pounds with substitution on the 3-aryl ring were less potent (**30**, **32**) or more toxic (**33**, **40**) than the unsubstituted compounds. When R_2 was furyl or pyridyl instead of phenyl, both potency and toxicity were reduced; when R_2 was thienyl, there was either no change (**39**) or increased toxicity (**45**).

Compounds with electron-donating substituents on the 2-aryl ring were more potent as a group than compounds with electron-withdrawing substituents.

The most potent compound of this series, **42**, also had the largest separation between spasmolytic and lethal effects, a 225-fold ratio, comparable to that of atropine but without its mydriatic and antisalivary effects.

In general, the results of these studies lend further support to the idea that the parasympatholytic action of atropine and its analogs is closely connected with the existence of a free alcoholic OH at the β-carbon.[10] The 2,3-diarylacrylates appear to share the desirable spasmolytic properties of the previously described 2-arylacrylates, but have the additional advantage of greater potency and wider margin of safety.

Acknowledgments.—We are indebted to Miss Margaret Carroll and her staff for microanalysis.

(10) W. F. Von Oettingen, "Therapeutic Agents of Pyrrole and Pyridine Group," Edwards, Ann Arbor, Mich., 1936, pp 141–168.

Spasmolytics. III. 3-Tropanyl 2,3-Diarylacrylates. A Case History of π–σ Structure–Function Correlation[1a]

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The use of partition and polar parameters to relate chemical structures and biological activity is illustrated for a series of spasmolytic 3-tropanyl 2,3-diarylacrylates. The methods developed by Hansch and coworkers were used, and meaningful correlations were obtained which involved π and the Hammett σ effect related to the ortho position of the α-phenyl ring. This relationship was found early in the synthetic work and provided guidance and limits for further synthetic work.

During the chemical synthetic and biological testing programs which followed the discovery of potent antispasmodic activity for certain of the 3-tropanyl 2,3-diarylacrylates (Table I),[2] the original publications of Hansch and coworkers[3] came to our attention. We recognized that a prompt application of Hansch's correlative techniques, if successful, promised to give valuable guidance to our synthetic efforts, and to reduce the number of compounds which we would need to synthesize and test.

Accordingly, we provided the experimental data for 9 members of the series to Professor Hansch, who subjected these data to a multiple parameter analysis, using π and Hammett σ constants (directed both to the side chain and to the ortho position—see arrow in the structure in Table I).[4] The linear response with respect to the substituent effect on electron density at the ortho position was straightforward and, in hindsight, should not have required regression analysis to be noted. Actually, without the systematic approach developed by Hansch, we would not have found this correlation, as the use of the Hammett σ constant in the customary sense (directed to the side chain) gave only a poor straight line. The use of Otsu's ER[5] constants did not give meaningful correlations in this series.

Using this lead to guide our syntheses, we then prepared compounds suggested by reference to tables of Hammett σ constants, choosing substituents preferably from those with high negative values, but also adding a few with positive values to test the suggested correlation.

Our final group of compounds numbered 24 (see Table I), and included some with heterocyclic rings substituted for the β-phenyl ring. Preliminary correlations showed the need to eliminate the 4 compounds with substituents in the β-phenyl ring from the regression analyses (eq 1 and 2, Table II). These compounds were either more toxic or less active spasmolytics than the unsubstituted compounds. The remaining 20 compounds gave slightly better correlations (eq 3 and 4). Removal of the only ortho-substituted compound and the 4-hydroxy derivative resulted in a significant correlation involving σ^2 and σ terms (referred to the ortho position; see eq 5 and 6). Further refinement was obtained by eliminating all heterocyclic analogs to give eq 7. This equation is plotted in Figure 2,[6] together with the actual experimental data.

Our arrival at this point led us to stop work with this series of antispasmodic agents, with what we consider to be a high probability that we will not have missed an outstandingly active molecule by not preparing "just a few more analogs." Since the synthesis and testing of each additional analog means an outlay of more than $2,000, this is valuable information.

