Enamine Derivatives of Malonic Acid with Pharmacologic Activities

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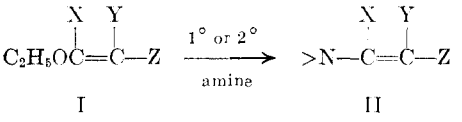
A number of enamines corresponding to II have been prepared and characterized. Many of these compounds displayed muscle relaxant and sedative properties when tested in mice. Reduction of diethyl (4-hydroxy-4-phenylpiperidyl) methylenemalonate with lithium aluminum hydride gave 2-(4-hydroxy-4-phenylpiperidyl)-2-propen-1-ol. Catalytic hydrogenation of diethyl piperidylmethylenemalonate resulted in the reductive cleavage of the C–N bond. Reaction with methyl iodide also caused cleavage of the C–N bond with subsequent formation of the methyl quaternary ammonium iodide. Aminomethylenemalonates and cyanoacrylates of type II reacted with benzamidine with the expulsion of the amine moiety to form pyrimidines. The formation of benzimidazole and 2-methylbenzimidazole occurred when *o*-phenylenediamine underwent reaction in boiling ethanol with ethoxymethylenemalononitrile and ethyl(2-cyano-3-ethoxy)crotonate, respectively.

The reaction of primary and secondary amines with ethoxymethylene compounds of type I resulted in the displacement of the ethoxy group by the amino function to give enamines of type II.



I II

X = H or CH_3; Y = $CO_2C_2H_5$, CO_2CH_3, CN, or $COCH_3$; Z = $CO_2C_2H_5$, CN, or $COCH_3$; >N = primary or secondary amine

Some of these type II compounds displayed interesting central nervous system activity and muscle relaxing properties.[1] In order to determine the effect of structure on activity in such compounds, the amino portion of the molecule, as well as substituents X, Y, and Z, were varied. In general, these reactions were carried out according to the method of Claisen.[2] The compounds prepared are recorded in Tables I–IV.

Pharmacological Results.—The compounds listed in Table I proved to be pharmacologically the most interesting. They showed muscle relaxation and sedative properties and had very low toxicity. Among the more active members of the series were compounds **25**, **30**, **33**, **36**, **39**, and **41**. All of these compounds have X = H and Y = dialkylamino or polymethylenimino. In other compounds where Y = monoalkylamino or arylamino, there was little or no observable activity. Substitution of an H with a methyl group in X in the more active compounds decreased the activity.

The compounds listed in Table II showed a high degree of toxicity with one member (**83**) causing death in mice when given orally at 50 mg./kg. Many of the compounds tested produced a depression of spontaneous motor activity. The types of activity observed for the most active compounds are CNS stimulation for compounds **77**, **86**, and **92**; depression for **60**, **66**, **78**, and **79**; muscle relaxation for **60** and **85**; and analgesia for **78**.

The substituted malononitriles of Table III were for the most part very toxic, producing convulsions and death, and were therefore not studied extensively.

The two principal methods used in screening the compounds listed in Tables I–IV are described in the Pharmacolgical Methods section.

(1) A similar observation was reported by E. A. Steck [*J. Org. Chem.*, **27**, 306 (1962)] while the present work was in progress.

(2) L. Claisen, *Ann.*, **297**, 77 (1897).

Pharmacological Methods. Muscle Relaxant Activity Screen.—Compounds in Tables I–IV were administered either orally or intraperitoneally at a number of dose levels to groups of 12 male mice. At various times after the administration of the compounds, each animal was handled in the following manner: The mouse was placed in the palm of one hand, and each limb was gently pulled out to an extended position. Muscle relaxation was considered present if the limb remained in the extended position for 5 sec.

Spontaneous Motor Response as a Screen for Central Nervous System Activity.—The effect of compounds in Tables I–IV on spontaneous motor activity in mice was used as a rapid objective measure of the presence or absence of pharmacologic activity. Both central nervous system stimulants and depressants have been detected by this method.[3a–e] Groups of 5 male mice weighing 15–23 g. were placed in a photoelectric activity chamber immediately after administration of the compounds. A count of the number of crossings of a beam of light was taken at 15 and 30 min. at which time the experiment was terminated. Suitable controls were run with the media that had been used as suspending or solubilizing agents. An arbitrary dose of 200 mg./kg. was used initially and then doses were halved until the effectiveness was considerably reduced. At the same time that this test was carried out, other animals were injected, observed, and the subjective impressions of activity were recorded.

Chemistry.—Although the compounds were prepared principally for pharmacological evaluation, certain facts concerning their chemistry were uncovered and are worthy of mention here.

Diethyl [(4-hydroxy-4-phenylpiperidyl)methylene]-malonate (**42**) was reduced with lithium aluminum hydride. The product of the reaction was identified by the n.m.r. spectrum and elemental analysis as 2-[(4-hydroxy-4-phenyl)piperidyl]-2-propen-1-ol. This is in accord with the recent finding of Gannon and Steck,[4] who showed unequivocally that the reduction of diethyl 2-naphthylaminomethylenemalonate with lithium aluminum hydride afforded 2-(2-naphthylaminomethyl)-2-propen-1-ol. It was previously reported by Shivalkar and Sunthankar[5] that the product of the latter reduction is 3-(2-naphthylamino)allyl alcohol, formed "as the result of partial hydrogenolysis." No partial hydrogenolysis was observed in the case studied by us.

