The Addition Reaction of Dinitrogen Trioxide with Cinnamyl Acetate

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A number of investigations[1-4] have been carried out into the reaction between dinitrogen trioxide and unsaturated compounds, and it is well known that the dimer of the nitro-nitroso compound is the main product in those reactions. In an earlier paper[5] from our laboratory, it was demonstrated, however, that not the nitro-nitroso compound but nitro-alcohol and nitro-olefin were formed in the reaction between methyl crotonate and dinitrogen trioxide. The present study was undertaken, firstly, to examine whether or not only the nitro-nitroso compound is obtained in the addition reaction of dinitrogen trioxide to cinnamyl acetate (I) and, secondly, to synthesize from the reaction products 2-amino-1-phenyl-1, 3-propanediol, which is an important intermediate for synthesizing chloramphenicol.

Fodor et al.[6] examined the reaction of dinitrogen trioxide with compound I according to the technique presented by Bruckner[3] and obtained the dimer of the nitro-nitroso compound, from which chloramphenicol could be derived. In the present study, however, through a close examination of this reaction under Bruckners condition, two reaction products were isolated; they are white and relatively stable crystals and unstable yellow oil. The crystalline substance was found, through its elemental analysis and through the fact that it becomes blue when dissolved in benzene, to be the dimer of the nitro-nitroso compound (IIa). Although the purification of the oily substance by vacuum distillation was unsuccessful, it was purified chromatographically by the use of silica gel as the adsorbent. We assigned the structure IIb to the second oily product on the basis of the elemental analysis, its infrared spectrum and Liebermann's nitroso reaction, which indicated the presence of -NO and/or -ONO groups. The infrared spectrum of the oil indicated the presence of both -ONO (1659 cm^{-1}) and $-NO_2$ groups (1561 and 1367 cm^{-1}).[7] Compound IIb gradually lost nitrous acid at room temperature, forming β-nitro cinnamyl acetate (III). When the benzene solution of IIb was passed through a alumina column or warmed with sodium acetate for one or two hours, compound III, was quantitatively obtained. For the purpose of synthesizing 2-amino-1-phenyl-1, 3-propanediol, it is recommended that the crude product be directly transformed into compound III without isolation.

The ratio of IIa to IIb formed by the addition of nitrogen trioxide to cinnamyl acetate was greatly influenced by the solvent used and by the other experimental conditions. Toluene was the best among the solvents tried (i. e. toluene, ether and cyclohexane) for minimizing the product, IIb. The IIa/IIb ratio decreased progressively when the solvent was changed in the following order: toluene—cyclohexane—ether. With 20 mol. of toluene to cinnamyl acetate, the main product was IIa. The decrease in the amount of toluene greatly affected the relative amounts of IIa and IIb formed. For example, the use of less than 10 mol. of toluene yielded IIb in a greater quantity than IIa. When the reaction temperature was raised higher than 0°C, the formation of IIb also increased.

Compound IIa and compound III obtained from IIb underwent substitution or addition reaction to yield, finally, 2-amino-1-phenyl-1, 3-propanediol. Figure 1 illustrates the entire process adopted in this research. When IIa was treated with sodium methylate at 0°C, the nitroso group of IIa was converted into the methoxy group and compound IV was obtained in a 76% yield.

As an analogous reaction of this type, it was found in our laboratory that 1-methoxy-2-nitro-1-phenylethane (XI) was obtained directly

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[1] H. Wieland, *Ber.*, **36**, 2558 (1903).

[2] H. Wieland, *Ann.*, **328**, 154 (1903); **329**, 239 (1903); **424**, 71 (1921).

[3] V. Bruckner, ibid., **518**, 226 (1935).

[4] V. Bruckner, G. Fodor, J. Kiss and J. Kovacs, *J. Chem. Soc.*, **1948**, 885; G. Fodor, J. Kiss and M. Szekerke, *J. Org. Chem.*, **15**, 227 (1950). The reaction between nitrogen oxide and unsaturated compounds was reviewed by J. L. Riebsomer, *Chem. Revs.*, **36**, 157 (1954).

