TABLE II

HYDROLYSIS OF 2-PROPOXYMETHYLMERCAPTOPYRIDINE 1-OXIDE AT 30°

pH	% Hydrolyzed[a]	
	5 Hours	75 Hours
5.2	0	<3.5
4.1	0	<9.5
3.1	<0.5	4.0
2.2	5.0	19.0
1.3	25.0	65.0
−0.6	91.0	87[b]

[a] Determined as pyridinethione by colorimetric analysis of complex with ferric chloride. [b] Low figure probably due to further decomposition of pyridinethione in strong acid medium.

and *p*H of 2.2: isopropoxy < ethoxy < propoxy < "isooctyloxy" < dodecyloxy < octadecyloxy.[7]

The alkylmercaptomethyl derivatives (Vb) were very resistant to hydrolysis. Thus, the propylmercaptomethyl compound (Vb, R = C_3H_7) showed only 3.5% hydrolysis in 4*N* acid at 30° after forty-one hours.

EXPERIMENTAL

Chloromethylalkyl ethers (IVa) *and sulfides* (IVb). Methyl chloromethyl ether was obtained from Matheson, Coleman and Bell and methyl chloromethyl sulfide was obtained from Stauffer Chemical Corp. The remaining chloromethyl ethers and sulfides were prepared by methods summarized by Walker.[8]

Alkylation of 2-pyridinethiol 1-oxide. Reaction A. By use of the sodium salt (III). The sodium salt of 2-pyridinethiol 1-oxide (0.05–0.50 mole) was slurried in acetone (1,4-dioxane and 1,2-dimethoxyethane were also used successfully) using 200–300 ml. of solvent per 0.1 mole. While stirring, an equimolar quantity of the appropriate alkylchloromethyl ether or sulfide was added slowly. The mixture was then refluxed for 1 to 2.5 hr. and cooled. Sodium chloride was then filtered off, and the solvent evaporated under vacuum. (For the less soluble products, a hot filtration was required.) The products were isolated as oils which generally crystallized upon cooling. They were then purified by recrystallization in or extraction with hydrocarbon solvents or isopropyl ether. The ethoxy, *n*-propoxy, dodecyloxy, octadecyloxy, and methylmercapto derivatives were prepared by this procedure. Yields, melting points, and analyses are given in Table I.

Reaction B. By use of the free acid (I). 2-Pyridinethiol 1-oxide (0.25–0.4 mole) was dissolved in 250–400 ml. of dry benzene. An equimolar quantity of the appropriate alkylchloromethyl ether or mercaptan was slowly added while stirring. The solution was then heated to 61–62° for 1.5 to 3 hr. After cooling the crystalline hydrochloride product was washed with benzene and dried. Recrystallization was effected from acetone and from a 1:1 mixed solvent of hexane and methylene chloride. The methoxy, isopropoxy, "isooctyloxy", and propylmercapto derivatives were prepared by this procedure. Yields, melting points, and analyses are given in Table I.

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Some Basically Substituted Acrylic Acid Derivatives

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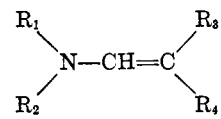
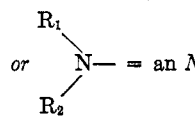
A number of basically substituted, unsaturated compounds have stimulant effects on the central nervous system. Included in this group are: arecoline,[2] lysergic acid derivatives (such as LSD-25[3] and LAE-32[4]), 1.4-bis(1-pyrrolidyl)-2-butyne,[5] β-amino-acroleins,[6,7] and nalorphine.[8] It was decided to probe the area of basically substituted acrylic acid derivatives, exemplified by I, for such activity. Varying, but definite, central stimulant effects were found in the series. Evidence of cardiovascular-renal actions and a suggestion of anti-inflammatory effects were also uncovered. Unfortunately, the potency was not at a practical level of utility in any instance.



I

R_1 = H and R_2 = alkyl, aralkyl, or heteryl group



or R_1R_2N— = an *N*-heteryl moiety

R_3 = H, CN, $COOC_2H_5$
R_4 = CN, $COOC_2H_5$

The greater number of compounds were of a basically substituted α-carbethoxy acrylic ester type (I, with R_3 = R_4 = $CO_2C_2H_5$). These were

