# Substituent Effects on Ester Carbonyl Absorption and Chemoreceptor Responses Initiated by Tropanyl Phenylacetates[1]

S. L. FRIESS AND F. J. FASH

*Division of Biochemistry, Naval Medical Research Institute, Bethesda, Maryland 20014*

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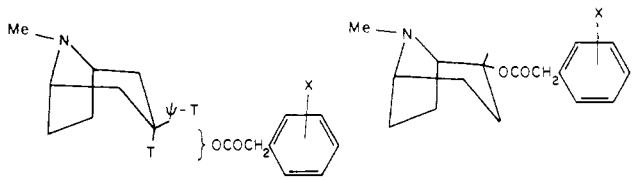
Recent work[2] on toxic interactions of monosubstituted phenylacetate esters in the 3-tropanyl (tropine and $\psi$-tropine) and 2-$\alpha$-tropanyl series with CNS receptor systems in the mouse has pointed to a rather systematic dependence of potency on certain structural features of the ester. In general, the order of decreasing potency in CNS stimulation/blockade and acute toxicity at constant substitution X runs in the sequence 3-tropanyl (transoid) > 3-tropanyl ($\psi$, cisoid) $\geq$ 2-$\alpha$-tropanyl (transoid). With progressive change in X, it is noted that relatively electronegative substituents (X = Cl, $NO_2$, etc.) on the aryl nucleus of 3-tropanyl esters confer significantly larger increments of toxicity on the parent structure (X = H) than do electropositive substituents (*e.g.*, $OCH_3$). This latter aspect of the structure–activity relationship raises the question of the degree to which the aryl substituent X may alter the total electron-density profile of the ester, and in turn the manner in which this alteration may be reflected in a change in effective interaction of a given ester with chemoreceptor surfaces controlling the onset of the convulsion–paralysis syndrome in the mouse. In particular, the point as to whether ring substituents are able to exert remote electronic effects on the $\pi$-electron distribution function of the –OCO– group, through the aryl ring and the insulating methylene linkage, and thereby alter the strength of interaction of this high-density locus with a potential charge site in a tissue receptor seemed amenable to probing by infrared absorption measurements of the C=O stretching vibrations in the esters. To the extent that electron supply toward or electron withdrawal from the C=O locus by substituent X changes the $\pi$-electron profile, a corresponding change in $\lambda_{C=O}$ would be expected. This possibility has now been tested, with the results described below.




3-Tropanyl esters | 2-α-Tropanyl esters (Transoid)

| Group X | Series T | Series ψ-T |
|---|---|---|
| H | I | I-ψ |
| m-$NO_2$ | II | II-ψ |
| p-$NO_2$ | III | III-ψ |
| o-F | IV | IV-ψ |
| m-F | V | |
| m-Cl | VI | |
| p-Cl | VII | VII-ψ |
| m-Br | VIII | VIII-ψ |
| o-$CH_3$ | IX | IX-ψ |
| m-$CH_3$ | | X-ψ |
| p-$CH_3$ | XI | XI-ψ |
| p-$CH_3$·MeI | XII | |
| m-$OCH_3$ | XIII | XIII-ψ |
| p-$OCH_3$ | | XIV-ψ |

| Group X | Ester |
|---|---|
| p-$NO_2$ | XV |
| p-$CH_3$ | XVI |

First, the spectra of all esters studied contained the characteristic absorption peak corresponding to the C=O stretching vibration in the expected[3] $\lambda_{C=O}$ region, 5.7–5.8 $\mu$. This peak for each ester appeared invariant in position as the ester concentration in $CHCl_3$ varied from 1–5% (w/v), with a reproducibility in peak wavelength of the order of 0.01 $\mu$. Additionally, the OH bond[4] and potential H-bonding bands[4,5] characteristic of the parent amino alcohols, tropine, and $\psi$-tropine, were missing from the ester spectra.

