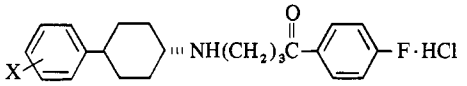
Table VIII. 4'-Fluoro-4-[4-arylcyclohexylamino]butyrophenone Hydrochlorides



Compd	X	Yield, %	Mp, °C	Formula[a]
17a	*p*-F	43[b]	193-197	$C_{22}H_{26}ClF_2NO$[c]
17a	*p*-F[d]	49[e]	190.5-195	$C_{22}H_{26}ClF_2NO$[f]
17b	*m*-F	55	197-200	$C_{22}H_{26}ClF_2NO$
17c	*p*-Cl	41	214-217	$C_{22}H_{26}Cl_2FNO$[c]
17d	*o*-CH_3	49	194-198	$C_{23}H_{29}ClFNO$[g]
17e	*m*-CH_3	35[b]	195-198	$C_{23}H_{29}ClFNO$
17f	*p*-CH_3	41	227-230	$C_{23}H_{29}ClFNO$[h]
17g	*o*-OCH_3	45	223-235	$C_{23}H_{29}ClFNO_2$
17h	*m*-OCH_3	58	183-185	$C_{23}H_{29}ClFNO_2$
17i	*p*-OCH_3	26[b]	191-193	$C_{23}H_{29}ClFNO_2$
17j	*m*-CF_3	36[b]	197-201	$C_{23}H_{26}ClF_4NO$[f]
17k	*p*-CF_3	26	206-210	$C_{23}H_{26}ClF_4NO$[f]
17l	*p*-F, *o*-CH_3	52	215-218	$C_{23}H_{28}ClF_2NO \cdot 0.5H_2O$
17m	*p*-NO_2	46	231-232	$C_{22}H_{26}ClFN_2O$

[a] Analyses for C, H, N within 0.4% of theoretical values unless specified. [b] Recrystallized from MeOH-EtOAc. [c] Analysis for C, H only. [d] Cis compound. [e] Recrystallized from CH_2Cl_2-EtOAc. [f] Analysis for C, H, Cl. [g] *Anal.* Calcd: C, 70.84; H, 7.50. Found: C, 71.32; H, 8.09. [h] Satisfactory analysis could not be obtained; ir and nmr in agreement with structures.

MeOH was then removed *in vacuo* and the residue dissolved in 100 ml of hot H_2O. The solution was then made strongly basic and extracted with Et_2O. The organic layer was taken to dryness, the residue dissolved in a small amount of Et_2O and this treated with 4.9 *N* HCl in Et_2O. There was obtained 4.78 g (99%) of hydrochloride. The analytical sample melted at 293-294°. *Anal.* ($C_{12}H_{17}N_2O$) C, H, N.

***trans*-4-Arylcyclohexylpiperidine Tosylates (17) (Table VII).** To a solution of 6.7 mmoles (1.64 g) of the amine hydrochloride in 30 ml of EtOH there was added 1.7 ml of 4.18 *N* NaOMe in MeOH. Following 1 hr stirring, there was added 1 ml (2.17 g) of 1,5-diiodopentane and 1.65 g of K_2CO_3. The mixture was stirred overnight at reflux and the solvent then removed *in vacuo*. The residue was taken up in H_2O and Et_2O (material insoluble in either phase was discarded). The organic layer was washed with H_2O and brine and taken to dryness; in several cases this was recrystallized. The residue was dissolved in ether and treated with 1 equiv of *p*-$CH_3C_6H_4SO_3H$ dissolved in ether. The precipitated tosyl salt was recrystallized from CH_2Cl_2-EtOAc.

General Procedure for Preparation of *p*-Fluorobutyrophenone (Table VIII). A suspension of 10 mmoles of the appropriate amine hydrochloride in 40 ml of DMF was treated with an equivalent (0.43 g) of 57% NaH in mineral oil. At the end of 1 hr there was added 1.70 g of KI, 2.82 g of K_2CO_3, and 2.86 g of 4-chloro-*p*-fluorobutyrophenone 2,2-dimethylpropylene ketal. The mixture was stirred overnight in an oil bath at 90°. The solvent was removed under oil pump vacuum and the residue dissolved in C_6H_6 and H_2O. The organic layer was washed with H_2O and brine and taken to dryness.

