Agents Acting on the Central Nervous System. XII. 3-*t*-Aminopropiophenones as Central Muscle Relaxants and Diuretics[1,2]

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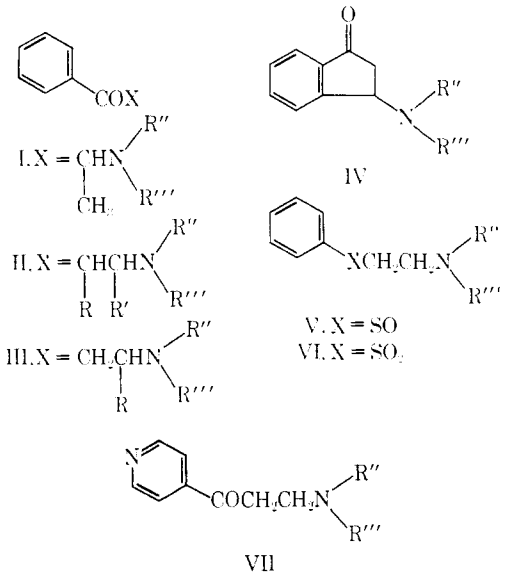
The syntheses and pharmacological evaluation of a series of 2- and 3-*t*-aminopropiophenones and of certain 3- and 4-*t*-aminobutyrophenones, 2-*t*-aminoethyl aryl sulfoxides and sulfones, 3-*t*-amino-1-(4-pyridyl)propan-1-one, and 3-*t*-aminoindan-1-one are presented. The 3-*t*-aminopropiophenones have been found to possess diverse types of biological activities, which include central depressant, adrenergic receptor blocking, central muscle relaxant, local anesthetic, diuretic, antifungal, and antiviral activities; and their structure–activity relationships are discussed. 4′-Fluoro-3-(1-piperidyl)propiophenone (**1**) has powerful central muscle relaxant activity, being twice as effective as mephenesin; 2′,4′-dimethyl-3-(4-morpholinyl)propiophenone (**17**) is diuretic and 4′-fluoro-3-(4-morpholinyl)propiophenone (**5**) is antifungal.

In an exploratory study carried out in this laboratory in search of central muscle relaxants, it was found that certain 3-aminopropiophenones[3] possessed significant activity. This led to a synthesis of compounds of the type I–VII and their biological evaluation.



R, R′ = alkyl groups
R″, R‴ = alkyl groups or they may form part of a polymethylene ring which may carry a hetro atom

Synthetic steps leading to 2-*t*-aminopropiophenones (I) and 3-*t*-aminopropiophenones[4] (II, R = R′ = H) are described in the Experimental Section. Reduction with $NaBH_4$ or LAH gave the corresponding propanols. Two diastereoisomeric propanols, the *threo* and *erythro*, can be formed by reduction of I; tlc showed the presence of two products in each case. Testing was carried out with the mixture of the diastereoisomers.

The 3-*t*-aminobutyrophenones (III, R = CH_3) were synthesized by Michael addition of secondary amines to appropriate crotonophenones, and 2′,4′-dimethyl-4-(4-morpholinyl)butyrophenone (**59**) by reaction of 2′,4′-dimethyl-4-chlorobutyrophenone with morpholine.

3-*t*-Aminopropiophenones showed significant central muscle relaxant activity, whereas the corresponding propanols and 2-*t*-aminopropiophenones did not possess this activity. It appears likely that this difference in their biological activity may be related to the ability of the 3-*t*-aminopropiophenones to undergo facile retro-Michael reaction,[5] leading to the generation of a reactive aryl vinyl ketone, which in the biophase could react with nucleophilic sites. Therefore, in an SAR study, apart from introducing substituents of different stereoelectronic character on the phenyl radical and in the alkyl chain, it seemed of interest to introduce such changes in the molecule as would alter the electronegativity at position 1 and thus their propensity to undergo retro-Michael reaction. Compounds of the type IV, V, VI, and VII were thus prepared. 3-*t*-Aminoindan-1-ones (IV) were prepared by the condensation of 3-bromoindan-1-ones with secondary amines. The bromoindanones were obtained by bromination of indan-1-ones with NBS.[6]

Ir spectra of 4′-butoxy-4′-fluoro- and 4′-methyl-3-piperidylpropiophenones showed CO absorption at 1672, 1682, and 1684 cm^{-1}, while 4′-trifluoromethyl-, 4′-methylsulfinyl-, and 4′-methylsulfonyl-3-piperidylpropiophenones showed CO absorption at 1695, 1690, and 1690 cm^{-1}, respectively, thus showing that F and CH_3 had a similar order of electron-donating effect in these compounds.

The difficulty in obtaining 2-aminoethyl aryl sulfones (V) by means of Mannich reaction on an aryl alkyl sul-

(1) Communication No. 1388 from the Central Drug Research Institute, Lucknow, India.

(2) For the preceding paper of this series: S. K. Chatterji, S. Mukerji, B. C. Gautam, and Nitya Anand, *Indian J. Chem.*, **6**, 235 (1968).

(3) (a) J. Pórszász, K. Nádor, K. Gibiszer Pórszász, and T. Barankay, *Acta Physiol. Acad. Sci. Hung.*, **18**, 149 (1960); (b) M. Yokoyama, S. Toyoshima, and T. Morishita, Japanese Patent 20,390 (Sept 10, 1965); *Chem. Abstr.*, **63**, 16313 (1965).

(4) Roman numerals refer to the types of compounds synthesized, while Arabic numerals refer to the specific compounds.

(5) A retro-Michael reaction has been implicated to explain the *in vivo* antiamebic activity of some 3-*t*-aminoketones of emetine by D. E. Clark, R. F. K., Meredith, A. C. Ritchie, and T. Walker [*J. Chem. Soc.*, 2400 (1962)].

(6) W. Treibs and W. Schroth, *Justus Liebigs Ann. Chem.*, **639**, 204 (1961).

fone experienced by us and also reported earlier,[7] was circumvented by the Michael addition of secondary amines to aryl vinyl sulfones.[8] 2-Aminoethyl aryl sulfoxides (VI) were synthesized by condensation of the appropriate thiophenols with 2-chloroethanol, followed by treatment with $SOCl_2$ to form 2-chloroethyl phenyl sulfides, oxidation with HNO_3 to the corresponding sulfoxides[9] and condensation with the appropriate amines.

1-(4-Pyridyl)-3-(1-piperidyl)propan-1-one (**30**) was obtained by the condensation of 4-acetylpyridine with paraformaldehyde and piperidine.

Biological Activity.—Although most of the compounds described in this paper were screened for their biological activity, the results of only those compounds are described that have shown significant activity and have a bearing on the SAR.

Pharmacological Activity. Methods.—The gross behavioral effects were observed in mice by intraperitoneal administration at different dose levels.

Effects on somatic reflexes were studied in chloralosed (80 mg/kg iv) cats according to the method of Witkin, *et al.*,[10] and De Salva and Oester[11] using mephenesin as the standard drug. Local anesthetic activity was determined in rabbits according to the method of Kuna and Seeler[12] using a 1.2% saline solution of the compounds and the hemolytic activity was measured *in vitro* following the method of Domino, *et al.*[13]

Results and Discussion

The results of the testing of some compounds are recorded in Table I. The 2-*t*-aminopropiophenones and the corresponding propanols in general showed stimulation as indicated by hyperreflexia, alertness, irritability, increase in spontaneous motor activity, piloerection, Straub-tail phenomenon, and convulsions. On the other hand, the 3-*t*-aminopropiophenones caused a marked reduction of voluntary motor activity (in some cases after an initial transient increase in motility), sedation, tachypnea, salivation, lachrymation, and ataxia, ending in complete inhibition of the righting reflex. Death occurred due to respiratory arrest. The gross observational effects indicated the possibility of some of these 3-*t*-aminopropiophenones possessing a central muscle relaxant action. In the corresponding propanols, this central depressant action was greatly reduced and some of these even showed a certain amount of stimulant action.