[5] K. Yamagishi and Y. Ishibiki, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **81**, 971 (1960).

[6] G. Fodor, I. Toth, E. Kovacs and J. Kiss, *Izvest. Akad. Nauk., U. S. S. R.*, **441** (1955).

[7] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley & Sons, Inc., New York, N. Y. (1958), p. 298.

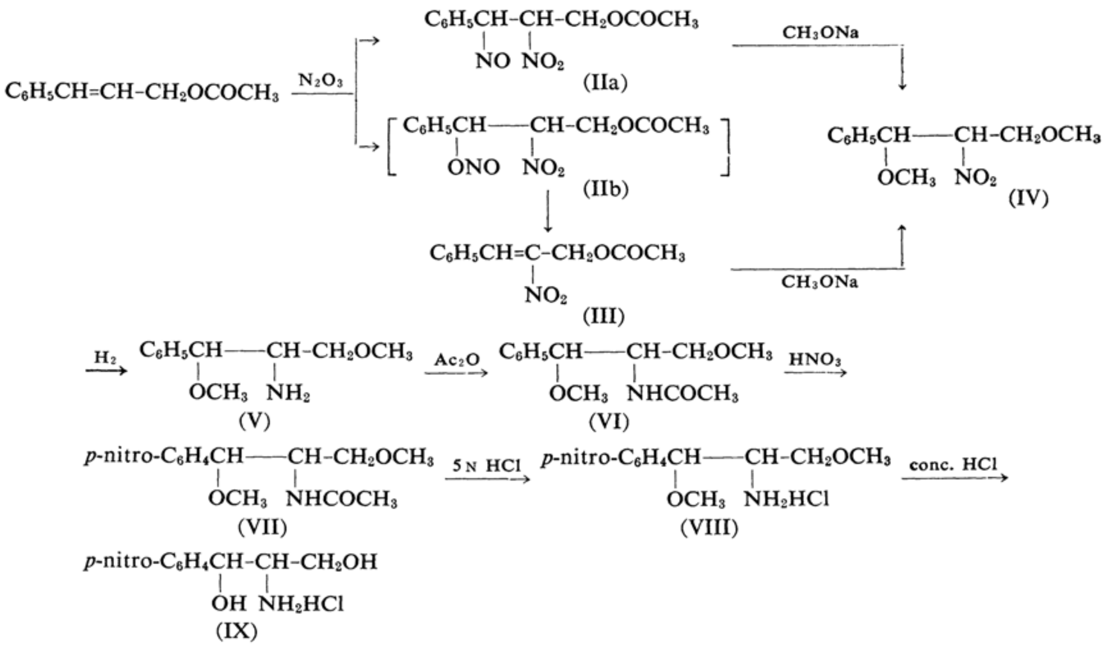
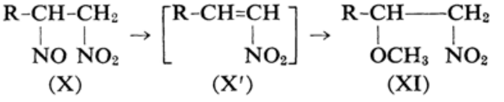


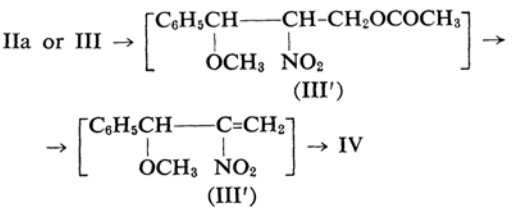
Fig. 1

in a good yield by the reaction of 1-nitroso-2-nitro-1-phenylethane (X) with sodium methylate. Meisenheimer[8] and Rosenmund[9] reported that ω-nitrostyrene (X′) reacted with sodium alcoholate to afford 1-alkoxy-2-nitro-1-phenylethane. Moreover, Wieland[1] described how compound X was transformed into compound X′ through treatment with sodium methylate. Therefore, it may be supposed that the reaction between X and sodium methylate would proceed via ω-nitrostyrene, as is described below (1):



$R=C_6H_5$ (1)

When sodium methylate was added to compound III, the same reaction product IV was obtained. A new finding in this reaction was that the acetyl group of compound IIa or III was transformed into the methoxy group. Probably, with one mole of sodium methylate, IIa or III may be changed into compound III′ which then may be transformed into compound III″ by losing acetic acid,[10] and finally compound IV may be formed with the excess sodium methylate.



