cis	A	210–213	dil EtOH	35	$C_{17}H_{27}N_3 \cdot 3HCl \cdot 0.5H_2O$	12.3	0/5	0/5
5e	CH_3	H	$CH_2C_6H_5$	cis	A	180–182	EtOH	52	$C_{19}H_{22}N_2 \cdot 2HCl$	35.3	0/5	0/5
5f	CH_3	H	$CH_2COC_6H_5$	cis	A	201–204	dil EtOH	48	$C_{20}H_{20}N_2O \cdot 2HCl$	29.8	0/5	0/5
5g	CH_3	H	CPTP[j]	cis	B			44	$C_{27}H_{28}ClN_3S$	96.9 (56.6)	0/5	2/5
5h	CH_3	H	$(CH_2)_3CH(C_6H_4\text{-}p\text{-}F)_2$	cis	B	193–197	dil EtOH	41	$C_{28}H_{30}F_2N_2 \cdot 2HCl$	90.7 (−73.0)	0/5	1/5
5i	H	H	$(CH_2)_3COC_6H_4\text{-}p\text{-}F$	cis	B	199–203	dil EtOH	52	$C_{21}H_{23}FN_2O \cdot 2HCl$	77.7 (−6.0)	2/5	3/5
5j	F	H	$(CH_2)_3COC_6H_4\text{-}p\text{-}F$	cis	B	172–175	dil EtOH	59	$C_{21}H_{22}F_2N_2O \cdot 2HCl$	91.2 (47.2)	4/5	4/5
5k	CH_3	H	$(CH_2)_3COC_6H_4\text{-}p\text{-}F$	cis	B	202–205	dil EtOH	60	$C_{22}H_{25}FN_2O \cdot 2HCl$	97.8 (75.9)	5/5	5/5
5l	C_2H_5	H	$(CH_2)_3COC_6H_4\text{-}p\text{-}F$	cis	B	191–195	dil EtOH	57	$C_{23}H_{27}FN_2O \cdot 2HCl \cdot 0.75H_2O$	44.0	0/5	0/5
5m	CH_3O	H	$(CH_2)_3COC_6H_4\text{-}p\text{-}F$	cis	B	214–216	dil EtOH	49	$C_{22}H_{25}FN_2O_2 \cdot 2HCl$	96.7 (61.7)	5/5	3/5
6a	CH_3	CH_3	$(CH_2)_3COC_6H_4\text{-}p\text{-}F$	cis	*d*	141–144	dil EtOH	38	$C_{23}H_{27}FN_2O \cdot 2HCl$	95.8 (55.8)	4/5	5/5
6b	CH_3	C_2H_5	$(CH_2)_3COC_6H_4\text{-}p\text{-}F$	cis	*e*	149–153	EtOH	46	$C_{24}H_{29}FN_2O \cdot 2HCl$	92.9 (34.0)	5/5	5/5
6c	CH_3	$CH_2C_6H_5$	$(CH_2)_3COC_6H_4\text{-}p\text{-}F$	cis	*e*	112–115	EtOH	42	$C_{29}H_{31}FN_2O \cdot 2HCl$	70.5	4/5	0/5
6d	CH_3	$COCH_3$	$(CH_2)_3COC_6H_4\text{-}p\text{-}F$	cis	*f*	164-166	EtOH	64	$C_{24}H_{27}FN_2O_2 \cdot C_4H_4O_4$[c]	21.7	0/5	0/5
7a	F	H	$CH_2C_6H_5$	trans	*g*	92–94	*n*-hexane	72	$C_{18}H_{19}FN_2$	76.1	0/5	0/5
7b	CH_3	H	$CH_2C_6H_5$	trans	*g*	249–255	dil EtOH	51	$C_{19}H_{22}N_2 \cdot 2HCl$	17.9	0/5	1/5
10a	CH_3	H	CH_3	trans	A	241–245	dil EtOH	42	$C_{13}H_{18}N_2 \cdot 2HCl$	79.7	0/5	0/5
10b	CH_3	H	CH_2CH_2OH	trans	A	201–205	dil EtOH	31	$C_{14}H_{20}N_2O \cdot 2HCl \cdot 0.25H_2O$	−5.6	0/5	0/5
10c	CH_3	H	$CH_2CH_2COCH_3$	trans	C	201–205	dil EtOH	39	$C_{16}H_{22}F_2N_2O \cdot 2HCl$	−15.5	0/5	1/5
10d	F	H	$(CH_2)_3COC_6H_4\text{-}p\text{-}F$	trans	B	141–145	dil EtOH	46	$C_{21}H_{22}F_2N_2O \cdot 2HCl \cdot 2.75H_2O$	92.2	1/5	4/5
10e	CH_3	H	$(CH_2)_3COC_6H_4\text{-}p\text{-}F$	trans	B	192–195	dil EtOH	41	$C_{22}H_{25}FN_2O \cdot 2HCl \cdot H_2O$	86.5	3/5	4/5
11a	F	CH_3	$(CH_2)_3COC_6H_4\text{-}p\text{-}F$	trans	*d*	87–90	AcOEt	44	$C_{22}H_{24}F_2N_2O \cdot C_4H_4O_4$[c]	92.7	1/5	4/5
11b	CH_3	CH_3	$(CH_2)_3COC_6H_4\text{-}p\text{-}F$	trans	*d*	151–152	AcOEt	52	$C_{23}H_{27}FN_2O \cdot C_4H_4O_4 \cdot 0.25H_2O$	97.4	2/5	5/5
1 (carbidine)				cis						37.6	0/5	0/5
chlorpromazine										97.4 (67.6)	5/5	5/5

