[Communication from the Chemical Institute of the Serbian Academy of Sciences
and the Chemical Institute of the Faculty of Sciences in
Belgrade (Yugoslavia)]

REACTIONS OF BISAMIDES. I. SYNTHESIS OF DERIVATIVES OF α-NITRO-β-AMINO ACIDS

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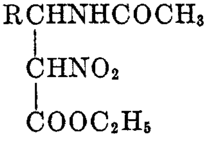
Received December 18, 1951

When benzaldehyde, ethyl nitroacetate, and acetamide or ammonium acetate are allowed to react in the presence of acetic anhydride, a compound of m.p. 140–141° is formed in yields up to 63%. Its molecular formula is $C_{13}H_{16}N_2O_5$, indicating that it is formed from equimolecular amounts of benzaldehyde, acetamide, and ethyl nitroacetate by loss of one molecule of water.

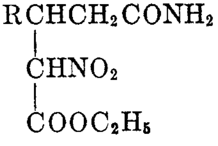
The same reaction occurs when using, instead of benzaldehyde, other aromatic aldehydes, such as veratraldehyde, acetylvanillin, piperonal, *o*-nitrobenzaldehyde and others.

Structural formulas I and II can be proposed for the products obtained in this way:



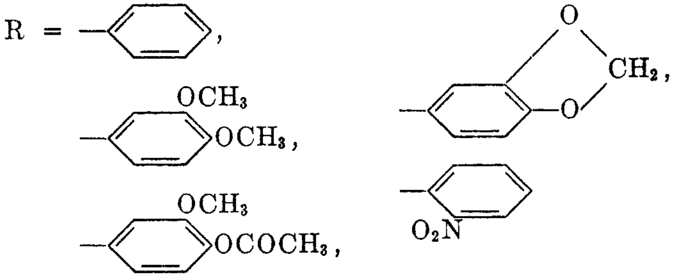
$$\begin{array}{l} RCHNHCOCH_3 \\ \;\;| \\ \;\;CHNO_2 \\ \;\;| \\ \;\;COOC_2H_5 \end{array}$$

I



$$\begin{array}{l} RCHCH_2CONH_2 \\ \;\;| \\ \;\;CHNO_2 \\ \;\;| \\ \;\;COOC_2H_5 \end{array}$$

II



When heating the isolated products with an aqueous solution of alkali (20% KOH), we obtained ammonia as the first product, while the solution itself had a faint smell of the particular aldehyde used for the synthesis (benzaldehyde for R = C_6H_5). When the alkaline solutions are acidified, hydrogen cyanide and acetic acid as well as the acids corresponding to the aldehydes used in the reaction separate in considerable amounts (benzoic acid for R = C_6H_5 in yields of approx. 74% and more).

The liberation of ammonia in this degradation is no indication for the structure, since compounds of type I as well as of type II should on saponification yield ammonia in any case. In the first case (I) we should obtain β-amino acids,

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[1] This communication is the subject of the dissertation for the degree of Doctor of Philosophy of Miss Jelena Bojanović at the Chemical Institute of the Serbian Academy of Sciences.

which, when heated, lose ammonia easily (as β-phenylalanine) (1); in the second case (II) ammonia is formed from the amide group.

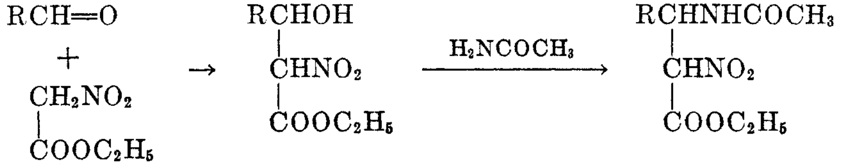
The presence of the secondary nitro group was established by its reduction[2] as well as by the behavior of these substances towards alkali hydroxides. Like other esters of α- and β-primary and secondary aliphatic nitrocarboxylic acids, these compounds dissolve in alkalis, giving yellow solutions, though they themselves and in alcohol solution are colorless. By action of mineral acids the solution decolorizes and the unchanged compounds are recovered. It is likely that the hydrogen cyanide originates from the secondary nitro group as well, similar to the decomposition of nitroacetic acid to methazonic acid which further decomposes yielding carbon dioxide, hydrocyanic acid, ammonia, nitric acid, and hydroxylamine (2, 3).

