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SYNTHESIS OF COMPOUNDS RELATED TO THE BARBITURIC ACIDS

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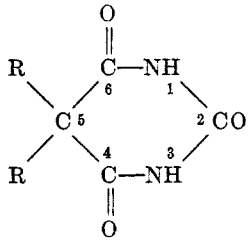
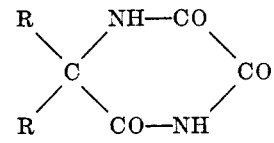
In the search for new pharmacologically useful drugs we have been exploring three variations in the barbituric acid structure (I), represented by formulas II, III, and IV.



I



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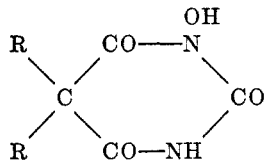

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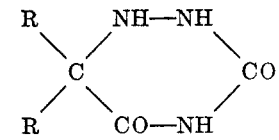
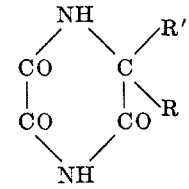


IV

Formula II is derived from the barbituric acid nucleus by interchanging the 6-carbonyl group with the 1-imino group and has the structure of a piperazine-2,3,6-trione. This nucleus was studied by Bornwater (1) who reported the synthesis of 5-benzyl-2,3,6-piperazinetrione by reacting oxalyl chloride with DL-β-phenylalanine amide. We were unable to repeat this work. Bergmann and co-workers (2, 3) obtained the 5-benzyl derivative by a multi-step procedure in what seemed to be a low over-all yield. We have found that ethyl oxalate condenses with DL-β-phenylalanine amide in ethanol in the presence of sodium methoxide to give the sodium salt of the trione, from which a 60% yield of the free trione can be isolated. We used this method for the preparation of the piperazinetriones described in Table I. Further studies revealed the interesting fact that the sodium salts of the triones are unstable in aqueous solution and are hydrolyzed completely in as little time as one hour. This might explain the failure of Clarke and Francis (4) to isolate any trione from the reaction between α-ethoxalylamidophenylacetamide and sodium ethoxide. Even under our most favorable conditions for isolation of the triones some hydrolysis occurred and we obtained the corresponding oxalamidoacid amides. For example, ethyl oxalate on reaction with α-aminoisobutyramide (V) in the presence of sodium methoxide gave α-oxalamidoisobutyramide (VII) along with the trione (VI). This compound, after esterification with diazomethane (VIII), was cyclized with sodium methoxide to the trione.

