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REACTIONS OF BISAMIDES. V. SYNTHESIS OF DERIVATIVES OF β-ARYL-β-AMINO ACIDS

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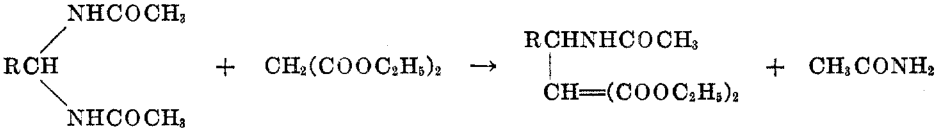
Free β-aryl-β-aminopropionic acids have been obtained hitherto in the following ways:

(a) by Rodionow's method, applying the Knoevenagel reaction (1–5); (b) by the addition of hydroxylamine to cinnamic acids (11); (c) by the hydrogenation of β-keto acids in the presence of platinum and palladium as catalysts in an alcoholic solution of ammonia (12); (d) from arylhydramide and malonic acid (2, 13); (e) by heating cinnamic acid and ammonia at 100° in sealed tubes using stannic chloride as a condensing agent (14); (f) by addition of ammonia on arylidenemalonic acids or their esters (15).

According to Rodionow, in the Knoevenagel reaction the oxamines are formed first, which then react with malonic acid giving β-aryl-β-aminoethane-α,α-dicarboxylic acids. By action of mineral acids and heat, these acids decompose with loss of carbon dioxide, yielding β-aryl-β-aminopropionic acids. The arylidenemonocarboxylic acids are obtained with loss of carbon dioxide and ammonia, as illustrated by the equations:

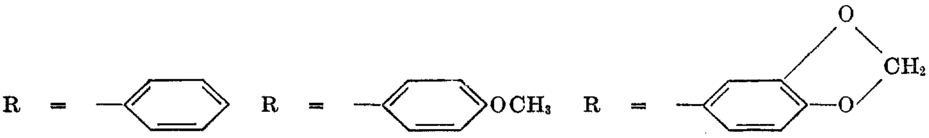
$$\begin{array}{l}\mathrm{RCHO + NH_3 \rightarrow RCH(OH)NH_2}\\ \mathrm{RCH(OH)NH_2 + CH_2(COOH)_2 \rightarrow RCH(NH_2)CH{=}(COOH)_2}\\ \mathrm{RCH(NH_2)CH{=}(COOH)_2 \rightarrow RCH(NH_2)CH_2COOH}\\ \mathrm{RCH(NH_2)CH{=}(COOH)_2 \rightarrow RCH{=}CHCOOH}\end{array}$$

In our previous studies on the reactions of bisamides, we found that bisamides react readily with compounds possessing an active methylene group. In the present work we have investigated the reactions of bisamides with diethyl malonate and have found that the same reactions occur as with ethyl nitroacetate (6), nitromethane (7), and acetoacetic ester (8), *i.e.* in these reactions the diethyl esters of β-aryl-β-acylamino-ethane-α,α-dicarboxylic acids (I) are formed according to the following scheme:

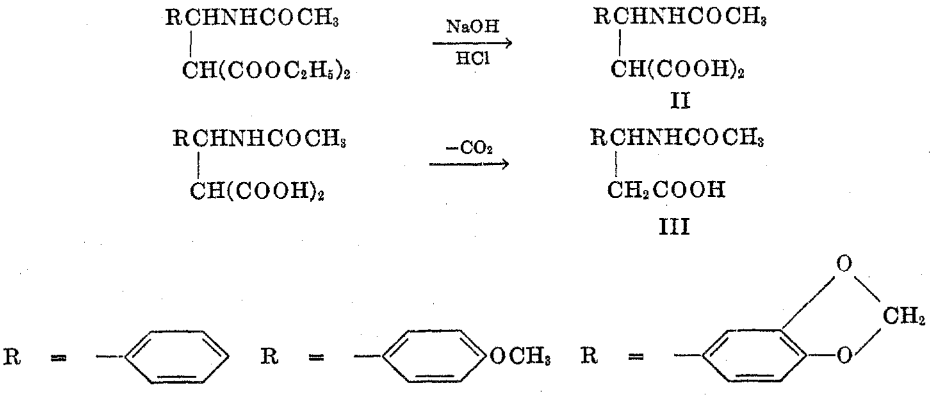


$$\mathrm{RCH}\begin{array}{l}\diagup\mathrm{NHCOCH_3}\\ \diagdown\mathrm{NHCOCH_3}\end{array} + \mathrm{CH_2(COOC_2H_5)_2} \rightarrow \begin{array}{l}\mathrm{RCHNHCOCH_3}\\ \quad|\\ \mathrm{CH{=}(COOC_2H_5)_2}\end{array} + \mathrm{CH_3CONH_2}$$

