Spasmolytics. II. 3-Tropanyl 2,3-Diarylacrylates[1]

HENRY C. CALDWELL,* JOSEPH A. FINKELSTEIN, PHILIP P. GOLDMAN, ANDREW J. SIVAK, JACK SCHLOSSER, CAROL PELIKAN, AND WILLIAM G. GROVES

Research and Development Division, Smith Kline and French Laboratories, Philadelphia, Pennsylvania 19101

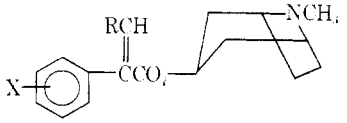
Received May 25, 1970

Twenty-six tropine esters of 2,3-diarylacrylic acids were prepared by standard methods. 3-Tropanyl and 2-(3 and 4-hydroxyphenyl)-3-phenylacrylates were prepared by selective hydrolysis of their respective 3- and 4-acetoxy derivatives. The compounds were potent spasmolytics (fecal pellet inhibition) but devoid of mydriatic activity in mice po. 3-Tropanyl 2-(2 and 3-methoxyphenyl)-3-phenylacrylates were as potent as atropine in the fecal pellet inhibition test.

The synthesis and pharmacological properties of a series of 3-tropanyl-2-arylacrylates and a series of 3-tropanyl-2-arylhydracrylates were recently described.[2a]

The hydracrylates, like atropine, produced typical anticholinergic effects in mice—mydriasis[2b] and salivary suppression—and spasmolytic activity as measured by reduction in mouse fecal pellet count.[3] In contrast, the acrylates were nonmydriatic and had weak or absent antisalivary activity, but did show spasmolytic activity.

This virtually complete separation of antisalivary and mydriatic properties from spasmolytic properties had not been reported previously in compounds related to atropine. The most potent of these, 3-tropanyl-2-(4-chlorophenyl) acrylic acid (Ia) was about one-seventh as potent as atropine as a spasmolytic. In this paper, we describe the preparation and pharmacological evaluation of analogs of Ia with a 3-aryl group (Ib).



Ia, X = 4Cl; R = H
Ib, R = Ar

Experimental Section

Where analyses are indicated by elements only, the analytical results obtained for those elements were within ±0.4% of the calculated values.

Chemistry.—Melting points were determined in open capillary tubes using the Thomas-Hoover Uni-Melt and are uncorrected.

Substituted Phenylacetic Acids.—4-Chloro- and 4-bromophenylacetic acid were prepared from the nitriles by acid hydrolyses.[4] 4-Hydroxy-3,5-dinitrophenylacetic acid was prepared by a published method.[5] The others were available commercially. The aromatic aldehydes were all available commercially.

2,3-Diarylacrylic Acids (Table I).—2,3-Diphenylacetic acid was purchased. The other acids were prepared by modifying the method of Buckles, *et al.*,[6] which uses equimolar amounts of the aromatic aldehyde, the phenylacetic acid, and $N(Et)_3$, and 4 *M* portions of Ac_2O. In most cases the reactive mixture was heated at 100° for 2–7 hr. We found the product could be isolated with less manipulation by cooling the reaction mixture, acidifying the HCl and filtering the precipitate. Ketcham and Jambotkar[7] also acidified at this stage by their method. In a few cases heating was not necessary. For example **7** and **10** were formed at ambient temperature after mixing in an ice bath. No HCl was added to **10** because it precipitated out of the reaction mixture. In general the reaction mixtures darkened considerably before they were worked up. In most cases the product was dissolved in EtOH, decolorized with activated charcoal, and diluted with warm H_2O to the cloud point. Acid **20** was prepared from acid **14** by pyridine·HCl demethylation.

3-Tropanyl 2,3-Diarylacrylates.[8]—The 3-tropanyl 2,3-diarylacrylates listed in Table II were prepared by several different methods which are illustrated as follows.