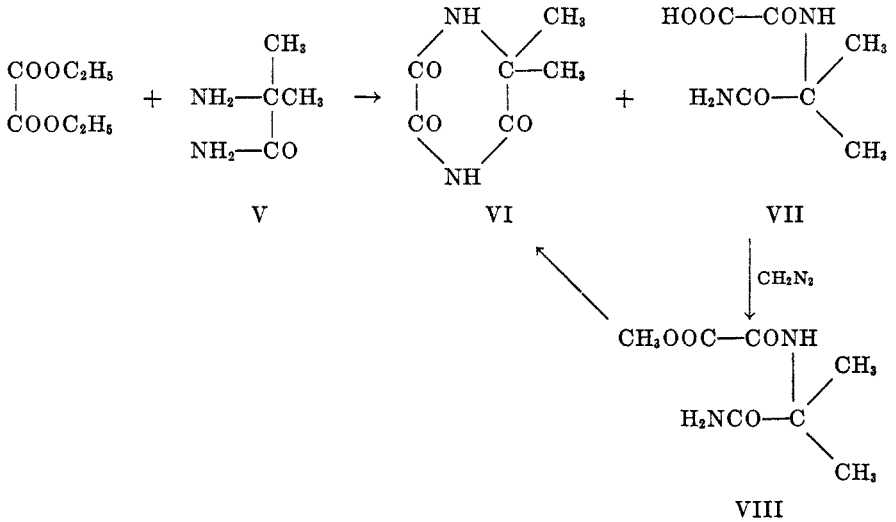
TABLE I

5-SUBSTITUTED-2,3,6-PIPERAZINETRIONES



R	R′	M.P., °C.	YIELD, %	EMPIRICAL FORMULA	ANALYSES					
					Calc'd			Found		
					C	H	N	C	H	N
$C_6H_5CH_2$—[a]	H	252–255 (dec.)	60	$C_{11}H_{10}N_2O_3$	60.6	4.6	12.8	60.6	4.9	13.0
CH_3—	CH_3—	280–284 (dec.)	72	$C_6H_8N_2O_3$	46.2	5.1	17.9	46.3	5.3	17.7
C_2H_5—	H	196–200 (dec.)	62	$C_6H_8N_2O_3$	46.2	5.1	17.9	46.2	5.3	17.9
$(CH_3)_2CHCH_2$—	H	222–224 (dec.)	4	$C_8H_{12}N_2O_3$	52.2	6.5	15.2	52.6	6.3	15.3
C_6H_5—	H	232–236 (dec.)	64	$C_{10}H_8N_2O_3$	58.8	3.9	13.7	58.9	4.1	13.8

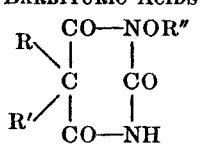
[a] Bornwater (1) reports m.p. 170° (dec.) for this compound prepared by a different method. Bergmann and co-workers (2, 3) report m.p. 265° (corr. dec.) for a sample made by still another method.



Formula III possesses the barbituric acid nucleus with the added feature of a hydroxyl group attached to a nitrogen atom. This substitution confers on the molecule the properties of a cyclic hydroxamic acid. So far as we are aware, no representatives of this series have been reported in the literature. These compounds were prepared by reacting the appropriately substituted malonyl chlorides with benzyloxyurea followed by hydrogenolysis of the benzyl groups. The hydroxy derivatives, together with the intermediate benzyloxy compounds are listed in Table II.

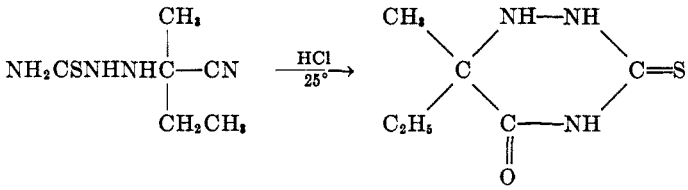
TABLE II

BARBITURIC ACIDS



R	R′	R″	M.P., °C.	EMPIRICAL FORMULA	ANALYSES						YIELD, %
					Calc'd			Found			
					C	H	N	C	H	N	
C_2H_5—	C_2H_5—	$C_6H_5CH_2$—	111–113	$C_{15}H_{18}N_2O_4$	62.0	6.2	9.7	62.2	6.5	9.7	40
C_2H_5—	C_6H_5—	$C_6H_5CH_2$—	100–103	$C_{19}H_{18}N_2O_4$	67.5	5.3	8.3	67.6	5.5	8.3	62
C_2H_5—	$(CH_3)_2CH$—	$C_6H_5CH_2$—	91–92	$C_{16}H_{20}N_2O_4$	63.2	6.6	9.2	63.5	6.7	9.0	34
C_2H_5—	$CH_3(CH_2)_2CH_2$—	$C_6H_5CH_2$—	oil	$C_{17}H_{22}N_2O_4$							
C_2H_5—	C_2H_5—	H	143–146	$C_8H_{12}N_2O_4$	48.0	6.0	14.0	48.3	6.3	14.0	36
C_2H_5—	C_6H_5—	H	161–163	$C_{12}H_{12}N_2O_4$	58.1	4.8	11.3	58.1	5.0	11.4	62
C_2H_5—	$(CH_3)_2CH$—	H	141–143	$C_9H_{14}N_2O_4$	50.4	6.5	13.1	50.3	6.9	13.2	70
C_2H_5—	$CH_3(CH_2)_2CH_2$—	H	107–109	$C_{10}H_{16}N_2O_4$	52.7	7.0	12.3	52.5	7.2	12.2	33

In formula IV an imino group has replaced the carbonyl group in the 6-position of barbituric acid. Compounds with this structure belong to the *as*-triazine-3,5-dione series. Table IV lists the members of this class which we have prepared. They were made by the method of Bailey (9) which involves the cyclization of an ester of α-semicarbazido-α,α-dialkylacetic acid. It is of interest to note that when 2-thiosemicarbazido-2-methylbutyronitrile (IX) was treated with fuming hydrochloric acid a 30% yield of the corresponding thiotriazinedione (X) was obtained directly.



