Central Nervous System Depressants. V. Polyhydroxy and Methoxyphenyl Ketones, Carbinols, and Derivatives

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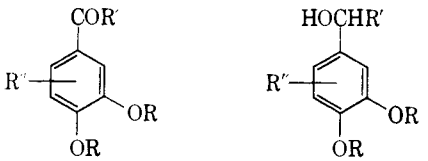
A number of ketones and carbinols (types I and II) were prepared by a variety of methods. Most of these compounds were found to be CNS depressants by gross observation of intact mice and rats and by avoidance behavior studies. XVIII has received clinical study as a tranquilizer. Several compounds had a relaxing effect on the cat uterus. Compound XIX has been studied in the clinic in dysmenorrhea and premature labor.

In continuation of our investigation of compounds having depressant effects on the central nervous system[1] a number of phenyl ketones (I) and carbinols (II) having hydroxyl or alkoxyl substituents in the 3- and 4-positions were studied (Table I).



I II

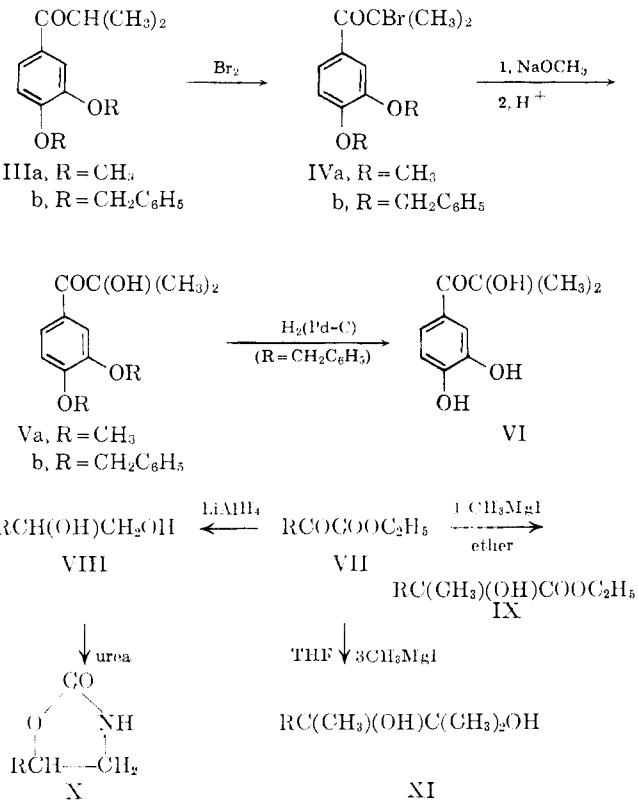
R'' = H, OH, OR

Some of the compounds were available, or had been reported in the literature. Others were prepared by methods which are described in the Experimental section.

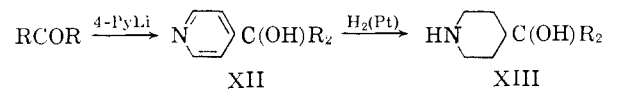
In general the 3,4-dimethoxyphenyl alkyl ketones (I, R = CH_3, R' = alkyl, and R'' = H) were prepared by the Friedel–Crafts reaction with veratrole and the appropriate acid chloride. However, in two cases (R' = *t*-Bu and cyclopropyl), this method was not applicable, since pivaloyl chloride is not stable to aluminum chloride[2] and the cyclopropane ring is opened by this reagent.[3] The 3',4'-dimethoxy-2,2-dimethylpropiophenone was prepared in excellent yield by methylating 3',4'-dimethoxy-2-methylpropiophenone (IIIa).

Cyclopropyl 3,4-dimethoxyphenyl ketone (**17**) was prepared by ring closure using the method of Close.[4] Some of the 3',4'-dihydroxyphenylalkyl ketones (*e.g.*, I, R and R'' = H, R' = isopropyl) were made by the Fries rearrangement on pyrocatechol esters, but better yields were usually obtained by demethylating the corresponding 3,4-dimethoxyphenyl ketones with pyridine hydrochloride. This failed, however, with the cyclopropyl ketone. The α-hydroxy ketones were prepared *via* the bromoketones using the epoxy ether synthesis of Stevens.[5]

Ethyl 3,4-dimethoxyphenylglyoxylate[6] (VII) [R = 3,4-$(CH_3O)_2C_6H_3$] was the key intermediate for another series of carbinols. A number of carbonates and carbamates of VIII and XI were prepared.



Two compounds containing two 3,4-dimethoxyphenyl groups were made by the reaction of 4-pyridyllithium with 3,3',4,4'-tetramethoxybenzophenone followed by reduction of the heterocyclic ring.[7]



XII XIII

R = 3,4-$(CH_3O)_2C_6H_3$

Several 3',4',5'-trialkoxyaceto- (and benzo) phenones were obtained by the reaction of the appropriate dialkylcadmium reagents on the trialkoxybenzoyl chloride.[8] This method worked quite well in some cases but in the preparation of 3,4,5-trimethoxybenzophenone some 4-hydroxy-3,5-dimethoxybenzophenone was obtained as reported by Koelsch and Flesch.[9] It is not clear whether the cleavage of the 4-methoxyl was brought about by the diphenylcadmium itself or by magnesium halides in the mixture. In other cases

(1) Paper IV of this series: R. B. Moffett and P. H. Seay, *J. Med. Pharm. Chem.*, **2**, 229 (1960).

(2) R. Baltzly, W. S. Ide, and A. P. Phillips, *J. Am. Chem. Soc.*, **77**, 2522 (1955).

(3) C. A. Thomas, "Anhydrous Aluminum Chloride in Organic Chemistry," 501, Reinhold Publishing Corp., New York, N. Y., 1941, p. 501.

(4) W. J. Close, *J. Am. Chem. Soc.*, **79**, 1455 (1957).

(5) See C. L. Stevens and R. L. McLean, *ibid.*, **81**, 119 (1959), for key references.

(6) K. Kindler, W. Metzenbrf, and Dsebi-yui-Kwok, *Ber.*, **76**, 308 (1943).

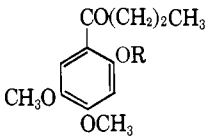
(7) Experimental work by Mr. D. A. Lyttle in these laboratories.

(8) E. C. Horning and J. Koo, *J. Am. Chem. Soc.*, **73**, 5826 (1951).

(9) C. F. Koelsch and R. N. Flesch, *J. Org. Chem.*, **20**, 1270 (1955).

where the yield of desired product was low (notably 4′-allyloxy-3′,5′-dimethoxyacetophenone), it is probable that similar cleavage occurred to some extent.

2′,4′,5′-Trimethoxybutyrophenone (XIV, R = CH_3) was prepared by methylation of 2′,4′,5′-trihydroxybutyrophenone with diazomethane,[10] and 2′-hydroxy-4′,5′-

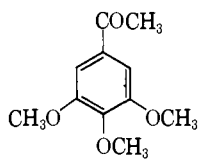


XIV

dimethoxybutyrophenone (XIV, R = H) was prepared in poor yield, by the reaction of 3,4-dimethoxyphenol with butyronitrile in the presence of zinc chloride.[11] We have obtained both these compounds by methylation of the commercially available trihydroxybutyrophenone. The former (XIV, R = CH_3) was obtained in good yield using methyl sulfate and sodium hydroxide in methanol and the latter (XIV, R = H) using methyl sulfate with potassium carbonate. A number of new derivatives (oximes, etc.) of available carbonyl compounds were made and are reported in the Experimental section.

Pharmacology.—The compounds reported in this paper as well as a considerable number of analogous known ketones, carbinols, and derivatives were tested for effects on the central nervous system. By gross observation of intact mice and rats most of them were found to be depressants. This was confirmed in some cases by testing their effect on motor activity[1] of mice and particularly by their effects on classical avoidance behavior in rats (see Table I and paper to be published by Dr. D. G. Anger).

Particularly noteworthy is the activity of 3′,4′,5′-trimethoxyacetophenone[8] (Table I, no. 33).



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This showed depression in intact mice at about one-fourth of its LD_{50} and was outstanding in the classical avoidance test. It has been tested in schizophrenic patients but, although it may have some activity as a tranquilizer, it is much less active than chlorpromazine in psychotic states.

Many of the compounds were tested as inhibitors of catechol O-methyltransferase *in vitro*.[12] The more active of these are mentioned in footnotes to Table I. Those compounds having *o*-dihydroxy groups were highly active,[13] while those with one phenolic (or acetoxy) group were less active. Preliminary testing showed that completely methylated compounds were

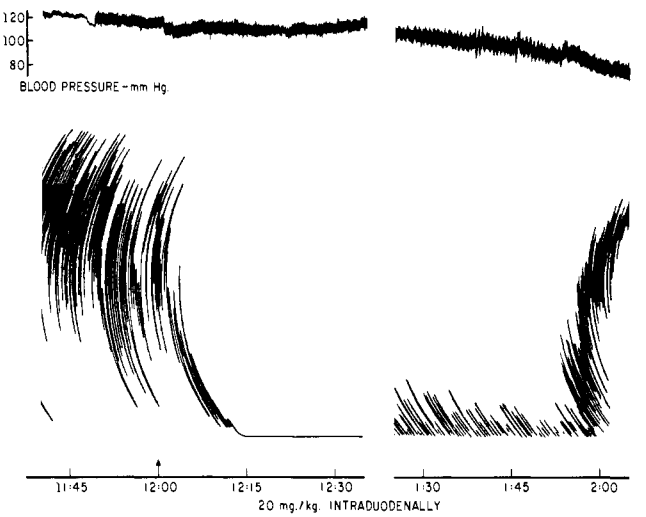
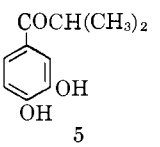


Fig. 1.—Uterine motility of XIX.

inactive, and for this reason few of the latter were tested. Likewise, several of these compounds inhibited 5-hydroxytryptophane decarboxylase *in vitro*.[14] The most active tested was 3,4-dihydroxy-5-methoxybenzaloxime (Table I, no. 44), which gave 100% inhibition at 10^{-2} *M* concentration.