Efforts to hydrogenate the double bond in diethyl piperidylmethylenemalonate (**33**) catalytically with

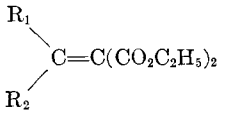
(3) (a) W. J. Kinnard, Jr., and C. J. Carr, *J. Pharmacol. Expil. Therap.*, **121**, 354 (1957); (b) P. Dews, *Brit. J. Pharmacol.*, **8**, 46 (1953); (c) L. Garberg and F. Sandberg, *Acta Pharmacol. Toxicol.*, **16**, 367 (1960); (d) J. Borsy, E. Csányi, and I. Lázár, *Arch. Intern. Pharmacodyn.*, **124**, 180 (1960); (e) B. B. Brown, *ibid.*, **128**, 391 (1960).

(4) W. F. Gannon and E. A. Steck, *J. Org. Chem.*, **27**, 4137 (1962).

(5) R. L. Shivalkar and S. V. Sunthankar, *J. Am. Chem. Soc.*, **82**, 718 (1960).

TABLE I

DIETHYL AMINOMETHYLENE AND AMINOETHYLIDENE MALONATES



No.	R_1	R_2	M.p. or b.p., °C. (mm.)	Recrystn. solvent[a]	% yield	Formula	% Calcd. C	% Calcd. H	% Calcd. N	% Found C	% Found H	% Found N
1	n-C_3H_7NH	H	134–135		80	$C_{11}H_{19}NO_4$	57.62	8.35	6.11	57.40	8.42	6.12
2	OC_5H_9NH[b]	H	51–53	D	67	$C_{13}H_{17}NO_5$	58.42	6.41	5.24	58.51	6.37	5.11
3	$(C_2H_5)_2N(CH_2)_2NH$	H	94–96	F–G	86	$C_{18}H_{30}N_2O_8$	53.72	7.51	6.96	53.72	7.26	6.89
4	$CH_3CONH(CH_2)_2NH$	H	79–80	H–J	60	$C_{12}H_{20}N_2O_5$	52.93	7.40	10.29	52.76	7.42	10.29
5	$C_6H_5(CH_2)_2NH$[d]	H	190–195 (1.2)		55	$C_{16}H_{21}NO_4$	65.95	7.27	4.81	65.94	7.39	4.64
6	$C_6H_5CH(CH_3)NH$	H	186–188 (1.0)		67	$C_{17}H_{23}NO_4$	66.86	7.59	4.59	66.59	7.28	4.69
7	$C_6H_5C(CH_3)(n\text{-}C_3H_7)CH_2NH$	H	204–208 (0.8)		65	$C_{20}H_{29}NO_4$	69.13	8.41	4.03	68.98	8.33	4.22
8	$3,4\text{-}Cl_2C_6H_3C(CH_3)(n\text{-}C_3H_7)CH_2NH$	H	>195 (0.8)		98	$C_{20}H_{27}Cl_2NO_4$	57.69	6.54	3.37	57.66	6.37	3.47
9	cyclo-C_5H_9NH	H	154–155 (0.4)		75	$C_{13}H_{21}NO_4$	61.15	8.29	5.49	61.03	8.16	5.44
10	cyclo-$C_6H_{11}NH$	H	153–155 (0.25)		59	$C_{14}H_{23}NO_4$	62.43	8.61	5.20	62.42	8.65	5.11
11	$OC_4H_8N(CH_2)_2NH$[b]	H	125		99	$C_{18}H_{28}N_2O_9$[c]	51.91	6.78	6.73	51.74	6.68	6.69
12	$C_5H_{10}N$[b]	H	104	H	98	$C_{19}H_{30}N_2O_8$[c]	55.06	7.30	6.76	55.31	7.08	6.93
13	$OC_4H_8N(CH_2)_2NH$[b]	H	115	H–J	72	$C_{19}H_{30}N_2O_9$[c]	53.01	7.03	6.51	52.71	6.87	6.73
14	$C_4H_8N(CH_2)_2NH$[b]	H	113	H	77	$C_{18}H_{28}N_2O_8$[c]	53.99	7.05	7.00	54.20	6.99	7.20
15	$2,5(CH_3O)_2C_6H_3NH$	H	80–81	F–K	75	$C_{16}H_{21}NO_6$	59.43	6.55	4.33	59.43	6.50	4.45
16	$2\text{-}HOCOC_6H_4NH$	H	156–157	F	69	$C_{15}H_{17}NO_6$	58.63	5.58	4.56	58.74	5.66	4.56
17	$2\text{-}CH_3OCOC_6H_4NH$	H	57	J	89	$C_{16}H_{19}NO_6$	59.80	5.96	4.36	59.84	6.09	4.32
18	$(C_2H_5O_2C)_2C{=}CHNH(CH_2)_2NH$	H	125	F	72	$C_{18}H_{28}N_2O_8$	53.99	7.05	7.00	54.29	6.91	6.84
19	$2\text{-}C_6H_5NHC_6H_4NH$	H	97–98	F	86	$C_{20}H_{22}N_2O_4$	67.78	6.26	7.91	67.54	6.39	8.02
20	$(C_2H_5O_2C)_2C{=}CHNHC_6H_4\text{-}3\text{-}NH$	H	109	F	92	$C_{23}H_{28}N_2O_8$	58.92	6.29	6.25	59.12	6.07	6.11
21	$(C_2H_5O_2C)_2C{=}CHNHC_6H_4\text{-}4(C_6H_4\text{-}4\text{-}NH)$	H	163–164	F	10	$C_{28}H_{32}N_2O_8$	64.11	6.15	5.34	63.81	6.05	5.43
22	$C_6H_5CH_2NCH{=}C(CO_2C_2H_5)_2$ $\vert$ $(CH_2)_2NCH_2C_6H_5$	H	77–78	H–L	43	$C_{32}H_{40}N_2O_8$	66.19	6.94	4.82	66.27	6.88	5.00
