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STUDIES ON THE NEF REACTION. II. THE SYNTHESIS OF NORCAMPHOR AND PHENYLNORCAMPHOR

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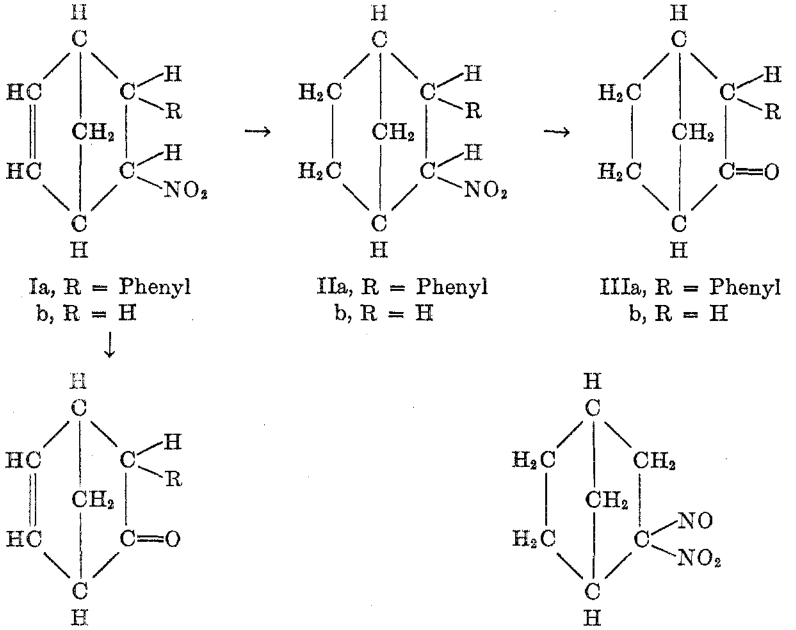
In a previous study of synthetic applications of the Nef reaction (1), it was found that 2-nitro-3-phenylbicyclo[2.2.1]heptene-5 (Ia) could not be converted to the ketone IVa. Since certain 4-nitro-5-phenylcyclohexenes were converted to the corresponding ketones in high yield, a further study of this anomalous behavior was undertaken with a simpler analog, 2-nitrobicyclo[2.2.1]heptene-5 (Ib).



Ia, R = Phenyl
b, R = H

IIa, R = Phenyl
b, R = H

IIIa, R = Phenyl
b, R = H

IVa, R = Phenyl
b, R = H

V

As in the case of Ia, the usual blue-green coloration did not appear when the sodium salt of Ib was added to a cold, dilute solution of hydrochloric acid. No ketonic material could be isolated from the reaction mixture. However, it was found that 2-nitronorcamphane (IIb) was converted smoothly to norcamphor (IIIb) under the same conditions. With this encouraging result, the phenyl-substituted series was reinvestigated. The dihydro derivative, IIa, was converted to phenylnorcamphor (IIIa) by the Nef reaction. Recently van Tamelen and

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[1] Abstracted in part from a thesis submitted by C. H. Hemminger in partial fulfillment of the requirements for the degree of Bachelor of Arts, Princeton University, May, 1952.

Thiede (2) reported a similar case; 2-methyl-3-nitrobicyclo[2.2.1]heptene-5 could not be converted to a ketone while the dihydro derivative gave apocamphenilone in good yield.

The failure of derivatives of 2-nitrobicyclo[2.2.1]heptene-5 to undergo the Nef reaction is not due to the presence of the olefinic bond *per se*, since compounds possessing an olefinic bond in the same position relative to the nitro group but lacking the methylene bridge can be transformed into ketones in good yield (1). It seems more likely that the reaction fails because of the geometry of the bicyclo[2.2.1]heptene-5 ring system as a whole.

A white solid, melting with decomposition to a blue liquid, was isolated in yields up to 20% in the synthesis of norcamphor from IIb. Slow addition of the *aci*-salt to an ethanolic solution of hydrochloric acid seemed to give the highest yield of the by-product. The infrared absorption spectrum showed the presence of a nitro group and the absence of hydroxyl and carbonyl groups. Elementary analysis indicated the empirical formula $C_7H_{10}N_2O_3$. The compound was identified as the dimeric form of 2-nitro-2-nitrosonorcamphane by a synthesis of this pseudonitrole from 2-nitronorcamphane and nitrous acid. The product formed was identical with the unknown by-product of the Nef reaction. Pseudonitroles often exist as colorless dimers which melt to blue monomers (3). The formation of a pseudonitrole was quite unexpected since it would indicate the presence of nitrous acid in the course of the Nef reaction. A strong test for nitrous acid was obtained in the Nef reaction mixture during the synthesis of norcamphor. A synthesis of 6-(4-methoxyphenyl)-3-cyclohexen-1-one (1) was repeated, and the reaction mixture was found to contain traces of nitrous acid by the test described by Feigl (4). However, it appears that nitrous acid does not participate in the Nef reaction since in the above reaction no diminution in yield was noted when a five-fold excess of urea was dissolved in the dilute acid prior to the addition of the sodium salt of 4-nitro-5-(4-methoxyphenyl)cyclohexene. More studies on the mechanism of the Nef reaction will be published shortly.