3′,4′-Methylenedioxy-2-methylpropiophenone (Table I, no. 8) showed an interesting spectrum of biological properties. Intraperitoneally in intact mice it was rather nontoxic (LD_{50} 1000 mg./kg.) but showed stimulation at 100, stimulation followed by depression at 300, and convulsions followed by 4 hr. of sleep at 1000 mg./kg. Intraperitoneally in rats (LD_{50} 1000 mg./kg.) it showed depression at all doses from 200 to 1000 mg./kg. It was extremely active in prolonging the sleeping time of mice given small doses of hexobarbital[1] (≫ 2000% increase in sleeping time at 200 mg./kg., 1000% increase at 100 mg./kg., 660% increase at 50 mg./kg., and 360% increase at 25 mg./kg. given either intraperitoneally or orally). However, this compound was found to be an active inhibitor of the metabolism of hexobarbital *in vivo*, and this may account for its high activity in potentiating hexobarbital.

In the course of screening these compounds it was found that some of them had an interesting relaxing effect on the motility of the cat uterus (Table I). The most interesting compound was 3′,4′-dihydroxy-2-methylpropiophenone (Table I, no. 5). This produced relaxation of the uterus, lasting about 30 min., without altering blood pressure, at 1 and 2 mg./kg. intravenously; or relaxation lasting about 2 hr. at 20 mg./kg. intraduodenally (Fig. 1). This compound was tested clinically and produced a definite decrease in uterine activity in premature labor but tolerance seemed to develop. It had no effect in dysmenorrhea in double blind studies.



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(10) B. D. Astill, D. W. Fassett, and R. L. Roudabush, *Biochem. J.*, **72**, 451 (1959).

(11) G. H. Jones, J. B. D. Mackenzie, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 562 (1949).

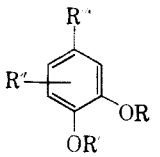
(12) J. Axelrod, *Science*, **126**, 400 (1957).

(13) J. Axelrod and M. Laroche, *ibid.*, **130**, 800 (1959).

(14) C. T. Clark, A. Weissbach, and S. Udenfriend, *J. Biol. Chem.*, **210**, 139 (1954).

TABLE I

PHARMACOLOGICAL ACTIVITY



No.	R	R′	R″	R‴	Mouse LD_{50},[a] mg./kg.	CNS depression,[b] mg./kg.	Uterine activity[c]
1[d]	CH_3	H	H	$COCH_3$	650	—[e]	—
2[d]	CH_3	CH_3	H	$COCH_3$			++
3[f]	H	H	H	$COCH_2CH_3$	650	100[g,h]	—
4[i]	CH_3	CH_3	H	$COCH_2CH_3$	>1000	100[j,k]	++
5[l]	H	H	H	$COCH(CH_3)_2$	650	100[g,m,n]	+++
6	CH_3	H	K	$COCH(CH_3)_2$	>1000	300[o]	+++
7[p]	CH_3	CH_3	H	$COCH(CH_3)_2$	420	100[q]	+++
8		$—CH_2—$	H	$COCH(CH_3)_2$	1000	300[r]	—
9[f]	H	H	H	$CO(CH_2)_2CH_3$	650	30[s]	—
10[f]	H	H	H	$COCH_2CH(CH_3)_2$	650	100[h,t]	—
11	H	H	H	$COCH(CH_3)C_2H_5$	560	100	+
12	CH_3	CH_3	H	$COCH(CH_3)C_2H_5$	530	30[g,u]	++
13	H	H	H	$COC(CH_3)_3$	530	—[v,w,x,y]	+
14	CH_3	CH_3	H	$COC(CH_3)_3$	650	—	++
15	H	H	H	$COCH(C_2H_5)CH(CH_3)_2$	200	—	—
16	CH_3	CH_3	H	$COCH(C_2H_5)CH(CH_3)_2$	>1000	100	+
17	CH_3	CH_3	H	$COCHCH_2CH_2$	>1000	100[z,aa]	++
18	H	H	H	$COCH(CH_2)_3CH_2$	650	100[bb]	—
19[cc]	CH_3	CH_3	H	$COCH(CH_2)_3CH_2$	>1000	100	
20	CH_3	CH_3	H	$COC(CH_3)_2Br$	>1000	—	—
21	CH_3	CH_3	H	$COC(CH_3)_2OH$	650	30[dd]	—
22	H	H	H	$COC(CH_3)_2OH$	650	—[ee]	—
23[ff]	CH_3	H	H	$COCH(OH)_2$	200	—	
24[gg]	CH_3	CH_3	H	$COCOOCH_2CH_3$	>1000	—	—
25	CH_3	CH_3	H	$C(=NNH_2)CONHNH_2$	650	—	—
26[d]	CH_3	CH_3	H	CO-3,4-$(OCH_3)_2C_6H_3$	>1000	—[hh,ii]	—
27[d]	H	H	2-OH	$COCH_3$	650	100[ii,kk]	—
28[ll]	H	CH_3	2-OCH_3	$COCH_3$	767	200	
29	CH_3	CH_3	2-OCH_3	$COCH_3$	650	—	—
30[mm]	H	H	5-OH	$COCH_3$	870	300[nn]	—
31[oo]	CH_3	H	5-OH	$COCH_3$	650	100	—
32[d]	CH_3	H	5-OCH_3	$COCH_3$	650	—[pp]	—
33[qq]	CH_3	CH_3	5-OCH_3	$COCH_3$	>1000	300[o]	—
34[rr]	CH_3	CH_3	5-OCH_3	$C(CH_3)=NOH$	650	200[ss]	—
35	CH_2CH_3	CH_2CH_3	5-OCH_2CH_3	$COCH_3$	>1000	—[tt]	
36	CH_3	$CH_2CH=CH_2$	5-OCH_3	$COCH_3$	1000	—[ii]	
37		$—CH_2—$	5-OCH_3	$COCH_3$	167	—	
38[d]	CH_3	CH_3	5-OCH_3	COC_2H_5	1000	100[ii]	—
39[d]	H	H	6-OH	$CO(CH_2)_2CH_3$	530	—	
40[uu]	CH_3	CH_3	6-OH	$CO(CH_2)_2CH_3$	>1000	—	
41[vv]	CH_3	CH_3	6-OCH_3	$CO(CH_2)_2CH_3$	1000	300	
42[ww]	CH_3	CH_3	5-OCH_3	$COC\equiv N$	65	10	—
43[tt]	H	H	5-OCH_3	CHO	650	—[xx]	
44	H	H	5-OCH_3	$CH=NOH$	650	—[uu]	
45[d]	CH_3	H	5-OCH_3	CHO	1000	300	—
46[zz]	CH_3	H	5-OCH_3	$CH=NOH$	1000	300[aaa]	
47	CH_3	H	5-OCH_3	$CH=NOCH_2COOH$	>1000	—[bbb]	
48[d]	CH_3	CH_3	5-OCH_3	CHO	>1000	300	—
49	CH_3	CH_3	5-OCH_3	$CH=NOCH_2COOH$	>1000	—	
50[ccc]	CH_3	H	5-OCH_3	COC_6H_5	>1000	300[ddd]	
51[eee]	CH_3	CH_3	5-OCH_3	COC_6H_5	>1000	300	
52[eee]	CH_3	CH_3	H	$CH(OH)CH(CH_3)_2$	650	—[g,v,fff]	+
53[d]	CH_3	CH_3	5-OCH_3	CH_2OH	>1000	300	
54	CH_3	CH_3	5-OCH_3	CH_2OCONH_2	930	100[hh]	
55[ggg]	CH_3	CH_3	5-OCH_3	$CH(CH_3)OH$	>1000	300	
56	CH_3	CH_3	5-OCH_3	$CH(CH_3)OCONH_2$	>1000	300[hhh,iii]	
57	CH_3	CH_3	H	$C(CH_3)(OH)COOC_2H_5$	650	100	—
58[jjj]	CH_3	CH_2	H	$CH(OH)CH_2OH$	>1000	300	—
59	CH_3	CH_3	H	$—CHCH_2OCO$	>1000	—	—
60	CH_3	CH_3	H	$CH(OH)CH_2OCONH_2$	>1000	300[k]	++
61	CH_3	CH_3	H	$—CHCH_2NHCO$	1000	300	
62[kkk]	CH_3	CH_3	H	$C(CH_3)(OH)C(CH_3)_2OH$	>1000	100	++
63	CH_3	CH_2	H	$—C(CH_3)C(CH_3)_2O—CO$	650	—	
64	CH_3	H	5-OCH_3	$CH(C_6H_5)OH$	>1000	—	
65	CH_3	CH_3	5-OCH_3	$CH(C_6H_5)OH$	>1000	300	

