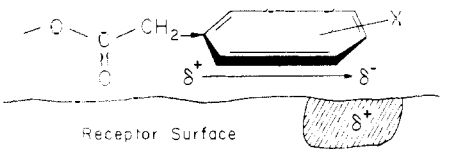
tropine and ψ-tropine. It is seen from Table I that the deviations in position of $\lambda_{C=O}$ afforded by substitution of either relatively electronegative (NO_2, F, Cl, Br) or electropositive (CH_3, OCH_3) substituents on the aryl nucleus of tropine- or ψ-tropine-series esters are quite small, ranging in maximum excursion to only several hundredths of a micron from the reference 5.77 μ value. Indeed, the mean excursion (absolute) noted for electronegatively substituted esters is ± 0.01 μ for the tropine series,[6] and ± 0.01 μ for the ψ-tropine series; for electropositive substitution, the corresponding mean excursions from the same reference level are ± 0.02 μ for each of the two series. In contrast, with these small variations in $\lambda_{C=O}$ induced by aryl substitution, the final column of Table I illustrates the very considerable influence of substituents X on biological potency. For this purpose, brief groups of previously documented[2] LD_{50} values (intravenous) in mice are cited as representative indexes of biological potency of the esters, with tabulation of data in units of μmoles of ester/kg of body weight. Noteworthy increments of toxic potency occur on substitution of the aryl ring by *m*-Cl (VI) and *p*-Cl (VII) groups.

Further from Table I, it is to be noted that hexahydrogenation of the aryl ring in either parent ester I or I-ψ produces an exaltation of $+0.02$ μ in the wavelength of the carbonyl-stretching vibration. Also, comparing substitution effects in the 3-tropanyl (transoid) series with these in the 2-α-tropanyl (transoid) series reveals that (1) ester III *vs.* ester XV at constant *p*-NO_2 substitution demonstrates a negative (-0.03 μ) displacement in peak position on shifting series, and (2) ester XI *vs.* ester XVI at constant *p*-CH_3 substitution also shows a negative (-0.04 μ) displacement in peak position on shifting series. Finally, it can be seen that esters containing the electronegative $CHCl_2$ grouping in replacement of the entire $CH_2C_6H_4X$ residue of compounds I–XIV also show a negative (-0.04 μ) displacement in peak position from the reference 5.77 μ level of the phenylacetates.

Accordingly, it seems clear that electronic perturbations produced by monosubstitution of I or I-ψ are only minimally reflected in electron-density changes about the region of the carbonyl function, as inferred from the tiny alterations in $\lambda_{C=O}$. Therefore, with esters I–XIV in each stereochemical series, the pronounced effects of aryl group substitution on potency of interaction with central and peripheral chemoreceptors in tissues and intact animals must be taken as reflecting the result of alterations in the electron-density map of the aryl residue itself, with little or no proliferation in effect beyond the insulating methylene link. In this event, the biological effects of distortion in electron-density pattern within the ring by relatively electronegative substituents which increase toxic potency[2] in the mouse may best be interpreted by (1) a direct interaction between the aryl ring and an electron-poor region of a tissue receptor surface; and (2) specific displacement of ring π-electron density away from the linking $-CH_2-$ group, for facilitation of interaction of esters with this type of receptor. These conditions are pictured schematically below. In this interaction diagram, the dominant electron-displacement mechanism activated jointly by X and tissue receptors has previously been inferred[2] to be of the inductive variety, stemming from studies with positional isomers. Further, this picture is consonant with the abrupt loss of ability to evoke stereospecific responses from mouse receptor systems when the phenyl ring of I and I-ψ is hexahydrogenated,[3] since the π bonding of an aryl locus to a localized charge center on a tissue surface as one contributor to tropine *vs.* ψ-tropine-series specificity is denied to the cyclohexyl esters.



Ester–receptor interaction model

[6] In this assessment the deviation of ester VII from the reference level has not been included, since it derives from measurements in a different solvent system.

Experimental Section

All of the esters for which data have been given in Table I were available in analytical purity as crystalline hydrochloride (XII as the methiodide) samples from previous studies[2] in this series. Solutions of esters in Fisher Spectranalyzed $CHCl_3$ were prepared just before use at a concentration level near 5% (w/v) and serially diluted with the same solvent for recording of spectra over the concentration range 1–5% (w/v). With the *p*-Cl ester VII, limited solubility precluded the use of pure $CHCl_3$ as solvent. For this ester, an equivolume mixture of $CHCl_3$ and Fluorobube was employed.