Method A. 3-Tropanyl 2-(4-Methoxyphenyl)-3-phenylacrylate·HCl (31).—A suspension of 4.38 g (0.172 mole) of 2-(4-methoxyphenyl)-3-phenylacrylic acid, 70 ml of dry C_6H_6, and 30 ml (0.414 mole) of $SOCl_2$ was warmed gently until a solution was obtained. The clear solution was refluxed for 1.5 hr and the excess $SOCl_2$ and C_6H_6 were removed at an aspirator. Three separate portions of dry C_6H_6 were added and removed in like manner. To this oil was added 34.3 g (0.155 mole) of tropine·HBr and the mixture was chilled. To this mixture was added 25 ml of dry pyridine and the mixture was stirred for 0.5 hr at room temperature and then at 60–70° for 1 hr. The mixture solidified during this process and 10 ml of dry pyridine was added. Then H_2O (100 ml) was added and the solution was warmed and treated with activated charcoal. The solution was cooled, made basic with 10% NaOH, extracted into Et_2O, and dried. The HCl salt was formed in the usual manner. See Table II for additional details.

Method B. Tropanyl 2-(3-Acetoxyphenyl)-3-phenylacrylate (41).—A mixture of 17.1 g (0.0713 mole) of 2-(3-hydroxyphenyl)-3-phenylacrylic acid, 20.8 ml (0.150 mole) of Ac_2O, and 1 drop of H_2SO_4 was heated on the steam bath for 45 min and evaporated to dryness at the aspirator. Dry C_6H_6 (45 ml) and $SOCl_2$ (15 ml, 0.027 mole) were added and treated as in method A to give the oily acid chloride which was dissolved in 50 ml of dry C_6H_6 and added to a solution of 20.1 g (0.1426 mole) of tropine in 100 ml of dry C_6H_6. The mixture was heated at reflux temperature for 5 hr and filtered. The filtrate was washed (H_2O) and evaporated. Crystallization from C_6H_6 gave 17.2 g (59.4%) of product, mp 118.5–120.5°.

Method C. 3-Tropanyl 2-(3-Hydroxyphenyl)-3-phenylacrylate (48).—To a solution of 3.05 g (0.0076 mole) of **41** in 70 ml of warm MeOH was added 4 drops of saturated Na_2CO_3 in 20 ml of H_2O. After standing at ambient temperature for 6 hr, the precipitate was collected and recrystallized from MeOH to give 2.5 g (91%) of product, mp 214.5–216° dec.

Method D. 3-Tropanyl 2-(4-Aminophenyl)-3-phenylacrylate·HCl·1.25H_2O (47).—A warm solution of 15.5 g (0.0346 mole) of 3-tropanyl-2-(4-nitrophenyl)-3-phenylacrylate·HCl·H_2O (**35**) in MeOH (250 ml) was hydrogenated over Raney Ni at 3 atm until the calculated amount of H_2 was absorbed (3–6 hr). The reaction mixture was warmed to dissolve crystallized product, filtered, and cooled to give 13 g (93%) of yellow solid.

* To whom correspondence should be addressed.

(1) Presented at the 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970.

(2) (a) H. C. Caldwell, J. A. Finkelstein, D. Arbokov, C. Pelikan, and W. G. Groves, *J. Med. Chem.*, **12**, 477 (1969); (b) H. R. Ing, G. S. Dawes, and I. Wajda, *J. Pharmacol. Exp. Ther.*, **85**, 85 (1945).

(3) P. A. J. Janssen, A. H. Jageneau, and J. Huyens, *J. Med. Pharm. Chem.*, **1**, 299 (1959).

(4) H. Gilman and A. H. Blatt, "Organic Synthesis," Collected Vol. I, 2nd ed, Wiley, New York, N. Y., 1944, p 436.

(5) J. H. Wilkinson, *Biochem. J.*, **63**, 601 (1956).

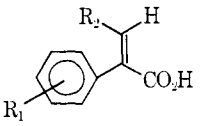
(6) R. E. Buckles, M. P. Bellis, and W. D. Coder, Jr., *J. Amer. Chem. Soc.*, **73**, 4972 (1951).

(7) R. Ketcham and D. Jambotkar, *J. Org. Chem.*, **28**, 1034 (1963).

(8) H. C. Caldwell and W. G. Groves, U. S. Patents 3,317,544, 3,351,550 (1967), and 3,458,507 (1969).

