Synthesis of Some Disubstituted Cyanoacetamides as Potential Anticonvulsants

By HERBERT F. SCHWARTZ, II, LEE F. WORRELL, and JAIME N. DELGADO

A series of 17 cyanoacetamides was synthesized for pharmacologic evaluation. Several synthetic methods were studied: *C*-alkylation, acylation of amines by ester, and acylation of amines by amides. The *C*-alkylation of cyanoacetamides was investigated in several solvent systems using various bases, and the results are reported. This method was adopted for the alkylation of the cyanoacetamides in a pressure-reaction vessel and utilized formamide and/or dimethylsulfoxide as solvent with potassium hydroxide as the basic reagent. Several of the compounds were obtained by the pyrolytic acylation of amine by amide.

IN AN EARLIER paper Schwartz and Doerge (1) reported the preparation and investigation of some disubstituted malondiamides. Preliminary pharmacological studies showed several of these to possess anticonvulsant activity and simultaneously to be devoid of sedative-hypnotic properties. Furthermore, the disubstituted cyanoacetamide intermediates used in the preparation of the malondiamides were observed to possess higher anticonvulsant activity and, like the malondiamides, to be devoid of sedative-hypnotic activity. Table I summarizes these pharmacological data (2).

The significant activity of 2-ethyl-2-propyl- and 2,2-diethylcyanoacetamide against both electroshock and subcutaneous pentylenetetrazol tests suggests that further molecular modification might lead to more active compounds. Such modification might serve as the basis for the study of structure-activity relationships among cyanoacetamides. Accordingly, a series of *N*-alkylated and similar *N*-cyclic derivatives from the aforementioned ethylpropyl-, and diethylcyanoacetamides was prepared by several synthetic methods which involved *C*-alkylation, aminolysis, and the acylation of amines by amides.

Since preliminary and previous laboratory experience and literature surveys indicated classical methods of *C*-alkylation and *N*-alkylation to be undesirable and impractical in the preparation of these disubstituted cyanoacetamides, alternate synthetic methods were studied.

DISCUSSION

C-Alkylation.—The *C*-alkylation of cyanoacetamides was investigated in several solvents using various bases by preparing previously known mono- and disubstituted cyanoacetamides and several related esters with the hope of finding a more suitable method.

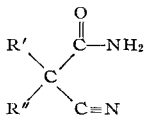
Under the conditions described under *Experimental*, cyanoacetamide has been found to act in a manner qualitatively similar to other active methylene compounds and on an acidity and reactivity basis, theoretically, may be categorized with malonic ester. The initial introduction of low molecular weight primary substituents (R-X less than 4 carbon atoms) into these types of compounds produced a mixture of monoalkylated and dialkylated product with starting material. Such mixtures are known to be difficult to purify by ordinary fractional distillation. The corresponding cyanoacetamides, although solids, are relatively water soluble and also produce a mixture which is difficult to separate by fractional crystallization.

Table II summarizes the results of this work. Since primary alkyl halides were used, dialkylation was the main side reaction detected. *N*-Alkylation was not observed.

Of the 17 compounds listed in Tables III and IV, only compound *2* (*N*-methyl-2,2-diethylcyanoacetamide) has previously been reported in the literature. Fourteen of the 16 compounds were prepared by application of the method of *C*-alkylation described above, utilizing potassium hydroxide in formamide or dimethylsulfoxide or in admixtures of these. Most of the desired compounds are derivatives of either diethyl- or ethylpropylcyanoacetamide and may be derived from their common intermediate ethylcyanoacetamide. Initially all reactions were carried out in formamide because of its lesser tendency toward dialkylation. Furthermore, when ethyl bromide was the alkylating agent, no diethylcyanoacetamide was produced and purification was easily accomplished. In earlier work, therefore, conversion to dialkylated compound was accomplished in a separate step, starting with purified ethylcyanoacetamide in formamide solution. In several instances it was possible to add the second set of reagents and to introduce the second alkyl substituent after having allowed the first stage to become essentially neutral, without separating and isolating the intermediate. Since dialkylation is of no concern when diethylcyanoacetamide is the desired product, and since dimethylsulfoxide supported a more vigorous reaction and gave excellent yields, this solvent was ultimately chosen for dialkylation in those situations when the alkyl groups were identical. When they

Received April 25, 1966, from the Pharmaceutical Chemistry Laboratories, College of Pharmacy, University of Texas, Austin 78712.
Accepted for publication September 20, 1966.
Presented to the Medicinal Chemistry Section, A.PH.A. Academy of Pharmaceutical Sciences, Dallas meeting, April 1966.

TABLE I.—PHARMACOLOGICAL DATA ON CYANOACETAMIDES STUDIED[a,e,f]



Compd.	R′	R″	Max. Tolerated Oral Dose, mg./Kg.	SED[b]	SMES[c]	RSCM[d]
2658 L	C_2H_5	C_2H_5	200	0	3+	4+
2655 L	C_2H_5	n-C_3H_7	75	0	2+	3+
2663 L	C_2H_5	i-C_3H_7	80	0	4+	+
2659 L	C_2H_5	n-C_4H_9	70	0	+	0
2652 L	C_2H_5	i-C_4H_9	125	0	3+	2+
2660 L	C_2H_5	n-C_5H_{11}	125	0	4+	+
2654 L	C_2H_5	i-C_5H_{11}	175	0	2+	0

