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A CYCLIC HYDROXAMIC ACID FROM 1,3-CYCLOHEXANEDIONE AND ω-NITROSTYRENE

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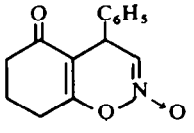
Abstract—The condensation of 1,3-cyclohexanedione and ω-nitrostyrene formed the lactam **6** from which **2** and **3** were obtained. Synthesis of 3-phenyl-4,5,6,7-tetrahydroindol-4-one by another method confirmed the structure assigned to **3**.

THE reaction of ω-nitrostyrene with 1,3-cyclohexanedione takes an abnormal course, and the product was formulated as the oxazine **1**.[2] The adduct from 1-nitropropene and 1,3-cyclohexanedione was assumed to be an analog of **1**.[2] Reduction of **1** with hydrogen and Raney Ni provided **2**. Dehydrogenation of **2** formed 3-phenyl-4,5,6,7-tetrahydroindol-4-one, **3**.[2] Hydrolysis of **1** provided a keto acid **4** that was converted to α-phenylsuberic acid by a Wolff-Kishner reduction.[2] Subsequent synthesis of α-phenylsuberic acid by another route furnished an authentic sample[3] with physical properties in agreement with those reported by Stetter and Hoehne.[2] Nitroethylene reacted with 1,3-cyclohexanedione to form a normal Michael addition product **5**.[2]



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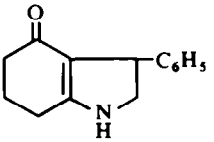

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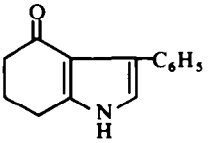

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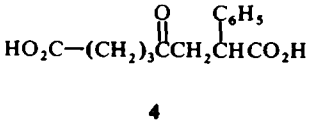

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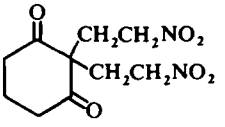

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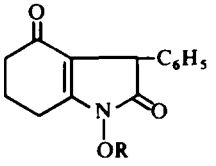


6: R = H
7: R = Ac

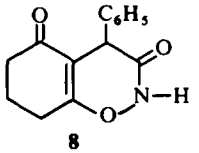
The structures **1**, **2**, and **3** were not accompanied by spectral data, and having an interest in unusual reactions of the nitro group,[4,5] we have investigated these compounds. The condensation of 1,3-cyclohexanedione and ω-nitrostyrene furnished a product, $C_{14}H_{13}NO_3$—in agreement with Stetter and Hoehne, for which the IR spectrum showed a broad absorption due to an OH group at 2·93–3·20 μ and two bands in the CO region at 5·89 and 6·13 μ. The absorption at 5·89 μ is indicative of a lactam, and the band at 6·13 μ is suggestive of a CO group. The compound gave a positive ferric chloride test. These preliminary observations are not accommodated by **1**. Formation of **4** clearly limits the C atoms to which oxygen may be bonded in the product of the condensation. Consequently, we propose the cyclic hydroxamic acid **6**

for the structure of the product. Hydrolysis of **6** would be expected to produce the keto acid **4** by analogy to the reaction of another vinylogous imide.[6]

Spectral data for precise analogs of **6** do not appear to be available. The absorption at 5·89 and 6·13 μ in the IR spectrum of **6** is similar to data reported for vinylogous imides.[7-9] Absorption in the UV spectrum at 268 mμ (ε = 10,800) is similar to the UV spectrum of a vinylogous imide.[7,8] The NMR spectrum of **6** contained a triplet (J = 2·0 c/s) at δ 4·98 for the C-3 proton. Irradiation at δ 2·69 collapsed the triplet to a singlet, thereby establishing coupling between the C-3 and C-7 protons. A determination of the mol. wt. of **6** obviates the consideration of dimers for its structure.

Acetylation of the hydroxamic acid **6** yielded a monoacetate **7**. The NMR spectrum of **7** showed two peaks for the acetate protons at δ 1·82 and 2·02. By irradiation at δ 2·71 the two triplets at δ 5·01 (J = 2·3 c/s) and 5·10 (J = 2·3 c/s) became singlets, establishing coupling between the C-3 and C-7 protons. These results are attributed to restricted rotation about the N—O bond in **7**. An interesting study of a barrier to rotation about the N—O bond in esters has been reported by Larkin.[10]

Other structures for the product of the condensation are possible. Structure **8** was excluded because the acetyl derivative is not an N-acetyl derivative. Structure **9** is also feasible.[11] The rearrangement of a nitro group to an oximino lactone function has never been established, although that possibility has been suggested.[12] If **9** were the