I



By partial saponification, these esters yield the free acylamino dicarboxylic acids (II), which, when heated above the melting point, yield, with evolution of carbon dioxide, the β-acylamino-monocarboxylic acids (III).



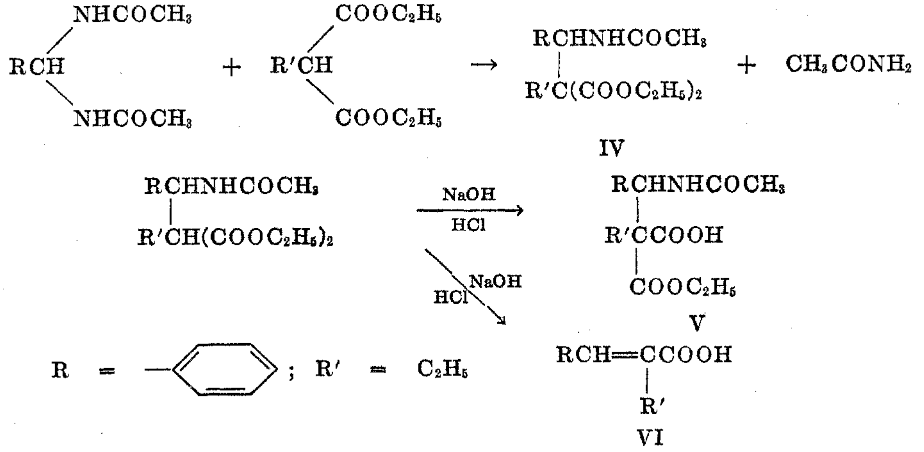
$$\begin{matrix}\mathrm{RCHNHCOCH_3}\\ |\\ \mathrm{CH(COOC_2H_5)_2}\end{matrix} \xrightarrow[\mathrm{HCl}]{\mathrm{NaOH}} \begin{matrix}\mathrm{RCHNHCOCH_3}\\ |\\ \mathrm{CH(COOH)_2}\\ \text{II}\end{matrix}$$

$$\begin{matrix}\mathrm{RCHNHCOCH_3}\\ |\\ \mathrm{CH(COOH)_2}\end{matrix} \xrightarrow{-\mathrm{CO_2}} \begin{matrix}\mathrm{RCHNHCOCH_3}\\ |\\ \mathrm{CH_2COOH}\\ \text{III}\end{matrix}$$

Contrary to Rodionow and others, Goldstein (9) and Boehm (10) are of the opinion that by saponification of the diethyl esters of β-aryl-β-amino-ethane-α,α-dicarboxylic acids, it is not possible to isolate the corresponding dicarboxylic acids, because of their instability and the easy loss of carbon dioxide, *i.e.*, that by the condensation of arylaldehydes ammonia and malonic acid, β-aryl-β-aminoethane-α,α-dicarboxylic acids are not obtained, but only the acid ammonium-salts of the arylidene malonic acids (10).

We have found, however, that the acylamino derivatives of the dicarboxylic acids are very stable compounds, which decompose only when heated above their melting point, yielding the corresponding acylamino-monocarboxylic acids, with loss of carbon dioxide.

