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APPLICATION OF THE BRUCKNER METHOD TO THE SYNTHESIS OF PHENANTHRIDINES—IV[1]

STRUCTURE OF THE SO-CALLED NITROSITES FROM THE ADDITION OF DINITROGEN TRIOXIDE TO 1-ARYLCYCLOHEXENES

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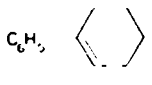
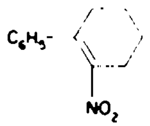
Abstract—The solid byproducts formed in the addition of dinitrogen trioxide to 1-arylcyclohexenes have been shown to be 3-nitro-2-aryl-2-cyclohexenone oximes arising from nitrosation of 2-nitro-1-arylcyclohexenes.

The first paper[2] of this series reported the formation of a yellow solid, m.p. 224° (decomp) by the reaction of 1-phenylcyclohexene (I) with dinitrogen trioxide under certain conditions. Under other conditions, the predominant product was 2-nitro-1-phenylcyclohexene (II). The solid dissolved in cold alcoholic alkali, yielding a deep red solution, from which it was recovered unchanged by acidification. It afforded an acetate with acetic anhydride in pyridine, from which again it was regenerated by mild hydrolysis. Oxidation of the yellow solid gave a good yield of benzoic acid. These data and preliminary analytical results on the solid led to the tentative formulation[2] of its structure as 2-nitro-1-nitroso-1-phenylcyclohexane (III). Analogous compounds were obtained from the addition of dinitrogen trioxide to 1-*o*, 1-*m* and 1-*p*-tolyl and 1-*m*-methoxyphenylcyclohexenes.[2] However structure III was not entirely compatible with the properties observed for the yellow solid, m.p. 224° (decomp). Further investigations leading to a revision of the tentative formulation are reported in this paper.



I



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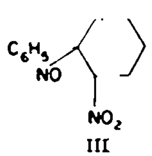
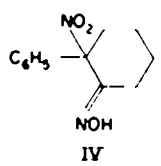


III



IV

A plausible alternate structure IV suggested by Prof. D. H. R. Barton[3] would also explain the properties of the yellow solid. The oxime IV would presumably arise by rearrangement of the intermediate normal nitrosite III[3] and isomerization of the

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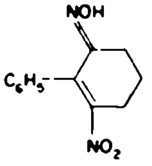
[1] Part III, T. R. Govindachari, K. Nagarajan, B. R. Pai and V. N. Sundararajan, *Chem. Ber.* 91 2053 (1958).

[2] T. R. Govindachari, K. Nagarajan, B. R. Pai and N. Arumugam, *J. Chem. Soc.* 4280 (1956).

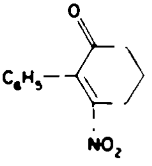
[3] We are thankful to Prof. Barton, Imperial College of Technology, London, for his suggestion.

secondary nitroso compound to the oxime. The compound indeed contained one active hydrogen and its I.R. spectrum showed, in addition to the bands at 1344 and 1508 cm^{-1} characteristic of the nitro group, a band at 3226 cm^{-1} indicative of the presence of a hydroxyl group. The compound was shown to be an oxime by acid hydrolysis to a crystalline ketone, m.p. 109–110° from which it could be regenerated in quantitative yield by treatment with hydroxylamine in pyridine solution. The ketone was further characterized as its semicarbazone and 2,4-dinitrophenylhydrazone. However the I.R. spectrum of the ketone ($\nu_{C=O}$ 1685, $\nu_{C=C}$ 1645 cm^{-1}) and the U.V. spectrum of its 2,4-dinitrophenylhydrazone (λ_{max} 380 mμ)[4] were consistent with an α,β-unsaturated cyclohexanone structure, rather than with the saturated cyclohexanone corresponding to IV. Results of repeated, careful analysis of the ketone, its oxime and other derivatives were in definite agreement with the molecular formula of $C_{12}H_{11}NO_3$ for the ketone and $C_{12}H_{12}N_2O_3$ for the oxime, supporting the presence of a double bond, inferred from spectral evidence. The N.M.R. spectrum of the ketone[5] showed the double bond to be tetrasubstituted, since peaks were observed only in the phenyl and ring methylene regions with an intensity ratio of 5:6. The peaks due to the methylene groups were resolved into three groups of equal area and the line positions of two of these groups were in the allylic region.