In light of the wide spectrum of types of correlations found by Hansch and coworkers,[7] it is interesting to

(1) (a) Presented at the 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970. (b) To whom inquiries should be addressed.

(2) H. C. Caldwell, J. A. Finkelstein, Philip P. Goldman, Andrew J. Sivak, Jack Schlosser, Carol Pelikan, and William G. Groves; *J. Med. Chem.*, **13**, 1076 (1970).

(3) See C. Hansch, *Accounts Chem. Res.*, **2**, 232 (1969), for ref and a review of this field.

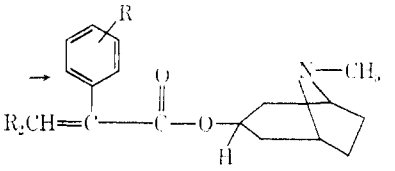
(4) For a similar use of σ constants directed to the ortho position see C. Hansch, P. P. Maloney, T. Fujita, and R. M. Muir, *Nature (London)*, **194**, 178 (1962).

(5) T. Yamamoto and T. Otsu, *Chem. Ind.*, 787 (1967).

(6) X-Plot obtained by use of IBM 'STATPACK' "SCATTER" program, printed on an IBM 2741 electric typewriter terminal for BASIC timesharing system.

(7) For a comprehensive review see chapter by C. Hansch in the forthcoming book "Drug Design," Vol. 1, E. J. Ariëns, Ed., Academic Press, New York, N. Y.

TABLE I: 3-TROPANYL 2,3-DIARYLACRYLATES[a]



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Compd	R_1	R_2	Fecal pellet ED_{50}[a] mg/kg po	σ[b]	σ_0[c]	π[d]	Obsd log 1/c	Pred[e] log 1/c	Dev
1	3-CH_3O	Ph	1.8	0.12	−0.27	−0.12	5.320	4.882	0.438
2	2-CH_3O	Ph	2.4	−0.27	0.12	−0.33	5.200		
3	3-OH	Ph	4.4	0	−0.36	−0.49	4.920	4.889	0.031
4	3,4(CH_3O)$_2$	Ph	5.2	−0.12	−0.12	0.08	4.890	4.827	0.063
5	4-NH_2	Ph	5.7	−0.66	−0.16	−1.23	4.800	4.847	−0.047
6	3-*i*-BuNH	Ph	7.8	−0.34	−0.64	0.72	4.730	4.785	−0.055
7	4-C_2H_5	Ph	7.3	−0.15	−0.04	0.97	4.710	4.776	−0.066
8	H	Ph	7.2	0	0	0	4.680	4.744	−0.064
9	3-NH_2	Ph	8.2	−0.16	−0.66	−1.23	4.650	4.770	−0.120
10	4-CH_3O	Ph	9.7	−0.27	0.12	−0.04	4.590	4.625	−0.035
11	3,4,5-(CH_3O)$_3$	Ph	12	0.08	0.08	0.20	4.560	4.669	−0.109
12	4-Cl	Ph	17	0.23	0.37	0.70	4.350	4.266	0.084
13	4-Cl	2-Thienyl	21	0.23	0.37	0.38	4.270		
14	4-CH_3O	2-Thienyl	25	−0.27	0.12	−0.36	4.190		
15	4-CH_3CO_2	Ph	29	0.31	0.39	−0.64	4.150	4.231	−0.081
16	4-CF_3	Ph	43	0.55	0.42	1.20	3.990	4.176	−0.186
17	4-OH	Ph	42	−0.36	0	−0.61	3.940		
18	4-Cl	4-Pyridyl	69	0.23	0.37	−0.78	3.740		
19	4-Cl	2-Furyl	75	0.23	0.37	0.05	3.700		
20	4-NO_2	Ph	82	0.78	0.71	0.24	3.680	3.534	0.146
21	4-Cl	4-CH_3OPh	16	0.23	0.37	0.66	4.41		
22	4-CH_3O	4-CH_3OPh	>16	−0.27	0.12	−0.08	4.41		
23	H	4-Cl-Ph	100	0	0	0.70	3.58		
24	4-CH_3O	4-Cl-Ph	>108	−0.27	0.12	0.66	3.58		

