(63.9 g, 0.200 mole) was added to the deep red ylide solution and the mixture was stirred at reflux for 2 hr. After cooling the reaction mixture to 5°, 100 ml of H<sub>2</sub>O was carefully added, then the aqueous phase was adjusted to pH 3 with 3 N aqueous HCl. The layers were separate and the aqueous layer was extracted with two 250-ml portions of C<sub>6</sub>H<sub>6</sub> to remove unreacted ketone and Ph<sub>3</sub>PO. The aqueous phase was clarified with Darco G-60, neutralized with 3 N aqueous KOH, and extracted throughly with C<sub>6</sub>H<sub>6</sub> to provide 46.3 g (54%) of 19, a 1:1 mixture of geometric isomers.

The trans isomer was isolated by conversion to the dioxalate salt in 50% aqueous EtOH. One recrystallization from the same solvent pair afforded pure trans-19 dioxalate: mp 181-181.5° dec. Anal. (C<sub>22</sub>H<sub>27</sub>N<sub>3</sub>O<sub>2</sub>S<sub>2</sub>·2C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>·H<sub>2</sub>O) C, H, N.

The free base from *trans*-19 dioxalate, when treated with maleic acid in MeCN, provided *trans*-19 dimaleate: mp 150–153°; uv max (EtOH) 302 m $\mu$  (log  $\epsilon$  3.9). Anal. (C<sub>22</sub>H<sub>27</sub>N<sub>3</sub>O<sub>2</sub>S<sub>2</sub>·2C<sub>4</sub>H<sub>4</sub>-O<sub>4</sub>) C, H, N.

The cis isomer was isolated by neutralization of the oxalate mother liquor to pH 10 with 3 N aqueous KOH, extracting thoroughly with CH<sub>2</sub>Cl<sub>2</sub>, and treatment of the enriched free base mixture with p-toluenesulfonic acid in hot MeOH. A single recrystallization from MeOH provided pure cis-19 ditosylate: mp 207-208°, uv max (EtOH) 261, 310 m $\mu$  (log  $\epsilon$  4.2, 3.9). Anal. (C<sub>22</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>S<sub>2</sub>·2C<sub>1</sub>H<sub>8</sub>O<sub>3</sub>2) C, H, N.

Methylation of trans-19.—A solution of the free base of trans-19 (172 mg) in 4 ml of 97% HCO<sub>2</sub>H and 4 ml of 37% formalin was heated at reflux for 30 min. The residue was dissolved in CH<sub>2</sub>Cl<sub>z</sub>, washed with 1 N aqueous KOH, dried (MgSO<sub>4</sub>), then evaporated to an oil which crystallized from *i*-PrOH, mp 119–121°. One recrystallization afforded a product which was identical with trans-4.

Methylation of cis-19.--In the same manner cis-19 (free base) was converted to cis-4, mp 145-147°.

**3-(4-Methyl-1-piperazinyl)propyltriphenylphosphonium Bro**mide Hydrobromide.—1-Methylpiperazine (10.0 g, 0.100 mole) was added carefully to a stirred slurry of 3-bromopropyltriphenylphosphonium bromide<sup>15</sup> (46.4 g, 0.100 mole) in 100 ml of *i*-PrOH. When heated to reflux, a deep red solution was obtained. After 2 hr at reflux, the solution was chilled to 5°. The crystalline product was filtered, washed with cold *i*-PrOH, and dried

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 $(100^\circ, 0.3 \text{ mm})$  to provide 38.7 g (69%) of material, mp  $244^\circ$  dec. Anal.  $(C_{26}H_{23}BrN_2P \cdot HBr) C$ , H, Br. Upon standing in air this salt quickly absorbs 1 equiv of  $H_2O$ , which readily dissociates on vacuum drying.

cis-N,N-Dimethyl-9-{3-[4-(2-hydroxyethyl)-1-piperazinyl]propylidene}thioxanthene-2-sulfonamide (20) Dimaleate.—A solution of cis-19 free base (4.30 g, 0.010 mole) in 10 ml of anhydrous MeOH at 0° was treated with 1.0 ml of ethylene oxide under N<sub>2</sub>. After heating the solution at reflux for 4 hr, the solvent was removed and the residue was treated with 2 equiv of maleic acid in EtOH to afford the crystalline dinaleate salt. Two recrystallizations from MeCN and one recrystallization from EtOH provided 2.38 g (33%) of pure 20 dimaleate: mp 126-128°; ir (KBr) 2.95  $\mu$  (OH); nv max (EtOH) 308 m $\mu$  (log  $\epsilon$  3.9). Anal. (C<sub>24</sub>H<sub>31</sub>N<sub>3</sub>O<sub>3</sub>S<sub>2</sub>·2C<sub>4</sub>H<sub>4</sub>O<sub>4</sub>) C, H, N.