[a] Analyses were obtained for C, H, N and, when those elements were presented, for F or S. The results obtained for these elements were within ±0.4% of the theoretical values. [b] No. of positive effects/no. tested. [c] Maleate. [d–g] See the corresponding procedure under the Experimental Section. [h] 100 mg/kg (10 mg/kg) po. [i] 100 mg/kg po. [j] CPTP = 2-chlorophenothiazin-10-ylpropyl.

Table II. Effects of 2-Substituted 2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole Derivatives on Methamphetamine-Induced Sterotyped Behavior



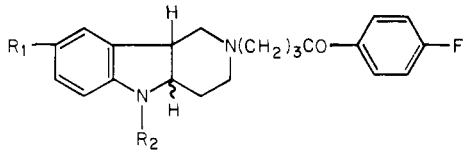
compd	R_1	R_2	R_3	4a,9b rel confign	dose, mg/kg	stereotyp behav
5i	H	H	$(CH_2)_3COC_6H_4$-*p*-F	cis	1.0	0[a]
					2.0	0
					5.0	0
					10.0	−
5j	F	H	$(CH_2)_3COC_6H_4$-*p*-F	cis	1.0	0
					2.0	0
					5.0	−
					10.0	− −
5k	CH_3	H	$(CH_2)_3COC_6H_4$-*p*-F	cis	1.0	0
					2.0	+ +
					5.0	+ + +
					10.0	+ +
5l	C_2H_5	H	$(CH_2)_3COC_6H_4$-*p*-F	cis	2.0	+
					5.0	+ + +
					10.0	+ + +
5m	CH_3O	H	$(CH_2)_3COC_6H_4$-*p*-F	cis	1.0	0
					2.0	0
					5.0	0
					10.0	−
6a	CH_3	CH_3	$(CH_2)_3COC_6H_4$-*p*-F	cis	1.0	0
					2.0	0
					5.0	+ +
					10.0	+ +
6b	CH_3	C_2H_5	$(CH_2)_3COC_6H_4$-*p*-F	cis	1.0	0
					2.0	0
					5.0	+
					10.0	+ + +
6c	CH_3	$CH_2C_6H_5$	$(CH_2)_3COC_6H_4$-*p*-F	cis	1.0	0
					2.0	0
					5.0	0
					10.0	0
5g	CH_3	H	CPTP[b]	cis	1.0	0
					2.0	0
					5.0	0
					10.0	0
10e	CH_3	H	$(CH_2)_3COC_6H_4$-*p*-F	trans	1.0	−
					2.0	− −
					5.0	− − −
					10.0	− − −
15 (FBPMTPI·HCl)[c]					1.0	0
					2.0	0
					5.0	0
					10.0	0
1 (carbidine)					1.0	0
					2.0	+
					5.0	+ +
					10.0	+ + +
haloperidol					0.1	0
					0.2	−
					0.5	− − −
					1.0	− − −
chlorpromazine					2.0	0
					5.0	− −
					10.0	− − −