[a] Groups of four mice (albino-Upjohn strain, 18-22 g.) were injected intraperitoneally with test compound dissolved or suspended in 0.25% aqueous methylcellulose. The dose decreased in 0.5 log units from 1000 mg./kg. until complete killing and living doses were obtained, the LD_{50} was estimated by the method of Spearman and Karber "Statistical Method in Biological Assay," Hafner Publishing Co., New York, N. Y., 1952, p. 524. The values are approximations with an accuracy of about +100% to −50%. [b] Mice (or rats)

were observed during the toxicity tests (footnote a). The lowest dose at which significant depression was noted in mice is recorded in this column. Depression at doses greater than 40% of the LD_{50} is not considered significant and is indicated as negative (−). Groups of four rats were injected intraperitoneally with test compound at the calculated mouse LD_{50}. The dose was subsequently halved or doubled in order to obtain a dose at which all animals lived and a dose at which at least one animal died. Observations of behavior were made intermittently over a 4-hr. period. For the most part the rat studies were not carried to doses as low as 40% of the LD_{50} but in cases where depression was noted at such doses it is recorded in footnotes. Any other significant activities on the CNS of mice or rats are also noted in footnotes in this column. [c] This test is a modification of that described by M. L. Clary, A. Cameron, and B. N. Craver [*Proc. Soc. Exptl. Biol. Med.*, **77**, 778 (1951)]. Cats are injected intravenously at 1 and 2 mg./kg. of the compound. Relaxation or stimulation of the uterus is recorded on a kymograph and any change in blood pressure is also noted. Compounds producing some relaxation at 2 mg./kg. but not at 1 mg./kg. are given a plus (+) rating. Those producing some relaxation at both 1 and 2 mg./kg. are given two plus (++) and those showing more relaxation are given three plus (+++) rating. [d] This compound is well known in the literature or is available commercially, but is included for comparison. [e] Depression in rats at 325 mg./kg. (32.5% of the rat LD_{50}). [f] K. W. Rosemund and H. Lohfert, *Ber.*, **61**, 2601 (1928). [g] Depression in rats at 50 mg./kg. (10% of the rat LD_{50}). [h] Sleep in rats at 200 mg./kg. (40% of the rat LD_{50}). [i] R. D. Haworth and D. Woodcock, *J. Chem. Soc.*, 809 (1938). [j] Depression in rats at 125 mg./kg. (36% of the rat LD_{50}). [k] Motor activity of mice: 50% decrease at 200 mg./kg. [l] See ref. 21. [m] Catechol O-methyltransferase inhibition: 67% at 10^{-3} *M*. 5-Hydroxytryptophane decarboxylase 50% inhibition (I_{50}) at 4×10^{-3} *M*. [n] Sleep in rats at 400 mg./kg. (80% of rat LD_{50}). [o] Motor activity of mice 50% decrease at 300 mg./kg. [p] See ref. 18. [q] Depression in rats at 100 mg./kg. (30% of rat LD_{50}). [r] Depression in rats at 200 mg./kg. (20% of rat LD_{50}). [s] Motor activity of mice 50% decrease at 150 mg./kg. [t] Depression in rats at 100 mg./kg. (25% of the rat LD_{50}). [u] Sleep in rats at 300 mg./kg. (60% of rat LD_{50}). [v] Sleep in mice at 300 mg./kg. [w] Muscle relaxant in mice at 200 mg./kg. [x] Depression in rats at 100 mg./kg. (15% of the rat LD_{50}). [y] Sleep in rats at 400 mg./kg. (60% of the rat LD_{50}). [z] Motor activity of mice 50% decrease at 100 mg./kg. [aa] Depression in rats at 50 mg./kg. (6.3% of the rat LD_{50}). [bb] Depression in rats at 165 mg./kg. (40% of rat LD_{50}). [cc] See ref. 19. [dd] Motor activity of mice 50% decrease at 250 mg./kg. [ee] Catechol O-methyltransferase inhibition 100% at 10^{-3} *M*, 50% (I_{50}) at 8.2×10^{-6} *M*. [ff] R. B. Moffett, B. B. Tiffany, B. D. Aspergren, and R. V. Heinzelman, *J. Am. Chem. Soc.*, **79**, 1687 (1957). [gg] See ref. 6. [hh] Depression in rats at 500 mg./kg. (<50% of rat LD_{50}). [ii] Motor activity of mice 50% decrease at 50 mg./kg. [jj] Sleep in rats at 500 mg./kg. (65% of rat LD_{50}). [kk] Catechol O-methyltransferase inhibition 100% at 10^{-3} *M*, 50% (I_{50}) at 3×10^{-6} *M*. [ll] I. K. Brand and H. Collischonn, *J. prakt. Chem.*, **103**, 329 (1922). [mm] F. Mauthner, *ibid.*, **115**, 137 (1927). [nn] Catechol O-methyltransferase inhibition 100% at 10^{-3} *M*, 50% (I_{50}) at $3 \times 1.6 \times 10^{-6}$ *M*. 5-Hydroxytryptophane decarboxylase inhibition 80% at 10^{-2} *M*. Tryptophane 5-hydroxylation (liver) inhibition 92% at 10^{-5} *M*, 50% (I_{50}) at 8×10^{-7} *M*, determined by the method of R. A. Freedland, I. M. Wadzinski, and H. A. Waisman [*Biochem. Biophys. Res. Commun.*, **5**, 94 (1961)]. [oo] See ref. 31. [pp] Catechol O-methyltransferase inhibition 100% at 10^{-3} *M*. [qq] See ref. 8. [rr] E. Späth, *Monatsh.*, **40**, 129 (1919). [ss] Motor activity of mice 50% decrease at 120 mg./kg. [tt] Motor activity of mice 50% decrease at 175 mg./kg. [uu] See ref. 11. [vv] See ref. 10. [ww] J. T. Marsh and H. Stephen, *J. Chem. Soc.*, **127**, 1633 (1925). [xx] Catechol O-methyltransferase inhibition 100% at 10^{-3} *M*, 50% (I_{50}) at 4.6×10^{-6} *M*. [yy] Catechol O-methyltransferase inhibition 100% at 10^{-3} *M*, 50% (I_{50}) at 4×10^{-6} *M*. [zz] See ref. 33 and 34. [aaa] Catechol O-methyltransferase inhibition 81% at 10^{-3} *M*, 50% (I_{50}) at 2×10^{-4} *M*. [bbb] Catechol O-methyltransferase inhibition 85% at 10^{-3} *M*, 50% (I_{50}) at 10^{-4} *M*. [ccc] See ref. 9 and 10 and Experimental. [ddd] Catechol O-methyltransferase inhibition 90% at 10^{-3} *M*, 50% (I_{50}) at 2×10^{-5} *M*. [eee] G. Norcross and H. T. Openshaw, *J. Chem. Soc.*, 1174 (1949). [fff] Sleep in rats at 100 mg./kg. (20% of the rat LD_{50}). [ggg] See ref. 27. [hhh] Depression in rats at 280 mg./kg. (30% of the rat LD_{50}). [iii] Sleep in rats at 560 mg./kg. (60% of the rat LD_{50}). [jjj] See ref. 22. [kkk] See ref. 25 and Experimental.

Experimental[15]

4′-Hydroxy-3′-methoxy-2-methylpropiophenone (6).—A mixture of 117 g. (0.94 mole) of guaiacol and 100 g. (0.94 mole) of isobutyryl chloride was heated on a steam bath until the evolution of hydrogen chloride practically ceased. The crude ester was then dissolved in 900 ml. of nitrobenzene and 250 g. (1.8 moles) of aluminum chloride was added with stirring in portions at such a rate that the temperature did not rise above 50°. The mixture was stirred at room temperature for 3 hr. and then cautiously heated on a steam bath to 90° and kept at this temperature for 30 min. After cooling, it was poured into ice and 200 ml. of concentrated hydrochloric acid. The mixture was steam distilled to remove the nitrobenzene, cooled, and extracted with ether. The ether solution was washed with water and then extracted with 1 l. of 10% aqueous sodium hydroxide in three portions. The basic aqueous solution was washed with ether and acidified with hydrochloric acid. The product was extracted with ether, washed with water, and dried over sodium sulfate. After filtration, the ether was removed and the product was distilled. The first fractions (57 g.) crystallized in the receiver; b.p. 118° (0.07 mm.). Then an orange-colored oil of unknown structure distilled, b.p. 145–150° (0.07 mm.). The crystalline fractions were recrystallized from toluene, giving 26.3 g. (14.4%) of white crystals, m.p. 95–97.5°. A m.m.p. with 3′,4′-dihydroxy-2-methylpropiophenone gave a depression (64–75°). A small sample was recrystallized again from toluene giving crystals of the same melting point. The infrared spectrum supports the proposed structure rather than the *ortho* isomer (2′-hydroxy-3′-methoxy-2-methylpropiophenone) having major bands at 3310, 1665, 1600, 1585, 1511, 1275, 1182, 1148, 779, and 754 cm.$^{-1}$ in Nujol mull and showing no evidence of chelation. The n.m.r. spectrum[16] also supports this structure showing the hydrogens *ortho* to the carbonyl as a multiplet centered at 454 c.p.s., the *meta* hydrogen as a doublet centered at 417 ($J = 9$), the phenolic hydrogen as a broad absorption at 402, the methoxy hydrogens as a singlet at 233, α-hydrogen as a septuplet centered at 211, and the β-hydrogens as a doublet at 72 c.p.s. ($J = 7$) relative to internal tetramethylsilane.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26; neut. equiv., 194.2. Found: C, 68.16; N, 7.69; neut. equiv., 195.

