[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Studies of Imidazoles. VII. Substituted 1-Phenethylimidazoles and Related Compounds*,[1]

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A series of 1-aralkylimidazoles, 2-mercaptoimidazoles, and 2-substituted mercaptoimidazoles is described. 1-Homoveratryl-2-methylmercaptoimidazole was found to possess marked local anesthetic and appreciable bronchodilator activities. The 1-phenethylimidazoles and also 1-benzyl and 1-(3-phenylpropyl)imidazole caused effects on blood pressure and heart rate of experimental animals of about the same kind and magnitude as ephedrine.

1-Benzylimidazole,[2] when tested in anesthetized cats and dogs, was found to have a pharmacological activity closely resembling that of ephedrine. 1-Phenethylimidazole had even greater pressor activity. These observations led us to prepare a series of substituted 1-phenethylimidazoles and related compounds to test as possible broncholdilator agents.

The preparation of the compounds described in the accompanying tables involved methods previously reported.[3] In general the reaction sequence was as follows: An appropriate amine was heated with chloroacetal to form an *N*-substituted aminoacetal (Table I). The aminoacetal was allowed to react with thiocyanic acid to yield a 1-substituted-2-mercaptoimidazole (Table II). This was either desulfurized with Raney nickel to produce a 1-substituted imidazole (Table III) or was allowed to react with methyl iodide to yield a 1-substituted-2-methylmercaptoimidazole (Table IV).

The compounds of Table III generally had appreciable bronchodilator activities, but at the same time they almost all caused marked elevations of the blood pressure of experimental animals. For this reason they were not intensively tested. Some of the 2-methylmercaptoimidazoles of Table IV, and particularly 1-homoveratryl-2-methylmercaptoimidazole, had good bronchodilator activity and little or no effect on blood pressure or heart rate.

1-Homoveratryl-2-methylmercaptoimidazole underwent preliminary testing in the clinic, but the results were disappointing. During the clinical observation the compound was discovered to be a potent local anesthetic, and its apparent bronchodilator activity could probably be ascribed to its local anesthetic effects.

Several additional 1-homoveratryl-2-alkyl and aralkylmercaptoimidazoles were prepared and are presented in Table V. They were pharmacologically less interesting than the methylmercapto compound.

At first impression it may be thought that the effects of the 1-β-phenylethylimidazoles (Table III) on blood pressure and heart rate are due to the β-phenethylamine fragment present in the structures; or that perhaps the imidazole ring is degraded in the animal body with formation of an

* This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

(1) Preceding paper, R. G. Jones, *J. Am. Chem. Soc.*, **74**, 1085 (1952).

(2) R. G. Jones, *J. Am. Chem. Soc.*, **71**, 383 (1949).

(3) R. G. Jones, E. C. Kornfeld, K. C. McLaughlin, and R. C. Anderson, *J. Am. Chem. Soc.*, **71**, 4000 (1949).