[a] The symbols have the following meanings: − − −, marked antagonism (>75%); − −, moderate antagonism (50-75%), −, slight antagonism (25-50%); 0, no interaction (0-25%); +, slight potentiation (25-50%); ++, moderate potentiation (50-75%); + + +, marked potentiation (>75%). [b] CPTP = 2-chlorophenothiazin-10-ylpropyl. [c] FBPMTPI·HCl = 2-[3-(*p*-fluorobenzoyl)propyl]-8-methyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole hydrochloride.

caused catalepsy similar to the existing neuroleptics. These activities were slightly less potent than those of chlorpromazine. Thus, **5k** is a new compound having not only the neuroleptic properties, which are considerably more potent than **1**, but also some thymoleptic-like properties.

As to the trans compounds, the butyrophenone derivatives **10d**, **10e**, **11a**, and **11b** showed marked activities in the primary tests but strongly antagonized the methamphetamine-induced stereotyped behavior at 10 mg/kg sc. It is interesting that the cis (**5k**) and trans isomers (**10e**) exhibited the opposite effect on the stereotyped behavior. These *trans*-butyrophenone derivatives showed potent CNS-depressing activities and, in particular, exhibited more potent inhibition of self-stimulation in comparison

Table III. Comparative CNS Activities of Butyrophenone Derivatives



compd	R_1	R_2	4a,9b rel confign	ED_{50}, mg/kg: antimeth[b] mice, po	antiapomorph rats, po	locomot act. mice, po	catalepsy mice, po	active avoid. mice, po	self-stimulation: rats, po	self-stimulation: rats, ip
5k	CH_3	H	cis	23.8 (13.3-42.4)[a]	16.5 (9.94-22.6)	9.30 (5.62-15.3)	15.3 (10.9-21.3)	10.0 (5.52-19.7)	61.8 (26.2-119)	3.16 (1.80-5.53)
6a	CH_3	CH_3	cis			10.2 (4.26-24.2)	40.3 (21.9-75.2)	20.1 (10.1-39.9)	30.0 (18.8-47.7)	
10d	F	H	trans			7.12 (2.63-24.3)	8.08 (5.05-12.9)	5.19 (3.32-9.06)	4.54 (2.58-7.98)	
10e	CH_3	H	trans			9.73 (6.57-14.2)	7.18 (4.51-11.4)	9.73 (6.57-14.2)	6.28 (3.14-12.6)	
11a	F	CH_3	trans			12.8 (7.56-21.7)	30.7 (8.62-109)	4.58 (2.73-7.67)	7.37 (4.06-13.4)	
11b	CH_3	CH_3	trans			14.5 (7.58-27.7)	55.9 (30.9-101)	11.5 (6.16-21.5)	8.44 (5.67-12.6)	
1 (carbidine)				>100	>100	150 (81.0-279)	>150	119 (46.5-516)	>100	60.3 (16.4-222)
chloropromazine				13.3 (6.90-25.7)	3.25 (2.36-4.00)	7.42 (3.21-17.1)	9.97 (6.20-16.0)	5.59 (3.75-8.34)	7.04 (5.25-9.43)	2.10 (1.20-3.57)

[a] 95% confidence limits. [b] Antimeth = antimethamphetamine.

with the cis compounds **5k** and 6a. Introduction of a methyl group in the 5 position reduced the cataleptic activity, which is regarded as a measure of extrapyramidal side effects in clinical use;[8] so 11a is a neuroleptic approximately as potent as chlorpromazine but with less cataleptic potential.

On the basis of these results, **5k** and 11a are worth further studying and, in particular, the former has a unique pharmacological profile as a new neuroleptic. Further studies of this compound will be published elsewhere.