It has also been established that diethyl ethylmalonate reacts in the same way as diethyl malonate, with the only difference that upon partial saponification of the diester, only one ester group is removed (contrary to the assumption of Rodionow, *et al.*) while upon total saponification by means of alkali, α-alkylcinnamic acid is obtained (VI):

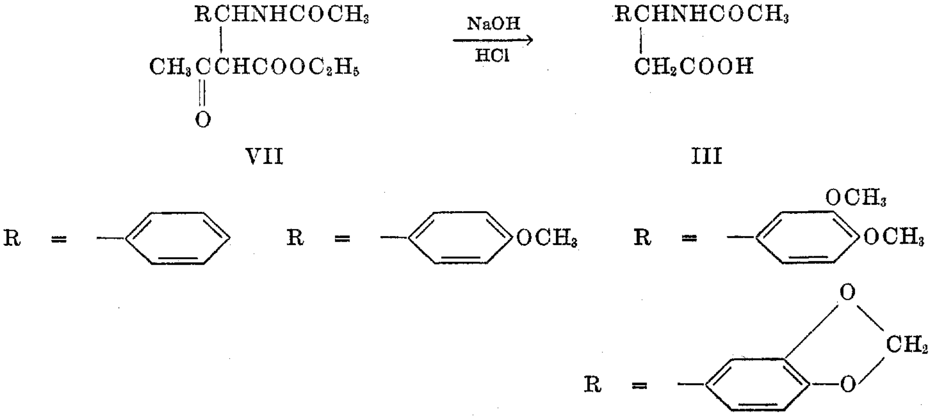


$$\mathrm{RCH}\begin{matrix}\diagup\mathrm{NHCOCH_3}\\ \diagdown\mathrm{NHCOCH_3}\end{matrix} + \mathrm{R'CH}\begin{matrix}\diagup\mathrm{COOC_2H_5}\\ \diagdown\mathrm{COOC_2H_5}\end{matrix} \rightarrow \begin{matrix}\mathrm{RCHNHCOCH_3}\\ |\\ \mathrm{R'C(COOC_2H_5)_2}\\ \text{IV}\end{matrix} + \mathrm{CH_3CONH_2}$$

$$\begin{matrix}\mathrm{RCHNHCOCH_3}\\ |\\ \mathrm{R'CH(COOC_2H_5)_2}\end{matrix} \xrightarrow[\mathrm{HCl}]{\mathrm{NaOH}} \begin{matrix}\mathrm{RCHNHCOCH_3}\\ |\\ \mathrm{R'CCOOH}\\ |\\ \mathrm{COOC_2H_5}\\ \text{V}\end{matrix}$$

$$\xrightarrow[\mathrm{HCl}]{\mathrm{NaOH}} \begin{matrix}\mathrm{RCH{=}CCOOH}\\ |\\ \mathrm{R'}\\ \text{VI}\end{matrix} \qquad \mathrm{R'} = \mathrm{C_2H_5}$$

We have also obtained the β-aryl-β-acylaminopropionic acids, in quantitative yields, by partial saponification of α-carbethoxy-β-aryl-β-acylaminoethyl methyl ketones (VII), prepared by the action of acetoacetic ester on bisamides (8):



$$\underset{\text{VII}}{\begin{array}{l}\text{RCHNHCOCH}_3\\ \quad|\\ \text{CH}_3\overset{\|}{\text{C}}\text{CHCOOC}_2\text{H}_5\\ \quad \text{O}\end{array}} \xrightarrow[\text{HCl}]{\text{NaOH}} \underset{\text{III}}{\begin{array}{l}\text{RCHNHCOCH}_3\\ |\\ \text{CH}_2\text{COOH}\end{array}}$$

Our attempts to obtain the corresponding ketones by partial saponification, *i.e.* by ketonic hydrolysis, of the α-carbethoxy-β-aryl-β-acylaminoethyl methyl ketones were unsuccessful; in the presence of alkali of various concentrations and at low temperatures the β-aryl-β-acylamino-propionic acids are always obtained in quantitative yields, while on heating, the above mentioned ketones are decomposed.

EXPERIMENTAL

The melting points are uncorrected.

1. Diethyl ester of β-phenyl-β-acetylaminoethane-α,α-dicarboxylic acid (I, R = C_6H_5). *A. Prepared by the condensation of benzylidenebisacetamide with diethyl malonate in acetic anhydride.* Benzylidenebisacetamide (10.3 g., 0.05 mole), 8 g. (0.05 mole) of diethyl malonate and 25 cc. of acetic anhydride are heated in a flask equipped with an air condenser for 3 hours in an oil-bath at 150–155°. Prolonged heating leads to benzylidene diethyl malonate, *e.g.*, after heating for 9 hours the yield falls to 11%. The acetic anhydride is removed *in vacuo* (14 mm.) and to the remaining viscous mass 100 cc. of water is added with stirring, causing white crystals to separate. The precipitate is filtered and washed with cold water and a little ether. The crude product weighs 8.9 g., m.p. 83°. From the ether used for washing another 0.7 g. is obtained. The total yield is 9.5 g. (62.1%) of crude product. After recrystallization from 50% ethyl alcohol the compound has the constant melting point 85°. The crystals are readily soluble in alcohol and acetone, sparingly soluble in ether, and insoluble in water.