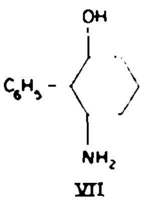
Reduction of the ketone with sodium borohydride afforded a mixture of products from which a small amount of a neutral crystalline alcohol, $C_{12}H_{15}NO_3$ was obtained. Reduction of both the carbonyl group and the double bond must have taken place.[6] Lithium aluminium hydride reduction yielded a mixture of oily amines, separated by fractional crystallization of the hydrochlorides. Two isomeric crystalline hydrochlorides, $C_{12}H_{18}ClNO$, m.p. 327-330° (decomp) and m.p. 241° respectively, were thus obtained and both were found to be resistant to cleavage by sodium metaperiodate, indicating the absence of a vicinal 1,2-aminoalcohol system. The evidence cited so far would be consistent only with structure VII for the amino alcohols,[7] thus leading to structures VI and V for the ketone and the 'yellow solid' oxime, respectively.



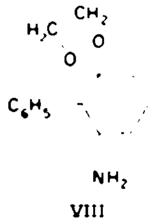
V



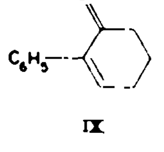
VI



VII



VIII



IX

[4] The presence of a nitro group adjacent to the carbonyl group in the ketone from IV may be expected to have an effect on the U.V. maximum of its 2,4-dinitrophenylhydrazone. However for a model compound, α-nitroacetone 2,4-dinitrophenylhydrazone (λ_{max} 350 mμ), this effect was shown to be hypsochromic rather than bathochromic.

[5] We are grateful to Prof. J. D. Roberts, California Institute of Technology, Pasadena, for the use of the N.M.R. spectrometer.

[6] cf. D. H. R. Barton, P. deMayo and M. Shafiq, *J. Chem. Soc.* 929 (1957).

[7] The stereochemistry of these compounds has not yet been studied.

Further proof was obtained by the following alternate sequence of reactions: the ketone VI was converted into its ethylene ketal which was then reduced to the amino-ketal VIII.[7] Attempted hydrolysis of VIII with hot 4 N hydrochloric acid led to the formation of a neutral ketone identified as 2-phenyl-2-cyclohexenone (IX). Evidently ketal cleavage is accompanied by elimination of the elements of ammonia from the resultant β-aminoketone system.[8] The 1,3-disposition of nitro and carbonyl groups in the ketone VI was thus further substantiated. In analogy with V, the solids obtained from the addition of dinitrogen trioxide to other 1-arylcyclohexenes must be formulated as 2-aryl-3-nitro-2-cyclohexenone oximes and the ketones derived therefrom as 2-aryl-3-nitro-2-cyclohexenones.

The reaction of dinitrogen trioxide with 1-phenylcyclohexene presumably gives an unstable nitrosite which decomposes to give 2-nitro-1-phenylcyclohexene (II). Oxime V may be formed by nitrosation of the reactive methylene group at position 6 in II. Treatment of an ethereal solution of II with dinitrogen trioxide did not yield V; thus in the experimental procedure described previously,[2] the oxime V was not formed prior to but during the sodium methoxide treatment employed for separating the neutral product II from any acidic product that may be formed in the addition of dinitrogen trioxide to 1-phenylcyclohexene (I). This would explain the erratic yields of V that were encountered in experiments performed[9] subsequent to the original publication,[2] since the ether solution of the products at that stage (see Experimental) would contain varying amounts of oxides of nitrogen depending upon the extent of washing of the ether layer, duration of drying etc. Confirmation of the possible intermediacy of II in the formation of the oxime V was obtained by treatment of II with amyl nitrite in the presence of an equivalent of sodium methoxide, whereby a fair yield of V was obtained.

EXPERIMENTAL

Melting points are uncorrected. Ultra-violet absorption spectra were measured with a Beckmann Model DU Spectrophotometer. Infra-red spectra were measured by Mr. S. Selvavinayakam using a Perkin-Elmer Infracord Spectrophotometer.