23	$(CH_3)_2N$	H	108–110 (0.1)		58	$C_{10}H_{17}NO_4$	55.80	7.96	6.51	55.60	7.98	6.51
24	$(n\text{-}C_3H_7)_2N$	H	124–125 (0.15)		51	$C_{14}H_{25}NO_4$	61.96	9.29	5.16	61.60	9.25	5.11
25	$(i\text{-}C_3H_7)_2N$	H	122 (0.15)		48	$C_{14}H_{25}NO_4$	61.96	9.29	5.16	61.73	9.00	5.08
26	$(C_6H_5CH_2)_2N$	H	65–66	L	66	$C_{22}H_{25}NO_4$	71.91	6.86	3.81	72.05	6.71	4.05
27	$(\text{cyclo-}C_6H_{11})_2N$	H	195–196 (0.6)		66	$C_{20}H_{33}NO_4$	68.34	9.46	3.99	68.40	9.46	3.91
28	$C_6H_5CH_2CH(CH_3)NCH_3$	H	186–188 (0.6)		94	$C_{18}H_{25}NO_4$	67.69	7.89	4.39	67.78	7.87	4.55
29	$C_6H_5CH_2C(CH_3)_2NH$	H	200–203 (0.7)		63	$C_{18}H_{25}NO_4$	67.69	7.89	4.39	68.10	8.07	4.26
30	C_4H_8N[b]	H	140–141 (0.1)		58	$C_{12}H_{19}NO_4$	59.73	7.94	5.81	59.44	7.98	5.78
31	$2,5\text{-}(CH_3)_2C_4H_6N$[b]	H	155–160 (0.5)		45	$C_{14}H_{23}NO_4$	62.42	8.61	5.20	62.21	8.68	5.13
32	C_4H_8N[b]	CH_3	105–106	D	70	$C_{13}H_{21}NO_4$	61.15	8.29	5.49	61.38	8.24	5.50
33	$C_5H_{10}N$[b,e]	H	39–40	J	89	$C_{13}H_{21}NO_4$	61.15	8.29	5.49	61.37	8.07	5.63
34	$C_5H_{10}N$[b]	CH_3	64–65	D–J	78	$C_{14}H_{23}NO_4$	62.43	8.61	5.20	62.37	8.63	5.19
35	$2\text{-}CH_3C_5H_8N$[b]	H	144–148 (0.14)		42	$C_{14}H_{23}NO_4$	62.43	8.61	5.20	62.24	8.59	5.06
36	OC_4H_8N[b,e]	H	66–67.5	D	80	$C_{12}H_{19}NO_5$	56.02	7.44	5.44	56.08	7.43	5.58
37	OC_4H_8N[b]	CH_3	93.5–95	D	62	$C_{13}H_{21}NO_5$	57.55	7.80	5.16	57.58	7.72	5.19
38	SC_4H_8N[b]	H	43–44 188–189 (1)	J	63	$C_{12}H_{19}NO_4S$	52.73	6.79	5.13	52.75	6.79	5.07
39	$3,5\text{-}(CH_3)_2OC_4H_6N$[b]	H	159–164 (0.14)		42	$C_{14}H_{23}NO_5$	58.93	8.13	4.91	58.45	8.29	4.86
40	$2,6\text{-}(CH_3)_2OC_4H_6N$[b]	H	155–156 (0.25)		71	$C_{14}H_{23}NO_5$	58.93	8.13	4.91	58.66	8.16	4.85
41	$C_6H_{12}N$[b]	H	138–142 (0.15)		78	$C_{14}H_{23}NO_4$	62.43	8.61	5.20	62.19	8.66	5.24
42	$4\text{-}OH\text{-}4\text{-}C_6H_5C_5H_8N$[b]	H	118–119	F	80	$C_{19}H_{25}NO_5$	65.67	7.25	4.03	65.57	6.97	4.11
43	$4\text{-}C_6H_5\text{-}(\Delta^3\text{-}C_5H_7N)$[b]	H	68–69	F	33	$C_{19}H_{23}NO_4$	69.28	7.04	4.25	69.51	7.14	4.52
44	$CH_3NC_4H_8N$[b,f]	H	61–62	J	49	$C_{13}H_{22}N_2O_4$	57.76	8.20	10.36	57.52	8.02	10.38
45	$C_2H_5NC_4H_8N$[b]	H	52.5–53.5	J	62	$C_{14}H_{24}N_2O_4$	59.13	8.51	9.85	59.12	8.44	9.94
46	$(C_2H_5O_2C)_2C{=}CHNC_4H_8N$[b]	H	115–122	H–J	47	$C_{20}H_{30}N_2O_8$	56.32	7.09	6.57	56.52	7.22	6.55
47	CH_3CONH[g]	H	52–53.5	D	10	$C_{10}H_{18}NO_5$	52.39	6.60	6.11	52.64	6.77	5.93
48	C_2H_5OCONH[g]	H	36.5–37.5	J	20	$C_{11}H_{17}NO_6$	50.96	6.61	5.40	51.25	6.59	5.30
49	$3\text{-}oxo\text{-}OC_4H_6N$[b]	H	180–184 (0.4)		16	$C_{12}H_{17}NO_6$	53.13	6.32	5.16	52.99	6.57	5.16
50	$H_2NCONHNH$	H	180	F	92	$C_9H_{16}N_3O_6$	44.08	6.17	17.14	43.80	5.93	17.45
51	$H_2NCSNHNH$	H	171–173	B	98	$C_5H_{13}N_3O_4S$	41.37	5.79	16.08	41.53	5.74	16.11
52	$2\text{-}H_2N\text{-}5\text{-}Cl\text{-}C_6H_3C(C_6H_5){=}NNH$	H	143.5–144	D	72	$C_{21}H_{22}ClN_3O_4$	60.65	5.33	10.10	60.83	5.31	10.10
53	$2\text{-}HOC_6H_4CH{=}NNH$	H	115–116	F	84	$C_{15}H_{18}N_2O_5$	58.81	5.92	9.15	58.95	5.72	9.28