Experimental Section

Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. NMR spectra were taken in Me_2SO-d_6 solution with a Varian HA-100 spectrometer using Me_4Si as an internal standard. Where the analyses are indicated only by the symbols of the elements, the analytical results were within ±0.4% of theoretical values. Organic extracts were dried over $MgSO_4$.

8-Ethyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (3d) Hydrochloride. A mixture of **2d**·HCl (16.3 g, 0.05 mol) and 5% Pd/C (2 g) in 70% EtOH (150 mL) was catalytically hydrogenated at 70 °C under ordinary pressure. After the theoretical amount of H_2 was absorbed, the catalyst was filtered. The filtrate was cooled, and the resulting precipitates were collected and recrystallized from 70% EtOH to give **3d**·HCl (8.8 g, 75%), mp 256–258 °C. Anal. ($C_{13}H_{16}N_2$·HCl) C, H, Cl, N.

***cis*-2,3,4,4a,5,9b-Hexahydro-1*H*-pyrido[4,3-*b*]indoles 4a–d and 4e.** Into a mixture of concentrated HCl (370 mL) and H_2O (250 mL) were added **3** (0.25 mol) and PtO_2 (1.3 g), and the mixture was submitted to catalytic hydrogenation at 70 °C under ordinary pressure. After the theoretical amount of H_2 was absorbed, the catalyst was filtered. The filtrate was made alkaline with NaOH and extracted with benzene. The extract was dried and concentrated. Solid residues (crude **4a** and **4d**) were recrystallized from benzene and *n*-hexane. Oily residues were converted into the oxalates (**4b** and **4c**) and recrystallized from EtOH or purified by chromatography on silica gel with $CHCl_3$–MeOH (30:1) (**4e**). **4a**: mp 99–101 °C; yield 54%. Anal. ($C_{11}H_{14}N_2$) C, H, N. **4b**·dioxalate: mp 169–171 °C dec; yield 34%. Anal. ($C_{11}H_{13}FN_2$·$2C_2H_2O_4$) C, H, F, N. **4c**·dioxalate: mp 188–189 °C; yield 74%. Anal. ($C_{12}H_{16}N_2$·$2C_2H_2O_4$) C, H, N. **4d**: mp 82–85 °C; yield 65%. Anal. ($C_{13}H_{18}N_2$) C, H, N. **4e**: yield 52%. Anal. ($C_{12}H_{16}N_2O$) C, H, N.

***cis*- or *trans*-2-Substituted 2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole Derivatives 5 and 10. Procedure A.** A mixture of **4** (or **9**) (0.01 mol), appropriate alkyl halide (or methyl benzenesulfonate) (0.012 mol), and triethylamine (0.015 mol) in toluene (50 mL) was heated under reflux for 1–15 h. After being cooled, the reaction mixture was washed with H_2O, dried, and concentrated in vacuo. The residue was converted into the hydrochloride with ethanolic HCl and recrystallized from a suitable solvent.

Procedure B. A mixture of **4** (or **9**) (0.01 mol), appropriate alkyl halide (0.013 mol), potassium carbonate (0.03 mol), and potassium iodide (0.01 mol) in methyl ethyl ketone (100 mL) was heated under reflux for 10–25 h. The insoluble matter was removed by filtration and the filtrate was concentrated. The residue was converted into the hydrochloride with ethanolic HCl and recrystallized from a suitable solvent or purified by chromatography on silica gel with $CHCl_3$–EtOH (20:1) in **5g**.

Procedure C. A mixture of **4c** (or **9b**) (2 g, 0.011 mol) and methyl vinyl ketone (0.9 g, 0.013 mol) in benzene (50 mL) was refluxed for 1 h. After the reaction mixture was concentrated, the residue was converted into salt and recrystallized from a suitable solvent.

***cis*- or *trans*-8-Substituted 2-[3-(*p*-fluorobenzoyl)propyl]-5-methyl-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole (6a, 11a, and 11b).** A solution of **5k** (or **10d** or **10e**) (0.01 mol) in a mixture of 37% HCHO (1 g, 0.012 mol), HCOOH (1.2 g, 0.026 mol), and H_2O (10 mL) was heated under reflux for 15 min. The reaction mixture was made alkaline with dilute NaOH and extracted with benzene. The extract was washed with H_2O, dried, and concentrated. The residue was purified by chromatography on silica gel (20 g) with $CHCl_3$–EtOH (200:1), converted into salt, and recrystallized from a suitable solvent.

