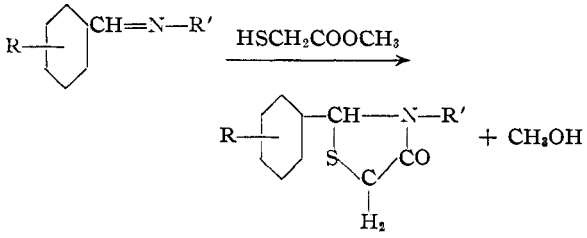
[CONTRIBUTION FROM STERLING-WINTHROP RESEARCH INSTITUTE]

The Preparation of 4-Thiazolidones. III. The Reaction of Methyl Thioglycolate with Benzylidene Dialkylaminoalkylamines

BY ALEXANDER R. SURREY

Recently it has been shown that 2,3-diaryl- and/or 3-alkyl-2-aryl-4-thiazolidones may be easily prepared by the reaction of thioglycolic acid[1] or of thioglycolic esters[1d] with Schiff bases. In continuation of a general investigation on the synthesis of 4-thiazolidones, a series of 2-aryl-3-dialkylaminoalkyl derivatives was prepared to make them available for pharmacological studies.

A convenient method of synthesis,[1b] involving the reaction of methyl thioglycolate with the appropriate benzylidene dialkylaminoalkylamine (Table I), was employed for this purpose. However, in some instances the intermediate anils were not isolated and the crude material was used directly in the next step.



In contrast to the benzylidene anilines,[1b] the anils in the present series react with a thioglycolic ester to give good yields of the 2,3-disubstituted 4-thiazolidones. When the reaction was carried out in refluxing Skellysolve E (b. p. 120°) with a separator connected to the apparatus, the methanol which formed during the reaction was collected as a distinct layer in the separator. Heating was discontinued when no further separation of methanol was noted, which in most instances approached the theory. With lower-boiling petroleum fractions as a solvent, the reaction proceeded in the expected manner. However, the separation of methanol could not be observed.

In most cases, after removal of the solvent by distillation, the crude residue was dissolved in ether, and the 2-aryl-3-dialkylaminoalkyl-4-thiazolidone was extracted with dilute hydrochloric acid. The base obtained from the acid extract was then converted to the crystalline hydrochloride (Table II).

In the preparation of 3-(3-diethylamino-2-hydroxypropyl)-2-phenyl-4-thiazolidone two isomeric crystalline bases and hydrochlorides were obtained. Although two possible racemic mixtures can also be formed in the preparation of the corresponding 2-(4-methoxyphenyl) derivative, only one compound was isolated.

(1) (a) Erlenmeyer and Oberlin, *Helv. Chim. Acta*, **30**, 1329 (1947); (b) Surrey, THIS JOURNAL, **69**, 2911 (1947); (c) Surrey, *ibid.*, **70**, 4262 (1947); (d) Troutman and Long, *ibid.*, **70**, 3436 (1947).

Preliminary pharmacological studies[2] indicate that several of the 2-aryl-3-dialkylaminoalkyl-4-thiazolidones reported in this paper show marked local anesthetic activity. 3-(2-Dibutylaminoethyl)-2-(4-chlorophenyl)-4-thiazolidone, (Win 2126) 3-(2-dibutylaminoethyl-2-(3,4-methylenedioxyphenyl)-4-thiazolidone (Win 2777) and 3-(2-diethylaminoethyl-2-(3,4-methylenedioxyphenyl)-4-thiazolidone (Win 2125) are the most active compounds studied in this series. Win 2777 is much more active than procaine while Win 2125 is as active as procaine and also shows activity as a topical anesthetic (cornea). The compounds reported are very stable to heat, acid or base and in most instances are non-irritating.

Experimental[3]

Preparation of Benzylidene-dialkylaminoalkylamines. (Table I).—Equimolecular quantities of the appropriate aromatic aldehyde and dialkylaminoalkylamine in benzene were refluxed with a water separator connected to the apparatus. When the reaction was completed the benzene was removed and the product was distilled under reduced pressure.

Preparation of 2-Aryl-3-dialkylaminoalkyl-4-thiazolidone Hydrochlorides.—The general procedure for the preparation of the compounds described in Table II is described below.

Equimolecular quantities (0.1 mole) of the benzylidene dialkylaminoalkylamine (Table I) and methyl thioglycolate[4] in 150 ml. of Skellysolve E were refluxed until approximately the theoretical amount of methanol was collected in a separator connected to the apparatus. After distilling the solvent *in vacuo*, the residue was dissolved in ether, and the desired product was extracted with dilute hydrochloric acid solution. The base, obtained from the acid extracts, was dissolved in acetone and alcoholic hydrogen chloride was added. Where necessary, dry ether was added and the solution was allowed to stand at room temperature. The solid hydrochloride which precipitated was purified by recrystallization.