Effect on Somatic Reflexes.—Quite early in this work it was found that 4′-fluoro-3-(1-piperidyl)propiophenone (**1**) had marked central muscle relaxant activity. It selectively blocked the polysynaptic reflexes at 5 to 10 mg/kg iv without having any effect on the monosynaptic patellar reflex. It produced flaccid paralysis in unanesthetized animals. This molecule was, therefore, used as the prototype and the results recorded in Table I show the effect of structural modifications on the biological activity.

It was found that changing the position of F to position 2′ (**8**) considerably reduced the activity. Replacing F by Me (**12**), OBu (**15**), and 2′,4′-Me_2 (**16**) groups gave compounds which had significant activity though of a lower order than that of the F analog. Replacing it by electron-withdrawing substituents like CH_3SO (**21**), CH_3SO_2 (**22**), NO_2 (**23**), and CF_3 (**24**), however, caused complete loss of this activity. An F substituent in an aromatic system has a dual effect—it can withdraw electrons by its inductive effect and donate electrons by its mesomeric effect. The biological activity indicated that the radical in these compounds had an electron-releasing effect, which is also supported by the ir spectral study reported above. Another variation studied to determine the role of electronic character of the substituent in the aryl residue was a study of the activity of 1-(4-pyridyl)-3-(1-piperidyl)propan-1-one (**30**), this compound had no central muscle relaxant or CNS depressant action. This would indicate that electron-withdrawing groups in 4′ position of the propiophenones reduced the central muscle relaxant activity.

Reduction of the ketones to the alcohols (**31–36**) led to a considerable drop in activity. Replacement of CO by SO or SO_2 (**26**, **27**) completely obviated the central muscle relaxant activity. Some of these compounds, *e.g.*, 4-methylphenyl 2-(4-morpholinyl)ethyl sulfoxide (**26**) and its 4-fluoro analog (**81**), however, had moderate anticonvulsant activity. The position of the piperidyl residue in relation to the CO function had a marked effect on the activity. The corresponding 2-piperidylpropiophenone (**37**) had no depressant or central muscle relaxant activity. Introduction of Me on either of the alkanone residue (**9**, **10**) considerably reduced the activity. Replacement of $C_5H_{10}N$ by morpholino (**5**) had a similar effect. Ring enlargement to the corresponding hexamethyleneimino residue (**7**) caused a certain amount of reduction of this activity; compound **7**, however, had significant adrenergic receptor blocking activity. Introduction of Me at position 2 (**2**) or 3 (**3**) or Ph at position 4 (**4**) of the piperidyl residue caused reduction in activity. The 4-phenylpiperidyl compound (**4**), however, had a significant central depressant, antiamphetamine, and adrenergic receptor blocking activity.

The cyclization of the alkanone residue to form a 3-piperidylindan-1-one (**29**) also abolished the central muscle relaxant activity.

Hemolytic and Local Anesthetic Activities.—As mephenesin is known to cause hemolysis, the hemolytic activity of our compounds was investigated and compared with that of mephenesin (Table I). Some of the compounds (**1**, **2**, **5**, and **7**) which had significant central muscle relaxant activity, had much less hemolytic activity than mephenesin. Like mephenesin, many of these compounds showed local anesthetic activity. However, there was no correlation between the local anesthetic activity and the central muscle relaxant action of these compounds.

4′-Fluoro-3-(1-piperidyl)propiophenone (**1**) because of its potent central muscle relaxant activity, and 2′,4′-

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(8) G. Kränzlein, J. Heyna, and W. Schumacher, German Patent 842,198 (June 23, 1952); *Chem. Abstr.*, **47**, 11244 (1953).

(9) E. L. Holmes, C. K. Ingold, and E. H. Ingold, *J. Chem. Soc.*, 1684 (1926).

(10) L. B. Witkin, P. Spitaletta, and A. J. Plummer, *Arch. Int. Pharmacodyn. Ther.*, **124**, 105 (1960).

(11) S. J. De Salva and Y. T. Oester, *ibid.*, **124**, 255 (1960).

(12) S. Kuna and A. O. Seeler, *J. Pharmacol.*, **90**, 181 (1947).

(13) E. F. Domino, K. R. Unna, and J. Kerwin, *J. Pharmacol. Exp. Ther.*, **105**, 486 (1952).

TABLE I

Compound[a]	Yield, %	Bp or mp, °C	Formula	Analysis	LD_{50}, mg/kg mice ip	Effect on flexed reflex: Dose, mg/kg iv	Block % of mephenesin	Duration (min)	Local anesthetic activity and duration (min)	Hemolytic activity *in vitro* (dog blood at 0.66%)	Other noteworthy effects
Mephenesin						31	100	100	Complete (20)	++++	
4′-Fluoro-3-(1-piperidyl)-propiophenone (**1**)	65	181–190[c]	$C_{14}H_{18}FNO \cdot HCl$	N	151	10	239	100	Complete (30)	0	Depressant, marked central muscle relaxant action
4′-Fluoro-3-(2-methyl-1-piperidyl)propiophenone	60	180	$C_{15}H_{20}FNO \cdot HCl$	C,H,N	151	10	110	60	Partial	0	Depressant, mild diuretic and analgesic
4′-Fluoro-3-(3-methyl-1-piperidyl)propiophenone	78	181	$C_{15}H_{20}FNO \cdot HCl$	C,H,N	134	10	0				Depressant, weak antireserpine activity at 20 mg/kg ip
4′-Fluoro-3-(4-phenyl-1-piperidyl)propiophenone	55	188	$C_{20}H_{22}FNO \cdot HCl$	C,H,N	186	10	91		Complete (15)		Depressant, adrenolytic, antiamphetamine (toxicity 70% protection at 40 mg/kg ip and po)[d]
4′-Fluoro-3-(4-morpholinyl)propiophenone	65	215[b]	$C_{13}H_{16}FNO_2 \cdot HCl$	N	1000	10	135	40	0	++	Depressant
4′-Fluoro-3-(2-tetrahydroisoquinolinyl)-propiophenone	60	178	$C_{18}H_{16}FNO \cdot HBr$	N	400	10	15	15	Complete (10)	+++	Depressant
4′-Fluoro-3-(1-hexamethyleneimino)propiophenone	69	162	$C_{15}H_{20}FNO \cdot HCl$	C,H,N	190	5	1111	760	0	0	Depressant, hypotensive, weak anticonvulsant, antiadrenergic ganglion blocking and mild antiamphetamine activity
2′-Fluoro-3-(1-piperidyl)propiophenone	62	182	$C_{14}H_{18}FNO \cdot HCl$	C,H,N	100	10	40	50	Complete (10)		Mild anticonvulsant
4′-Fluoro-2-methyl-3-(1-piperidyl)propiophenone	55	188[c]	$C_{15}H_{20}FNO \cdot HCl$	C,H,N	222	5	70	60	0	0	Depressant
4′-Fluoro-3-(1-piperidyl)butyrophenone	80	151	$C_{15}H_{20}FNO \cdot HCl$	C,H,N	210	10	20	20			Tremors
4′-Fluoro-3-(4-phenyl-1-piperazinyl)butyrophenone (**11**)	70	164–165	$C_{20}H_{23}FN_2O \cdot 2HCl$	C,H,N	200						Depressant anti-electroshock, anti-amphetamine, blocked CAR at 40 mg/kg ip
4′-Methyl-3-(1-piperidyl)propiophenone	65	175[d]	$C_{15}H_{21}NO \cdot HCl$	C,H,N	134	10	50	760	Complete (7)		Depressant
4′-Ethoxy-3-(1-hexamethyleneimino)propiophenone	61	163	$C_{17}H_{25}NO_2 \cdot HCl$	N	175	5	118	90			Stimulant
4′-Ethoxy-2-methyl-3-(hexamethyleneimino)propiophenone	70	156	$C_{18}H_{27}NO_2 \cdot HCl$	N	300	5	50	100			Stimulant
4′-*n*-Butoxy-3-(1-piperidyl)propiophenone	61	175[c]	$C_{18}H_{27}NO_2 \cdot HCl$	N	130	2.5	80	30	Complete (25)	++++	Depressant
2′,4′-Dimethyl-3-(1-piperidyl)propiophenone	40	177	$C_{16}H_{23}NO \cdot HCl$	N	150	5 5	137 93	90 760	Complete (12)	++++	Depressant
2′,4′-Dimethyl-3-(4-morpholinyl)propiophenone	45	204	$C_{15}H_{21}NO_2 \cdot HCl$	N	500	10	91	50	Complete	++++	Depressant, significant diuretic in rats and dogs
2′,4′-Dimethyl-2-methyl-3-(1-piperidyl)propiophenone	48	174	$C_{17}H_{25}NO \cdot HCl$	C,H,N	175	5	88	45	Complete (12)	++++	
3′,4′-Dichloro-3-(1-piperidyl)propiophenone	52	241	$C_{14}H_{15}Cl_2NO \cdot HCl$	C,H,N	500	5	33	60			Depressant
3′,4′-Dichloro-3-(4-morpholinyl)propiophenone	63	160	$C_{13}H_{15}Cl_2NO_2 \cdot HCl$	C,H,N		5	0		Complete (5)		
4′-Methylsulfinyl-3-(1-piperidyl)propiophenone (**21**)	67	212	$C_{15}H_{21}NO_2S \cdot HCl$	C,H,N	100	10	0				Weak anticonvulsant
4′-Methylsulfonyl-3-(1-piperidyl)propiophenone	85	218	$C_{15}H_{21}NO_3S \cdot HCl$	C,H,N	400	10	9				Depressant
4′-Nitro-3-(1-piperidyl)-propiophenone	62	201[e]	$C_{14}H_{18}N_2O_3 \cdot HCl$	N	91						Weak anticonvulsant and antiamphetamine
4′-Trifluoromethyl-3-(1-piperidyl)propiophenone	79	197	$C_{15}H_{18}F_3NO \cdot HCl$	C,H,N	210	10	0				

