[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

# DIALKYL THIAZOLIDIONES

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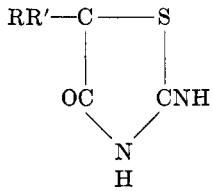
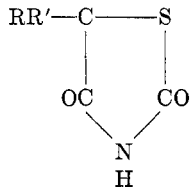
It seems significant that a wide group of organic compounds exhibiting sedative action, such as the dialkylacetyl ureas, the halogenated dialkylacetamides, the alkaryl hydantoins,* the dialkyl homophthalimides,[1] the dialkyl barbituric acids, the dialkyldiketotetrahydro oxazoles,[2] the dialkyl-dioxotetrahydro pyridines,[3] and dialkyl rhodanines,[4] contain the group $RR'{=}\overset{|}{C}{-}CO{-}NH{-}$. Although many series of organic compounds exhibiting sedative action which do not contain this group exist, the synthesis and pharmacological study of additional compounds containing such a group seemed desirable.

At the time this investigation was completed, little chemical data and no pharmacological reports were available concerning the 5,5-dialkyl-2-imino-4-thiazolidones or the 5,5-dialkyl-2,4-thiazolidiones.



5,5-Dialkyl-2-imino-4-thiazolidone



5,5-Dialkyl-2,4-thiazolidione

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* Of the many hydantoins described, only phenylethyl hydantoin possesses sufficient hypnotic action to come within the range of clinical usefulness.

[1] LUMIERE AND PERRIN, *Bull. soc. chim.* [4], **35**, 1022 (1924) describe diethyl-, ethylpropyl-, dipropyl-, and diallyl homophthalimide.

[2] (*a*) ALTWEGG AND EBIN, *U. S. Patent* 1,375,949, describe phenylmethyl-, phenylethyl-, dipropyl-, and diallyl-2,4-diketotetrahydro oxazole; and (*b*) ERLENMEYER AND KLEIBER, *Helv. Chim. Acta*, **21**, 111 (1938), describe the diethyl-2,4-diketotetrahydro oxazole.

[3] SCHNIDER, *U. S. Patent* 2,090,237, and PREISWERK AND SCHNIDER, *U. S. Patent* 2,090,068, describe a large group of 3,3-dialkyl-2,4-dioxotetrahydro pyridines.

[4] (*a*) LEONARD, *Medd. K. Vetenskapsakad. Nobelinst.* **4**, No. 14, 1–13 (1921), describes 5,5-diethyl rhodanine, and (*b*) ERLENMEYER AND KLEIBER, *Helv. Chim. Acta*, **21**, 111 (1938), describe 5,5-dimethyl and 5,5-diethyl rhodanine.

This paper, which covers the synthesis and pharmacological study of certain of the thiazolidones and thiazolidiones, is a report on a portion of a research directed to increasing our knowledge on the relationship of chemical structures and hypnotic action. This study was directed chiefly to the preparation and evaluation of unsymmetrical thiazolidiones, since it has been our experience in the field of barbituric acids that the unsymmetrically substituted derivatives are more effective than the symmetrically substituted ones. Inasmuch as the corresponding 5,5-dialkyl-2-imino-4-thiazolidones were the intermediates from which the thiazolidiones were prepared, they also were pharmacologically tested.

After our experimental work was completed, Erlenmeyer and von Meyenburg[5] reported the preparation of 5,5-diethyl-, 5,5-dipropyl-, 5,5-diallyl-, and 5,5-phenylethyl-2,4-thiazolidiones. These investigators state that several of these compounds had been pharmacologically tested and found to have a sedative action which was comparable to that of the dialkyl barbituric acids.

Our pharmacological studies show that the thiazolidiones have a marked sedative and anesthetic action of brief duration. Only the data obtained after the intravenous administration of the sodium salts of the 2,4-thiazolidiones are reported, although these compounds also were administered orally and intraperitoneally. The brevity of the effect is indicative of rapid destruction by the body. Critical animal tests, however, brought out the fact that these dialkyl 2,4-thiazolidiones do not give particular promise of clinical usefulness, at least after intravenous administration, due to the fact that they either produce tremors or convulsions. While it is impossible to make a broad prediction that all of the possible dialkyl 2,4-thiazolidiones will produce convulsions or tremors, their presence following administration of these five representative members leads us to believe that such a response may be expected from the other members. No statement is made by Erlenmeyer and von Meyenburg as to whether their compounds produced tremors or convulsions, although our study included one of the compounds which they tested.