3-(3-Diethylamino-2-hydroxypropyl)-2-phenyl-4-thiazolidone.—A solution of 23.4 g. of benzylidene 3-diethylamino-2-hydroxypropylamine and 11 g. of methyl thioglycolate in 150 ml. of Skellysolve E was treated as described above. The crude crystalline hydrochloride (16 g.) melted at 120–125°. After several recrystallizations from isopropanol, the product melted at 155.6–160.9° cor.

Anal. Calcd. for $C_{16}H_{25}ClN_2O_2S$: S, 9.29; Cl^-, 10.30. Found: S, 9.23; Cl^-, 10.12.

A sample of the hydrochloride was converted to base which solidified on standing. After recrystallization from Skellysolve A it melted at 58.8–60° cor.

Anal. Calcd. for $C_{16}H_{24}N_2O_2S$: S, 10.37. Found: S, 10.55.

(2) The author is indebted to Dr. F. P. Luduena and Miss J. Sherndal for the local anesthetic testing, the details of which will be published elsewhere.

(3) All melting points and boiling points are uncorrected unless otherwise specified. The corrected melting point determinations and analyses recorded were performed by the analytical staff of these laboratories under the direction of M. E. Auerbach.

(4) Baker, *et al.*, *J. Org. Chem.*, **12**, 144 (1947).

TABLE I

BENZYLIDENE DIALKYLAMINOALKYLAMINES, R—C$_6$H$_4$—CH=N—R′

R	R′	B. p., °C.	Mm.	$n^{25}D$	Nitrogen analyses, %[a] Calcd.	Found
H	$CH_2CH_2N(CH_3)_2$	132–133	12	1.5330	15.91	15.61
H	$CH_2CH_2N(C_2H_5)_2$	82–83[b]	0.1	1.5231	13.73	13.61
4-Cl	$CH_2CH_2N(C_4H_9)_2$	147–150	.5	1.5198	9.50	9.36
4-OCH_3	$CH_2CH_2N(C_2H_5)_2$	120–125	.3	1.5367	11.96	11.83
3,4-Di-OCH_3	$CH_2CH_2N(C_2H_5)_2$	140–145	.35	1.5460	10.59	10.29
3,4-O_2CH_2	$CH_2CH_2N(C_2H_5)_2$	132–133	.2	1.5463	11.29	11.07
4-N-$(CH_3)_2$	$CH_2CH_2N(C_2H_5)_2$	140–150	.2–0.4	1.5778	11.31	11.31[c]
H	$CH_2CH_2CH_2N(C_2H_5)_2$	105	.1	1.5196	12.85	12.80
3,4-O_2CH_2	$CH_2CH_2CH_2N(C_2H_5)_2$	155	.4	1.5402	10.68	10.64
H	$CH_2CHOHCH_2N(C_2H_5)_2$	137–139	.6	1.5313	11.97	11.62
4-OCH_3	$CH_2CHOHCH_2N(C_2H_5)_2$	160–163	.3	1.5419	10.61	10.50

[a] Basic nitrogen by the Toennies and Callan method [*J. Biol. Chem.*, 125, 259 (1938)]. [b] Described in German Patent 559,500, June 26, 1928, b. p. 128° at 7 mm. [c] Titrated for only two nitrogen atoms by this method.

