INDOLE DERIVATIVES

LVI. REACTION OF INDOLEALDEHYDE WITH

NITROACETIC ACID ESTER

L. Kh. Vinograd and N. N. Suvorov

It is shown that the reaction of indolealdehyde with nitroacetic acid esters leads to esters of 4-indolyl-3,5-dicarboxyisoxazoline N-oxide. 4-Indolyl-3,5-isoxazolinedicarboxylic acid N-oxide was obtained by hydrogenolysis of the dibenzyl ester.

The reaction of aldehydes with nitroacetic acid esters can be depicted by the scheme



Depending on the nature of the aldehyde and the conditions used, hydroxynitroesters III [1-3], unstable dinitroglutaric acid esters V [1,3], or isoxazoline N-oxides VI [3, 4] are obtained. Saponification of VI gives isoxazolecarboxylic acids VII (R' = H).

We were able to show that nitroacetic acid esters react with indoleal dehyde in the presence of sodium acetate in dimethyl formamide at 40-50°C.

The chief reaction product is isoxazoline N-oxide VI (R = Ind, R' = Me, Bz).* In addition, a small amount of nitroolefin IV (R = Ind, R' = Bz). Thin-layer chromatography made it possible to observe that the amount of this nitroolefin becomes appreciable only at the end of the process, when the formation of the isoxazoline is almost complete. Since the transformations described are difficult to conceive without the intermediate formation of nitroolefin IV, one has to assume that this extremely reactive product reacts rapidly, as soon as it forms, with nitroester II and does not build up to an appreciable concentration. It can be detected only when its reaction partner – nitroacetic acid ester – is used up. This assumption was previously expressed in [5], but the nitroolefin could not be detected.

1-Acetylindole-3-aldehyde was similarly converted to the corresponding isoxazoline N-oxide [VI (R = 1-acetyl-3-indolyl, R' = Bz)]. The same compound was obtained by treatment of nitroolefin IV (R = Ind, R' = Bz) with acetic anhydride and sodium acetate. Acetylation of IV with a mixture of acetic anhydride and pyridine proceeds without complications and gives nitroolefin IV (R = 1-acetyl-3-indolyl, R' = Bz). The conversion of IV to VI can be explained by assuming that the step I + II \rightleftharpoons IV is reversible. In this connection, one should note the observations of Umezawa and Zen [6], who indicated that nitroolefin IV (R = C₆H₅, R' = Et) is converted to an isoxazoline derivative. The nitroacetic acid ester here could only be formed from the corresponding nitroolefin.

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1505-1507, November, 1970. Original article submitted June 2, 1969.

© 1973 Consultants Bureau, a division of Plenum Publishing Corporation, 227 West 17th Street, New York, N. Y. 10011. All rights reserved. This article cannot be reproduced for any purpose whatsoever without permission of the publisher. A copy of this article is available from the publisher for \$15.00.

^{*}The following abbreviations are used in this paper: Me = methyl, Et = ethyl, Bz = benzyl, and Ind = 3-indolyl.

The PMR spectrum of VI (R = Ind, R' = Bz) contains two doublets at 5.4-5.6 ppm, characteristic for CH-CH systems. These signals disappear when the diester is converted to the diamide of acid VII, since ammonolysis is accompanied by cleavage of water and conversion of the isoxazoline N-oxide to an isoxazole.

The isoxazoline N-oxide nucleus is preserved during hydrogenolysis of dibenzyl ester VI (R = Ind, R' = Bz), and acid VI (R = Ind, R' = H) is formed. Attention is drawn to the rather high strength of this acid: a 5% aqueous solution has a pH of 1.5. The acid forms a crystalline adduct with two molecules of dioxane. Acids of the isoxazoline N-oxide series have not been obtained up to now since the usual methods of saponification of the esters of isoxazolinecarboxylic acid N-oxides are always accompanied by dehydration and give acids of the isoxazole series (VII).

Nitroolefin IV (R = Ind, R' = Bz), formed in the reaction, was isolated by chromatography on silica gel. Its structure was confirmed by synthesis via the method described for the corresponding methyl ester.

 $\begin{array}{ccc} C_2H_5OCH = & ccoor \\ I \\ VII \\ NO_2 \end{array} \begin{array}{ccc} + & ind CH = ccoor \\ I \\ I \\ V \\ I \\ NO_2 \end{array} \begin{array}{ccc} R = Me, Bz \\ I \\ V \\ NO_2 \end{array}$

EXPERIMENTAL

The PMR spectra were obtained with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. The IR spectra in mineral oil were obtained with a UR-10 spectrophotometer. Thin-layer chromatography was carried out on plates with a loose layer of aqueous (20%) silicic acid. A mixture of benzene and ether (50:1) was used for development. The substances were detected after spraying the plates with 10% phosphomolybdic acid in alcohol and subsequent heating at 110-120° for 15 min.