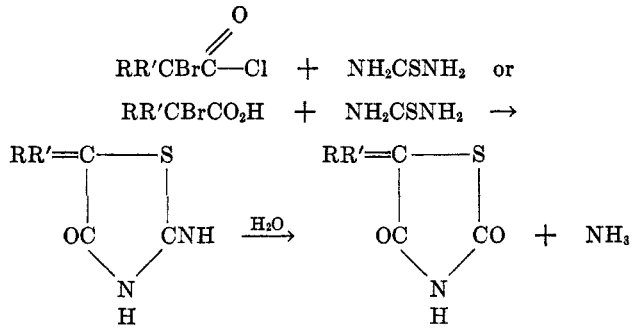
The imino derivatives, which are soluble in both dilute acids and in dilute alkalis, contrary to what might be expected, exhibited a moderate amount of sedative action when administered orally to white rats. The effectiveness of the imino derivatives of this series is in marked contrast to the lack of activity of the imino barbituric acids.

It was concluded, on the basis of the above study, that dialkyl derivatives of the 2,4-thiazolidione nucleus are less satisfactory than the corresponding barbituric acid derivatives for the production of sedation.

[5] ERLENMEYER AND VON MEYENBURG, *Helv. Chim. Acta*, **20**, 1388 (1937).

## EXPERIMENTAL

The 5,5-dialkyl-2-imino-4-thiazolidones were prepared either by condensing thiourea with dialkyl substituted bromoacetic acids or with dialkyl substituted bromoacetyl chlorides, and hydrolyzed to form the corresponding thiazolidione.



The substituted acetic acids were obtained by hydrolyzing the corresponding substituted malonic esters in dilute potassium hydroxide solution. After refluxing for several hours, the alcohol was removed by distillation *in vacuo*, and the residue was treated with water. The aqueous solution was acidified, and the substituted malonic acid which separated was extracted with ether. The malonic acids were heated to about 170°, in order to split out carbon dioxide, and thus form the corresponding acetic acids.

The dialkyl-substituted $\alpha$-bromoacetic acids were obtained by heating the acetic acids with bromine following the general procedure given for the preparation of $\alpha$-bromo-*n*-caproic acid.[6] Two of the $\alpha$-bromoacetic acids prepared have not been described in the literature. They are ethylisobutylbromoacetic acid, which boils at 121–125° at 2.5 mm., and ethyl-1-methylbutylbromoacetic acid, which boils at 120–125° at 1 mm.

The dialkyl-substituted bromoacetyl chlorides were prepared by converting the acetic acids into their acid chlorides by means of thionyl chloride and treating the acetyl chlorides with bromine.[7]

5,5-Ethyl-*n*-propyl-, 5,5-ethylisobutyl-, and 5,5-ethyl-1-methylbutyl-2-imino-4-thiazolidones were prepared by condensing the corresponding substituted bromoacetic acids with thiourea, using the method which Markley and Reid[8] employed in the preparation of diphenylisothiohydantoin. This is illustrated in the following preparation of 5,5-ethyl-1-methylbutyl-2-imino-4-thiazolidone.

A mixture of 23.5 g. (0.1 mol) ethyl 1-methylbutylbromoacetic acid, 7.6 g. (0.1 mol) thiourea, 3.8 g. (0.046 mol) anhydrous sodium acetate and 110 cc. absolute ethyl alcohol was refluxed for three hours. The alcohol was removed by distillation *in vacuo*, the residue was treated with water, and sodium bicarbonate was added until the mixture was neutral to litmus. The solid 5,5-ethyl-1-methylbutyl-2-imino-4-thiazolidone was filtered, washed with water, dried *in vacuo*, and weighed

[6] *Organic Syntheses*, Coll. Vol. I, p. 108.

[7] *D.R.P.* 158,220; *Chem. Zentr.*, **1905**, I, 635.

[8] MARKLEY AND REID, *J. Am. Chem. Soc.*, **52**, 2137 (1930).