3-*Nitro-2-phenyl-2-cyclohexenone oxime*

(*a*) *From* 1-*phenylcyclohexene*. A mixture of saturated aqueous solution of sodium nitrite (50 ml) and 1-phenylcyclohexene (2 g) in ether (50 ml) was cooled in ice-water and treated with 4N H_2SO_4 added in drops till the blue colour changed to yellow. After the mixture was left aside for several hours, the ether layer was separated, washed well with water and dried (Na_2SO_4). The combined ether extracts from 5 such experiments were treated with a solution of sodium methoxide (2·5 g) in absolute methanol (35 ml) with vigorous shaking.[3] Water (40 ml) was added to the solution with stirring and the deep red aqueous layer separated. Acidification of the alkaline solution and crystallization of the precipitate from alcohol gave the *oxime* V (0·5 3 g) as yellow needles, m.p. 227 228° (decomp) (Found: C, 62·0, 62·1, 62·2; H, 5·2, 5·2, 5·4; N, 11·8, 11·9; active H, 0·38. $C_{12}H_{12}N_2O_3$ requires: C, 62·1; H, 5·2; N, 12·1; 1 active H, 0·43%). The *acetate* was made in quantitative yield by the action of acetic anhydride in pyridine at 100° for 1 hr and was obtained by crystallization from aqueous methanol as light brown needles, m.p. 103 -104° (Found: C, 61·4, 61·1; H, 5·2, 5·2; N, 10·7. $C_{14}H_{14}N_2O_4$ requires: C, 61·3; H, 5·1; N, 10·2%). Hydrolysis of the acetate using 10% methanolic potassium hydroxide at 30° for 1 hr regenerated the oxime in good yield.

(b) *From* 2-*nitro*-1-*phenylcyclohexene*. A mixture of 2-nitro-1-phenylcyclohexene[2] (5 g) and amyl nitrite (5 g) in dry methanol (25 ml) was treated with a solution of sodium (1·5 g) in methanol (20 ml). The reaction mixture was left overnight at room temp and then poured into excess water. The solution

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[8] H. Cromwell, Q. T. Wiles and O. C. Schroeder, *J. Amer. Chem. Soc.* **64**, 2432 (1942).

[9] V. N. Sundararajan, Ph.D. Thesis, Madras University, August (1957).

was cooled and repeatedly extracted with ether. The aqueous alkaline layer was then cooled well and made acidic with HCl, when a yellow solid (3 g) was precipitated. Crystallization of this material from methanol yielded needles of the oxime (1·1 g), m.p. and mixed m.p. 227° (decomp).

3-*Nitro-2-phenyl-2-cyclohexenone*

A suspension of the oxime (2 g) in 4 N H_2SO_4, (40 ml) and dioxane (20 ml) was refluxed for 2 hr. The solid dissolved gradually and an oily layer separated. The mixture was poured into ice-water and the precipitate filtered and washed with water. This was dissolved in boiling methanol (100 ml), decolourized with animal charcoal and filtered. The filtrate was concentrated to 20 ml, treated with water to turbidity and cooled. The precipitate was filtered and washed with benzene to leave a little (ca. 0·1 g) of the original oxime, m.p. 220-225°. The benzene filtrate was evaporated to give the *ketone* VI (1 g), m.p. 105 106°, which on a second crystallization from methanol, formed glistening yellow plates, m.p. 109-110° (Found: C, 66·3, 66·4; H, 5·1, 5·0; N, 6·3, 6·4. $C_{12}H_{11}NO_3$ requires: C, 66·4; H, 5·1; N, 6·5%). The ketone (0·1 g) and hydroxylamine hydrochloride (0·1 g) in alcohol (1 ml) and pyridine (1 ml) heated at 100° for 1·5 hr, afforded, after crystallization from alcohol, yellow needles of the oxime (0·1 g), m.p. and mixed m.p. with V, 226–227° (decomp). The *semicarbazone* made by the sodium acetate procedure, on crystallization from aqueous alcohol, formed golden yellow needles, m.p. 207-208° (decomp) (Found: C, 56·7; H, 4·7. $C_{13}H_{14}N_4O_3$ requires: C, 56·9; H, 5·1%). The 2,4-*dinitrophenylhydrazone* was obtained as orange plates (from benzene–alcohol), m.p. 202–203°, λ_{max} 380 mμ (log ε 4·45) (Found: C, 54·1, H, 3·5. $C_{18}H_{15}N_5O_6$ requires: C, 54·4; H, 3·8%).

Sodium borohydride reduction of ketone VI

A solution of the ketone (0·2 g) in methanol (10 ml) was reduced with sodium borohydride (0·2 g) to give the crude product (0·15 g) as a gum. Fractional crystallization of the petroleum ether (b.p. 40 60°) soluble fraction of the product gave crystals (20 mg) which were recrystallized from the same solvent to give the *nitroalcohol*, m.p. 110°, with softening above 103°, depressed by admixture with the ketone VI (Found: C, 65·1; H, 6·7. $C_{12}H_{15}NO_3$ requires: C, 65·2; H, 6·8%).