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TABLE I

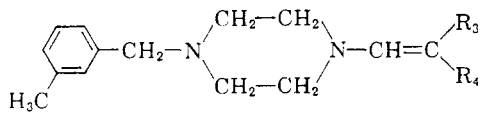
DIETHYL [BASICALLY SUBSTITUTED) METHYLENEMALONATE TYPES

Diethyl (Subst.) Methylenemalonates	Appearance[a]	M.P.[b]	Solvent[c]	Absorption Maxima		Calcd.			Found		
				Ultraviolet[d]	Infrared[e]	C	H	N	C	H	N
3-Diethylaminopropylamino	Pale yellow oil	[f]			5.94; 6.05; 6.20; 6.85; 7.02; 7.25[g]	57.34	8.88	10.29	57.10	9.31	10.35
4-Carboxybutylamino	Nacreous platelets	76–77	B-H	223 (3.51); 279 (3.71)	5.80; 5.97; 6.16; 6.32; 7.00	54.34	7.37	4.88	54.45	7.34	5.05
Benzhydrylamino	Leaflets	78.5–79	H	284 (4.41)	5.95; 6.09; 6.13; 6.17 (s); 6.95	71.37	6.56	3.96	71.61	6.69	4.06
(1,2,3,4-Tetrahydro-2-naphthyl) amino	Needles	88.5–89	H	218 (3.25); 281 (3.42)	5.94; 6.20	68.11	7.30	4.42	68.33	7.45	4.40
4-Ethoxycarbonyl-1-piperazinyl	Viscous, golden oil	[h]		284 (3.35)	5.91; 6.27; 7.01; 7.76[g]	54.86	7.37	8.53	55.01	7.43	8.31
4-Methyl-1-piperazinyl	Creamy blades	63–64	H	287 (3.34)	5.87; 6.00; 6.32	57.76	8.20	10.36	57.65	8.36	10.25
4-Benzyl-1-piperazinyl	Parallelepipeds	66.5–67	Pet	286 (3.35)	5.85; 5.95; 6.19			8.09			8.32
4-(2-Methylbenzyl)-1-piperazinyl	Creamy, prismatic needles	86.5–87.5	Pe	287 (4.37)	5.81; 5.90; 6.14	66.65	7.85	7.77	66.80	7.75	7.68
4-(3-Methylbenzyl)-1-piperazinyl	Platelets	59–60	Pe	288 (4.33)	5.85; 5.95; 6.25				66.68	7.69	8.00
4-(4-Methylbenzyl)-1-piperazinyl	Creamy, prismatic needles	72.5–73	Pe	287 (4.32)	5.82; 5.90; 6.23				66.81	7.75	7.63
1,8,8-Trimethyl-3-azabicyclo-[3.2.1]octan-3-yl	Viscous, golden oil	[i]		248 (3.79); 292 (4.34)	5.99; 6.33; 7.23; 7.32[j]	19.79[k]		4.32	19.38[k]		4.44
2-Pyrimidylamino	Creamy, prismatic needles	102–103[l]	Hp	309 (4.45)	5.93; 6.08; 6.40; 6.93	54.33	5.70	15.84	54.18	5.86	15.98
2-Thiazolylamino	Feathery needles	60–61	Hp	214 (3.09); 323 (4.42)	5.95; 6.10; 6.27	11.87[m]		10.37	11.63[m]		10.37

[a] Colorless, unless otherwise specified. [b] Uncorrected. [c] B, benzene; H, hexane; Hp, heptane; Pe, pentane; Pet, low-boiling petroleum ether. [d] Wave lengths in mμ (log ε); methanol as solvent; Cary, Model 14 used. [e] Wave lengths in μ; Nujol mulls unless stated otherwise; shoulder, (s); Perkin-Elmer, Model 21 was used. [f] B.p. 137–140° (0.5 mm.); n_D^{25} 1.5002. [g] Neat. [h] B.p. 163–165° (0.025 mm.); n_D^{28} 1.5202. [i] B.p. 148–152° (0.1 mm.); n_D^{28} 1.5235. [j] Chloroform. [k] Oxygen. [l] Recently reported by R. L. Shivalkar and S. V. Sunthankar, *J. Am. Chem. Soc.*, **82**, 718 (1960), as yellow needles m.p. 113°. [m] Sulfur.

prepared by interaction of the requisite basic compound with diethyl ethoxymethylenemalonate, essentially after the method of Claisen.[9] Use of secondary amines in this connection has been limited[10–12]; however, diethyl arylaminomethylenemalonates have been recommended for the identification of anilines.[13] The yields of purified products, tabulated (Table I) as diethyl (basically substituted) methylenomalonates, exceeded 90%.

The other variants on structure I were limited to the use of 1-(3-methylbenzyl)piperazine for the basic portion of the desired structures because diethyl 4-(3-methylbenzyl)-1-piperazinylmethylenemalonate had shown the most interesting profile of pharmacological actions of the stimulant series in Table I. These compounds have structures II–IV; unfortunately, none exhibited effects worthy of clinical evaluation. The first two examples were made by the Claisen method.[9,12,14–16] Ethyl 3-[4-(3-methylbenzyl)-1-piperazinyl]acrylate(IV) was obtained by the addition of the piperazine derivative to ethyl propiolate.[17,18] These several reactions gave yields which approached the theoretical.



