Synthesis and Biological Screening of Aminotropone Derivatives

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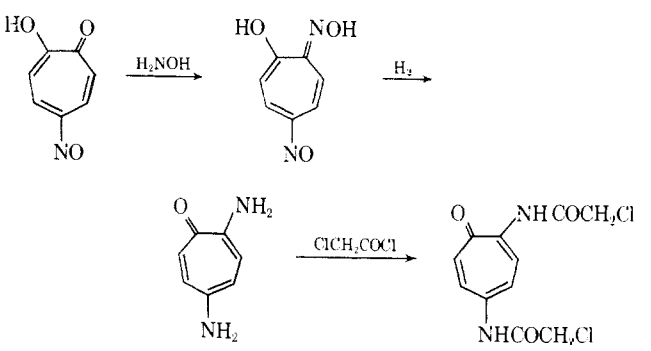
A series of basic derivatives of 2-aminotropone, 2,5-diaminotropone, and 5-aminotropolone were synthesized and tested pharmacologically. Some 2-dialkylaminoalkylaminotropones exhibited significant activity on arterial blood pressure and the N,N-disubstituted 2-glycinamidotropones exhibited coronary vasodilator activity. Structure–activity relationships were examined.

The alkaloid colchicine was isolated in 1820 and its structure was established by Dewar[1] and Tarbell, *et al.*,[2] after 1945. Since then, in view of the outstanding effect of colchicine on mitosis, the action of many other colchicine derivatives has been tested. Pauson[3] reported that in several compounds in which the tropono id ring has been rearranged to a benzenoid system, activity was retained and toxicity decreased. He concluded that the troponoid ring has little significance for antimitotic activity. More recently, Belleau[4] studied the troponoid ring for its activity at the adrenergic receptor level and Krapcho[5] studied the pharmacological activities of some benzotropones. Since the troponoid ring occurs in natural structures and is not relevant to antimitotic activity, and since very little is known about the pharmacology of troponoid derivatives, we decided to synthesize a series of 2-aminotropone, 2,5-diaminotropone, and 5-aminotropolone derivatives and study their pharmacological properties.

Chemistry.—The derivatives of 2-amino- and 2-aminoalkylaminotropones (Table I) were prepared by nucleophilic substitution[6] of the methoxyl group with primary or secondary amines on 2-methoxytropone[7] and 2-methoxy-5-acetamidotropone,[8] respectively. The derivatives of 2-glycinamido- and 2,5-bis(glycinamido)tropone and of 5-glycinamidotropolone (Table II) were obtained by condensation of the corresponding chloroacetamidotropones and -tropolones with secondary amines. 2-Chloroacetamidotropone was prepared by acylation of 2-aminotropone[9] with chloroacetyl chloride; 2,5-bis(chloroacetamido)tropone was obtained according to Scheme I by condensation of the crude 2,5-diaminotropone hydrochloride[10] with chloroacetyl chloride. 5-Chloroacetamidotropolone was similarly obtained from 5-aminotropolone.[8]

The basic esters of N-(2-troponyl)-β-alanine (Table III) were prepared by condensing N-(2-troponyl)-β-alanine with dialkylaminoethyl chloride. N,2-Troponyl-β-alanine was described by Matsumoto,[11] who

SCHEME I



hydrolyzed N-(2-troponyl)-β-propionitrile, obtained by adding acrylonitrile to 2-aminotropone. We prepared the N-(2-troponyl)-β-propionitrile by condensing 2-methoxytropone with β-aminopropionitrile.

N-(2-Troponyl)ethylurethan and N-(3,4,5-trimethoxybenzoyl)-2-aminotropone were secured by condensation (in pyridine) of 2-aminotropone with either ethyl chlorocarbonate or 3,4,5-trimethoxybenzoyl chloride. The 2-phthalimidotropone was prepared by condensation of 2-aminotropone with phthalic anhydride.