TABLE I

2,3-DIARYLACRYLIC ACIDS



Compd	R_1	R_2	Mp, °C	Recrystn solvent[a]	Yield, %	Formula	Analyses
1	4-Cl	Ph	181–184[b]	A	59	$C_{15}H_{11}ClO_2$	
2	H	4-ClPh	203–204	A	21.5	$C_{15}H_{11}ClO_2$	
3	4-CH_3O	Ph	149–150[c]	A	66.5	$C_{16}H_{14}O_3$	
4	4-CH_3O	4-ClPh	183–184	A	57	$C_{16}H_{13}ClO_3$	C H Cl[e]
5	4-Cl	4-CH_3O-Ph	222–223	A	32	$C_{16}H_{13}ClO_3$	C H Cl[f]
6	4-CF_3	Ph	220–221	A	38	$C_{16}H_{11}F_3O_2$	C H[g]
7	4-NO_2	Ph	224.5–225.5[c]	B	29	$C_{15}H_{11}NO_4$	
8	4-Cl	2-Furyl	212–213	A	37	$C_{13}H_9ClO_3$	C H Cl
9	4-C_2H_5	Ph	168–169.5	A	45	$C_{17}H_{16}O_2$	C H[h]
10	4-Cl	4-Pyridyl	278–279	C	44	$C_{14}H_{10}ClNO_2$	C H N[i]
11	4-Cl	2-Thienyl	222–223	A	66	$C_{13}H_9ClSO_2$	C H Cl
12	4-CH_3O	4-CH_3O-Ph	215.5–216.5[c]	D	25	$C_{17}H_{16}O_4$	
13	2-CH_3O	Ph	143–144	A	66	$C_{16}H_{14}O_3$	C H
14	3-CH_3O	Ph	155–156[d]	A	86	$C_{16}H_{14}O_3$	C H
15	3,4-$(CH_3O)_2$	Ph	151.5–152.5[d]	A	53	$C_{17}H_{16}O_4$	C H
16	3,4,5-$(CH_3O)_3$	Ph	208–210	E	43.2	$C_{18}H_{18}O_5$	C H
17	4-CH_3O	2-Thienyl	200–201	A	47	$C_{14}H_{12}SO_3$	C H S
18	4-OH	Ph	222–223	F	49	$C_{15}H_{12}O_3$	C H
19	3-NO_2	Ph[d]	224–225	G	80	$C_{15}H_{11}NO_4$	C H N
20	3-OH	Ph	181–182.5	H	41.5	$C_{15}H_{12}O_3$	C H
21	4-Cl	4-ClPh	176.5–177.5	I	23	$C_{15}H_{10}Cl_2O_2$	C H Cl
22	4-Cl	2-ClPh	185–186.5	I	24	$C_{15}H_{10}Cl_2O_2$	C H Cl
23	4-Cl	2-CH_3OPh	219.5–220.5	A	50	$C_{16}H_{13}ClO_3$	C H Cl
24	4-Br	Ph	190–191.5[d]	A	41.5	$C_{15}H_{11}BrO_2$	C H Br
25	4-OH, 3,5-diNO_2	Ph	189–190	J	56	$C_{12}H_{15}N_2O_7$	C H N[j]
26	4-CH_3O	2-CH_3O-Ph	202–203	A	62.5	$C_{17}H_{16}O_4$	C H
27	4-CH_3O	2-NO_2-Ph	174–175[k]	A	71	$C_{16}H_{13}NO_5$	