trans-N,N-Dimethyl-9- $\frac{3}{4}-\frac{4}{2}-\frac{1}{2}$ 

cis-4-[3-(2-N,N-Dimethylsulfamoylthioxanthen-9-ylidene)propyl]-N-methyl-1-piperazinepropionamide (22) Dihydrochloride.—A solution of cis-19 ditosylate (1.55 g, 0.002 mole) and 3-chloro-N-methylpropionamide<sup>16</sup> (0.49 g, 0.002 mole) in 5.0 ml of DMF under N<sub>2</sub> was stirred at 80° for 48 hr with 1.7 g of K<sub>2</sub>CO<sub>3</sub>. Upon cooling the reaction mixture was filtered, the filtrate was diluted with 4 vol of H<sub>2</sub>O, and the product was isolated with CHCl<sub>3</sub>. The crude base was treated with dry HCl in *i*-PrOH and the precipitated solid was recrystallized from *i*-PrOH to afford 0.69 g (57%) of 22 dihydrochloride: mp 244.5-246° dec, ir (KBr) 5.92  $\mu$  (amide I), uv max (EtOH) 310 m $\mu$ (log  $\epsilon$  4.0). Anal. (C<sub>26</sub>H<sub>34</sub>N<sub>4</sub>O<sub>3</sub>S<sub>2</sub>·2HCl) C, H, N.

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## 4'-Fluoro-4-(1,4,5,6-tetrahydroazepino[4,5-b]indol-3(2H)-yl)butyrophenones

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The preparation and pharmacology of a new series of 4'-fluoro-4-(1,4,5,6-tetrahydroazepino[4,5-b]indol-3(2H)-yl)-butyrophenones is discussed. These compounds possess a high degree of interesting CNS depressant activity.

The discovery in  $1959^{1}$  that a series of butyrophenone derivatives had pronounced CNS depressant activity in several mammalian species resulted in the preparation of a large number of related compounds. Several of these, the most notable being haloperidol, have been found to have useful antipsychotic activity in man.<sup>2</sup>

Chemically the more active members of this series are derived from six-membered heterocyclic nuclei, usually piperidine or piperazine, with the 4-(4'-fluoro)butyrophenone substituent at N-1 and a variety of substituents at the 4 position.<sup>3,4</sup> In this communication we will present a major departure from this general theme: a series of 4-(4-fluoro)butyrophenones derived from the centrally active hexahydroazepino [4,5-b] indoles<sup>5</sup> in which the butyrophenone moiety is attached to N-3 of the seven-membered heterocyclic ring. The compounds were prepared by alkylating the appropriate base with 4-chloro-4'-fluorobutyrophenone and are listed in Table I.

## **Experimental Section**

**Pharmacology.** Methods.—Carworth Farms male, albino mice (CF-1) weighing 18-22 g were used for all studies reported

P. A. J. Janssen, C. Van de Westeringh, A. H. M. Jageneau, P. J. A. Demoen, B. K. F. Hermans, G. H. P. Van Daele, K. H. L. Schellekens, C. A. M. Vander Eycken, and C. J. E. Niemegeers, J. Med Pharm. Chem., 1, 281 (1959).

<sup>(2)</sup> P. A. J. Janssen, C. J. E. Niemegeers, and K. H. L. Schellekens, Arzneim.-Forsch., 15, 104 (1965).

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Analyses

C, H, F, N C, H, Cl, F, N

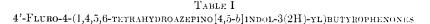
C, H, F, N

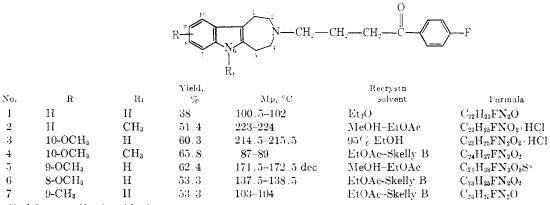
C, H, F, N

C, H, F, N

C, H, Cl, F, N

C, H, F, N, S





<sup>a</sup> Cyclohexanesulfamic acid salt.

here. The test compounds were dissolved or suspended in  $0.25 \frac{C}{C}$ , aqueous methylcellulose solution and administered intraperitoneally. Procedures for measuring acute toxicity (LD<sub>20</sub>) and the effect of the test compounds on overt behavior, loss of righting reflex (LRR<sub>50</sub>), traction (Tr<sub>50</sub>), chinney (Ch<sub>50</sub>), dish (D<sub>50</sub>), pedestal (P<sub>50</sub>), fighting behavior (FM<sub>30</sub>), and antagonism of nicotine-induced running (R), tonic-extensor convulsions (TE), and death (D), have been described previously.<sup>6</sup> Other test procedures used for this series of compounds are described below.