Both of the unsubstituted phenylacetates I and I-$\psi$ were found to display sharp absorption peaks at 5.77 $\mu$. This peak value was therefore taken as each series reference, and the $\lambda_{C=O}$ values for the corresponding peaks of the other esters were tabulated in terms of algebraic deviations from this reference position in each amino alcohol series. This tabulation is summarized in Table I, which includes data for the available ester I–XIV in each tropanyl series, for the unsubstituted cyclohexylacetate esters, for the 2-$\alpha$-tropanyl esters XV and XVI, and finally for the dichloroacetate esters of

TABLE I

$\lambda_{C=O}$ AND MOUSE $LD_{50}$ VALUES FOR TROPANYL PHENYLACETATES AND RELATED ESTERS

| Ester hydrochlorides | $\lambda_{C=O}$ deviations from ref[a] peak, $\mu$: Tropine (transoid) | ψ-Tropine (cisoid) | Mouse $LD_{50}$ values,[c] μmoles/kg: Tropine | ψ-Tropine |
|---|---|---|---|---|
| I and I-ψ | 0.00 | 0.00 | 77.8 ± 2.7 | 142.9 ± 5.4 |
| II and II-ψ | 0.00 | +0.01 | | |
| III and III-ψ | −0.01 | −0.01 | | |
| IV and IV-ψ | 0.00 | +0.01 | | |
| V | +0.01 | | | |
| VI | +0.01 | | 53.6 ± 1.5 | 76.9 ± 0.6 |
| VII and VII-ψ | −0.08[b] | 0.00 | 18.5 ± 3.6 | 32.7 ± 1.2 |
| VIII and VIII-ψ | 0.00 | 0.00 | | |
| IX and IX-ψ | +0.04 | −0.01 | | |
| X-ψ | | +0.02 | 65.5 ± 6.5 | 105.5 ± 7.1 |
| XI and XI-ψ | +0.01 | −0.06 | 74.2 ± 1.6 | 127.5 ± 1.6 |
| XII | +0.02 | | | |
| XIII and XIII-ψ | +0.01 | +0.01 | | |
| XIV-ψ | | +0.01 | | |
| XV | −0.04 | | | |
| XVI | −0.03 | | | |
| Cyclohexylacetates | +0.02 | +0.02 | 119.3 ± 5.3 | 112.6 ± 4.0 |
| Dichloroacetates | −0.04 | −0.04 | | |

[a] Reference level of $\lambda_{C=O}$ 5.77 $\mu$ as found for the unsubstituted phenylacetates I and I-$\psi$; spectra taken in $CHCl_3$ unless otherwise indicated. [b] Spectrum taken in 50% $CHCl_3$–50% Fluorolube (vol) because of low solubility in $CHCl_3$ alone. [c] Previously documented; see leading references.[2]

(1) From Bureau of Medicine and Surgery, Navy Department, Research task MR005.06.0002. The opinions in this paper are those of the authors and do not necessarily reflect the views of the Navy Department or the naval service at large.

(2) Leading references: (a) S. L. Friess, R. C. Durant, H. D. Baldridge, Jr., and L. J. Reber, *Toxicol. Appl. Pharmacol.*, **7**, 694 (1965); (b) S. L. Friess, H. D. Baldridge, Jr., R. C. Durant, and L. J. Reber, *ibid.*, **7**, 794 (1965).

(3) R. T. Conley, "Infrared Spectroscopy," Allyn and Bacon, Inc., Boston, Mass., 1966, p 145.

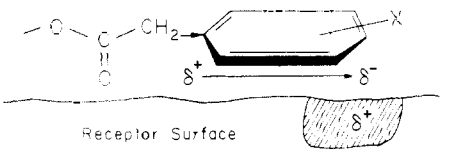
(4) B. L. Zenitz, C. M. Martini, M. Priznar, and F. C. Nachod, *J. Am. Chem. Soc.*, **74**, 5564 (1952).

(5) S. Archer and T. R. Lewis, *Chem. Ind.* (London), 853 (1954).

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 those 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[7] 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,[8] 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 Fluorolube 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. Martin, and P. M. Pohoski, *Toxicol. Appl. Pharmacol.*, in press.
(8) S. L. Friess, L. J. Reber, and R. C. Doran, *ibid.*, **8**, 88 (1966).

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

ARMANDO NOVELLI AND ALBERTO M. DE SANTIS

*Departamento de Química Orgánica, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Buenos Aires, República Argentina*

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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. Herbst 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).