Electronic Effects of *para*-Substituents on the Local Anesthetic Activity of 2-Diethylaminoethyl Benzoate and Related Compounds[1a,1b]

ALVIN M. GALINSKY, JAMES E. GEARIEN, ALFRED J. PERKINS, AND STANLEY V. SUSINA

Departments of Chemistry and Pharmacy, University of Illinois, College of Pharmacy, Chicago, Illinois

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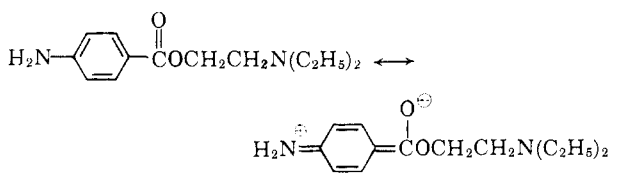
The infrared spectra of a number of diethylaminoethyl *p*-substituted benzoates, cinnamates and β-phenylpropionates were correlated with their activity as local anesthetics. In general, their potencies as local anesthetics could be related to the bond order of the carbonyl portion of their ester groups.

A number of *p*-substituted benzoic acid esters are known to possess local anesthetic activity. The electronic structure of the ester group in each of these compounds is dependent upon the resonance effects of the aromatic substituents. Electron repelling substituents in the *para* position of these esters would be expected, through their inductive effect or through resonance, to decrease the relative bond order of the carbonyl portion of the ester group while electron attracting groups would be expected to have the opposite effect.



It might be expected that changes in bond order of the carbonyl portion of the ester group would affect local anesthetic activity. If desensitization occurs, as suggested by Nachmansohn,[2] by a competition with acetylcholine for an enzyme site, changes in the bond order of the carbonyl portion of the ester group could influence local anesthetic activity. Compounds whose *p*-substituents gave rise to a lower carbonyl bond order might be expected to have a higher affinity for the enzyme site and therefore compete more favorably for it than acetylcholine or any biologically active chemical. It also is possible that the resonance and inductive effects of the electron repelling substituents may give rise to structures possessing solubility and adsorptive properties which are quite close to those required for maximum local anesthetic activity. Thus it appeared that an attempt to correlate the local anesthetic activity of a group of 2-diethylaminoethyl esters of *p*-substituted benzoic acids, with the bond order of the carbonyl group might prove helpful in a correlation of chemical structure and pharmacological activity.

While many 2-diethylaminoethyl *p*-substituted benzoates have been tested for local anesthetic activity, a review of the published data indicated that no single method of testing has been employed nor have all their pharmacological activities been related to any single local anesthetic. It seemed necessary, therefore, to prepare a number of 2-diethylaminoethyl *p*-substituted benzoates and to reevaluate their local anesthetic activity. This pharmacological evaluation should utilize a uniform method of testing which would compare their activities to a single standard. In this evaluation, it was considered more reasonable to measure their potencies over a fixed period of time rather than their durations of action, since this latter measurement might be more closely related to some detoxification mechanism. For this reason, it was decided that pharmacological testing designed to determine their ED_{50} values should be undertaken. A modification of the classical method of Bulbring and Wajda[3] for determining ED_{50} values of infiltration local anesthetics was employed for this purpose.

Although qualitative predictions can be made of the relative inductive and resonance effects upon the bond order in a group of closely related molecules, an objective measurement of a physical property related to bond order is always helpful. In this case the stretching frequency of the C=O bond was used for this purpose, since this frequency is related through its force constant to the bond strength and, therefore, to the bond order. The lower the bond order the lower should be the frequency of the carbonyl absorption. Soloway and Fries[4] have demonstrated that the C=O stretching frequency of a number of *p*-substituted acetophenones varied with the type of substituent and that the magnitude of the shift in frequency was related to the electron donating or withdrawing character of the group.