Pharmacology (Table IV). Toxicity.—The acute toxicity was determined intraperitoneally in mice. The animals which showed symptoms of CNS excitation (tremors, convulsions) died within 1 hr of administration of the compounds. The animals which showed hypnotic or depressive effects died within 24 hr of administration of compounds.

Effects on Blood Pressure and on Respiration.—Disubstituted 2-aminoalkylaminotropones exhibited a significant activity on arterial blood pressure and on respiration. This activity was influenced by the distance between the two nitrogen atoms, by the type of substitution at the terminal nitrogen atom, and by the introduction into position 5 of an acetamido group. With an ethylene chain between the two nitrogen atoms, hypertensive activity was found. With a propylene chain, hypotensive activity appeared. The hypertensive activity decreased and the hypotensive activity increased with the lengthening of the chains at the terminal nitrogen atom. The maximum hypertensive activity was shown by compound **37** and the maximum hypotensive activity by **6**. All compounds showed a stimulant effect on respiration. With an acetamido group in position 5, the stimulant effect on respiration disappeared, while only a slight hypotensive activity remained (**8**, **10**–**12**). No effect on blood pressure was

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(3) P. L. Pauson, *Chem. Rev.*, **55**, 121 (1955).

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(8) T. Nozoe and S. Seto, *Proc. Japan Acad.*, **27**, 188 (1951).

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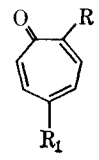
(10) T. Nozoe, M. Sato, and T. Matsuda, *Sci. Rept. Tohoku Univ., First Ser.*, **37**, 407 (1953).

(11) Y. Matsumoto, *Sankyo Kenkyusho Nempo*, **16**, 33 (1964).