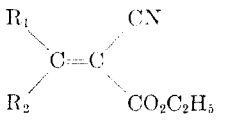
TABLE I (*Continued*)

No.	R_1	R_2	M.p. or b.p., °C.	Recrystn. solvent[a]	% yield	Formula	% Calcd. C	% Calcd. H	% Calcd. N	% Found C	% Found H	% Found N
54	2-$HOC_6H_4C(CH_3)$=NNH	H	102–103	F	87	$C_{16}H_{20}N_2O_5$	59.99	6.29	8.75	59.81	6.10	8.63
55	$C_6H_5NHNC_6H_8$	H	127–128[d]	F	61	$C_{20}H_{22}N_2O_2$	67.78	6.26	7.91	67.96	6.11	7.76

[a] A = benzene, B = 2-ethoxyethanol, C = chloroform, D = cyclohexane, E = 1,4-dioxane, F = ethanol, G = ether, H = ethyl acetate, I = methanol, J = petroleum ether, K = water, and L = hexane. [b] OC_5H_5NH = furfurylamino, OC_4H_8N = morpholino, $C_5H_{10}N$ = piperidino, C_4H_8N = pyrrolidinyl, $(CH_3)_2C_4H_6N$ = dimethylpyrrolidinyl, $CH_3C_5H_9N$ = methylpiperidino, SC_4H_8N = thiamorpholino, $(CH_3)_2OC_4H_6N$ = dimethylmorpholino, $C_6H_{12}N$ = hexahydroazepinyl, $C_6H_5C_5H_8N$ = phenylpiperidino, (Δ^3-C_5H_7N) = 1,2,5,6-tetrahydro-1-pyridyl, NC_4H_8N = piperazinyl, and oxo-OC_4H_6N = oxomorpholino. [c] Analyzed as the maleate salt. [d] L. H Groves and G. A. Swan [*J. Chem. Soc.*, 650 (1952)] reported b.p. 206–208° (1.2 mm.). [e] C. D. Hurd and L. T. Sherwood, Jr. [*J. Org. Chem.*, **13**, 471 (1948)] reported m.p. for **33** *ca.* room temperature and 64–66° for **36**. [f] Stock reported m.p. 63–64°, see ref. 1. [g] Equimolar equivalents of reactants were heated together without diluent for 2.5 hr. at 180°.

