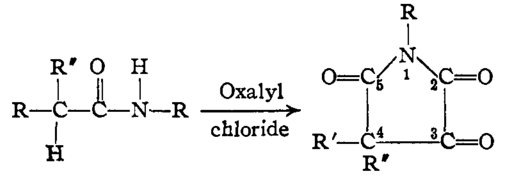
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF DELAWARE]

Trialkylpyrrolidinetriones

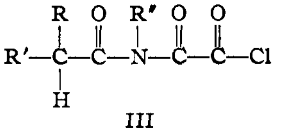
BY GLENN S. SKINNER AND JAMES F. PERKINS, JR.

The mono- and dialkylpyrrolidinetriones have been formulated as hydroxymaleimides. However, the enolic form of trialkylpyrrolidinetriones (II) is not possible. Since a search of the literature failed to reveal any trialkylpyrrolidinetriones, it seemed desirable to synthesize representative types for the purpose of observing their infrared absorption, color, stability and pharmacological behavior. The method of synthesis was adapted from that used for the preparation of 1,4-diphenylpyrrolidinetrione.[1]



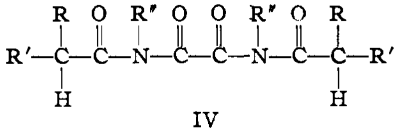
I II

The preparation of the needed trialkylacetamides (I) proceeded smoothly in all cases to give fair yields (Table I). However, marked differences are to be noted in the yields of trialkylpyrrolidinetriones (Table II). In general, better yields were obtained if an aromatic radical is present, especially at position 1. If all three radicals are aliphatic, uniformly poor yields resulted. In such cases this may be attributed partly to resistance to ring closure as evidenced by the formation of the oxamic acid chlorides (III) which were identified by hydrolysis to the oxamic acids. Evidence for the reaction of the oxamic acid chloride with a second molecule of the amide was also found (IV).



$$R'-\underset{H}{\overset{R}{C}}-\overset{O}{\overset{\|}{C}}-\overset{R'}{N}-\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}-Cl$$

III



$$R'-\underset{H}{\overset{R}{C}}-\overset{O}{\overset{\|}{C}}-\overset{R'}{N}-\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}-\overset{R'}{N}-\overset{O}{\overset{\|}{C}}-\underset{H}{\overset{R}{C}}-R'$$

IV

The trialkylpyrrolidinetriones are easily hydrolyzed to the original amides by alkali at room temperature. They yield N,N'-diphenyloxamide and the original amide with evolution of heat when treated with aniline. As these compounds cannot enolize, this relatively easy splitting of the ring cannot be attributed to an enolic form.

The infrared absorption data,[2] of which a typical portion is included here, show with remarkable agreement the occurrence of three carbonyl bands at the following positions: 5.6, 5.8 and 6.0 μ. The band at 5.8 μ is characteristic of aldehydes and ketones and therefore should be attributed to the carbonyl at position 3. The data were obtained for a suspension of the solids in Nujol and are referable to the solid state. The same absorption bands were also noted for 1,4,4-triethyl-2,3,5-pyrrolidinetrione which was used as the pure liquid. A solid suspension of 1,4-diphenyl-2,3,5-pyrrolidinetrione likewise gave the characteristic bands for three carbonyls but no evidence for an enolic hydroxyl. This compound in pyridine solution also gave no absorption attributable to an enolic hydroxyl. In all cases in which a phenyl group is linked to nitrogen there is an absorption band at 6.7 μ. If this radical is ethyl there is an absorption band at 14.1 μ.

The trialkylpyrrolidinetriones are almost colorless if the radicals are aliphatic but the color deepens to brilliant lemon-yellow as the number of aromatic radicals is increased. In general, they crystallize more easily if the radicals are phenyl groups. They also crystallize more readily if the radicals at position 4 are alike (Table II). The slower crystallization or non-crystallization of compounds with unlike groups at position 4 may be due partly to isomerism. In the case of 1,4-diphenyl-4-ethylpyrrolidinetrione two crystalline isomers having similar absorption bands (see Fig. 1) were isolated. The absorption for the higher melting isomer was depressed at 5.8 and 6.0 μ while that of the lower melting isomer was depressed at 5.6 and 5.8 μ. It would be interesting to know whether other multifunctional *cis-trans* isomers also manifest this inverted depression.