Benzyl Nitroacetate (II, R = Bz). This was obtained according to [7]. High-vacuum distillation was replaced by crystallization at -5° . The crystals were washed with a cold hexane-absolute alcohol mixture (9:1), dried in vacuo, and stored in a refrigerator. The product was obtained in 52% yield, based on nitromethane, and had mp 37°, R_f 0.75, ν_{max} 1755 (CO) and 1565 cm⁻¹ (NO₂).

Benzyl α-Nitro-β-ethoxyacrylate (VIII, R = Bz). This was obtained in 34.3% yield via the method in [8] and had mp 72-74° (from diisopropyl ether); ν_{max} 1720 (CO), 1650 (C=C), 1570 cm⁻¹ (NO₂); δ (CDCl₃): 1.37 (triplet, CH₃); 4.25 (quartet, CH₂CH₃); 5.22 (singlet, CH₂C₆H₅); 7.33 (broad singlet, C₆H₅); 7.55 ppm (singlet, CH=C).

Benzyl α-Nitro-β-aminoacrylate. A mixture of 1 g of VIII and 3 ml of concentrated ammonium hydroxide was stirred for 1 h, and the mixture was filtered to give 0.87 g (98%) of a product with mp 108.5-109.5° (from ethyl acetate). Found %: C 54.0; H 4.5; N 12.6. $C_{10}H_{10}N_2O_4$. Calculated %: C 54.0; H 4.5; N 12.6. ν_{max} 3400, 3225 (NH₂), 1710 (CO), 1660 (C=C), 1570 or 1585 cm⁻¹ (NO₂).

 $\frac{3,5-\text{Dicarboxy-4-(3-indolyl)isoxazoline N-Oxide Dibenzyl Ester (VI, R = Ind, R' = Bz).}{(0.01 \text{ mole}) \text{ of indolealdehyde } (R_f 0.07), 1.95 g (0.01 \text{ mole}) \text{ of benzyl nitroacetate, and 0.2 g of ammonium acetate was heated for 30 min at 180° in 10 ml of dimethylformamide. The mixture was cooled, diluted with water, and filtered to give 1.2 g (51.2%) of a product (colorless crystals that darken in light) with mp 153-154° (from alcohol) and R_f 0.38. Found %: C 68.7; H 4.6; N 5.9. C₂₇H₂₂N₂O₆. Calculated %: C 68.9; H 4.7; N 5.9. <math>\nu_{\text{max}}$ 3445 (NH), 1767, 1748 (CO), 1640 cm⁻¹ (C=N); δ (pyridine): 4.9 (doublet, CH₂C₆H₅); 5.2 (singlet, CH₂C₆H₅); 5.4-5.6 ppm (two doublets, CH-CH).

 $\frac{3,5-\text{Dicarboxy-4-}(3-\text{indolyl})\text{isoxazoline N-Oxide Dimethyl Ester (VI, R = Ind, R' = Me).} \text{This was obtained in 60.8\% yield in the same way that was used to obtain the dibenzyl ester (heating for 1 h at 80°) from methyl nitroacetate [9] and had mp 195-197° (from alcohol). Found %: C 56.7; H 4.5; N 8.8. C₁₅H₁₄N₂O₆. Calculated %: C 56.6; H 4.4; N 8.8. <math>\nu_{\text{max}}$ 3380 (NH), 1750 broad (CO), 1460 cm⁻¹ (C=N); δ (C₅D₅N): 3.42 (singlet, CH₃); 3.68 (singlet, CH₃); 5.45-5.69 ppm (two doublets, CH-CH).

<u>Benzyl α -Nitro- β (3-indolyl)acrylate (IV, R = Ind, R' = Bz).</u> A. A mixture of 11.7 g (0.1 mole) of indole and 23.5 g (0.1 mole) of benzyl α -nitro- β -ethoxyacrylate (VIII) was stirred; after 20 min a transparent red liquid formed and immediately began to crystallize. After washing with benzene and alcohol, 22.1 g (68.7%) of red crystals with mp 165° (from benzene) and R_f 0.48 were obtained. Found %: C 67.2; H 4.0; N 8.6. C₁₃H₁₄N₂O₄. Calculated %: C 67.1; H 4.4; N 8.7. ν_{max} 3240 (NH), 1710 (CO), 1600-1500 cm⁻¹ (NO₂).

B. The mother liquor from crystallization of 3,5-dicarboxy-4-(3-indolyl)isoxazoline N-oxide dibenzyl ester was evaporated and chromatographed with a column filled with silica gel. Evaporation of the benzene eluate gave 12 mg of red crystals that had the same melting point, R_f value, and IR spectrum as the sample obtained via method A.

Benzyl α-Nitro-β-(1-acetyl-3-indolyl)acrylate. Benzyl α-nitro-β-(3-indolyl)acrylate (1.6 g) was dissolved in 20 ml of acetic anhydride and 10 ml of pyridine. The next morning the solution was poured into ice water, and the resulting mixture was stirred for 3 h and filtered to give 1.37 g (76%) of lemon-yellow crystals with mp 143-145° (from ethyl acetate). Found %: C 66.1; H 4.5; N 7.5. $C_{20}H_{16}N_2O_5$. Calculated %: C 65.9; H 4.4; N 7.7. ν_{max} 1745, 1725 (CO), 1647 (C=C), 1555 or 1535 cm⁻¹ (NO₂); δ(CDCl₃): 2.62 (singlet, COCH₃); 5.35 (singlet, CH₂C₆H₅); 7.39 (broad singlet, C₆H₅); 7.35-8.45 (multiplet, 4H of the indole ring); 7.78 ppm (singlet, superimposition of indole >NH and >CH=C).