[a] A, EtOH–H_2O; B, C_6H_6–hexane; C, MeOH; D, AcOH; E, MeOH–EtOH; F, *i*-PrOH–H_2O; G, heated in EtOH and filtered; H, C_6H_6–Me_2CO; I, Et_2O–petr ether; J, treated solution of Na salt with charcoal and pptd with HCl; K, *i*-PrOH; L, H_2O; M, EtOH–hexane; N, *i*-PrOH–EtOH; O, salt formed in MeOH–Et_2O was pure; P, *i*-PrOH–hexane; Q, MeOH–H_2O; R, EtOH; S, EtOH–petr ether; T, dioxane–Et_2O; U, C_6H_6. [b] V. Chandra and V. B. Srivastava [*J. Indian Chem. Soc.*, **43**, 433 (1966)] report mp 180–181°. [c] Lit.[7] mp (**3**) 150°, mp (**7**) 221–224°, mp (**12**) 216–217°. [d] J. I. G. Cadogan, E. D. Dwell, and P. W. Inward [*J. Chem. Soc.*, 4164, (1962)] report mp (**24**) 198°, mp (**19**) 228.5–229°, mp (**14**) 156°, mp (**15**) 156°. [e] Calcd for 0.25 H_2O. [f] ($C_{16}H_{13}ClO_3$): Calcd C, 60.56; H, 4.54; Cl, 12.28. Found: C, 65.81; H, 4.48; Cl, 13.68. [g] ($C_{16}H_{11}F_3O_2$): Calcd C, 65.75; H, 3.79 Found: C, 66.27; H, 3.89. [h] ($C_{17}H_{16}O_2$): Calcd C, 80.93; H, 6.39. Found: C, 80.34; H, 6.50. [i] ($C_{14}H_{10}ClNO_2$): Calcd C, 64.75; H, 3.88; N, 5.39. Found: C, 64.14; H, 3.75; N, 5.34. [j] ($C_{12}H_{15}N_2O_7$): Calcd C, 54.5; H, 3.05; N, 8.04. Found: C, 53.57; H, 3.00; N, 8.34. [k] R. Pschorr, O. Wolfes, and W. Buchow [*Ber.*, **33** 172 (1900)] report mp 177°.

Method E. 3-Tropanyl 2-(3,4-Dimethoxyphenyl)-3-phenylacrylate 2-(4-Hydroxybenzoyl)benzoate Salt (43).—A solution of 48 g (0.168 mole) of 2-(3,4-dimethoxyphenyl)-3-phenylacrylic acid, 25 ml (0.4 mole) of $SOCl_2$, and 150 ml of dry C_6H_6 was treated as in method A to give the oily acid chloride which was dissolved in 100 ml of dry C_6H_6 and added in 20 min to a solution of azeotropically dried tropine (47.5 g, 0.336 mole) in 100 ml of dry C_6H_6. The mixture was heated at reflux temperature for 5 hr, filtered, treated with activated charcoal, and evaporated to give the free base. An Et_2O solution of this base was mixed with 40.5 g (0.168 mole) of 2-(4-hydroxybenzoyl)benzoic acid and warm *i*-PrOH. The product was recrystallized, yield 48.5 g (40%).

Method F. 3-Tropanyl 2-(3-Isobutylaminophenyl)-3-phenylacrylate·2HCl·H_2O (49) was made by the general method of Emerson and Mohrman.[9] A warm solution of 5 g of 3-tropanyl-2-(3-nitrophenyl)-3-phenylacrylate·HCl, 2.52 g of isobutyraldehyde, and 0.232 g of NaOAc in MeOH (75 ml) was hydrogenated over Raney Ni. It was converted into the dihydrochloride salt *via* the free base.

Pharmacological Methods.—The drugs were administered orally by stomach tube in all cases.

MLD and Observation of Overt Effects.—Groups of 3 mice were administered various doses of test drug. Observations for behavioral changes, impairment of reflexes, mydriasis, and lethality were made. The lowest dose causing death was defined as the MLD. Measurements of pupil diameter served to indicate possible anticholinergic activity.

Spasmolytic Activity.—A modification of Janssen's method was used.[3] Potency was expressed as the dose that reduced 5-hr fecal pellet count in mice by 50% as compared with a control group (ED_{50}).

Anticholinergic Effects.—The method of Pulewka as modified by Ing, *et al.*,[2b] was used to quantitate mydriatic activity. Pupil diameter was measured in arbitrary units at 15- to 30-min intervals for about 5 hr. Antisalivary activity was studied in some of the compounds by using all-or-none blockade of furtrethonium iodide-induced salivation in mice. The ED_{50} was the dose that protected 50% of the mice.

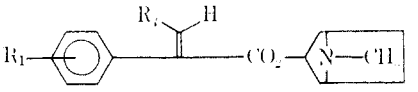
Results

The 3-tropanyl 2,3-diarylacrylates exhibited spasmolytic properties similar to those previously reported for 3-tropanyl 2-arylacrylates. The spasmolytic effects of both classes of compounds are distinct from those of atropine in that no evidence of anticholinergic effect such as mydriasis was seen. Three compounds in the present series, **28**, **29**, and **20**, were also tested for antisalivary activity; none was active. Thus, in tests with

(9) W. S. Emerson and H. W. Mohrman, *J. Amer. Chem. Soc.*, **62**, 69 (1940).