A mixture of the residue and 20 ml of 2.5 *N* HCl in 40 ml of MeOH was stirred at room temp for 2 hr. The bulk of the solvent was removed *in vacuo* and the solid collected on a filter. The cake was washed once with Et_2O and recrystallized to constant mp from MeOH-2.5 *N* HCl.

***trans*-4'-Fluoro-4-[4-(*p*-fluorophenyl)cyclohexylmethylamino]-butyrophenone hydrochloride (17n)** was prepared in 60% yield by the above procedure. The product was recrystallized from CH_2Cl_2-EtOAc, mp 206-207.5°. *Anal.* ($C_{23}H_{28}ClF_2N$) C, H, N.

***cis*-4'-Fluoro-4-[4-(*p*-fluorophenyl)cyclohexylmethylamino]-butyrophenone hydrochloride (17o)** was prepared in 39% yield by the above procedure. The product was recrystallized from CH_2Cl_2-EtOAc to mp 191.5-193.5°. *Anal.* ($C_{23}H_{28}ClF_2N$) C, H, N.

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Central Nervous System Agents. 4.[1] Analogs of 3-Amino-2-phenylpropiophenone

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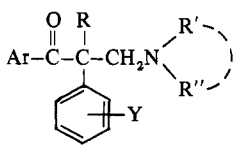
Thirty-one 1-aryl-2-phenyl-3-aminopropanones (I) have been tested in a battery of pharmacological screens designed to detect central nervous system activity. In general these Mannich bases seem to be stimulants. Most of these compounds and intermediates have not been previously reported.

Since the time of Mannich, scattered references have appeared to Mannich bases of the general formula I.[2] A con-

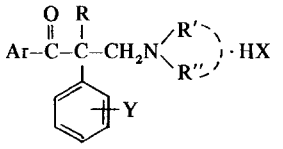


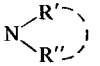
I

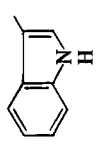
siderable number of this type of compound has been tested in animals in our laboratories. In general we have confirmed the reports by Huebner[2g] and Hofmann[2h] of CNS stimulant properties in this series, and we have extended the observations to many new compounds using a battery of pharmacological tests. Table I lists the results of the most significant testing. That many of these compounds are stimulants is shown by the low dose at which stimulation was observed in intact mice as compared with the relatively high dose causing death or loss of righting reflex (generally >100-200 mg/kg). The potency is also indicated by the low dose which prevented nicotine-induced convulsions.

From these data it seems that the most potent stimulants have small substituents on the amine (H, Me, or cyclic with 3 or 4 carbons). While azetidine and pyrrolidine compounds are quite active (**5**, **6**, **16**, **17**, **18**, **19**, and **26**), compounds with the diethylamine group (**4**) or piperidine group (**9**) are much less active. It should be noted, however, that **9** was tested as a free base and thus may be more slowly absorbed