Hammett's[5] *sigma* constants have frequently been used as a quantitative measure of the inductive and resonance contribution to particular structures. Insofar as local anesthetic activities and carbonyl bond order is concerned, the infrared frequency gives a much better correlation with ED_{50} than the sigma values for the substituent groups studied in this work. The spectra of the compounds prepared and evaluated pharmacologically were determined on a Beckman IR-4 spectrophotometer. Compounds capable of intermolecular hydrogen bonding were determined in dilute solution. Those compounds that could not enter into intermolecular hydrogen bonding showed no significant difference in carbonyl absorption frequency whether determined in solution or in a potassium bromide disk. These compounds are shown in Table I with their carbonyl absorption frequencies and ED_{50} values.

(1) (a) Abstracted from a thesis submitted by A. M. Galinsky to the Graduate College of the University of Illinois in partial fulfillment of the requirements for the Degree of Doctor of Philosophy; (b) presented before the Division of Medicinal Chemistry, 141st National Meeting, American Chemical Society, Washington, D. C., March 21–29, 1962.

(2) D. Nachmansohn, "Chemical and Molecular Basis of Nerve Activity," Academic Press, New York, N. Y., 1959.

(3) E. Bulbring and I. Wajda, *J. Pharmacol. Exptl. Therap.*, **85**, 78 (1945).

(4) A. H. Soloway and S. L. Fries, *J. Am. Chem. Soc.*, **73**, 5000 (1951).

(5) L. P. Hammett, "Physical Organic Chemistry," 1st Ed., McGraw-Hill, New York, N. Y., 1940, p. 184.

TABLE I

CORRELATION OF ABSORPTION FREQUENCIES WITH LOCAL ANESTHETIC POTENCIES. BENZOATES

2-Diethylaminoethyl substituted benzoate	ED_{50}, mmoles/100 ml.	Absorption frequency, cm.$^{-1}$
1. *p*-Ethoxy[a]	0.012	1708
2. *p*-Dimethylamino	.019	1697
3. *p*-Methoxy[a]	.060	1708
4. *p*-Amino[b]	.075	1711
5. *p*-Hydroxy[c]	.125	1714
6. *p*-Acetamido[d]	.53	..
7. Benzoate[e]	.60	1727
8. *p*-Nitro[d]	.74	1731

[a] H. Vanderhaege, P. Kolosy, and M. Claesen, *J. Pharm. Pharmacol.*, **6**, 119 (1954). [b] Commercially available U.S.P. grade was used in this study. [c] R. Fusco, S. Chiavarelli, G. Palazzo, and D. Bovet, *Gazz. Chim. Ital.*, **78**, 951 (1948). [d] A. Einhorn and E. Uhlfelder, *Ann.*, **371**, 138 (1909). [e] E. S. Cook and C. W. Kreke, *J. Am. Chem. Soc.*, **62**, 1951 (1940).

As may be seen from the ED_{50} values and the infrared spectra of this series of compounds, there is a marked correlation between local anesthetic potency and the bond order of the carbonyl portion of the ester group as measured by C=O stretching frequency. Of these compounds, only 2-diethylaminoethyl *p*-ethoxybenzoate deviates from the local anesthetic activity that might be predicted from its infrared spectrum.

Attempts to relate the local anesthetic activity of 2-diethylaminoethyl *p*-chlorobenzoate[6] to the bond order of the carbonyl portion of the ester group were unsuccessful. The compound appeared to possess an ED_{50} of 0.090 mmole/% and a carbonyl absorption frequency of 1729 cm.$^{-1}$. Further pharmacological study, however, indicated that animals treated with an "effective" dose of the compound did not regain their sensitivity to pain and that desensitization was probably accompanied by nerve damage. It seemed probable, therefore, that the low ED_{50} measured was more the result of a toxic manifestation than a true measure of the compound's local anesthetic potency.