**Potentiation of Ethanol Narcosis.**—A subhypnotic dose of EtOH (5 ml/kg of a 50% aqueous solution) was administered orally to groups of six mice 30 min after the test compound. Thirty minutes later each mouse was examined for loss of righting reflex. The dose of test compound was decreased in 0.3 log intervals; the number of animals in each group that exhibited loss of righting reflex was used as a quantal response parameter for calculating the effect dose (ED<sub>50</sub>) of the test compound.<sup>7</sup>

**Potentiation of Pentobarbital Narcosis.**—A nonmarcotic dose of pentobarbital (10 mg/kg) was administered intravenously to groups of six mice 30 nin after the test compound. The dose of test compound was decreased in 0.5 log intervals; the number of animals in each group exhibiting loss of righting reflex 15 min after the pentobarbital injection was used to calculate the effective dose ( $ED_{50}$ ) of test compound.<sup>7</sup>

**Catalepsy.**—The ability of the test compounds to produce a cataleptic state in mice was determined. Thirty minutes after the administration of the test compound to groups of six nice the animals were placed so that their forepaws rested on a 5-cm high pedestal. The number of seconds to a maximum of 30 sec that each monse remained in this position was recorded. The dose of test compound was decreased at 0.5 log intervals; the effective dose (ED<sub>50</sub>) which produced catalepsy was determined.<sup>5</sup>

**Ptosis.**—Groups of six mice were used for this test. Thirty minutes after injection of the test compound each monse was placed on a pedestal and observed for 10 sec. The degree of ptosis was rated on a scale of 1 (eyes open) to 4 (eyes completely closed). The dose of test compound was decreased in 0.5 log intervals; the effective dose, determined graphically, was that dose of test compound required to give a total score of 15 per group of six mice.

Antagonism of Apomorphine-Induced Cage Climbing.—The ability of compounds to antagonize the apomorphine-induced cage climbing phenomenon was determined in groups of four mice. Apomorphine (2.5 mg/kg) was injected intraperitoneally 30 min after administration of the test compound, and the mice were placed in a wire-mesh cage. Fifteen minutes later the number of seconds ont of a 60-sec observation period that at least three of the four mice were standing upright or had climbed from the bottom of the eage was recorded. Doses of the test compounds were decreased in 0.5 log intervals until no antagonism of the cage climbing response was observed.<sup>3</sup> Antagonism of d-Amphetamine-Induced Aggregation Toxicity. — Thirty minutes after administration of the test compound mice were injected intraperitoneally with a dose of d-amphetamine (10 mg/kg) which would be lethal to all control animals under the conditions of this experiment. The mice were immediately aggregated in groups of ten in plastic cages with perforated metal tops. The cages measured  $13 \times 16 \times 12$  cm and were kept at an internal temperature of  $32^{\circ}$  in a cabinet maintained at  $2^{\circ}$ . After 4 hr of aggregation the number of dead mice was recorded. The dose of test compound was decreased at  $0.5 \log$  intervals.<sup>†</sup>

Effect on Body Temperature.—The body temperature of mice was measured 30 min after administration of the test compound. Body temperature was measured with an intraperitoncal thermiister probe on a Tri-R electronic thermometer. The average temperature for groups of six mice was calculated.

**Chemistry.**—Melting points, taken in a capillary tube, are corrected. The structures of all compounds were supported by ir, uv, and umr spectra. Skellysolve B is a commercial hexane, bp 60–70°, made by Skelly Oil Co., Kansas City, Mo. The silica gel used for chromatography was obtained from E. Merck A.G., Darmstadt, Germany.

4'-Fluoro-4-(1,4,5,6-tetrahydroazepino [4,5-b]indol-3(2H)-yl)butyrophenone (1).—A stirred mixture of 1,2,3,4,5,6-hexahydroazepino [4,5-b]indole<sup>3</sup> (18.6 g, 0.100 mole), 4-chloro-4'-fluorobutyrophenone (28.0 g, 0.140 mole), anhydrous Na<sub>2</sub>CO<sub>3</sub> (32 g), 4-methyl-2-pentanone (1.15 l.), and a few crystals of KI was refluxed under N<sub>2</sub> for 15 hr, cooled, poured into H<sub>2</sub>O, and extracted (Et<sub>2</sub>O). The extract was dried (K<sub>2</sub>CO<sub>3</sub>) and concentrated *in vacuo*. The oily residue was chroniatographed on silica gel (1.8 kg) with Et<sub>3</sub>NH-EtOAc (2:98). The product thus obtained was recrystallized from Et<sub>2</sub>O to give 13.3 g (38%) of 1.