Table I. Pharmacology



No.	Ar	Y	R		HX	LD_{50},[a] mg/kg	Stimulation,[a,b] mg/kg	Traction,[a] Tr_{50}	Chimney,[a] Ch_{50}	Dish,[a] D_{50}	Electroshock,[c] PD_{50}	Nicotine Antag,[a] AD_{50}	Misc
1	C_6H_5	H	H	$-NH_2$	HCl[d]	126	30	32	20	20	18	3.9	
2	C_6H_5	H	H	$-NHCH_3$	$C_4H_4O_4$[a]	142	30	40	>25	12.5	16	12	*f*
3	C_6H_5	H	H	$-N(CH_3)_2$	HCl[g]	234		45	>25	36	20	7	*f*
4	C_6H_5	H	H	$-N(CH_2CH_3)_2$	HCl[h]	133	30	63	45	23	28	11	
5	C_6H_5	H	H	$-NCH_2CH_2CH_2$	$C_4H_4O_4$[e]	100	10	89	50	45	>50	6.3	
6	C_6H_5	H	H	$-N(CH_2)_5CH_2$	HCl[i]	133	10	89	45	50	32	10	*f*
7	C_6H_5	H	H	$-NCH_2CH{=}CHCH_2$	HCl	200	10	71	>50	>50	71	20	
8	C_6H_5	H	H	$-N(CH_2)_5C(CH_3)_2$	HCl	142	10	56	45	40	>50	25	
9	C_6H_5	H	H	$-N(CH_2)_4CH_2$	Base[j]	562		>200	>200	>200	>200	57	
10	C_6H_5	H	H	$-NCH_2CH_2SCH_2CH_2$	Base	>1000		>200	>200	112	>200	89	
11	C_6H_5	H	H	$-NCH_2CH_2N(CH_3)CH_2CH_2$	2HCl	178	30	100	63	>100	56	18	
12	C_6H_5	H	H	$-NHCHCHCH_2CH_2NCH_2CH_2$ (CH$_2$ bridge)	Base	56	30	36	8	>50	>25	8	
13	C_6H_5	H	H	$-NCH_2CHCH_2CH_2CHCH_2CH_2$ (CH$_2$ bridge)	Base	>1000	300	>200	178	126	>200	25	
14	C_6H_5	H	H	$-N(CH_2)_5C(CH_2)_4CH_2$	HCl	178		>200	126	100	200	18	
15	C_6H_5	H	H	$-NCH_2CH_2C(OH)(C_6H_5)CH_2CH_2$	HCl	>1000	100	>200	89	>200	>200	79	
16	C_6H_5	H	CH_3	$-N(CH_2)_5CH_2$	HCl	142	10	63	50	>50	32	8	
17	C_6H_5	*m*-F	H	$-N(CH_2)_5CH_2$	HCl	159	10	100	63	>100	56	18	
18	*m*-FC_6H_4	H	H	$-N(CH_2)_5CH_2$	HCl	142	10	63	>50	36	40	5.6	*k*
19	*m*-FC_6H_4	*m*-F	H	$-N(CH_2)_5CH_2$	HCl	178	10	159	>100	36	72	18	*k*
20	*p*-ClC_6H_4	H	H	$-N(CH_2)_5CH_2$	Base[l]	562	100	>200	>200	112	>200	63	
21	*o*-ClC_6H_4	*o*-Cl	H	$-N(CH_2)_5CH_2$	HCl	178		159	100	18	178	79	
22	*p*-ClC_6H_4	*p*-Cl	H	$-N(CH_2)_5CH_2$	HCl	75	30	>200	50	72	>200	29	
23	*p*-$(OH)C_6H_4$	H	H	$-N(CH_2)_4CH_2$	Base[m]	>1000							
24	*p*-$(OCH_3)C_6H_4$	*p*-(OCH_3)	H	$-N(CH_3)_2$	HCl[n]	75	30						*f*
25	3,4,5-$(OCH_3)_3C_6H_2$	H	H	$-N(CH_2)_5CH_2$	HCl	142	30	72	50	45	>50	>50	*k*
26		H	H	$-N(CH_2)_5CH_2$	HCl	178	10	72	>50	>50	>50	23	*o*



27	H	H	$-N(CH_3)_2$	Base	>1000		>200	>200	20		126
28	H	H	$-N(CH_2)_5CH_2$	Base	750		>200	100	36		100
29	H	H	$-N(CH_2)_4CH_2$	Base	>1000	300[p]	>200	>200	3.6		159
30	H	H	$-NCH_2CH_2OCH_2CH_2$	Base	>1000		>200	>200	36		173
31	H	H	$-NCH_2CH_2N(CH_3)CH_2CH_2$	Base	1000	[q]	>200	126	28		50

[a]Carworth Farms male, albino mice (CF-1) weighing 18–22 g were used for all studies reported here. The test compds were dissolved or suspended in 0.25% aqueous methylcellulose soln and administered ip. Procedures for measuring acute toxicity (LD_{50}) and the effects of the compound on overt behavior, traction (Tr_{50}), chimney (Ch_{50}), dish (D_{50}), and antagonism of nicotine-induced tonic extensor convulsions (TE) have been described previously.[3] [b]The lowest dose showing definite CNS stimulation is given. A blank indicates no stimulation was observed. [c]Procedures for the antagonism of electroshock convulsions are described.[4] [d]See ref 5. [e]Maleate salt. [f]Anorexigenic activity was observed in dogs with a potency about 1/35 that of amphetamine. [g]See ref 6. [h]See ref 2b. [i]See ref 7. [j]See ref 2a. [k]Anorexigenic activity was observed in dogs with a potency about 0.1 that of amphetamine. [l]See ref 8. [m]See ref 9. [n]See ref 10. [o]In rat, ip LD_{50} 141, stimulation at 12.5 mg/kg. [p]Depression was observed in some mice at 100 mg/kg. [q]Depression was observed at 300 mg/kg.