[a] The male albino rat, dosed orally, was used in all the tests. [b] SED, sedative: the ability of the compound to control the stimulating action of 30 mg./Kg. ephedrine sulfate injected subcutaneously is recorded on a kymographic record. [c] SMES, supramaximal electroshock test: the ability of the compound to abolish the hind limb extensor reflex produced by a current of 150 ma. delivered for 0.3 sec. to the brain *via* the optic pathway is recorded. [d] RSCM, rat subcutaneous pentylenetetrazol test: the ability of the compound to block completely the convulsions produced by pentylenetetrazol injected subcutaneously at a level of 70 mg./Kg. is noted. [e] Rating system: in all the tests, 0 to + indicates essentially no detectable activity of the compound to produce the desired effect. A rating of 2+ to 3+ indicates fair to good activity. A 4+ rating indicates complete control of desired effect and from an activity standpoint is the maximum attainable rating. [f] These pharmacological data abstracted from a personal communication to R. F. Doerge from R. W. Cunningham, then with Lederle Laboratories, Division of American Cyanamid Co.

were dissimilar, the usual order of alkylation for this series became ethyl- then propyl-, stepwise in the same reaction vessel, in formamide, without isolation of the intermediate.

Both *N*-methyl-2-ethylcyanoacetamide and *N*-dimethyl-2-ethylcyanoacetamide failed to react with the addition of the second portion of base and propyl bromide. Reversal of the order of introduction of the alkyl groups provided *N*-dimethyl-2-ethyl-2-propylcyanoacetamide in a slightly depressed yield but the corresponding *N*-methyl-compound was obtained in low yield and poor quality. Conversion of *N*-methylcyanoacetamide by a single molar quantity of propyl bromide gave a mixture of propyl- and dipropyl-substituted product. The desired *N*-methyl-2-ethyl-2-propylcyanoacetamide was ultimately obtained in fair to good yield by ethylating *N*-methyl-2-propylcyanoacetamide.

Generally, enolate salts appeared to be considerably less soluble in dimethylsulfoxide than in formamide, and their solubility was noted to decrease with increase in the weight of the *N* substituent. In those instances when precipitation of the enolate became troublesome, it was found advantageous to add the more polar formamide as an aid in solvation. Homogeneous solutions or satisfactory results were obtained in most instances with a 1:3 ratio of formamide to dimethylsulfoxide.

The propylation of 1-(2-cyanobutyryl)-piperidine in formamide failed until a mixture of formamide and dimethylsulfoxide was used.

Acylation of Amine by Ester.—Several of the desired members of the series arose by applying the aminolysis reaction to unsubstituted ester to obtain *N*-alkylated unsubstituted amide which was later *C*-alkylated. All of the piperidine, pyrrolidine, and morpholine derivatives were prepared in this manner. Of these unalkylated amide intermediates only 1-(2-cyanoacetyl)-pyrrolidine has not been found in the literature.[1]

[1] Compound *10* is not shown in tables.

Acylation of Amine by Amide.—The Galat-Elion acylation method (10) applied to disubstituted cyanoacetamides produced three substances not previously reported in the literature (Table IV): *N* - methyl - 2,2 - diethylcyanoacetamide,[2,3] *N*-methyl - 2 - ethyl - 2 - propylcyanoacetamide,[2] *N* - propyl - 2,2 - diethylcyanoacetamide, and *N*-propyl - 2 - ethyl - 2 - propylcyanoacetamide. Additionally, attempts were made to prepare *N* - dimethyl - 2,2 - diethylcyanoacetamide[2] and 1 - (2- cyano - 2 - ethylbutyryl) - piperidine.[2] The heating period varied from 4 to 6 hr. but occasionally, guided by the lack of precipitated ammonium chloride, the reaction time was extended overnight. The external (mantle) temperature was maintained so that the liquid appeared to be boiling gently, usually between 190° and 230°. Each reagent was melted separately and maintained in a molten condition for a period of time to insure minimal water content. Since disubstituted cyanoacetamides sublime readily, an attempt was made to counteract this loss by starting with 10% excess. Attempts to *N*-dialkylate using secondary amine salts, in a similar manner, repeatedly gave depressed yields of *N*-monoalkylated product. Considerable dealkylation apparently had taken place under these conditions (11, 12). The carbon and hydrogen analysis of *N*-methyl-2-ethyl-2-propylcyanoacetamide prepared by this method was no better than when prepared by *C*-alkylation as in Table III.

EXPERIMENTAL[4]

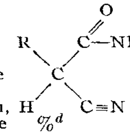
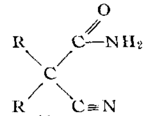
Unsubstituted amide intermediates were prepared from ester by a method similar to that to

[2] Preparation of this compound is possible *via* the unsubstituted ester to *N*-alkylated amide, then *C*-alkylation *via* the novel method.

[3] Known compound (9).

[4] Melting point determinations were made using a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Elemental analyses were conducted by Dr. K. W. Zimmerman, University of Melbourne, Melbourne, Australia, and by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