***cis*-2-[3-(*p*-Fluorobenzoyl)propyl]-5-ethyl- (or benzyl) 8-methyl-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole (6b and 6c) Dihydrochloride.** A mixture of **5k** (3.5 g, 0.01 mol), ethyl iodide (or benzyl bromide) (0.012 mol), and triethylamine (1.3 g, 0.013 mol) in toluene (50 mL) was heated under reflux for 15 h. The reaction mixture was washed with H_2O, dried, and concentrated. The residue was converted into the dihydrochloride with ethanolic HCl and recrystallized from EtOH.

***cis*-2-[3-(*p*-Fluorobenzoyl)propyl]-5-acetyl-8-methyl-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole (6b) Fumarate.** A mixture of **5k** (3.5 g, 0.01 mol) and Ac_2O (2.6 g, 0.026 mol) in benzene (30 mL) was heated under reflux for 1.5 h. The reaction mixture was washed with dilute NaOH and H_2O, dried,

and concentrated. The residue was converted into the fumarate and recrystallized from EtOH to give **6d**·fumarate (2.8 g, 64%), mp 164–166 °C.

***trans*-2-Benzyl-8-methyl-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole (7b) Dihydrochloride.** To a cooled mixture of **2c** (34 g, 0.123 mol) and sodium borohydride (9.36 g, 0.246 mol) in tetrahydrofuran (THF; 300 mL) was added a solution of boron trifluoride etherate (46.9 g, 0.33 mol) in THF (60 mL) under N_2 during 1 h. The reaction mixture was stirred for 30 min at room temperature and then refluxed for 4 h. To the cooled mixture was added 6 N HCl (200 mL), and THF was removed in vacuo. To the residual solution was added dioxane (150 mL), and the mixture was heated under reflux for 1 h and concentrated. The residue was made alkaline with dilute NaOH and extracted with $CHCl_3$. The extract was dried and concentrated. The residue was converted to the hydrochloride and recrystallized from 80% EtOH to give 7b·HCl (23.2 g, 54%), mp 250–255 °C.

***trans*- or *cis*-2-Benzyl-8-fluoro-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole (8b and 8a).** Crude **7a** (27 g) was prepared from **2b** (30 g) by the same procedure for the preparation of **7b**.

A mixture of the crude **7a** (27 g) and Ac_2O (25 g) in benzene (60 mL) was refluxed for 1.5 h. The reaction mixture was washed with dilute NaOH and H_2O and dried. The solvent was removed in vacuo and the residue was recrystallized from EtOH to give 8b (8.5 g, 24.4%). The mother liquor was concentrated and the residue was chromatographed on silica gel (60 g). The product obtained from the earlier fraction of $CHCl_3$ elution was recrystallized from EtOH to give 8a (1.4 g, 4%). **8a**: mp 139–140 °C. Anal. ($C_{20}H_{21}FN_2O$) C, H, N. **8b**: mp 157–159 °C. Anal. ($C_{20}H_{21}FN_2O$) C, H, N.

A solution of 8a (1.3 g, 0.004 mol) in a mixture of concentrated HCl (4.2 mL) and H_2O (2 mL) was heated under reflux for 1.5 h. The reaction mixture was made alkaline with NaOH and extracted with benzene. The extract was concentrated and to the residue was added Pd/C (0.2 g) and 50% EtOH (20 mL). The mixture was catalytically hydrogenated at 60 °C under ordinary pressure. After the theoretical amount of H_2 was absorbed, the catalyst and the solvent were removed and the residue was recrystallized from benzene and *n*-hexane to give 4b (0.51 g, 67%).

***trans*-2-Benzyl-8-fluoro-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole (7a).** A solution of 8b (2.6 g, 0.008 mol) in a mixture of concentrated HCl (9.5 mL) and H_2O (5 mL) was heated under reflux for 2 h. The solution was made alkaline with dilute NaOH and extracted with benzene. The extract was dried and concentrated. The residue was recrystallized from *n*-hexane to give 7a (1.7 g, 75%), mp 92–94 °C.