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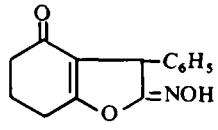

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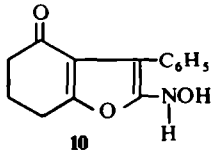

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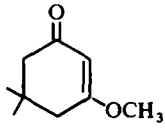

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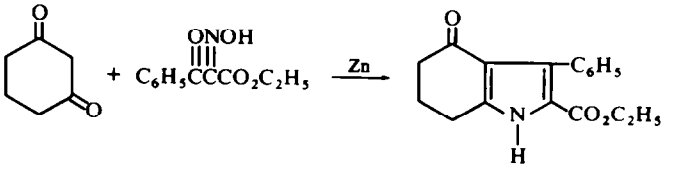
product of the condensation, the available information on aminofurans that has been summarized by Katritzky and Lagowski[13] indicates that tautomerism of **9** to **10** would occur. The spectral data of the condensation product is not compatible with the aminofuran **10**. Both structures **8** and **9** have a structural feature in common with the enol ether **11** for which there is prominent absorption at 251 mμ (ε = 14,900) in the UV spectrum.[14] The product of the condensation does not have the UV spectrum characteristic of an enol ether derived from a cyclic β-diketone.

Reduction of the hydroxamic acid **6** using the procedure of Setter and Hoehne[2] with hydrogen and Raney Ni provided the vinylogous amide, **2**. Hydrogenolysis of the OH group in **6** with Raney Ni is in agreement with comparable transformations.[15] Vinylogous amides are resistant to reduction by hydrogen and Raney Ni,[16] so the survival of **2** under these conditions is plausible. Conversion of the C-2 CO group to a methylene group with hydrogen and Raney Ni is an exceptional case, since the

survival of lactams under these conditions has been amply demonstrated.[15,17] However, the reduction of the lactam **6** is not without precedent. The unusual hydrogenolysis of oxoannotinine to annotinine with platinum and hydrogen at low pressure and room temperature has been reported[18] and confirmed.[19] Other examples of the reduction of lactams to amines under similar conditions have been described.[20]

The absorption at 3·18 and 6·32 μ in the IR spectrum of **2** is characteristic of β-amino-α,β-unsaturated ketones.[21-23] The UV spectrum of **2** with a max at 308 mμ is typical of vinylogous amides with the grouping —NH—C=C—CO—.[16,21,22] The UV spectrum of **2** was unchanged by alkali, but the max underwent a hypsochromic shift in acid, indicating that **2** is in the keto form.[24] Raney Ni is known to promote dimerization,[25] but the mol. wt. of **2** excludes that reaction. The NMR spectrum substantiates the structure that has been assigned to **2**.

Dehydrogenation of **2** to **3** was accomplished under mild conditions.[2] The functional groups of **3** were readily identified in the IR spectrum at 3·14 and 6·13 μ. Synthesis of **3** according to a method (Eq. 1) developed by Schoen and Pachter[26] established the structure of **3**. Saponification of **12** and decarboxylation of the acid **13**



(1)

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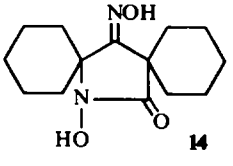
provided 3-phenyl-4,5,6,7-tetrahydroindol-4-one for which the properties and spectra are in agreement with those reported for **3**.

The complexity of the reaction of primary nitroalkanes with alkali is illustrated by the decomposition of 1-nitro-2-phenylethane by sodium hydroxide to six products and several unidentified compounds.[27] The condensation of cyclohexanone and nitromethane with secondary amines produced the lactam **14** in which a primary nitro group



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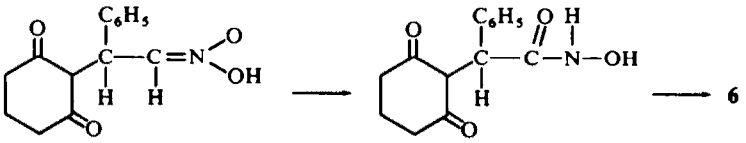
was converted to a cyclic hydroxamic acid.[15] The mechanism that was suggested to account for this conversion was intricate. The formation of **6** at room temperature from a Michael reaction is unique for the ease with which the reaction occurs. Presumably the adduct **15**, a nitronic acid or its tautomer, is an intermediate, and **16** is a plausible predecessor of **6**. The conversion, **15** → **16**, remains unexplained; speculation of the transfer of oxygen from N to C implicates a small heterocyclic ring. A

rather similar transformation was proposed elsewhere to account for the conversion of the anion derived from a secondary nitro group to a CO group.[28]