from the mouse peritoneum. An exception is compound **12**, which contains a large amine moiety and is quite active. However, it is also quite toxic. Fluorine substituents on the benzene rings had little effect (**17**, **18**, **19**) but chlorine was detrimental (**20**, **21**, and **22**). The low CNS activity of the last five compounds in the table, containing the indole nucleus, is surprising in view of their relationship to CNS active indoles such as α-ethyltryptamine (etryptamine) which shows CNS stimulation in mice at 30 mg/kg and antagonizes nicotine-induced tonic extensor convulsions at 5.6 mg/kg. A few of the compounds (**9**, **14**, and **19**) showed some promise as anorexigenics having activity on the order of 0.1 that of amphetamine.

These compounds were synthesized from the corresponding aryl benzyl ketone either directly by the Mannich reaction[2a] (methods A or C) or indirectly by the addition of an amine to 2-phenylacrylophenone[2e,7] (method B) which was in turn prepared *via* a Mannich base. The latter method usually gave better results. These methods are illustrated in the Experimental Section and the new compounds are given in Table II or in the Experimental Section.

Experimental Section†

Method B. 3-(1-Azetidinyl)-2-phenylpropiophenone (5). To 13.2 g (0.15 mole) of 2-phenylacrylophenone[7] was added 6.8 ml (0.1 mole) of azetidine giving a soln which soon crystallized. After standing for 7 hr, the solid was recrystallized from 75 ml of hexane yielding 20.3 g (77%) of white crystals, mp 80.5–82°.

***d*-2-Phenyl-3-(1-pyrrolidinyl)propiophenone Hydrochloride (6d).** The *d*-10-camphorsulfonate salt of 2-phenyl-3-(1-pyrrolidinyl)propiophenone was prepd in EtOAc from 168 g (0.6 mole) of *dl* base[2] and 139.5 g (0.6 mole) of *d*-10-camphorsulfonic acid. This was recrystallized 11 times from EtOAc giving 2.6 g of white cryst, mp 145–146.5°, $[\alpha]^{25}D$ +61.6 ± 2° (α_0^{25} +1.35 ± 0.03° (*c* 0.0219 g in 2 ml of MeOH). *Anal.* C, H, N, S.

A soln of 2.1 g of this salt was converted to the hydrochloride on a column of 100 ml of Amberlite XE-208 resin in the chloride form. The product was eluted with 90% EtOH giving 1.3 g of crystalline solid, $[\alpha]^{25}D$ +65°. This was recrystallized three times from EtCOMe yielding 0.16 g of white crystals, mp 157–159°, $[\alpha]^{25}D$ +171 ± 3° (α_0^{25} +3.45 ± 0.05°, *c* 0.0202 g in 2 ml of MeOH). The rotation remained unchanged after the last recrystallization.

2-Phenyl-3-(3-quinuclidinylamino)propiophenone (12). To a soln of 25 g (0.126 mole) of 3-aminoquinuclidine dihydrochloride and 25.4 g (0.252 mole) of Et_3N in 100 ml of MeOH was added 26.2 g (0.126 mole) of 2-phenylacrylophenone. After standing for 5 days, the soln was concd to dryness and the residue was dissolved in cold dil HCl. The acid soln was washed with Et_2O and basified with cold NaOH. The resulting oil was extd with Et_2O, washed (water and sat NaCl soln), and dried (Na_2SO_4). Filtration and removal of the ether gave 36 g of a syrup which crystallized on standing, mp 90–95°. This was recrystallized from EtOAc yielding 19 g (45%) of white crystals, mp 98.5–100°.