TABLE I

2-AMINO- AND 2-AMINOALKYLAMINOTROPONE DERIVATIVES

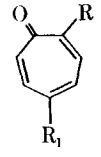


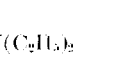
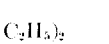
No.	R	R_1	Method	Bp, °C (mm) base	Crystn solvent[a]	Mp, °C	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % Cl	Found, % C	Found, % H	Found, % N	Found, % N
1	$NHCH_2CH_2N(C_2H_5)_2$	H	A	155–165 (1)	E	195–198[c]	38	$C_{13}H_{20}N_2O\cdot 2HCl$	53.24	7.56	9.55	24.18	52.73	7.66	9.73	24.06
2	$NHCH_2CH_2N[CH(CH_3)_2]_2$	H	A	165–175 (1.5)	E	207–211[c]	63	$C_{15}H_{24}N_2O\cdot 2HCl$	56.07	8.16	8.72	22.07	55.94	7.94	8.50	22.40
3	$NHCH_2CH_2N$(morpholino)	H	A	148–150 (0.2)	M	240–243	41	$C_{13}H_{18}N_2O_2\cdot 2HCl$	50.82	6.56	9.12	23.08	51.20	6.70	9.27	23.34
4	$NHCH_2CH_2N$(pyrrolidino)	H	A	162–165 (0.2)	M	220–225	50	$C_{14}H_{20}N_2O\cdot 2HCl$	55.08	7.26	9.18	23.23	55.32	7.08	9.01	22.84
5	$NHCH_2CH_2CH_2N(CH_3)_2$	H	A	130–132 (0.25)	I	174–177[b,c]	46	$C_{12}H_{18}N_2O\cdot 2HCl$	51.62	7.22	10.03	25.40	51.47	7.72	9.87	24.79
6	$NHCH_2CH_2CH_2N(C_2H_5)_2$	H	A	142–143	I	162–165[b]	59	$C_{14}H_{22}N_2O\cdot 2HCl$	54.72	7.87	9.12	23.08	54.15	8.33	8.91	23.07
7	$NHCH_2CH_2N(CH_3)_2$	$NHCOCH_3$	B	(0.2)	Ac–Et	127–128	62	$C_{13}H_{19}N_3O_2$	62.62	7.68	16.85		62.44	7.97	17.07	
8	$NHCH_2CH_2N(C_2H_5)_2$	$NHCOCH_3$	B		Ac–Et	112–114	63	$C_{15}H_{23}N_3O_2$	64.95	8.36	15.15		64.70	8.14	14.88	
9	$NHCH_2CH_2N$(morpholino)	$NHCOCH_3$	B[n]		Ac–Et	93–97[d]	55	$C_{15}H_{21}N_3O_3$	61.83	7.26	14.42		61.66	7.39	14.33	
10	$NHCH_2CH_2N$(pyrrolidino)	$NHCOCH_3$	B[n]		Ac–Et	106–108[d]	76	$C_{16}H_{23}N_3O_2$	66.40	8.01	14.52		66.54	8.30	14.26	
11	$NHCH_2CH_2CH_2N(CH_3)_2$	$NHCOCH_3$	B[e]			64–67[d]	43	$C_{14}H_{21}N_3O_2$	63.84	8.04	15.96		63.94	8.32	15.96	
					Ew	217–218[c]		$C_{14}H_{21}N_3O_2\cdot C_6H_3N_3O_7$[i]	48.78	4.91	17.07		48.34	4.99	17.25	
12	$NHCH_2CH_2CH_2N(C_2H_5)_2$	$NHCOCH_3$	B[f]			87–91[d]	37	$C_{16}H_{25}N_3O_2\cdot C_6H_3O_7$	54.64	6.88	8.69		54.81	6.67	8.77	
13	$NHCH_3$	$NHCOCH_3$	B[g,h]		Ew	187–189	75	$C_{10}H_{12}N_2O_2$	62.48	6.29	14.57		62.32	6.59	14.62	
14	NHC_2H_5	$NHCOCH_3$	B[g,h]		Ew	198–200	76	$C_{11}H_{14}N_2O_2$	64.05	6.84	13.58		64.03	6.79	13.49	
15	$N(C_2H_5)_2$	$NHCOCH_3$	B[g,i]		E	140–142	76	$C_{13}H_{18}N_2O_2$	66.65	7.75	11.96		66.50	7.85	11.77	
16	NH(pyrrolidino)	$NHCOCH_3$	B[h,k]		E	179–181	42	$C_{15}H_{20}N_2O_2$	69.20	7.74	10.76		69.34	7.36	10.72	
17	NHC_6H_5	$NHCOCH_3$	B[l,m]		E	199–201	59	$C_{15}H_{14}N_2O_2$	70.85	5.55	11.02		71.17	5.35	11.18	

[a] M = methanol, I = 2-propanol, Ac = acetone, Et = ethyl ether, E = EtOH, Ew = 95% EtOH. [b] In sealed capillary tube. [c] Decomposition. [d] Softening point. [e] The product was purified through the corresponding citrate. [f] The crude base obtained from the reaction mixture was repeatedly washed with ligroin, then chromatographed (eluting mixture C_6H_6–MeOH, 10:1). The citrate salt was obtained in 1:1 MeOH–acetone, then it was purified twice by fractional precipitation with EtOAc. Crystallized without passing over column. [h] The reaction was carried out at room temperature for 8 days. [i] The picrate was obtained in 95% EtOH. The reaction was carried out in EtOH at room temperature for 16 days. [k] Eluted with CH_2Cl_2. [l] The reaction was carried out without solvent at 150° for 4 hr. [m] Eluted with $CHCl_3$–Me_2CO, 10:1. [n] Eluted with C_6H_6–MeOH, 10:1.