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EXPERIMENTAL

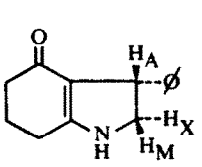
IR spectra were determined with the compounds in discs of KBr on a Beckman IR-5 spectrophotometer. UV spectra of compounds in 95% EtOH were obtained on a Cary Model 14 instrument. NMR spectra were recorded on a varian HA-100 spectrometer. Chemical shifts are given in ppm (δ) downfield from TMS as the internal reference. Mass spectra were taken with a Hitachi–Perkin–Elmer RMU-6E mass spectrometer. Microanalyses were by Dr. A. Bernhardt, Mulheim, Germany and Berkeley Analytical Laboratory, Berkeley, California. M.ps. were taken with total immersion thermometers.

N-Hydroxy-3-phenyl-4,5,6,7-tetrahydrooxindol-4-one (**6**). The condensation of 1,3-cyclohexanedione and ω-nitrostyrene by NaOMe was done according to the procedure of Stetter and Hoehne.[2] The product must be purified promptly to avoid extensive decomposition, and the yield was 45–50%. Recrystallization from MeOH gave the cyclic **6**, m.p. (variable) 167–168° dec (lit.[2] 165–167°); λ_{max} 2·96–3·20 (OH), 5·89 (τ-lactam CO) and 6·13 μ (conjugated C=O); λ_{max} 268 mμ (ε = 10,800); NMR (DMSO-d_6) 2·03 (m), 2·21 (m), 2·69 (m) (C-6, -5 and -7 methylenes), 4·98 (t, J = 2·0 c/s, C-3 H), 7·24 (s, Ph protons) and 10·20 (s, N—OH). Irradiation of the multiplet centered at δ 2·69 caused a collapse of the triplet at δ 4·98 to a singlet; mol wt 243 (mass spectrum). (Found: C, 69·23; H, 5·43; N, 5·81. $C_{14}H_{13}NO_3$ requires: C, 69·13; H, 5·38; N, 5·75%). The hydroxamic acid gave a purple color with $FeCl_3$ in EtOH.

The hydroxamic acid **6** (2·73 g) was treated with a soln of Ac_2O (1·70 g) and pyridine (17 ml) at room temp for 3 hr. Addition of cold water precipitated a solid that was isolated by filtration. Recrystallization from EtOH provided 1·23 g (40% yield) of crystals, m.p. 165–166°; λ_{max} 5·68 (acetate) 5·95 (τ-lactam) and 6·05 μ (conjugated CO); NMR ($CDCl_3$) 1·82, 2·12 (both s, OAc) 2·12 (m), 2·30 (m), 2·71 (m) (C-6, -5 and -7 methylenes), 5·01 (t, J = 2·3 c/s), 5·10 (t, J = 2·3 c/s, C-3 H) and 7·25 (s, Ph protons). Irradiation of the multiplet centered at δ 2·71 changed the triplets at δ 5·01 and 5·10 to singlets. (Found: C, 67·59; H, 5·20; N, 4·88. $C_{16}H_{15}NO_4$ requires: C, 67·36; H, 5·30; N, 4·91%).

3-Phenyl-2,3,4,5,6,7-hexahydroindol-4-one (**2**). The acid **6** (6·0 g), Raney Ni (4 g) and EtOH (300 ml) were placed in a Parr hydrogenation unit with H_2 at 3 atm and room temp for 6 hr.[2] The catalyst was removed by filtration, and the solvent was removed with a vacuum evaporator. Recrystallization of the residue from acetone gave **2** (54% yield), m.p. 196–197° dec (lit.[2] 195–197°); λ_{max} 3·18 (NH) and 6·32 μ (conjugated CO); λ_{max} 308 mμ (ε = 21,600); mol wt 213 (mass spectrum). (Found: C, 78·76; H, 7·02; N, 6·58; $C_{14}H_{15}NO$ requires: C, 78·85; H, 7·08; N, 6·57%). The UV spectrum of **2** was not changed by the addition of 10% NaOH aq. The addition of 6N HCl caused a shift of the max to 293 mμ (ε = 17,700).

The NMR spectrum ($CDCl_3$) showed peaks at δ 1·95 (m, C-6 methylene), 2·23 (m, C-5 and -7 methylenes), 6·35 (broad, NH), 7·15 (m, Ph hydrogens). The three protons at C-2 and C-3 gave an AMX pattern that has been discussed by Abraham and Thomas.[29] The protons were tentatively assigned: H_A at δ 3·29 (q, J_{AX} = 5c/s, J_{AM} = 11 c/s), H_M at δ 3·83 (t, $J_{AM} = J_{MX}$ = 11 c/s) and H_X at δ 4·24 (q, J_{AX} = 5 c/s, J_{MX} = 11 c/s).