The relatively easy formation of the corresponding acids, or rather aldehydes, by this degradation, is best explained if we suppose that the compounds synthetized have the structure I. On saponification, the salts of the *aci*-form are obtained first, and then the saponification of the ester group occurs yielding the salts of the derivatives of the nitroacetic acid. Further saponification of the amide group results in α-nitro-β-amino derivatives of hydrocinnamic acids. Finally, ammonia is eliminated, which is followed by the oxidation to the corresponding acids.

On the basis of the degradation products obtained, we assume that the compounds synthesized have the structural formula I, *i.e.*, they are the derivatives of α-nitro-β-amino acids.

Their formation can be explained in the following four ways:

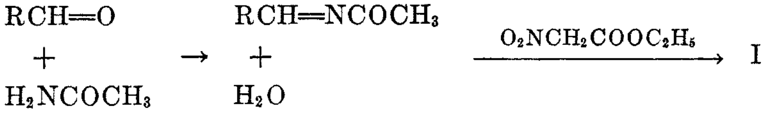
(a) The aldehyde reacts with nitroacetic acid ester giving the addition product III, which then condenses with acetamide to yield I.



$$\begin{array}{c} RCH{=}O \\ + \\ CH_2NO_2 \\ | \\ COOC_2H_5 \end{array} \rightarrow \begin{array}{c} RCHOH \\ | \\ CHNO_2 \\ | \\ COOC_2H_5 \end{array} \xrightarrow{H_2NCOCH_3} \begin{array}{c} RCHNHCOCH_3 \\ | \\ CHNO_2 \\ | \\ COOC_2H_5 \end{array}$$

III I

(b) The aldehyde reacts first with acetamide giving the acetimino derivative IV (4), to which nitroacetic acid ester is then added giving I.



$$\begin{array}{c} RCH{=}O \\ + \\ H_2NCOCH_3 \end{array} \rightarrow \begin{array}{c} RCH{=}NCOCH_3 \\ + \\ H_2O \end{array} \xrightarrow{O_2NCH_2COOC_2H_5} I$$

IV

(c) The aldehyde reacts with acetamide yielding the addition product V, which then condenses with ethyl nitroacetate to yield I.

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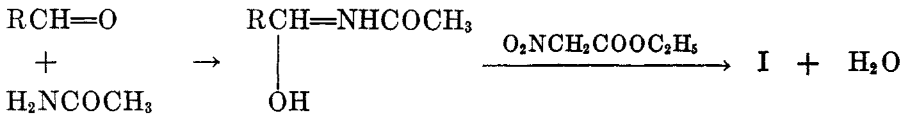
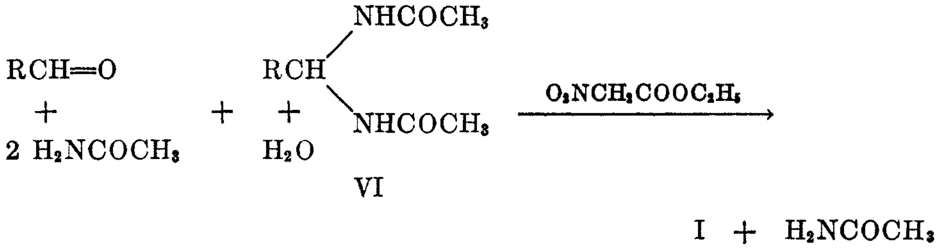
[2] These reductions will be reported in further publications.



$$\mathrm{RCH{=}O} + \mathrm{H_2NCOCH_3} \rightarrow \mathrm{RCH(OH){=}NHCOCH_3} \xrightarrow{\mathrm{O_2NCH_2COOC_2H_5}} \mathrm{I} + \mathrm{H_2O}$$

V

(d) Two molecules of acetamide condense with the aldehyde to yield the bisamide VI, this being followed by an exchange of one acetamido group with the ethyl nitroacetate, giving again I.



$$\mathrm{RCH{=}O} + 2\,\mathrm{H_2NCOCH_3} \rightarrow \mathrm{RCH(NHCOCH_3)_2} + \mathrm{H_2O} \xrightarrow{\mathrm{O_2NCH_2COOC_2H_5}} \mathrm{I} + \mathrm{H_2NCOCH_3}$$