TABLE II.—*C*-ALKYLATION IN SEVERAL SOLVENTS USING VARIOUS BASES

Expt.	Solvent	Vol. Solvent,[a] ml.	Alkyl Halide, Gm.	Basic Reagent[b]	Substrate	Ratio[c]	Size of Run, mole	Products  %[d]	Products  %
1	Formamide	30	Benzyl chloride	Potassium hydroxide	Cyanoacetamide	1:1:1.1	0.1	43–46[e]	26–28[h]
2	Formamide	30	Benzyl chloride	Sodium methoxide	Cyanoacetamide	1:1:1.1	0.1	17–34[e]	34–36[h]
3	Formamide	60	Benzyl chloride	Sodium carbonate	Cyanoacetamide	1:1:1.1	0.1	17–32[e]	1–7[h]
4	Formamide	30	Benzyl chloride	Potassium phenoxide	Cyanoacetamide	1:1:1.1	0.1	35[e]	9[h]
5	Formamide	40	Ethyl bromide	Potassium hydroxide	Cyanoacetamide	1:1:1.1	0.4	62–74[f]	0
6	Formamide	40	Ethyl bromide	Potassium hydroxide	Cyanoacetamide	1:2:2.2	0.2	29–49[f]	0–8[i]
7	Formamide	40	Ethyl bromide	Sodium hydroxide	Cyanoacetamide	1:1:1.1	0.2	58–71[f]	0
8	Formamide	20	Ethyl bromide	Sodium methoxide	Cyanoacetamide	1:1:1.1	0.2	38–45[f]	0
9	Formamide	30	Ethyl bromide	Potassium hydroxide	2-Ethylcyano-acetamide	1:1:1.1	0.2	...	69–75
10	Formamide	90	Propyl bromide	Potassium hydroxide	2-Ethylcyano-acetamide	1:1:1.1	0.3	...	77
11	Dimethyl-sulfoxide	60	Benzyl chloride	Sodium methoxide	Cyanoacetamide	1:1:1.1	0.1	17–31[e]	30–32[h]
12	Dimethyl-sulfoxide	20	Benzyl chloride	Potassium hydroxide	Cyanoacetamide	1:1:1.1	0.1	23–29[e]	27–30[h]
13	Dimethyl-sulfoxide	40	Benzyl chloride	Potassium hydroxide	Cyanoacetamide	1:2:2.2	0.1	3[e]	94[h]
14	Dimethyl-sulfoxide	60	Ethyl bromide	Potassium hydroxide	Cyanoacetamide	1:1:1.1	0.2	53–58[f]	0–4[j]
15	Dimethyl-sulfoxide	60	Ethyl bromide	Potassium hydroxide	Cyanoacetamide	1:2:2.2	0.1	0	64–78[j]
16	*N,N*-Dimethyl-formamide	30	Benzyl chloride	Potassium hydroxide	Cyanoacetamide	1:1:1.1	0.1	23–25[e]	32–33[h]
17	Ethylene-diamine	30	Benzyl chloride	Potassium hydroxide	Cyanoacetamide	1:1:1.1	0.1	16–18[e]	15–21[h]
18	Ethanol 99.5%	80	Ethyl bromide	Potassium hydroxide	Cyanoacetamide	1:1:1.1	0.4	59[f]	23[j]
19	Formamide	100	*n*-Butyl bromide	Potassium hydroxide	Ethyl acetoacetate	1:1:1.1	0.3	Ethyl butyl-acetoacetate 39–49[g]	Ethyl dibutyl-acetoacetate 0

[a] The volume of solvent stated is for the size of run indicated and in the ratio shown. Since quantities larger than those shown have not been attempted, caution is urged when exceeding these conditions by the pressure-bottle method. [b] Potassium and sodium hydroxide were in pellet form. Sodium methoxide was commercial powder. [c] Amide or ester, basic reagent, alkyl halide, respectively. [d] Identity confirmations were by melting point and mixed melting point (Mel-Temp apparatus) of known samples based on carbon and hydrogen determinations and infrared analyses. Pressure-bottle reaction at room temperature unless otherwise specified. [e] M.p. 127–128°. Shimo and Asami report 128–130°, 38–43% yield (3). [f] M.p. 112–113°. Shimo and Asami report 105–108°, 42–65% yield (3). Shimo, Wakamatsu, and Inoue report 112.5–113.5°, 24% yield (4). Schwartz and Doerge report 113–114°, 36–46% yield (1). [g] Heated to about 95°, b.p. 113–115°/15 mm., n_D^{23} 1.4297. Zaugg *et al.* report 95–100°/10 mm., 59–72% yield (5). Marvel and Hager report 112–117°/16 mm., 69–72% yield (6). [h] M.p. 165–165.5°. Shimo and Asami report 162–164°, 59–74% yield based on dialkylation as the main reaction (7). [i] Stepwise addition of base and alkyl halide without isolation of monosubstituted product gives only diethylcyanoacetamide (69%). [j] M.p. 120–121°. Schwartz and Doerge report 121.5–122°, 62% yield (1). Doerge and Wilson report 120–121°, 63% yield (8).

be given for 1-(cyanoacetyl)-pyrrolidine. Unspecified, known, *C*-alkylated intermediates were prepared by the *C*-alkylation methods below.

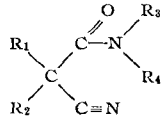
1 - (2 - Cyanobutyryl) - piperidine.—Potassium hydroxide (26 Gm. of 85%; 0.4 mole) and 1-(cyanoacetyl)-piperidine (61 Gm.; 0.4 mole) were added to 120 ml. of formamide contained in a 500-ml. Pyrex pressure-bottle.[5] The container was stoppered and placed on a Parr apparatus, and shaken for 1 hr. at which time ethyl bromide (48 Gm.; 0.44 mole) was added and shaking resumed. The container and cage soon became hot and potassium bromide began to precipitate. After 4 hr. of shaking, the reaction was essentially completed and had cooled. The bromide was removed and the filtrate diluted with a volume of water equal to about 1/4 of its original volume. Refrigeration (−10° to −17°) for 12 to 24 hr. gave 60 Gm. (83%) of crystals which when recrystallized from a mixture of ether and petroleum ether or from isopropanol–water had a melting point of 59–60°.

Anal.—Calcd. for $C_{10}H_{16}N_2O$: C, 66.63; H, 8.95. Found: C, 67.17; H, 8.97.