B. Prepared by direct heating of benzylidenebisacetamide and diethyl malonate. Benzylidenebisacetamide (10.3 g., 0.05 mole) and 24 g. (0.15 mole) of diethyl malonate are mixed and heated for 3 hours in an oil-bath at 180°. After the reaction mixture has cooled, the unreacted bisamide and the separated acetamide are filtered, and the excess of diethyl malonate is removed *in vacuo* (14 mm.). After several days the remaining syrup begins to crystallize. The crystals are washed with a little ether and after several crystallizations from 50% alcohol, 1.7 g. of the pure product is obtained (yield 11.1%). The melting point of the mixture of the products obtained according to *A* and *B* does not show any depression.

Anal. Calc'd for $C_{16}H_{21}NO_5$: C, 62.54; H, 6.84; N, 4.56.
Found: C, 62.71; H, 7.11; N, 4.67.

2. β-Phenyl-β-acetylaminopropionic acid (III, R = C_6H_5). *A. Prepared from the diethyl ester of β-phenyl-α-acetylamino-ethane-α,α-dicarboxylic acid.* The ester (5 g.) and 40 cc. of a 10% aqueous solution of sodium hydroxide are allowed to stand at room temperature for 24 hours. The solution is neutralized with 10% hydrochloric acid using Congo Red as an indicator, and the water is evaporated *in vacuo.* The remaining solid product is extracted several times with a little absolute ethyl alcohol. The dicarboxylic acid thus obtained is an amorphous hygroscopic compound, readily soluble in alcohol, insoluble in ether, melting at 75°. By heating above its melting point it loses carbon dioxide, solidifies, and melts then at 150–164°. The molecular weight, determined by titration, was 265 (Calc'd 251). The complete transformation of the dicarboxylic acid into the monocarboxylic is achieved by heating first at 75°, and then for 3 hours at 115–120°, until it solidifies completely. The β-phenyl-β-acetylaminopropionic acid obtained in this way is recrystallized from water and has the constant melting point of 164°. Yield, 3.2 g. (97%, based on the diester).

B. Prepared from α-carbethoxy-β-acetylaminophenylethyl methyl ketone (VII, R = C_6H_5). The ketone (5 g.) obtained from benzylidenebisacetamide and acetoacetic ester (8) and 40 cc. of a 10% sodium hydroxide solution are mixed. After standing for 3 days the solution is neutralized with 10% hydrochloric acid. After half an hour the white crystalline product is filtered and washed with water. There is obtained 3.5 g. (93.7%) of the crude product, m.p. 159–161°. After several crystallizations from water it has the constant m.p. 164–165°. The mixture melting point of this product with the material obtained according to *2 A* is not depressed. Posner has obtained this compound by acylation of β-phenyl-β-aminopropionic acid; m.p. 161–162° (16).

Anal. Calc'd for $C_{11}H_{13}NO_3$: C, 63.77; H, 6.28; N, 6.77.
Found: C, 63.95; H, 6.40; N, 6.99.

3. Diethyl ester of β-(4-methoxyphenyl)-β-acetylaminoethane α,α-dicarboxylic acid (I, R = $C_6H_4OCH_3$). Anisylidenebisacetamide (12 g., 0.05 mole), 8 g. (0.05 mole) of diethyl malonate, and 50 cc. of acetic anhydride are treated according to the procedure *1 A*, yielding 7.6 g. (44.5%) of crude product which is recrystallized from 80 cc. of 50% alcohol until the melting point is unchanged (m.p. 95°).

Anal. Calc'd for $C_{17}H_{23}NO_6$: C, 60.56; H, 6.82; N, 4.18.
Found: C, 60.49; H, 7.01; N, 4.32.