Pharmacological screening tests made by Eli Lilly and Company indicate that neither the amides nor the pyrrolidinetriones offer promise as hypnotics, analgesics or anticonvulsants. Amide 6 produced severe convulsions in rats, amide 11 gave a slight analgesia and amide 10 gave slight hypnosis. Of the trialkylpyrrolidinetriones only compounds 1 and 2 gave slight hypnosis, none of them gave protection as an anticonvulsant, and 15 produced ataxia.

Experimental

N,α,α-Trialkylacetamides.—These compounds were prepared from the acid chlorides and the amines. All of the needed acid chlorides were made from the dialkylacetic acids and thionyl chloride. The following have not been described: 2-*s*-amylethylacetyl chloride, yield, 90%; b. p., 87–89° (25 mm.); $n^{25}\text{D}$ 1.4364; α-phenybutyryl chloride, yield, 97%; b. p. 125–127° (36.5 mm.), 146–149° (110 mm.); $n^{25}\text{D}$ 1.5146. In the case of the inexpensive amines, one mole of the acid chloride was added dropwise to a stirred and cooled solution of two moles of

---

[1] Figee, *Rec. trav. chim.*, **34**, 289 (1915).

[2] Measurements by Janet Hucks.

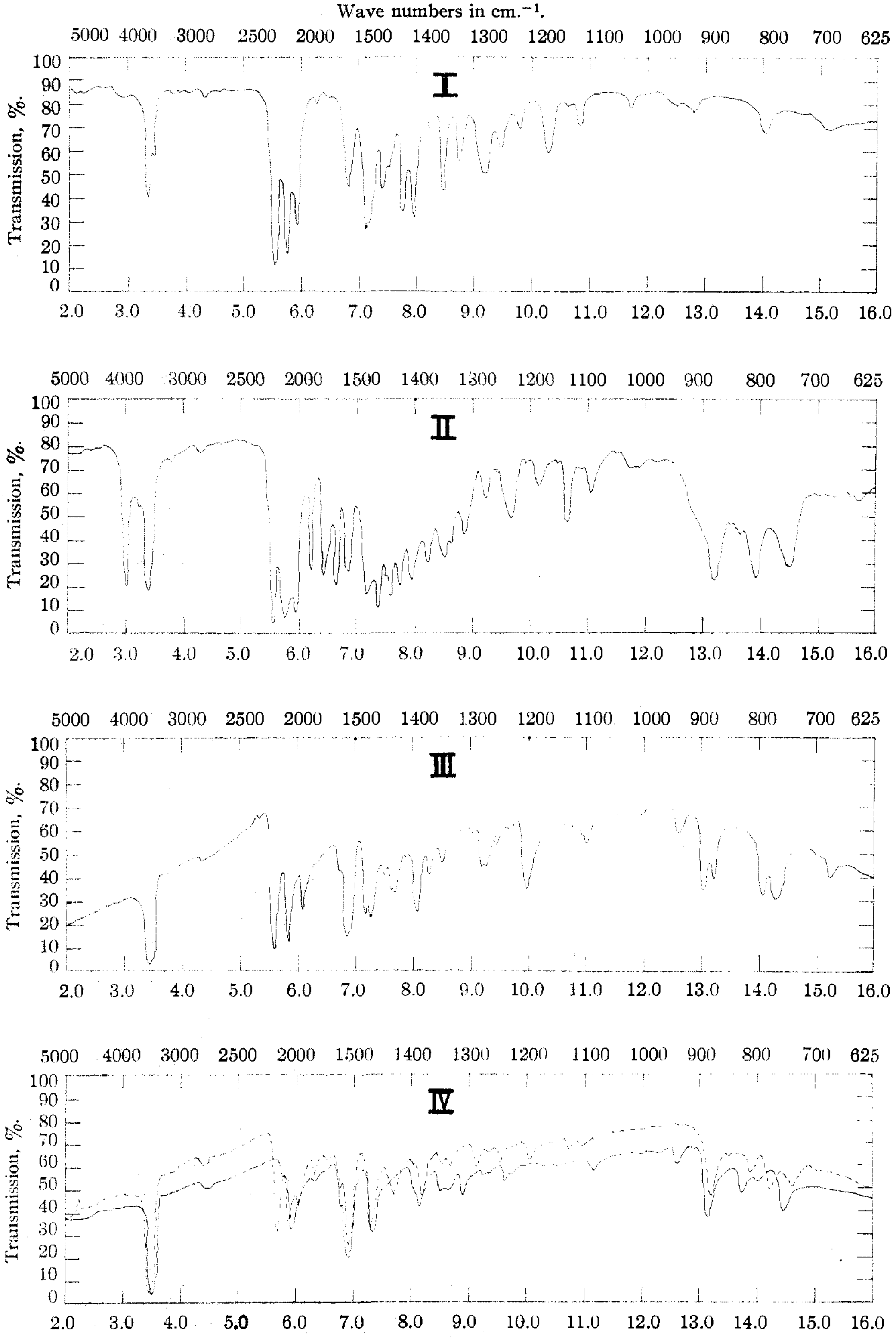


Fig. 1.—Infrared absorption spectra of pyrrolidinetriones: I, 1,4,4-triethyl- (pure liquid); II, 4,4-diethyl-1-phenyl- (Nujol mull); III, 1-ethyl-4,4-diphenyl- (Nujol mull); IV, isomeric 4-ethyl-1,4-diphenyl- (dotted line, m. p. 129–130°; solid line, m. p. 114.5–115.5°, Nujol mull).

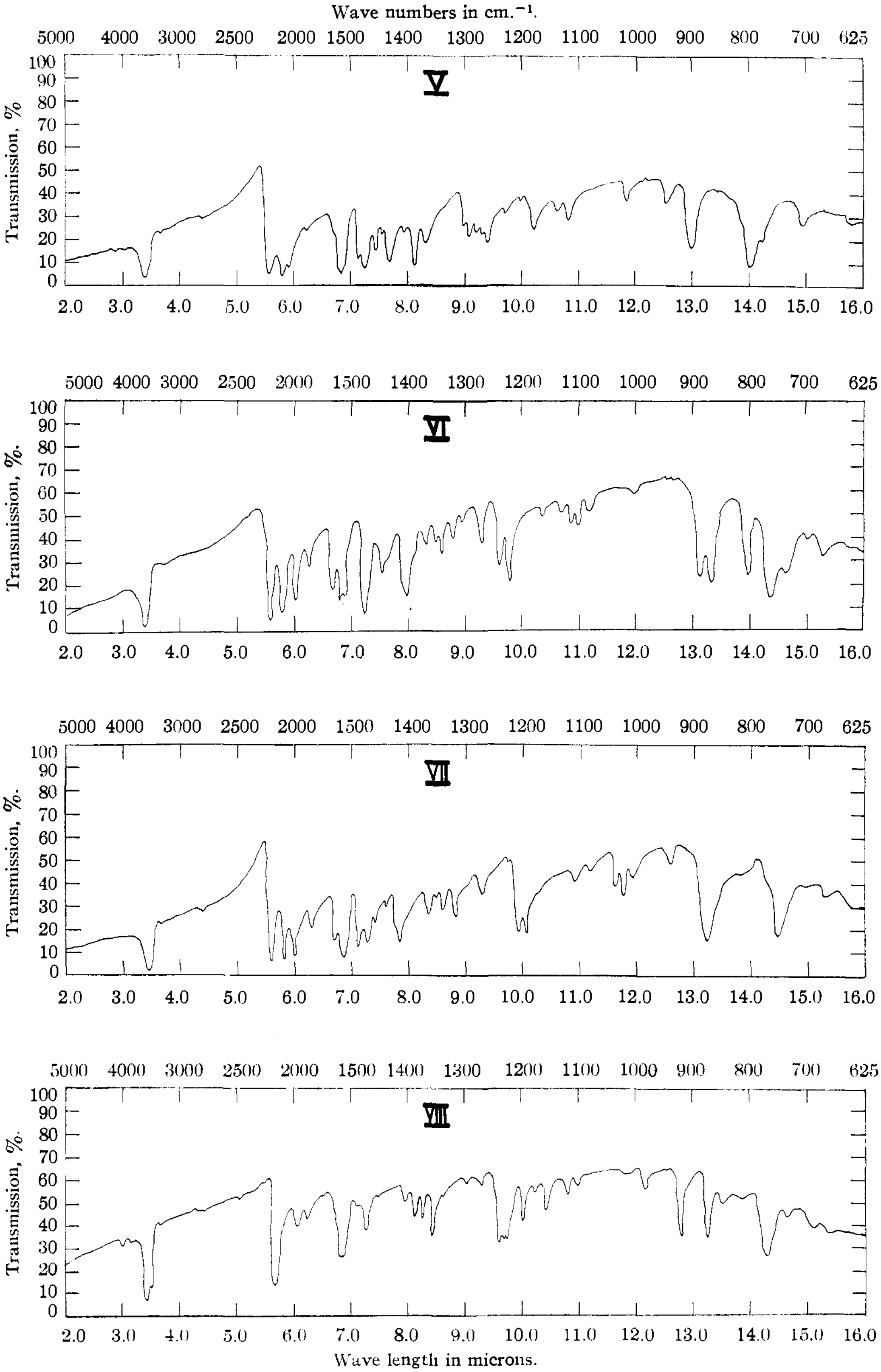
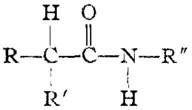


