The Synthesis of Some Ethyl 3-(1,2-Dialkylhydrazino)propanoates and Their Cyclization to 1,2-Dialkyl-3-pyrazolidinones

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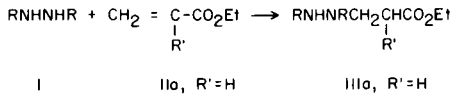
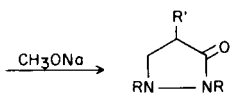
The preparation of several ethyl 3-(1,2-dialkylhydrazino)propanoates (III) by the reaction of 1,2-dialkylhydrazines with acrylates is described. Compound III is accompanied by small amounts of the bis addition products (V) in the reactions of ethyl acrylate with a few of the hydrazines. Cyclization of III to 1,2-dialkyl-3-pyrazolidinones (IV) was achieved with sodium methoxide. 1,2-Dialkyl-5-methyl-3-pyrazolidinones were obtained directly from 1,2-dialkylhydrazines and ethyl crotonate. A procedure for the preparation of 1,2-di-(2-ethoxycarbonylethyl)hydrazines is also given.

The addition of ammonia and amines to the carbon-carbon double bond of acrylates is well documented (1). Hydrazine reacts with ethyl methacrylate to form 4-methyl-3-pyrazolidinone (2) although no yield data are given. More recently, the reaction of methylhydrazine with α,β-unsaturated acids or esters to give 1-methyl-3-pyrazolidinones has been reported (3). The 3-pyrazolidinones obtained in the latter two reactions presumably arise by addition of the hydrazine to the double bond of the acrylate followed by ring closure.

The addition of 1,2-dialkylhydrazines (I) to ethyl acrylate (IIa) and ethyl methacrylate (IIb) has been used to prepare a series of ethyl 3-(1,2-dialkylhydrazino)-propanoates (IIIa, b) in good yield. Cyclization of III by means of sodium methoxide in hexane afforded high yields of the corresponding 1,2-dialkyl-3-pyrazolidinones (IVa, b).

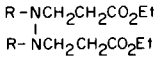


I IIa, R'=H; b, R'=CH_3 IIIa, R'=H; b, R'=CH_3



IVa, R'=H; b, R'=CH_3

The physical properties and analyses of these compounds are recorded in Tables I and II. In the reaction of ethyl acrylate with 1,2-dimethyl-, 1,2-diethyl- and 1,2-di-*n*-propylhydrazines, small amounts of the corresponding bis addition products (V) accompanied IIIa and were readily separated by distillation.



V

The bis compounds V were obtained in high yields by using a 4:1 molar ratio of ethyl acrylate to the 1,2-dialkylhydrazine (see Table IV). Analysis (vpc) of the products resulting from the reaction of 1,2-dimethylhydrazine with ethyl acrylate and ethyl methacrylate showed some contamination by the corresponding 3-pyrazolidinones (see Table I).

Several different methods of cyclizing the adducts III to the cyclization compounds IV were tried including: (1) refluxing in ethanol, (2) refluxing in ethanol containing an excess of triethylamine and (3) refluxing in hexane containing a catalytic amount of sodium methoxide. Only the latter method was generally satisfactory as evidenced by the high yields of IV and it was therefore used routinely.

A time-composition study of the addition of 1,2-dialkylhydrazines to ethyl crotonate was made by means of vpc. In this way it was learned that the addition to crotonate is much slower than the additions to either acrylate or methacrylate, however the adducts once formed cyclize faster to 1,2-dialkyl-5-methyl-3-pyrazolidinones (VI) than the corresponding uncatalyzed cyclization of III to IV. For this reason it was impossible to isolate

TABLE I

Ethyl 3-(1,2-Dialkylhydrazino)propanoates

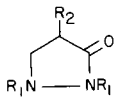
$$R_1NHNCH_2CHCO_2CH_2CH_3$$
$$\quad R_1 \quad\; R_2$$

R_1	R_2	Stirring time (hr.)	Reflux time (hr.)	b.p. °C (mm. Hg)	n_D(°C)	Yield (a) %	Analytical data Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	H	18	0	87-88 (12)	1.4371 (20.5)	79	52.48	10.07	17.48	52.30	10.17	17.59
		17	3	45-47 (0.3) (b), (c)		82.5 (d)						
CH_3	CH_3	15	4	41 (0.35) (c), (e)		77.4						
		8 (f)	0	82-82.5 (10)	1.4342 (20)	32.0	55.15	10.41	16.08	55.23	10.54	16.29
CH_2CH_3	H	16	4	67-69 (0.4) 104-106 (12)	1.4410 (20.7)	76.3 (g)	57.42	10.71	14.88	57.43	10.69	14.87
CH_2CH_3	CH_3	20	4	58.5 (0.4)	1.4392 (20.5)	74.9	59.37	10.96	13.85	59.24	11.01	13.99
$CH_2CH_2CH_3$	H	15	2	68-69 (0.4)	1.4392 (21.1)	69.1 (h)	61.08	11.18	12.95	61.22	11.04	13.11
$CH_2CH_2CH_3$	CH_3	20	0	68-69 (0.3)	1.43.65 (21.9)	28.3	62.57	11.38	12.16	62.61	11.37	12.28
$CH(CH_3)_2$	H	24	7	63 (0.3)	1.4371 (21)	77.1	61.08	11.18	12.95	61.17	11.36	12.93
$CH(CH_3)_2$	CH_3	17	7	63 (0.5)	1.4371 (20)	10.5	62.57	11.38	12.16	62.40	11.37	12.23