4. β-(4-Methoxyphenyl)-β-acetylaminopropionic acid (III, R = $C_6H_4OCH_3$). *A.* The ester (5 g.) is saponified according to *2 A.* The melting point of the dicarboxylic acid is 82–84°. By prolonged heating above its melting point β-(4-methoxyphenyl)-β-acetylaminopropionic acid is formed, m.p. 171–173° (yield quantitative).

B. Prepared from α-carbethoxy-β-acetylamino-β-(4-methoxyphenyl)ethyl methyl ketone (VII, R = $C_6H_4OCH_3$). The ketone (5 g.) obtained from anisylidenebisacetamide is saponified according to *2 B.* The product obtained by recrystallization from water melts at 174–175°. There is no depression in melting point when this acid is mixed with the product obtained in *4 A.*

Anal. Calc'd for $C_{12}H_{15}NO_4$: N, 5.91. Found: N, 6.05.

5. Diethyl ester of β-(3,4-methylenedioxyphenyl)-β-acetaminoethane-α, α-dicarboxylic acid (III, R = $C_6H_3O_2CH_2$). Piperylidenebisacetamide (12.5 g., 0.05 mole), 8 g. (0.05 mole) of diethyl malonate, and 25 cc. of acetic anhydride are treated according to *1 A.* The red-colored crude product, m.p. 95°, is dissolved in a little warm acetone and precipitated with ether. The colorless crystals thus obtained are recrystallized from 50% alcohol until the melting point is unchanged. The yield is 9.25 g. or 52.6%.

Anal. Calc'd for $C_{17}H_{21}NO_7$: C, 58.11; H, 5.98; N, 4.00.
Found: C, 57.90; H, 6.04; N, 4.35.

6. β-(3,4-Methylenedioxyphenyl)-β-acetylaminopropionic acid (III, R = $C_6H_3O_2CH_2$). *A. Prepared from the diethyl ester of β-(3,4-methylenedioxyphenyl)-β-acetylaminoethane-α,α-dicarboxylic acid.* The ester obtained according to *5* (5 g.) is saponified and treated as described in *2 A.* The dicarboxylic acid thus obtained melts at 84–86°. On longer heating it loses carbon dioxide and is transformed quantitatively into the monocarboxylic acid which, recrystallized from water, gives white crystals, melting point 103–105°.

B. Prepared from α-carbethoxy-β-acetylamino-β-(3,4-methylenedioxyphenyl)ethyl methyl ketone (VII, R = $C_6H_3O_2CH_2$). The ketone (5 g.) obtained from the corresponding bisamide and acetoacetic ester is saponified as described in *2 B*. The crude acid is recrystallized from water, m.p. 104–105°. The yield is 3.5 g. or 89.7%. The mixture melting point of this product with the material obtained according to *6 A* does not show any depression.

Anal. Calc'd for $C_{12}H_{13}NO_5$: N, 5.58. Found: N, 5.72.

7. β-(3,4-Dimethoxyphenyl)-β-acetylaminopropionic acid [III, R = $C_6H_3(OCH_3)_2$]. The ketone (5 g.) obtained from the corresponding bisamide and acetoacetic acid (8) is saponified as described in *2 B*. There is obtained 3.4 g. (yield 85.8%) of β-(3,4-dimethoxyphenyl)-β-acetylaminopropionic acid, m.p. 164–165°.

Anal. Calc'd for $C_{13}H_{17}NO_5$: N, 5.24. Found: N, 5.32.

8. Monoethylester of β-phenyl-β-acetylamino-α-ethylethane α,α-dicarboxylic acid (V, R = C_6H_5; R′ = C_2H_5). Benzylidenebisacetamide (10.3 g., 0.05 mole), 9.4 g. (0.05 mole) of diethyl ethylmalonate, and 25 cc. of acetic anhydride are heated for 5 hours at 150–155°. The acetic anhydride is evaporated *in vacuo* and the excess ethyl diethyl malonate is removed by steam-distillation. The remaining oil is extracted with ether, dried over sodium sulphate, and the ether removed by distillation. The syrupy product (12.8 g.) thus obtained is the crude diethyl ester of β-phenyl-β-acetylamino-α-ethylethane-α,α-dicarboxylic acid (IV). It is not further purified, but is partially saponified. The crude ester is dissolved in 100 cc. of alcohol, and to this solution 60 cc. of a 10% sodium hydroxide solution is added. After standing for 3 days at room temperature, the solution is neutralized with 10% hydrochloric acid, and the alcohol is removed *in vacuo*. On cooling, white crystals separate, which are filtered, washed with cold water and a little ether, and recrystallized from 96% alcohol. The yield is 2.4 g. or 20.5% (based on the crude diethyl ester) of the pure monoethyl ester of β-phenyl-β-acetylamino-α-ethylethane-α,α-dicarboxylic acid, melting at 184°.