TABLE II

ETHYL AMINOMETHYLENE AND AMINOETHYLIDENE CYANOACETATES



No.	R_1	R_2	M.p., °C.	Recrystn.[a] solvent	% yield	Formula	% Calcd. C	% Calcd. H	% Calcd. N	% Found C	% Found H	% Found N
56	H_2N[b]	CH_3	189–190	F	83	$C_7H_{10}N_2O_2$	54.53	6.54	18.17	54.84	6.38	18.12
57	$HO(CH_2)_2NH$	H	75	C–J	97	$C_8H_{12}N_2O_3$	52.16	6.57	15.21	52.08	6.23	15.15
58	$CH_3CO_2(CH_2)_2NH$[c]	H	104–105	I–K	82	$C_{10}H_{14}N_2O_4$	53.09	6.24	12.38	53.05	6.20	12.46
59	cyclo-C_5H_9NH	CH_3	52–59	J	58	$C_{12}H_{18}N_2O_2$	64.84	8.16	12.60	64.92	8.49	12.42
60	cyclo-$C_6H_{11}NH$	H	105–106.5	J	99	$C_{12}H_{18}N_2O_2$	64.84	8.16	12.60	64.54	8.13	12.58
61	cyclo-$C_7H_{13}NH$	CH_3	74.5–75.5	J	77	$C_{14}H_{22}N_2O_2$	67.17	8.86	11.19	67.10	8.70	10.90
62	cyclo-$C_8H_{15}NH$	H	94–98	F–K	43	$C_{14}H_{22}N_2O_2$	67.17	8.86	11.19	67.23	8.68	11.23
63	2-$CH_3OC_6H_4NH$	H	150	F	79	$C_{13}H_{14}N_2O_3$	63.40	5.73	11.38	63.17	5.93	11.32
64	2-$CH_3OC_6N_4NH$	CH_3	90.5–92	F–J	11	$C_{14}H_{16}N_2O_3$	64.60	6.20	10.76	64.47	6.49	10.55
65	2-$NO_2C_6H_4NH$	H	171	F	29	$C_{12}H_{11}N_3O_4$	55.17	4.24	16.09	54.99	4.31	15.97
66	2-$HCO_2C_6H_4NH$	H	237	B–K	99	$C_{13}H_{12}N_2O_4$	59.99	4.65	10.77	59.90	4.33	10.80
67	2,5-$(CH_3O)_2C_6H_3NH$	H	132	F–K	99	$C_{14}H_{16}N_2O_4$	60.86	5.84	10.14	60.68	5.75	10.11
68	2,5-$(CH_3O)_2C_6H_3NH$	CH_3	173–174	F–K	28	$C_{15}H_{18}N_2O_4$	62.05	6.25	9.65	61.75	6.05	9.62
69	2-$CH_3OCOC_6H_4NH$	H	103	F	77	$C_{14}H_{14}N_2O_4$	61.31	5.15	10.21	61.15	5.02	10.27
70	5-Cl-2,4-$(CH_3O)_2C_6H_2NH$	H	178–179	F	50	$C_{14}H_{15}ClN_2O_4$	51.11	4.87	9.02	54.08	4.67	9.32
71	2-(CH_3O)-5-$(C_6H_5NHCO)C_6H_3NH$	H	260–261	E–K	33	$C_{20}H_{19}N_3O_4$	65.74	5.24	11.50	65.74	5.18	11.30
72	$NC(C_2H_5O_2C)C$=$CHNH(CH_2)_2NH$	H	145	F	60	$C_{13}H_{18}N_4O_4$	54.89	5.92	18.29	54.57	5.84	18.06
73	$(C_2H_5)_2N(CH_2)_2NH$	H	80–81	D	99	$C_{12}H_{21}N_3O_2$	60.22	8.85	17.56	60.67	8.72	17.46
74	$(C_2H_5)_2N(CH_2)_2NH$	CH_3	53.5–55	J	95	$C_{13}H_{23}N_3O_2$	61.63	9.15	16.59	61.52	9.31	16.61
75	2-$C_6H_5NHC_6H_4NH$	H	116–117	F	47	$C_{18}H_{17}N_3O_2$	70.34	5.58	13.67	70.19	5.63	13.76
76	2-$H_2NC_6H_4NH$	H	141–142	I	95	$C_{12}H_{13}N_3O_2$	62.32	5.67	18.17	62.02	5.61	17.62
77	2-$H_2NC_6H_4NH$	CH_3	122.5–123.5	F–J	41	$C_{13}H_{15}N_3O_2$	63.66	6.16	17.13	63.70	6.42	16.87
78	4-$(CH_3)_2NC_6H_4NH$[d]	H	133	F	90	$C_{14}H_{17}N_3O_2$	64.84	6.61	16.21	64.82	6.59	16.16
79	3-[(NC)$(C_2H_5O_2C)$C=$CHNH]C_6H_4NH$	H	188	F	62	$C_{18}H_{18}N_4O_4$	61.01	5.12	15.81	60.89	5.09	15.76
80	$(HOCH_2CH_2)_2N$	H	97–98.5	F–J	96	$C_{10}H_{16}N_2O_4$	52.62	7.07	12.27	52.38	7.01	12.39
81	$C_6H_5CH_2C(CH_3)_2NCH_3$	H	79–80	F–K	94	$C_{17}H_{22}N_2O_2$	71.30	7.74	9.78	71.53	7.71	9.82
82	$(C_6H_5CH_2)_2N$	H	78–79	F–K	94	$C_{20}H_{20}N_2O_2$	74.97	6.29	8.74	74.76	6.29	8.67
83	$C_5H_{10}N$[e,f]	H	65–66	F–K	99	$C_{11}H_{16}N_2O_2$	63.44	7.74	13.45	63.34	7.86	13.52
84	OC_4H_8N[e]	H	140–141	F	92	$C_{10}H_{14}N_2O_3$	57.13	6.71	13.33	57.12	6.80	13.47
85	2,6-$(CH_3)_2OC_4H_6N$[e]	H	90	K	47	$C_{12}H_{18}N_2O_3$	60.48	7.61	11.76	60.47	7.63	12.12
86	2,6-$(CH_3)_2OC_4H_6N$[e]	CH_3	124.5–125.5	F–J	24	$C_{13}H_{20}N_2O_3$	61.88	7.99	11.10	61.83	8.13	11.19
87	$C_6H_{12}N$[e]	H	59–60	F–K	95	$C_{12}H_{18}N_2O_2$	64.84	8.16	12.60	65.09	8.38	12.50
88	$CH_3NC_4H_8N$[e]	H	83–84	D	99	$C_{11}H_{17}N_3O_2$	59.17	7.68	18.82	59.53	7.68	18.82
89	$HO(CH_2)_2NC_4H_8N$[e]	H	108.5	A	72	$C_{12}H_{19}N_3O_3$	56.90	7.56	16.59	56.89	7.43	16.67
90	$CH_3CO_2(CH_2)_2NC_4H_8N$[e,g]	H	124	K	85	$C_{14}H_{21}N_3O_4$	56.93	7.17	14.23	56.83	7.16	14.25
91	$C_6H_5CH_2NC_4H_8N$[e]	H	94–95	F–J	19	$C_{17}H_{24}N_3O_2$	68.20	7.07	14.04	68.24	6.79	14.23
92	H_2NNH[h]	H	90–91	F	84	$C_7H_9N_3O_2$	46.44	5.85	27.08	46.73	5.74	27.36