Fig. 1.—V, 1,4-diethyl-4-phenyl- (Nujol mull); VI, 1,4,4-triphenyl- (Nujol mull); VII, 1,4-diphenyl- (Nujol mull); VIII, 4,4-diphenyl -(Nujol mull).

TABLE I

ALKYLACETAMIDES



$$\mathrm{R{-}\overset{H}{\underset{R'}{C}}{-}\overset{O}{\overset{\|}{C}}{-}\underset{H}{N}{-}R''}$$

Crystallized from solvents as follows: water, 1; alcohol, 2, 4, 7, 10, 15, 17, 19, 22, 23, 24, 25; benzene, 3, 5, 8, 9, 11, 12, 13, 18, 20, 21; ligroin, 5.

	R	R′	R″	M. p., °C.	Yield, %	Nitrogen, % Calcd.	Nitrogen, % Found
1	C_4H_9–	C_2H_5–	H–	101.5–102[a]	88		
2	C_4H_9–	C_2H_5–	C_2H_5–	58–59[a]	90		
3	C_4H_9–	C_2H_5–	C_6H_5–	88–89	87	6.38	6.27
4	C_4H_9–	C_2H_5–	$C_6H_5CH_2$–	49–50[d]	88	6.00	6.07
5	C_4H_9–	C_2H_5–	$C_6H_5CH_2CH_2$–	60.5–61.5	93	5.65	5.76
6	C_2H_5–	C_2H_5–	C_2H_5–	83.0	86	9.77	9.94
7	C_2H_5–	C_2H_5–	C_6H_5–	126–127[b]	92		
8	C_2H_5–	C_2H_5–	$C_6H_5CH_2$–	82.5–83[c]	84		
9	C_2H_5–	C_2H_5–	$C_6H_5CH_2CH_2$–	83	84	6.38	6.19
10	C_6H_5–	C_2H_5–	C_2H_5–	58–60	92	7.32	7.36
11	C_6H_5–	C_2H_5–	C_6H_5–	91–92	89	5.85	5.81
12	C_6H_5–	C_2H_5–	$C_6H_5CH_2$–	77–78	82	5.52	5.58
13	C_6H_5–	C_2H_5–	$C_6H_5CH_2CH_2$–	78–79	82	5.23	5.22
14	s-C_5H_{11}–	C_2H_5–	C_2H_5–	[e]	80	7.55	7.68
15	s-C_5H_{11}–	C_2H_5–	C_6H_5–	75–77[f]	85	6.00	6.15
16	s-C_5H_{11}–	C_2H_5–	$C_6H_5CH_2$–	[g]	84	5.66	5.64
17	s-C_5H_{11}–	C_2H_5–	$C_6H_5CH_2CH_2$–	68–70[h]	81	5.35	5.38
18	C_6H_5–	C_6H_5–	C_2H_5–	134.5–135.5	85	5.85	5.73
19	C_6H_5–	C_6H_5–	C_6H_5–	180–181[i]	88		
20	C_6H_5–	C_6H_5–	$C_6H_5CH_2$–	127–128	83	4.64	4.67
21	C_6H_5–	C_6H_5–	$C_6H_5CH_2CH_2$–	112–112.5	80	4.43	4.47
22	C_4H_9–	C_2H_5–	iso-C_3H_7–	99–101[j]	81	7.55	7.50
23	C_2H_5–	C_2H_5–	iso-C_3H_7–	145–147[k]	91	8.90	8.92
24	C_6H_5–	C_2H_5–	Br–C_6H_4–	192.5–193	90	4.39	4.36
25	C_6H_5–	C_6H_5–	H–	168–169[l]	91		