IX X

A preliminary general screening by the pharmacology department showed that these compounds have a low order of activity.

Acknowledgment. The authors express their appreciation to Mr. Louis Brancone and his co-workers for the microanalyses, to Mr. W. L. McEwen and his associates for the preparation of some of the intermediates, and to Dr. R. W. Cunningham and Dr. B. K. Harned and their associates for the pharmacological evaluation of the compounds described.

EXPERIMENTAL

5,5-Mono- and di-substituted 2,3,6-piperazinetriones. The five members of this group (Table I) were made by the following general procedure: equimolecular amounts of ethyl oxalate and the required amino acid amide were heated to reflux in ethanol and a solution of slightly more than one equivalent of sodium methoxide in ethanol was added during 15–20 minutes. Refluxing was then continued for an additional 20 minutes. The sodium salts of the products separated during this period or upon cooling. The solids were filtered and added with stirring to the calculated amounts of dilute hydrochloric acid. The triones were filtered and recrystallized from water. In the case of 5-isobutyl-2,3,6-piperazinetrione which was found to be insoluble in the common solvents, the crude material was dissolved in one equivalent of dilute alkali and the solution was filtered and quickly neutralized with hydrochloric acid. With the exception of the isobutyl derivative, the yields ranged from 60–70%. The isobutyl derivative was isolated in about a 4% yield and was accompanied by oily substances possessing a strong caproic acid-like stench.

The triones are characterized by the extreme ease with which they are hydrolyzed in aqueous alkali. In the early runs the crude sodium salts of the triones which had precipitated during the reaction were first dissolved in water and then neutralized. This procedure led to erratic results and poor yields of triones. Strong acidification of these solutions (*p*H 1 or below) gave good yields of the oxalamidoacid amides. When a solution of 5-benzyl-2,3,6-piperazinetrione in one molar-equivalent of 0.2 *M* sodium hydroxide was allowed to stand at 25° for one hour, the trione was completely hydrolyzed. The hydrolysis products from 5-benzyl-2,3,6-piperazinetrione and from 5,5-dimethyl-2,3,6-piperazinetrione are described below:

α-Oxalamido-β-phenylpropionamide was obtained in the form of white crystals after recrystallization from water; m.p. 169–171° (dec.); yield 36%.

Anal. Calc'd for $C_{11}H_{12}N_2O_4$: C, 56.0; H, 5.1; N, 11.9.
Found: C, 55.6; H, 5.2; N, 11.9.

α-Oxalamidoisobutyramide formed colorless crystals from water and melted at 211–212° (dec.); yield 60%.

Anal. Calc'd for $C_6H_{10}N_2O_4$: C, 41.3; H, 5.7; N, 16.1.
Found: C, 41.4; H, 6.0; N, 16.1.

Conversion of α-oxalamidoisobutyramide into 5,5-dimethyl-2,3,6-piperazinetrione. The aforementioned oxalamidoamide (1.9 g.) was esterified with ethereal diazomethane in methanol. The crude methyl ester was dissolved in 20 cc. of ethanol, the solution was heated to reflux, and a solution of 0.65 g. of sodium methoxide in 10 cc. of ethanol was added during ten minutes. The mixture was refluxed an additional two hours, cooled, and the solid was filtered, dissolved in water, and acidified to *p*H 4 to 4.5. On cooling in ice 0.3 g. (18%) of white crystals separated; m.p. 278–283° (dec.). No depression resulted on admixture with a sample of the trione prepared from the previously described general procedure.

5,5-Disubstituted-1-benzyloxybarbituric acids. Four derivatives (Table II) belonging to this series were made by the following general procedure: to a suspension of 0.09 mole of N-benzyloxyurea (5) in 400 cc. of dry toluene was added 0.086 mole of disubstituted malonyl chloride.[1] This mixture was refluxed until the evolution of hydrogen chloride ceased (about one hour), and then was evaporated to dryness *in vacuo*. The oils that remained usually solidified and were recrystallized from 50% ethyl alcohol. The benzyloxy derivatives give a negative ferric chloride test.