[a] See footnote *a* of Table I. [b] F. S. Eberts, Jr., *Biochem. Pharmacol.*, **8**, 367 (1961). [c] Prepared by heating **57** in excess acetic anhydride. [d] F. B. Dains, O. O. Malleis, and J. T. Meyers [*J. Am. Chem. Soc.*, **35**, 970 (1913)] reported 134°. [e] See footnote *b* of Table I. [f] T. Cuvigny and H. Normant [*Bull. Soc. Chim. France*, 2423 (1961)] reported 62°. [g] Prepared by heating **89** in excess acetic anhydride. [h] P. Schmidt and J. Druey [*Helv. Chim. Acta*, **39**, 986 (1956)] reported 89–90°.

platinum black in glacial acetic acid resulted in a reductive cleavage of the molecule to give diethyl methylmalonate. A similar result was reported by Baker and Schlesinger.[6]

Attempts to form quaternary salts of some compounds listed in Tables I and II were unsuccessful. For example, treatment of diethyl piperidylmethylenemalonate in boiling isobutyl alcohol with methyl iodide resulted in C–N bond cleavage exclusively, with the subsequent formation of 1,1-dimethylpiperidinium diodide. Diethyl morpholinylmethylenemalonate (**36**) and diethyl 4-methylpiperazinylmethylenemalonate (**44**) underwent a similar C–N bond cleavage, with the formation of 4,4-dimethylmorpholinium iodide and 1,1,4,4-tetramethylpiperazinium diiodide, respectively.

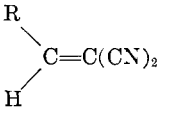
An attempt to add ketene to diethyl [(4-hydroxy-4-phenylpiperidyl)methylene]malonate by bubbling ketene into an acetone solution of the enamine resulted only in unchanged starting material. Opitz, *et al.*,[7] have reported that addition of ketene to certain enamines gives cyclobutanones.

(6) R. H. Baker and A. H. Schlesinger, *J. Am. Chem. Soc.*, **68**, 2009 (1946).

(7) G. Opitz, M. Kleemann, and F. Zimmermann, *Angew. Chem.*, **74**, 32 (1962).

TABLE III

AMINOMETHYLENE MALONONITRILES



No.	R	M.p., °C.	Recrystn.[a] solvent	% yield	Formula	% Calcd. C	% Calcd. H	% Calcd. N	% Found C	% Found H	% Found N
93	$C_5H_{10}N$[b,c]	92–93	F	84	$C_9H_{11}N_3$	67.05	6.88	26.07	66.80	6.76	26.15
94	OC_4H_8N[b,c]	149–150	F	69	$C_8H_9N_3O$	58.88	5.56	25.75	59.03	5.72	26.00
95	2,6-$(CH_3)_2OC_4H_6N$[c]	128–129	K	52	$C_{10}H_{13}N_3O$	62.80	6.85	21.98	62.80	6.84	22.31
96	cyclo-$C_6H_{11}NH$	177.5–178.5	F–K	78	$C_{10}H_{13}N_3$	68.54	7.48	23.98	68.44	7.41	24.11
97	2-$CH_3OC_6H_4NH$	163–164	F	91	$C_{11}H_9N_3O$	66.32	4.55	21.10	66.31	4.45	21.30
98	2,5-$(CH_3O)_2C_6H_3NH$	196–197	H	93	$C_{12}H_{11}N_3O_2$	62.87	4.84	18.33	62.40	4.80	18.31
99	3-ClC_6H_4NH[d]	200–201	I	95	$C_{10}H_6ClN_3$	58.95	2.97	20.63	58.44	3.05	20.88
100	4-$(CH_3)_2NC_6H_4NH$	270–271.5	E–K	80	$C_{12}H_{12}N_4$	67.90	5.70	26.40	67.78	5.86	26.67
101	$(NC)_2C{=}CHNH(CH_2)_2NH$	237–238	B–K	61	$C_{10}H_8N_6$	56.59	3.80	39.61	56.56	3.95	39.38

[a] See footnote *a* of Table I. [b] A. T. Shulgin [U. S. Patent 3,057,864 (Oct. 9, 1962)] reported m.p. 90–92° for **93** and 148–150° for **94**. [c] See footnote *b* of Table I. [d] C. C. Price and V. Boekelheide [*J. Am. Chem. Soc.*, **68**, 1246 (1946)] reported 198–199°.