N - Dimethyl - 2 - ethylcyanoacetamide.—*N* - Dimethylcyanoacetamide (22.4 Gm.; 0.2 mole) and potassium hydroxide (13.0 Gm. of 85%; 0.2 mole) were added to 40 ml. of formamide contained in a 500-ml. Pyrex pressure-bottle. The container and its contents were shaken on a Parr apparatus for 1 hr., after which time ethyl bromide (24.0 Gm.; 0.22 mole) was added and the shaking resumed. The exothermic reaction began in a few minutes. The shaking was continued for 4 hr. during which time potassium bromide precipitated and the reaction mixture cooled. After the shaking period, the precipitate was separated, the reaction mixture and the filtrate neutralized with diluted hydrochloric acid, then transferred to a Rinco evaporator operating under vacuum and steam. After the low boiling substances had been removed, the

[5] Tested to 125 lb.

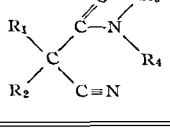
TABLE III.—2,2-DIALKYLCYANOACETAMIDES BY *C*-ALKYLATION[a]



No.	R_1	R_2	R_3	R_4	Formula	Calcd.	Found	Amide Substrate	Recrystallizing Solvent	Refract. Index, M.p./B.p. °C.	Yield, %
1	H	C_3H_7	CH_3	H	$C_7H_{12}ON_2$	C, 59.97 H, 8.63	60.07 8.55	*N*-Methyl-cyanoacetamide	Water or aqueous ethanol	65.5–66.5	41
2[b]	C_2H_5	C_2H_5	CH_3	H	$C_8H_{14}ON_2$	C, 62.30 H, 9.15	62.70 9.21	*N*-Methyl-cyanoacetamide[c]	Water	97–98	84
3	C_3H_7	C_2H_5	CH_3	H	$C_9H_{16}ON_2$	C, 64.25 H, 9.59	64.52 10.38	*N*-Methyl-2-propyl-cyanoacetamide	Water or isopropyl ether	86.5–87.5	68–82
4	C_3H_7	C_3H_7	CH_3	H	$C_{10}H_{18}ON_2$	C, 65.89 H, 9.98	66.10 9.80	*N*-Methyl-cyanoacetamide	Water or aqueous ethanol	111–112	16
7	H	C_2H_5	CH_3	CH_3	$C_7H_{12}ON_2$	C, 59.97 H, 8.63	60.02 8.65	*N*-Dimethyl-cyanoacetamide		120–121 at 4 mm. n_D^{23} 1.4616	43–48
8	C_2H_5	C_2H_5	CH_3	CH_3	$C_9H_{16}ON_2$	C, 64.25 H, 9.59	64.31 9.77	*N*-Dimethyl-cyanoacetamide[d]		92–93 at 7mm. n_D^{23} 1.4606	48
9	C_2H_5	C_3H_7	CH_3	CH_3	$C_{10}H_{18}ON_2$	C, 65.89 H, 9.96	66.31 10.24	*N*-Dimethyl-cyanoacetamide[d,e]		111–112 at 4 mm. n_D^{23} 1.4605	44[g]
11	H	C_2H_5	N⟨ ⟩		$C_9H_{14}ON_2$	C, 65.03 H, 8.49	65.18 8.20	1-(Cyanoacetyl)-pyrrolidine		160–161 at 8 mm. n_D^{24} 1.4868	70–89
12	C_2H_5	C_2H_5	N⟨ ⟩		$C_{11}H_{18}ON_2$	C, 68.00 H, 9.34	67.84 9.25	1-(2-Cyanobutyryl)-pyrrolidine[d]		127–128 at 3 mm. n_D^{24} 1.4816	31–47
13	C_2H_5	C_3H_7	N⟨ ⟩		$C_{12}H_{20}ON_2$	C, 69.19 H, 9.68	69.43 9.73	1-(2-Cyanobutyryl)-pyrrolidine[d,f]		133–134 at 3 mm. n_D^{24} 1.4810	70
14	H	C_2H_5	N⟨ ⟩		$C_{10}H_{16}ON_2$	C, 66.63 H, 8.95	67.17 8.97	1-(Cyanoacetyl)-piperidine	Isopropanol or ether–pet. ether	59–60	83–100
15	C_2H_5	C_2H_5	N⟨ ⟩		$C_{12}H_{20}ON_2$	C, 69.19 H, 9.68	69.00 9.56	1-(Cyanoacetyl)-piperidine[c]		122–123 at 6 mm. n_D^{21} 1.4846	82–95[g]
16	C_3H_7	C_2H_5	N⟨ ⟩		$C_{13}H_{22}ON_2$	C, 70.23 H, 9.97	69.77 9.93	1-(2-Cyanobutyryl)-piperidine[d]		137–138 at 3 mm. n_D^{23} 1.4829	78–100
17	H	C_2H_5	N⟨ ⟩O		$C_9H_{14}O_2N_2$	C, 59.32 H, 7.74	59.47 7.91	4-(Cyanoacetyl)-morpholine		164–165 at 4 mm. n_D^{24} 1.4915	69
18	C_2H_5	C_2H_5	N⟨ ⟩O		$C_{11}H_{18}O_2N_2$	C, 62.83 H, 8.63	62.93 8.82	4-(Cyanoacetyl)-morpholine		138–139 at 5 mm. n_D^{23} 1.4858 m.p. 35–36°	43[g,h]

[a] Solvent formamide unless otherwise specified. [b] Conrad and Zart report m.p. 102° (9). [c] Solvent dimethylsulfoxide. [d] Solvent a mixture of formamide and dimethylsulfoxide. [e] Propyl bromide, then ethyl bromide. [f] With formamide–dimethylsulfoxide mixture obtained 79% yield. [g] Two consecutive steps without isolation of monoalkyl intermediate, yield based on dialkylated product. [h] With formamide–dimethylsulfoxide mixture obtained 55% yield.