[a] Blicke and Centolella (THIS JOURNAL, **60**, 2925 (1938); Raper (*J. Chem. Soc.*, 91, 1837 (1907)). [b] M. Freund and P. Hermann, *Ber.*, **23**, 191 (1890). [c] Dermer and King (*J. Org. Chem.*, **8**, 169 (1943)) reported 76–77°. [d] B. p. 189–191° (3 mm.). [e] B. p. 123–125 (3.5 mm.); n^{25}D 1.4480. [f] B. p. 172–175 (4.5 mm.). [g] B. p. 178–180 (4.5 mm.); n^{25}D 1.5070. [h] B. p. 178–180 (6.0 mm.). [i] H. Staudinger, *Ber.*, **38**, 1737 (1905). [j] Softens at 80°. [k] Softens at 115°. [l] Klingemann, *Ann.*, **275**, 85 (1893).

the amine in a dry solvent such as benzene or petroleum ether. Only one mole of the more expensive amines was used. To solutions of these one mole of aqueous alkali and one mole of the acid chloride were added simultaneously in a dropwise manner. The use of dry pyridine gave similar yields (Table I).

1,4,4-Trialkyl-2,3,5-pyrrolidinetriones.—In a typical experiment the alkylated acetamide (0.10 mole) and 150 cc. of dry benzene were placed in a 500-cc. three-necked flask fitted by ground glass joints to a mercury-seal stirrer, a dropping funnel, and a condenser. The stirred solution or suspension was heated to 60° and the oxalyl chloride (0.125 mole) was added dropwise in twenty minutes. The stirring was continued in the case of the insoluble amides, *e.g.*, N-benzyl-α,α-diphenylacetamide, until solution resulted. In case the amide, *e.g.*, N,α,α-triphenylacetamide, gave an insoluble pyrrolidinetrione the mixture was stirred until the completion of the reaction as evidenced by titration of hydrogen chloride evolved. The time for completion of the reaction varied from about eight hours in the case of N,α,α-triphenylacetamide to about twenty-four hours in the case of N,α,α-triethylacetamide. The addition of oxalyl chloride at 60° is preferable to the addition at room temperature followed by heating at 60°, *e. g.*, the yields from N,α-diethyl-α-phenylacetamide were thereby increased from 50 to 66%. The liquid pyrrolidinetriones were isolated by distillation and the solid products were isolated by distillation of the benzene and crystallization from the appropriate solvent (Table II).

As an example of the behavior toward aniline, 4.0 g. of 4,4-diphenyl-1-ethylpyrrolidinetrione was thoroughly mixed with 2.2 g. of freshly distilled aniline. Heat was evolved and a solid separated from the solution. After heating for fifteen minutes in a steam-bath and cooling in ice the product was filtered, washed once with a minimum of aniline, and then with toluene· yield of N,N′-diphenyloxamide 3.4 g., m. p. 247–249.[3] This when mixed with an authentic sample gave no depression of the melting point. From the filtrate there was obtained by treatment with ice and an excess of hydrochloric acid 3.1 g. of crude diphenyl-N-ethylacetamide, m. p. 131–133°. This after crystallization from benzene melted at 134.5–135.5° (no. 18, Table I).