TABLE II

3-TROPANYL 2,3-DIARYLACRYLATES



Compd	R_1	R_2	Salt	Recrystn solvent[a]	Mp, °C[b]	Yield, %	Formula	Analyses
28	4-Cl	Ph	HCl	L	254–255	60	$C_{23}H_{24}ClNO_2 \cdot HCl \cdot 1.5H_2O$	C H Cl N
29	H	Ph	HCl	L	255–256.5	41.6	$C_{23}H_{25}NO_2 \cdot HCl \cdot H_2O$	C H Cl N
30	H	4-Cl-Ph	HCl	L	230–231.5	48	$C_{23}H_{24}ClNO_2 \cdot HCl \cdot H_2O$	C H Cl N
31	4-CH_3O	Ph	HCl	N	264–265	61	$C_{24}H_{27}NO_3 \cdot HCl$	C H Cl N
32	4-CH_3O	4-ClPh	HCl	E	279–280	54.5	$C_{24}H_{26}ClNO_3 \cdot HCl$	C H Cl N
33	4-Cl	4-CH_3OPh	HCl	K	244.5–245.5	32	$C_{24}H_{26}ClNO_3 \cdot HCl$	C H N
34	4-CF_3	Ph	HCl	N	262–263	56	$C_{24}H_{24}F_3NO_2 \cdot HCl \cdot 0.25H_2O$	C H Cl N
35	4-NO_2	Ph	HCl	E	255–256	49.3	$C_{23}H_{24}N_2O_4 \cdot HCl \cdot H_2O$	C H Cl N
36	4-Cl	2-Furyl	HCl	L	244–244.5	35.5	$C_{21}H_{22}ClNO_3 \cdot HCl$	C H Cl N
37	4-C_2H_5	Ph	HCl	F	245–246	40.6	$C_{25}H_{29}NO_2 \cdot HCl \cdot H_2O$	C H Cl N
38	4-Cl	4-Pyridyl	B[c]	M	202.5–203.5	26	$C_{22}H_{23}ClN_2O_2 \cdot C_{14}H_{10}O_4$	C H Cl N
39	4-Cl	2-Thienyl	HCl	R	270–271.5	62.1	$C_{21}H_{22}ClNO_2S \cdot HCl \cdot 0.5H_2O$	C H Cl N
40	4-CH_3O	4-CH_3OPh	HCl	N	241.5–242.5	56	$C_{25}H_{29}NO_4 \cdot HCl$	C H Cl N
41	3-CH_3CO_2	Ph		U	118.5–120.5	59.4	$C_{25}H_{27}NO_4$	C H N
42	3-CH_3O	Ph	HCl	P	182–183.5	41.7	$C_{24}H_{27}NO_3 \cdot HCl$	C H Cl N
43	3,4-$(CH_3O)_2$	Ph	B[c]	N	180–181	40	$C_{25}H_{29}NO_4 \cdot C_{14}H_{10}O_4$	C H N
44	3,4,5-$(CH_3O)_3$	Ph		K	125–126.5	27.6	$C_{26}H_{31}NO_5$	C H N
45	4-CH_3O	2-Thienyl	HCl	O	264–265	74.3	$C_{22}H_{25}NO_3S \cdot HCl$	C H Cl N
46	4-CH_3CO_2	Ph	HCl	L	274–275	44	$C_{25}H_{27}NO_4 \cdot HCl$	C H Cl N
47	4-NH_2	Ph	HCl	E	260–261	93	$C_{23}H_{26}N_2O_2 \cdot HCl \cdot 1.25H_2O$	C H Cl N
48	3-OH	Ph		Q	214.5–216	91	$C_{23}H_{25}NO_3$	C H N
49	3-*i*-BuNH	Ph	2HCl	S	247–248.5	42.5	$C_{27}H_{34}N_2O_2 \cdot 2HCl \cdot H_2O$	C H Cl N
50	3-NH_2	Ph	HCl	R	230–231	80	$C_{23}H_{26}N_2O_2 \cdot HCl$	C H Cl N
51	2-CH_3O	Ph	HCl	T	219–220	45	$C_{24}H_{27}NO_3 \cdot HCl$	C H Cl N
52	4-OH[d]	Ph		C	221.5–223	73[e]	$C_{23}H_{25}NO_3$	C H N
53	3-NO_2	Ph	HCl	C	264.5–265	53	$C_{23}H_{24}N_2O_4 \cdot HCl$	C H N Cl