TABLE I

N-SUBSTITUTED AMINOACETALS

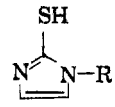
$RNHCH_2CH(OC_2H_5)_2$

R	B.P., °C./mm.	n_D^{25}	Yield, %	Formula	Analyses: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
$C_5H_{11}CH(CH_3)$[a]	117–121/10	1.4289	64.3	$C_{13}H_{29}NO_2$	67.48	67.05	12.63	12.03	6.05	6.34
$C_5H_{11}CH(CH_3)$[b]	125–129/10	1.4283	53	$C_{13}H_{29}NO_2$	[b]					
$C_6H_5CH_2CH(CH_3)$	154–159/8	1.4839	68.3	$C_{15}H_{25}NO_2$	71.67	71.40	10.03	9.80	5.57	5.75
p-$CH_3OC_6H_4CH_2CH_2$	170/4	1.4923	77	$C_{15}H_{25}NO_3$	67.38	67.11	9.43	9.41	5.24	5.25
3,4-$(CH_3O)_2C_6H_3CH_2CH_2$	190–191/3	1.5015	62	$C_{16}H_{27}NO_4$	64.62	64.37	9.15	9.15	4.71	4.49
o-$ClC_6H_4CH_2CH_2$	130–135/1	1.5020	53	$C_{14}H_{22}ClNO_2$	61.87	61.59	8.15	8.02	5.15	5.17
p-$ClC_6H_4CH_2CH_2$	140–145/1.5	1.4983	61	$C_{14}H_{22}ClNO_2$	61.87	61.60	8.15	8.20	5.15	5.13
2,4-$(Cl)_2C_6H_3CH_2CH_2$	160–165/2	1.5131	46	$C_{14}H_{21}Cl_2NO_2$	54.91	54.97	6.91	7.17	4.57	4.42
3,4-$(Cl)_2C_6H_3CH_2CH_2$	151–152/1	1.5203	41.2	$C_{14}H_{21}Cl_2NO_2$	54.91	54.74	6.91	6.41	4.57	4.88
$C_6H_5CH_2CH_2CH_2$	163/4	1.4849	73.5	$C_{15}H_{25}NO_2$	71.67	71.41	10.03	10.10	5.57	5.61
$(CH_3)_2CHCH_2CH_2$	100–102/10	1.4250	75	$C_{11}H_{25}NO_2$	64.98	65.30	12.39	12.17	6.89	7.05
$CH_3(CH_2)_6CH_2$	97/0.25	1.4311	73	$C_{14}H_{31}NO_2$	68.52	69.05	12.73	12.58	5.71	5.67

[a] 4-Methyl-2-hexyl. [b] 2-Heptyl, see ref. 3.

TABLE II

1-SUBSTITUTED 2-MERCAPTOIMIDAZOLES



R	M.P., °C.[a]	Yield, %	Formula	Analyses: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
$C_5H_{11}CH(CH_3)$[b]	82	53	$C_{10}H_{18}N_2S$	60.58	60.45	9.15	9.20	14.13	14.03
$C_5H_{11}CH(CH_3)$[c]	75–76	45	$C_{10}H_{18}N_2S$	[c]					
$C_6H_5CH_2CH(CH_3)$	126–126.5	86.5	$C_{12}H_{14}N_2S$	66.02	66.39	6.46	6.61	12.83	12.91
p-$CH_3OC_6H_4CH_2CH_2$	152	87.2	$C_{12}H_{14}N_2OS$	61.51	61.80	6.02	5.78	11.96	11.99
3,4-$(CH_3O)_2C_6H_3CH_2CH_2$	171	66.4	$C_{13}H_{16}N_2O_2S$	59.06	59.29	6.09	6.08	10.60	10.26
o-$ClC_6H_4CH_2CH_2$	140.5	83	$C_{11}H_{11}ClN_2S$	55.34	55.35	4.65	4.63	11.74	11.50
p-$ClC_6H_4CH_2CH_2$	202–203	79	$C_{11}H_{11}ClN_2S$	55.34	55.60	4.65	4.64	11.74	11.77
2,4-$(Cl)_2C_6H_3CH_2CH_2$	179.5–180	71.5	$C_{11}H_{10}Cl_2N_2S$	48.36	48 35	3.69	3.65	10.26	10.10
3,4-$(Cl)_2C_6H_3CH_2CH_2$	153–154	62	$C_{11}H_{10}Cl_2N_2S$	48.36	48.29	3.69	3.79	10.26	10.24
$C_6H_5CH_2CH_2CH_2$	113–114	81.5	$C_{12}H_{14}N_2S$	66.01	65.74	6.46	6.47	12.83	12.65
$(CH_3)_2CHCH_2CH_2$	95–96	78	$C_8H_{14}N_2S$	56.42	56.04	8.29	8.31	16.45	16.29
$CH_3(CH_2)_6CH_2$	57–57.5	87.5	$C_{11}H_{20}N_2S$	62.21	62.31	9.49	9.57	13.19	12.96

[a] Melting points were taken on a Fisher-Johns apparatus and are uncorrected. [b] 4-Methyl-2-hexyl. [c] 2-Heptyl, see ref. 3.