3,5-Dicarboxy-4-(1-acetyl-3-indolyl)isoxazoline N-Oxide Dibenzyl Ester. A. A solution of 0.935 g (0.005 mole) of N-acetylindolealdehyde, 2.34 g (0.012 mole) of benzyl nitroacetate, and 0.1 g of ammonium acetate in 7 ml of dimethylformamide was heated for 2 h at 50°, cooled, 20 ml of alcohol was added, and, after 24 h, 1.44 g (56.2%) of colorless crystals with mp 162-164° was filtered. Found %: C 67.8; H 4.7; N 5.6. $C_{29}H_{24}N_2O_7$. Calculated %: C 68.0; H 4.7; N 5.4. ν_{max} 1777, 1735, 1714 (CO), 1650 (C=N) cm⁻¹; δ (deuterated dimethylformamide): 2.61 (singlet, COCH₃); 5.0-5.3 (two doublets, CH-CH); 5.35 (singlet, CH₂C₆H₅); 7.0-8.4 ppm (multiplet, aromatic protons).

B. A mixture of 7 g of benzyl α -nitro- β -indolylacrylate, 10.5 g of anhydrous sodium acetate, and 50 ml of acetic anhydride was heated for 3 h at 103° and then poured into an ice-water mixture to give 2.2 g of light-brown crystals with mp 158-160° (from ethyl acetate) that do not depress the melting point of a sample obtained via method B (their IR spectra also coincided).

 $\frac{4-(3-\text{Indolyl})\text{isoxazole}-3,5-\text{dicarboxamide.}}{(1\text{ g})\text{ was added to 5 ml of 25\% ammonium hydroxide, and the resulting suspension was agitated periodically. After 7 days the mixture was filtered to give 0.27 g (61.2%) of colorless crystals with mp 260° (from aqueous formamide). Found %: C 57.7; H 4.0; N 20.3. C₁₃H₁₀N₄O₃. Calculated %: C 57.8; H 3.7; N 20.7. <math>\nu_{\text{max}}$ 3410, 3320, 3260, 3180 (NH, NH₂), 1685 (CO) cm⁻¹. δ (dimethylformamide): no signals from 3.7 to 6.8 ppm.

<u>3,5-Dicarboxy-4-(3-indolyl)isoxazoline N-Oxide (VI, R = Ind, R' = H).</u> A suspension of 0.68 g of 3,5dicarboxy-4-(3-indolyl)isoxazoline N-oxide dibenzyl ester in 30 ml of absolute alcohol was hydrogenated over 1 g of 5% Pd/C at 20° (760 mm). After 4 h, about 100 ml of hydrogen was absorbed, and the starting ester had dissolved. The catalyst was filtered, and the filtrate was evaporated. The residue was triturated with dioxane and washed with chloroform to give 0.66 g (97%) of colorless crystals of the oxonium salt with mp 105-106° (decomp.). Found %: C 53.9; H 5.8; N 5.9. C₁₃H₁₀N₂O₆ · 2C₄H₈O₂. Calculated %: C 54.1; H 5.6; N 6.0. ν_{max} 3415, 3375 (NH), 2500-3000 (broad) (COOH), 1740, 1710 (CO), 1630 (C=N), cm⁻¹; δ (CD₃OD): 3.62 (singlet, CH₂); 5.17-5.41 (two doublets, CH-CH); 6.85-7.65 ppm (multiplet, aromatic protons).

LITERATURE CITED

- 1. V. M. Rodionov and V. M. Belikov, Dokl. Akad. Nauk SSSR, <u>93</u>, 827 (1953); K. K. Babievskii, V. M. Belikov, and N. A. Tikhonova, Izv. AN SSSR, Otd. Khim. Nauk, 89 (1965).
- 2. S. Umezawa and S. Zen, Bull. Chem. Soc. Japan, 36, 1143 (1963).
- 3. A. Dornow and G. Wiehler, Ann., 578, 113 (1952).
- 4. S. Umezawa and S. Zen, Bull. Chem. Soc. Japan, <u>36</u>, 1150 (1963).
- 5. A. Dornow and A. Frese, Ann., <u>578</u>, 122 (1952).
- 6. S. Umezawa and S. Zen, Bull. Chem. Soc. Japan, <u>33</u>, 1016 (1963).
- 7. A. Taylor, British Patent No. 835,521; Chem. Abstr., <u>54</u>, 24,555d (1960).
- 8. A. Taylor, British Patent No. 842,797; Chem. Abstr., 55, 1533a (1961).
- 9. V. E. Matthews and D. G. Kubler, J. Org. Chem., 25, 266 (1960).