TABLE IV.—2,2-DIALKYLCYANOACETAMIDES—ACYLATION OF AMINES BY AMIDES



No.	R_1	R_2	R_3	R_4	Formula	Calcd.	Found	Amide Substrate	Recrystallizing Solvent	Refract. Index, M.p./B.p.	Yield, %
2[a,b]	C_2H_5	C_2H_5	CH_3	H	$C_8H_{14}ON_2$	C, 62.30 H, 9.15	62.70 9.21	2,2-Diethyl-cyanoacetamide	Water	97–95°	38–61
3[b]	C_3H_7	C_2H_5	CH_3	H	$C_9H_{16}ON_2$	C, 64.25 H, 9.59	64.52 10.38	2-Ethyl-2-propylcyano-acetamide	Isopropanol or ether–pet. ether	86.5–87.5°	60–62
5	C_2H_5	C_2H_5	C_3H_7	H	$C_{10}H_{18}ON_2$	C, 65.89 H, 9.96	65.46 9.85	2,2-Diethyl-cyanoacetamide	Aqueous isopropanol	71–71.5°	69–78
6	C_3H_7	C_2H_5	C_3H_7	H	$C_{11}H_{20}ON_2$	C, 67.30 H, 10.27	67.61 10.47	2-Ethyl-2-propylcyano-acetamide	Aqueous ethanol or isopropanol	65.5–66.5°	70–90

[a] Conrad and Zart report m.p. 102° (9). [b] Also prepared by *C*-alkylation method.

material was fractionated under reduced pressure, using a 14-cm. heated column with multiple receiver. Pure *N*-dimethyl-2-ethylcyanoacetamide distilled between 120–121° at 4 mm. pressure (n_D^{23} = 1.4616, 13.5 Gm.; 48.3%).

Anal.—Calcd. for $C_7H_{12}N_2O$: C, 59.97; H, 8.63. Found: C, 60.02; H, 8.65.

4-(2-Cyanobutyryl)-morpholine.—This compound was prepared in 69% yield from 4-(cyanoacetyl)-morpholine in the same manner as *N*-dimethyl-2-ethylcyanoacetamide above, except that the formamide solvent was increased to 80 ml. for 0.2 mole (b.p. 164–165° at 4 mm., n_D^{24} = 1.4915).

Anal.—Calcd. for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.74. Found: C, 59.47; H, 7.91.

1-(2-Cyanobutyryl)-pyrrolidine.—This substance was prepared in 70–89% yield from 1-(cyanoacetyl)-pyrrolidine in an identical manner using 80 ml. of formamide for 0.2 mole (b.p. 160–161° at 8 mm., n_D^{24} = 1.4868).

Anal.—Calcd. for $C_9H_{14}N_2O$: C, 65.03; H, 8.49. Found: C, 65.18; H, 8.20.

N - Methyl - 2 - ethyl - 2 - propylcyanoacetamide.[6]—Except for the change of starting amide *N*-methyl-2-propylcyanoacetamide (56.8 Gm.; 0.4 mole) the preparation was almost identical with that for 1-(2-cyanobutyryl)-piperidine. The filtered reaction product was neutralized with a minimum of diluted hydrochloric acid. Sufficient isopropyl alcohol was then added to obtain a homogeneous solution which was chilled to produce crystals (55 Gm.; 81.8%). The melting point after recrystallization was 86.5–87.5°.

Anal.—Calcd. for $C_9H_{16}N_2O$: C, 64.25; H, 9.59. Found: C, 64.52; H, 10.38.

N - Methyl - 2 - propylcyanoacetamide and N-Methyl - 2,2 - dipropylcyanoacetamide.—Potassium hydroxide (13.0 Gm. of 85%; 0.02 mole) and *N*-methylcyanoacetamide (19.6 Gm.; 0.2 mole) were added to 60 ml. of formamide contained in a 500-ml. Pyrex pressure-bottle. The container was stoppered, placed on a Parr apparatus, and shaken for 1 hr. The dissolution was exothermic and complete, and gave an orange-colored solution. Propyl bromide (27 Gm.; 0.22 mole) was added and the two-phase mixture returned to the shaker. Within a few minutes the container and its protective cage became warm, and potassium bromide began to precipitate. The shaking was continued for 4 hr., after which time the bromide was removed and the filtrate shaken with an equal volume of hot water. The resulting two layers were separated and when chilled (−10° to −17°) for 12 to 24 hr. yielded crystals.

Alternatively, the filtrate was diluted with a volume of water equal to about 1/4 of its original volume and refrigerated as above. Extraction of the resulting crystals (16 Gm.; 57%) with hot water gave 41% of *N*-methyl-2,2-dipropylcyanoacetamide and 16% of *N*-methyl-2-propylcyanoacetamide based on starting amide. The latter was recrystallized from aqueous ethanol or from diisopropyl ether, m.p. 65.5–66.5°.

Anal.—Calcd. for $C_7H_{12}N_2O$: C, 59.97; H, 8.63. Found: C, 60.07; H, 8.55.

N-methyl-2,2-dipropylcyanoacetamide was recrystallized from hot water or hot aqueous ethanol, m.p. 111–112°.

[6] Also prepared by acylation of the amine by the amide.

Anal.—Calcd. for $C_{10}H_{18}N_2O$: C, 65.89; H, 9.98. Found: C, 66.10; H, 9.80.