***trans*-8-Fluoro- (or methyl) 2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole (9a and 9b).** A mixture of **7** (0.02 mol) and 5% Pd/C (1 g) in 50% EtOH (100 mL) was submitted to catalytic hydrogenation at 60 °C under ordinary pressure. After the theoretical amount of H_2 was absorbed, the catalyst and the solvent were removed. To the residue was added dilute NH_4OH, and the solution was extracted with benzene. The extract was dried and concentrated. The residue was recrystallized from a suitable solvent. **9a**: mp 121–123 °C (benzene–*n*-hexane); yield 82%. Anal. ($C_{11}H_{13}FN_2$) C, H, F, N. **9b**: mp 100–102 °C (ether–*n*-hexane); yield 78%. Anal. ($C_{12}H_{16}N_2$) C, H, N.

***cis*- or *trans*-2-Benzoyl-8-methyl-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole (12a and 12b).** To a solution of 4c (or **9b**) (10 g, 0.053 mol) and triethylamine (10.7 g, 0.106 mol) in benzene (200 mL) was added benzoyl chloride (8.19 g, 0.059 mol) dropwise at room temperature; after the addition was completed, the reaction mixture was stirred for 1 h. The precipitate was filtered and the filtrate was extracted with dilute HCl. The acidic layer was made alkaline with Na_2CO_3 and extracted with benzene. The extract was dried and concentrated. The residue was chromatographed on silica gel (40 g) and elution with $CHCl_3$–EtOH (100:1) gave crude **12a** (or **12b**). Crude 12a was converted into the hydrochloride with ethanolic HCl and recrystallized from EtOH. Crude **12b** was recrystallized from benzene and *n*-hexane.

12a·HCl: mp 185–190 °C; yield 58%. Anal. ($C_{19}H_{20}N_2O$·HCl) C, H, Cl, N. **12b**: mp 169–171 °C; yield 51%. Anal. ($C_{19}H_{20}N_2O$) C, H, N.

***cis*- or *trans*-2-Benzoyl-5,8-dimethyl-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole (13a and 13b).** After adding 37% aqueous HCHO (3.24 g, 0.04 mol) to a solution of **12** (2.9 g, 0.01 mol) in EtOH (60 mL), the resulting solution was stirred at room temperature for 30 min, then treated with Raney Ni (0.2 g), and finally catalytically hydrogenated at ordinary temperature and pressure. After the theoretical amount of H_2 was absorbed, the catalyst and the solvent were removed. The residue was recrystallized from AcOEt. **13a**: mp 150–152 °C; yield 45%. Anal. ($C_{20}H_{22}N_2O$) C, H, N. **13b**: mp 165–167 °C; yield 75%. Anal. ($C_{20}H_{22}N_2O$) C, H, N.

***cis*- or *trans*-2-Benzoyl-5,8-dimethyl-2,3,4,4a,5,9b-hexahydro-1*H*-pyrido[4,3-*b*]indole Methiodide (14a and 14b).** A solution of **13** (3.1 g, 0.01 mol) and an excess of methyl iodide in AcOEt (40 mL) was heated under reflux for 8 h. The separated quarternary ammonium salt was collected and recrystallized from a suitable solvent. **14a**: mp 169–171 °C (EtOH); yield 31%; NMR δ 3.41, 3.52 (s, each 3 H, N-CH_3). Anal. ($C_{20}H_{22}N_2O$·CH_3I) C, H, I, N. **14b**: mp 234–235 °C (dilute EtOH); yield 76%; NMR δ 3.23, 3.63 (s, each 3 H, N-CH_3). Anal. ($C_{20}H_{22}N_2O$·CH_3I) C, H, I, N.

Pharmacology Methods. Animals and Materials. Adult male STD-ddy mice and male Wister HLA rats were employed in the experiments. Test compounds were dissolved or suspended in 0.5% aqueous tragacanth and administered. All doses of the compounds are expressed as the form (salt or base) indicated in Table I.