## **Results and Discussion**

The activities of the subject compounds on the various pharmacologic parameters studied are listed in Tables II and III. The activities of the antipsychotics, thioridazine (8) and haloperidol (9). are included for comparison. In general the 4'-fluoro-4-(1,4,5,6-tetrahydroazepino [4,5-b]indol-3(2H)-yl) butyrophenones are relatively nontoxic and produce little neurologic deficit at doses which depress overt behavior. In the tests (Tr, Ch, D, and P) which measure effects on simple reflexes and behavior they are highly active and compare favorably with the standard compounds. The compounds also effectively depress isolation-induced fighting behavior and antagonize nicotine-induced tonic-extensor convulsions and death. The subject compounds induce prosis at higher dose levels than thioridazine. Potentiation of ethanol- and pentobarbital-induced narcosis by the subject compounds was somewhat less than by either thioridazine or haloperidol which suggests a diminished sedative effect for

<sup>(6)</sup> G. A. Youngdale, D. G. Anger, W. C. Anthony, J. P. DeVanzo, M. E. Greig, R. V. Heinzelman, H. H. Keasling, and J. Szmuszkovicz, J. Med. Chem., 7, 415 (1964).

<sup>(7)</sup> The effective dose (ED<sub>60</sub>) was calculated by the method of Spearman and Karber, see D. J. Finney, "Statistical Methods in Biological Assay," Hafner Publishing Co., New York, N. Y., 1952

		<b>  _ _ _ _ ,</b>						,								
										Potentiation		Antagonism				
											Pento-	/	Nicotine			
Compd.	$LD_{50}$	LRR50	Tr50	$Ch_{50}$	$D_{50}$	$\mathbf{P}_{50}$	$FM_{50}$	Catalepsy	Ptosis	Ethanol	barbital	R	TE	D	d-Amphetamine	Apomorphine
1	316	>100	32	4	4	6	10	>25	4.0	12	14.7	23	3	4	1.8	5.6
<b>2</b>	562	159	18	3.5	2.5	3.9	7.9	> 30	6.7	6.8	14.7	6	2.5	2.8	22.4	3.0
3	233	>200	16	2.8	0.8	5.6	5.0	>30	4.5	6.8	12.1	14	0.6	0.6	30	10
4	562	>200	>200	20	2.8	5.6	20	>30	1.6	18	100	89	1.6	1.8	1.4	17.8
<b>5</b>	562	>100	25	<b>2</b>	1.4	3	7.1	> 30	5.5	5.6	14.7	>13	8	9	22.4	5.6
6	>1000	>200	25	10	0.8	4	12.6	>30	10	6.8	21.5	>13	8	9	>30	>30
7	>1000	>200	142	6	5.6	9	20	>30	21	5.6	>30	32	5.6	5.6	>30	>30
8	65	56	20	5.6	$^{2}$	8	10	6.3	2.1	2.8	8.3	>13	<b>2.2</b>	<b>2.2</b>	2.0	5.6
9	56	$>\!25$	8	1.3	1.3	2.2	2.9	3.5		0.9	6.8	>13	9	7	0.16	0.1

TABLE 1I Pharmacological Activities of 4'-Fluoro-4-(1,4,5,6-tetrahydroazepino[4,5-b]indol-3(2H)-yl)butyrophenonesª

<sup>a</sup> See text for an explanation of the symbols. Values are ED<sub>50</sub>'s expressed in mg/kg.

TABLE III Effect of 4'-Fluoro-4-(1,4,5,6-tetrahydroazepino[4,5-b]indol-3(2H)-yl)butyrophenones on Normal Body Temperature											
Dose,	Body temp, °C										
mg/kg	1	2	3	4	5	6	7	8	9		
0	35.5	35.2	35.2	37.8	35.2	35.2	35.2	35.5	35.5		
3	34.7	35.2			34.8	35.3		36.0	35.4		
6.3	33.9			37.1				34.4	33.0		
10		31.5	31.5		32.5	33.2	35.2				
12.5	33.1			36.4				32.2	30.4		
25	30.8			35.5				31.3			
30		27.9	28.0		<b>29.9</b>	31.3	32.1				

the series. All of the compounds effectively lowered the body temperature of normal mice (Table III): the more active derivatives (1, 2, 3, and 5) had about the same potency as thioridazine. Compounds 1, 2, 3, and 5 were good antagonists of apomorphine-induced cage climbing and were about as active as thioridazine in this test. Two compounds (1 and 4) antagonized *d*-amphetamineinduced aggregation toxicity as effectively as thioridazine; the others were much less active in this test. Of particular significance was the inability of the subject compounds to produce catalepsy in mice at low doses, since it has been suggested that there may be a correlation between the production of catalepsy in animals and of extrapyramidal stimulation in man.<sup>8</sup> Both thioridazine and haloperidol are active in this test.