The local anesthetic properties and the infrared spectrum of 2-diethylaminoethyl *p*-acetamidobenzoate were also studied. The infrared spectrum of this compound showed one weak and two strong peaks in the region of carbonyl absorption which was not further resolved. It was impossible, therefore, to assign unequivocally the exact absorption frequency of the carbonyl moiety belonging to the ester group. The ED_{50} of this compound was 0.53 mmole/100 ml. which, as might be predicted, denoted an activity somewhat lower than either 2-diethylaminoethyl *p*-aminobenzoate or the similar ester of *p*-hydroxybenzoic acid. It also demonstrated slightly more activity than 2-diethylaminoethyl benzoate. This might be predicted from the result obtained with the other compounds in this series, since the acetyl group would reduce the resonance effect of the amino group.

In order to examine further the electronic effects of substituents upon local anesthetic activity, it seemed desirable to prepare a compound in which the ester group would be isolated from the usual inductive or resonance effects of the *para* substituent and to compare this compound with those of similar structure in which the *para* substituent could enter into resonance with the ester group. Previous observations[7,8] that cinnamate esters were better local anesthetics than phenylpropionate esters offered a valuable clue in devising such molecules. Furthermore, use of phenylpropionate esters and cinnamate esters permits a comparison of molecules with an equal number of carbon atoms. Therefore, the 2-diethylaminoethyl esters of β-(*p*-aminophenyl)-propionic acid, *p*-nitrocinnamic acid and *p*-aminocinnamic acid were prepared and tested for local anesthetic activity. Their ED_{50} values and carbonyl absorption frequencies are shown in Table II.

TABLE II

CORRELATION OF ABSORPTION FREQUENCIES WITH LOCAL ANESTHETIC POTENCIES. II. CINNAMATES AND PHENYLPROPIONATE

Compound	ED_{50}, mmoles/100 ml.	Absorption frequency, cm.$^{-1}$
1. 2-Diethylaminoethyl *p*-aminocinnamate	0.063	1710
2. 2-Diethylaminoethyl *p*-aminophenylpropionate	.27	1725
3. 2-Diethylaminoethyl *p*-nitrocinnamate[a]	.66	1731

[a] See footnote 7.

From these data it may be seen that the aminophenylpropionate ester is less potent and has a higher carbonyl absorption frequency than the aminocinnamate ester. As a consequence, it appeared that the amino group was most effective when it was in conjugation with the carbonyl moiety and could, through resonance, decrease the relative bond order of the latter. It is also interesting to note that, although the length of the conjugated system is extended in the cinnamates as compared to the benzoates, both the pharmacological activity (ED_{50}) and the C=O absorption frequencies are very nearly alike in the *p*-amino compounds and in the *p*-nitro compounds. This strengthens our hypothesis that the ester group is at least part of the biologically active portion of these local anesthetic molecules and is probably involved in the binding of the local anesthetic to the enzyme site.

Experimental[9]

2-Diethylaminoethyl *p*-Dimethylaminobenzoate.—In a pressure bottle, 0.15 g. of platinum oxide and 20 ml. of 95% ethanol were subjected to hydrogen at a pressure 0.35 kg./cm.^{2} until the catalyst became black (5 min.). A solution of 27.3 g. (0.1 mole) of 2-diethylaminoethyl *p*-aminobenzoate hydrochloride in 3 ml. of concentrated hydrochloric acid and 80 ml. of 95% ethanol was cooled to 5°. A 37% aqueous formaldehyde solution (17.0 ml.; 0.2 mole) was also cooled to 5° and added dropwise to the alcoholic solution. The cold solution was then added to the reduced platinum oxide and the entire mixture was hydrogenated at a pressure of 2.46 kg./cm.^{2} for 5 hr. After the hydrogenation was completed, the catalyst was removed by filtration and the solvent was evaporated. The sirupy residue was dissolved in cold water and the pH of this solution was adjusted to 9 with sodium carbonate solution. The separated oil was extracted with ether and the ethereal extract was dried over anhydrous sodium sulfate. Subsequent distillation gave 18.2 g. (65%) of an oil which distilled at 146–148° (0.02 mm.).