Statistics. The ED_{50} values were calculated according to the method of Litchfield and Wilcoxon.[9]

Effect on Locomotor Activity in Mice. The effect of the compounds on locomotor activity was examined in mice using an Animex activity meter according to the modified method of Svensson and Thieme.[10] A group of five mice was used for each dose of the compounds. At an appropriate time after oral administration of test compounds, each mouse was put into the cage on Animex and the locomotor activity was measured for 3 min. Average suppression of the locomotor activity by each dose of test compounds was expressed as percent inhibition of control, and the ED_{50} of each compound, defined as the dose which caused 50% inhibition, was calculated.

Muscle Relaxation. Test compound, 100 mg, was administered po to a group of five mice and the effect was evaluated 20 min after the administration according to the modified method of Courvoisier et al.[11] When forepaws of a mouse are placed on a taut horizontal wire, the normal response is for the mouse to draw the hind paws up to the wire. The reaction was considered to be positive if the mouse failed to grasp the wire with the hind paws in less than 5 s at least once in three trails.

Catalepsy in Mice. Groups of five mice were tested for catalepsy according to the modified method of Courvoisier et al.[11] Each mouse was forced to put its forepaws on a rubber cap of 2.8 cm in height. The mice which failed to remove their paws from the cap within 30 s were considered to be cataleptic. The ED_{50} in this test is the dose which causes catalepsy in 50% of the mice.

Effect on Methamphetamine-Induced Stereotyped Behavior. This test was carried out by a modified method of Nayler and Costall.[12] Groups of six rats (200–250 g) were injected ip with graded doses of test compounds, followed 20 min later by an ip injection of methamphetamine, 2 mg/kg, and they were observed for stereotyped behavior at 30-min intervals for 3 h and then 1-h intervals for a further 3 h. The intensity of the stereotypy was evaluated by assessing the components of this behavior, i.e., sniffing, exploratory activity, head movement, gnawing, licking, and back locomotion, with an arbitrary score from 0 to 2, "0" referring to absent, "1" to moderate, and "2" to marked manifestation of each component. The sums of the scores for these components of stereotypy were used to quantitatively evaluate the effect of test compounds on the stereotyped behavior induced by methamphetamine. The results are expressed as the symbols representing the percent potentiation or antagonism and are given in Table II.

Effect on Apomorphine-Induced Gnawing in Rats. Groups of six rats were injected iv with 1 mg/kg of apomorphine hydrochloride 1 h after sc injection of test compounds, and at 5, 10, and 20 min after apomorphine hydrochloride the rats were

observed for gnawing movement for 1 min. Absence of the typical gnawing movement during at least one of the three observation periods was regarded as a positive effect.[13] The ED_{50} in this test is defined as the dose which suppresses the gnawing movement in 50% of the rats. Furthermore, the ability of **5k** to enhance the action of apomorphine hydrochloride was examined. Rats were injected iv with 0.05 mg/kg of apomorphine hydrochloride, a dose too small to induce gnawing by itself, 1 h after a sc injection of **5k** and observed for the incidence of gnawing for 20 min.

Effect on Methamphetamine-Induced Hyperactivity in Mice. The suppression of methamphetamine-induced hyperactivity was examined according to the modified method of Ueki et al.[14] At 100 min after oral administration of test compounds, five groups of three mice were injected with methamphetamine (5 mg/kg, ip), and 10 min thereafter the locomotor activity was measured with a photocell activity counter for 20 min. The ED_{50} in this test is the dose which reduces the average counts of the treated mice to half the count of control animals.

Effect on Active Avoidance in Mice. Effect of test compounds on one-way active avoidance in mice was examined using a box with two compartments, darkened and lighted, as described previously.[15] Mice were previously trained to avoid electroshocks from the floor by moving from the darkened compartment to the lighted one in response to a warning stimulus. This test was carried out using for each group 10 mice which could avoid the shock at a rate more than 80% in 20 trials. The results are expressed as the ED_{50} values, defined as the dose that causes a 50% inhibition in the rate of the avoidance response.