5,5-Disubstituted-1-hydroxybarbituric acids. The 5,5-disubstituted-1-benzyloxybarbituric acids were hydrogenolyzed to the corresponding 1-hydroxy derivatives with atmospheric hydrogen and platinum oxide in ethanol (Table II). After filtration of the catalyst the ethanolic filtrates were evaporated to dryness *in vacuo*. The products generally solidified on standing and were recrystallized from water. The hydroxy derivatives give a wine-red color with alcoholic ferric chloride.

α,α-Disubstituted semicarbazidoacetonitriles (Table III). To a mixture of 0.78 mole of the required semicarbazone in 280 cc. of 100% hydrocyanic acid was added 1 cc. of concentrated hydrochloric acid followed by 70 cc. of water. The suspension was stirred at 20° for four hours. During this period all but a few grams of the semicarbazone dissolved. The solution was then stored at 20° overnight and evaporated to dryness *in vacuo* below 25°. The crude products were sufficiently pure for use in the next step.

2-Semicarbazido-2-methylbutyramide hydrochloride. A solution of 5 g. (0.032 mole) of 2-semicarbazido-2-methylbutyronitrile in 60 cc. of dry ethanol was saturated with hydrogen chloride at 0°. This mixture was stored at 20–25° for six days. The solid that crystallized was filtered and dried *in vacuo*; yield, 4.5 g. (67%); m.p. 190–193°. For analysis, a sample was recrystallized from methanol-ether; m.p. 191–193° (dec.).

Anal. Calc'd for $C_6H_{15}ClN_4O_2$: C, 34.2; H, 7.1; Cl, 16.9; N, 26.6.
Found: C, 34.3; H, 7.1; Cl, 16.9; N, 26.4.

2-Semicarbazido-2-isobutyramide.[2] A suspension of 10 g. (0.07 mole) of semicarbazidoisobutyronitrile in 60 cc. of dry ethanol was saturated with hydrogen chloride at 0°. At first a clear solution resulted, followed by a separation of a solid (nitrile hydrochloride). Upon refluxing the mixture for one hour a clear solution was obtained, whereupon the hydrochloride of the product began to crystallize. The mixture was cooled and the solid filtered; yield, 8 g. (58%); m.p. 194–196°. Neutralization of a concentrated aqueous solution of the hydrochloride with ammonia gave the free base; m.p., 196–200° (dec.). After one recrystallization from water the m.p. was 199–202° (dec.).

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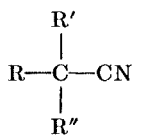
[1] The malonyl chlorides were prepared from the malonic acids with phosphorus pentachloride and purified by vacuum distillation.

[2] Thiele and Stange (6) prepared this compound by a different procedure and give 205–206° (dec.) as their m.p.

TABLE III

TRISUBSTITUTED ACETONITRILES



R	R′	R″	M.P., °C.	RECRYSTALLIZATION SOLVENT	EMPIRICAL FORMULA	ANALYSES						YIELD, %
						Calc'd			Found			
						C	H	N	C	H	N	
CH_3—	CH_3—	$NH_2CONHNH$—	141–143	Ether-methanol	$C_5H_{10}N_4O$ (6)							90
CH_3—	C_2H_5—	$NH_2CONHNH$—	120–122	Ether-methanol	$C_6H_{12}N_4O$	46.1	7.7	35.9	46.3	8.0	35.6	90
C_2H_5—	C_2H_5—	$NH_2CONHNH$—	124–126	Ether-methanol	$C_7H_{14}N_4O$ (7)							90
CH_3—	C_2H_5—	$NH_2CSNHNH$—	133–135	Benzene	$C_6H_{12}N_4S$	41.8	7.0	32.6	41.9	7.1	32.3	77
CH_3—	$(CH_3)_2CH$—	$NH_2CONHNH$—	126–127	Ether-methanol	$C_7H_{14}N_4O$	49.4	8.2	32.9	49.1	8.3	32.5	95

Anal. Calc'd for $C_5H_{12}N_4O_2$: C, 37.5; H, 7.5; N, 35.0.
Found: C, 37.8; H, 7.6; N, 34.6.