VI

Our attempts to obtain the compounds of formula III from aldehyde and ethyl nitroacetate in acetic anhydride in the absence of any other reagent were unsuccessful. The attempts to condense the aldehyde with acetamide in the presence of acetic anyhdride, in order to obtain the acetimino derivatives IV, were likewise unsuccessful. By condensing the above mentioned aldehydes with acetamide in the presence of acetic anhydride in order to prepare V, we have, invariably, obtained the corresponding bisamides VI in satisfactory yields.[3]

The formation of bisamides from aldehydes and amides in the presence of acetic anhydride suggested to us that the synthesis of the compounds of the type illustrated by formula I occurs only according to the scheme (d). To confirm this, we have prepared the corresponding bisamides VI and treated them with ethyl nitroacetate in the presence of acetic anhydride. The compounds obtained in this way were identical with the compounds obtained from the reaction mixture consisting of aldehyde, acetamide or ammonium acetate and ethyl nitroacetate, the only difference being that the yields with bisamides were as high as 85%, while those in the reaction of the mixture mentioned above did not exceed 63%.

The synthesis from bisamides proves that the products synthesized actually have structure I, and are, therefore, the derivatives of α-nitro-β-amino acids.

In this way we synthesized up to now the following members of this class of compounds: ethyl α-nitro-β-acetylamino-β-phenylpropionate, α-nitro-β-acetylamino-β-(3,4-methoxyphenyl)propionic acid, α-nitro-β-acetylamino-β-(3,4-methylenedioxyphenyl)propionic acid, α-nitro-β-acetylamino-β-(*o*-nitrophenyl)propi-

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[3] This method of preparing bisamides from amides and aldehydes with acetic anhydride has not been described in the literature. Bisamides have been obtained previously by direct heating of amide and aldehydes (4, 6, 9), or by heating amide and aldehyde with addition of hydrochloric acid (10), or by adding to this mixture acetic acid (8), or pyridine and piperidine (11), from nitriles (12, 13, 14) and finally from mercury acetamide and trithioformaldehyde (10).

onic acid, and α-nitro-β-acetylamino-β-(3-methoxy-4-acetoxyphenyl)propionic acid.

The substances are crystalline, colorless solids (the nitro derivative has a light green color). Their melting points range from 132° to 141° (decomposition). They dissolve easily in alcohol and acetone, with great difficulty in ether and water. With alkalis they give colored solutions (salts of the *aci*-form) from which they can be regenerated by adding mineral acids.

To our knowledge, the class of α-nitro-β-amino acids, as well as their derivatives, has not been described so far. We are at present extending the studies of these compounds, both in the aliphatic and the aromatic series.

Little is known about the reactivity of bisamides. It is mentioned in the literature that they react easily with dilute mineral acids, giving back the initial components, *i.e.* the aldehydes and amides (5). Heated with alkalis, they remain unchanged (5). By heating derivatives of bisformamide, triarylamine, formyldiarylamine, diarylamine, and formylmonoarylamine are obtained (15, 16). With hypochloric acid N-dichloro and N-monochloro derivatives are obtained (9). Benzylidenediformamide heated with benzaldehyde gives tetraphenylpyrazine (7).

We found that bisamides are very reactive substances. They react not only with ethyl nitroacetate, but also with other compounds possessing active hydrogen atoms, such as malonic esters, alkylmalonic esters, acetoacetic esters, cyanoacetic esters, acetylene, and others; this will be the subject of further communications.

Both syntheses described, either starting with bisamides or by heating a mixture of aldehyde and acetamide (or ammonium acetate), can be used for preparative purposes.

EXPERIMENTAL

The melting points are uncorrected.

1. *α-Nitro-β-acetylamino-β-phenylpropionic acid ethyl ester* (I, R = C_6H_5). *A. Prepared from benzaldehyde, ammonium acetate, and ethyl nitroacetate.* Freshly distilled acetic anhydride (20.4 g., $\frac{1}{5}$ mole) is mixed, in a 100-cc. flask equipped with an air-condenser and calcium chloride tube, with 5.3 g. ($\frac{1}{25}$ mole) of ethyl nitroacetate, prepared by the Bouveault and Wahl method (17), and 21.2 g. ($\frac{1}{5}$ mole) of freshly distilled benzaldehyde. To this solution 3.1 g. ($\frac{1}{25}$ mole) of ammonium acetate is added which causes some warming of the reaction mixture and the solution turns faint yellow. The mixture is heated for 7 hours on a water-bath. In some experiments in the beginning a crystalline mass is formed which, however, disappears on further heating. After the reaction mixture is cooled, it is poured into 500 cc. of cold water and the mixture is allowed to stand for 24 hours, in order to hydrolyze the excess anhydride. During this time the separated oil first starts to crystallize. The liquid is decanted and the crystalline mass is washed with a little ether and filtered. The crude product weighs 7.08 g. (63%) and melts at 139°. After crystallization from 90% ethyl alcohol, colorless, hexagonal plates of m.p. 140.5–141° (dec.) are obtained.