TABLE

CONSTANTS OF 2-IMINO-4-THIAZOLIDONES AND OF 2,4-THIAZOLIDONES

| 5, 5-ALKYL SUBSTITUENTS | 2-IMINO-4-THIAZOLIDONE | | | 2,4-THIAZOLIDIONE | | | INTRAVENOUS ADMINISTRATION OF SODIUM SALT OF DISUBSTITUTED 2,4-THIAZOLIDIONES IN WHITE RATS | | |
|---|---|---|---|---|---|---|---|---|---|
| | M.p., °C.[a] | % Nitrogen | | M.p., °C.[a] | % Nitrogen | | M.E.D., mg./kg. | M.L.D., mg./kg. | Average duration of M.E.D., min. |
| | | Calc'd | Found | | Calc'd | Found | | | |
| Diethyl | 237–238[b] | 16.27 | 16.05 16.15 | 78.0–78.5[c] | 8.09 | 8.14 8.22 | 200[d] | 600 | 120 |
| Ethyl-*n*-propyl | 220–222 | 15.04 | 14.98 14.91 | oil | 7.49 | 7.58 7.62 | 100[e] | 400 | 75 |
| Ethyl-isobutyl | 225–227 | 14.00 | 14.08 14.08 | oil | 6.97 | 7.01 7.13 | 100[e] | 325 | 30 |
| Ethyl-*sec.*-butyl | 215–216 | 14.00 | 14.01 13.91 | 70–72 | 6.97 | 6.89 7.03 | 100[e] | 300 | 60 |
| Ethyl-1-methylbutyl | 229–231 | 13.08 | 13.00 13.07 | 105–107 | 6.51 | 6.52 6.69 | 50–100[e] | 250 | 30 |

[a] Anschütz thermometer used. [b] CLEMMENSEN AND HEITMAN, *Am. Chem. J.*, *40*, 280 (1908), report the m.p. as 224°, while ERLENMEYER AND VON MEYENBURG, *Helv. Chim. Acta*, *20*, 1388 (1937), give 233.5° (corr.).

[c] ERLENMEYER AND VON MEYENBURG report this compound melts at 76°. [d] Produces tremors. [e] Convulsions.

16 g. (79% yield). After several recrystallizations from dilute alcohol it melted at 229–231°.

Diethyl-2-imino-4-thiazolidone[9] and ethyl-sec.-butyl-2-imino-4-thiazolidone were prepared by condensing the dialkyl substituted bromoacetyl chlorides with thiourea. A mixture of the bromoacetyl chloride and thiourea was warmed to initiate the reaction, which was then allowed to proceed spontaneously. All of the 2-imino-4-thiazolidones were crystalline solids which were purified by crystallization from dilute alcohol. They are but slightly soluble in water but dissolve in dilute acids and bases. The constants of the five 2-imino-4-thiazolidones which were prepared, are given in the accompanying table.

The 5,5-dialkyl-2,4-thiazolidones were obtained from the 2-imino-4-thiazolidones by hydrolysis of the 2-imino group. The method used is illustrated in the hydrolysis of 5,5-ethyl-1-methylbutyl-2-imino-4-thiazolidone. Four and one-half grams (0.021 mol) of the latter was dissolved in a solution of 10 cc. of 1:1 hydrochloric acid and 90 cc. of distilled water. The solution was refluxed for two hours, and on cooling, the oil which had formed solidified. The crude 2,4-thiazolidione was filtered, washed with petroleum ether; it weighed 3.0 g. and melted at 99–100°. After several recrystallizations from dilute alcohol it melted at 105–107° and weighed 2.5 g. (55%). The crystalline 2,4-thiazolidiones described in the accompanying table were purified by recrystallization from alcohol.

Ethyl-*n*-propyl- and ethylisobutyl-2,4-thiazolidiones would not crystallize on standing for some time. They were purified by extracting them from their chloroform solutions with dilute sodium hydroxide solution. The pH of the solutions was then lowered to about 9.0 (colorimetrically), decolorizing carbon was added, and the solutions were filtered. On acidification, oils were obtained, which were extracted with chloroform, and after the chloroform solutions had been washed free of mineral acid, the thiazolidiones recovered by evaporation of the chloroform.

## CONCLUSION

Two additional series of compounds containing the group $RR'{=}\overset{|}{C}{-}CO{-}NH{-}$ as part of a heterocyclic ring, the 5,5-dialkyl-2-imino-4-thiazolidones, and the 5,5-dialkyl-2,4-thiazolidiones were found to exert hypnotic action when administered orally to white rats.

The prevalence of tremors or convulsions after the intravenous administration of sodium salts of the thiazolidiones makes it unlikely that they will be of practical importance.

The following new compounds were prepared: ethylisobutyl- and ethyl-1-methylbutyl-bromoacetic acids; ethyl-*n*-propyl-, ethylisobutyl-, ethyl-*sec.*-butyl-, and ethyl-1-methylbutyl-2-imino-4-thiazolidones; and ethyl-*n*-propyl-, ethylisobutyl-, ethyl-*sec.*-butyl-, and ethyl-1-methylbutyl-2,4-thiazolidiones.

[9] CLEMMENSEN AND HEITMAN, *Am. Chem. J.*, **40**, 280 (1908).