2-Semicarbazido-2-ethylbutyramide. 2-Semicarbazido-2-ethylbutyronitrile (7) (30 g., 0.17 mole) was dissolved in 200 cc. of fuming hydrochloric acid at 0°. The solution was stored at 20–25° for six days, filtered, and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in the minimum amount of cold water and ammonia was added to neutralization. The resulting solid was filtered and dried; yield, 15 g. (47%); m.p., 157–161°.

A sample of this material was recrystallized twice from *n*-propyl alcohol; m.p. 164–166°.

Anal. Calc'd for $C_7H_{16}N_4O_2$: C, 44.7; H, 8.5; N, 29.8.
Found: C, 44.9; H, 8.7; N, 29.8.

2-Semicarbazido-2-methylisovaleramide was prepared from the nitrile in the manner described for 2-semicarbazido-2-ethylbutyramide. The crude material was recrystallized from ethanol; m.p. 201–203°; yield, 32%.

Anal. Calc'd for $C_7H_{16}N_4O_2$: C, 44.7; H, 8.5; N, 29.8.
Found: 45.0; H, 8.8; N, 30.1.

Semicarbazidoisobutyric acid (*8*, *9*). A solution of 30 g. (0.153 mole) of semicarbazidoisobutyramide and 92 cc. (0.45 mole) of 5 *N* sodium hydroxide plus 400 cc. of water was refluxed until the evolution of ammonia ceased (three hours). The solution was cooled and 6 *N* hydrochloric acid was added until *p*H 3.2 was reached. The resulting solid was filtered, washed with ice-water, and dried; yield, 12 g. (50%); m.p. 183–186° (dec.).

A sample of this product was recrystallized from ethanol; m.p. 186–188° (dec.).

Anal. Calc'd for $C_5H_{11}N_3O_3$: C, 37.3; H, 6.8; N, 26.1.
Found: C, 37.7; H, 7.3; N, 25.7.

2-Semicarbazido-2-methylbutyric acid was prepared in the same manner; after one recrystallization from methanol the m.p. was 156–158°; yield, 72%.

Anal. Calc'd for $C_6H_{13}N_3O_3$: C, 41.1; H, 7.4; N, 24.0.
Found: C, 41.4; H, 7.5; N, 24.4.

2-Semicarbazido-2-ethylbutyric acid. A solution of 9 g. (0.047 mole) of the corresponding amide and 15 cc. (0.072 mole) of 5 *N* sodium hydroxide in 50 cc. of water was heated on a steam-bath for 75 minutes, and then acidified to *p*H 3.5 with 6 *N* hydrochloric acid. The solid that precipitated was filtered and air-dried; yield, 5.2 g. (59%); m.p. 130–131° (dec.).

After one recrystallization from water the m.p. was 130–132° (dec.).

Anal. Calc'd for $C_7H_{15}N_3O_3$: C, 44.5; H, 7.9; N, 22.2.
Found: C, 44.7; H, 7.9; N, 22.5.

2-Semicarbazido-2-methylisovaleric acid was prepared in the manner described for 2-semicarbazido-2-ethylbutyric acid. A sample recrystallized from water melted at 174–176° (dec.); yield, 82%.

Anal. Calc'd for $C_7H_{15}N_3O_3$: C, 44.5; H, 7.9; N, 22.2.
Found: C, 44.5; H, 7.9; N, 22.0.

Ethyl semicarbazidoisobutyrate. A suspension of 11 g. (0.062 mole) of semicarbazidoisobutyric acid in 250 cc. of ethanol saturated with hydrogen chloride was refluxed for five hours. The solution was evaporated to dryness *in vacuo* and the residue was dissolved in a small amount of ice-water. This solution was made neutral with ammonia and concentrated to about one-third the volume *in vacuo* and the ester was extracted with chloroform. The chloroform layer was dried over magnesium sulfate, then evaporated to dryness *in vacuo*. The residue was recrystallized from benzene; yield, 5.5 g. (47%); m.p. 98–100°.[3]

Methyl 2-semicarbazido-2-ethylbutyrate was made by the addition of an ethereal solution of diazomethane to a methanolic solution containing 2-semicarbazido-2-ethylbutyric acid. The product was recrystallized from ethyl acetate; m.p. 102–105°; yield, 85%.

Anal. Calc'd for $C_8H_{17}N_3O_3$: C, 47.3; H, 8.4; N, 20.7.
Found: C, 47.4; H, 8.4; N, 20.9.