Spectra were obtained with the Beckman IR8 infrared spectrophotometer, employing an Irtran-2 liquid cell with 0.025-mm spacing. All spectra were scanned against solvent spectra obtained with the same cell. Particular care was taken in measurement of the position of the $\lambda_{C=O}$ value for the carbonyl-stretching vibration near 5.8 μ. Observed wavelengths were corrected in absolute value by use of a calibrating spectrum taken with a standard polystyrene film.

(7) S. L. Friess, T. J. Fass, H. V. Kelly, B. L. Macia, and P. M. Polasko, *Toxicol. Appl. Pharmacol.*, in press.
(8) S. L. Friess, L. J. Reber, and R. C. Usnac, *Science*, **8**, 88 (1965).

Methoxy Derivatives of 5,5-Diphenylhydantoin and 5-Phenyl-5-benzylhydantoin

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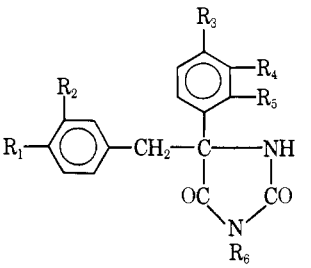
5,5-Disubstituted hydantoins have pharmacological activity as hypnotics,[1] anticonvulsants,[2] hypoglycemics,[3] etc. The systematic introduction of methoxy groups in 5,5-disubstituted hydantoins, that have an important pharmacological effect in some other drugs, was considered of interest by us. Methoxy and dioxymethylene derivatives of 5,5-diphenylhydantoin and methoxy derivatives of 5-phenyl-5-benzylhydantoin were obtained. The advantages of using DMF as a

(1) R. H. Hebst and F. B. Johnson, *J. Am. Chem. Soc.*, **54**, 2463 (1932).
(2) (a) V. S. Patkar and P. F. Smith, *J. Org. Chem.*, **20**, 125 (1965); (b) C. Enebäck and J. Alberty, *Arzneimittel-Forsch.*, **15**, 1231 (1965); (c) H. H. Merrit and F. J. Putnam, *Epilepsia*, **3**, 51 (1945).
(3) J. C. Lombardino and C. F. Gerber, *J. Med. Chem.*, **7**, 97 (1964).

TABLE I

METHOXY DERIVATIVES OF 5-PHENYL-5-BENZYLHYDANTOIN



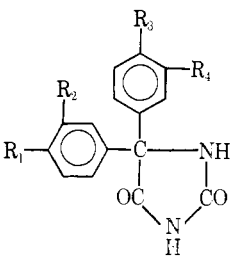
R_1	R_2	R_3	R_4	R_5	R_6	Yield, %	Mp, °C	Formula	Analyses
H	H	H	H	H	H	100	214–215	$C_{16}H_{14}N_2O_2$	C, H, N
H	H	OCH_3	H	H	H	60	226–227	$C_{17}H_{16}N_2O_3$	C, H, N
H	H	OCH_3	OCH_3	H	H	100	217–218	$C_{18}H_{18}N_2O_4$	C, H, N
OCH_3	H	OCH_3	H	H	H	80	231–232	$C_{18}H_{18}N_2O_4$	C, H, N
OCH_3	OCH_3	OCH_3	H	H	H	80	246–247	$C_{19}H_{20}N_2O_5$	C, H, N
OCH_3	H	OCH_3	OCH_3	H	H	80	232–233	$C_{19}H_{20}N_2O_5$	C, H, N
OCH_3	OCH_3	OCH_3	OCH_3	H	H	80	212–213	$C_{20}H_{22}N_2O_6$	C, H, N
OCH_3	OCH_3	H	H	H	H	85	208–209	$C_{18}H_{18}N_2O_4$	C, H, N
H	H	OCH_3	OCH_3	OCH_3	H	80	232–233	$C_{19}H_{20}N_2O_5$	C, H, N
OCH_3	OCH_3	OCH_3	OCH_3	OCH_3	H	40	283–284	$C_{21}H_{24}N_2O_7$	C, H, N
H	H	H	H	H	CH_3	95	202–203	$C_{17}H_{16}N_2O_2$	N
H	H	OCH_3	H	H	CH_3	95	195–196	$C_{18}H_{18}N_2O_3$	N
H	H	OCH_3	OCH_3	H	CH_3	95	174–175	$C_{19}H_{20}N_2O_4$	N
OCH_3	H	OCH_3	H	H	CH_3	95	185–186	$C_{19}H_{20}N_2O_4$	N
OCH_3	OCH_3	OCH_3	H	H	CH_3	95	195–196	$C_{20}H_{22}N_2O_5$	N
OCH_3	H	OCH_3	OCH_3	H	CH_3	95	167–168	$C_{20}H_{22}N_2O_5$	N
OCH_3	OCH_3	OCH_3	OCH_3	H	CH_3	95	201–202	$C_{21}H_{24}N_2O_6$	N

solvent in preparing the latter hydantoins has been already noted in a previous communication.[4]