Acylalkyloxamic Acid Chlorides.—The distillation of the various reaction products, excepting those in which the N-alkyl group was phenyl or isopropyl, gave small amounts of acid chlorides boiling lower than the alkylpyrrolidinetriones. Three of these acid chlorides were hydrolyzed by cold water to the dialkylacetic acid and the alkyloxamic acid: ethyloxamic acid, m. p. 131–132° (calcd. for $C_4H_7O_3N$: N, 11.92. Found: N, 11.75); Heintz[4] reported m. p. 120°. Benzyloxamic acid, m. p. 128–129°; Guareschi[5] reported m. p. 128–129°. β-Phenylethyloxamic acid, m. p. 130–130.5°. Calcd. for $C_{10}H_{11}O_3N$: N, 7.24. Found: N, 7.11. The dialkylacetic acid com-

---

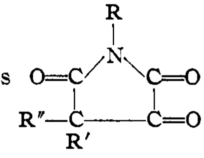
[3] Meyer and Seeliger, *Ber.*, **29**, 2640 (1896).

[4] Heintz, *Ann.*, **127**, 47 (1863).

[5] Guareschi, *Atti. reale accad. sci. Torino*, **27**, 1 (1891)

TABLE II

ALKYLPYRROLIDINETRIONES



Crystallized from solvents as follows: benzene, 3, 4, 5, 19, 20, 22, 23; alcohol, 15, 16, 17, 18, 24, 25; carbon disulfide, 21; ethyl acetate, 26.

	R	R′	R″	M. p., °C.	B. p., °C.	Mm.	$n^{25}D$	Yield, %	Nitrogen, % Calcd.	Nitrogen, % Found
1	C_2H_5–	C_2H_5–	C_2H_5–	....	151–153	4.4	1.5290	29	7.09	6.99
2	*i*-C_3H_7	C_2H_5–	C_2H_5–	....	148–151	4.8	1.5230	41	6.59	6.64
3	C_6H_5–	C_2H_5–	C_2H_5–	46–48	196–199	2.0	....	61	5.70	5.58
4	$C_6H_5CH_2$–	C_2H_5–	C_2H_5–	75–76	206–208	2.6	....	65	5.43	5.42
5	$C_6H_5CH_2CH_2$–	C_2H_5–	C_2H_5–	91–91.5	207–209	2.0	....	60	5.12	5.06
6	C_2H_5–	C_2H_5–	C_4H_9–	....	178–179	3.0	1.5186	46	6.18	6.21
7	*i*-C_3H_7	C_2H_5–	C_4H_9–	....	152–154	3.2	1.5119	33	5.85	5.87
8	C_6H_5–	C_2H_5–	C_4H_9–	....	196–198	3.0	1.5637	69	5.12	5.02
9	$C_6H_5CH_2$–	C_2H_5–	C_4H_9–	....	215–218	3.8	1.5531	52	4.87	4.87
10	$C_6H_5CH_2CH_2$–	C_2H_5–	C_4H_9–	....	219–222	2.5	1.5290	50	4.64	4.57
11	C_2H_5–	C_2H_5–	*s*-C_5H_{11}–	....	172–175	4.8	1.5211	31	5.85	5.88
12	C_6H_5–	C_2H_5–	*s*-C_5H_{11}–	....	204–206	4.7	1.5619	85	4.85	4.94
13	$C_6H_5CH_2$–	C_2H_5–	*s*-C_5H_{11}–	....	212–216	4.8	1.5250	81	4.64	4.77
14	$C_6H_5CH_2CH_2$–	C_2H_5–	*s*-C_5H_{11}–	....	215–218	4.3	....	40	4.42	4.50
15	C_2H_5–	C_2H_5–	C_6H_5–	84.5–85.5	.....	...	....	66	5.72	5.64
16	C_6H_5–	C_2H_5–	C_6H_5–	114.5–115.5	.....	...	....	27	4.76	4.75
17	C_6H_5–	C_2H_5–	C_6H_5–	129–130	.....	...	....	57	4.76	4.89
18	$C_6H_5CH_2$–	C_2H_5–	C_6H_5–	118–119	.....	...	....	81	4.55	4.53
19	$C_6H_5CH_2CH_2$–	C_2H_5–	C_6H_5–	113–115	.....	...	....	75	4.35	4.42
20	*p*-BrC_6H_5–	C_2H_5–	C_6H_5–	129–131	.....	...	....	65	3.76	3.77
21	C_2H_5–	C_6H_5–	C_6H_5–	164–165	.....	...	....	80	4.77	4.80
22	C_6H_5–	C_6H_5–	C_6H_5–	232–233	.....	...	....	86	4.11	4.12
23	$C_6H_5CH_2$–	C_6H_5–	C_6H_5–	158–158.5	.....	...	....	86	3.93	4.06
24	$C_6H_5CH_2CH_2$–	C_6H_5–	C_6H_5–	140–141	.....	...	....	81	3.79	3.69
25	H–	C_6H_5–	C_6H_5–	141–142	.....	...	....	77	5.27	5.39
26	C_6H_5–	C_6H_5–	H–	236–237[a]	.....	...	....	90		