3′,4′-Dimethoxy-2-methylbutyrophenone (12).—To a solution of 138.2 g. (1 mole) of veratrole in 500 ml. of benzene was added portionwise with stirring 160 g. (1.2 moles) of aluminum chloride. Then 120.6 g. (1 mole) of α-methylbutyryl chloride was added dropwise during 30 min. The mixture was stirred under reflux for 30 min. more, cooled, and poured into ice containing 120 ml. of concentrated hydrochloric acid. The mixture was steam distilled to remove the benzene and any remaining veratrol. The remaining oil was extracted with ether, and the ether solutions were washed successively with water, 10% sodium hydroxide solution, twice again with water, and then dried over sodium sulfate. After filtration, the solvent was removed and the residue was distilled. After removal of a small forerun, the product distilled at 101° (0.025 mm.) giving 146.9 g. (66%) of colorless liquid; $n^{25}D$ 1.5409.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.06; H, 8.19.

3′,4′-Dihydroxy-2-methylbutyrophenone (11).—A mixture of 67 g. (0.3 mole) of 3′,4′-dimethoxy-2-methylbutyrophenone and 200 g. of pyridine hydrochloride was heated under nitrogen with stirring at 200–220° for 1 hr. After cooling, the mixture was dissolved in water, acidified with hydrochloric acid, and extracted with ether. The ether solution was washed with water and then extracted well with 10% aqueous sodium hydroxide solution. The basic solution was acidified with hydrochloric acid liberating an oil. This was extracted with ether, and the ether solution was washed with water, saturated sodium chloride solution, and dried over sodium sulfate. After filtration and removal of the ether, the residue was distilled, giving 51.8 g. (89%) of a yellow viscous oil, b.p. 157° (0.05 mm.). The product could not be crystallized but was redistilled through a 15-cm. [1/8-in. (3.2

(15) Melting points were taken in capillary tubes with a partial immersion thermometer. Calibration of the apparatus against standard compounds showed no need for correction. Infrared spectra were obtained on all pure compounds and unless otherwise noted were in accordance with the proposed structures.

(16) This n.m.r. spectrum was determined in deuterated chloroform solution with a Varian A-60 spectrometer.

mm.) helices] column. A middle fraction of 15.1 g. of light yellow viscous oil was cut, b.p. 157° (0.02 mm.).

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26; neut. equiv., 194.22. Found: C, 67.67; H, 7.27; neut. equiv., 197.7.

3′,4′-Dimethoxy-2-ethyl-3-methylbutyrophenone (16).—This was prepared as described above for 3′,4′-dimethoxy-2-methylbutyrophenone from 145.2 g. (1.05 moles) of veratrole, 500 ml. of benzene, 168 g. (1.26 moles) of aluminum chloride, and 56.1 g. (1.05 moles) of 2-ethyl-3-methylbutyryl chloride.[17] The product was distilled, giving 102 g. (39%) of colorless liquid, b.p. 117° (0.025 mm.); $n^{25}D$ 1.5329.

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.96; H, 8.86. Found: C, 72.33; H, 8.63.

3′,4′-Dihydroxy-2-ethyl-3-methylbutyrophenone (15) was prepared as described above for 3′,4′-dihydroxy-2-methylbutyrophenone from 62.5 g. (0.25 mole) of 3′,4′-dimethoxy-2-ethyl-3-methylbutyrophenone and 170 g. of pyridine hydrochloride. The product was distilled, b.p. 135° (0.025 mm.), and the middle fraction was recrystallized from benzene, giving 16.8 g. (30%) of nearly white solid, m.p. 97–99°. Further recrystallization of a small sample yielded white crystals, m.p. 100–101.5°.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16; neut. equiv., 222.27. Found: C, 70.25; H, 8.23; neut. equiv., 225.

3′,4′-Dimethoxy-2,2-dimethylpropiophenone (14).—To a suspension of 10 g. (0.25 mole) of sodium amide in 385 ml. of dry toluene was added a solution of 45.9 g. (0.22 mole) of 3′,4′-dimethoxy-2-methylpropiophenone[18] in 65 ml. of toluene. After heating under reflux with stirring for 3.5 hr., 31.2 ml. (0.5 mole) of methyl iodide was added during 10 min. The mixture was heated under reflux for an additional 2.5 hr., cooled, and washed three times with water. The water layers were extracted with toluene which was added to the original toluene solution and distilled under reduced pressure. After removing the solvent, the product distilled smoothly at 111° (0.1 mm.), giving 47.7 g. (97.4%) of light yellow liquid; $n^{25}D$ 1.5355. This was redistilled through a 15 cm. (1/8-in. helices) packed column giving 46.6 g. (95%) as a nearly colorless liquid, b.p. 106° (0.06 mm.), all fractions of which (except a very small forerun) had $n^{25}D$ 1.5359.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.45; H, 8.21.

3′,4′-Dihydroxy-2,2-dimethylpropiophenone (13) was prepared from 29.5 g. (0.132 mole) of 3′,4′-dimethoxy-2,2-dimethylpropiophenone and 100 g. of pyridine hydrochloride as described above for 3′,4′-dihydroxy-2-methylbutyrophenone. On working up the reaction mixture and removing the solvent, the product crystallized, giving 22.6 g. (88%) of brown crystals, m.p. 125–127°. This was recrystallized from toluene, then dissolved in methanol, boiled with decolorizing charcoal (Darco), filtered, concentrated, and diluted with toluene. The solution was boiled until the temperature reached 100° (vol. about 100 ml.) and cooled. The resulting crystals were collected, washed with benzene, and dried, giving 17.8 g. of nearly white crystals, m.p. 127–129.5°.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 68.11; H, 7.25.

Cyclopentyl 3,4-dihydroxyphenyl ketone (18) was prepared from 56.9 g. (0.262 mole) of cyclopentyl 3,4-dimethoxyphenyl ketone[19] and 170 g. (1.48 moles) of pyridine hydrochloride as described above for **11**. The product was distilled under reduced pressure, giving a solid which was recrystallized once from aqueous methanol and twice from benzene, yielding 24.8 g. (45.9%) of white crystals, m.p. 99–101°.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84; neut. equiv., 206.23. Found: C, 70.18; H, 7.23; neut. equiv., 210.

Cyclopropyl 3,4-Dimethoxyphenyl Ketone (17).—A mixture of 141 g. (1.05 moles) of aluminum chloride and 570 ml. of carbon disulfide was cooled in an ice bath to 10°. Then a solution of 141 g. (1.0 mole) of γ-chlorobutyryl chloride in 138.2 g. (1.0 mole) of veratrole was slowly added with stirring and cooling at such a rate that the temperature was kept below 20°. The mixture was stirred at room temperature for 20 min. and poured into ice–water. The intermediate 4-chloro-3′,4′-dimethoxybutyrophenone was extracted with benzene and washed with water, and the solvent was distilled under reduced pressure. To the residue was added a solution of 100 g. of 85% potassium hydroxide in 396 ml. of methanol and the mixture was shaken for 30 min. The solvent was distilled under reduced pressure giving a crystalline residue. This was shaken with ether and washed twice with water, then with saturated sodium chloride solution, and dried over sodium sulfate. Filtration and distillation of the ether gave an oil which crystallized on addition of hexane, giving 82.5 g. of yellow crystals, m.p. 80–82°. This was recrystallized from 200 ml. of methylcyclohexane, yielding 77 g. (37.4%) of yellow crystals, m.p. 84–85.5°.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84; Cl, 0.00. Found: C, 69.73; H, 7.06; Cl, 0.07.

2-Methyl-3′,4′-methylenedioxypropiophenone (8).—Isopropylmagnesium chloride was prepared from 36.5 g. (1.5 moles) of magnesium, 118 g. (1.5 moles) of isopropyl chloride, and 175 ml. of absolute ether. To this was added slowly with stirring a solution of 73.5 g. (0.5 mole) of 3,4-methylenedioxybenzonitrile[20] in 300 ml. of benzene. After stirring under reflux for 16 hr., the mixture was poured into a mixture of ice and 150 ml. of concentrated hydrochloric acid and steam distilled for 3 hr. After removing the solvent, 6 l. of distillate containing a small amount of oil was collected and extracted with ether. The ether solution was washed with saturated salt solution and dried over sodium sulfate. After filtration and removal of the solvent, the product was distilled through a 15 cm. (1/8-in. helices) column giving 10.7 g. (11.2%) of very pale yellow oil, b.p. 130° (11 mm.); $n^{25}D$ 1.5472.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.87; H, 6.30. Found: C, 69.01; H, 6.71.

2-Bromo-3′,4′-dimethoxy-2-methylpropiophenone (20).—To 58.4 g. (0.28 mole) of 3′,4′-dimethoxy-2-methylpropiophenone[18] in 40 ml. of acetic acid containing 4 drops of a saturated solution of hydrogen bromide in acetic acid was added 44.8 g. (0.28 mole) of bromine in 40 ml. of acetic acid at such a rate as to keep a slight excess of bromine present (20–30 min.). The solution was stirred an additional hour and diluted with 325 ml. of ice–water. The mixture was extracted with methylene chloride and the methylene chloride layer washed with water to neutrality, dried over sodium sulfate, filtered, and concentrated to yield a sirup. The sirup was dissolved in 40 ml. of acetone and cooled to yield 43.4 g. (80.3%) of crystals, m.p. 47.5–48.5°.