Compound IV was reduced to V in the presence of a Raney nickel catalyst in methyl alcohol at 40°C under the pressure of 110 atm. of hydrogen. Glittering white crystals (VI) were obtained by the acetylation of V. After the introduction of the nitro group at the para position of the benzene ring by the known method,[11] VII (m. p. 109—110°C) was obtained. Compound VII seems to be *dl-erythro*-2-acetoamido-1, 3-dimethoxy-1-(*p*-nitrophenyl)-propane, because Gabor et al.[11] reported that the melting point of the threo form of VII was 129—130°C. Compound VII was hydrolyzed into compound VIII with 5 N hydrochloric acid; then, after the hydrolysis of VIII with concentrated hydrochloric acid, white crystals were obtained. The melting point of this end product was 209°C, which agreed with the melting point of *dl-erythro*-2-amino-1-(*p*-nitrophenyl)-1, 3-propanediol hydrochloride.[12] As has been described above (reaction 1), the nitroso group was converted into the methoxy group, probably via nitro-olefin (trans form) through the action of sodium methylate. Therefore, it seems likely that compound IIa

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[8] J. Meisenheimer and F. Heim, *Ber.*, **38**, 466 (1905).

[9] K. W. Rosenmund, ibid., **46**, 1034 (1913).

[10] G. D. Buckley and J. L. Charlich, *J. Chem. Soc.*, **1947**, 1473.

[11] V. Gabor, J. Kollonitsch and A. Hajos, *Acta Chim. Acad. Sci.*, **10**, 239 (1956).

[12] Sueo Tatsuoka (Takeda Pharmaceutical Industries Co.), Japanese Pat. 1524 (1952).

reacts with sodium methylate to afford IV via an intermediate, III. This is the reason why the erythro form was obtained in the reaction of IIa with sodium methylate.

Experimental[13]

3-Acetoxy-1-nitroso-2-nitro-1-phenylpropane (IIa). —To a mixture of 30 g. (0.17 mol.) of cinnamyl acetate (b. p. 102—103°C/0.2 mmHg, n_D^{25} 1.5391) in 430 ml. of toluene and 94 g. (1.4 mol.) of sodium nitrite in 100 ml. of water, 370 ml. of 20% sulfuric acid (0.85 mol.) was stirred in drop by drop at 0°C for 6—7 hr. The stirring was then continued for thirty minutes after the addition had been completed. The precipitate in the toluene layer was filtered and washed with cold water, and then with ether. A white powder of IIa, 21 g. (49%), was obtained; m. p. 116—117°C (decomp.) (lit.[6] 124°C).

Found: N, 11.01. Calcd. for $C_{11}H_{12}O_5N_2$: N, 11.11%.

3-Acetoxy-2-nitro-1-phenyl-1-propyl-nitrite (IIb). —The filtrate of the toluene layer, which is free from IIa, contained unreacted cinnamyl acetate and compound IIb. It was neutralized with a 5% sodium dicarbonate solution and dried over magnesium sulfate. By removing toluene under reduced pressure, 9 g. of a crude red oil was obtained. The crude oil was dissolved in anhydrous benzene, passed through a silica gel column, and eluted with benzene. First, the unreacted cinnamyl acetate (2.5 g.) was eluted, and then the second fraction was collected. When the solvent was removed, 5.4 g. of IIb was obtained as a pale yellow oil. The infrared spectrum showed bands at 1561, 1367 cm^{-1} (NO_2) and 1659 cm^{-1} (ONO).

Found: C, 49.55; H, 4.71; N, 10.22. Cacld. for $C_{11}H_{12}O_6N_2$: C, 49.25; H, 4.51; N, 10.45%.