TABLE II

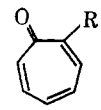
GLYCINAMIDOTROPONES AND -TROPOLONES

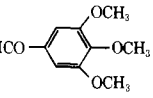


No.	R	R_1	Method	Reaction time, hr	Crystn solvent[a]	Mp, °C	Yield, %	Formula	Calcd, % C	H	N	Cl	Found, % C	H	N	Cl
18	$NHCOCH_2N(CH_3)_2$	H	C[c]	17	E	210–212[b]	67	$C_{11}H_{14}N_2O_2 \cdot HCl$	54.43	6.23	11.54	14.60	53.90	6.26	11.75	14.51
19	$NHCOCH_2N(C_2H_5)_2$	H	C	0.5	I	190–193[b]	30	$C_{13}H_{18}N_2O_2 \cdot HCl$	57.68	7.07	10.34	13.09	57.70	6.77	10.25	13.08
20	$NHCOCH_2N(n\text{-}C_4H_9)_2$	H	C	1	I–Et	164–166[b]	41	$C_{17}H_{26}N_2O_2 \cdot HCl$	62.47	8.33	8.57	10.84	62.20	8.77	8.70	10.89
21		H	C	0.25	M	218–220[b]	49	$C_{13}H_{16}N_2O_3 \cdot HCl$[d]	54.84	6.02	9.84	12.45	54.80	5.97	9.81	12.24
22		H	C	0.25	E–M	250–252[b]	77	$C_{14}H_{18}N_2O_2 \cdot HCl$[e]	59.52	6.78	9.91	12.54	60.11	6.58	10.24	12.74
23		H	C	0.25	E	229–230[b]	53	$C_{13}H_{16}N_2O_2 \cdot HCl$	58.10	6.38	10.42	13.19	57.72	6.74	10.54	13.18
24	$NHCOCH_2N(C_2H_5)_2$	$NHCOCH_2N(C_2H_5)_2$	D	8	B–L	122–123	60	$C_{19}H_{30}N_4O_3$	62.95	8.34	15.46		63.17	8.63	15.75	
25			D	2	B–L	179–181	65	$C_{19}H_{26}N_4O_5$	58.45	6.71	14.35		58.61	6.78	14.16	
26			D	1.5	B–L	147–148	81	$C_{20}H_{30}N_4O_3$	65.26	7.82	14.50		65.42	8.06	14.51	
27	OH	$NHCOCH_2N(C_2H_5)_2$	E	1.5	E	212–213[b]	36	$C_{13}H_{18}N_2O_3 \cdot HCl$	54.45	6.68	9.77	12.36	53.96	6.49	9.62	12.32
28	OH	$NHCOCH_2N(n\text{-}C_4H_9)_2$	E	2	E	215–217[b]	40	$C_{17}H_{26}N_2O_3 \cdot HCl$	59.55	7.94	8.17	10.34	59.80	8.29	8.40	10.54
29	OH		E	2	E–W	238–242[b]	80	$C_{13}H_{16}N_2O_4 \cdot HCl$	51.92	5.70	9.32	11.79	51.73	5.83	9.05	12.03
30	OH		E	1	Ew	252–254	60	$C_{13}H_{18}N_2O_2 \cdot HCl$	56.28	6.41	9.38	11.87	55.97	6.24	9.31	11.99

[a] M = MeOH, E = EtOH, Et = ethyl ether, B = benzene, L = ligroin, W = H_2O, Ew = 95% EtOH, I = 2-propanol. [b] Decomposition. [c] The reaction was carried out at 25°. [d] The base, crystallized from benzene–ligroin, melted at 95–96°. *Anal.* Calcd: N, 11.28. Found: N, 11.50. [e] The base, crystallized from EtOH, melted at 108–109°. *Anal.* Calcd: N, 11.37. Found: N, 11.27.

