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REACTIONS OF BISAMIDES. II. SYNTHESIS OF DERIVATIVES OF α -NITRO- β -AMINO HYDROCARBONS

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In a previous communication (1) we have reported that derivatives of α nitro- β -amino acids are obtained by reaction of bisamides with ethyl nitroacetate.

Pursuing further the studies on the reactivity of bisamides toward compounds possessing active hydrogen atoms, we have found that nitromethane reacted similar to ethyl nitroacetate, *i.e.*, that one amide group of the bisamide could be substituted by the nitromethane group. This reaction yields derivatives of the class of α -nitro- β -amino hydrocarbons (II) according to the following scheme:



In the cases and under the conditions which we have so far studied, ethyl nitroacetate is much more reactive than nitromethane. This is shown in the duration of the reaction and the yields of the compounds obtained by the reaction. Thus, for instance, by heating equimolecular quantities of benzylidenebisacetamide (I, $R = C_6 H_5$) and ethyl nitroacetate for 7 hours, the corresponding α -nitro- β amino acid (III, $R = C_6 H_5$) is obtained in yields up to 85%, while by heating the same bisamide for 34 hours with 16 times its weight of nitromethane, α -nitro- β acetylaminophenylethane (II, $R = C_{\rm f} H_{\rm b}$) is obtained in yields up to 32%(calculated after subtracting the regenerated bisamide). The lower yields are probably due not only to the lower reactivity of nitromethane but also to the fact that the compound formed decomposes on long heating in acetic anhydride, since our attempts to obtain the corresponding α -nitro- β -amino hydrocarbons from 3,4-dimethoxybenzylidene-, 4-methoxybenzylidene-, and 3,4-methylenedioxybenzylidene-bisacetamide and nitromethane (under the same conditions as with benzylidenebisacetamide) failed to give the expected results. Decomposition also occurred when pure α -nitro- β -acetylaminophenylethane was heated in acetic anhydride.

Since only benzylidenebisacetamide with nitromethane in the presence of acetic anhydride yielded the corresponding derivative of α -nitro- β -amino hydrocarbons, we have tried to obtain the others from the corresponding derivatives of the α -nitro- β -amino acids.

By partial saponification of these acids we have actually obtained the derivatives of α -nitro- β -amino hydrocarbons in very good yields (up to 96%).



Thus, by partial saponification we have obtained α -nitro- β -acetylamino- β -phenylethane (II, R = C₆H₅), α -nitro- β -acetylamino- β -(3,4-dimethoxyphenyl)ethane [II, R = C₆H₅(OCH₃)₂], and α -nitro- β -acetylamino- β -(3-methoxy-4-hydroxyphenyl)ethane [II, R = C₆H₃(OH)OCH₃].

The product obtained by the reaction between nitromethane and benzylidenebisacetamide proved to be identical with the product obtained by partial saponification of ethyl α -nitro- β -acetylamino- β -phenylpropionate.

Consequently, the best method for preparing these hydrocarbons consists in partial saponification of the α -nitro- β -acetylamino acids.

The hydrocarbons are solid, colorless substances which crystallize well. Heated above their melting point, they decompose. They are easily soluble in alcohol and acetone and with difficulty in ether and water. They dissolve in alkalis, giving yellow solutions (salts of *aci*-form), from which they are regenerated unchanged with mineral acids. When diluted sulphuric acid is added to a mixture of the alkaline solution and potassium nitrite, the solution turns red (salts of nitrole acids).

When heating the new compounds with aqueous solutions of alkali hydroxides, ammonia is evolved, and on acidifying these solutions with mineral acids, hydrogen cyanide, acetic acid, and acids corresponding to the aldehydes used for the synthesis of bisamides are formed (benzoic acid for $R = C_6H_5$).

Members of this class of compounds have been synthesized previously in different ways. Worrall (2), when studying the addition of amino and hydrazino bases to nitrostyrene, obtained α -nitro- β -arylaminoethanes, as illustrated by the equation:

By action of ammonia on nitrostyrene he obtained, however, α, α' -diphenyl- β, β' -dinitrodiethylamine, since ammonia reacts with two moles of nitrostyrene:

 $\begin{array}{cccc} 2 \ \mathrm{C_6H_5CH}{\longrightarrow} \mathrm{CHNO_2} &+ \ \mathrm{NH_3} & \rightarrow & \mathrm{C_6H_5CHCH_2NO_2} \\ & & & & & \\ & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & \\ & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & \\ & & & & & & \\ & & & & & & \\ & & &$

The same author (3) also obtained α -nitro- β -phenylamino- β -arylethanes as intermediaries in the synthesis of unsaturated nitro compounds by the Knoevenagel reaction (4), *i.e.*,



Our attempts to synthesize anyl derivatives of α -nitro- β -acetylamino hydrocarbons by the addition of acetamide to nitrostyrene gave negative results. Likewise, attempts to obtain the compounds mentioned by the action of the aldehyde in excess on the corresponding acetyl derivatives in the course of the synthesis of nitrostyrene were unsuccessful.

It is therefore evident that in our cases acetamide does not react in the same manner as described by Worrall for ammonia or amines.

EXPERIMENTAL

The melting points are uncorrected.