TABLE II

2-ARYL-3-DIALKYLAMINOALKYL-4-THIAZOLIDONES, R—C$_6$H$_4$—CH(S—C(=O)—CH$_2$)—N—R′ HYDROCHLORIDES

R	R′	Yield, %	Recryst. solvent	M. p., °C. (cor.)	Analyses, % Sulfur Calcd.	Found	Chlorine[a] Calcd.	Found	Win No.
H	$CH_2CH_2N(CH_3)_2$	70	Ethanol	219.2–221.1	11.18	11.08	12.37	12.20	2035
H	$CH_2CH_2N(C_2H_5)_2$	78[b]	Isopropanol	152–153.2	10.18	10.18	11.26	10.96	2131
4-Cl	$CH_2CH_2N(C_4H_9)_2$	53	Acetone	118.4–120.2	7.91	7.74	8.75	8.61	2126
4-OCH_3	$CH_2CH_2N(C_2H_5)_2$	50	Isopropanol	152.2–153.2	9.29	9.41	10.28	10.01	2530
3,4-Di-OCH_3	$CH_2CH_2N(C_2H_5)_2$	45	Isopropanol	137–138	8.55	8.38	9.48	9.45	2501
3,4-O_2CH_2	$CH_2CH_2N(C_2H_5)_2$	56	Isopropanol	144.8–146.4	8.93	8.88	9.88	9.75	2125
3,4-O_2CH_2	$CH_2CH_2N(C_4H_9)_2$	24[c]	Acetone-ether	125.5–127.3	7.71	7.52	8.52	8.52	2777
3,4,5-Tri-OCH_3	$CH_2CH_2N(C_2H_5)_2$	37[c]	Isopropanol	165.7–166.5	7.92	7.97	8.76	8.75	2503
4-N$(CH_3)_2$	$CH_2CH_2N(C_2H_5)_2$	66	Isopropanol	161–162.4	8.96	8.92	9.91	9.67	2195
4-NO_2	$CH_2CH_2N(C_2H_5)_2$	53[c]	Ethanol	194.1–194.9	8.91	9.10	9.85	9.66	2502
4-NH_2	$CH_2CH_2N(C_2H_5)_2$	54	Isopropanol	185.5–186.5	9.72	9.55	10.75	10.58	2531
H	$CH_2CH_2CH_2N(C_2H_5)_2$	30	Isopropanol	151.2–153.2	9.75	9.72	10.78	10.64	2095
3,4-O_2CH_2	$CH_2CH_2CH_2N(C_2H_5)_2$	10[d]	Isopropanol	171.6–173.8	8.60	8.43	9.51	9.32	2687
H	$CH_2CHOHCH_2N(C_2H_5)_2$		Ethanol-ether	143.2–144	9.30	9.22	10.28	10.22	2130
4-OCH_3	$CH_2CHOHCH_2N(C_2H_5)_2$	30	Isopropanol	168.7–170.5	8.58	8.38	9.48	9.37	2124

[a] Ionic chlorine. [b] The base of this compound was reported by Troutman and Long, Ref. 1d. [c] Yield based on substituted benzaldehyde. [d] Yield of crude base was 74%.

The hydrochloride prepared from the crystalline base melted at 160–161°.

In another experiment the crude base solidified on standing. It was recrystallized from Skellysolve A, m. p. 74.2–75.6° cor.

Anal. Found: S, 10.42.

The hydrochloride prepared from this base melted at 143.2–144° cor. A mixed melting point with the higher melting hydrochloride was depressed.

3-(2-Diethylaminoethyl)-2-(4-nitrophenyl)-4-thiazolidone Hydrochloride (Win 2502).—A mixture of 30.2 g. of 4-nitrobenzaldehyde and 23.6 g. of 2-diethylaminoethylamine in 150 ml. of Skellysolve E was refluxed for three hours (2.4 ml. of water collected). After allowing to cool, 21.8 g. of methyl thioglycolate was added to the reaction mixture and refluxing continued for seventeen hours. At the end of this time approximately 9 ml. of methanol had separated. The solvent was decanted from the oily layer which separated and the latter was dissolved in 250 ml. of acetone and filtered with Norite. Alcoholic hydrogen chloride was added to the filtrate to give 45 g. of a yellow solid. Recrystallization from ethanol yielded 38 g. (53%) of product melting at 194.1–194.9° cor.

2-(4-Aminophenyl)-3-(2-diethylaminoethyl)-4-thiazolidone Hydrochloride (Win 2531).—A mixture of 36 g. of the above nitro base, 150 ml. of water, 250 ml. of ethanol, 140 g. of iron filings and 3.6 ml. of acetic acid was refluxed with stirring for one hour. An additional 7 ml. of acetic acid was added and refluxing continued for two hours longer. The mixture was basified with sodium carbonate and filtered hot. The ethanol was removed by distillation and the aqueous mixture was extracted with ether. After drying and removing the ether by distillation 25 g. of the crude base was obtained which yielded 18 g. of hydrochloride.

A sample of this hydrochloride was converted to the base which solidified on standing. After recrystallization from Skellysolve B it melted at 62.8–64.4° cor.

Anal. Calcd. for $C_{15}H_{23}N_3OS$: S, 10.93. Found: S, 11.02.

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Summary

The preparation of a series of 2-aryl-3-dialkylaminoalkyl-4-thiazolidones by the reaction of methyl thioglycolate with several benzylidene dialkylaminoalkylamines is reported.

Several of the compounds reported showed marked local anesthetic activity.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF TEXAS]

A New Method for the Preparation of α-Bromoesters[1]

BY J. R. DICE AND J. N. BOWDEN[2]

The reaction of the metal salts of carboxylic acids with chlorine or bromine to yield an alkyl or aryl halide and carbon dioxide[3] is well known. Recently, Hunsdiecker[4] employed this reaction in the preparation of α-bromo aliphatic acids from the half-esters of ω,ω'-dicarboxylic acids. There are no reports in the literature of the use of the metal salts of the half acid esters of alkylmalonic acids in this synthesis.