Table I (*Continued*)

Compound[g]	Yield, %	Bp or mp, °C	Formula	Analysis	LD_{50} mg/kg mice ip	Effect on flexe-reflux: Dose mg/kg iv	Block % of Meph-enesin	Duration (min)	Local anesthetic activity and duration (min)	Hemolytic activity *in vitro* (dog blood at 0.66%)	Other noteworthy effects
4-Methylphenyl 2-(1-piperidyl)ethyl sulfoxide	63	211	$C_{14}H_{21}NOS \cdot HCl$	C,H,N	62	10	0		0		
4-Methylphenyl 2-(4-morpholinyl)ethyl sulfoxide	68	217	$C_{13}H_{19}NO_3S \cdot HCl$	C,H,N	800	10	60	60			Weak anticonvulsant
4-Fluorophenyl 2-(1-piperidyl)ethyl sulfone	89	218	$C_{13}H_{18}FNO_2S \cdot HCl$	C,H,N	280	10	20	25			Weak analgetic, anticonvulsant
4-Fluorophenyl 2-(4-morpholinyl)ethyl sulfone	81	238	$C_{12}H_{16}FNO_3S \cdot HCl$	C,H,N	800	10	30	60			Depressant
3-(1-Piperidyl)-5-methylindan-1-one	44	207	$C_{15}H_{19}NO \cdot HCl$	C,H,N	422	10	0				
1-(4-Pyridyl)-3-(1-piperidyl)propan-1-one	45	Oil	$C_{13}H_{18}N_2O$	C,H,N		10	0				
1-(4-Fluorophenyl)-3-(1-piperidyl)propan-1-ol (**31**)	87	54	$C_{14}H_{20}FNO$	C,H,N	200	10	0		0	0	Hyperreflexia
1-(4-Fluorophenyl)-3-(2-methyl-1-piperidyl)propan-1-ol	83	137	$C_{15}H_{22}FNO \cdot HCl$	C,H,N	150	10	80	60			Caused a nonspecific block of reflexes
1-(4-Fluorophenyl)-2-methyl-3-(1-piperidyl)propan-1-ol	91	182	$C_{15}H_{22}FNO \cdot HCl$	C,H,N	295	10	0		0	0	Depressant
1-(4-Methylphenyl)-3-(1-piperidyl)propan-1-ol	89	82	$C_{15}H_{23}NO$	C,H,N	250	5	50	25	Complete (10)	0	Stimulant
1-(4-Methylphenyl)-2-methyl-3-(1-piperidyl)propan-1-ol	87	175	$C_{16}H_{25}NO \cdot HCl$	C,H,N	200	5	40	30	Complete (12)	0	Stimulant
1-(2,4-Dimethylphenyl)-2-methyl-3-(1-piperidyl)propan-1-ol	90	212	$C_{17}H_{27}NO \cdot HCl$	C,H,N	150	5	60	35	Complete (15)	0	
4′-Fluoro-2-(1-piperidyl)propiophenone	79	156 (6 mm)	$C_{14}H_{18}FNO$	N	350						
4′-Methyl-2-(1-piperidyl)propiophenone	88	168 (5 mm) 211	$C_{15}H_{21}NO$ $C_{15}H_{21}NO \cdot HCl$	N N	200	5	0		Complete (5)	+++	Stimulant
4′-Hydroxy-2-(4-morpholinyl)propiophenone	70	206	$C_{13}H_{17}NO_3 \cdot HBr$	N	750	10			0	++	Stimulant
2′,4′-Dimethyl-2-(1-piperidyl)propiophenone	86	158	$C_{16}H_{23}NO \cdot HCl$	C,H,N	250	10	100	40	Complete (15)	++++	
3′,4′-Dihydroxy-2-(1-piperidyl)propiophenone (**41**)	76	234	$C_{14}H_{19}NO_3 \cdot HBr$	N	300	10	0	0	0	0	

[a] E. D. Taylor and W. L. Nobles, *J. Amer. Pharm. Ass. Sci. Ed.*, **49**, 317 (1960), mp 190°; [b] *ibid.*, mp. 215–217°; [c] L. Beregi, P. Hugon, and J. C. Le Douarec, French Patent M1459 (Sept. 24, 1962); *Chem. Abstr.*, **60**, 1716 (1964), mp. 208–209°; [d] D. W. Adamson, P. A. Barrett, J. W. Billinghurst, and T. S. G. Jones, *J. Chem. Soc.*, 312 (1958), mp 175°; [e] E. Profft, *Chem. Tech.*, **4**, 241 (1952), mp. 175–176°; [f] W. B. Wheatley, W. E. Fitzgibbon Jr., and L. C. Cheney, *J. Amer. Chem. Soc.*, **76**, 4490 (1954), mp. 198–200°. [g] The compounds are listed in numerical order (**1**–**41**) with the number of every tenth compound being given in parentheses after the name.

dimethyl-3-(4-morpholinyl)propiophenone (**17**), in view of its diuretic activity, were studied in detail.

4′-Fluoro-3-(1-piperidyl)propiophenone (1).—In mice (ip) it produced paralysis followed by ataxia at increasing doses. There was dragging of hind limbs, loss of righting reflex, loss of pinna reflex, but corneal reflex was intact. At lethal doses gasping respiration and cyanosis were observed. The compound was well absorbed orally, LD_{50} by this route being 350 mg/kg. Rabbits at 10 mg/kg iv showed complete flaccid paralysis of the hind limbs (hind drop) after an initial rigidity. The knee-jerk response was normal, pinna reflex was absent, and corneal reflex was intact. No head drop was seen.

In rats at a dose of 12.5 mg/kg ip **1** produced a weak analgetic activity. At 0.25 LD_{40} in mice it caused 100% potentiation of the hypnosis produced by 40 mg/kg ip of Na pentobarbital. At a dose of 10 mg/kg ip **1** antagonized 75% amphetamine (100 mg/kg ip) induced toxicity in grouped mice. At this dose in rats it showed 15% block of the conditioned avoidance reflex. At 50 mg/kg ip it blocked the tonic extensor component of the convulsions caused by pentylenetetrazole (90 mg/kg sc) and strychnine sulfate (1.5 mg/kg sc), and at 30 mg/kg ip it prevented the tonic extensor phase of the electroshock seizure (48 MA, 0.2 sec). Its local anesthetic activity was of the same order as of procaine·HCl. It had weak antihistaminic activity.