TABLE III



No.	R	Method	Crystn solvent[a]	Mp, °C	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
31	$NHCH_2CH_2COOCH_2CH_2N(CH_3)_2$	F	Et–P	50–51	46	$C_{14}H_{20}N_2O_3$	63.61	7.63	10.60	63.61	7.76	10.59
32	$NHCH_2CH_2COOCH_2CH_2N(C_2H_5)_2$	F[b]	Ac–E	108–110[c]	56	$C_{16}H_{24}N_2O_3 \cdot C_6H_8O_7$	54.53	6.66	5.78	54.76	7.00	5.97
33	$NHCH_2CH_2COOCH_2CH_2N$ 	F[d]	Ac–Ae	163–166	61	$C_{17}H_{24}N_2O_3 \cdot 2HCl$	54.11	6.95	7.42	54.39	6.84	7.43
34	$NHCOOC_2H_5$	G	L	71–72	61	$C_{10}H_{11}NO_3$	62.15	5.74	7.25	62.20	5.71	7.29
35		G	M	148–50	57	$C_{17}H_{17}NO_5$	64.75	5.43	4.44	64.65	5.19	4.29
36			E–W	195–197	22	$C_{15}H_9NO_3$	71.71	3.61	5.58	72.01	3.61	3.48

[a] Et = ethyl ether, P = petroleum ether (bp 40–60°), Ac = acetone, E = EtOH, Ae = EtOAc, L = ligroin, M = MeOH, W = H_2O. [b] The citrate was obtained by treating the oily base with citric acid in 2-propanol and crystallization from acetone. [c] Decomposition. [d] The ice-cooled solution of the base in EtOAc was treated with HCl to give the dihydrochloride which was crystallized from anhydrous 2-propanol. *Anal.* Calcd: Cl, 18.79. Found: Cl, 18.94. Treatment with 1 molar equiv of HCl gave the monohydrochloride which was crystallized from acetone–EtOAc, mp 89–92°. *Anal.* Calcd for $C_{17}H_{24}N_2O_3 \cdot HCl$: N, 8.22; Cl, 10.40. Found: N, 8.42; Cl, 10.18.

exhibited by morpholino derivatives (**3**, **9**). The glycinamido derivatives **19**, **28**, and **30** showed a slight hypotensive effect and **18**, **21**, **23**, **27**, and **30** showed a stimulant effect on respiration; no relation between structure and activity could be inferred from these observations.

Coronary Vasodilator Activity.—The N-disubstituted 2-glycinamidotropones (**18–23**) exhibited significant coronary vasodilator activity; when there was another glycinamido group in position 5, this activity disappeared. The N-disubstituted 5-glycinamidotropolones **27–30** showed slight or no activity. Slight activity was observed with 2-aminoalkylaminotropones **1**, **3–5** and the 2-diethylaminotropone **15**.

Miscellaneous Activities.—No activity was observed when the compounds were tested for smooth muscle relaxing activity and for anticonvulsant activity. Some compounds exhibited antiinflammatory activity against formalin edema, but were ineffective as analgetics in the Randall–Selitto test.[12] No *in vitro* bacteriostatic activity was observed.

Experimental Section[13]

2-(β-Diethylaminoethylamino)tropone Dihydrochloride (1). Method A.—A mixture of 2-methoxytropone (4.12 g, 0.03 mole) and N,N-diethylethylenediamine (3.83 g, 0.033 mole) in anhydrous benzene (30 ml) was refluxed for 2 hr. The solvent was evaporated, and the residue was distilled at 160–165° (1 mm). The ethereal solution of the base was acidified (ethanolic HCl), and the precipitated salt was collected and recrystallized (Table I).

2-(β-Dimethylaminoethylamino-5-acetamido)tropone (7). Method B.—A mixture of 2-methoxy-5-acetamidotropone (4.83 g, 0.025 mole) and N,N-dimethylethylenediamine (2.31 g, 0.026 mole) in methanol (50 ml) was refluxed for 2 hr. The solvent was evaporated, the residue was washed with ether and dissolved in cold acetone, and the solution was filtered. The solvent was removed, and the residue was redissolved in a minimum of C_6H_6–MeOH (10:1), passed over an Al_2O_3 column, and eluted with C_6H_6–MeOH (20:1). The eluate was evaporated to dryness, and the residue was crystallized (Table I).