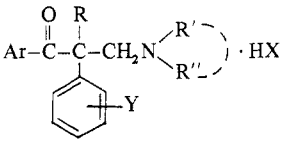
2-Methyl-2-phenyl-3-(1-pyrrolidinyl)propiophenone Hydrochloride (16). To a cold soln of 7.8 ml (0.1 mole) of pyrrolidine in 100 ml of 95% EtOH was slowly added 7.2 ml (0.09 mole) of 37% aqueous CH_2O, followed by 15.5 g (0.373 mole) of 2-phenylpropiophenone. The soln was heated under reflux for 22 hr, dild with water, and extd with Et_2O. The Et_2O soln was washed (H_2O and satd NaCl soln) and dried (K_2CO_3). After filtration, the soln was acidified with ethanolic HCl. The resulting oil was separated and crystallized on shaking with Et_2O. Two recrystns from *i*-PrOH yielded 2.94 g (12.2%) of white crystals, mp 194–196.5°.

2-Phenylpropiophenone.‡ A soln of 20.8 g (0.1 mole) of 2-

†Melting points were taken in capillary tubes with a partial immersion thermometer. Calibration of the apparatus against standard compounds showed no need for correction. Ir (Nujol mull) and usually nmr spectra (in DMSO-d_6 or $CDCl_3$) were obtained on pure compounds and were in accordance with the proposed structure. Where analyses are indicated only by symbols of the elements of functions, analytical results obtained for these elements or functions were within ±0.4% of theoretical.

‡This was first prepared by Meyer and Oelkers[11] and has since been made by numerous methods. The present new synthesis seems to be one of the most convenient.

Table II. Chemistry



No.[a]	Method of prepn	Yield, %[b]	Mp, °C[c]	Crystallization solvent	Formula	Anal.[c]
2	B[d]	22	134.5-135.5	*i*-PrOH	$C_{20}H_{21}NO_5$	C, H, N
5b	B	77	80.5-82	Hexane	$C_{18}H_{19}NO$	C, H, N
5	*e*	96	135-136	*i*-PrOH	$C_{22}H_{23}NO_5$	C, H, N
6d[f]	*g*		157-159	EtCOMe	$C_{19}H_{22}ClNO$	C, H
7b	B	96	99-101	*i*-PrOH	$C_{19}H_{19}NO$	C, H, N
7	*h*	93	151-154.5	*i*-PrOH	$C_{19}H_{20}ClNO$	C, H, Cl, N
8	B[i]	82	153-156	*i*-PrOH-Et_2O	$C_{21}H_{26}ClNO$	C, H, Cl, N
10	B	89	106-107	*i*-PrOH	$C_{19}H_{21}NOS$	C, H, N, S
11	B[j]	87	203-207 dec	EtOH	$C_{20}H_{26}Cl_2N_2O$	C, H, Cl, N
12	B[g]	45	98.5-100	EtOAc	$C_{22}H_{20}N_2O$	C, H, N
13	B	84	113-115	EtOH	$C_{23}H_{27}NO$	C, H, N
14b	B	60	71-72.5	*i*-PrOH	$C_{24}H_{29}NO$	C, H, N
14	*h*	96	169-170	*i*-PrOH	$C_{24}H_{30}ClNO$	C, H, Cl, N
15b	B	81	142.5-144.5	EtOH	$C_{26}H_{27}NO_2$	C, H, N
15	*h*	75	201-202.5	MeOH-Et_2O	$C_{26}H_{28}ClNO_2$	C, H, Cl, N
16	A[g]	12.5	194.5-196.5	*i*-PrOH	$C_{20}H_{24}ClNO$	C, H, Cl, N
17b	A[g]	50	102.5-104	95% EtOH	$C_{19}H_{20}FNO$	C, H, F, N
17	*k*	77	166.5-168	EtOH	$C_{19}H_{21}ClFNO$	C, H, Cl, F, N
18b	A	42	85-86.5	95% EtOH	$C_{19}H_{20}FNO$	C, H, F, N
18	*k*	82	159-160	*i*-PrOH	$C_{19}H_{21}ClFNO$	C, H, Cl, F, N
19b	A	33	85-86	Hexane	$C_{19}H_{19}F_2NO$	C, H, F, N
19	*k*	58	153-154	*i*-PrOH	$C_{19}H_{20}ClF_2NO$	C, H, Cl, F, N
21	B[g]	40	135-136	EtCOMe	$C_{19}H_{20}Cl_3NO$	C, H, Cl, N
22	B[l]	96	161-162	EtCOMe	$C_{19}H_{20}Cl_3NO$	C, H, Cl, N
25b	A	44	112.5-114	*i*-PrOH	$C_{22}H_{27}NO_4$	C, H, N
25	*k*	97	168-169.5 dec	95% EtOH	$C_{22}H_{28}ClNO_4$	C, H, N, Cl
26b	A[m]	100	119.5-121	MeOH	$C_{17}H_{19}NOS$	C, H, N, S
26	*k*	90	168-170	*i*-PrOH	$C_{17}H_{20}ClNOS$	C, H, Cl, N, S
27	C[n]	39	186.5-187.5	EtOAc	$C_{19}H_{20}N_2O$	C, H, N
28	C[o]	49[o]	141.5-144.5	EtOAc	$C_{21}H_{22}N_2O$	C, H, N
29	C[g]	54	172.5-173.5	EtOAc-hexane	$C_{22}H_{24}N_2O$	C, H, N
30	C[p]	6.1	167-169	EtOAc	$C_{21}H_{22}N_2O_2$	C, H, N
31	B[g]	47	183.5-184.5	EtOAc-hexane	$C_{22}H_{25}N_3O$	C, H, N