In chloralosed (80 mg/kg iv) cats at 10 mg/kg **1** completely abolished the flexer and linguomandibular reflex for 60–90 min, but was without any effect on the monosynaptic patellar reflex. At 10 mg/kg iv it also abolished the facilitation of the patellar reflex produced by reticular formation stimulation and by the contralateral sciatic nerve stimulation and potentiated the inhibition of patellar reflex produced by the ipsilateral

Table II
Diuretic Action of 17 in Rats

Compound	Dose, mg/kg	Mean urine volume, ml/day	Mean Na+ output μequiv/day	Mean K+ output μequiv/day	Mean Cl− output μequiv/day
Control[a]		10.70	0.46	1.50	1.50
Hydrochlorothiazide	2.5	23.20	1.80	2.70	3.50
17	2.0	18.0	0.80	2.80	2.80

[a] Sixteen animals were used in each group.

Table III
Diuretic Action of 17 in Dogs

Compound	Dose, mg/kg	Mean urine volume, ml/kg per day	Mean Na+ output μequiv/kg per day	Mean K+ output μequiv/kg per day
Control[a]		20.32	0.528	1.09
Hydrochlorothiazide[b]	25	38.15	3.07	2.87
17[b]	25	31.65	1.77	3.06

[a] Number of animals used was 30. [b] Number of animals used was 8.

sciatic nerve stimulation. These results showed that this compound has a specific polysynaptic blocking activity both at the spinal and supra-spinal levels. It is about twice as potent as mephenesin as a centrally acting muscle relaxant in the laboratory animals. Moreover, unlike mephenesin, it had no hemolytic activity which gives this compound a distinct advantage over mephenesin as a central muscle relaxant.

Diuretic Activity.—In routine pharmacological screening in rats 2′,4′-dimethyl-3-(4-morpholinyl)propiophenone (**17**) was found to possess significant diuretic activity and also produced a mild hypotensive response. This is an interesting new structural lead for diuretic activity. This led to the synthesis of analogs and homologs of this compound, and to a detailed analysis of the diuretic activity of this compound. A number of compounds which include **5, 16, 49, 50, 53, 54, 55, 58, 59, 60, 62, 64, 74,** and **80,** were tested for diuretic activity. Surprisingly none of these compounds had any diuretic activity and all molecular modifications carried out so far resulted in a loss of this activity. The diuretic activity of **17** thus seems to be very specific for this molecular structure. Its LD_{50} in rats was 140 mg/kg ip and 920 mg/kg po. The results of the diuretic testing of **17** in rats and dogs are recorded in Tables II and III, respectively. The urine output with **17** was comparable to that with hydrochlorothiazide. However greater K excretion as compared to Na seems a disadvantage.

Antimicrobial Activity.—Selected compounds were also submitted to antimicrobial screening. The compounds did not show significant antibacterial activity but some of them showed significant antifungal activity.

Antiviral Activity.—Some of the compounds (**1, 5, 6, 9, 16,** and **103**) were tested against Ranikhet disease virus and Vaccinia virus in chorioallantoic membrane culture. None of the compounds showed activity against Vaccinia virus but two of them (**1** and **5**) showed activity against Ranikhet disease virus. Compound **1** was tested when given to the cultures before, along with, and after inoculation of the virus. It was found that 75 μg/ml of **1** could significantly inhibit the virus growth when given within 1 hr of infection with 0.064 HA units/ml of the virus.

Antifungal Activity.—The results of antifungal screening are recorded in Table IV. Some of the compounds had a broad spectrum antifungal activity, being particularly active against dermatophytes. In general the 3-morpholino- and 3-piperidinopropiophenones **1, 5, 16, 17, 49, 50, 60,** and **80** showed good antifungal activity. Activity was abolished if CO was reduced to CHOH (**74**) or if CO was replaced by SO (**81**) or SO_2 (**28**). Branching at C-2 (**55**) decreased the activity but branching at C-3 (**58**) did not materially effect the activity. Increasing the alkyl chain to 3 C atoms as in butyrophenones (**59**) resulted in a complete loss of activity. 4′-Fluoro-3-(4-morpholinyl)-propiophenone (**5**) was also tested against a number of other fungi. It was found to inhibit markedly the growth of *Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitids,* and *Nocardia asteroides,* thus being active both against dermatophytes and systemic fungi with a rather poor activity against yeast-like fungi.

Experimental Section

The compounds were checked routinely by ir spectroscopy; tlc was carried out on silica gel G plates and the spots detected by exposure to I_2 vapors; the melting points were determined in an H_2SO_4 bath and are uncorrected.

The preparations described below illustrate the general methods of synthesis employed. Those new compounds for which the biological activity data is described are included in Table I; others are described in Table V; the intermediates not reported before are described in the procedures.

2-*t*-Aminopropiophenones.—All the propiophenones used were prepared by known methods. The synthesis of **3′,4′-dimethoxy-2-(4-methyl-1-piperazinyl)propiophenone (105)** is typical of the general method followed for the preparation of various 2-*t*-aminopropiophenones listed in Tables I and V.

A solution of *N*-methylpiperazine (10.00 g, 0.10 mol) in dry C_6H_6 (10 ml) was added dropwise to an ice-cold solution of 2-bromopropioveratrone (13.65 g, 0.05 mol) in dry C_6H_6 (100 ml), and the mixture was allowed to stand at room temperature for 8 hr, followed by heating on a steam-bath for 2 hr. *N*-Methylpiperazine·HBr was filtered, and the filtrate was washed with H_2O, and then extracted with 2 *N* HCl. The acid layer was basified with NH_4OH, extracted with Et_2O, the extract dried (Na_2SO_4), and the solvent removed. The residue was distilled under vacuum to give the required compound, yield 12.90 g (88.4%).

Compound **105** was also prepared by refluxing *N*-methylpiperazine (5.00 g, 0.05 mol) and 2-bromopropioveratrone (13.65 g, 0.05 mol) in C_6H_6 (100 ml) in the presence of anhydrous K_2CO_3 (15 g) and working up in the usual manner, yield 11.95 g (80%).

3′,4′-Dihydroxy-2-(4-methyl-1-piperazinyl)propiophenone (106).—A solution of **105** (5.84 g, 0.02 mol) in 48% HBr (10 ml) was gently refluxed for 6 hr. Excess HBr was removed under

Table IV

Compound	*Candida albicans*	*Cryptococcus neoformans*	*Trichophyton mentagrophytes*	*Microsporum canis*	*Aspergillus niger*
49	+[a]	1:40,000	1:320,000	1:160,000	+
50	1:20,000	1:80,000	1:160,000	1:320,000	1:40,000
80	+	1:80,000	1:40,000	1:80,000	1:40,000
60	1:40,000	1:40,000	1:160,000	1:320,000	1:20,000
17	+	+	1:320,000	1:160,000	+
74	+	+	+	+	+
16	+	+	1:80,000	1:160,000	1:20,000
55	+	+	1:160,000	1:160,000	+
59	+	+	+	+	+
58	+	1:40,000	1:320,000	1:160,000	1:40,000
62	+	+	1:20,000	1:40,000	+
64	+	+	+	+	+
26	+	+	+	+	+
28	+	+	+	+	+
85	+	+	+	+	+
5	+	+	1:160,000	1:160,000	+
1	+	+	1:160,000	1:320,000	+

[a] + = Good growth, no activity Maximum concentration of the compound tested was 1:10,000. The compound did not alter the pH of the broth.

reduced pressure and the residue was crystallized from EtOH–Et_2O to give **106** as light grey needles, yield 6.65 g.

2-*t*-Amino-1-phenylpropan-1-ols.—These were prepared from the corresponding propiophenones (I) by reduction with LAH (Et_2O) and worked up in the usual way.

3-*t*-Aminopropiophenones.—The synthesis of 4′-fluoro-3-(1-hexamethyleneimino)propiophenone (7) is representative of the general procedure[14] followed for the synthesis of 3-*t*-aminopropiophenones.

A solution of 4-fluoroacetophenone (6.90 g, 0.05 mol), hexamethyleneimine·HCl (6.78 g, 0.05 mol) and paraformaldehyde (2.25 g, 0.075 mol) in absolute EtOH (70 ml) containing a few drops of concentrated HCl, was refluxed for 2 hr. After cooling the solution and adding a further quantity of paraformaldehyde (1.50 g, 0.05 mol), the refluxing was continued for another 3 hr. The mixture was then concentrated under reduced pressure, H_2O was added to the residue, and the oil which separated was extracted with Et_2O. The Et_2O layer was extracted with 3 *N* HCl (3 × 50 ml); the acid layer was basified with NH_4OH; the liberated base was extracted with Et_2O; the extract was dried (Na_2SO_4); the solvent was removed; and the residue was converted into its hydrochloride, yield 9.75 g.