2-Chloroacetamidotropone.—Chloroacetyl chloride (1.65 ml, 0.021 mole) was added to a stirred mixture of 2-aminotropone (2.43 g, 0.02 mole) and K_2CO_3 (3.45 g, 0.025 mole) in acetone (30 ml) at 0°, and the mixture was refluxed for 30 min. Inorganic salts were filtered and washed with dry acetone. The filtrate was evaporated to dryness, and the residue was washed with ice-cold methanol; yield 2.33 g (59%), mp 127–129°. The product was satisfactory for the next step. Crystallization from methanol gave pure material, mp 128–129°.

Anal. Calcd for $C_9H_8ClNO_2$: C, 54.69; H, 4.08; Cl, 17.90. Found: C, 54.51; H, 4.09; Cl, 18.39.

2-Diethylaminoacetamidotropone Hydrochloride (19). Method C.—A mixture of 2-chloroacetamidotropone (3.95 g, 0.02 mole), and Et_2NH (3.21 g, 0.044 mole) in benzene (30 ml) was refluxed for 30 min. After cooling, it was filtered, and the solution was washed with H_2O, dried, and evaporated to dryness *in vacuo*. The residue was dissolved in ether, the solution was filtered and acidified with ethanolic HCl, and the precipitated salt crystallized (Table II).

2,5-Bis(chloroacetamido)tropone.—A mixture of 5-nitrosotropolone[8] (12.08 g, 0.08 mole), $NaHCO_3$ (7.06 g, 0.084 mole), and $NH_2OH \cdot HCl$ (5.84 g, 0.084 mole) in MeOH (80 ml) was refluxed and stirred at 45–50° under N_2 for 20 min. After rapid cooling with ice, still under N_2, the mixture was filtered, the residue was washed with MeOH, and the filtrates were evaporated to dryness *in vacuo* at 40°. The residue was extracted (hot EtOAc saturated with H_2O, three 300-, 50-, and 50-ml portions). Each fraction of the extract was then rapidly passed through an Al_2O_3 column (40 g, 2-cm diameter), and the column was eluted with 150 ml of the same solvent. The eluate was evaporated to dryness *in vacuo*, yielding 11 g (82%) of crude tropoquinone dioxime, mp 173–174° dec (lit.[10] 183° dec). The crude dioxime (6.64 g, 0.04 mole) suspended in MeOH (80 ml) was hydrogenated (10% Pd–C) at room temperature and pressure. The hydrogenation mixture was acidified with concentrated HCl (8 ml), filtered, and evaporated *in vacuo* at 40°. To the chilled solution of the residue (2,5-diaminotropone hydrochloride) in 50% aqueous AcOH (60 ml), a solution of NaOAc (18 g) in water (30 ml) was added. The ice-cooled mixture was treated with chloroacetyl chloride (7.6 ml, 0.1 mole), stirred until it returned to room temperature, filtered with charcoal, and diluted with 0.5 *N* HCl (300 ml). After 15 hr at 0°, the precipitate was filtered, dried, and extracted in a Soxhlet apparatus with ethyl acetate. The solvent was evaporated, and the residue was crystallized from dioxane to yield 2.0 g of product, mp 175–180° dec (after recrystallizing from acetonitrile, mp 180–181°).

Anal. Calcd for $C_{11}H_{10}Cl_2N_2O_3$: C, 45.62; H, 3.49; Cl, 24.53; N, 9.69. Found: C, 45.92; H, 3.71; Cl, 24.54; N, 9.43.

2,5-Bis(diethylaminoacetamido)tropone (24). Method D.—A mixture of 2,5-bis(chloroacetamido)tropone (5.78 g, 0.02 mole) and anhydrous Et_2NH (7.30 g, 0.1 mole) in benzene (100 ml) was

(12) L. O. Randall and J. J. Selitto, *Arch. Intern. Pharmacodyn.*, **111**, 409 (1957).