[a]Numbers correspond to those in Table I. A "b" after the number indicates a free base corresponding to the salt of Table I. [b]Yields of salts are calcd from the Mannich bases if the bases were purified. Yields of free bases (or salts if bases were not purified) are calcd from the corresponding desoxybenzoin (methods A or C) or from the corresponding 2-phenylacrylophenone (method B). Unless otherwise indicated, yields are reported for material melting not less than 2° below the highest mp obtd. [c]See footnote †. [d]The free base failed to crystallize. A slight excess of maleic acid was added to an ethereal soln of the crude base and the resulting maleate was recrystd from *i*-PrOH. The hydrochloride has been reported, ref 2e. [e]A warm soln of **5b** and a slight excess of maleic acid in *i*-PrOH crystallized on cooling giving the maleate salt. [f]**6d** is the dextro (+) rotating optical isomer corresponding to **6** of Table I. [g]Preparation described in the Experimental Section. [h]The free base was converted to the hydrochloride in *i*-PrOH with a slight excess of ethanolic HCl. [i]The free base failed to crystallize even after standing for 6 weeks. It was converted to the hydrochloride in *i*-PrOH with ethanolic HCl and diluted with Et_2O. [j]The free base was not purified but was converted to the dihydrochloride in EtOH. [k]Prepared from the free base in abs Et_2O with ethanolic HCl. [l]Prepared as described in the Experimental Section for **21**. [m]The Mannich base crystd from the reaction mixt and was collected, washed (*i*-PrOH), and dried. [n]Dimethylamine hydrochloride and sodium acetate were used in place of the free amine. About 13% of 1-(indol-3-yl)-2-phenyl-1-propenone was isolated. [o]About 35% of 1-(indol-3-yl)-2-phenyl-1-propenone and 49% of crude **27** were isolated. [p]A yield of 51.2% of 1-(indol-3-yl)-2-phenyl-1-propenone was isolated.

phenylacrylophenone[7] in 100 ml of MeOH was hydrogenated with 0.2 g of PtO_2 at 3.5 kg/cm² and room temp. After filtration and evaporation, the product was crystallized from 50 ml of pentane yielding 15.8 g (75%) of white crystals, mp 48-50°.

2-(*m*-Fluorophenyl)acetophenone.§ *m*-Fluorobenzylmagnesium chloride was prepd from 18.2 g (0.75 g-atom) of Mg, 108 g (0.75 mole) of *m*-fluorobenzyl chloride, and 375 ml of abs Et_2O. To this was slowly added 51.5 g (0.5 mole) of benzonitrile in 375 ml of abs Et_2O. After refluxing 2.5 hr and standing overnight, the mixt was poured onto ice and 120 ml of concd HCl. After standing for 1 hr, the product was extd with ether and CH_2Cl_2, washed (H_2O and satd NaCl), and dried (Na_2SO_4). Filtration and evaporation gave 131.3 g of crude product, mp 45-48°. Recrystallization from 160 ml of methylcyclohexane yielded 97.3 g (92%) of crystals, mp 47.5-49.5°