Anal. Calcd. for $C_{12}H_{15}BrO_3$: Br, 27.83. Found: Br, 27.54.

2-Hydroxy-3′,4′-dimethoxy-2-methylpropiophenone (21).—A solution of 2.87 g. (0.01 mole) of 2-bromo-3′,4′-dimethoxy-2-methylpropiophenone in 60 ml. of absolute methanol was added dropwise over 5 min. at 0–5° to a solution of sodium methoxide from 0.46 g. (0.02 g.-atom) of sodium in 15 ml. of absolute methanol. The mixture was stirred overnight at room temperature, diluted with 50 ml. of water, and extracted with methylene chloride. The methylene chloride solution was washed with water to neutrality, dried over potassium carbonate, filtered, and concentrated to a sirup. The compound gave a negative Beilstein test and had an infrared spectrum consistent with the structure, 1-(3,4-dimethoxyphenyl)-1-methoxy-2-methyl-1,2-epoxypropane. Attempts to crystallize the sirup were unsuccessful.

To 0.950 g. of this sirup in 5.0 ml. of methanol was added 3.0 ml. of 65% aqueous methanol containing 1/2 drop of concentrated sulfuric acid. The solution was stirred for 1 hr. at room temperature and then diluted with 8 ml. of water. The solution was made slightly basic with dilute potassium hydroxide, saturated with sodium chloride, and extracted with ether. The ether solution was dried over anhydrous sodium sulfate, filtered, and concentrated to give 0.63 g. of a sirup. This was combined with 0.8 g. of sirup from previous runs and dried in an oven. The semicrystalline mass was recrystallized from ether, giving a nearly quantitative yield of material, m.p. 66.5–70°. Recrystallization of a sample gave crystals, m.p. 69–70.5°.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19; OCH_3, 27.6. Found: C, 64.28; H, 7.37; OCH_3, 27.98.

3′,4′-Dibenzyloxy-2-methylpropiophenone (IIIb).—A mixture of 29.6 g. of 3′,4′-dihydroxy-2-methylpropiophenone,[21] 500 ml. of methanol, 22 g. of potassium carbonate, and 46.0 g. (41.8 ml.) of benzyl chloride was heated with vigorous stirring for 20 hr. at 73°. The mixture was cooled, water was added, and methanol was removed under reduced pressure. The mixture was extracted with ether and washed with 10% sodium hydroxide solution, water, and was dried over sodium sulfate. The filtered solution was concentrated to a thick sirup and distilled in a total immersion flask of 226–237° (0.08 mm.). A small sample crys-

(17) G. Stopp, Jr., and J. L. Johnson, *J. Am. Chem. Soc.*, **80**, 915 (1958).

(18) C. Noreross and H. T. Openshaw, *J. Chem. Soc.*, 1174 (1949).

(19) R. J. S. Beer, T. Broadhurst, A. Robertson, and L. McGrath, *ibid.*, 4351 (1952).

(20) E. Marcus, *Ber.*, **24**, 3650 (1891).

(21) Prepared as described in our U. S. Patent 2,929,848 (1960).

tallized on standing. Two recrystallizations from isopropyl alcohol gave crystals, m.p. 59–60°.

Anal. Calcd. for $C_{24}H_{24}O_3$: C, 79.97; H, 6.71. Found: C, 79.52; H, 6.68.

2,3′,4′-Trihydroxy-2-methylpropiophenone (22).—To 28.4 g. (0.079 mole) of 3′,4′-dibenzyloxy-2-methylpropiophenone in 11.5 ml. of acetic acid containing 2 drops of saturated hydrogen bromide in acetic acid was added 12.6 g. of bromine in 11.5 ml. of acetic acid at such a rate that only a slight excess of bromine was present (about 35 min.). The solution was stirred an additional hour, and water was added. This solution was extracted with methylene chloride and the organic layer was washed with saturated sodium bicarbonate until basic and then with water until neutral. After drying, filtration, and concentration, 38.7 g. of crude 2-bromo-3′,4′-dibenzyloxy-2-methylpropiophenone (IVb) was obtained as a sirup.

A solution of sodium methoxide from 3.4 g. of sodium and 75 ml. of absolute methanol was cooled to 0–5°, and a solution of 32.7 g. of the above sirup in 45 ml. of absolute methanol was added dropwise with stirring. The mixture stood overnight at room temperature and was then diluted with water and extracted with methylene chloride. The organic layer was washed with water, dried, and concentrated to yield 23.0 g. of sirup which was distilled in a total immersion flask at 211–215° (0.01 mm.), giving 1-(3,4-dibenzyloxyphenyl)-1-methoxy-2-methyl-1,2-epoxypropane as a noncrystallizable sirup.

A solution of 11.5 g. of this sirup in 59 ml. of methanol was added during 15 min. to 35 ml. of 65% aqueous methanol containing 4 drops of concentrated sulfuric acid. Water (24 ml.) was added and the solution was held at room temperature for 1 hr. An additional 90 ml. of water was added and the solution was made basic with dilute potassium hydroxide. The solution was saturated with sodium chloride and extracted with ether, and the ether was dried and concentrated to yield 8.7 g. of 2-hydroxy-3′,4′-dibenzyloxy-2-methylpropiophenone as a sirup which would not crystallize, even after chromatography.

A mixture of 7.7 g. of this sirup, 200 ml. of 95% alcohol, and 750 mg. of 5% palladium-on-charcoal catalyst was shaken with hydrogen for 1 hr. at which time the theoretical amount of hydrogen had been taken up. The mixture was filtered and concentrated to yield 5.3 g. of sirup. The sirup was dissolved in acetone, treated with charcoal, filtered, and concentrated to give again a sirup (4.1 g.). Upon standing the sirup crystallized and was recrystallized from ether, yielding 1.16 g. of crystals, m.p. 136.5–139.5°.

Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.25; H, 6.35.

3′,4′-Dimethoxyphenylglyoxylic Acid Hydrazide Hydrazone (25).—To a solution of 25.0 g. (0.105 mole) of ethyl 3,4-dimethoxyphenylglyoxylate[6] in 625 ml. of absolute ethanol was added 25.0 g. (0.5 mole) of hydrazine hydrate. The solution was refluxed for 3 hr. and cooled in the refrigerator. The resulting crystals were collected, washed with cold absolute ethanol, and recrystallized from absolute ethanol giving 16.0 g. (63.6%) of product, m.p. 136–139°, λ_{max}^{EtOH} 283 mμ (ε 12,100) and 304 mμ (ε 11,200).

Anal. Calcd. for $C_{10}H_{14}N_4O_3$: C, 50.3; H, 5.93; N, 23.5. Found: C, 50.22; H, 5.91; N, 22.76.

1-(3,4-Dimethoxyphenyl)ethane-1,2-diol Cyclic Carbonate (59).—To 0.99 g. (0.005 mole) of 1-(3,4-dimethoxyphenyl)-ethane-1,2-diol[22] in 50 ml. of pyridine, cooled to 0–5°, was added dropwise 1.56 g. (0.01 mole) of phenyl chloroformate. The reaction mixture was stirred overnight at room temperature and poured onto 600 g. of ice. The resulting mixture was extracted with methylene chloride and the organic layer washed with cold *N* hydrochloric acid and then with water. The solution was dried over sodium sulfate, filtered, and concentrated to dryness to give 2.1 g. of sirup. This material was chromatographed on 200 g. of Florisil, taking four 200-ml. fractions of the concentration of solvent as follows: 1, 3, 6, 10, 15, 20, and 25% acetone in hexane. Fractions 20–25 (0.706 g.) were combined and crystallized from isopropyl alcohol to yield 0.450 g. of crystals, m.p. 80.5–84°.

Anal. Calcd. for $C_{11}H_{12}O_5$: C, 58.92; H, 5.40. Found: C, 59.28; H, 5.72.

1-(3,4-Dimethoxyphenyl)ethane-1,2-diol 2-Carbamate (60).—A mixture of 3.32 g. of 1-(3,4-dimethoxyphenyl)ethane-1,2-diol cyclic carbonate and liquid ammonia was stirred under reflux and the ammonia was allowed to evaporate overnight. The resulting solid was recrystallized from 2-propanol, giving 1.32 g. of crystals, m.p. 102–105.5°. Another treatment of the mother liquors with ammonia gave an additional 1.13 g. of material, m.p. 102.5–106°. The total yield was 2.45 g. (68.7%).

Anal. Calcd. for $C_{11}H_{15}NO_5$: C, 54.76; H, 6.27; N, 5.81. Found: C, 54.62; H, 6.60; N, 5.63.

The opening of this type compound to give the primary carbamate rather than the secondary has been demonstrated by Baizer, *et al.*[23]

5-(3,4-Dimethoxyphenyl)-2-oxazolidinone (61).—A mixture of 1.98 g. (0.01 mole) of 1-(3,4-dimethoxyphenyl)ethane-1,2-diol[22] and 1.2 g. (0.02 mole) of urea was heated at 190° for 5 hr. under an air condenser. The molten mass was poured into 20 ml. of ice–water and the mixture was extracted with methylene chloride. The organic layer was dried, filtered, and concentrated to yield 1.9 g. of sirup, which was chromatographed over 200 g. of Florisil, taking six 200-ml. fractions of each of the following: 5, 10, 15, 20, 25, 40, and 80% acetone in hexane, and acetone. Fractions 29–39 were combined and crystallized from acetone–hexane, yielding 400 mg., m.p. 113–115.5°. Recrystallization from acetone–hexane gave pure material, m.p. 121–121.5°.