Effect on Self-stimulation in Rats. Effect of test compounds on intracranial self-stimulation behavior was studied in rats with chronic electrodes implanted in the lateral posterior hypothalamus.[16] The rats which showed a constant lever-pressing response of 50–100/min were selected for the test. Groups of eight rats were used. In the test, self-stimulation rates were counted for 10 min before and 1, 2, 4, 6, 8, and 24 h after po or ip administration of test compounds. The ED_{50} in this test is the dose which causes 50% or more inhibition of the rate of the self-stimulation in 50% of the rats.

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References and Notes

(1) W. M. Herrmann and J. Fabricius, *Dis. Nerv. Syst.*, **35** (7, section 2), 28 (1974).
(2) N. K. Barkov, A. Geller, and M. E. Jarvik, *Psychopharmacologia*, **21**, 82 (1971).
(3) N. K. Barkov, *Farmakol. Toksikol.*, **34**, 647 (1971).
(4) L. Valzelli, S. Consolo and C. Morpurgo in "Antidepressant Drugs", S. Garattini and M. N. G. Dures, Ed., Excerpta Medica, Amsterdam, 1966, p 61.
(5) A. Smith, *J. Chem. Soc.*, 1 (1970).
(6) J. G. Berger, S. R. Teller, C. D. Adams, and L. F. Guggenberger, *Tetrahedron Lett.*, 1807 (1975).
(7) R. H. Johnson and J. P. Oswald (to Abbott Laboratories), U.S. Patent 3 466 293 (1969).
(8) O. Hornykiewicz, C. H. Markham, W. G. Clark, and R. M. Fleming in "Principles of Psychoparmacology", W. G. Clark, Ed., Academic Press, New York, 1970, p 585.
(9) J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).
(10) T. H. Svensson and G. Thieme, *Psychopharmacologia*, **14**, 157 (1969).
(11) S. Courvoisier, R. Ducrot, and L. Julou in "Psychotropic Drugs", S. Garattini and V. Ghetti, Ed., 1975, p 373.
(12) R. J. Naylor and B. Costall, *Life Sci.*, **10**, 909 (1971).
(13) P. A. J. Janssen, C. J. E. Niemegeers, and K. H. L. Schellekens, *Arzneim.-Forsch.*, **15**, 104 (1955).
(14) S. Ueki, H. Sugano, N. Sato, J. Iwaki, H. Yonemura, T. Fukuda, H. Yamada, S. Nurimoto, G. Hayashi and Y. Kowa, *Nippon Yakurigaku Zasshi*, **61**, 421 (1965).
(15) M. Oka and M. Shimizu, *Jpn. J. Pharmacol.*, **25**, 121 (1975).
(16) C. Kamei, Y. Masuda, and M. Shimizu, *Jpn. J. Pharmacol.*, **24**, 613 (1974).

Glycerides as Prodrugs. 1. Synthesis and Antiinflammatory Activity of 1,3-Bis(alkanoyl)-2-(*O*-acetylsalicyloyl)glycerides (Aspirin Triglycerides)[1]

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A series of 1,3-bis(alkanoyl)-2-(*O*-acetylsalicyloyl)glycerides (aspirin triglycerides) having aspirin at the 2 position of glycerol and fatty acids at the 1 and 3 positions was prepared. The compounds were administered orally and tested for efficacy in the rat paw edema test, and the stomachs were examined for the presence of lesions. The results showed that the members of this series in which the fatty acids are of intermediate chain length (C_4–C_{12}) do not cause gastric lesions and have essentially all the systemic activity associated with aspirin.

Despite the enormous amount of work that has been done on development of antiinflammatory drugs, the classical remedy aspirin remains the drug of first choice in the treatment of arthritis. Although traditional and familiar, aspirin is not an innocuous substance. It causes a variety of side effects which limit its usefulness, often obliging the patient to switch to other medications which frequently have a similar profile of side effects. The primary unwanted effect is direct gastric irritation, due to contact of solid aspirin (or of concentrated solutions of aspirin) with the gastric mucosa. It has been reported recently[3] that aspirin in antiarthritic doses causes endoscopically observable gastric erosion in 39% of the patients tested over a 4-week period. Many attempts have been made to develop aspirin derivatives and formulations which will yield adequate blood levels after oral administration without causing gastric irritation. We wish to report on a novel approach to this problem, in which

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