N - Dimethyl - 2,2 - diethylcyanoacetamide.—*N*-Dimethylcyanoacetamide (22.4 Gm.; 0.2 mole) and potassium hydroxide (13.0 Gm. of 85%; 0.2 mole) were added to 80 ml. of solvent (formamide–dimethylsulfoxide, 1:3). At the end of 2 hr. shaking on a Parr apparatus, a small amount of basic reagent remained undissolved, and some metal enolate had precipitated. To this mixture, contained in a Pyrex glass pressure-bottle, was added ethyl bromide (24.0 Gm.; 0.22 mole) and the shaking continued. As the ethyl bromide reacted and the temperature rose, all insoluble material dissolved, and the mixture became a biphasic liquid. As the reaction progressed, potassium bromide precipitated and the liquid became homogeneous. At the end of 4 hr. insoluble bromide was removed and the filtrate returned to the reaction flask. The pattern of adding reagents was repeated: potassium hydroxide (13.0 Gm. of 85%; 0.2 mole) was added and the container shaken for 1 or 2 hr. Ethyl bromide (24.0 Gm.; 0.22 mole) was added and the mixture shaken for an additional 4 hr., after which time the insoluble bromide was removed. The filtrate was diluted with a volume of water equal to about 1/4 of its volume, neutralized with diluted hydrochloric acid, and extracted with 3 or more portions of ether. The combined ether extract was washed with water and dried over anhydrous sodium sulfate. Ether solvent was removed *via* the Rinco evaporator under reduced pressure. The residual oil was fractionally distilled under reduced pressure using a Fabco microdistillation apparatus with a heated column of about 14 cm. and a multiple receiver. Alternatively, the filtrate, after the removal of bromide, was neutralized with diluted hydrochloric acid, treated at the Rinco evaporator to remove low boiling substances, then fractionally distilled. Solvents distilled prior to the product. The yield was 48% of pure *N*-dimethyl-2,2-diethylcyanoacetamide obtained between 92–93° at 7 mm. pressure (n_D^{23} = 1.4606).

Anal.—Calcd. for $C_9H_{16}N_2O$: C, 64.25; H, 9.59. Found: C, 64.31; H, 9.77.

N - Dimethyl - 2 - ethyl - 2 - propylcyanoacetamide.—This compound was prepared in the same manner as *N*-dimethyl-2,2-diethylcyanoacetamide. Propyl bromide (27.0 Gm.; 0.22 mole) was added in the first step and ethyl bromide (24.0 Gm.; 0.22 mole) in the second. The crude yield was 44%; the pure product had a b.p. range of 111–112° at 4 mm. pressure (n_D^{23} = 1.4605).

Anal.—Calcd. for $C_{10}H_{18}N_2O$: C, 65.89; H, 9.96. Found: C, 66.31; H, 10.24.

1 - (2 - Cyano - 2 - ethylvaleryl) - piperidine and 1 - (2 - Cyano - 2 - ethylvaleryl)-pyrrolidine.—These compounds were both prepared in a manner analogous to the preparation of *N*-dimethyl-2,2-diethylcyanoacetamide except that since the starting materials were 1-(2-cyanobutyryl)-piperidine and 1-(2-cyanobutyryl)-pyrrolidine, respectively, only one step with base and alkyl halide was necessary. 1 - (2 - Cyano - 2 - ethylvaleryl)-piperidine was obtained almost quantitatively; the pure material boiled at 137–138° at 3.5 mm. pressure (n_D^{23} = 1.4829).

Anal.—Calcd. for $C_{13}H_{22}N_2O$: C, 70.23; H, 9.97. Found: C, 69.77; H, 9.93.

1 - (2 - Cyano - 2 - ethylvaleryl) - pyrrolidine (70–80% yield) distilled between 133–134° at 3 mm. pressure (n_D^{24} = 1.4810).

Anal.—Calcd. for $C_{12}H_{20}N_2O$: C, 69.19; H, 9.68. Found: C, 69.43; H, 9.73.

1 - (2 - Cyano - 2 - ethylbutyryl) - piperidine, 1-(2 - Cyano - 2 - ethylbutyryl)-pyrrolidine, and 4-(2 - Cyano - 2 - ethylbutyryl) - morpholine.—All three were prepared and isolated in essentially the same manner as *N*-dimethyl-2,2-diethylcyanoacetamide, with small differences in detail. 1-(2-Cyano-2-ethylbutyryl)-piperidine was prepared from 1-(cyanoacetyl)-piperidine by dialkylation, without isolation of the intermediate, in dimethylsulfoxide (60 ml./0.1 mole). The yield was 82–95%. The pure liquid distilled between 122–123° at 6 mm. (n_D^{23} = 1.4846).

Anal.—Calcd. for $C_{12}H_{20}N_2O$: C, 69.19; H, 9.68. Found: C, 69.00; H, 9.56.

1 - (2 - Cyano - 2 - ethylbutyryl) - pyrrolidine was prepared by monoalkylation of 1 - (2 - cyanobutyryl)-pyrrolidine in dimethylsulfoxide solvent (40 ml./0.1 mole). The vigorous reaction was moderated by chilling the enolate suspension to a solid prior to the addition of ethyl bromide. The pure substance boiled between 127–128° at 3 mm. (yield 31–47%, n_D^{24} = 1.4816).

Anal.—Calcd. for $C_{11}H_{18}N_2O$: C, 68.00; H, 9.34. Found: C, 67.84; H, 9.25.