B. Prepared from benzaldehyde, ethyl nitroacetate, and acetamide. The nitro ester (5.3 g., $\frac{1}{25}$ mole), 21.2 g. ($\frac{1}{5}$ mole) of benzaldehyde, 20.4 g. ($\frac{1}{5}$ mole) of acetic anhydride, and 4.7 g. ($\frac{1}{25}$ mole) of acetamide are mixed. The mixture does not warm up as under *A*. It is heated for 7 hours on a water-bath and after cooling poured into water. The crystals are filtered and washed with ether. The yield is 6.92 g. of crude product (61%), m.p. 139–140°. Recrystallized from 90% ethyl alcohol it melts at 140.5–141°. The melting point of the mixture of this product with the product described under *A* does not show any depression.

C. Prepared from benzylidene-bisacetamide. Ethyl nitroacetate (5.3 g., $\frac{1}{25}$ mole) and 7.7 g. ($\frac{1}{25}$ mole) of benzylidene-bisacetamide are introduced into 10.2 g. ($\frac{1}{10}$ mole) of acetic acid anhydride and heated for 7 hours on water-bath. The cooled mass is poured into cold water and crystals separate immediately. The precipitate is filtered and washed with ether. The crude product weighs 9.52 g. (yield 85%) and melts at 139.5°. Recrystallized from 90% ethyl alcohol it melts at 140–141°. The melting point of this product mixed with the product *A* does not show any depression.

Anal. Calc'd for $C_{13}H_{16}N_2O_5$: C, 55.69; H, 5.76; N, 9.99.
Found: C, 55.77; H, 5.87; N, 10.11.

2. *Ethyl α-nitro-β-acetylamino-β-(3,4-methoxyphenyl)propionate* [I, R = $C_6H_3(OCH_3)_2$]. *A. Prepared from veratraldehyde, ammonium acetate, and ethyl nitroacetate.* The nitro ester, (5.3 g., $\frac{1}{25}$ mole) and 6.2 g. ($\frac{1}{25}$ mole) of veratraldehyde (18) are introduced into 20.4 g. ($\frac{1}{5}$ mole) of acetic anhydride and to this mixture 3.1 g. ($\frac{1}{25}$ mole) of ammonium acetate is added. The solution warms up spontaneously and turns dark red. It is heated for 7 hours on a water-bath. The cooled solution is poured into water and allowed to stand for 24 hours. The liquid is decanted and the crystalline mass is filtered and washed with ether. There is obtained 5.52 g. of crude product (yield 41%), m.p. 133–135°. The crude product is dissolved in alcohol and ether is added until a slight turbidity is produced, and then it is left to crystallize. White crystal aggregates of ball form and of radial structure, m.p. 138° (dec.), are formed.

B. Prepared from 3,4-methoxybenzylidene-bisacetamide. The nitro ester, (5.3 g., $\frac{1}{25}$ mole), 10.7 g. ($\frac{1}{25}$ mole) of 3,4-methoxybenzylidene-bisacetamide, and 20.4 g. ($\frac{1}{5}$ mole) of acetic anhydride are heated for 7 hours on a water-bath. The solution is poured into water and the crystalline mass is separated by decantation and washed with ether. There is obtained 5.07 g. of crude product (yield 44%), m.p. 137°. When recrystallized several times from alcohol-ether, it melts at 138°. The melting point of this product mixed with the product under *A* does not show any depression.

Anal. Calc'd for $C_{15}H_{20}N_2O_7$: C, 52.92; H, 5.93; N, 8.23.
Found: C, 52.98; H, 6.04; N, 8.33.