Lithium aluminium hydride reduction of the ketone VI

A solution of the ketone (2 g) in tetrahydrofuran (10 ml) and ether (50 ml) was added during the course of 1 hr, to lithium aluminium hydride (3 g) in ether (50 ml). The mixture was stirred for 8 hr, left overnight and decomposed with water. The ether layer was decanted and the sludge extracted repeatedly with chloroform (3 × 150 ml). The combined extracts were evaporated and the residue taken up in ether (100 ml) and extracted with 2 N H_2SO_4 (50 ml). The aqueous layer was separated and the oily base (1·35 g) obtained from it by basification was converted into the hydrochloride. Fractional crystallization from alcohol–ether afforded as the less soluble fraction, a crop of crystals (70 mg), which on recrystallization yielded the hydrochloride of one isomer of 3-*amino-2-phenylcyclohexanol*, m.p. 327–330° (decomp) (Found: C, 63·8; H, 7·9; N, 6·0. $C_{12}H_{18}ClNO$ requires: C, 63·3; H, 7·9; N, 6·1%). The more soluble fraction was obtained from the mother liquors as stout crystals (0·8 g), m.p. 237–239°. Recrystallization from alcohol–ether gave an isomeric *hydrochloride*, m.p. 241° (Found: C, 63·3; H, 8·0, N, 5·9%).

Ethylene ketal of 3-*nitro-2-phenyl-2-cyclohexenone*

A mixture of the ketone VI (1 g) and *p*-toluenesulphonic acid (50 mg) in benzene (50 ml) containing ethylene glycol (4 ml) was refluxed for 2–3 hr. The solvents were then removed *in vacuo* and the residue taken up in ether. The ether layer was washed with sodium bicarbonate solution and then with water. The product obtained from the dried ether layer was crystallized from ether pet ether (b.p. 40–60°) to afford the *ketal* (0·8 g), m.p. 84° (Found: C, 64·1; H, 5·6. $C_{14}H_{15}NO_4$ requires: C, 64·4; H, 5·8%).

Ethylene ketal (VIII) *of* 3-*amino-2-phenylcyclohexanone*

A solution of the ketal (0·5 g) in ether was added during the course of ½ hr to lithium aluminium hydride (1 g) in ether (50 ml). After being left overnight, the mixture was decomposed with water and the basic product, obtained from the ether layer, was purified by one passage through dil HCl. The semisolid base (0·35 g) was converted into the hydrochloride. Fractional crystallization from alcohol–ether gave a less soluble crop of crystals which was recrystallized to give a hydrochloride of VIII,[7] m.p. 232° (decomp). From the mother liquors by dilution with more ether, an isomeric *hydrochloride* was obtained, m.p. 214-216° (decomp) (Found: C, 62·3; H, 7·1. $C_{14}H_{20}ClNO_2$ requires: C, 62·3; H, 7·4%).

Hydrolysis of the aminoketal VIII

A solution of the crude aminoketal (1 g) in 4N HCl (15 ml) was heated on the steam bath for 2 hr. The solution was diluted and extracted with ether. The ether extract was washed successively with water, aqueous sodium bicarbonate and again water. Removal of solvent from the ether layer and crystallization of the residue from ether gave colourless crystals of 2-phenyl-2-cyclohexenone (IX), m.p. 98° (Found: C, 83·3; H, 6·7. $C_{12}H_{12}O$ requires: C, 83·7; H, 7·0%), identical with an authentic specimen synthesized[10] by hydrolysis of its oxime obtained by the addition of nitrosyl chloride to 1-phenylcyclohexene. Identity was further confirmed by comparison of the oxime, m.p. 151° and 2,4-dinitrophenylhydrazone, m.p. 165-166° of the ketone with authentic samples.[10]

3-*Nitro*-2(o-*tolyl*)-2-*cyclohexenone oxime*

Treatment[2] of 1-(*o*-tolyl)cyclohexene (10 g) with dinitrogen trioxide gave as the alkali soluble fraction, the *oxime* (2 g) which formed yellow needles (from alcohol), m.p. 210° (decomp) (Found: C, 63·1; H, 5·9. $C_{13}H_{14}N_2O_3$ requires: C, 63·4; H, 5·7%) further characterized as its *acetate*, pale yellow needles (from aqueous methanol), m.p. 99° (Found: C, 62·7; H, 5·7. $C_{15}H_{16}N_2O_4$ requires: C, 62·5; H, 5·6%).