4 - (2 - Cyano - 2 - ethylbutyryl) - morpholine was obtained by dialkylation without isolation of intermediate in formamide (43% yield, 40 ml. of solvent/0.1 mole) or in a somewhat improved yield (55%) in formamide–dimethylsulfoxide mixture (40:60; 100 ml./0.2 mole). The purified product distilled between 138–139° at 5 mm. (n_D^{23} = 1.4858) and solidified on standing, m.p. 35–36°.

Anal.—Calcd. for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63. Found: C, 62.93; H, 8.82.

Acylation of Amine by Ester.—*1-(Cyanoacetyl)-pyrrolidine.*—Chilled ethyl cyanoacetate (22.6 Gm.; 0.2 mole) was added to an excess of pyrrolidine (28.5 Gm.; 0.4 mole) as it was being swirled in a flask. The rate of reaction was controlled by means of an ice bath. As the reaction vigor abated, the flask was permitted to stand with an occasional shaking. Within an hour the reaction mixture solidified. The crystals were collected by filtration. Further amounts of less pure crystals were obtained by chilling the mother liquor. The crude material was recrystallized from isopropanol and after purification melted at 71.5–72.5°. The crude yield with a twofold excess of amine was 90.5%; decreasing the amine to 10% excess depressed the yield to 68%.

Anal.—Calcd. for $C_7H_{10}N_2O$: C, 60.85; H, 7.30. Found: C, 60.42; H, 7.18.

Acylation of Amine by Amide.—*N-Propyl-2-ethyl-2-propylcyanoacetamide.*—The reaction apparatus consisted of a round-bottom, 1-neck distilling flask fitted with a Standard-Taper adapter, the plain end of which passed through a large rubber stopper closing the larger end of an inverted percolator (25 cm., 250 ml.). The flask was heated using a Glas-col mantle controlled by a Powerstat; the approximate temperature of the mantle was monitored using a Fisher pyrometer.

Dry propylamine hydrochloride (28.7 Gm.; 0.3 mole) placed in the dry flask was heated to melt. Mild suction was applied to the top of the inverted percolator. 2 - Ethyl - 2 - propylcyanoacetamide (50.9 Gm.; 0.33 mole) contained in a beaker was melted separately. Both chemicals were maintained molten for a period of time to insure minimal moisture content in order to reduce the hydrolysis reaction.

After pouring the amide into the amine, the temperature was raised and maintained at about 200° for 2 to 4 hr. The partially cooled reaction mixture was diluted with isopropanol and the insoluble ammonium chloride removed by filtration. Sublimed amide and ammonium chloride and condensed amine trapped in the upper chamber of the apparatus were discarded. Evaporation of the isopropanol solution gave a 70–90% yield of crude product. Fractional crystallization employing water and isopropanol enabled the separation of unchanged amide. Pure *N*-propyl-2-ethyl-2-propylcyanoacetamide melted at 65.5–66.5°.

Anal.—Calcd. for $C_{11}H_{20}N_2O$: C, 67.30; H, 10.27. Found: C, 67.61; H, 10.47.

N - propyl - 2,2 - diethylcyanoacetamide.—This compound was prepared in approximately the same manner by heating with the *secondary* amine salt and 2,2-diethylcyanoacetamide (69–78% yield, m.p. 71–71.5°).

Anal.—Calcd. for $C_{10}H_{18}N_2O$: C, 65.89; H, 9.96. Found: C, 65.46; H, 9.85.

N - Methyl - 2 - ethyl - 2 - propylcyanoacetamide.[7]—This substance was prepared by the method above by heating the amide with the *secondary* amine salt. The *N*-methyl product was obtained in 60–62% yield. The analysis of the compound prepared by this method was unacceptable.

SUMMARY

In the course of this investigation 17 new compounds have been synthesized: *N*-methyl-2-propylcyanoacetamide;[8] *N* - methyl - 2 - ethyl - 2 - propylcyanoacetamide; *N* - methyl - 2,2 - dipropylcyanoacetamide; *N* - propyl - 2,2 - diethylcyanoacetamide; *N* - propyl - 2 - ethyl - 2 - propylcyanoacetamide; *N* - dimethyl - 2 - ethylcyanoacetamide;[8] *N* - dimethyl - 2,2 - diethylcyanoacetamide; *N*-dimethyl - 2 - ethyl - 2 - propylcyanoacetamide; 1 - (cyanoacetyl) - pyrrolidine;[8] 1 - (2 - cyanobutyryl) - pyrrolidine;[8] 1 - (2 - cyano - 2 - ethylbutyryl) - pyrrolidine; 1 - (2 - cyano - 2 - ethylvaleryl) - pyrrolidine; 1 - (2 - cyanobutyryl)-piperidine;[8] 1 - (2 - cyano - 2 - ethylbutyryl)-piperidine; 1 - (2 - cyano - 2 - ethylvaleryl) - piperidine; 4 - (2 - cyano - butyryl) - morpholine;[8] 4 - (2 - cyano - 2 - ethylbutyryl) - morpholine. The pharmacological data and structure-activity relationships of 12 of these are discussed in a separate paper to be published.

Several synthetic methods were developed and applied to the preparation of these *N*-substituted-2,2-dialkylcyanoacetamides and *N*-cyclic dialkylated cyanoacetamides. *C*-Alkylation of 2-cyanoacetamide was accomplished by a method which utilized potassium hydroxide and the appropriate alkyl halide in formamide or in dimethylsulfoxide or in mixtures of these. These exothermic reactions were

[7] Prepared also by *C*-alkylation.
[8] Not tested for anticonvulsant activity.

conducted without additional heating, in a stoppered and shielded Pyrex pressure-vessel, by shaking on a Parr apparatus. Both mono- and dialkylations were accomplished within 4 to 8 hr. The results of the influence of several solvent systems and bases on the alkylation reaction are tabulated.