3-*t*-Amino-1-phenylpropan-1-ols.—These were prepared from the corresponding propanones by reduction with LAH (Et_2O) or $NaBH_4$ (MeOH) and the product worked up in the usual manner.

1-(4-*n*-Butoxyphenyl)-3-(1-piperidyl)prop-1-ene (134).—4′-*n*-Butoxy-3-(1-piperidyl)propiophenone (**15**) (2.25 g, 0.01 mol) was reduced with LAH (0.75 g, 0.02 mol) in Et_2O and worked up in the usual manner. The product after purification by chromatography over a column of basic alumina with C_6H_6 as eluant was obtained as a colorless viscous oil. *Anal.* ($C_{18}H_{27}NO$) C, H, N. Its hydrochloride had mp 197–198° (EtOH–Et_2O), uv λ_{max} C_2H_5OH 269 mμ (log ε = 4.24). *Anal.* ($C_{18}H_{27}NO \cdot HCl$) C, H.

4-Fluorophenyl 2-Hydroxyethyl Sulfide (135).—To a solution of 4-fluorobenzenethiol (64.5 g, 0.5 mol) in 10% NaOH (200 ml) was gradually added 2-chloroethanol (48.3 g, 0.6 mol), the reaction mixture was refluxed for 30 min and allowed to cool when an oily layer separated. It was then extracted with Et_2O (3 × 100 ml), the extract was washed with H_2O to neutrality and dried (Na_2SO_4). Removal of solvent furnished a colorless oil, bp 130° (10 mm), yield 77.5 g (90.2%). *Anal.* (C_8H_9FOS) C, H.

4-Fluorophenyl 2-Chloroethyl Sulfide (136).—To a vigorously stirred solution of **135** (17.2 g, 0.1 mol) in dry pyridine (7.9 g, 0.1 mol), $SOCl_2$ (14.28 g, 0.12 mol) was added dropwise. A precipitate was formed after about half of the $SOCl_2$ had been added but redissolved on further addition forming two layers. SO_2 was removed on a steam bath. The reaction mixture was cooled and extracted with Et_2O (3 × 50 ml). The extract was washed (10% Na_2CO_3 solution, H_2O), dried (Na_2SO_4), and solvent was removed. Distillation of the residue gave a colorless liquid, bp 120° (20 mm), yield 17.7 g (93%). *Anal.* (C_8H_8ClFS) C, H.

4-Fluorophenyl 2-Chloroethyl Sulfoxide (137).—Fuming HNO_3 (1.36 g) in Ac_2O (6 ml) was added slowly under stirring to a solution of **136** (7.62 g, 0.04 mol) in Ac_2O (25 ml) below 5°. The reaction mixture was kept at 0–5° for another 12 hr, diluted with H_2O, (200 ml), and rendered faintly alkaline with 2 *N* NaOH. It was then extracted with Et_2O, the extract washed with H_2O and dried (Na_2SO_4). Removal of solvent gave a colorless oil which tended to decompose on distillation under vacuum. It was, therefore, purified by passing through a small column of silica gel with C_6H_6 as eluant. *Anal.* (C_8H_8ClFOS) C, H.

4-Fluorophenyl 2-(4-Morpholinyl)ethyl Sulfoxide (81).—A solution of **137** (4.13 g, 0.02 mol) and morpholine (3.48 g, 0.04 mol) in C_6H_6 (40 ml) was refluxed for 12 hr and worked up in the usual way, yield 3.5 g.

Methylphenyl Vinyl Sulfone.—Methylphenyl vinyl sulfone was prepared according to Kränzlein, *et al.*,[8] mp 66° (lit.[8] mp 65–66°)

4-Fluorophenyl 2-Hydroxyethyl Sulfone (138).—Sodium 4-fluorobenzenesulfinate (18.2 g, 0.1 mol), prepared by the reduction of 4-fluorobenzenesulfonyl chloride,[15] was dissolved in 2 *N* NaOH (20 ml) and heated to 60°. 2-Chloroethanol (10.5 g, 0.14 mole) was then slowly added and the contents, were refluxed for 4 hr on a steam bath. The organic layer which separated was extracted with Et_2O, the extract washed with H_2O, and dried (Na_2SO_4). The solvent was removed and distillation of the residue under vacuum gave a colorless liquid, bp 202–203° (10 mm), yield 17.35 g (85%). *Anal.* ($C_8H_9FO_3S$), C, H.

4-Fluorophenyl Vinyl Sulfone (139).—Compound **138** (20.4 g, 0.1 mol) was added with stirring to concentrated H_2SO_4 (14.0 ml) at 50–70°. The contents were stirred for an additional 1 hr at room temperature and poured onto crushed ice, extracted with EtOAc to remove unreacted **138,** and the aqueous layer was basified with 2 *N* NaOH. The separated oil was extracted with EtOAc (3 × 50 ml), the extract washed (H_2O) to neutral and dried (Na_2SO_4) and the solvent removed. The residue was distilled under vacuum to give a colorless oil, bp 149–150° (5 mm), yield 10.6 g (57%). *Anal.* ($C_8H_7FO_2S$) C, H.

4-Fluorophenyl 2-(1-Piperidyl)ethyl Sulfone (27).—A solution of **139** (5.58 g, 0.03 mol) and piperidine (3.02 g, 0.036 mol), in EtOH (25 ml) containing AcOH (0.1 ml) was kept at room temperature for 30 hr. EtOH was removed by distillation under reduced pressure, H_2O was added, the oil taken up in Et_2O, and the organic layer extracted with 3 *N* HCl (3 × 30 ml). The acid layer was basified, extracted with Et_2O; the extract was washed with H_2O, dried (Na_2SO_4); the solvent was removed; the product was converted into its hydrochloride and crystallized from EtOH–Et_2O, yield 8.2 g.

4-Fluorocrotonophenone (140).—Crotonyl chloride (10.45 g,

(14) (a) C. Mannich and G. Heilner, *Ber.*, **55**, 356 (1922); (b) F. F. Blicke and J. H. Burckhalter, *J. Amer. Chem. Soc.*, **64**, 451 (1942).

(15) G. Oláh and A. Pavláth, *Acta Chim. Acad. Sci. Hung.*, **4**, 111 (1954).