Anal. Calcd. for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.07; H, 5.91; N, 6.29.

The formation of a 5-substituted rather than a 4-substituted 2-oxazolidinone in this type reaction has been demonstrated by Lunsford, *et al.*[24]

Ethyl 3′,4′-Dimethoxy-2-methylmadelate (57).—To a solution of methyl magnesium iodide from 7.29 g. (0.3 g.-atom) of magnesium, 18.7 ml. (0.3 mole) of methyl iodide, and 125 ml. of anhydrous ether was added, during 20 min., 23.8 g. (0.1 mole) of ethyl 3,4-dimethoxyphenylglyoxylate[6] in 200 ml. of ether. The mixture was refluxed for 75 min., cooled, and hydrolyzed with 180 ml. of 20% ammonium chloride. The ether layer was separated and the aqueous layer was extracted with an additional 400 ml. of ether. The combined extracts were dried over anhydrous magnesium sulfate and filtered, and the ether was removed. The residue was distilled, giving 21.3 g. of liquid, b.p. 134–140° (0.06 mm.); $n^{25}D$ 1.5240.

Anal. Calcd. for $C_{13}H_{18}O_5$: C, 61.40; H, 7.13. Found: C, 61.62; H, 7.37.

2-(3,4-Dimethoxyphenyl)-3-methylbutane-2,3-diol (62).—To 50 ml. of 3 *M* methylmagnesium bromide in ether was added dropwise during 25 min. under nitrogen 4.76 g. (0.02 mole) of ethyl 3,4-dimethoxyglyoxylate[6] in 75 ml. of tetrahydrofuran. The ether was removed by distillation, and the solution was heated at 60° for 4.5 hr., stirred overnight at room temperature, and refluxed for 5 hr. The mixture was hydrolyzed with a solution of 10 g. of ammonium chloride in 60 ml. of water. The organic layer was separated and the aqueous extracted with two 25-ml. portions of ether. The combined organic layers were washed with water and saturated sodium chloride and dried over anhydrous sodium sulfate. The mixture was filtered and concentrated to dryness to give a sirup. All attempts at obtaining crystals, including chromatography over Florisil or alumina, failed. A similar reaction using methyllithium also failed to yield crystals. The sirup was distilled in a falling film molecular still at 140–150° (30–120 μ). Kochetkov and Dudykina[25] prepared this by a different method and also report it to be an oil.

Anal: Calcd. for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.56; H, 8.55.

2-(3,4-Dimethoxyphenyl)-3-methylbutane-2,3-diol Cyclic Carbonate (63).—To a solution of 229 g. (0.0095 mole) of 2-(3,4-dimethoxyphenyl)-3-methylbutane-2,3-diol in 20 ml. of dry pyridine was added with stirring and cooling 3.0 g. (0.019 mole) of phenyl chloroformate. The mixture was allowed to warm to room temperature, stirred overnight, and poured on ice. The solid was collected, washed well with water, dried, and recrystallized from isopropyl alcohol, giving crystals, m.p. 72–74°. This was determined to be diphenyl carbonate by analysis and spectra. Extraction of the aqueous mother liquors with methylene chloride followed by washing with dilute hydrochloric acid and water gave, upon drying and concentration, a sirup weighing

(22) K. Freudenberg and E. Plankenhorn, *Chem. Ber.*, **80**, 149 (1947).

(23) M. M. Baizer, J. R. Clark, and J. Swidinsky, *J. Org. Chem.*, **22**, 1595 (1957).

(24) C. D. Lunsford, R. P. Mays, J. A. Richman, Jr., and R. S. Murphey, *J. Am. Chem. Soc.*, **82**, 1166 (1960).

(25) N. K. Kochetkov and N. V. Dudykina, *Zh. Obshch. Khim.*, **30**, 3054 (1960) [Engl. Transl., **30**, 3027 (1960)].

1.6 g. This was combined with the sirup obtained upon concentration of isopropyl alcohol filtrate and chromatographed on 200 g. of Florisil.

Four fractions were eluted using 200-ml. portions of methylene chloride. Then 15 fractions were taken using 200 ml. of hexane containing increasing (5 to 50%) amounts of acetone. Fractions 11 and 12 were recrystallized from isopropyl alcohol to give 0.51 g. of crystals, m.p. 75–77°. Recrystallization from aqueous isopropyl alcohol raised the m.p. to 81–82°.

Anal. Calcd. for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 63.33; H, 6.81.

4-Pyridylbis(3,4-dimethoxyphenyl)carbinol (XII).[7]—A solution of butyllithium from 2.09 g., (0.30 g.-atom) of lithium, 16.13 g. (0.15 mole) of butyl bromide, and 270 ml. of absolute ether was cooled to −60°, and 20.16 g. (0.1273 mole) of 4-bromopyridine in 120 ml. of dry ether was added with vigorous stirring during 30 min. A light tan solid precipitated. Then 24.20 g. of 3,4,3′,4′-tetramethoxybenzophenone in 480 ml. of tetrahydrofuran was added during 45 min. The solution was stirred at −60° for 1 hr., then allowed to stand at −45° overnight. It was then allowed to come slowly to 15° and 20 ml. of saturated ammonium chloride solution was added cautiously. Anhydrous potassium carbonate and magnesium sulfate were added to remove water, and the mixture was filtered. The filtrate was concentrated under reduced pressure and the residue crystallized. It was dissolved in 100 ml. of *N* hydrochloric acid and the solution was extracted with ethyl acetate to remove any starting material which might be present. The acid aqueous solution was placed under vacuum to remove ethyl acetate and was then made basic by addition of 52 ml. of 2 *N* sodium hydroxide. The red oil which separated soon crystallized. The crystalline material was collected, washed with water, and recrystallized from ethanol, giving 11.6 g. of solid, m.p. 178–179° (block). An additional yield of 9.0 g. (total yield 67.5%) was obtained by extracting the solid containing the drying agents with hot ethyl acetate and purifying as described above. The infrared and ultraviolet spectra were in agreement with the proposed structure. The hydroxyl shows in the infrared spectrum as highly bonded, so much so that it misled us for a time into believing we had lost the oxygen function. The Grignard test for active hydrogen was negative, probably for the same reason. However, n.m.r. confirmed the presence of hydroxyl.[26]

Anal. Calcd. for $C_{22}H_{23}NO_5$: C, 69.27; H, 6.08; N, 3.67; OCH_3, 32.5. Found: C, 69.09; H, 6.17; N, 3.82; OCH_3, 33.5.

4-Piperidylbis(3,4-dimethoxyphenyl)carbinol Hydrochloride (XII).[7]—A mixture of 13.27 g. (0.0348 mole) of 4-pyridylbis(3,4-dimethoxyphenyl)carbinol, 0.50 g. of platinum oxide, 100 ml. of methanol, and 17.4 ml. of 2 *N* hydrochloric acid was hydrogenated under 50 p.s.i. pressure. Hydrogen uptake was 96% of the calculated amount in 12 hr., by which time reduction had ceased. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure at 30°. The clear gum was crystallized from 2-propanol, giving 14.60 g. of solid. This was recrystallized from a mixture of 200 ml. of 2-propanol and 25 ml. of ethanol to give 12.79 g. of crystals, m.p. 245–246.5°.

Anal. Calcd. for $C_{22}H_{30}ClNO_5$: C, 62.33; H, 7.13; Cl, 8.36; N, 3.30. Found: C, 62.34; H, 7.60; Cl, 8.07; N, 3.33.

3,4,5-Trimethoxybenzyl Carbamate (54).—To a solution of 28.7 g. (0.145 mole) of 3,4,5-trimethoxybenzyl alcohol in 200 ml. of dry pyridine was added slowly during 15 min. with stirring and cooling 22.7 g. (0.145 mole) of phenyl chloroformate. After stirring overnight at room temperature the solution was filtered from pyridine hydrochloride and added slowly during 30 min. to 200 ml. of liquid ammonia. The mixture was allowed to reflux under a Dry Ice-cooled condenser for 7 hr. and then the ammonia was allowed to evaporate. The pyridine was distilled under reduced pressure and the residue was mixed with water and extracted well with ether. The ether solution was washed with cold 10% hydrochloric acid, water, cold 5% sodium hydroxide, then to neutrality with water, and dried over sodium sulfate. Filtration and removal of the ether gave 21.1 g. of light yellow crystalline solid which was recrystallized from 75 ml. of ethyl acetate, giving 12.7 g. of white crystals, m.p. 92–94°. This was recrystallized from 2-propanol, yielding 11.5 g. (35%) of white crystals, m.p. 117–119°.

Anal. Calcd. for $C_{11}H_{15}NO_5$: C, 54.76; H, 6.27; N, 5.81. Found: C, 55.06; H, 6.40; N, 5.74.

(26) This n.m.r. spectrum was determined in deuterated chloroform solution with a Varian DP-60 spectrometer.

1-(3,4,5-Trimethoxyphenyl)ethanol carbamate (56) was prepared in a similar way from 30.8 g. (0.145 mole) of 1-(3,4,5-trimethoxyphenyl)ethanol.[27] Removal of the ether gave 36.2 g. of waxy solid. Two recrystallizations from 2-propanol yielded 9.4 g. (25.4%) of white solid, m.p. 121–122°.