(a) Yield of product calculated on the basis of the pure adduct. (b) Analysis (vpc) indicated 80% of the adduct, 12% of the corresponding 3-pyrazolidinone and 8% of the bis adduct. (c) Analytical sample obtained by preparative vpc. (d) The bis adduct, identical to the compound described in Table IV, R=CH_3 was also obtained in 2.7% yield. (e) Analysis (vpc) indicated 78% of the adduct, 21% of the corresponding 3-pyrazolidinone and 1% of an unidentified product. (f) Addition carried out with ice bath cooling. (g) The bis adduct, identical to the compound described in Table IV, R=CH_3CH_2 was also obtained in 5.8% yield. (h) Accompanied by an 8.0% yield of the bis adduct which was identical to the compound described in Table IV, R=$CH_3CH_2CH_2$.

TABLE II

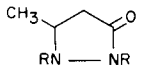
1,2-Dialkyl-3-pyrazolidinones



R_1	R_2	Reflux time hrs.	b.p. °C(mm. Hg)	n_D(°C)	Yield %	Analytical data: Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	H	18	43-45 (0.3)	1.4742 (23)	81.0	52.61	8.83	24.55	52.66	8.74	24.17
CH_3	CH_3	15	38-38.5 (0.35)	1.4700 (21.5)	90.5	56.21	9.44	21.86	56.20	9.25	21.97
CH_2CH_3	H	18	48.5-50 (0.3) 96-99 (8) 102-105 (12)	1.4693 (20.5)	75.0	59.13	9.92	19.70	59.12	10.09	19.64
CH_2CH_3	CH_3	16	51-51.5 (0.30)	1.4618 (22)	93.2	61.51	10.32	17.93	61.66	10.32	18.07
$CH_2CH_2CH_3$	H	17	65-66 (0.35)	1.4678 (20)	72.7	63.49	10.65	16.46	63.62	10.82	16.47
$CH_2CH_2CH_3$	CH_3	20	65.5-66.5 (0.25)	1.4615 (21.3)	67.0	65.18	10.94	15.20	65.07	11.22	14.98
$CH(CH_3)_2$	H	18	60 (0.48)	1.4669 (21)	69.6	63.49	10.65	16.46	63.59	10.85	16.51
$CH(CH_3)_2$	CH_3	20	49-50 (0.25)	1.4601 (22)	39.4	65.18	10.94	15.20	65.19	10.93	15.40

TABLE III

1,2-Dialkyl-5-methyl-3-pyrazolidinones



R	Reflux time hrs.	b.p. °C (mm. Hg)	n_D(°C)	Yield %	Analytical data Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	68	100-102 (19)	1.4681 (21.5)	80.3	56.23	9.44	21.86	56.24	9.34	21.94
CH_2CH_3	68	54-56 (0.2)	1.4604 (21)	75.3	61.50	10.33	17.94	61.67	10.67	17.85
$CH_2CH_2CH_3$	65	84-85 (1)	1.4598 (20.5)	64.6	65.18	10.94	15.20	65.07	10.83	15.34
$CH(CH_3)_2$	260 (a)	103.5-106.5 (10) (b)	1.4600 (19)	16.8	65.18	10.94	15.20	65.04	11.04	15.41

(a) After 108 hours a 3.5% yield of product (65% pure by vpc) was obtained. (b) Analysis (vpc) indicated a purity of 94%; the analytical sample was obtained by preparative vpc.