It was reasoned that if one mole of halogen would react with the metal salts of the monoesters of alkylmalonic acids in the same manner as with simple carboxylic acid salts, the product would be an α-haloester.

$$R-CH(COOC_2H_5)(COO\text{-Metal}) + X_2 \longrightarrow R-CHX-COOC_2H_5 + \text{Metal-X} + CO_2$$

To test this hypothesis the dry potassium salts of the monoesters of several alkylmalonic acids were treated with bromine. Although the expected α-bromoesters were obtained, the yields in most experiments were relatively low. In general, bromination of acid chlorides[5] would be a preferred route to these compounds. Compounds prepared by the new method were ethyl α-bromobutyrate, ethyl α-bromoisovalerate, ethyl α-bromocyclohexylacetate, ethyl α-bromocaproate and ethyl α-bromo-β-phenylpropionate.

Although silver salts have been used most frequently in the reaction, other metal salts such as mercury, copper or potassium also have been used successfully.[6] In this study the potassium salts were utilized throughout and carbon tetrachloride was used as solvent.

With the potassium salt of monoethyl malonate we obtained the same result in carbon tetrachloride as that reported by Freund[7] for aqueous solution; *i. e.*, a mixture of ethyl bromoacetate and ethyl dibromoacetate was formed. In this reaction hydrogen bromide was evolved during the addition of bromine. The liberation of hydrogen bromide is apparently caused by a substitution reaction which occurs prior to or simultaneously with decarboxylation. Substitution does not follow decarboxylation, since ethyl bromoacetate does not react visibly with bromine under the conditions of our experiment.

Experimental

Potassium Salts of Monoesters of Alkyl Malonic Acids.—The ethyl alkylmalonates used were prepared from ethyl malonate (b. p. 198° at 746 mm.) and the respective alkyl halides essentially as described by Adams and Johnson,[8] and they were redistilled before use. Potassium salts of the mono acid esters of these compounds were synthesized following the procedure of Freund.[7] To a solution of 0.15 mole of diethyl alkylmalonate in 100 ml. of absolute alcohol was added, with stirring, a solution of 8.7 g. (0.15 mole) of potassium hydroxide in 100 ml. of absolute alcohol. The solution was allowed to stand at room temperature for four to twelve hours; the *p*H of the final mixture had a value between 7 and 8 as measured with *p*-Hydrion paper. Any solids which formed were assumed to be the dipotassium salt of the alkylmalonic acid and were removed by filtration.

TABLE I

ETHYL α-BROMOESTERS

α-Bromoesters	Yield,[a] %	B. p., °C.	Mm.	$n^{25}D$	d^{25}_4
Acetate[b]	23	165–168	749		
Butyrate	36	177–180	745		
Caproate	67	208–209	748[c]	1.4468	1.2210
iso-Valerate	30	185–187	754[d]	1.4392	1.2325[e]
Cyclohexyl-acetate[f]	45	133–136	13	1.4708	1.1466
β-Phenyl-propionate	80	155–159	15	1.5180[g]	

[a] All yields are based on the weight of diethyl alkylmalonate employed. [b] Hydrogen bromide was evolved during the bromine addition and a 20% yield of ethyl dibromoacetate (b. p. 185–192° (749 mm.)) also was obtained. [c] 111–113° at 25 mm. [d] 105–115° at 25 mm. [e] Schleicher, *Ann.*, 267, 116 (1892), reported d^{12}_{12} to be 1.2276. [f] J. v. Braun, *Ber.*, 2184 (1923). [g] This compound decomposed on standing for twenty-four hours, so a density determination was not obtained.

(1) This work was supported by a grant from the Research Institute, the University of Texas, Project 186.

(2) From the M. A. Thesis of J. N. Bowden.

(3) Kleinberg, *Chem. Rev.*, **40**, 381 (1947).

(4) Hunsdiecker and Hunsdiecker, *Ber.*, **75**, 291 (1942).

(5) *Cf.* Bagard, *Bull. Soc. Chim. France*, [4] **1**, 310 (1907); Ingold, *J. Chem. Soc.*, **119**, 316 (1921); Schwenk and Papa, THIS JOURNAL, **70**, 3626 (1948).

(6) Hunsdiecker, Hunsdiecker and Vogt, U. S. Patent, 2,176,181 (1939); see also ref. 4.

(7) Freund, *Ber.*, **17**, 780 (1884).

(8) Adams and Johnson, "Elementary Laboratory Experiments in Organic Chemistry," The Macmillan Co., New York, N. Y., 1943, p. 329.