TABLE V

Compound[a]	Yield, %	Mp or bp, °C	Formula	Analysis
3′-Fluoro-3-(1-piperidyl)propiophenone (**42**)	61	167	$C_{14}H_{18}FNO \cdot HCl$	C,H,N,
3′-Fluoro-3-(4-phenyl-1-piperidyl)propiophenone	53	165	$C_{20}H_{22}FNO \cdot HCl$	C,H,N,
4′-Fluoro-2-methyl-3-(4-methyl-1-piperazinyl)propiophenone	63	165–166	$C_{15}H_{22}FN_2O \cdot 2HCl$	C,H,N,
4′-Fluoro-3-(2-methyl-1-piperidyl)butyrophenone	50	153	$C_{16}H_{22}FNO \cdot HCl$	C,H,N
4′-Fluoro-3-(4-hydroxy-4-phenyl-1-piperidyl)butyrophenone	65	215	$C_{21}H_{24}FNO_2 \cdot HCl$	C,H,N
4′-Fluoro-3-(4-morpholinyl)butyrophenone	73	167	$C_{14}H_{18}FNO_2 \cdot HCl$	C,H,N
4′-Fluoro-3-(hexamethyleneimino)butyrophenone	52	147	$C_{16}H_{22}FNO \cdot HCl$	C,H,N
4′-Methyl-3-(4-morpholinyl)propiophenone[c]	70	223[b]	$C_{14}H_{19}NO_2 \cdot HCl$	N
2′-Methyl-3-(4-morpholinyl)propiophenone	73	183	$C_{14}H_{19}NO_2HCl$	C,H,N
4′-Ethoxy-2-methyl-3-(1-piperidyl)propiophenone	60	181	$C_{17}H_{25}NO_2 \cdot HCl$	C,H,N
4′-Ethoxy-2-methyl-3-(4-methyl-1-piperazinyl)propiophenone (**52**)	57	196	$C_{17}H_{26}N_2O_2 \cdot 2HCl$	C,H,N
3′,4′-Dimethyl-3-(4-morpholinyl)propiophenone	42	174	$C_{15}H_{21}NO \cdot HCl$	C,H,N
2′,5′-Dimethyl-3-(4-morpholinyl)propiophenone	59	163	$C_{15}H_{21}NO_2HCl$	C,H,N
2′,4′-Dimethyl-2-methyl-3-(4-morpholinyl)propiophenone	55	187	$C_{16}H_{23}NO_2 \cdot HCl$	N
N-2-(4-Morpholinyl)ethyl 2,4-dimethylbenzenesulfonamide	48	228	$C_{14}H_{22}N_2O_3S \cdot HCl$	N
2′,4′-Dimethyl-3-(1-piperidyl)butyrophenone	75	176–177	$C_{17}H_{25}NO \cdot HCl$	C,H,N
2′,4′-Dimethyl-3-(4-morpholinyl)butyrophenone	78	153	$C_{16}H_{23}NO_2 \cdot HCl$	C,H,N
2′,4′-Dimethyl-4-(4-morpholinyl)butyrophenone	53	170	$C_{16}H_{23}NO_2 \cdot HCl$	C,H,N
2′,4′-Dimethoxy-3-(4-morpholinyl)propiophenone	58	171	$C_{15}H_{21}NO_4HCl$	N
3′,4′-Diethoxy-2-methyl-3-(1-piperidyl)propiophenone	51	182	$C_{19}H_{29}NO_3 \cdot HCl$	N
4′-Methylsulfinyl-3-(4-morpholinyl)propiophenone (**62**)	70	188	$C_{14}H_{19}NO_3S \cdot HCl$	C,H,N
4′-Methylsulfinyl-3-(4-methyl-1-piperazinyl)propiophenone	62	197–198	$C_{15}H_{22}N_2O_2S \cdot 2HCl$	C,H,N
4′-Methylsulfonyl-3-(4-morpholinyl)propiophenone	76	121	$C_{14}H_{19}NO_4S$	C,H,N
4′-Methylsulfonyl-3-(4-methyl-1-piperazinyl)propiophenone	61	219	$C_{15}H_{22}N_2O_3S \cdot 2HCl \cdot H_2O$	C,H,N
1-(4-Fluorophenyl)-3-(4-morpholinyl)propan-1-ol	83	178 (3 mm)	$C_{13}H_{18}FNO_2$	N
1-(4-Fluorophenyl)-3-(3-methyl-1-piperidyl)propan-1-ol	87	135	$C_{15}H_{22}FNO \cdot HCl$	C,H,N
1-(4-Methoxyphenyl)-2-methyl-3-(1-piperidyl)propan-1-ol	87	158–160 (10^{-3} mm)	$C_{16}H_{25}NO_2$	N
4′-Methoxy-2-methyl-3-(4-morpholinyl)propiophenone	75	170	$C_{15}H_{21}NO_3 \cdot HCl$	N
1-(4-Ethoxyphenyl)-3-(1-piperidyl)propan-1-ol	87	196–198 (3 mm)	$C_{18}H_{29}NO_2$	N
1-(4-Ethoxyphenyl)-3-(1-hexamethyleneimino)propan-1-ol	76	193 (2 mm)	$C_{17}H_{27}NO_2$	N
1-(4-Ethoxyphenyl)-2-methyl-3-(1-piperidyl)propan-1-ol (**72**)	89	162–163	$C_{17}H_{27}NO_2 \cdot HCl$	C,H,N
1-(4-Ethoxyphenyl)-2-methyl-3-(1-hexamethyleneimino)propan-1-ol	82	185 (3 mm)	$C_{19}H_{31}NO_2$	C,H,N
1-(2,4-Dimethylphenyl)-3-(4-morpholinyl)propan-1-ol	95	171–172	$C_{18}H_{25}NO \cdot HCl$	C,H,N
1-(3,4-Dimethoxyphenyl)-2-methyl-3-(1-piperidyl)propan-1-ol	81	191–192	$C_{18}H_{31}NO_3 \cdot HCl$	C,H,N
1-(4-Methylsulfinylphenyl)-3-(4-morpholinyl)propan-1-ol	80	208	$C_{14}H_{21}NO_3S \cdot HCl$	C,H,N
1-(4-Methylsulfinylphenyl)-3-(4-methyl-1-piperazinyl)propan-1-ol	78	240	$C_{15}H_{24}N_2O_2S \cdot 2HCl$	C,H,N
1-(4-Methylsulfonylphenyl)-3-(4-morpholinyl)propan-1-ol	85	226	$C_{14}H_{21}NO_4S \cdot HCl$	C,H,N
1-(4-Methylsulfonylphenyl)-3-(4-methyl-1-piperazinyl)propan-1-ol	71	222	$C_{15}H_{24}N_2O_3S \cdot 2HCl$	C,H,N
3-(4-Morpholinyl)-5-methylindan-1-one	49	176	$C_{14}H_{17}NO_2 \cdot HCl$	C,H,N
4-Fluorophenyl 2-(4-morpholinyl)ethyl sulfoxide	60	204	$C_{12}H_{16}FNO_2S \cdot HCl$	C,H,N
4-Methylphenyl 2-(4-methyl-1-piperazinyl)ethyl sulfoxide (**82**)	55	201	$C_{13}H_{22}N_2OS \cdot 2HCl \cdot H_2O$	C,H,N
4-Fluorophenyl 2-(4-methyl-1-piperazinyl)ethyl sulfone	73	239	$C_{13}H_{19}FN_2O_2S \cdot 2HCl \cdot H_2O$	C,H,N
4-Fluorophenyl 2-(4-phenyl-1-piperazinyl)ethyl sulfone	76	231	$C_{18}H_{21}FN_2O_2S \cdot HCl$	C,H,N
4-Methylphenyl 2-(4-morpholinyl)ethyl sulfone	71	65	$C_{13}H_{19}NO_3S$	C,H,N
4-Methylphenyl 2-(4-methyl-1-piperazinyl)ethyl sulfone	73	72	$C_{14}H_{22}N_2O_2S$	C,H,N
4-Methylphenyl 2-(*N*-1,2,3,4-tetrahydroisoquinolinyl)ethyl sulfone	75	235	$C_{18}H_{21}NO_2S \cdot HCl$	C,H,N
2-(1-Hexamethyleneimino)propiophenone	39	162 (2 mm)	$C_{15}H_{21}NO$	N
4′-Fluoro-2-(1-pyrrolidyl)propiophenone	73	144 (4 mm)	$C_{13}H_{16}FNO$	N
4′-Fluoro-2-(4-morpholinyl)propiophenone	81	71	$C_{13}H_{16}FNO_2$	C,H,N
4′-Fluoro-2-(4-methyl-1-piperazinyl)propiophenone	85	157 (3 mm)	$C_{14}H_{19}FN_2O$	N
4′-Chloro-2-(1-pyrrolidyl)propiophenone (**92**)	54	168 (5 mm)[b]	$C_{13}H_{16}ClNO$	N
4′-Methyl-2-(pyrrolidyl)propiophenone	67	150 (4 mm)	$C_{14}H_{19}NO$	N
4′-Methoxy-2-(4-methyl-1-piperazinyl)propiophenone	50	54	$C_{15}H_{24}N_2O_2$	N
		238	$C_{15}H_{24}N_2O_2 \cdot 2HCl$	N
4′-Methoxy-2-(1-hexamethyleneimino)propiophenone	74	206 (5 mm)	$C_{16}H_{23}NO_2$	N
		240	$C_{16}H_{23}NO_2 \cdot HCl$	N
4′-Ethoxy-2-methylaminopropiophenone	62	152 (2 mm)	$C_{12}H_{17}NO_2$	N
4′-Ethoxy-2-(1-pyrrolidyl)propiophenone	75	176 (2 mm)	$C_{15}H_{21}NO_2$	N
4′-Ethoxy-2-(4-methyl-1-piperazinyl)propiophenone	53	47	$C_{16}H_{24}N_2O_2$	N
		207	$C_{16}H_{24}N_2O_2 \cdot 2HCl$	N
4′-Ethoxy-2-(1-hexamethyleneimino)propiophenone	77	192 (2 mm)	$C_{17}H_{25}NO_2$	N
		177	$C_{17}H_{25}NO_2 \cdot HCl$	C,H,N
4′-Ethoxy-2-(4-methyl-1-homopiperazinyl)propiophenone	73	190 (3 mm)	$C_{17}H_{26}N_2O_2$	N
4′-Hydroxy-2-dimethylaminopropiophenone	46	195	$C_{11}H_{15}NO_2 \cdot HBr$	N
4′-Hydroxy-2-(1-pyrrolidyl)propiophenone (**102**)	54	202	$C_{13}H_{17}NO_2 \cdot HBr$	C,H,N
4′-Hydroxy-2-(1-hexamethyleneimino)propiophenone	65	205	$C_{15}H_{23}NO_2 \cdot HBr$	N
3′,4′-Dimethoxy-2-(1-pyrrolidyl)propiophenone	77	192 (3 mm)	$C_{15}H_{21}NO_2$	N
		205	$C_{15}H_{21}NO_2 \cdot HCl$	N