(13) Melting points were determined in open glass capillaries, except when otherwise indicated (Büchi apparatus), and are uncorrected. Alumina, Merck, standardized according to Brockmann, was used for chromatographic columns.

TABLE IV

PHARMACOLOGICAL ACTIVITIES OF DERIVATIVES OF TROPONES AND TROPOLONES

No.	LD_{50}, mg/kg ip	Effect[a] on— Blood pressure mg/kg[b]	Response[c]	Respiration[d]	Coronary vasodilatator act., μg/ml[e]	Anti-inflam act., mg/kg[f]
37[g]	150[h]	2	↑	+	10	...
1	150	15	↑	+	0.1	...
2	200[h]	40	↓	+	...	100
3	100		—	+	10	50
4	300		—	+	10	75
5	160[i]	8	↓	+	10	...
6	150	4	↓	—	...	...
7	75		—	—	...	...
8	75[h]	40	↓ *i*	—	...	...
9	200[h]		— *i*	—	...	...
10	120[h]	40	↓	—	...	...
11	600[h]	40	↓ *i*	—	...	...
12	500[i]	40	↓ *i*	—	...	...
13	200[h]	*k*			...	...
14	420	*k*			...	100
15	300		—	—	10	75
16	300[l]	*k*			...	...
17	800	*k*			...	200
18	200		—	+	0.01	...
19	300[l]	65	↓	—	0.001	...
20	600		—	—	0.001[m]	...
21	200[l]		—	+	0.01	...
22	200[l]		—	—	0.316[m]	...
23	250		—	+	0.10	60
24	350[h]		— *i*	—	10	17.5
25	900[h]		— *i*	—	10	...
26	1500[n]		— *i*	—	1	100
27	420[h]		—	+	...	...
28	210[h]	10	↓	—	...	...
29	750[o]		—	—	10	...
30	450[h,o]	50	↓	+	...	...
31	2500		— *i*	—	10	...
32	1800[h]		— *i*	—	...	...
33	350[h]	*k*			...	...
34	100[l]	*k*			...	25
35	750	*k*			...	200
36	350	*k*			...	90

[a] In mice. [b] Minimal effective dose producing a ≥20 mm blood pressure response at least over 10 min. [c] ↑, hypertensive effect; ↓, hypotensive effect; —, no effect. [d] —, no effect; +, stimulant effect. [e] Minimal effective concentration in the perfusion liquid (Ringer–Looke) which gave a mean increase in coronary flow of 20 ml/min over the early 20 min. [f] Minimal effective dose which provoked a statistically significant diminution of edema over 3 hr ($P \leq 0.01$). [g] 2-(β-Dimethylaminoethylamino)tropone: N. Soma, J. Nakazawa, T. Watanabe, Y. Sato, and G. Sunagawa, *Chem. Pharm. Bull.* (Tokyo), **13**, 457 (1965). [h] Clonic convulsions. [i] Tremors. [j] In rabbit. [k] Not tested. [l] Hypnosis. [m] Heart contractions were decreased. [n] Tremors. [o] Tonic convulsions.

refluxed for 8 hr. After cooling, the mixture was filtered, washed with saturated NaCl, dried, and evaporated to dryness *in vacuo*. The residue, dissolved in the minimum of benzene, was passed over Al_2O_3 and eluted with benzene. The eluate was evaporated to dryness *in vacuo*, and the residue was crystallized (Table II).

5-Chloroacetamidotropolone.—A solution of 5.4 g (0.04 mole) of 5-aminotropolone and 12 g of NaOAc, in 100 ml of H_2O and 8 ml of AcOH, was prepared by gently warming. After the solution had been cooled in ice, 6 ml (about 0.075 mole) of chloroacetyl chloride was added with vigorous shaking, and the mixture was finally placed in the cold until the separated oily material had solidified. The solid was collected, washed with water, dried, and exhausted in a Soxhlet apparatus with $CHCl_3$. After evaporation of the solvent the residue was crystallized from H_2O to give 1.98 g (23%) of the product, mp 165°.