TABLE III

1-SUBSTITUTED IMIDAZOLES

R	B.P., °C./mm.	n_D^{25}	Yield, %	Formula	Analyses: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
$C_5H_{11}CH(CH_3)$[a]	91–92/1	1.4731	65	$C_{10}H_{18}N_2$	72.24	72.16	10.91	11.18	16.85	16.65
$C_5H_{11}CH(CH_3)$[b,c]	118–119/3	1.4705	66	$C_{10}H_{18}N_2$	[d]					
$C_6H_5CH_2CH(CH_3)$	133/1	1.5535	65.5	$C_{12}H_{14}N_2$	77.37	77.28	7.58	7.69	15.04	15.12
p-$CH_3OC_6H_4CH_2CH_2$	158/0.5	1.5261	54.5	$C_{12}H_{14}N_2O$	71.26	71.00	6.98	7.08	13.85	13.61
3,4-$(CH_3O)_2C_6H_3CH_2CH_2$	195/1[e]	1.5659	60	$C_{13}H_{16}N_2O_2$	67.22	67.08	6.94	7.05	12.06	11.94
o-$ClC_6H_4CH_2CH_2$	139–140/1	1.5689	58.5	$C_{11}H_{11}ClN_2$	63.92	63.64	5.36	5.22	13.55	13.65
p-$ClC_6H_4CH_2CH_2$	159–161/1	[f]	73.7	$C_{11}H_{11}ClN_2$	63.92	63.95	5.36	5.51	13.55	13.49
2,4-$(Cl)_2C_6H_3CH_2CH_2$	152/0.25	1.5798	63	$C_{11}H_{10}Cl_2N_2$	54.79	54.87	4.18	4.34	11.62	11.70
3,4-$(Cl)_2C_6H_3CH_2CH_2$	221/1.25	1.5800	70	$C_{11}H_{10}Cl_2N_2$	54.79	54.75	4.18	4.03	11.62	11.82
$C_6H_5CH_2CH_2CH_2$	141/1	1.5547	68	$C_{12}H_{14}N_2$	77.37	77.23	7.58	7.52	15.04	15.21
$(CH_3)_2CHCH_2CH_2$	108/8	1.4742	70.3	$C_8H_{14}N_2$	69.52	69.95	10.21	10.27	20.27	20.12
$CH_3(CH_2)_6CH_2$	115–117/0.25	1.4781	35	$C_{11}H_{20}N_2$	73.28	73.52	11.18	11.19	15.54	15.60

[a] 4-Methyl-2-hexyl. [b] 2-Heptyl. [c] In this one case the mercaptoimidazole was desulfurized by treatment with nitric acid-sodium nitrite. [d] Analyzed as the hydrochloride salt. Calcd. for $C_{10}H_{19}ClN_2$: N, 13.82; Found, N, 13.51. [e] The liquid crystallized; m.p. 71–72°. [f] The liquid crystallized; m.p. 72–72.5°.

active β-phenethylamine. That such is not necessarily the case was indicated by the fact that 1-benzylimidazole and 1-(3-phenylpropyl)imidazole (Table III) were highly active in raising the blood pressure and increasing the heart rate of experimental animals. Thus, the pharmacological activities appear to be associated with the 1-substituted imidazole structure, and these compounds may be considered as a new class of potent pressor substances.

EXPERIMENTAL

Substituted phenylethylamines. The majority of the amines used in this investigation were commercially available. Those that appear not to have been described previously were prepared in the usual manner through the substituted benzyl cyanides with subsequent reduction to the amine.

2,4-Dichlorobenzyl cyanide. A mixture of 162 g. (3.3 moles) of sodium cyanide, 586.5 g. (3.0 moles) of 2,4-dichlorobenzyl chloride, 500 ml. of ethanol, and 500 ml. of water was refluxed 8 hr. After removing the ethanol by distillation, the product was extracted with diethyl ether. Removal of the ether yielded a residue which on recrystallization from ethanol provided 368 g. of the nitrile as a tan solid; m.p. 59–60°. An additional 65 g. of the product was recovered from the ethanol filtrate; 78% yield.

Anal. Calcd. for $C_8H_5Cl_2N$: C, 51.64; H, 2.71; N, 7.53. Found: C, 51.81; H, 2.89; N, 7.62.

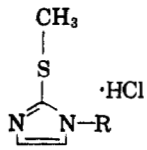
In a like manner, 3,4-dichlorobenzyl cyanide was prepared in 55% yield; m.p. 37–37.5°.

Anal. Calcd. for $C_8H_5Cl_2N$: C, 51.64; H, 2.71; N, 7.53. Found: C, 51.88; H, 2.75; N, 7.61.