Pharmacological Evaluation.—The pharmacological test was carried out using the method of Swinyard, *et al.*,[5] on rats. The drugs were administered as a suspension in tragacanth gum by a gastric catheter (15 mg/kg). The tests were compared to those with 5,5-diphenylhydantoin used as control. The anticonvulsant action was lowered when a phenyl group was replaced by a benzyl group. The introduction of methoxyl groups increased the drug efficacy. The action of bis(3,4-dimethoxyphenyl)hydantoin was similar to that of 5,5-diphenylhydantoin but delayed the appearance of the anticonvulsant effect. With 5,5-diphenylhydantoin the anticonvulsant effect appeared after approximately 3–4 hr, while with the tetramethoxy compound it was observed only after 6–7 hr.

TABLE II

METHOXY AND DIOXYMETHYLENE DERIVATIVES OF 5,5-DIPHENYLHYDANTOIN



R_1	R_2	R_3	R_4	Mp, °C	Formula	Analyses
OCH_3	H	H	H	220–221	$C_{16}H_{16}N_2O_3$	C, H, N
OCH_3	H	OCH_3	H	236–237	$C_{17}H_{16}N_2O_4$	C, H, N
O_2CH_2		H	H	210–211	$C_{16}H_{12}N_2O_4$	C, H, N
O_2CH_2		OCH_3	H	234–235	$C_{17}H_{14}N_2O_5$	C, H, N
O_2CH_2		O_2CH_2		222–223	$C_{17}H_{12}N_2O_6$	C, H, N

Experimental Section

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.3% of the theoretical values.

Methoxy Derivatives of Deoxybenzoin.—P_2O_5 (1 mole) and 1.8 moles of H_3PO_4 (*d* 1.71) were heated at 120° with continuous stirring for 4 hr. After cooling to 60–70°, 0.33 mole of the acid (phenylacetic, 4-methoxyphenylacetic, 3,4-dimethoxyphenylacetic) and 0.33 mole of the methoxybenzene of choice (methoxybenzene, 1,2-dimethoxybenzene, 1,2,3-trimethoxybenzene) were added to the polyphosphoric acid. The mixture was heated at 65–70° for 2 hr and then at 80–85° during 1 hr. The reaction mixture was cooled and poured slowly into water with stirring. The solid was filtered, washed (H_2O, 10% NaOH, H_2O), and recrystallized (EtOH); yield 70–80%.

2,3,4-Trimethoxydeoxybenzoin, mp 50°. *Anal.* ($C_{17}H_{18}O_4$) C, H.

2,3,4,3′,4′-Pentamethoxydeoxybenzoin, mp 86°. *Anal.* ($C_{19}H_{22}O_6$) C, H.

Methoxy Derivatives of 5-Phenyl-5-benzylhydantoin. General Method.—A suspension containing 27% of $(NH_4)_2CO_3$ and 11% of KCN in 75 ml of H_2O was added to a solution of 5 g of the deoxybenzoin derivative in 75 ml of DMF.[6] The mixture was heated at 80–90° for 2 hr and then at 90–100° for 8 hr. H_2O (80 ml) was added and the mixture was filtered. The filtrate was acidified with 10% HCl, and the hydantoin was collected by filtration. The crude product was purified by dissolving it in 10% NaOH, precipitating by acidification to pH 3, and recrystallization (EtOH); yield 40–100% (Table I).

The 3,N-methyl derivatives were obtained by the usual method.[7]

Derivatives of 5,5-Diphenylhydantoin. General Method.—Urea (1 g) was dissolved in a boiling solution of Na (0.4 g) in

(4) A. Novelli and A. De Santis, *Bol. Soc. Quim. Perú*, **30**, 155 (1964).

(5) E. A. Swinyard, W. C. Brown, and L. S. Goodman, *J. Pharmacol. Exptl. Therap.*, **106**, 319 (1952).

(6) To obtain hydantoin from cholestanone, J. W. Cremlyn and M. Chisholm [*J. Chem. Soc.*, 5117 (1965)] have used the same solvent, but have found that the product was the N-formyl derivative of the amino acid.