Table V (*Continued*)

Compound[d]	Yield %	Mp or bp, °C	Formula	Analysis
3′,4′-Dimethoxy-2-(4-methyl-1-piperazinyl)propiophenone	88	196–197 (2 mm)	$C_{16}H_{24}N_2O_3$	C,H,N
3′,4′-Dihydroxy-2-(4-methyl-1-piperazinyl)propiophenone	75	167	$C_{14}H_{22}N_2O_3 \cdot 2HBr \cdot H_2O$	C,H,N
3′,4′-Dihydroxy-2-(4-phenyl-1-piperazinyl)propiophenone	83	193–195	$C_{19}H_{22}N_2O_3 \cdot 2HBr$	C,H,N
1-Phenyl-2-(1-piperidyl)propan-1-ol	85	150 (2 mm)	$C_{14}H_{21}NO$	N
		171	$C_{14}H_{21}NO \cdot HCl$	N
1-Phenyl-2-(4-methyl-1-piperazinyl)propan-1-ol	82	133	$C_{14}H_{22}N_2O$	N
		249	$C_{14}H_{22}N_2O \cdot HCl$	N
1-Phenyl-2-(1-hexamethyleneimino)propan-1-ol	87	176 (3 mm)	$C_{15}H_{23}NO$	N
1-(4-Fluorophenyl)-2-(1-pyrrolidyl)propan-1-ol	71	83	$C_{13}H_{18}FNO$	N
1-(4-Fluorophenyl)-2-(1-piperidyl)propan-1-ol (**112**)	84	113	$C_{14}H_{20}FNO$	N
		196	$C_{14}H_{20}FNO$	N
1-(4-Fluorophenyl)-2-(4-morpholinyl)propan-1-ol	90	95	$C_{13}H_{18}FNO$	N
1-(4-Fluorophenyl)-2-(4-methyl-1-piperazinyl)propan-1-ol	84	83[e]	$C_{14}H_{21}FN_2O$	N
		145[e]	$C_{14}H_{21}FN_2O$	N
1-(4-Chlorophenyl)-2-(1-pyrrolidyl)propan-1-ol	79	165 (3 mm)	$C_{13}H_{18}ClNO$	N
		212	$C_{13}H_{18}ClNO \cdot HCl$	N
1-(4-Methylphenyl)-2-(1-pyrrolidyl)propan-1-ol	79	175 (5 mm)	$C_{14}H_{21}NO$	N
1-(4-Methylphenyl)-2-(1-piperidyl)propan-1-ol	83	152 (2 mm)	$C_{15}H_{23}NO$	N
		190	$C_{15}H_{23}NO \cdot HCl$	N
1-(4-Methoxyphenyl)-2-dimethylaminopropan-1-ol	61	140 (2 mm)	$C_{12}H_{19}NO_2$	N
1-(4-Methoxyphenyl)-2-diethylaminopropan-1-ol	74	155 (3 mm)	$C_{14}H_{23}NO_2$	N
		161	$C_{14}H_{23}NO_2 \cdot HCl$	N
1-(4-Methoxyphenyl)-2-(1-piperidyl)propan-1-ol	82	185 (3 mm)	$C_{15}H_{23}NO_2$	N
		187	$C_{15}H_{23}NO_2 \cdot HCl$	N
1-(4-Methoxyphenyl)-2-(4-morpholinyl)propan-1-ol	79	99	$C_{14}H_{21}NO_3$	N
1-(4-Methoxyphenyl)-2-(1-hexamethyleneimino)propan-1-ol (**122**)	88	178 (3 mm)	$C_{14}H_{25}NO_2$	N
1-(4-Ethoxyphenyl)-2-methylaminopropan-1-ol	59	150 (3 mm)	$C_{12}H_{19}NO_2$	N
1-(4-Ethoxyphenyl)-2-diethylaminopropan-1-ol	76	162 (3 mm)	$C_{15}H_{25}NO_2$	N
		163	$C_{15}H_{25}NO_2 \cdot HCl$	N
1-(4-Ethoxyphenyl)-2-(1-pyrrolidyl)propan-1-ol	60	88	$C_{15}H_{23}NO_2$	N
1-(4-Ethoxyphenyl)-2-(4-morpholinyl)propan-1-ol	70	73–74	$C_{15}H_{23}NO_3$	N
		164	$C_{15}H_{23}NO_3 \cdot HCl$	N
4′-Ethoxy-2-(4-methyl-1-piperazinyl)propiophenone	71	89[e]	$C_{16}H_{26}N_2O_2$	C,H,N
		142–143[e]	$C_{16}H_{26}N_2O_2$	C,H,N
1-(4-Ethoxyphenyl)-2-(1-hexamethyleneimino)propan-1-ol	75	57	$C_{17}H_{27}NO_2$	N
		212	$C_{17}H_{27}NO_2 \cdot HCl$	C,H,N
1-(4-Ethoxyphenyl)-2-(4-methyl-1-homopiperazinyl)propan-1-ol	77	198 (3 mm)	$C_{17}H_{28}N_2O_2$	N
1-(4-Hydroxyphenyl)-2-(1-piperidyl)propan-1-ol	75	78	$C_{14}H_{21}NO_2$	N
		208	$C_{14}H_{21}NO_2HCl$	N
1-(2,4-Dimethylphenyl)-2-(1-piperidyl)propan-1-ol	91	189	$C_{16}H_{25}NO \cdot HCl$	C,H,N
1-(3,4-Dimethoxyphenyl)-2-(1-pyrrolidyl)propan-1-ol (**132**)	90	196 (5 mm)	$C_{15}H_{23}NO_2$	N
1-(3,4-Dimethoxyphenyl)-2-(1-piperidyl)propan-1-ol	92	195 (3 mm)	$C_{16}H_{24}NO_3$	N
		241	$C_{16}H_{24}NO_3 \cdot HCl$	N

[a] J. J. Denton, R. J. Turner, W. B. Neier, V. A. Lawson, and H. P. Schedl, *J. Amer. Chem. Soc.*, **71**, 2048 (1949), mp 224°. [b] A. J. Rottendorf, Chemische Fabrik, Belgian Patent 622,585 (Jan. 15, 1963); *Chem. Abstr.*, **59**, 2723 (1963), bp 117–119° (0.05 mm). [c] Distereoisomers were separated by fractional crystallization. [d] The compounds are listed in numerical order (**42–133**) with the number of every tenth compound being given in parentheses after the name.

0.1 mol) was added under vigorous stirring to a suspension of anhydrous $AlCl_3$ (13.35 g, 0.1 mol) in PhF (11.5 g, 0.12 mol) to 0° over a period of 30 min. After another 15 min the contents were worked up in the usual manner and the product distilled, bp 140° (10 mm), yield (based on crotonyl chloride) 9.85 g (60%). *Anal.* ($C_{10}H_{19}FO$) C, H.