Anal. Calcd. for $C_{12}H_{17}NO_5$: C, 56.46; H, 6.71; N, 5.49; O, 31.34. Found: C, 56.09; H, 6.69; N, 5.67; O, 31.25.

3′,4′,5′-Triethoxyacetophenone (35).—A mixture of 50 g. (0.1 mole) of 3,4,5-triethoxybenzoic acid, 125 ml. of benzene, and 22 ml. (0.3 mole) of thionyl chloride was heated under reflux for 2.5 hr. The solvent was removed under reduced pressure and benzene was added and removed, leaving crude acid chloride. Dimethylcadmium mixture was prepared from 7.3 g. (0.3 g.-atom) of magnesium, 31.4 g. (0.33 mole) of methyl bromide, 550 ml. of absolute ether, and 55 g. (0.3 mole) of cadmium chloride. The ether was distilled under reduced pressure and 200 ml. of dry benzene was added. Then the above acid chloride in 200 ml. of benzene was slowly added with vigorous stirring and the mixture was refluxed for 2.5 hr. A solution of 50 g. of ammonium chloride in 300 ml. of water was added slowly. The aqueous layer was extracted with ether and the combined benzene and ether solution was washed with water, cold 5% aqueous sodium hydroxide, water, saturated sodium chloride, and dried over sodium sulfate. After filtration and removal of the solvent the product was distilled, b.p. 126° (0.2 mm.), giving 34.55 g. of solid, m.p. 54–58°. This was recrystallized from 150 ml. of hexane, yielding 29.24 g. (58%) of white crystals, m.p. 62–63°.

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 66.64; H, 7.99; O, 25.37. Found: C, 66.98; H, 8.31; O, 25.59.

3,4,5-Trimethoxybenzophenone (51) and 4-Hydroxy-3,5-dimethoxybenzophenone (50).[28]—The reaction of 252.3 g. (1.067 moles) of 3,4,5-trimethoxybenzoyl chloride with diphenylcadmium [from 48.6 g. (2 g.-atom) of magnesium, 215 ml. (2.05 moles) of bromobenzene, and 48.6 g. (2 moles) of cadmium chloride] was carried out essentially as described by Koelsch and Flesch.[9] Yields of 188.5 g. (65%) of 3,4,5-trimethoxybenzophenone, m.p. 75–76°, and 36 g. (13%) of 4-hydroxy-3,5-dimethoxybenzophenone, m.p. 122–123.5°, were obtained. Koelsch and Flesch[9] and Klemm, *et al.*,[29] indicated doubt about the position of the hydroxyl group in the latter compound. We established this as the 4-position by n.m.r.[26] which shows the hydrogens of the unsubstituted phenyl ring as a multiplet centered at 448 c.p.s., the *ortho* hydrogens on the substituted ring as a singlet at 423, the *para* phenolic hydrogen as a broad absorption at 376, and the methoxyl hydrogens as a singlet at 230 c.p.s. relative to internal tetramethylsilane.

3,4,5-Trimethoxybenzhydrol (65) and 4-Hydroxy-3,5-dimethoxybenzhydrol (64).[28]—An ether solution of 157.2 g. (0.28 mole) of somewhat crude 3,4,5-trimethoxybenzophenone was added slowly to 23.1 g. (0.58 mole) of lithium aluminum hydride in ether. After stirring under reflux for 2 hr. 171 ml. of ethyl acetate was added slowly followed cautiously by ice–water. The mixture was acidified with hydrochloric acid. The ether solution was washed with sodium bicarbonate, then with water, and concentrated. Much of the 3,4,5-trimethoxybenzhydrol separated at this point and was collected as 75.4 g. of white solid having a negative ferric chloride test, m.p. 107–110°. Further concentration of the ether solution gave 30.1 g. of yellow solid with a positive test with ferric chloride. This was dissolved in chloroform, extracted with 5% aqueous sodium hydroxide, washed with water, dried over magnesium sulfate, filtered, and evaporated. Trituration with ether yielded an additional 14.5 g. of 3,4,5-trimethoxybenzhydrol, m.p. 113–114°; total yield 57%.

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 69.93; H, 6.67.

Acidification of the above sodium hydroxide extract gave a solid which was crystallized twice from ethanol; yield of 4-hydroxy-3,5-dimethoxybenzhydrol, 4.8 g. (3.2%), m.p. 154–155°. It is not clear whether this resulted from some 4-hydroxy-3,5-dimethoxybenzophenone in the starting material (see above) or whether further demethylation occurred during the reaction with lithium aluminum hydride.

Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.21; H, 6.20; O, 24.59. Found: C, 69.49; H, 6.25; O, 24.12.

(27) F. Mauthner and G. Szonyi, *J. prakt. Chem.*, **92**, 194 (1915).

(28) These were prepared by Dr. Leonard R. Worden in these laboratories.

(29) L. H. Klemm, H. J. Wolbert, and B. T. Ho, *J. Org. Chem.*, **24**, 952 (1959).

4-Allyloxy-3,5-dimethoxybenzoic Acid.—To 75.8 g. (0.38 mole) of syringic acid in 500 ml. of methanol was added in portions alternately during 3 hr. with stirring under reflux 172.1 g. (1.42 moles) of allyl bromide and 250.3 g. (1.14 moles) of 25% methanolic sodium methoxide. After refluxing for 3 hr. more, most of the solvent was distilled under reduced pressure and 142 ml. of methanol and 142.5 ml. of 20% aqueous sodium hydroxide were added. After refluxing for 2 hr. part of the solvent was distilled, water was added, and the mixture was extracted twice with ether. The aqueous solution was acidified with hydrochloric acid and the resulting solid was collected, washed with water, and dried, giving 77.6 g. (86%) of white solid, m.p. 114–117°. Recrystallization from aqueous ethanol yielded 69.2 g. of white crystals, m.p. 115.5–117°.

Anal. Calcd. for $C_{12}H_{13}O_5$: C, 60.50; H, 5.92. Found: C, 60.41; H, 5.91.

4′-Allyloxy-3′,5′-dimethoxyacetophenone (36).—A mixture of 39.4 g. (0.165 mole) of 4-allyloxy-3,5-dimethoxybenzoic acid, 200 ml. of benzene, and 20 ml. (0.28 mole) of thionyl chloride was heated under reflux for 3 hr. The solvent was distilled under reduced pressure, more benzene was added and distilled, leaving the crude acid chloride as a light yellow gum.

Dimethylcadmium was prepared from 5.2 g. (0.214 g.-atom) of magnesium, 22.4 g. (0.236 mole) of methyl bromide, 420 ml. of absolute ether, and 39.2 g. (0.214 mole) of cadmium chloride. The ether was distilled under reduced pressure and 150 ml. of dry benzene was added. To this was added with rapid stirring the above acid chloride in 200 ml. of benzene and the mixture was refluxed for 3 hr. A solution of 36 g. of ammonium chloride in 220 ml. of water was added slowly and the aqueous layer was extracted with ether and the benzene. The extracts were washed with water, aqueous sodium hydroxide, water, saturated sodium chloride, and dried over sodium sulfate. After filtration and removal of the solvent the product was distilled, giving 15.2 g. (39%) of solid, m.p. 50–57°. Recrystallization from hexane, methylcyclohexane, and twice from aqueous ethanol furnished 6.0 g. of white crystals, m.p. 60–62°.

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83; O, 27.09. Found: C, 66.14; H, 6.88; O, 27.45.

2′,4′,5′-Trimethoxybutyrophenone (41).[10]—To 39.2 g. (0.2 mole) of 2′,4′,5′-trihydroxybutyrophenone and 250 ml. of methanol was added in portions alternately during 3 hr. with stirring under reflux 186 ml. (2 moles) of dimethyl sulfate and a solution of 120 g. (3 moles) of sodium hydroxide in 200 ml. of water. After refluxing for 1.5 hr. more, the mixture was diluted with ice–water and most of the methanol was distilled under reduced pressure. It was then extracted with ether and the ether solution was washed with aqueous sodium hydroxide, then with water, and dried over sodium sulfate. Filtration and removal of the solvent gave 44.1 g. of yellow crystals, m.p. 70–75°. This was recrystallized from methylcyclohexane, yielding 39.65 g. (83.4%) of white crystals, m.p. 78.5–80°.

Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.46; H, 7.30.

2′-Hydroxy-4′,5′-dimethoxybutyrophenone (40).[11]—A mixture of 78.5 g. (0.4 mole) of 2′,4′,5′-trihydroxybutyrophenone, 276 g. (2 moles) of potassium carbonate, 189 g. (1.5 moles) of dimethyl sulfate, and 1 l. of dry benzene was heated with stirring under reflux for 15.5 hr. The mixture was diluted with water and acidified with hydrochloric acid. The benzene layer was washed with water and extracted with aqueous sodium hydroxide. Acidification of the basic solutions gave 57 g. of phenolic material melting too high for the desired compound. The benzene solution was concentrated to yield 26.6 g. of light yellow solid, m.p. 68.5–75°. This was recrystallized from methanol and then from heptane, giving 22.0 g. of white crystals, m.p. 77–78°. A mixture melting point with 2′,4′,5′-trimethoxybutyrophenone gave a depression (57–71°). Although the infrared spectrum does not show the OH group, this is not surprising since the group is highly bonded. The n.m.r.[26] clearly supports the proposed structure. It shows the phenolic hydrogen as a sharp singlet at 760 c.p.s., the aromatic hydrogen as 2 singlets at 422 and 383, the methoxyl hydrogens as 2 singlets at 233 and 231, and the hydrogens of the butyryl side chain as a triplet centered at 172, a sextuplet centered at 106, and a triplet centered at 219 c.p.s. relative to internal tetramethylsilane.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19; O, 28.54. Found: C, 64.37; H, 7.24; O, 27.26.