Anal. Calcd. for $C_{15}H_{24}N_2O_2$: C, 68.20; H, 9.09; N, 10.61. Found: C, 68.29; H, 9.11; N, 10.58.

(6) H. Vanderhaege, *J. Pharm. Pharmacol.*, **6**, 55 (1954).

(7) L. L. Sulya, *Microfilm Abstr.*, **4**, No. 2, 47 (1949).

(8) E. R. Andrews, M. G. Van Campen, and E. L. Schuman, *J. Am. Chem. Soc.*, **75**, 4004 (1953).

(9) Microanalyses were performed by Weiler and Strauss, Microanalytical Laboratory, Oxford, England. Melting points are corrected and were determined on a Thomas-Hoover capillary melting point apparatus.

2-Diethylaminoethyl *p*-Nitrophenylpropionate.—A mixture of 10.0 g. (0.05 mole) of *p*-nitrophenylpropionic acid[10] and 25 ml. of thionyl chloride was allowed to reflux for 2 hr. The excess thionyl chloride was removed by distillation and the residue was treated with 60 ml. of dry benzene. A solution of 18.0 g. (0.15 moles) of 2-diethylaminoethanol in 60 ml. of dry benzene was slowly added to the acid chloride solution. When the addition was completed, the mixture was refluxed for 2 hr. and filtered. The filtrate, when distilled, yielded 10.0 g. (66%) of a viscous yellow oil which boiled between 167–169° (0.1 mm.). This oil, dissolved in 100 ml. of anhydrous ether, was converted to its hydrochloride by treatment with anhydrous hydrogen chloride. The salt was filtered and recrystallized from acetone by the addition of isopropyl ether. The white, crystalline product melted at 131–132°.

Anal. Calcd. for $C_{15}H_{23}ClN_2O_4$: C, 54.46; H, 7.01; N, 8.47. Found: 54.96; H, 7.19; N, 8.38.

2-Diethylaminoethyl *p*-Aminophenylpropionate.—2-Diethylaminoethyl *p*-nitrophenylpropionate hydrochloride (11.2 g., 0.034 mole) was dissolved in 30 ml. of water. Saturated sodium carbonate solution was added in sufficient quantity to raise the pH of the solution to 9. The oil that separated was extracted with three 30-ml. portions of ether. After drying with anhydrous sodium sulfate, 0.1 g. of platinum oxide, or 0.5 g. of W-2 Raney nickel catalyst was added, and the compound was reduced at a hydrogen pressure of 2.1 kg./cm.^{2} and 34° for 3 hr. After filtration, the solvent was removed by evaporation and the remaining yellow oil was distilled. The product distilled at 160–162° (0.2 mm.) and weighed 6.7 g. (75%).

Anal. Calcd. for $C_{15}H_{24}N_2O_3$: C, 68.20; H, 9.09; N, 10.61. Found: C, 68.44; H, 9.41; N, 10.61.

Infrared Spectra.—All infrared spectra were obtained on a Beckman IR-4 infrared spectrophotometer. In the region of carbonyl absorption the frequencies were measured using a period of 8, spectral slit width 5 cm.$^{-1}$ and a gain of 100×. A speed of 0.02 μ/min. was employed.

Pharmacology.—A solution of the hydrochloride[11] or hydriodide of the test compound, in known molar concentration, and 1.5 μg./ml. of epinephrine hydrochloride in normal saline solution was prepared. A 0.25 ml. dose of this solution was injected intracutaneously in the anterior area of each of 2 guinea pigs whose backs had been previously clipped. An identical dose of the same solution was injected into the posterior area of each of 2 other guinea pigs. The borders of the resultant wheals were outlined with an indelible pencil. At the end of a 5 min. period, each animal was probed with a pin in the area outside the zone of the wheal. After observing the normal response of the animal to the stimulus, a total of 6 probes were applied to the area inside the wheal at intervals of 3–5 sec. The number of probes to which the guinea pig failed to respond was recorded.