When the reaction was carried out at 7—10°C, no IIa was obtained; the only reaction product was IIb (22 g.). When the reaction was carried out at 0°C, however, using 200 ml. of toluene and the other experimental conditions were not varied, 4.5 g. of IIa and 23 g. of IIb were obtained. When 450 ml. of ether was employed instead of toluene and the other experimental conditions were not varied, a small amount of IIa (1.8 g.) was obtained, while most of the reaction product was IIb (20 g.). When 450 ml. of cyclohexane was used as the solvent, 8 g. of IIa and 18 g. of IIb were formed from 30 g. of cinnamyl acetate.

Compound IIb, if desired, could be isolated as has been mentioned above. However, IIb was highly unstable. It is, therefore, recommended that, after neutralizing it with a sodium bicarbonate solution and removing the solvent, the crude product be directly transformed into compound III without the isolation of IIb.

β-Nitro Cinnamyl Acetate (III).—A mixture of 3 g. of the crude product of IIb and 1.5 g. of sodium acetate in 100 ml. of benzene was warmed at 60—80°C for 5 hr. When the mixture was poured into cold water, yellow needle crystals were formed. 1.8 g. of III was obtained; m. p. 81.5—82°C (recrystallized from alcohol and water (15 : 5)). Compound III was also obtained by passing the benzene solution of the crude product of IIb through an alumina column.

Found: C, 59.76; H, 4.95; N, 6.57. Calcd. for $C_{11}H_{11}O_4N$: C, 59.72; H, 5.01; N, 6.33%.

1-Nitroso-2-nitro-1-phenylethane (X).—To a mixture of 160 g. (1.53 mol.) of styrene in 900 ml. of ether and 570 g. (8.3 mol.) of sodium nitrite in 570 ml. of water, 1500 g. of 20% sulfuric acid was added drop by drop in the course of four or five hours at about 0°C. When the addition of sulfuric acid was complete, the precipitate present in the ether layer was filtered off and washed thoroughly with cold water in order to remove the inorganic salt; then it was washed with ether. One hundred and sixty-eight grams (61%) of X was obtained; m. p. 130°C (lit.[8] m. p. 129°C).

Found: N, 15.63. Calcd. for $C_8H_8O_3N_2$: N, 15.56%.

1-Methoxy-2-nitro-1-phenylethane (XI). — To a suspension of 9 g. (0.025 mol.) of compound X in 50 ml. of anhydrous methyl alcohol, sodium methylate prepared from 2.3 g. of sodium and 50 ml. of methyl alcohol was added with a rapid agitation at −5°C. The temperature immediately rose from −5°C to 7°C, and the reaction was completed within one or two minutes. A clear red solution was obtained. After it had been neutralized with carbon dioxide, the mixture was poured into a large amount of water and extracted with three 30-ml. portions of ether. The ether solution was dried over anhydrous magnesium sulfate, and the ether was removed. The nitro ether was distilled at 0.3 mmHg; b. p. 90—91°C (lit.[9] 140—141°C at 15 mmHg), n_D^{20} 1.5190. Yield: 4.9 g. (55%).

Found: C, 59.71; H, 6.11; N, 7.85. Calcd. for $C_9H_{11}O_3N$: C, 59.66; H, 6.08; N, 7.74%.

***dl-erythro*-1, 3-Dimethoxy-2-nitro-1-phenylpropane (IV).**—*Procedure from IIa.*—Sodium methylate which had been prepared from 4.6 g. (0.2 g.-atom) of sodium and 118 ml. of methyl alcohol was added quickly at −5°C to a suspension of 25.2 g. (0.1 mol.) of IIa in 100 ml. of anhydrous methyl alcohol. The reaction proceeded spontaneously, and the mixture became transparent. After it had been neutralized with carbon dioxide, the mixture was poured into a large amount of water and extracted three times with 50 ml. of ether. Anhydrous magnesium sulfate was then added to the ether extract. Compound IV was purified by distillation at 118°C/0.08 mmHg, m. p. 58—59°C (recrystallized from water and methyl alcohol (1 : 1)). Yield: 17 g. (76%).