(7) H. Bilts, *Ber.*, **41**, 1379 (1908).

50 ml of EtOH. The benzil employed (2 g) was added in small portions and the mixture was refluxed for 50 min. Most of the EtOH was removed by distillation and H_2O (100 ml) was added. The mixture stood overnight and was filtered, the filtrate was acidified with 10% HCl, and the solid was filtered off, washed, and recrystallized (EtOH); yield 70–75% (Table II).

The methoxybenzil derivatives were prepared by condensing the respective aldehydes,[8] and the product was then oxidized with $CuSO_4$ solution in pyridine on a boiling-water bath.[9]

Acknowledgment.—This work was carried out with a grant from the C.N.I.C.y T.

(8) N. J. Leonard, R. T. Rapala, H. L. Herzog, and E. R. Blout, *J. Am. Chem. Soc.*, **71**, 2997 (1949).

(9) H. T. Clarke and E. E. Dreger, "Organic Syntheses," Coll. Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1958, p 87.

Synthesis of 3,5-Bishydroxymethyl-6-methyl-2-pyridone, an Isomer of Pyridoxine

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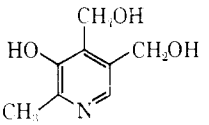
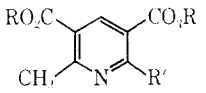
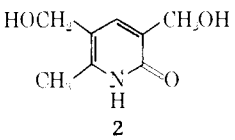
A number of positional isomers of pyridoxine (**1**) have been prepared[1] and a theory concerning the structure–activity relationship for the vitamin B_6 like compounds has been proposed.[2] The preparation and biological testing of 3,5-bishydroxymethyl-6-methyl-2-pyridone (**2**) are now described.



1



3, R′ = OH; R = H
4, R′ = OH; R = Et
5, R′ = OCH_2Ph; R = H



2

⇌ hydroxypyridine tautomer

The known dibasic acid[3] **3** was converted to the diethyl ester **4** on treatment with ethanol and sulfuric acid in refluxing benzene. Reaction with $POCl_3$ followed by sodium in benzyl alcohol yielded the corresponding benzyl ether dibenzyl ester. Reduction of the benzyl ether diacid **5**, which was easier to handle than the diester, with lithium aluminum hydride afforded the ether diol which was hydrogenolyzed to give the required pyridoxine isomer.

Compound **2** exhibited no vitamin B_6 like activity against *Saccharomyces carlsbergensis* in the range 5–500 ng/ml which is consistent with the proposed structure–activity theory.[2] It showed a slight anti-B_6 activity which did not merit further investigation on higher organisms.

(1) (a) R. G. Jones, *J. Am. Chem. Soc.*, **74**, 1489 (1952); (b) F. Hoffman, Swiss Patent 224,314; *Chem. Abstr.*, **43**, 1811g (1949); (c) D. Heyl, E. Luz, and S. A. Harris, *J. Am. Chem. Soc.*, **76**, 4474 (1956); (d) D. B. McCormick, M. E. Gregory, and E. E. Snell, *J. Biol. Chem.*, **236**, 2085 (1961); (e) B. van der Wal, Th. J. de Boer, and H. O. Huisman, *Rec. Trav. Chim.*, **80**, 221 (1961).

(2) E. E. Snell, *Vitamins Hormones*, **16**, 77 (1958).

(3) J. L. Simonsen, *J. Chem. Soc.*, 1022 (1908); G. Errera, *Ber.*, **33**, 2969 (1900).

Experimental Section[4]

3,5-Dicarboethoxy-6-methyl-2-pyridone (**4**). 6-Methyl-2-pyridone-3,5-dicarboxylic acid (19.7 g, 0.1 mole) was refluxed with absolute EtOH (300 ml), PhH (300 ml), and concentrated H_2SO_4 (5.5 ml) below a Soxhlet containing 40 g of Molecular Sieves, Union Carbide 4A, for 7 days.[5] Reduction to half-volume by evaporation under reduced pressure and cooling gave the diester as white needles: recrystallized from EtOH, mp 196–198°; 17 g (68%); ir (KCl) (cm^{-1}) 1670, 1703, 1725; nmr ($CDCl_3$) (ppm) 1.24 (*s* 1), 5.62 (*q* 4), 7.2 (*s* 3), 8.65 (*tr* 6). *Anal.* ($C_{12}H_{15}NO_5$) C, H, N.