TABLE IV

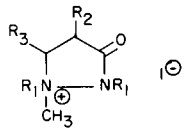
1,2-Dialkyl-1,2-di-(2-ethoxycarbonylethyl)hydrazines

$CH_3CH_2O_2CCH_2CH_2NRNRCH_2CH_2CO_2CH_2CH_3$

R	Reflux time hrs.	b.p. °C (mm. Hg)	n_D (°C)	Yield %	Analytical data Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3	24	90-92 (0.2)	1.4480 (22)	80.6	55.36	9.29	10.76	55.49	9.19	10.98
CH_2CH_3	24	103-104 (0.28)	1.4486 (20)	88.0	58.31	9.79	9.71	58.14	10.09	10.03
$CH_2CH_2CH_3$	48	108.5-110 (0.2)	1.4490 (21.5)	63.5	60.74	10.19	8.85	61.01	10.20	9.08

TABLE V

1,2-Dialkyl-3-pyrazolidinone Methiodides



R_1	R_2	R_3	M.P. °C	Recrystn. solvent	Analytical data Calcd. N	Calcd. I	Found N	Found I
CH_3	H	H	190.5-193	MeOH	10.94	49.56	11.12	49.51
CH_3	CH_3	H	286-287 (a)	MeOH	10.37	46.97	10.57	46.81
CH_3	H	CH_3	238-239	MeOH	10.37	46.97	10.57	46.79
CH_2CH_3	H	H	164-165	EtOH	9.86	44.66	9.74	44.96
CH_2CH_3	CH_3	H	191.5-192.5 (b)	EtOH	9.39	42.56	9.26	42.81
CH_2CH_3	H	CH_3	167-169.5	EtOH	9.39	42.56	9.45	42.49
$CH_2CH_2CH_3$	H	H	129-130.5	EtOH	8.97	40.64	9.07	40.36
$CH_2CH_2CH_3$	CH_3	H	135.5-138	Me_2CO	8.59	38.90	8.59	38.86
$CH_2CH_2CH_3$	H	CH_3	121.5-124.5	Me_2CO	8.59	38.90	8.42	38.98
$CH(CH_3)_2$	H	H	188-188.5 (b)	EtOH	8.97	40.64	8.74	40.25
$CH(CH_3)_2$	CH_3	H	208.5-209.5 (a)	EtOH	8.59	38.90	8.77	39.11

(a) Determined in a sealed tube. (b) Melting with decomposition.

pure addition products. Good yields of VI were realized by refluxing ethyl crotonate with 1,2-dimethyl-, 1,2-diethyl- and 1,2-di-*n*-propylhydrazines in ethanol for about 65 hours. A poor (17%) yield of the 1,2-diisopropyl analog was obtained after 10 days of heating. The yield of cyclized product decreases as the size of the alkyl group on the nitrogen atoms increases, clearly showing a steric effect for this reaction (see Table III).

With one exception the 1,2-dialkyl-3-pyrazolidinones gave crystalline methiodides upon treatment with methyl iodide in tetrahydrofuran (Table V). The preparation of a sufficient quantity of the pure methiodide of 1,2-diisopropyl-5-methyl-3-pyrazolidinone was unsuccessful. The reluctance of this compound to undergo quaternization is probably steric in nature.

The infrared spectral studies showed characteristic carbonyl absorption bands at 5.72 μ for the ethyl 3-(1,2-dialkylhydrazino)propanoates, 5.73 μ for the 1,2-dialkyl-1,2-di-(2-ethoxycarbonylethyl)hydrazines, and at 5.88 μ for the 1,2-dialkyl-3-pyrazolidinones.

In a forthcoming paper, the active-methylene and other reactions of the 1,2-dialkyl-3-pyrazolidinones will be reported.

EXPERIMENTAL

Microanalyses were performed by Dr. Kurt Eder, Geneva, Switzerland. Infrared spectra were recorded on a Beckman IR-8 spectrophotometer. Melting points were taken on a Fisher-Johns apparatus and are corrected while boiling points are uncorrected. The vpc analyses were obtained with an Aerograph A-700 Autoprep gas chromatograph using a 20 ft. x 3/8 in. aluminum column packed with 30% Silicone Gum Rubber SE on Chromosorb W (45-60 mesh); helium was used as the carrier gas and percentage compositions refer to the relative areas observed for the different components.

1,2-Dialkylhydrazines (I).

1,2-Diethyl-, 1,2-dipropyl- and 1,2-diisopropylhydrazines were prepared by the method of Renaud and Leitch (4).

1,2-Dimethylhydrazine.