II. R_3 = CN; R_4 = $CO_2C_2H_5$
III. R_3 = R_4 = CN
IV. R_3 = $CO_2C_2H_5$; R_4 = H

EXPERIMENTAL

A. Intermediates. 1-Benzylpiperazine,[19] 1-ethoxycarbonyl piperazine,[20] camphidine,[21] ethyl propiolate,[17] and diethyl 2-pyridylaminomethylenemalonate[22] were made by published methods.

1-(2-Methylbenzyl)- and 1-(4-methylbenzyl)piperazine preparation. 1-(2-Methylbenzyl)piperazine was prepared from α-chloro-o-xylene and piperazine hydrochloride.[23] The colorless oil was obtained in 84.5% yield, b.p. 77–80° (0.15 mm.). Similarly, the 1-(4-methylbenzyl) isomer was made in 86% yield. The colorless oil, b.p. 78–83° (0.12 mm.), solidified to a mass of plates, m.p. 36–37°.

Anal. Calcd. for $C_{12}H_{18}N_2$: N, 14.73. Found: N, 14.60 (2-methyl); N, 14.40 (4-methyl).

All other compounds were purchased.

B. Diethyl aminomethylenemalonates. The products of this group have been assembled in Table I, together with pertinent data for characterization. In the preparation of the more highly basic types, diethyl ethoxymethylenemalonate was refluxed with the base in heptane.[9,22] Ordinarily, 100 ml. of heptane was used to suspend or dissolve each 0.1 mole of starting material, and the mixtures were refluxed for 4–6 hr. Some of the reactions were sufficiently exothermic to cause ebullition. At the end of the heating period, the solvent was removed and the residual oils degassed at 0.5 mm. to give nearly quantitative yields of the unsaturated esters, which were readily purified. 2-Aminothiazole and 2-aminopyrimidine were interacted directly with diethyl ethoxymethylenemalonate after the method used[22] for 2-aminopyridine. In these cases, the reactions were run by placing the flask in a bath preheated to 125° and raising the temperature to 140° to ensure steady distillation of the alcohol formed. At the end of the reaction (2–3 hr.), the molten products were poured out to cool. Crude yields of 95% or more resulted, and the compounds were readily crystallized.

C. Other basically substituted acrylic acid derivatives. Ethyl 4-(3-methylbenzyl)-1-piperazinylmethylenecyanoacetate (II). 1-(3-Methylbenzyl)piperazine and ethyl ethoxymethylenecyanoacetate were interacted in refluxing heptane for 3 hr. Removal of the solvent left a 97% yield of the desired compound; it crystallized from hexane as pale, dull yellow blades, m.p. 108–108.5°; $\lambda_{max}^{CH_3OH}$ 283 mμ (log ε 3.47); λ_{max}^{Nujol} 4.55, 5.92, 6.22 μ.

Anal. Calcd. for $C_{18}H_{23}N_3O_2$: C, 68.98; H, 7.40; N, 13.41. Found: C, 69.11; H, 7.58; N, 13.46.

4-(3-Methylbenzyl)-1-piperazinylmethylenemalononitrile (III) was prepared from the requisite piperazine derivative and ethoxymethylenemalononitrile in heptane (4 hr. of refluxing) in quantitative yield. It separated from cyclohexane as nacreous platelets, m.p. 114.5–115.5°; $\lambda_{max}^{CH_3OH}$ 282 mμ (log ε 3.38); λ_{max}^{Nujol} 3.00; 4.56, 4.60, 6.13, 6.88 μ.

Anal. Calcd. for $C_{16}H_{18}N_4$: C, 72.13; H, 6.81; N, 21.03. Found: C, 71.88; H, 6.85; N, 20.75.

Ethyl 3-[4-(3-methylbenzyl)-1-piperazinyl]acrylate, (IV) was formed in 97.5% yield by the highly exothermic reaction[17] of ethyl propiolate in heptane. It passed over as a viscous, golden oil of b.p. 168–173° (0.1 mm.); n_D^{28} 1.5639; $\lambda_{max}^{CH_3OH}$ 290 mμ (log ε 3.56); $\lambda_{max}^{CHCl_3}$ 3.46, 3.61, 5.92, 6.22, 6.90 μ.

Anal. Calcd. for $C_{17}H_{24}N_2O_2$: C, 70.70; H, 8.39; N, 9.71. Found: C, 70.88; H, 8.25; N, 9.33.

Acknowledgment. Determinations of spectra and a number of analyses were carried out by Mrs. M. Christie. Dr. W. M. Govier and associates did the pharmacologic screening.

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