[a] Figee, *Rec. trav. chim.*, **34** 289 (1915).

ponents of the hydrolysates were identified by conversion to the anilides (Table I).

The formation of the oxamic acid derivative was the chief reaction when the oxalyl chloride was added at room temperature to α-*n*-butyl-N,α-diethylacetamide. After heating sixteen hours at 60° and removal of benzene and the excess of oxalyl chloride, the residue was hydrolyzed with cold water. From 25.7 g. (0.150 mole) of the amide 9.0 g. (0.063 mole) of the dialkylacetic acid, 7.0 g. (0.059 mole) of ethyloxamic acid and 4.0 g. (0.017 mole) of the pyrrolidinetrione were isolated.

N,N′-Diisopropyloxamide.—The distillation of the reaction product of diethyl-N-isopropylacetamide and oxalyl chloride gave a fraction, b. p. 120–130° (5 mm.), from which separated a small amount of a crystalline product, m. p. 213–215°. Therefore in another experiment the reaction product from 25.0 g. (0.159 mole) of diethyl-N-isopropylacetamide and 25.1 g. (0.198 mole) of oxalyl chloride after removal of the benzene and excess of oxalyl chloride under diminished pressure was stirred with 150 cc. of water for ten hours and then allowed to stand for several days at room temperature. The mixture was extracted with benzene and 3.0 g. (0.017 mole) of N,N′-diisopropyloxamide[6] m. p. 213–215° separated from the residue after the distillation of the benzene. Distillation of the filtrate under diminished pressure gave 10 g. (0.063 mole) of unreacted amide, 4.0 g. (0.035 mole) of diethylacetic acid which was identified by conversion to the anilide, m. p. 126–127°, and 4.6 g. of the pyrrolidinetriene.

Isomeric 1,4-Diphenyl-4-ethylpyrrolidinetriones.—The crude 1,4-diphenyl-4-ethylpyrrolidinetrione (31.0 g.) melted at 118–124° indicating that it was a mixture. Crystallization from hot alcohol gave 9.5 g. of material, m. p. 112–115°. The filtrate cooled in an ice-bath to yield 19.5 g. of material, m. p. 127–130°. Further recrystallization from absolute alcohol gave m. p. 114.5–115.5° and m. p. 129–130°, respectively (16 and 17, Table II). Although the trialkylpyrrolidinetriones are recovered unchanged from suspension in cold water or cold hydrochloric acid, they are immediately hydrolyzed by cold 10% sodium hydroxide solution. The two isomers when similarly hydrolyzed by alkali gave the identical ethylphenyl-N-phenylacetamide, m. p. 91–92°.

Summary

1. Twenty-five trialkylpyrrolidinetriones and nineteen trialkylacetamides are reported.

2. The pharmacological action and infrared absorption of the trialkylpyrrolidinetriones have been investigated.

3. The formation of oxamic acid chlorides and a diacyldialkyloxamide has been noted.

RECEIVED APRIL 25, 1950

---

[6] Dermer and Hutcheson, *Proc. Okla. Acad. Sci.*, **23**, 60 (1943).