[a] See ref 2 for description of this test. [b] σ values taken from Jaffe, *Chem. Rev.*, **53**, 222 (1953). [c] Electronic effect is related to the ortho position of the α-phenyl ring—hence, for a para substituent a meta constant is used and *vice versa*. See ref 4 for a similar treatment. [d] π values from the phenylacetic acid and phenyl series where available; otherwise from the phenoxyacetic acid series [T. Fujita, J. Iwasa, and C. Hansch, *J. Amer. Chem. Soc.*, **86**, 5175 (1964)]. [e] Predicted by eq 7.

TABLE II: EQUATIONS OBTAINED BY REGRESSION ANALYSIS[a]

Eq		N[c]	s[d]	r[e]	R^2[f]
1	$\text{Log}\frac{1}{c}$[b] $= 4.373 - 0.602\sigma_{sc}$[g]	24	0.4756	0.3857	0.1488
	95% CI[i] (±0.201) (±0.637)				
2	$\text{Log}\frac{1}{c} = 4.443 - 0.880\sigma_0$[h]	24	0.4196	0.5809	0.3374
	(±0.182) (±0.545)				
3	$\text{Log}\frac{1}{c} = 4.459 - 0.759\sigma_{sc}$	20	0.4209	0.5334	0.2845
	(±0.198) (±0.596)				
4	$\text{Log}\frac{1}{c} = 4.508 - 0.921\sigma_0$	20	0.3638	0.6824	0.4656
	(±0.173) (±0.488)				
5	$\text{Log}\frac{1}{c} = 4.497 - 0.955\sigma_0$	18	0.2968	0.7824	0.6121
	(±0.150) (±0.403)				
6	$\text{Log}\frac{1}{c} = 4.652 - 1.105\sigma_0^2 - 0.987\sigma_0$[j]	18	0.2456	0.8666	0.7509
	(±0.170) (±0.814) (±0.336)				
7	$\text{Log}\frac{1}{c} = 4.744 - 1.215\sigma_0^2 - 0.842\sigma_0$[k]	14	0.1670	0.9295	0.8641
	(±0.131) (±0.583) (±0.255)				

[a] Using computer program H3A, developed by C. H. Hansch and co-workers; this program uses double precision and matrix inversion to obtain the equations. It can be run on an IBM 360-40 computer, and has been adapted to the BASIC language for time sharing by Smith Kline & French Laboratories. [b] Log 1/c = log of the reciprocal of the charcoal meal test[2] ED_{50} expressed in moles/kg. [c] N = number of compounds used in the regression. [d] s = standard deviation. [e] r = correlation coefficient. [f] R^2 = fraction of data accommodated by this model. [g] σ_{sc} = σ effect directed to the side chain of the α-phenyl ring. [h] σ_0 = σ effect directed to the ortho position of the α-phenyl ring. [i] 95% Confidence interval. [j] Ideal σ_0 = −0.445. [k] Ideal σ_0 = −0.346.

speculate about the relative lack of significance for the partition factor, and the high dependence upon polar factors in our series.

Since our compounds have log P values higher than atropine by about 3.0 log units [$>CHCH_2OH$, log $P \cong -0.29$; $>C = C(C_6H_5)H$, log $P \cong 2.7$; for atropine, experimental value of log $P = 1.8$[8] so $1.8 + (2.7 + 0.29) = 4.8$], the range in log P caused by substitutions ranging from OH to CF_3 only alters the 4.3 value ± 1.2 log units, and all of these analogs therefore have log P values higher than atropine. The roughly equivalent antispasmodic activity for atropine and some of these compounds indicates that the partition factor plays only a small role in the antispasmodic activity of this series of compounds.