β-(3,4-Dichlorophenyl)ethylamine. A solution of 186 g. (1.0 mole) of 3,4-dichlorobenzyl cyanide in 500 ml. of diethyl ether was added slowly to a stirred suspension of 38 g. (1.0 mole) of lithium aluminum hydride in 2 l. of ether at such a rate as to maintain gentle boiling. The mixture was then decomposed by the cautious addition of 25 ml. of

TABLE IV

1-SUBSTITUTED 2-METHYLMERCAPTOIMIDAZOLE HYDROCHLORIDES

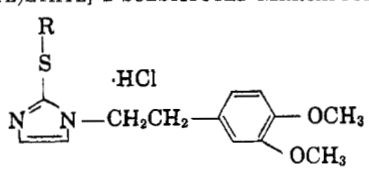


R	M.P., °C.	Yield, %	Formula	Analyses					
				Carbon, %		Hydrogen, %		Nitrogen, %	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
$C_6H_{11}CH(CH_3)$[a]	152–154	49.5	$C_{11}H_{21}ClN_2S$	53.09	52.80	8.50	8.25	11.26	11.02
$C_6H_{11}CH(CH_3)$[b]	142–143	81.5	$C_{11}H_{21}ClN_2S$	53.09	53.39	8.50	8.51	11.26	11.31
$C_6H_5CH_2CH(CH_3)$	164–164.5	86	$C_{13}H_{17}ClN_2S$	58.09	58.39	6.37	6.18	10.42	10.43
p-$CH_3OC_6H_4CH_2CH_2$	158–159	58.5	$C_{13}H_{17}ClN_2OS$	54.82	54.79	6.02	6.03	9.83	9.90
3,4-$(CH_3O)_2C_6H_3CH_2CH_2$	149–150	58	$C_{14}H_{19}ClN_2O_2S$	53.41	53.53	6.08	6.15	8.89	9.12
o-$ClC_6H_4CH_2CH_2$	128–129	64	$C_{12}H_{14}Cl_2N_2S$	49.83	49.91	4.88	5.12	9.68	9.83
p-$ClC_6H_4CH_2CH_2$	171–172	39.5	$C_{12}H_{14}Cl_2N_2S$	49.83	49.93	4.88	4.65	9.68	9.86
2,4-$(Cl)_2C_6H_3CH_2CH_2$	188	56	$C_{12}H_{13}Cl_3N_2S$	44.52	44.70	4.05	4.26	8.65	8.93
3,4-$(Cl)_2C_6H_3CH_2CH_2$	173.5	52	$C_{12}H_{13}Cl_3N_2S$	44.52	44.73	4.05	3.99	8.65	8.68
$C_6H_5CH_2CH_2CH_2$	95–96	76	$C_{13}H_{17}ClN_2S$	58.09	58.35	6.37	6.29	10.42	10.49
$(CH_3)_2CHCH_2CH_2$	130–131	78.5	$C_9H_{17}ClN_2S$	48.96	48.94	7.76	7.51	12.69	12.48
$CH_3(CH_2)_6CH_2$	117–118	69	$C_{12}H_{23}ClN_2S$	54.83	55.08	8.82	8.24	10.66	10.53
C_6H_{11}[c]	166–167	76	$C_{10}H_{17}ClN_2S$	51.59	51.74	7.36	7.14	12.03	12.20
$C_6H_5CH_2$	169–170	82.3	$C_{11}H_{13}ClN_2S$	54.87	55.33	5.44	5.59	11.63	11.71

[a] 4-Methyl-2-hexyl. [b] 2-Heptyl. [c] Cyclohexyl.

TABLE V

1-[β-(3,4-DIMETHOXYPHENYL)ETHYL]-2-SUBSTITUTED MERCAPTOIMIDAZOLE HYDROCHLORIDES



R	M.P., °C.	Yield, %	Formula	Analyses					
				Carbon, %		Hydrogen, %		Nitrogen, %	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
$CH_3CH_2CH_2$	117–118	70	$C_{16}H_{23}ClN_2O_2S$	56.04	56.17	6.76	6.81	8.17	8.13
$CH_3(CH_2)_4CH_2$	108–109	72	$C_{19}H_{29}ClN_2O_2S$	59.27	59.29	7.59	7.32	7.27	7.38
$CH_3CH_2CO_2CH_2CH_2$	107–108	64	$C_{18}H_{25}ClN_2O_4S$	53.92	53.54	6.28	6.40	6.98	7.08
$C_6H_5CH_2$	129–130	82	$C_{20}H_{23}ClN_2O_2S$	61.44	61.40	5.93	6.08	7.16	7.29
$C_6H_5CHCH_2$ | OH	151–152	74	$C_{21}H_{25}ClN_2O_3S$	59.91	59.45	5.98	6.20	6.65	6.41