TABLE IV

MISCELLANEOUS ENAMINES

No.	Compound	B.p., °C. (mm.)	% yield	Formula	% Calcd. C	% Calcd. H	% Calcd. N	% Found C	% Found H	% Found N
102	$C_4H_8NCH{=}C(COCH_3)CO_2C_2H_5$[a]	153 (0.4)	52	$C_{11}H_{17}NO_5$	62.54	8.11	6.63	62.77	8.40	6.67
103	$OC_4H_8NCH{=}C(COCH_3)CO_2C_2H_5$[a]	143–145 (0.06)	53	$C_{11}H_{17}NO_4$	58.13	7.54	6.16	58.19	7.32	6.00
104	$C_5H_{10}NCH{=}C(COCH_3)CO_2CH_3$[a]	145–146 (0.25)	40	$C_{11}H_{17}NO_3$	62.54	8.11	6.63	62.67	8.28	6.36

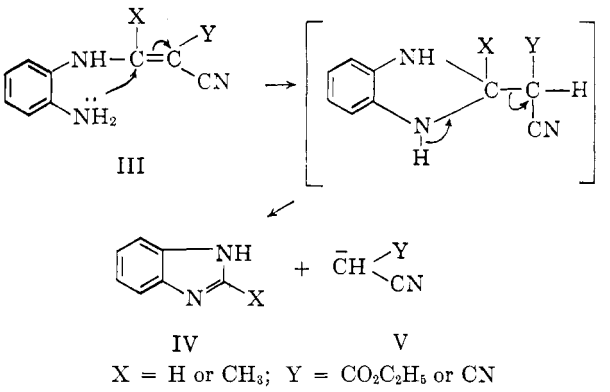
[a] See footnote *b* of Table I.

The reaction of both diethyl piperidylmethylenemalonate and diethyl morpholinylmethylenemalonate with benzamidine gave 5-carbethoxy-4-hydroxy-2-phenylpyrimidine. Some hydrolysis occurred in the latter reaction, leading to the formation of 5-carboxy-4-hydroxy-2-phenylpyrimidine. The reaction of diethyl ethoxymethylenemalonate with benzamidine has also been reported to give 5-carbethoxy-4-hydroxy-2-phenylpyrimidine.[8]

In a similar fashion, it was found that diethyl ethoxyethylidenecyanoacetate reacted with benzamidine under comparable conditions to give 5-cyano-4-hydroxy-6-methyl-2-phenylpyrimidine. During the formation of the pyrimidine ring in the compounds mentioned, displacement of the amino function occurs with considerable facility as does displacement of the ethoxy group.

Heating a solution of *o*-phenylenediamine and ethoxymethylenemalononitrile in boiling ethanol resulted in the expulsion of the malononitrile moiety with a concomitant ring closure to form benzimidazole. Heating an ethanolic solution of *o*-phenylenediamine and ethyl 3-ethoxy-2-cyanocrotonate under reflux led to the formation of 2-methylbenzimidazole. In the former reaction, it is possible to isolate (2-aminoanilinomethylene)malononitrile if the reaction is carried out at room temperature. In the latter reaction, ethyl (2-aminoanilinomethylene)cyanoacetate (**76**) can be obtained if the reaction time is reduced. Formation of these two enamines must occur prior to the formation of benzimidazoles. In each case, attack of the primary amino nitrogen on the β-carbon of enamine III, accompanied by the elimination of the resonance-stabilized anion V, results in the ring closure. The tendency to form the aromatic benzimidazole system IV must act as a strong driving force which favors this reaction.

(8) P. C. Mitter and J. C. Bardhan, *J. Chem. Soc*., 2179 (1923).



III

IV V

X = H or CH_3; Y = $CO_2C_2H_5$ or CN

Experimental[9]

Generally, the enamines listed in Tables I–IV were prepared by heating under reflux an ethanolic solution of the appropriate amine and ethoxymethylene compound. An example is given below. Any significant departures from this procedure are indicated in the footnotes of the tables.

Diethyl Pyrrolidylmethylenemalonate (30).—A solution of 14.2 g. of pyrrolidine and 43.2 g. of diethyl ethoxymethylenemalonate in 50 ml. of absolute ethanol was heated under reflux for 1 hr. The solvent was removed *in vacuo* on a rotary evaporator. The residual oil (47 g.) was distilled through a Claisen head. After an initial forerun of 11.1 g., b.p. 40–145° (0.15 mm.), there was obtained 28.2 g. of product, b.p. 140–141° (0.1 mm.).

Reduction of Diethyl [(4-Hydroxy-4-phenylpiperidyl)methylene]malonate (42) with Lithium Aluminum Hydride.—A mixture of 3.5 g. of diethyl[(4-hydroxy-4-phenylpiperidyl)methylene]-malonate, 200 ml. of anhydrous ether, and 2 g. of lithium aluminum hydride was heated under reflux for 2 hr. and was left standing overnight at room temperature. The excess hydride was decomposed by the slow addition of 6 ml. of water. The resulting granular solid was washed twice with 200 ml. of ether. The combined ethereal solutions were concentrated to give 2.5 g. of colorless oil, which crystallized on standing. Recrystallization from ethanol afforded 1.5 g. of 2-(4-hydroxy-4-phenylpiperi-

(9) Melting points were taken in capillary tubes (Thomas–Hoover capillary melting point apparatus) on a corrected basis.

dyl)-2-propen-1-ol, m.p. 74–75°. The n.m.r. spectrum was consistent with the proposed structure, with the expected hydrogen ratio of 2:2, peaks occurring at 3.06 (for $=CH_2$) and at 4.1 τ (for the methylene group of CH_2OH).

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.61; H, 8.29; N, 5.77.

The **picrate,** formed in methanol on addition of a methanol solution of picric acid, decomposed violently with a brilliant purple flash at 243°, with gradual darkening above 150°.