Ethyl 2-semicarbazido-2-methylbutyrate was prepared by the method given above. The recrystallized product melted at 114–116°; yield, 46%.

Anal. Calc'd for $C_8H_{17}N_3O_3$: C, 47.3; H, 8.4; N, 20.7.
Found: C, 47.5; H, 8.6; N, 20.5.

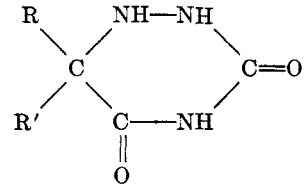
Methyl 2-semicarbazido-2-methylisovalerate was also prepared by esterification with diazomethane. The product was recrystallized from benzene; m.p. 114–116°; yield, 59%.

Anal. Calc'd for $C_8H_{17}N_3O_3$: C, 47.3; H, 8.4; N, 20.7.
Found: C, 47.6; H, 8.5; N, 21.0.

6,6-Dialkyldihydro-as-triazine-3,5-(2H,4H)diones. To a solution of 0.126 mole of the required semicarbazidoester in 210 cc. of dry methanol was added 0.14 mole of 95% sodium methoxide. The mixture was heated to boiling, then evaporated to dryness *in vacuo*. The residue was dissolved in a small amount of ice-water and the solution was acidified with 6 *N* hydrochloric acid. The resulting product was filtered and recrystallized from ethanol. The data are summarized in Table IV.

TABLE IV

5,5-DISUBSTITUTED TRIAZINE DIONES



R	R′	M.P., °C.	EMPIRICAL FORMULA	YIELD, %	ANALYSES					
					Calc'd			Found		
					C	H	N	C	H	N
CH_3—	CH_3—	228–230	$C_5H_9N_3O_2$ (9)	44						
CH_3—	C_2H_5—	218–220	$C_6H_{11}N_3O_2$	50	45.9	7.1	26.7	45.9	7.2	26.6
C_2H_5—	C_2H_5—	215–217	$C_7H_{13}N_3O_2$	81	49.1	7.6	24.6	49.4	7.5	24.4
CH_3—	$(CH_3)_2CH$—	196–199	$C_7H_{13}N_3O_2$	75	49.1	7.6	24.6	49.4	7.8	24.4

6-Ethyl-6-methyl-3-thiodihydro-as-triazine-3,5-(2H,4H)dione. A solution of 195 g. (1.13 moles) of 2-thiosemicarbazido-2-methylbutyronitrile in 1300 cc. of fuming hydrochloric acid was stored at 20–25° for nine days. It was then evaporated *in vacuo* to one-third its volume. The solid that separated was filtered, washed with water then dried on a steam-bath; yield, 36.5 g.; m.p. 174–176°. Evaporation of the filtrate to dryness followed by washing the residue with water gave 20 g. more of product (28% over-all yield). Recrystallization of the product from water gave m.p. 176–177°.

Anal. Calc'd for $C_6H_{13}N_3OS$: C, 41.6; H, 6.4; N, 24.3; S, 18.5.
Found: C, 41.8; H, 6.6; N, 24.3; S, 18.2.

SUMMARY

The synthesis of a number of compounds structurally related to the barbituric acids has been described.

PEARL RIVER, NEW YORK

[3] Bailey (9) reports m.p. 97° for this compound.

REFERENCES

(1) BORNWATER, *Rec. trav. chim.*, **36**, 250 (1917).
(2) BERGMANN AND MIEKELEY, *Ann.*, **458**, 40 (1927).
(3) BERGMANN AND ENSSLIN, *Hoppe-Seyler's Z. physiol. Chem.*, **174**, 76 (1928).
(4) CLARKE AND FRANCIS, *J. Chem. Soc.*, **99**, 319 (1911).
(5) BEHREND AND LEUCHS, *Ann.*, **257**, 203 (1890).
(6) THIELE AND STANGE, *Ann.*, **283**, 1 (1894).
(7) BERGER, *J. prakt. Chem.*, **152**, 267 (1938).
(8) THIELE AND BAILEY, *Ann.*, **303**, 75 (1898).
(9) BAILEY, *Am. Chem. J.*, **28**, 387 (1902).