3. *Ethyl α-nitro-β-acetylamino-β-(3-methoxy-4-acetoxyphenyl)propionate* (I, R = $C_6H_3OCH_3OCOCH_3$). *A. Prepared from acetylvanillin, ammonium acetate, and ethyl nitroacetate.* The nitro ester, (5.3 g., $\frac{1}{25}$ mole), 7.8 g. ($\frac{1}{25}$ mole) of acetylvanillin [obtained by the method of Pschorr (19)], 20.4 g. ($\frac{1}{5}$ mole) of acetic anhydride, and 3.1 g. ($\frac{1}{25}$ mole) of ammonium acetate are heated on a water-bath for 7 hours. The yellow oily liquid is poured into 500 cc. of cold water and allowed to stand for 24 hours; then the liquid is decanted and the crystals filtered and washed with ether. There is obtained 5.94 g. of crude product (yield 40%), m.p. 128°. By recrystallization from 96% ethyl alcohol the compound is obtained in colorless, hexagonal crystals of m.p. 132° (dec.).

B. Prepared from 3-methoxy-4-acetoxybenzylidene-bisacetamide and ethyl nitroacetate. The nitro ester, (5.3 g., $\frac{1}{25}$ mole), 11.8 g. ($\frac{1}{25}$ mole) of 3-methoxy-4-acetoxybenzylidene-bisacetamide, and 20.4 g. of acetic anhydride are heated on a water bath for 7 hours, and worked up as above under *A*. There is obtained 6.35 g. of crude product (yield 43%), m.p. 129.5°. Recrystallized from 96% ethyl alcohol, it had m.p. 132°. No depression in melting point when mixed with the product under *A*.

Anal. Calc'd for $C_{16}H_{20}N_2O_8$: C, 52.16; H, 5.48; N, 7.60.
Found: C, 51.79; H, 5.52; N, 7.72.

4. *Ethyl α-nitro-β-acetylamino-β-(3,4-methylendioxyphenyl)propionate* [I, R = $C_6H_3(O_2CH_2)$]. *Prepared from piperonal, ammonium acetate, and ethyl nitroacetate.* The nitro ester (5.3 g., $\frac{1}{25}$ mole), 6.2 g. ($\frac{1}{25}$ mole) of piperonal, 20.4 g. ($\frac{1}{5}$ mole) of acetic anhydride, and 3.1 g. ($\frac{1}{25}$ mole) of ammonium acetate are heated for 8½ hours on a water-bath. The cooled mass is poured into water, and after some time the separated oily liquid starts

to crystallize. The supernatant solution is decanted and the crystalline mass washed with ether. There is obtained 6.38 g. of crude substance (yield 49%), m.p. 123°. Recrystallization from ethyl alcohol yields colorless, hexagonal crystals in the form of rosettes, of m.p. 129° (dec.).

Anal. Calc'd for $C_{14}H_{16}N_2O_7$: N, 8.63. Found: N, 8.82.

5. *Ethyl α-nitro-β-acetylamino-β-(o-nitrophenyl)propionate* (I, R = $C_6H_4NO_2$). *Prepared from o-nitrobenzaldehyde, ammonium acetate, and ethyl nitroacetate.* The nitro ester, (5.3 g., $\frac{1}{25}$ mole) and 6 g. ($\frac{1}{25}$ mole) of *o*-nitrobenzaldehyde are introduced into 20.4 g. ($\frac{1}{5}$ mole) of acetic anhydride. To this mixture 3.1 g. ($\frac{1}{25}$ mole) of ammonium acetate is added and the mixture is heated for 7 hours on a water-bath. The cooled mass is poured into cold water. After it is allowed to stand for 24 hours, the crystalline mass is separated from water, washed with ether, and filtered. There is obtained 1.6 g. of crude product (yield 12%), m.p. 135–136°. Recrystallization from ethyl alcohol gives hexagonal tablet crystals of protracted form and clear green color, m.p. 135–136° (dec.).

Anal. Calc'd for $C_{13}H_{15}N_3O_7$: N, 12.92. Found: N, 12.70.

6. *Degradation of ethyl α-nitro-β-acetylamino-β-phenylpropionate by alkaline hydroxide.* The ester (2.5 g.) is refluxed with 15 cc. of 20% potassium hydroxide until ammonia ceases to evolve. The liquid is then cooled and neutralized with 20% hydrochloric acid to Congo Red, while the hydrogen cyanide evolved is carried into a sodium hydroxide solution by an air current. The precipitated benzoic acid is filtered and washed with cold water. There is obtained 0.8 g. of benzoic acid (yield 74%), m.p. 121°. In the filtrate the acetic acid is identified in the usual way.