The test of 6 probes to the area of the wheal was repeated on each guinea pig at 5 min. intervals for a total period of 1 hr. The number of times the probe failed to elicit a response in all 4 animals was added and the sum was divided by the total number of possible responses. The quotient, expressed in terms of per cent, was plotted on probit-logarithm graph paper against the molar concentration of the compound in the dose administered. Using the same 4 animals, a second concentration of the test compound was administered except that the injection sites (anterior-posterior) were reversed in each animal. In a similar manner additional concentrations of the test compound were employed until a well defined dose-response curve was obtained. The molar ED_{50} for each compound, the concentration at which the plotted line intersected the line of 50% response (probit 5), was then determined.

(10) F. Von Kunek and E. Pacsu, *Ber.*, **51**, 855 (1918).

(11) For those compounds isolated as the water insoluble free base, an equivalent amount of hydrochloric acid was added.

Structures Related to Morphine. XXV.[1a] 5-Propyl- and 5,9-Dipropyl-6,7-benzomorphans and a Pharmacologic Summary[1b]

J. HARRISON AGER, S. E. FULLERTON, AND EVERETTE L. MAY

National Institutes of Health, Bethesda 14, Maryland

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Cyclization of 4-propyl- and 3,4-dipropyl-2-(*p*-methoxybenzyl)-1-methyl-1,2,5,6-tetrahydropyridines (III) obtained in the Stevens rearrangement of the quaternary compounds (II) has produced the expected benzomorphans (IV) and (V). Compounds Va and Vb have been converted to open nitrogen analogs VIa and VIb which show significant diuretic activity in the rat. A tabular summary of the analgesic activity, acute toxicity (mice) and morphine-abstinence-suppressing capacity (monkey) of various 2′-hydroxy-2-methyl-6,7-benzomorphans is presented. In this series a pronounced, consistent separation of analgesic activity and physical dependence property has been achieved.

2′-Hydroxy-2-methyl-6,7-benzomorphans, a relatively new class of analgesic agents synthesized in our laboratory to date, include the 5-methyl[2]; 5-ethyl[3]; α- and β-5,9-dimethyl; 5,9-diethyl; 5-ethyl-9-methyl; and 5-methyl-9-ethyl derivatives.[1,4] Of the monoalkyl compounds the 5-ethyl analog was far more effective in mice than the 5-methyl. In the α-dialkyl series maximum activity was shown by the 5-methyl-9-ethyl derivative, while the 5-ethyl-9-methyl proved to be the most potent β-compound.[1,4] Thus, it appeared that a combined total of three carbon atoms in the 5 and 9 positions might be optimal for analgesic activity in this type of structure. To obtain additional information on this point, 5,9-dipropyl- and 5-propyl-2′-hydroxy-2-methyl-6,7-benzomorphane (IV and V) have been synthesized. A pharmacologic summary is also included in this report along with details of the conversion of V to corresponding open nitrogen derivatives (VI) desired for testing as diuretics.

Compounds IV and V were synthesized by the Stevens rearrangement method described previously.[1,5,6]

(1) (a) Paper XXIV, S. E. Fullerton, J. H. Ager, and E. L. May, *J. Org. Chem.*, **27**, 2554 (1962); (b) In honor of Dr. Erich Mosettig, deceased June, 1962.

(2) J. C. Murphy, J. H. Ager, and E. L. May, *J. Org. Chem.*, **25**, 1386 (1960).

(3) S. Saito and E. L. May, *ibid.*, **27**, 948 (1962).

(4) For a leading reference and for details of the stereochemistry of the 5,9-dialkyl compounds, *cf.* S. E. Fullerton, E. L. May, and E. D. Becker, *ibid.*, **27**, 2144 (1962).

(5) E. M. Fry and E. L. May, *ibid.*, **26**, 2592 (1961).

(6) J. H. Ager and E. L. May, *ibid.*, **27**, 245 (1962).