4′-Fluoro-3-(4-phenyl-1-piperazinyl)butyrophenone (11).—A solution of **140** (4.92 g, 0.03 mol) and *N*-phenylpiperazine 4.86 g, 0.03 mol) in EtOH (35 ml) containing AcOH (5 drops) was left at room temperature for 30 hr, and the product worked up in the usual way. The residual oil was chromatographed over basic alumina (Grade I) using C_6H_6 as eluant. Compound **11** was eluted first, and converted into its dihydrochloride, yield 8.25 g.

2′,4′-Dimethyl-4-(4-morpholinyl)butyrophenone (59).—A solution of 4-chloro-2′,4′-dimethylbutyrophenone[16] (6.31 g, 0.03 mol) and morpholine (2.61 g, 0.03 mol) in C_6H_6 (60 ml) was refluxed for 12 hr and worked up as for **81**, and converted into its hydrochloride, yield 4.7 g.

5-Methylindan-1-one.—3-(3-Methylphenyl)propionic acid (8.4 g, 0.05 mol) was dissolved in PPA (160 g) and heated at 80° for 2 hr. After allowing to stand overnight at room temperature, it was poured over crushed ice, diluted with H_2O (300 ml); the separated oil was extracted with Et_2O; the extract was washed with 5% Na_2CO_3, dried (Na_2SO_4); the solvent was removed, and the residue crystallized from ligroin, mp 58° (lit.[17] mp 59–60°), yield 4.95 g (68%).

3-Bromo-5-methylindan-1-one (141).—A solution of 5-methylindan-1-one (2.92 g, 0.02 mol), NBS (3.84 g, 0.02 mol) and benzoyl peroxide (5 mg) in dry CCl_4 (75 ml) was refluxed for 4 hr and left overnight. The reaction mixture was chilled and succinimide precipitated during the reaction was removed by filtration. The filtrate was concentrated under reduced pressure and the residue was crystallized from C_6H_6–hexane, mp 63°, yield 2.7 g (60%). *Anal.* ($C_{10}H_9BrO$) C, H.

3-(1-Piperidyl)-5-methylindan-1-one (29).—A solution of **141** (2.25 g, 0.01 mol) in C_6H_6 (50 ml) was cooled to 5–10° and piperidine (1.70 g, 0.02 mol) in C_6H_6 (5 ml) was added dropwise with continuous stirring. The solution was stirred for another 30 min. Piperidine·HBr precipitated during the reaction was

(16) P. A. J. Janssen, *et al.*, *J. Med. Pharm. Chem.*, **1**, 281 (1959).

(17) J. v. Braun, G. Manz, and E. Reinsch, *Justus Liebigs Ann. Chem.*, **468**, 277 (1929).

filtered off and the filtrate was worked up in the usual way, and converted into its hydrochloride, yield 1.17 g.

N-(2-(4-Morpholinyl)ethyl)-2,4-dimethylbenzenesulfonamide (56).—To a solution of 2,4-dimethylbenzenesulfonamide 15.55 g, 0.03 mol) in 10% NaOH (30 ml) was added 2-morpholinoethyl chloride·HCl 15.52 g, 0.03 mol) and the mixture was refluxed for 3 hr. The mixture was cooled and extracted with Et_2O to remove unreacted morpholinoethyl chloride. The aqueous layer was acidified and extracted with EtOAc to remove unreacted dimethylbenzenesulfonamide. The acid layer was then basified to pH 7.5 and extracted with EtOAc, washed with H_2O, dried (Na_2SO_4), and the solvent was removed. The residual oil was converted into its hydrochloride, yield 4.8 g.

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1,2,3,4,5,6-Hexahydro-6-phenyl-2,6-methano-3-benzazocines. II[1-3]

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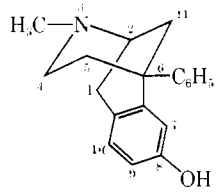
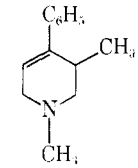
The synthesis of racemic 1,2,3,4,5,6-hexahydro-3,11β-dimethyl-6-phenyl-2,6-methano-3-benzazocin-8-ol (VIII) and of its optical isomers is described. Evidence is presented for the assignment of the β configuration of the 11-methyl substituent. The *l* isomer is a potent analgetic with mild nalorphine-like antagonistic properties in mice.

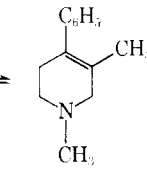
In the first paper of the series[1] the synthesis of 1,2,3,4,5,6-hexahydro-3-methyl-6-phenyl-2,6-methano-3-benzazocin-8-ol (I) was described. It was our hope that modification of the basic hexahydro-2,6-methano-3-benzazocine nucleus I would result in a more potent analgetic with interesting and advantageous properties. The synthetic scheme so successfully applied to the preparation of I again proved its value in the preparation of the corresponding compound with Me at C_{11}.[3]



I



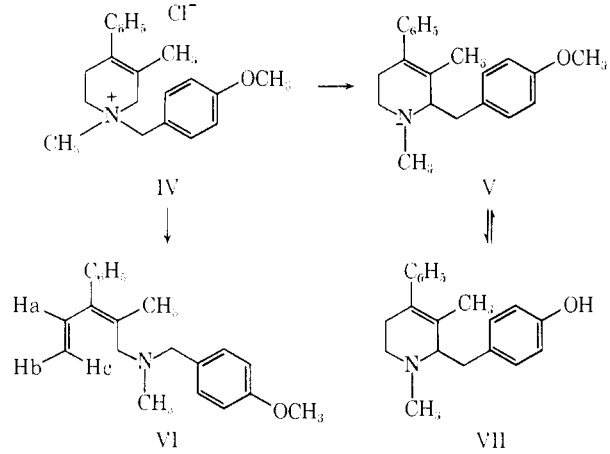
II



III

The required Δ^3-piperideine intermediate III was obtained by the procedure of Casy, *et al.*[4] These authors had prepared III by the acid-catalyzed dehydration of the *trans*-4-piperidinol obtained by the reaction of PhLi with 1,3-dimethyl-4-piperidone,[5] and found the dehydration product to be an equilibrated mixture of Δ^3- and Δ^4-piperideines.

Nmr spectral data showed that the initial dehydration product was an approximately equimolar mixture of II and III. Prolonged refluxing (48 hr) with HCl resulted in a mixture containing 85% of the required Δ^3-piperideine, III. The amount of III was estimated from the signal of the 3-Me substituent in the nmr spectrum of III in $CDCl_3$. It is interesting to note that this signal, which appeared as a triplet at δ 1.56 (J = 1.5 cps), is due to long range coupling with the CH_2 at the 5 position since it is found unchanged in the nmr spectrum of the 2-substituted derivative V.



IV V VI VII

Reaction of crude III with anisyl chloride in acetone gave the calculated yield of the desired crystalline quaternary ammonium salt IV and left the isomeric quaternary salt from the Δ^4-piperideine in solution.

The structure of IV was confirmed by its nmr spectrum in D_2O. The Stevens rearrangement[6] of IV to V proceeded in 65–75% yield (estimated by vpc) by stirring the dried quaternary salt IV and powdered KOH in refluxing toluene. For characterization, the crude 2-anisyl-Δ^3-piperideine derivative V was converted into the crystalline phenolic derivative, 2-(4-hydroxybenzyl)-1,3-dimethyl-4-phenyl-1,2,5,6-tetrahydropyridine VII, by short treatment with boiling 48% HBr. The pure Stevens base V was obtained from the phenol VII with CH_2N_2. The structures of the Stevens base V and of its corresponding phenol VII were confirmed by the nmr spectra. A minor product (about 5%) formed during the Stevens re-

(1) Part I. F. B. Block and F. H. Clarke, *J. Med. Chem.*, **12**, 845 (1969).

(2) Presented in part at the Symposium on Newer Analgetics and Narcotic Antagonists of the Medicinal Chemistry Section, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 9–14, 1967, Abstract M-15.

(3) Chemical Abstracts nomenclature. Part I of this series,[1] footnote 3.

(4) A. F. Casy, A. H. Beckett, and M. A. Iorio, *Tetrahedron*, **23**, 1165 (1967).

(5) A. Ziering and J. Lee, *J. Org. Chem.*, **12**, 911 (1947).

(6) See ref 1 for a further discussion of this reaction in the 4-phenyl-Δ^3-piperideine series.