[a] See footnote *a* of Table I. [b] Most of the compounds melted with decomposition. [c] B = 2-(4-hydroxybenzoyl)benzoate. [d] From hydrolysis of acetoxy compound (**46**). [e] See A. Englehardt and H. Wick *Arzneim. Forsch.*, 1, 217 (1957).

TABLE III

LETHAL, SPASMOLYTIC, AND MYDRIATIC EFFECTS IN MICE—2-SUBSTITUTED PHENYL 3-PHENYLACRYLATES[a]

Compd (free base)	R_1	Dose, mg/kg po — MLD	Dose, mg/kg po — Fecal pellet, ED_{50}
47	4-NH_2	512	5.7
37	4-CH_2CH_3	128	7.3
31	4-CH_3O	256	9.7
28	4-Cl	195	17
46	4-CH_3COO	917	29
52	4-OH	2150	42
34	4-CF_3	256	43
35	4-NO_2	162	82
42	3-CH_3O	384	1.8
48	3-OH	256	4.4
49	3-*i*-BuNH	128	7.8
50	3-NH_2	256	8.2
51	2-CH_3O	64	2.4
43	3,4-$(CH_3O)_2$	384	5.2
44	3,4,5-$(CH_3O)_3$	768	12
29	H	63	7.2
Atropine		620	2.5

[a] None of these compounds had a mydriatic effect except **28**, **29**, and **31** which produced mydriasis at lethal doses. Atropine was mydriatic at 0.75–1.3 mg/kg.

TABLE IV

LETHAL, SPASMOLYTIC, AND MYDRIATIC EFFECTS IN MICE—2-ARYL 3-SUBSTITUTED PHENYLACRYLATES[a]

Compd (free base)	R_1	R_2	Dose, mg/kg po — MLD	Dose, mg/kg po — Fecal pellet ED_{50}
33	4-Cl	4-CH_3O	32	16
30	H	4-Cl	512	100
32	4-CH_3O	4-Cl	384	>108
40	4-CH_3O	4-CH_3O	16	>16

[a] Compounds **32**, **33**, and **40** did not produce mydriasis, **30** produced mydriasis at 256 mg/kg.

TABLE V

LETHAL, SPASMOLYTIC, AND MYDRIATIC EFFECTS IN MICE—2-SUBSTITUTED PHENYL 3-HETEROCYCLIC ACRYLATES[a]

Compd (free base)	R_1	R_2	Dose, mg/kg po — MLD	Dose, mg/kg po — Fecal pellet ED_{50}
36	4-Cl	2-Furyl	512	75
38	4-Cl	4-Pyridyl	512	69
39	4-Cl	2-Thienyl	190	21
45	4-CH_3O	2-Thienyl	48	25

[a] Compounds **36** and **45** did not produce mydriasis. **38** produced mydriasis at 128 mg/kg, **39** at lethal doses.

other compounds, absence of mydriasis was taken as evidence of lack of anticholinergic activity.

Nearly all of the compounds possessed spasmolytic activity,[3] with a wide range of potency. In general, the 2,3-diarylacrylates were more potent than the 2-arylacrylates, and had a wider separation between spasmolytic and lethal effects. Whereas all of the 2-arylacrylates were considerably less potent than atropine, several 2,3-diarylacrylates were close to atropine in potency, in fact **42** and **51** were equipotent. Com-

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]

PAUL N. CRAIG, HENRY C. CALDWELL,[1b] AND WILLIAM G. GROVES

Smith Kline & French Laboratories, Philadelphia, Pennsylvania

Received May 25, 1970

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. Finkelsteln, Phillp 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.