Hydrolysis of the oxime (1 g) with 4N H_2SO_4 (20 ml) in dioxane (10 ml) for 2 hr gave 3-*nitro*-2-(o-*tolyl*)-2-*cyclohexenone* as pale yellow prisms, m.p. 119-121° (Found: C, 67·9; H, 5·4. $C_{13}H_{13}NO_3$ requires: C, 67·5; H, 5·6%), yielding a 2,4-*dinitrophenylhydrazone*, orange needles (from benzene–alcohol), m.p. 217° with slight softening above 209°, λ_{max} 380 mμ (log ϵ 4·48) (Found: C, 55·4; H, 4·2. $C_{19}H_{17}N_5O_6$ requires: C, 55·5; H, 4·1%).

3-*Nitro*-2-(m-*tolyl*)-2-*cyclohexenone oxime*

1-(*m*-Tolyl)cyclohexene (10 g) by treatment with dinitrogen trioxide[2] gave the *oxime* (2 g) which crystallized from alcohol in pale yellow needles, m.p. 195-197° (Found: C, 63·1; H, 5·4%), forming an *acetate*, m.p. 117° (Found: C, 62·6; H, 5·8%).

Acid hydrolysis of the oxime (1 g) as before gave 3-*nitro*-2-(m-*tolyl*)-2-*cyclohexenone* (0·5 g) as an oil which solidified after being left overnight in the ice-chest. Recrystallized from aqueous methanol, it formed pale yellow needles, m.p. 82-83° (Found: C, 67·4; H, 5·3%). The 2,4-*dinitrophenylhydrazone* was obtained as brownish red needles (from benzene-alcohol), m.p. 204-206° (decomp), λ_{max} 383 mμ (log ϵ 4·40) (Found: C, 55·3; H, 4·1%).

3-*Nitro*-2-(p-*tolyl*)-2-*cyclohexenone oxime*

Reaction of 1-(*p*-tolyl)cyclohexene (10 g) with dinitrogen trioxide gave the *oxime* (1·5 g) which was recrystallized from alcohol in yellow needles, m.p. 228° (decomp) (Found: C, 63·4; H, 5·7%), forming an *acetate*, colourless needles (from aqueous methanol), m.p. 79-81° (Found: C, 62·9; H, 5·7%).

Sulphuric acid hydrolysis of the oxime (1 g) yielded 3-*nitro*-2-(p-*tolyl*)-2-*cyclohexenone* (0·55 g), yellow needles, m.p. 98-100° (Found: C, 67·3; H, 5·4%), giving a 2,4-*dinitrophenylhydrazone*, orange needles, m.p. 215-216°, λ_{max} 383 mμ (log ϵ 4·60) (Found: C, 55·9; H, 4·1%).

3-*Nitro*-2-(m-*anisyl*)-2-*cyclohexenone oxime*

1-(*m*-Anisyl)cyclohexene (10 g) by treatment with dinitrogen trioxide[2] yielded as the alkali soluble product, the *oxime* (1·5 g), pale brown needles (from alcohol), m.p. 161° (Found: C, 59·4; H, 5·7. $C_{13}H_{14}N_2O_4$ requires: C, 59·5; H, 5·4%), further characterized as the *acetate*, colourless needles (from methanol) m.p. 137° (Found: C, 59·2; H, 5·6. $C_{15}H_{16}N_2O_5$ requires: C, 59·2; H, 5·3%).

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[10] David Ginsburg and Raphael Pappo, *J. Chem. Soc.* 516 (1951).

The above oxime (0·8 g), hydrolysed by hot sulphuric acid afforded 3-*nitro*-2-(m-*anisyl*)-2-*cyclohexenone* (0·4 g) as an oil which solidified after being left in the ice-chest. Recrystallized from benzene-pet ether (b.p. 40–60°) it formed yellow needles m.p. 67–69° (Found: C, 63·3; H, 4·9. $C_{13}H_{13}NO_4$ requires: C, 63·2; H, 5·3%). The 2,4-*dinitrophenylhydrazone* crystallized from benzene-alcohol as orange-red plates, m.p. 163–164°, λ_{max} 380 mμ (log ϵ 4·54) (Found: C, 53·7; H, 3·6. $C_{19}H_{17}N_5O_7$ requires: C, 53·4; H, 4·0%).

Nitroacetone 2,4-*dinitrophenlyhydrazone*

The *hydrazone* was made from nitroacetone[11] and was recrystallized from alcohol in glistening yellow plates, m.p. 137–139° (Found: C, 38·2; H, 2·9. $C_9H_9N_5O_6$ requires: C, 38·2; H, 3·2%).

Acknowledgement- We are grateful to Mr. S. Selvavinayakam for the microanalyses. We thank the Government of Madras for the award of a Research Assistantship (to V. N. S.).

[11] C. Harries, *Liebig Ann.* **319**, 251 (1901).