2-Chloro-3,5-dicarboethoxy-6-methylpyridine.—3,5-Dicarboethoxy-6-methyl-2-pyridone (15 g, 0.059 mole) and $POCl_3$ (75 ml) were refluxed together for 3.5 hr under anhydrous conditions. The cooled solution, in 5-ml portions, was cautiously added to ice water with shaking. The buff precipitate (15.3 g) was filtered and dried in a vacuum desiccator. Ether extraction of the filtrate afforded further material (1.14 g). Crystallization from EtOH–H_2O gave white needles: mp 53.5–54.5°; 14 g (85%); ir (KCl) (cm^{-1}) 1730; nmr ($CDCl_3$) (ppm) 1.5 (*s* 1), 5.65 (*q* 4), 7.2 (*s* 3), 8.6 (*tr* 6). *Anal.* ($C_{12}H_{14}ClNO_4$) C, H, Cl, N.

2-Benzoxy-6-methylpyridine-3,5-dicarboxylic Acid (**5**).—To Na (1.6 g, 0.0695 g-atom) dissolved in benzyl alcohol (200 ml) was added 2-chloro-3,5-dicarboethoxy-6-methylpyridine (11.5 g, 0.0425 mole) and the mixture stirred at about 18° for 17 hr. AcOH (4.2 ml, 0.07 mole) was added dropwise to the stirred solution and the bulk of the solvent was removed under reduced pressure. The residue was dissolved in absolute EtOH (75 ml), 10% aqueous NaOH (75 ml) was added, and the whole was refluxed for 3 hr. Evaporation to half-volume under reduced pressure and cautious acidification of the residual liquor with dilute HCl gave a white precipitate, 9.08 g (74%). Crystallization from EtOH–H_2O gave the analytical sample: softens 186–188°, decomposes 260°; ir (KCl) (cm^{-1}) 1695, 1720. *Anal.* ($C_{14}H_{13}NO_5$) C, H, N.

2-Benzoxy-3,5-bis(hydroxymethyl)-6-methylpyridine.—A solution of crude benzyl ether diacid (9 g, 0.0314 mole) in dry THF (500 ml) was refluxed for 3 hr below a Soxhlet containing $LiAlH_4$ (2.5 g, 0.060 mole). The mixture was cooled and stirred, and 7% aqueous NaOH (7.5 ml) was added dropwise. Filtration of the gray precipitate and evaporation of the filtrate under reduced pressure gave crude benzyl ether diol. Crystallization from petroleum ether (bp 40–60°) gave white needles: mp 86.5–87°; 3.14 g (38% first crop); ir (KCl) (cm^{-1}) 1200, 1000; nmr ($CDCl_3$) (ppm) 4.6 (*s* 2), 5.48 (*s* 2) 5.51 (*s* 2) 7.15 (*broad* 2). *Anal.* ($C_{15}H_{17}NO_3$) C, H, N.

3,5-Bishydroxymethyl-6-methyl-2-pyridone (**2**).—The benzyl ether diol (5.4 g, 0.021 mole) in absolute EtOH (100 ml) was shaken with 5% Pd–C (250 mg) under H_2 at the ambient temperature and pressure, resulting in an uptake of 505 ml of H_2 (equivalent to 2H/mole). Removal of the catalyst and evaporation of the liquor gave the pyridone in quantitative yield. Crystallization from EtOH gave fine white needles: mp 181–181.5°; ir (KCl) (cm^{-1}) 1650; nmr (D_2O) (ppm) 2.2 (*s* 1), 5.4 (*s* 4), 7.5 (*s* 3). *Anal.* ($C_8H_{11}NO_3$) C, H, N.

The **diacetate** was prepared in AcOH; mp 146–148° (C_8H_{11}); ir (KCl) (cm^{-1}) 1240, 1650, 1725. *Anal.* ($C_{12}H_{15}NO_5$) C, H, N.

Acknowledgment.—We thank Nederlands Instituut voor Volksvoeding for testing compound **2**.

(4) Melting points are uncorrected. The notation in parentheses used in describing nmr spectra refers to the type and proton integral of the signal.

(5) Y. Ito, *Nippon Zaryku Zasshi*, **83**, 195 (1962).

3-Aminomethyl-5-hydroxybenzo[*b*]thiophenes[1]

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In our continuing study of the synthesis and pharmacological properties of sulfur analogs of biologically

(1) Contribution No. 1516. Benzo[*b*]thiophene Derivatives. XI. Part X: E. Campaigne and T. Bosin, *J. Med. Chem.*, **10**, 945 (1967).