EXPERIMENTAL[2, 3]

Nitroethanol. Prepared according to the method of Gorski and Makarow (5).

Nitroethylene. Prepared according to the method of Buckley and Scaife (6).

2-Nitrobicyclo[2.2.1]heptene-5 (Ib).[4] A solution of 13.30 g. (0.18 mole) of nitroethylene in 200 ml. of dry benzene was added slowly to 100 g. (1.50 moles) of freshly-distilled cyclopentadiene in 150 ml. of benzene. The mixture was cooled in an ice-bath during the addition. After the reaction mixture had stood overnight, benzene and dicyclopentadiene were removed by distillation. 2-Nitrobicyclo[2.2.1]heptene-5 distilled as a colorless liquid, b.p. 92–94° (8 mm.), that solidified at room temperature. Yield 16.8 g. (67%).

2-Nitronorcamphane (IIb).[4] Repeated reductions of 2-nitrobicyclo[2.2.1]heptene-5 could not be carried out with consistent results. The absorption did not always stop or decrease significantly when the theoretical amount of hydrogen had been taken up. When the reductions were successful, yields up to 96% of 2-nitronorcamphane were obtained. The fol-

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[2] All melting points are corrected. All boiling points are uncorrected.

[3] Microanalyses by J. F. Alicino, Metuchen, New Jersey.

[4] Both Ib and IIb have been prepared previously by Alder and co-workers, *Ber.*, **71,** 2451 (1938), in unspecified yield.

lowing run is a typical example done on a small scale with a fair yield. A solution of 0.315 g. (2.27 millimoles) of 2-nitrobicyclo[2.2.1]heptene-5 in 5 ml. of glacial acetic acid was mixed with 23 mg. of platinum oxide and hydrogenated at room temperature and atmospheric pressure. The catalyst was removed by filtration. Since just the theoretical amount of hydrogen had been absorbed, no acid wash was necessary. The filtrate was concentrated and evaporatively distilled at 110° (0.2 mm.) to give 0.191 g. (60%) of waxy, white solid. 2-Nitronorcamphane was either a waxy solid or an oil after sublimation, n_D^{20} 1.4843.

Anal. Calc'd for $C_7H_{11}NO_2$: C, 59.55; H, 7.86; N, 9.92.

Found: C, 59.38; H, 7.81; N, 9.75.

Norcamphor (IIIb). A solution of the *aci*-salt was prepared by heating 3.40 g. (24 millimoles) of 2-nitronorcamphane in 60 ml. of 10% sodium hydroxide solution. The resultant solution was cooled and added quickly to a well-stirred solution of 40 ml. of concentrated hydrochloric acid in 500 ml. of water at room temperature. The blue reaction mixture was stirred until colorless (about 2 hours). The precipitated pseudonitrole dimer [0.11 g., m.p. 103.5–104.5° (dec.)] was removed by filtration. The aqueous solution was neutralized with 10% sodium hydroxide solution and steam-distilled. The distillate was saturated with sodium chloride and continuously extracted with ether for 8 hours. The ethereal solution was dried over magnesium sulfate, and the ether was removed through a 30-inch fractionating column packed with glass helices. The residue was a volatile, sharp-smelling yellow oil, 1.05 g. (40%), from which 0.36 g. of waxy, white norcamphor was obtained, m.p. 92.5–93.5° [reported (7) 93–94°; (8) 91–92°].

The *semicarbazone* was prepared in 79% yield according to the method of Shriner and Fuson (9) and recrystallized once from ethanol-water as white prisms, m.p. 196–196.5° (dec.) [reported (7) 196.5–197.5°].

The *2,4-dinitrophenylhydrazone* was prepared in 98.5% yield according to the method of Shriner and Fuson (10) and recrystallized from ethanol in two polymorphic forms. Orange prisms (A), m.p. 131.5–132.5°, crystallized from a concentrated ethanolic solution, and yellow prisms (B), m.p. 137–138°, crystallized from a dilute ethanolic solution.

Anal. Calc'd for $C_{13}H_{14}N_4O_4$: C, 53.79; H, 4.86; N, 19.30.

Found (A): C, 54.05; H, 4.95; N, 19.54.

Found (B): C, 53.72; H, 4.86; N, 19.41.