5-Cyano-6-hydroxy-4-methyl-2-phenylpyrimidine.—To a solution of 0.4 g. of sodium in 50 ml. of absolute ethanol was added 1.1 g. of benzamidine hydrochloride. After a few minutes, 1.3 g. of ethyl 3-ethoxy-2-cyanoacetate was added. The reaction mixture was heated under reflux for 2 hr. and then allowed to stand overnight at room temperature. After the addition of 25 ml. of water, the reaction mixture was neutralized with glacial acetic acid. A precipitate was deposited that amounted to 1 g. Dissolution of this material in concentrated ammonium hydroxide, followed by acidification with glacial acetic acid, afforded 0.8 g. of product, m.p. 290–291°.

Anal. Calcd. for $C_{12}H_9N_3O$: C, 68.23; H, 4.30; N, 19.90. Found: C, 68.59; H, 4.42; N, 20.03.

5-Carbethoxy-4-hydroxy-2-phenylpyrimidine.—To a solution of 1.38 g. of sodium in 100 ml. of absolute ethanol was added 6.25 g. of benzamidine hydrochloride, followed by 5.1 g. of diethyl piperidylmethylenemalonate. The reaction mixture was heated under reflux with stirring for 2 hr. After filtering the reaction mixture, the ethanol was removed from the filtrate *in vacuo* and the residue was acidified with glacial acetic acid. The precipitate that was deposited amounted to 1 g. Recrystallization from ethanol afforded 0.9 g. of product, m.p. 214–215°. A mixture melting point with an authentic sample gave no depression.

Diethyl morpholinylmethylenemalonate (5.1 g.) reacted with 3.0 g. of benzamidine hydrochloride under the same conditions to give 0.5 g. of 5-carbethoxy-4-hydroxy-2-phenylpyrimidine, m.p. 214–215°, and 1.2 g. of 5-carboxy-4-hydroxy-2-phenylpyrimidine, m.p. 270.5–271.5°.

Formation of Benzimidazole from *o*-Phenylenediamine and Ethoxymethylenemalononitrile.—A solution of 6.1 g. of ethoxymethylenemalononitrile and 5.2 g. of *o*-phenylenediamine in 75 ml. of absolute ethanol was heated under reflux for 1 hr. After removal of the solvent *in vacuo* on a rotary evaporator, the residual solid was washed with petroleum ether and amounted to 7 g., m.p. 171–173°. Comparison of the infrared spectra and a mixture melting point with benzimidazole showed the two materials to be identical.

Formation of 2-Methylbenzimidazole from *o*-Phenylenediamine and Ethyl 3-Ethoxy-2-cyanocrotonate.—A solution of 27.5 g. of ethyl 2-cyano-3-ethoxycrotonate and 16.2 g. of *o*-phenylenediamine in 50 ml. of absolute ethanol was heated under reflux for 7.5 hr. The solvent was removed *in vacuo* on a rotary evaporator. The residue amounted to 24 g., m.p. 150–160°. Several recrystallizations from ethyl acetate–petroleum ether afforded pure 2-methylbenzimidazole, m.p. 176–177° (lit.[10] m.p. 176°).

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(10) M. A. Phillips, *J. Chem. Soc.*, 2393 (1928).

Cyclic Analogs and Congeners of Succinyl Dicholine[1,2]

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Dicholine- and bis(N,N-dimethylhydraziniumethyl) esters of *cis*- and *trans*-cyclopropane- and cyclobutane-1,2-dicarboxylic acids have been prepared to study the effect of forcing the ester groups to assume a fixed conformation which would be similar to one of the conformations of succinyl dicholine. Biological test data are presented.

If the possible conformations of the succinic acid portion of succinyl dicholine are considered, it would be expected that *in vitro* a staggered conformation would be favored. The question then arises as to whether this conformation would also be favored for adsorption at an *in vivo* receptor surface. It was the purpose of the research reported herein to limit the degrees of rotational freedom about the two carbons alpha to the carboxyls of certain succinic acid congeners, thus forcing the ester groups to assume a fixed conformation which would be similar to one of the extreme conformations of succinyl dicholine. Inspection of Dreiding models of the dicholine esters of *cis*-cyclopropane- and of *cis*-cyclobutane-1,2-dicarboxylic acids indicates that they coincide (as regards the carbonyl groups) with the *eclipsed* form of the succinate ester. The *trans* isomers are nearly superimposable on the *staggered* conformation of the succinate ester. Since the cyclopropane and the cyclobutane rings are small, there should be a minimum of steric interference by the ring with the receptor surfaces involved, and it might be possible to evaluate the biological effects induced by the enforcement of specific conformations.

Tammelin[4] has prepared analogs of dicholine esters of saturated alkyl dicarboxylic acids from oxalic through adipic, in which one nitrogen–methyl of each choline was replaced by a primary amino group, forming a hydrazinium structure. These hydrazine analogs of choline esters possessed neuromuscular blocking activity, but they were in general less potent than the corresponding dicholine esters.[5] Nevertheless, it appeared that comparative studies of ammonium and hydrazinium

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(4) L. E. Tammelin, *Acta Chem. Scand.*, **10**, 1068 (1956).

(5) T. Fredriksson, *Acta Pharmacol. Toxicol.*, **13**, 86 (1957).