7. *3-Methoxy-4-acetoxybenzylidene-bisacetamide.*[4] Acetylvanillin (7.8 g., $\frac{1}{25}$ mole), 4.7 g. ($\frac{1}{12.5}$ mole) of acetamide, and 10.2 g. ($\frac{1}{10}$ mole) of acetic anhydride are heated for 7 hours on a water-bath. After cooling, 600 cc. of ether are added. The resulting crystals are filtered and washed with ether. There is obtained 4.03 g. of crude product (yield 34%), m.p. 211°. Recrystallized from 96% ethyl alcohol, this gave white, fibrous crystals, m.p. 212°.

Anal. Calc'd for $C_{14}H_{18}N_2O_5$: N, 9.52. Found: N, 9.70.

8. *3,4-Methoxybenzylidene-bisacetamide.*[4] Veratraldehyde (6.6 g., $\frac{1}{25}$ mole), 4.7 g. ($\frac{1}{12.5}$ mole) of acetamide, and 10.2 g. ($\frac{1}{10}$ mole) of acetic anhydride are heated on a water-bath for 10 hours. To the cooled mixture 600 cc. of ether is added. The crystals are filtered and washed with ether. There is obtained 5.43 g. of crude substance (yield 52%), m.p. 231–232°. Recrystallization from 96% ethyl alcohol gives white fibrous crystals of m.p. 233.5°.

Anal. Calc'd for $C_{13}H_{18}N_2O_4$: N, 10.52. Found: N, 10.77.

Acknowledgment. The authors acknowledge the valuable assistance of Miss M. Pavičić of the Faculty of Sciences, Belgrade, who performed the microanalyses reported in this paper.

SUMMARY

1. By the reaction of a mixture of aromatic aldehydes, amides, and ethyl nitroacetate in acetic anhydride, or by the action of the nitro ester on bisamides in acetic anhydride, a new class of compounds is obtained, namely the derivatives of α-nitro-β-amino acids, in satisfactory yields.

2. When heating esters of α-nitro-β-acetylamino acids with solutions of alkali hydroxides, the following degradation products are formed: ammonia, acetic acid, hydrogen cyanide, and the acids corresponding to the aldehydes used for the synthesis.

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[4] These bisamides are new compounds.

3. Bisamides can be obtained in good yields by heating aldehydes with amides or ammonium salts of carboxylic acids in acetic anhydride.

4. Bisamides react readily with compounds possessing active hydrogen atoms.

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REFERENCES

(1) POSNER, *Ber.*, **38**, 2316, 2321 (1905).
(2) MEISTER, *Ber.*, **40**, 3435 (1907).
(3) HANTZSCH AND VOIGT, *Ber.*, **45**, 85 (1912).
(4) MEHRA AND PANDYA, *Chem. Abstr.*, **34**, 1981 (1940).
(5) ROTH, *Ann.*, **154**, 72 (1870).
(6) SCHUSTER, *Ann.*, **154**, 80 (1870).
(7) BÜLOW, *Ber.*, **26**, 1972 (1893).
(8) BEHAL AND CHOAY, *Ann. chim.*, [6] **27**, 321 (1892).
(9) CHATTAWAY AND SWINTON, *J. Chem. Soc.*, **101**, 1206 (1912).
(10) PULVERMACHER, *Ber.*, **25**, 304, 310 (1892).
(11) NOYES AND FORMAN, *J. Am. Chem. Soc.*, **55**, 3493 (1933).
(12) PANDYA AND COLLABORATORS, *Chem. Abstr.*, **32**, 7434 (1938); **36**, 6144 (1942); **37**, 2725 (1943); **39**, 4595 (1945); **41**, 3774 (1947); **33**, 8589 (1939); **34**, 1981 (1940); **36**, 1308 (1942).
(13) HEPP AND SPIESS, *Ber.*, **9**, 1424 (1876).
(14) HEPP, *Ber.*, **10**, 1649 (1877).
(15) LEUCKART, *Ber.*, **18**, 2341 (1885).
(16) POLLARD AND YOUNG, *J. Org. Chem.*, **16**, 661 (1951).
(17) BOUVEAULT AND WAHL, *Bull. soc. chim.*, [3] **31**, 847 (1904).
(18) VON KOSTANECKI AND TAMBOR, *Ber.*, **39**, 4022 (1906).
(19) PSCHORR AND SIMULEANU, *Ber.*, **32**, 3045 (1899).