Method A. 2-(*m*-Fluorophenyl-3-(pyrrolidinyl)propiophenone (17b). A soln of 21.4 g (0.1 mole) of 2-(*m*-fluorophenyl)acetophenone, 12 ml of 37% aqueous CH_2O, and 9.5 ml (0.122 mole) of pyrrolidine in 100 ml of MeOH was allowed to stand for 3 days at room temp and evapd to dryness *in vacuo*. The residue was dissolved in dil HCl, washed (ether), and basified with dil NaOH. The resulting oil crystallized and was collected, washed (H_2O), dried, and recrystallized from 90 ml of 95% EtOH yielding 14.7 g (50%) of crystals, mp 102.5-104°.

3'-Fluoro-2-phenylacetophenone. This was prepd as the above 2-(*m*-fluorophenyl)acetophenone from 19.4 g (0.8 g-atom) of Mg, 100.8 g (0.8 mole) of benzyl chloride, 50 g (0.415 mole) of *m*-fluorobenzonitrile, and 750 ml of abs Et_2O. The product was recrystallized from hexane yielding 77.2 g (87%) of white crystals, mp 63-65°. *Anal.* C, H, F.

3'-Fluoro-2-(*m*-fluorophenyl)acetophenone. This was prepd as the above 2-(*m*-fluorophenyl)acetophenone from 19.4 g (0.8 g-atom) of Mg, 115 g (0.8 mole) of *m*-fluorobenzyl chloride, 50 g (0.415 mole) of *m*-fluorobenzonitrile, and 750 ml of abs Et_2O. The product was recrystallized from methylcyclohexane yielding 70 g (70%) of crystals, mp 49-50.5°. *Anal.* C, H; F, calcd 16.36, found 17.01.

2-Chloro-2-(*o*-chlorophenyl)acrylophenone. A soln of 53 g (0.2 mole) of 2'-chloro-2-(*o*-chlorophenyl)acetophenone,[13] 48 ml (0.6 mole) of 37% CH_2O, and 1 ml of pyrrolidine in 160 ml of

§ This has been reported by Fischer, *et al.*,[12] mp 47°, prepd by a different method. No yield of pure material was given.

MeOH was refluxed for 4 hr and allowed to stand for 3 days. Water was added, and the mixt was extd with Et_2O. The Et_2O soln was washed (dil HCl, dil $NaHCO_3$, H_2O, and satd NaCl) and dried (Na_2SO_4). After filtration and evaporation of the solvent, the product was distd giving 36.8 g of solid, bp 152° (0.1 mm). A sample was recrystallized from *i*-PrOH giving white crystals, mp 81–83°. *Anal.* C, H, Cl.

2′-Chloro-2-(*o*-chlorophenyl)-3-(1-pyrrolidinyl)propiophenone Hydrochloride (21). A mixt of 35 g (0.126 mole) of 2′-chloro-2-(*o*-chlorophenyl)acrylophenone and 12 ml (0.15 mole) of pyrrolidine was warmed to effect soln and allowed to stand for 4 days. The resulting oil was dissolved in Et_2O, washed (H_2O, satd NaCl), and dried (Na_2SO_4). After filtration, the soln was acidified with ethanolic HCl, and the resulting solid was crystallized from EtCOMe yielding 19.6 g of white crystals, mp 135–136°.

4′-Chloro-2-(*p*-chlorophenyl)acrylophenone. This was prepd as described above for the ortho isomer from 10 g (0.0378 mole) of 4-chloro-2-*p*-chlorophenyl)acetophenone,[13] 8.8 ml (0.11 mole) of 37% CH_2O, and 0.19 ml of piperidine in 35 ml of MeOH. The product was not distilled but was recrystallized from hexane yielding 7.2 g (69%) of white crystals, mp 80–83°. *Anal.* C, H, Cl