Found: C, 58.48; H, 6.63; 6.18. Calcd. for $C_{11}H_{15}O_4N$: C, 58.65; H, 6.71; N, 6.22%.

Procedure from III. — The same procedure as above was employed in the preparation of IV from III. Thus, 16.5 g. (70%) of IV was obtained from 22.1 g. of III in 100 ml. of methyl alcohol.

***dl-erythro*-2-Acetoamido-1,3-dimethoxy-1-phenylpropane (VI).**—Compound IV (13.7 g.) in 30 ml. of methyl alcohol was hydrogenated in an autoclave with 4 g. of Raney nickel at 40°C under an initial

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[13] Boiling points and melting points are uncorrected. infrared spectra were measured with a Perkin-Elmer Model 321 double-beam spectrophotometer.

pressure of 110 atm. Three molecular equivalents of hydrogen were absorved over a five-hour period. The solvent, methyl alcohol was removed under reduced pressure. The residue (7.5 g.) was mixed with 22.5 g. of acetic anhydride and warmed at 50°C. After the mixture had cooled, 5.0 g. of white crystals were obtained; m. p. 106°C (recrystallized from *n*-hexane and ethyl acetate (4 : 14)).

Found: C, 66.05; H, 8.10; N, 6.00. Calcd. for $C_{13}H_{19}O_3N$: C, 65.80; H, 8.07; N, 5.90%.

***dl-erythro*-2-Acetoamido-1, 3-dimethoxy-1-(*p*-nitrophenyl)-propane (VII).**—According to the method of Gabor,[11] from 2 g. of VI, 3.4 ml. of acetic anhydride and 10 ml. of fuming nitric acid, 1.1 g. of VII was obtained as pale-yellow-needle crystals, m. p. 109—110°C (from benzene).

Found: C, 55.98; H, 6.77; N, 9.69. Calcd. for $C_{13}H_{18}O_5N_2$: C, 55.31; H, 6.43; N, 9.92%.

***dl-erythro*-2-Amino-1, 3-dimethoxy-1-(*p*-nitrophenyl)-propane Hydrochloride (VIII).**—A 1.5 g. of sample of VII was mixed with 5 ml. of 5 N hydrochloric acid, and then the mixture was heated at 100°C for 4 hr. After the mixture had cooled, white crystals of VII (0.9 g.) were obtained; m. p. 216°C (from ethyl alcohol).

Found: C, 47.23; H, 6.27; N, 10.24. Calcd. for $C_{11}H_{16}O_4N_2 \cdot HCl$: C, 47.70; H, 6.15; N, 10.11%.

***dl-erythro*-2-Amino-1-(*p*-nitrophenyl)-1, 3-propanediol Hydrochloride (IX).**—The mixture of 0.8 g. of VIII and 15 ml. of concentrated hydrochloric acid was heated at 120—125°C for 2 hr. in the sealed tube. Then the solution was concentrated in a vacuum, and the residue was recrystallized from methyl alcohol. White crystals were obtained; m. p. 209°C (lit.[12] 206—208°C).

Found: C, 43.60; H, 5.12; N, 11.66. Calcd. for $C_9H_{12}O_4N_2 \cdot HCl$: C, 43.42; H, 5.22; N, 11.26%.

Summary

This study of the reaction between dinitrogen trioxide and cinnamyl acetate has indicated that the 3-acetoxy-2-nitro-1-phenyl-1-propylnitrite (IIb) is formed, in addition to 3-acetoxy-1-nitroso-2-nitro-1-phenylpropane (IIa), in yield depending on the experimental conditions. Those products have been transformed in good yields into 1, 3-dimethoxy-2-nitro-1-phenylpropane, from which *dl*-erythro-2-amino-1-(*p*-nitrophenyl)-1, 3-propanediol has been synthesized.

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