4′-Acetoxy-3′-iodo-5′-methoxyacetophenone.—A solution of 7.3 g. (0.025 mole) of 5-iodoacetovanillone[30] and 20 g. of potassium acetate in 100 ml. of acetic acid and 20 ml. of acetic anhydride was heated under reflux for 18 hr. Dilution with water gave 6.8 g. of the acetylated material, which, after recrystallization from ethanol and then from acetic anhydride, had m.p. 144–145.5°. This was identical with material prepared by acetylation of 5-iodoacetovanillone with acetic anhydride and a trace of sulfuric acid.

Anal. Calcd. for $C_{11}H_{11}IO_4$: C, 39.54; H, 3.32; I, 37.98. Found: C, 39.65; H, 3.75; I, 37.56.

3′,4′-Methylenedioxy-5′-methoxyacetophenone (37).—A mixture of 18.2 g. (0.1 mole) of 3′,4′-dihydroxy-5′-methoxyacetophenone,[31] 69.0 g. (0.5 mole) of potassium carbonate, 107.2 g. (0.4 mole) of methylene iodide, and 300 ml. of acetone was heated under reflux with stirring for 2 days. The mixture was filtered and the solid was extracted well with acetone. The acetone solution was concentrated nearly to dryness to a tan solid. This was extracted with ether and the ether solution was washed with cold aqueous sodium hydroxide. After washing with water and saturated sodium chloride, the ether solution was dried over sodium sulfate, filtered, and evaporated. The crystalline residue was washed with water and pentane, and dried, yielding 9.5 g. (48.5%) of solid, m.p. 82.5–83.5°. This was recrystallized from 85 ml. of 2-propanol, yielding 8.1 g. of white crystals, m.p. 82.5–83.5°.

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19; O, 32.96. Found: C, 61.91; H, 4.99; O, 32.56.

2-(Methylamino)-2′,3′,4′-trimethoxyacetophenone Hydrochloride.—This was prepared in 35% yield as described by Moed and Asscher,[32] m.p. 182–183.5° dec. These authors reported no melting point.

Anal. Calcd. for $C_{12}H_{18}ClNO_4$: C, 52.27; H, 6.58; Cl, 12.86; N, 5.08; O, 23.21. Found: C, 51.90; H, 6.50; Cl, 12.75; N, 4.83; O, 22.60.

3,4,5-Trimethoxybenzaldehyde O-Carboxymethyl Oxime (49).—A mixture of 19.6 g. (0.1 mole) of 3,4,5-trimethoxybenzaldehyde, 10.9 g. (0.1 mole) of aminoxyacetic acid hemihydrochloride, 4.1 g. (0.05 mole) of sodium acetate, 100 ml. of ethanol, and 50 ml. of water was kept at room temperature for several days and evaporated to dryness under reduced pressure. The gummy residue was dissolved in benzene, filtered, diluted with hexane, and cooled, giving 20.2 g. of white solid, m.p. 90–92°. This was recrystallized from benzene–hexane, giving 18.13 g. (70.5%) of white crystals, m.p. 100–103°.

Anal. Calcd. for $C_{12}H_{15}NO_6$: C, 53.53; H, 5.63; N, 5.20. Found: C, 53.59; H, 5.59; N, 5.17.

Syringaldehyde Oxime (46).—A mixture of 18.2 g. (0.1 mole) of syringaldehyde, 7.65 g. (0.11 mole) of hydroxylamine hydrochloride, 75 ml. of ethanol, and 24 ml. (0.12 mole) of 20% aqueous sodium hydroxide was heated under reflux for 2 hr. Most of the ethanol was distilled under reduced pressure and water was added, giving 16.6 g. (84.5%) of white cottony crystals, m.p. 125–127°. This was recrystallized from 100 ml. of ethyl acetate giving 11.42 g. of white needles, m.p. 126–127°.

Anal. Calcd. for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.46; H, 5.57; N, 7.15.

The material listed as this compound in *Chemical Abstracts*[33] (m.p. 91°) is actually 3,5-dimethoxy-4-ethoxybenzaldoxime as is clear in the original article.[34]

Syringaldehyde O-Carboxymethyl Oxime (47).—A mixture of 18.2 g. (0.1 mole) of syringaldehyde, 10.9 g. (0.1 mole) of aminoxyacetic acid hemihydrochloride, 4.1 g. (0.05 mole) of sodium acetate, 130 ml. of ethanol, and 50 ml. of water was allowed to stand for several hours and was evaporated to dryness under reduced pressure, giving a solid, m.p. 140–143°. This was recrystallized from 175 ml. of water, yielding 22.0 g. (86%) of white crystals, m.p. 146–147.5°.

Anal. Calcd. for $C_{11}H_{13}NO_6$: C, 51.76; H, 5.13; N, 5.49. Found: C, 51.44; H, 4.95; N, 5.41.

3,4-Dihydroxy-5-methoxybenzaldoxime (44).—A mixture of 80.8 g. (0.48 mole) of 3,4-dihydroxy-5-methoxybenzaldehyde,

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(32) H. D. Moed and M. Asscher, U. S. Patent 2,683,743 (1954).

(33) *Chem. Abstr.*, **39**, 5250 (1945).

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40.4 g. (0.58 mole) of hydroxylamine hydrochloride, 100 ml. of ethanol, and 200 ml. of 20% aqueous sodium hydroxide was heated under reflux for 4 hr. Most of the ethanol was distilled under reduced pressure, water was added, and the mixture was acidified with hydrochloric acid. The solid was collected, giving 67.5 g. of material, m.p. 140–143°. This was recrystallized several times from ethyl acetate and twice from water, yielding 49.4 g. (56%) of crystals, m.p. 153° dec.

Anal. Calcd. for $C_8H_9NO_4$: C, 52.46; H, 4.95; N, 7.65. Found: C, 52.65; H, 4.89; N, 7.67.

3,4-Diacetoxy-5-methoxybenzonitrile.—A mixture of 39.8 g. (0.218 mole) of 3,4-dihydroxy-5-methoxybenzaldoxime and 75 g. of acetic anhydride was heated until a vigorous reaction started. After the reaction subsided the mixture was again heated under reflux with stirring for 1 hr. The dark mixture was poured into ice-water, giving a dark solid, wt. 44.5 g. A sample was recrystallized from ethanol with the aid of Darco, giving crystals, m.p. 119.5–121°.

Anal. Calcd. for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45; N, 5.62. Found: C, 57.82; H, 4.05; N, 5.80.

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Antitumor Activity and Structural Relationships of Purine Derivatives and Related Compounds against Neoplasms in Experimental Animals

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A study of the various purines exhibiting antitumor activity has been made with special attention given to those compounds prepared in the author's laboratory over the past ten years. The antitumor activity of a number of purines is presented for the first time. Previously noted structure–activity relationships have been discussed and extended in view of possible binding sites on the purine molecule. Certain biochemical studies on the mode of action of the purines and purine analogs have been reviewed and several suggestions made for future synthetic work. Greater specificity of drug action and further biochemical studies on mechanisms of inhibition are needed.

The limited but encouraging success of certain simple purine derivatives and related compounds in the clinic[2a–d] against neoplastic diseases in man has stimulated the synthesis and study of a considerable number of potential purine antagonists in recent years. In our own laboratory over the past ten-year period approximately 1300 compounds (purines or related derivatives) have been prepared and evaluated under the auspices of the Cancer Chemotherapy National Service Center[2e] against various induced rodent tumors. It is now quite possible to classify most of the active compounds in various groups and to make certain general statements concerning structure and antitumor activity. In most instances preliminary screening was accomplished against Adenocarcinoma 755 since this tumor has been shown to be especially sensitive to inhibition by purines.[3] Adenocarcinoma 755 had earlier proved to be especially useful in the evaluation of structure–activity relationships of certain 4-aminopyrazolo[3,4-*d*]pyrimidines shown to possess antitumor activity in experimental mice.[4] Several previous studies of the antitumor activity of certain purine derivatives against this tumor have already appeared[3,5–7] and will be referred to often in the present report. In addition various structural derivatives of 6-purinethiol have been evaluated against Sarcoma 180 in mice.[8] Although there is certainly grave danger in extrapolating antitumor activity and structural relationships from one tumor to another, certain useful comparisons can be made. In the present work attention will be focused on functional group changes on the purine ring. The antitumor activity of purine nucleosides will only be referred to in the sense that D-ribose may be considered a 9-substituent. The antitumor activity of the various purine nucleoside-type antibiotics and active compounds prepared by changes in the carbohydrate moiety are beyond the scope of the present study.

From the point of view of the organic chemist the synthetic program was begun with the following goals. (1) Beginning with a lead "active" purine it was proposed to prepare a series of structurally related purines which could be evaluated to determine the maximum therapeutic index in experimental animals and therefore contribute to the careful selection of the most desirable derivative in a series for clinical investigation. (2) It was hoped to provide new purine derivatives which would exhibit antitumor action *via* different biochemical mechanisms. This would provide a powerful tool to combat the resistance often observed after prolonged

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