Anal. Calc'd for $C_{16}H_{21}NO_5$: C, 62.54; H, 6.84; N, 4.56.
Found: C, 62.59; H, 7.03; N, 4.77.

The molecular weight is determined by titration in alcoholic solution. Calc'd: 307; Found: 308.

9. α-Ethylcinnamic acid (VI, R′ = C_2H_5). The monoethyl ester of β-phenyl-β-acetylamino-α-ethylethane-α,α-dicarboxylic acid (3 g.) is dissolved in 50 cc. of 10% sodium hydroxide solution. Half of this solution is heated to boiling for 2 hours and on cooling is acidified with hydrochloric acid. The separated white crystals (yield 98%) of α-ethylcinnamic acid melt at 114–115°, in agreement with Posner (17). The remaining 25 cc. of the above solution is allowed to stand at room temperature for 60 days. On acidification with hydrochloric acid α-ethylcinnamic acid separates quantitatively; melting point 114–115°. The molecular weight determined by titration is 170. Calc'd, 176.

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SUMMARY

1. Arylidenebisamides react readily with diethyl malonate yielding diethyl esters of β-aryl-β-acylaminoethane-α,α-dicarboxylic acids. By partial saponification of these esters the corresponding dicarboxylic acids are obtained, which are converted into β-aryl-β-acylaminopropionic acids when heated above their melting points.

2. The products obtained by the reaction of arylidenebisamides with substituted malonic esters yield, by partial saponification, the monoesters of the corresponding dicarboxylic acids. The free acids cannot be isolated because on saponification α-substituted cinnamic acids are formed.

3. Partial saponification of the products obtained by condensing arylidenebisamides with acetoacetic ester, *i.e.* of α-carbethoxy-β-acylamino-β-aryl-ethyl methyl ketones (8) occurs exclusively in the direction of the β-aryl-β-acylamino propionic acids.

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REFERENCES

(1) KNOEVENAGEL, *Ber.*, **31**, 2596 (1898).
(2) RODIONOW AND MALEVINSKAJA, *Ber.*, **59**, 2952 (1926).
(3) RODIONOW AND FEDOROVA, *Ber.*, **60**, 804 (1927).
(4) RODIONOW AND POSTOVSKAJA, *J. Am. Chem. Soc.*, **51**, 841 (1929).
(5) RODIONOW, *J. Am. Chem. Soc.*, **51**, 847 (1929).
(6) STEFANOVIĆ AND BOJANOVIĆ, *J. Org. Chem.*, **17**, 816 (1952).
(7) STEFANOVIĆ, BOJANOVIĆ, AND SIROTANOVIĆ, *J. Org. Chem.*, **17**, 1110 (1952).
(8) STEFANOVIĆ AND STEFANOVIĆ, *J. Org. Chem.*, **17**, 1114 (1952).
(9) GOLDSTEIN, *Ber.*, **28**, 1450 (1895); *Ber.*, **29**, 813 (1896).
(10) BOEHM, *Chem. Zentr.*, **I**, 676 (1930); BOEHM AND GROHNWALD **II**, 1339 (1936).
(11) POSNER, *Ber.*, **36**, 4305 (1903); *Ber.*, **38**, 2316 (1905); *Ann.*, **389**, 1 (1912).
(12) KNOOP AND OESTERLIN, *Chem. Zentr.*, **I**, 1157 (1926).
(13) JOHNSON AND LIVAK, *J. Am. Chem. Soc.*, **58**, 299 (1936).
(14) ENKVIST, *Chem. Abstr.*, **41**, 4103 (1947).
(15) SCUDI, *J. Am. Chem. Soc.*, **57**, 1279 (1935).
(16) POSNER, *Ber.*, **38**, 2322 (1905).
(17) POSNER, *J. prakt. Chem.*, **82**, 436 (1910).