Benzyl Indol-3-yl Ketone. A soln of 287.6 g of *N,N*-dimethylphenylacetamide in 300 ml of PhH was cooled under N_2 to 10° and 108 ml of $POCl_3$ was added dropwise with stirring. After warming to 20°, 102.9 g (0.878 mole) of indole was slowly added keeping the temp below 48° by cooling. The mixt was then refluxed for 2 hr, cooled, and poured into 6 l. of H_2O. A soln of 307.5 g of NaOH in 914 ml of H_2O was added, and the mixt was stirred for 1 hr. The product was extd with Et_2O, washed (H_2O, satd NaCl), and evapd *in vacuo*. The residue was mixed with 200 g of NaOAc in 200 ml of H_2O and 3 l. of MeOH, refluxed for 3 hr, and cooled to near 0°. The solid was collected, washed (MeOH), and dried yielding 122.6 g of product, mp 206.5–209°. An addnl 45.5 g (total 81.5%) was obtained by concn of the filtrate. A sample was recrystd from EtOAc, mp 208–209°. *Anal.* C, H, N.

Method C. 1-(Indol-3-yl)-2-phenyl-1-propenone and 1-(Indol-3-yl)-2-phenyl-3-(1-piperidinyl)-1-propanone (29). A mixt (prepared under N_2 with cooling) of 50 ml of AcOH, 4.9 ml (0.05 mole) of piperidine, 11.76 g (0.05 mole) of benzyl indol-3-yl ketone, and 2 g (0.0666 mole) of paraformaldehyde was stirred at 100–110° for 3–5 hr, cooled, and concd *in vacuo* to half its vol. This was poured into ice water and the solid was collected, washed (H_2O), and dried giving 4.68 g of 1-(indol-3-yl)-2-phenyl-1-propenone, mp 175–181.5°. Recrystallization from EtOAc–hexane gave 1.17 g of crystals, mp 195–196.5°. *Anal.* C, H, N.

The aqueous filtrate was basified with NaOH giving free base which was collected, dried, and recrystallized from EtOAc yielding 8.99 g (54%) of **29**, mp 171.5–172.5°. Recrystallization from EtOAc–hexane raised the mp to 172.5–173.5°.

1-(Indol-3-yl)-3-(4-methyl-1-piperazinyl)-2-phenyl-1-propanone (31). A mixt of 6.33 g (0.0266 mole) of 1-(indol-3-yl)-2-phenyl-1-propenone and 20 ml of 1-methylpiperazine was heated under N_2 at 100° for 3 hr and poured into ice water. The resulting solid was dissolved in $CHCl_3$ and extd with dil HCl. The acid soln was basified with NaOH giving solid which was collected, washed (H_2O), dried, and recrystallized first from EtCOMe–cyclohexane and then from EtOAc–hexane yielding 4.3 g of **31**, mp 183.5–184.5°.

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Potential Bioreductive Alkylating Agents. 1. Benzoquinone Derivatives

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A series of benzoquinone derivatives with one or two side chains potentially capable of alkylation after bioreduction was synthesized. These compounds showed growth-inhibitory activity against adenocarcinoma 755 ascites cells and greatly prolonged the life-span of such tumor-bearing mice. Compounds of this series were also found to be potent inhibitors of the synthesis of both DNA and RNA in these neoplastic cells.

Mitomycin C, an antineoplastic agent active against tumors of both animals and man, has been shown to be a strong inhibitor of the synthesis of the nucleic acids.[1] Iyer and Szybalsky[2] presented evidence to indicate that mitomycins act as bifunctional alkylating agents which add across both strands of the DNA double helix to cause cross-linking. Schwartz, *et al.*,[3] demonstrated that the reduction of the benzoquinone ring of the mitomycins to dihydrobenzoquinone was an essential step for biological activity and Iyer and Szybalsky[4] showed that a NADPH (reduced form of nicotinamide-adenine dinucleotide phosphate) dependent quinone reductase system was involved in the reductive activation step. Recently, Kinoshita and coworkers[5] reported a positive correlation between both antineoplastic and antimicrobial activity of a series of mitomycin derivatives and their reduction potentials. These investigators[5] also provided evidence that the carbamyl group and the aziridine ring of the mitomycins were not essential for biological activity. The essential portions of the mitomycins were proposed to be the structures shown in formulas I and II (Scheme I). It is possible that charge delocalization of the dihydroquinone hydroxyl