The yield of norcamphor isolated in a pure state was low because of the high volatility of the compound. To determine more accurately the yield of norcamphor, the product of the Nef reaction was converted directly to the 2,4-dinitrophenylhydrazone. A solution of 1.00 g. (7.1 millimoles) of 2-nitronorcamphane in 50 ml. of 10% sodium hydroxide solution was prepared by refluxing for 1 hour followed by cooling. This solution was added quickly to 25 ml. of concentrated hydrochloric acid in 100 ml. of water. The reaction mixture was stirred at room temperature for 2½ hours. The white pseudonitrole dimer (100 mg.) was removed by filtration. The filtrate was treated with a solution prepared by mixing 1.60 g. of 2,4-dinitrophenylhydrazine with 8 ml. of concentrated sulfuric acid, adding 25 ml. of water dropwise to complete solution followed by 50 ml. of ethanol. The reaction mixture was refluxed for 15 minutes, cooled, and filtered. The 2,4-dinitrophenylhydrazone, 1.60 g. (80%), m.p. 125–129°, was recrystallized once from ethanol to give orange prisms, m.p. 130–131°. The yield of derivative obtained indicated a conversion of 2-nitronorcamphane to norcamphor of 80%.

2-Nitro-2-nitrosonorcamphane (V), precipitated in dimeric form during the Nef reaction, was obtained in small quantities when the solution of the *aci*-salt of 2-nitronorcamphane was added quickly to the acid, but when the *aci*-salt was added dropwise yields up to 20% of the pseudonitrole dimer were recovered. The white powder was sublimed at 120° (0.08 mm.) for analysis, m.p. 107.5–108.5° (dec.).

Anal. Calc'd for $C_7H_{10}N_2O_3$: C, 49.40; H, 5.92; N, 16.47.

Found: C, 49.46; H, 5.94; N, 16.42.

Recrystallization from chloroform-ethanol gave white prisms, m.p. 109.5–111.5° (dec.). An authentic sample of 2-nitro-2-nitrosonorcamphane (dimeric form) was prepared from

2-nitronorcamphane according to the method of Hickinbottom (11), m.p. 108.5–109.5° (dec.). A mixture melting point with the sample isolated from the Nef reaction showed no depression.

2-Nitro-3-phenylbicyclo[2.2.1]heptene-5 (Ia) was prepared according to the method of Allen, Bell, and Gates (12). B.p. 128° (0.2 mm.); n_D^{20} 1.5655 [reported (13) b.p. 136–138° (1–2 mm.); n_D^{20} 1.5641].

2-Nitro-3-phenylnorcamphane (IIa). A solution of 2.58 g. (12.0 millimoles) of 2-nitro-3-phenylbicyclo[2.2.1]heptene-5 in 10 ml. of glacial acetic acid was treated with 73 mg. of platinum oxide and hydrogenated at room temperature and atmospheric pressure. The reduction was stopped when 110% of the theoretical amount of hydrogen had been absorbed. The catalyst was removed by filtration. The filtrate was concentrated, dissolved in ether, washed twice with dilute hydrochloric acid solution followed by water, dried, and concentrated. Yield 2.28 g. (88%) of colorless oil that was evaporatively distilled, n_D^{20} 1.5531. Distillation gave a colorless liquid that was not analytically pure, b.p. 128–132° (0.3 mm.); n_D^{20} 1.5530.

Phenylnorcamphor (IIIa). A solution of sodium ethoxide prepared from 0.415 g. (18 millimoles) of sodium and 15 ml. of ethanol was added to 1.95 g. (9 millimoles) of 2-nitro-3-phenylnorcamphane in 15 ml. of ethanol and allowed to stand overnight covered with nitrogen. This ethanolic solution was added over 5 minutes to a well-stirred solution of 12 ml. of concentrated hydrochloric acid, 200 ml. of water, and 120 ml. of ethanol at 0° in a nitrogen atmosphere. When the addition was completed, the reaction mixture was stirred at 0° for 1 hour and then at room temperature for 5 hours. A small amount of blue-green tar remained insoluble. The reaction mixture was refluxed for 1 hour, cooled, and allowed to stand overnight. The solution was diluted to twice its volume with water and extracted with ether. The ethereal extracts were dried and concentrated to give 1.66 g. of pale yellow oil which could not be induced to crystallize.

The yellow oil (100 mg.) was converted directly to the *2,4-dinitrophenylhydrazone* according to the method of Shriner and Fuson (10). The crude yellow product, 140 mg. (71%), was recrystallized three times from ethanol to give yellow needles, m.p. 165–166° (dec.).

Anal. Calc'd for $C_{19}H_{18}N_4O_4$: C, 62.29; H, 4.95; N, 15.29.
Found: C, 62.20; H, 4.92; N, 15.05.

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SUMMARY

Norcamphor and phenylnorcamphor have been synthesized from 2-nitronorcamphane and 2-nitro-3-phenylnorcamphane, respectively, in good yield by the Nef reaction.

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