3-*Phenyl*-4,5,6,7-*tetrahydroindol*-4-*one* (**3**). The compound **2** (1 g) was placed in EtOH (50 ml) with Raney Ni (0·5 g). The mixture was maintained at the reflux temp for 2 hr. After filtration to remove the catalyst, the solvent was removed with a vacuum evaporator. The residue was crystallized from MeOH. The ketone **3** was a stable product (45% yield), m.p. 238–239°; λ_{max} 3·14 (NH) and 6·13 μ (conjugated CO); λ_{max} 218 (ε = 22,080), 242 (sh, ε = 8450), 263 (ε = 10,400) and 287 mμ (sh, ε = 6570); NMR (DMSO-d_6) 2·04 (m), 2·36 (t, J = 6 c/s), 2·80 (t, J = 6 c/s) (C-6, -5 and -7 methylenes, respectively), 6·91 (d, J = 2·5 c/s, C-2 H), 7·23 and 7·62 (both m, Ph protons) and 11·48 (broad, NH); mol wt 211 (mass spectrum). (Found: C, 79·60; H, 6·09; N, 6·74. $C_{14}H_{13}NO$ requires: C, 79·59; H, 6·20; N, 6·63%).

2-*Carbethoxy*-3-*phenyl*-4,5,6,7-*tetrahydroindol*-4-*one* (**12**). A procedure by Schoen and Pachter[2b] was used for the synthesis of **12**. Ethyl benzoylacetate (19·1 g, 0·1 mole) was dissolved in glacial AcOH (30 ml) and cooled to 5°. The soln was stirred efficiently, and a cold sat $NaNO_2$ aq (6·9 g, 0·1 mole) was added at a rate so that the temp did not exceed 10°. About 30 min were required for the addition. A solid formed, and after 15 min 1,3-cyclohexanedione (11·2 g, 0·1 mole) in glacial AcOH (35 ml) was added with swirling. The solid intermediate dissolved.

Zn dust (13·1 g, 0·2 g-atom) was added at such a rate that the mixture boiled within 3 min. The exothermic reaction continued at the b.p. until the addition of Zn dust was complete was maintained at the reflux temp for a total time of 1 hr. The mixture was cooled and poured on to ice. The gray solid was isolated by filtration. Recrystallization from EtOH provided 6·0 g (21% yield) of crystals, m.p. 194–195°; λ_{max} 3·16 (NH), 5·92 (ester CO), and 6·10 μ (conjugated CO). Found: N, 5·19. $C_{17}H_{17}NO_3$ requires: N, 4·94%).

A semicarbazone was prepared from the ketone in the usual way. Recrystallization from EtOH furnished crystals (88% yield), m.p. 275–277° dec. (Found: C, 63·66; H, 5·78; N, 16·28. $C_{18}H_{20}N_4O_3$ requires: C, 63·52; H, 5·92; N, 16·46%).

2-*Carboxy*-3-*phenyl*-4,5,6,7-*tetrahydroindol*-4-*one* (**13**). The ester **12** (5·2 g) was treated with NaOH (3·5 g) in a soln of water (20 ml) and EtOH (40 ml) at the reflux temp for 45 min. EtOH was removed with a vacuum evaporator, and water was added to dissolve the salt. The mixture was filtered, and the filtrate was acidified with HCl aq. The product was isolated by filtration. Recrystallization from EtOH 3·7 g (80% yield) of the acid, m.p. 238–239° dec. (Found: C, 70·59; H, 5·09; N, 5·49. $C_{15}H_{13}NO_3$ requires: C, 70·58; H, 5·13; N, 5·49%).

3-*Phenyl*-4,5,6,7-*tetrahydroindol*-4-*one* (**3**). The carboxylic acid **13**(2·62 g) was suspended in light paraffin oil (115 ml) under N_2. Decarboxylation occurred at 235–245°, and the temp was raised to 290° for 15 min.[2b] Upon cooling a solid separated that was isolated by filtration. The product was washed with low boiling pet ether on the filter funnel. Recrystallization furnished 1·88 g (87% yield; MeOH) of the ketone **3**, m.p. 238–239°. The mixture m.p. with the compound prepared according to procedures by Stetter and Hoehne was 238–239°. The IR spectrum, NMR spectrum, and the mass spectrum of the synthetic ketone were identical to the spectra of the ketone prepared according to the method of Stetter and Hoehne. (Found: C, 79·43; H, 6·22; N, 6·69. $C_{14}H_{13}NO$ requires: C, 79·59; H, 6·20; N, 6·63%).

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