1. α -Nitro- β -acetylamino- β -phenylethane (II, $R = C_6H_{\bar{s}}$). A. Prepared from benzylidenebisacetamide and nitromethane: In a 100-cc. flask equipped with a reflux condenser 4.1 g. (1/50 mole) of benzylidenebisacetamide, 20 g. of nitromethane, and 20 g. of acetic anhydride are mixed. The mixture is heated on a water-bath until the bisamide completely dissolves in 12-24 hours. The mixture is cooled to 0° when the unreacted bisamide separates. It is filtered, and the filtrate is distilled in vacuo until about 4/5 of the acetic anhydride is removed at the lowest possible temperature. On cooling, about 0.3 g. more of bisamide separates. It is filtered, and the remaining acetic anhydride is removed entirely in vacuo. To the cooled, yellowish oil cold water is added (about 80 cc.), and the mixture is allowed to stand for 24 hours. The solidified mass is filtered and washed with water and ether, yielding 1.2 g. (32%) of crude product melting at 132° (in other experiments 20-32% of the crude product was obtained). Recrystallization from 96% ethyl alcohol yields a product of m.p. 138-140°.

B. Prepared from ethyl α -nitro- β -acetylamino- β -phenylpropionate: The ester (5 g.), prepared as described earlier (1), is dissolved in the cold in 40 cc. of 10% sodium hydroxide and allowed to stand for 68 hours at 0°. The cold solution is neutralized with 10% hydrochloric acid to pH 5 when a crystalline substance separates. The crystals are filtered and washed with a little cold water, yielding 3.8 g. (88%) of crude substance melting at 138°. After recrystallizations from 96% ethyl alcohol, colorless, crystalline needles melting at 138–140° are obtained. The mixture melting point with the starting material is 117°. The melting point of a mixture of the products obtained according to A and B does not show any depression.

Anal. Cale'd for C₁₀H₁₂N₂O₈: C, 57.67; H, 5.82; N, 13.45.

Found: C, 57.78; H, 5.93; N, 13.60.

2. α -Nitro- β -acetylamino- β -(3-methoxy-4-hydroxyphenyl)ethane [III, R = C₆H₈(OCH₈)OH]. Ethyl α -nitro- β -acetylamino-3-methoxy-4-acetyloxyphenylpropionate (5 g.) (1) is dissolved in 60 cc. of 10% sodium hydroxide with cooling and allowed to stand for 68 hours at 0°. After neutralization with 10% hydrochloric acid to about pH 5, the crystals separated are filtered and washed with water. The crude product weighs 2.82 g. (94.7%) and melts at 151–152°. Recrystallization from 96% ethyl alcohol gives colorless, hexagonal crystals of m.p. 154°.

Anal. Calc'd for C₁₁H₁₄N₂O₅: C, 51.95; H, 5.56; N 11.02.

Found: C, 52.06; H, 5.67; N, 11.02.

3. α -Nitro- β -acetylamino- β -(β , 4-dimethoxyphenyl)ethane [III, R = C₆H₈(OCH₈)₂]. Ethyl α -nitro- β -acetylamino- β -(β , 4-dimethoxyphenyl)propionate (5 g.) is dissolved in the cold in 60 cc. of 10% sodium hydroxide and allowed to stand for 24 hours at 0°. The alkaline solution is neutralized with 10% hydrochloric acid to pH 5. The separated crystals are filtered and washed with water, giving 3.36 g. (85%) of crude product melting at 127°. The crude product is then recrystallized from 96% ethyl alcohol with the addition of ether, giving colorless, fibrous crystals melting at 132°.

Anal. Cale'd for C12H16N2O5 (268.30): N, 10.44. Found: N, 10.42.

4. Degradation of α -nitro- β -acetylamino- β -phenylethane by acetic anhydride. One gram of pure product melting at 138–140° is heated with 10 g. of acetic anhydride for 12 hours on a water-bath. The acetic anhydride is removed *in vacuo*, and the solid residue is washed with ether. One-half gram (50%) of starting material melting at 138–140° is thus recovered. When this material is heated again with 10 g. of acetic anhydride for 12 hours on a water-bath and the acetic anhydride is removed *in vacuo*, 0.2 g. (40%) of the starting substance, m.p. 138– 140°, is recovered.

SUMMARY

1. Bisamides react with nitromethane in a similar manner as with ethyl nitroacetate, yielding derivatives of α -nitro- β -amino hydrocarbons.

2. The reactivity of nitromethane toward bisamides is lower than that of ethyl nitroacetate.

3. α -Nitro- β -amino hydrocarbons decompose on heating in acetic anhydride.

4. The derivatives of α -nitro- β -amino hydrocarbons can be obtained in good yields (up to 95%) by partial saponification of the corresponding α -nitro- β -acetylamino acid esters.

5. By heating α -nitro- β -acetylamino hydrocarbons with aqueous solutions of alkalis the following degradation products are obtained: hydrogen cyanide, ammonia, acetic acid, and the acids corresponding to the aldehydes used in the synthesis of the bisamides.

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REFERENCES

(1) STEFANOVIĆ AND BOJANOVIĆ, J. Org. Chem., 17, 816 (1952).

(2) WORRALL, J. Am. Chem. Soc., 49, 1598 (1927).

(3) WORRALL, J. Am. Chem. Soc., 56, 1556 (1934).

(4) KNOEVENAGEL AND WALTER, Ber., 37, 4503 (1904).