ethanol, 40 ml. of water, 30 ml. of 20% aqueous sodium hydroxide, and 140 ml. of water. The granular inorganic salts were removed by filtration and washed with more ether. The combined ether solution was dried over anhydrous magnesium sulfate and the ether evaporated. Upon distillation, a small forerun was collected up to 118° (1.5 mm.) followed by a 54% yield of the product boiling at 118–120° (1.5 mm.); n_D^{25} 1.5650. The hydrochloride salt was prepared as a white, non-hygroscopic solid by treating an ether solution of the amine with anhydrous hydrogen chloride. A sample for analysis was recrystallized three times from ethanol-ether; m.p. 169–170°.

Anal. Calcd. for $C_8H_{10}Cl_3N$: C, 42.41; H, 4.45; N, 6.18. Found: C, 42.38; H, 4.46; N, 6.39.

In a similar manner β-(*o*-chlorophenyl)ethylamine was obtained in 63% yield; b.p. 94–95° (4–5 mm.); n_D^{25} 1.5483. The hydrochloride salt melted at 139–140°.

Anal. Calcd. for $C_8H_{11}Cl_2N$: C, 50.02; H, 5.77; N, 7.29. Found: C, 50.41; H, 5.65; N, 7.33.

β-(2,4-Dichlorophenyl)ethylamine, b.p. 114–120° (3 mm.), n_D^{25} 1.5639, was obtained in 67% yield. The hydrochloride salt melted at 164–165°.

Anal. Calcd. for $C_8H_{10}Cl_3N$: C, 42.41; H, 4.45; N, 6.18. Found: C, 42.26; H, 4.66; N, 6.48.

N-Substituted aminoacetals. These compounds, described in Table I, were all prepared by the same general procedure. The preparation of *N*-[β-(3,4-dimethoxyphenyl)ethyl]aminoacetaldehyde diethylacetal is described below:

A mixture of 91.8 g. (0.6 mole) of chloroacetaldehyde diethylacetal and 362 g. (2.0 moles) of homoveratrylamine was heated in a wax bath at 120° for 24 hr. After cooling to room temperature, 180 ml. of 50% aqueous sodium hydroxide was added. The oily organic phase was extracted into chloroform. The chloroform extract was washed with water and dried over anhydrous potassium carbonate. After removing the drying agent the chloroform was evaporated. Distillation of the residue gave 189 g. of unreacted homoveratrylamine and 110 g. of the desired acetal, b.p. 190–195° (3–4 mm.).

1-Substituted-2-mercaptoimidazoles. These compounds, pre-

sented in Table II, were obtained by the reaction of the substituted aminoacetals with thiocyanic acid. The preparation of 1-[β-(*o*-chlorophenyl)ethyl]-2-mercaptoimidazole is illustrative of this procedure:

To a solution of 57 g. (0.135 mole) of *N*-[β-(*o*-chlorophenyl)ethyl]aminoacetaldehyde diethylacetal in 125 ml. of ethanol was added 18.2 g. (0.16 mole) of potassium thiocyanate and 75 ml. (0.15 mole) of 2*N* hydrochloric acid. The mixture was heated on the steam bath for 4 hr., during which time most of the ethanol was allowed to evaporate. The dark, oily organic layer solidified on cooling. This was filtered and washed with water. The damp filter cake was dissolved in a solution of 5.4 g. of sodium hydroxide in 300 ml. of water. This solution was heated to boiling, treated with decolorizing carbon, filtered, and acidified with concentrated hydrochloric acid. The pink colored precipitate was filtered and washed with water. The sample for analysis was recrystallized from ethanol.

1-Substituted imidazoles. These compounds, described in Table III, were, with one exception as noted in the table, prepared by the Raney nickel desulfurization of the mercaptoimidazoles. The preparation of 1-[β-(*p*-methoxyphenyl)ethyl]imidazole serves to illustrate this procedure.