The most active member of the series, the 10methoxy derivative (3), was about twice as active in the mouse behavior tests and had a much more favorable therapeutic index than thioridazine. Compound 4 was qualitatively different from the other members of the series. It did not cause loss of righting reflex or traction at the highest dose tested. It was only slightly active in the chimney and fighting behavior tests, and in antag-

(8) S. Irwin, Psychopharmacologia, 9, 259 (1966).

onizing apomorphine cage climbing or potentiating EtOH and pentobarbital narcosis. It was, however, highly active in the dish and pedestal tests, in inducing ptosis, and in antagonizing *d*-amphetamine-induced aggregation toxicity and nicotine-induced TE and D.

It is interesting that, although the CNS activity of the compounds is qualitatively much different from that of the hexahydroazepino [4,3-b]indoles from which they were derived, the variation in potency with substitution on the indole nucleus seems to be similar. Methoxyl substitution at C-10 or methyl substitution at N-6 potentiated activity while substitution at other locations on the aromatic ring had little effect or deereased potency relative to the parent compound.

A comprehensive discussion of the pharmacology of 1 will be published at a later date.

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## Analogs of α-Methylphenethylamine (Amphetamine). I. Synthesis and Pharmacological Activity of Some Methoxy and/or Methyl Analogs<sup>1</sup>

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A series of amphetamine derivatives substituted on the benzene ring with MeO and/or Me groups was synthesized. The pharmacological activity of these compounds was evaluated for toxicity, effects on barbiturate sleeping time, and ability to disrupt mouse behavior. Those which were active in behavioral disruption *included* 1-(2,5-dimethoxy-4-methylphenyl)-, 1-(2,4,5-trimethoxyphenyl)-, 1-(2,4-dimethoxy-3-methylphenyl)-, and 1-(3,4-methylphenyl)-2-aminopropanes. In addition, <math>1-(3-methylphenyl)-2-aminopropane, structurally resembling <math>1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM), was found to be just as active and long lasting as DOM. The amphetamine derivatives either diminished or prolonged the barbiturate sleeping time. 1-(3,4-Methylenedioxyphenyl)-2-aminopropane and DOM were equally effective in decreasing the sleeping time, while <math>1-(2,4,6-trimethylphenyl)-and 1-(3,5-dimethyl-4-hydroxyphenyl)-2-aminopropanes were the most active in the potentiation of the sleeping time.

For many years, there has been interest in the structure of some known hallucinogens. Smythies, *et al.*,<sup>2</sup> have studied the structure-action relationship of a number of mescaline analogs on the behavior of rats. Some ring-substituted amphetamine derivatives have been studied in humans by Shulgin.<sup>3</sup> and in animals by Smythies. *et al.*,<sup>4</sup> and Beaton, *et al.*<sup>5</sup> Snyder and Richelson<sup>6</sup> proposed a common configuration for the action of different classes of some hallucinogens on the basis of steric factors. A correlation between hallucinogenic activities of these different classes of compounds with the electronic properties of the phenyl or indole nucleus was also presented by Snyder and Merril.<sup>7</sup>

In this study, a series of compounds related to amphetamine (1) and 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM or STP, 2) was synthesized and their pharmacological activity was evaluated for their effect on barbiturate sleeping time and their ability to disrupt mouse behavior. It was hoped that evaluation of the compounds in this series would provide information as to which of the substituents on DOM is essential for its action. These compounds included 1-(2-methoxy-4-methylphenyl)-2-aminopropane (3), 1-(3-methoxy-4-methylphenyl)-2-aminopropane (4), and

(7) S. H. Snyder and C. R. Merril, *ibid.*, **54**, 258 (1965).

<sup>(1)</sup> This work was supported by Grants MH-12959, U. S. Public Health Service, Bethesda, Md., and by the Britton Fund.

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<sup>(5)</sup> J. M. Beaton, J. R. Smythies, F. Benington, R. D. Morin, and L. C. Clark, Jr., *ibid.*, **220**, 800 (1968).

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