Many 2,2-disubstituted cyanoacetamides prepared by the above method were converted to *N*-alkyl-2,2-dialkylcyanoacetamides by a method similar to that of Galat and Elion (10) for the acylation of amine by amide. While this method was effective for *N*-alkyl derivatives, it failed for *N*-dialkyl products when using secondary amine salts. Recourse to acylation of amine by ester, using appropriate aliphatic secondary amine (or in the instances of cyclic derivatives, pyrrolidine, piperidine, and morpholine), provided the desired amides which were subsequently alkylated at C-2.

REFERENCES

(1) Schwartz, H. F., and Doerge, R. F., *J. Am. Pharm. Assoc., Sci. Ed.*, **44**, 80(1955).
(2) Cunningham, R. W., to Doerge, R. F., personal communication.
(3) Shimo, K., and Asami, R., *Sendai Japan Tohoku Univ., Sci. Rep.*, **9**, 328(1957).
(4) Shimo, K., Wakamatsu, S., and Inoue, T., *J. Am. Chem. Soc.*, **26**, 4868(1961).
(5) Zaugg, H. E., Dunnigan, D. A., Michaels, R. J., Swett, L. R., Wang, T. S., Sommers, A. H., and DeNet, R. W., *J. Org. Chem.*, **26**, 644(1961).
(6) Marvel, C. S., and Hager, F. D., *Org. Syn.*, **1**, 248 (1947).
(7) Shimo, K., and Asami, R., *Sendai Japan Tohoku Univ., Sci. Rep.*, **9**, 341(1957).
(8) Doerge, R. F., and Wilson, C. O., *J. Am. Pharm. Assoc., Sci. Ed.*, **40**, 407(1951).
(9) Conrad, M., and Zart, A., *Ann. Chem.*, **340**, 329 (1905).
(10) Galat, A., and Elion, G., *J. Am. Chem. Soc.*, **65**, 1566 (1943).
(11) Hurd, C. D., "The Pyrolysis of Carbon Compounds," A.C.S. Monograph 50, Chemical Catalog Co,. New York, N. Y., 1929, p. 310.
(12) Hickinbottom, W. J., "Reactions of Organic Compounds," Longmans Green and Co., New York, N. Y., 3rd ed., 1957, p. 416.

Lawsone Derivatives III

Cyclizations Involving Side Chains

By H. MACHATZKE, W. R. VAUGHAN*, CHARLOTTE L. WARREN, and G. R. WHITE

In continuing efforts to prepare a stable 3-ω-bis-β-chloroethyl aminoalkyl-2-hydroxy-1,4-naphthoquinone the preparation and reactions of several ω-substituted alkyllawsones have been examined. The ultimate objective of the research was not achieved as a consequence of unexpectedly facile cyclizations, either of the 3-side chain to the lawsone nucleus or by macrocyclic dimerization. The nature of these cyclizations is discussed, and the structures of the cyclic products are delineated.

THE OBJECTIVES of this continuing research have been discussed in a previous paper (1), and it should be noted in this respect that lawsone derivatives have for a considerable number of years been of interest as potential chemotherapeutic agents, particularly as antimalarials (2–4) and as antitumor compounds (1).

The purpose of the present paper is to report reactions which interfere with the preparation of 3-ω-bis-2′-hydroxyethylaminoalkyl-2-hydroxy-1,4-naphthoquinones. Two types of interfering cyclizations were encountered: (*a*) a previously recognized one in which a 3-ω-chloroalkyl-side chain closes to the 2- or 4-oxygen of 2-hydroxy-1,4-naphthoquinone (lawsone), and (*b*) an unexpected dimerization of a 3-ω-carboxyalkyllawsone to a macrolactide.

Received July 21, 1966, from the Department of Chemistry, University of Michigan, Ann Arbor.
Accepted for publication October 7, 1966.
This investigation was supported by research grant CA 02961 from the National Cancer Institute, U. S. Public Health Service, Bethesda, Md.
Previous paper: Machatzke, H., and Vaughan, W. R., *J. Pharm. Sci.*, **53**, 730(1964).
* Present address: Department of Chemistry, University of Connecticut, Storrs.

DISCUSSION

Four 3-ω-chloroalkyllawsones were investigated (I) as alkylating agents for bis-β-hydroxyethylamine (diethanolamine). And in each case the reaction desired was simple alkylation of diethanolamine, but in none was this achieved. In the case of I*a* simple cyclization to the 2-hydroxyl, as reported by Moser (4), was observed. But a mixture of II and the isomeric III (8, 9-benzo-7, 10-dioxo-2-oxabicyclo-[4.4.0]deca-1[6], 8[9]-diene and 9,10-benzo-7, 8-dioxo-2-oxabicyclo[4.4.0]-deca-1[6], 9[10]-diene, respectively) was shown to be present. The structure of III is assigned on the basis of its infrared spectrum, microanalysis, and acid isomerization[1] (5) to II. The formation of III in about 10% yield was demonstrated by comparision of the infrared spectrum of the product with spectra of pure II and pure III. And when I*b* was used in place of I*a*, the yield of III increased to about 40% at the expense of II. But when I*c* was used in place of I*a* with diethanolamine a considerably more complex reaction was encountered, with production of III accounting for but 14% of the initial I*c*, and the only other readily characterizable product (IV) being the result of 1,4-addition of diethanolamine to lawsone with reduction. Scheme I represents a rationale for the

[1] *Cf.* conversion of β-lapachone to α-lapachone.