The mercaptoimidazole, 11.7 g. (0.05 mole) was dissolved in 250 ml. of ethanol with gentle warming. To this solution was added an excess of ethanol-wet Raney nickel. Some frothing was noted. The resulting mixture was stirred under reflux for 5 hr. The mixture was filtered, and the filter cake washed with more ethanol. The combined filtrate and washings were concentrated *in vacuo*. The residue was dissolved in diethyl ether, and the ether solution washed with 100 ml. of 10% sodium hydroxide solution, and then with water. The alkaline wash, on acidification with concentrated hydrochloric acid, produced none of the original mercaptoimidazole. The ether solution, after drying over anhydrous magnesium sulfate, was evaporated and the residue distilled under reduced pressure. The product distilled at 158° (0.5 mm.) to give 5.5 g. of a clear, viscous liquid.

1-Substituted-2-methylmercaptoimidazole hydrochlorides. All of the compounds described in Table IV were prepared by the same general method.[4] The preparation of 1-(2-heptyl)-2-methylmercaptoimidazole hydrochloride illustrates this method.

There was added 21.3 g. (0.15 mole) of methyl iodide to a solution of 19.8 g. (0.1 mole) of 1-(2-heptyl)-2-mercaptoimidazole in 100 ml. of ethanol. The mixture became quite warm, and cooling in an ice bath was necessary. After the initial reaction had subsided, the flask was stoppered and kept overnight at room temperature. An excess of diethyl ether was added to complete the precipitation of the hydroiodide salt. This salt was removed by filtration and washed with more ether. The salt was added to a solution containing 4 g. of sodium hydroxide in 500 ml. of water. The organic phase was extracted into diethyl ether and washed twice with water. The ether solution was dried over anhydrous magnesium sulfate, and the drying agent then removed by filtering. The ethereal filtrate upon treatment with anhydrous hydrogen chloride precipitated the product as a white, crystalline solid. This was filtered and washed well with ether. The sample for analysis was recrystallized twice from a mixture of ethanol and ether.

1-[β-(3,4-Dimethoxyphenyl)ethyl]-2-substituted mercaptoimidazole hydrochlorides. These compounds, described in Table V, were prepared in a manner similar to the above, using the appropriate bromo compounds in place of methyl iodide.

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INDIANAPOLIS 6, IND.

(4) W. Marckwald, *Ber.*, 25, 2360 (1892).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF CALIFORNIA]

Reactivity of Organocadmium Reagents toward Halides Other than Acid Chlorides. Improvement of Conditions for the Reformatsky Reaction*,[1]

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The organocadmium reagent has been found to be considerably more inert than the Grignard reagent towards coupling with alkyl halides. In boiling ether solution, there was no significant rate of reaction of the cadmium reagent with either 2-iodooctane or allyl bromide. Reaction with a tertiary chloride is vigorous, but the principal products are the alkene resulting from dehydrohalogenation of the tertiary halide and the alkane corresponding to the alkylcadmium reagent. Reaction with α-bromo esters is also rapid, but in this instance the products are the alkyl bromide corresponding to the alkylcadmium reagent and the metal enolate (cadmium reagent) of the bromo ester. The reagent obtained from α-bromo esters in this way gives the same reactions as those observed in the Reformatsky reaction with zinc. An initial impression that the cadmium reagents give better yields in reaction with hindered ketones than are obtained in parallel Reformatsky reactions later proved to be a solvent effect. With hindered ketones, Reformatsky reactions in benzene-ether solvent give significantly better yields than in the conventional benzene or benzene-toluene solvent. Better yields were also realized in β-keto ester synthesis from a nitrile, zinc and α-bromo ester (Blaise reaction) when a benzene-ether solvent was used. Thermal cracking of three of the β-hydroxy-α,β-dialkyl esters prepared during this investigation yielded β,γ-unsaturated esters containing little, if any, of the α,β-unsaturated isomers.

In the initial investigation of the organocadmium reagents by Gilman and Nelson,[2] it was reported that these reagents exhibit a very low order of reactivity towards polar multiple bonds, but are re-

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(2) H. Gilman and J. F. Nelson, *Rec. trav. chim.*, 55, 518 (1936).