This compound was prepared in good yield by modification of the method of Hinman (5). Into a 3-liter flask equipped with a mechanical stirrer and a pressure-equalizing dropping funnel with teflon stopcock was placed 1100 ml. of tetrahydrofuran (THF) followed by 75 g. (1.978 moles) of lithium aluminum hydride. The dropping funnel was previously charged with 100 g. (0.568 mole) of *N,N'*-dicarbethoxyhydrazine and a small plug of cotton was placed between the compound and the stopcock in order to prevent it from becoming clogged. A Friedrichs condenser protected by a drying tube containing calcium chloride and soda lime was attached to the top of the dropping funnel. The reaction mixture was heated to reflux and when the condensed vapors had filled the dropping funnel, the saturated solution of *N,N'*-dicarbethoxyhydrazine in THF was added dropwise at a rate which equaled the rate of condensation of the THF at the condenser. After 15-18 hours the addition was complete and the reaction mixture was refluxed for 72 hours. After cooling to 0° by means of an ice-salt-water bath, about 250 ml. of a solution of 40% aqueous potassium hydroxide was added dropwise to decompose the reduction intermediates. The THF layer was separated and the remaining inorganic sludge was extracted 3 times with 100 ml. portions of THF. The combined THF layers were dried overnight over potassium hydroxide pellets and filtered. The solution was acidified to *p*H ~ 3 by the addition of 125 ml. of a saturated ethanolic hydrogen chloride solution and evaporated under reduced pressure. The residue was triturated with absolute ethanol and evaporated again. After another trituration and evaporation there remained 61 g. of crude dimethylhydrazine dihydrochloride.

Repetition of the above experiment gave another 56 g. of crude dimethylhydrazine dihydrochloride. The combined product (117 g.) was dissolved in 175 ml. of water and added dropwise through the top of a Claisen distillation flask which had been previously charged with 211 g. (5.28 moles) of sodium hydroxide pellets and arranged for distillation. Heat was evolved and the hydrazine began to distill. The distillation was continued until the vapor temperature reached 100°. The distillate was dried over potassium hydroxide pellets overnight, decanted and distilled from potassium hydroxide pellets, b.p. 80-95°. To the distillate was added 1.5 g. of calcium hydride and after standing overnight, 10 g. of potassium hydroxide pellets was added and the product was distilled again and afforded 57.4 g. (84.2%) of a colorless liquid, b.p. 82-82.5° (Lit. (6) b.p. 81° (747 mm.)). Analysis (vpc) indicated the presence of only one component.

Ethyl 3-(1,2-Dialkylhydrazino)propanoates (IIIa) and Ethyl 3-(1,2-Dialkylhydrazino)-2-methylpropanoates (IIIb).

A solution of 0.15 mole of ethyl acrylate or ethyl methacrylate in 9 ml. of absolute ethanol was added dropwise at room temperature to a stirred (magnetic) solution of 0.15 mole of 1,2-dialkylhydrazine in 18 ml. of absolute ethanol. After stirring overnight at room temperature the reaction mixture was refluxed by means of an oil bath for several hours. The ethanol was removed (rotary evaporator) and the residue distilled *in vacuo* to give IIIa or IIIb.

The results are given in Table I.

1,2-Dialkyl-3-pyrazolidinones (IVa) and 1,2-Dialkyl-4-methyl-3-pyrazolidinones (IVb).

A solution of 0.1 mole of IIIa or IIIb in hexane (100 ml. plus the amount of hexane necessary to fill the Dean-Stark tube) was dried by refluxing the solution under a Dean-Stark tube for 2 hours. The mixture was cooled, the Dean-Stark tube was removed, 600 mg. of sodium methoxide was added and the reaction mixture was refluxed for 15-20 hours. After cooling, 50 ml. of ether was added and the mixture was dried over magnesium sulfate. The spent drying agent was filtered and the solvents were distilled under reduced pressure on a water bath. Distillation of the residue at reduced pressure afforded IVa or IVb. The results are shown in Table II.

1,2-Dialkyl-5-methyl-3-pyrazolidinones (VI).

To a solution of 0.15 mole of 1,2-dialkylhydrazine in 18 ml. of of absolute ethanol was added dropwise a solution of 0.15 mole of ethyl crotonate in 9 ml. of absolute ethanol with stirring (magnetic) at room temperature. The mixture was then refluxed for at least 65 hours. The solvent was removed *in vacuo* and the residue was distilled at reduced pressure to give VI. The results are given in Table III.

1,2-Dialkyl-1,2-di-(2-ethoxycarbonylethyl)hydrazines (V).

To a magnetically stirred solution of 0.05 mole of 1,2-dialkyl-

hydrazine in 9 ml. of absolute ethanol was added slowly 0.2 mole of ethyl acrylate. After completion of the addition, the mixture was refluxed by means of an oil bath. The solvent was removed *in vacuo* (rotary evaporator) and the residue was distilled at reduced pressure to give V (see Table IV).

1,2-Dialkyl-3-pyrazolidinone Methiodides.

Two g. of methyl iodide was added to a solution of 1 g. of the 1,2-dialkyl-3-pyrazolidinone in 5 ml. of THF at room temperature and the mixture was allowed to stand until the salt crystallized. In cases where an oil separated, the mixture was placed in the refrigerator after scratching the oil with a glass rod. The crystals were filtered, washed with cold absolute ethanol and recrystallized. The results are recorded in Table V.

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