The significance of the electron density at the ortho position of this series (see formula, Table I, arrow) gives rise to several possibilities. First, models suggested the possibility of a slight spatial overlap between the π electron density at the ortho position and the carbonyl group π electrons. This could conceivably affect the rate of hydrolysis of these esters, and thus effect a stability change which might be important in the maintenance of a necessary drug concentration, or might be significant in some drug–receptor interaction involving the ester group. Second, the increased electron density at the ortho position of the α-phenyl ring may be involved in the actual binding at a receptor site (or enzyme surface) and may strengthen binding at a cationic (or partially electron deficient) site. Third, this effect may be reflected in an alteration of the rate of metabolic transformation in this series. The parabolic relationship found for σ (optimum value ≈ -0.346) is in line with the first and third of these possibilities, since kinetic processes are involved and easily lead to maximum effects. It is difficult to reconcile the second explanation with the parabolic relationship.

(8) Unpublished experimental value obtained by S. Anderson and C. Hansch.

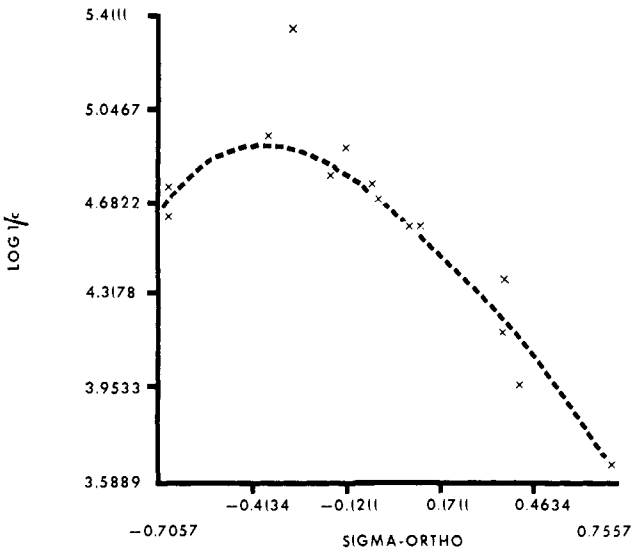

Figure 1.—Computer plot for eq 7, Table II.

Metabolic studies would be of value to help determine the reason for this relationship between biological activity and physical–chemical properties.

Acknowledgment.—The authors gratefully acknowledge the help given to this project by Professor Corwin H. Hansch.

New s-Triazine Derivatives as Depressants for Reticuloendothelial Hyperfunction Induced by Bacterial Endotoxin

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A series of 159 derivatives of s-triazine were synthesized and evaluated for their depressive effects on the reticuloendothelial hyperfunction induced by typhoid–paratyphoid vaccine. Among those, 20 derivatives were found to be as active as or superior to phenylbutazone. The most active depressants were 2-*n*-propyl-4,6-dicyclohexylamino-s-triazine (**9**), 2-amino-4-cyclohexylamino-6-(3-pyridyl)-s-triazine (**35**), and 2-ethyl-4,6-dipiperidino-s-triazine (**112**). These showed potent depressive effects on the reticuloendothelial hyperfunction as active as cortisone. Structure–activity relationships are discussed.

In recent years, reports have been published on the relationships between the phagocytic activity of the reticuloendothelial system (RES) and tumors,[1] inflammation,[2] or atherosclerosis.[3] The phagocytosis of the RES is enhanced systemically by means of bacterial polysaccharides, cholesterol, or inactive polymer colloids.[4] We found that some antiinflammatory drugs had an inhibitory effect on this hyperfunction of the RES. For the purpose of obtaining antiinflammatory or antiatherosclerotic drugs, many compounds were synthesized in our laboratory and screened with respect to the depressive effects on the hyperfunction of the RES. Recently, some s-triazine derivatives have been found to have reliable effects.

Some pharmacological activities of s-triazines have

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(4) R. K. Fred and M. L. Shore, *ibid.*, **1**, 1 (1967); E. L. Dobson, L. S. Kelly, and C. R. Finney, *ibid.*, **1**, 63 (1967); S. Ota, *Nippon Byori Gakkai Kaishi*, **48**, 799 (1959).