Anal. Calcd for $C_9H_8ClNO_3$: C, 49.45; H, 3.77; N, 6.55; Cl, 16.60. Found: C, 49.55; H, 3.58; N, 6.55; Cl, 16.46.

5-Diethylaminoacetamidotropolone Hydrochloride (27). Method E.—A mixture of 2.13 g (0.01 mole) of 5-chloroacetamidotropolone, 1.54 g (0.021 mole) of Et_2NH, and 40 ml of EtOH was refluxed for 1.5 hr. After concentration *in vacuo*, the residue was taken up in 30 ml of H_2O and 10 ml of 2 *N* HCl, and the solution was kept overnight at 0° to separate the unreacted chloroacetamidotropolone and impurities. The solution was filtered and concentrated to dryness *in vacuo*. The residual hydrochloride was purified by crystallization (Table II).

N-(2-Troponyl)-β-aminopropionitrile.—A mixture of 2-methoxytropone (4.12 g, 0.03 mole) and β-aminopropionitrile (2.8 g, 0.04 mole) was kept at room temperature for 1 day. The mixture, treated with ether, gave a solid which crystallized from EtOH to yield 3.9 g of the product, mp 125–126° (lit.[11] 124–125°).

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.94; H, 5.79; N, 16.08. Found: C, 68.92; H, 5.69; N, 15.99.

N-(2-Troponyl)-β-alanine β-Dimethylaminoethyl Ester (31). Method F.—A mixture of N-(2-troponyl)-β-alanine[11] (7.72 g, 0.04 mole), β-dimethylaminoethyl chloride hydrochloride (5.76 g, 0.04 mole), and 0.5 *N* sodium isopropoxide in 2-PrOH (160 ml) was stirred and heated to reflux during 15 min. After refluxing for 15 min, the mixture was evaporated to dryness *in vacuo*, and the residue was treated at 0° with a saturated K_2CO_3 solution, extracted ($CHCl_3$), and dried. After evaporation, the residue was dissolved in a minimum of benzene, passed over Al_2O_3 (50 g, 2-cm diameter), and eluted with benzene. The yellow eluate was evaporated to dryness *in vacuo*, and the residue was crystallized (Table III).

N-(2-Troponyl)ethylurethan (34). Method G.—Ethyl chlorocarbonate (3.25 g, 0.03 mole) was added slowly to a stirred and chilled solution of 2-aminotropone (3.99 g, 0.033 mole) in anhydrous pyridine (15 ml). After 15 hr at room temperature, the mixture was diluted with a large amount of benzene and washed with H_2O, dilute HCl, and H_2O. The benzene was dried (Na_2SO_4) and evaporated to dryness *in vacuo*, and the residue was crystallized (Table III).

2-Phthalimidotropone (36).—A mixture of 2-aminotropone (7.26 g, 0.06 mole) and phthalic anhydride (17.76 g, 0.12 mole) in AcOH was refluxed for 1 hr. After diluting with H_2O (450 ml), the mixture was again refluxed, cooled, and extracted ($CHCl_3$). The extract was washed (aqueous Na_2CO_3, H_2O) and dried (Na_2SO_4). After evaporation, the residue was crystallized (Table III).

Pharmacological Methods.—For all tests NMRI albino mice and Wistar albino rats were used. LD_{50} values were determined in mice intraperitoneally, and the mortality over 24 hr was recorded. The animals were also observed for qualitative signs of intoxication following the Irwin scheme. Antimicrobial and antifungal activity, smooth muscle relaxing activity, effects on blood pressure and on respiration, coronary vasodilatator activity, anticonvulsant activity, and antiinflammatory activity were determined according to the methods previously described.[14]

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(14) E. Massarani, D. Nardi, L. Degen, and M. J. Magistretti, *J. Med. Chem.*, **9**, 617 (1966).