

STRUCTURE OF THE 2:2 CONDENSATION PRODUCT OF  
NITROMETHANE AND CYCLOHEXANONE

Wayland E. Noland and Richard J. Sundberg<sup>1</sup>

School of Chemistry, University of Minnesota, Minneapolis 14, Minnesota

(Received 12 February 1962; in revised form 7 March 1962)

NITROMETHANE and cyclohexanone condense in refluxing solution in the presence of secondary amines to a colorless 2:2 product  $C_{14}H_{20}N_2O_3$  (I), m.p. 270-271° (sublimes).<sup>2,3</sup> Secondary amines used as catalysts include piperidine<sup>4</sup> (8-14,<sup>3</sup> 24%<sup>5</sup> yield), piperazine (47%),<sup>5</sup> pyrrolidine (23%),<sup>5</sup> morpholine (22%),<sup>5</sup> diethylamine (19%),<sup>2</sup> and di-n-propylamine,<sup>3</sup> but the primary amine, methylamine, gave no I.<sup>4</sup> Compound I has also been obtained from condensation of nitromethane with the other reaction products,<sup>2</sup> 1-(nitromethyl)cyclohexanol (4% yield),<sup>2</sup> and 1-(nitromethyl)cyclohexene,<sup>3</sup> and with the enamines 1-piperidinocyclohexene (10%)<sup>6</sup> and 1,4-bis(1-cyclohexenyl)piperazine (23%).<sup>5</sup>

Compounds analogous to I have been obtained from secondary amine-catalyzed condensations of nitromethane with 3-methyl (1% yield),<sup>4</sup> 4-methyl (5-40%),<sup>3-5</sup> 4-isopropyl (38%),<sup>5</sup> and 4-t-butyl (7-26%)<sup>5</sup> cyclohexanones, and

<sup>1</sup> National Science Foundation Fellow, June 1960-June 1962.

<sup>2</sup> A. Lambert and A. Lowe, J. Chem. Soc. 1517 (1947).

<sup>3</sup> D.V. Nightingale, D.A. Reich and F.B. Erickson, J. Org. Chem. **23**, 236 (1958).

<sup>4</sup> D.V. Nightingale, F.B. Erickson and J.M. Shackelford, J. Org. Chem. **17**, 1005 (1952).

<sup>5</sup> Shozo Miki (with Dorothy V. Nightingale), M.S. thesis, University of Missouri, Aug. 1961.

<sup>6</sup> Z. Eckstein, A. Sacha and W. Sobótka, Bull. Acad. Polon. Sci., Sér. Sci. Chim., géol. et géograph. **7**, 295 (1959); Roczniki Chem. **34**, 1329 (1960).

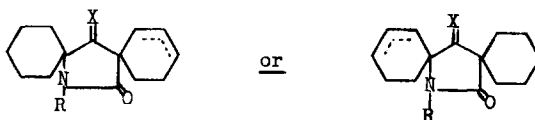
with cyclopentanone (7-24%),<sup>3,5</sup> cycloheptanone (51%),<sup>5</sup> and cyclooctanone (1%).<sup>5</sup> Extensive degradative studies of I have been carried out by Nightingale *et al.*<sup>3</sup>

We now wish to report that the nitromethane:cyclohexanone 2:2 product has structure I, only the position of the olefinic double bond and the stereochemistry of the oximino group being uncertain. Hydrolysis of the oximino group of I with dilute sulfuric acid gave the ketone  $C_{14}H_{19}NO_3$  (IV,<sup>7</sup> 91%),<sup>3</sup> m.p. 176.5-177.5° (sublimes). Oximation by long heating of IV with excess hydroxylamine hydrochloride in pyridine-ethanol gave  $C_{14}H_{20}N_2O_3$  (Ie, 93%), m.p. 262-264° (sublimes), probably a *syn* or *anti* isomer of I, having a Nujol infrared spectrum different from I, also obtained by thermal isomerization of I in refluxing xylene. Methylation (as with IV  $\rightarrow$  IVa)<sup>3</sup> of I and Ie gave isomeric N-methoxy derivatives  $C_{15}H_{22}N_2O_3$  (Id, quantitative; and If, 52%), both m.p. 185-186° (sublime), but having different Nujol infrared spectra. Similar methylation of IV (80%),<sup>3</sup> or the action of diazomethane on IV,<sup>8</sup> or hydrolysis of the oximino group of Id (76%) or If (50%) with dilute hydrochloric acid all gave the same N-methoxyketone  $C_{15}H_{21}NO_3$  (IVa), m.p. 95-96°. A second dimorphic form, m.p. 95-96°, having a different Nujol infrared spectrum, has also been observed. Hydrogenation of I (94%) or of Ie (75%) over Raney nickel at 2 atm gave the amine  $C_{14}H_{24}N_2O$  (II),<sup>3</sup> m.p. 196-197° (sublimes). Oxidation of II (30%) with chromium (VI) trioxide in acetic acid or (25%) with aqueous potassium permanganate gave the ketone  $C_{14}H_{21}NO_2$  (XV),<sup>3</sup> m.p. 241-242° (sublimes), identical with that obtained by hydrogenation of IV (86%)<sup>9</sup> or IVa (77%) over Raney nickel at

<sup>7</sup> Where appropriate, our usage of numbers corresponds to that of Professor Nightingale (ref. 3).

<sup>8</sup> Vernon D. Parker, unpublished work, University of Minnesota, 1959.

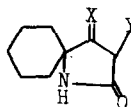
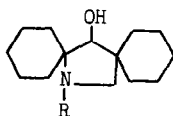
<sup>9</sup> This experiment was first performed in unstated yield by Roger D. Johnson, National Science Foundation Undergraduate Research Participant, summer 1959, with support from NSF grant G-8179.



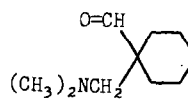
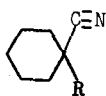
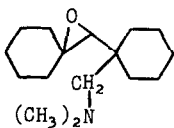
	<u>X</u>	<u>R</u>
I, Ie	NOH	OH
Id, If	NOH	OCH <sub>3</sub>
IV	O	OH
IVa	O	OCH <sub>3</sub>



	<u>X</u>	<u>X</u>
II	NH <sub>2</sub>	O
IIId	N(CH <sub>3</sub> ) <sub>2</sub>	XV
IIe	N(CH <sub>3</sub> ) <sub>3</sub> <sup>+</sup> I <sup>-</sup>	XVc
IIIf	OCH <sub>2</sub> CH <sub>2</sub> OH	NOH
XIV	OH	



	<u>R</u>	<u>X</u>	<u>Y</u>
V	H	NH	CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>
Vb	CH <sub>3</sub>	O	H
XI	CH <sub>3</sub> + CH <sub>3</sub> I	XXXVI	
		XXXVII	



XXX

	<u>R</u>
XXXIII	OH
XXXIV	NH <sub>2</sub>
XXXV	NHCOCH <sub>2</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>

XXXI

2 atm gave II (62%), identical with the sample from hydrogenation of I or Ie. These transformations establish the presence of an oximino and of an N-hydroxy group in I and Ie.

The atomic skeleton of II and IV (and, thus, of I) was established by degradation. Dimethylation<sup>10</sup> of II gave  $C_{16}H_{28}N_2O$  (IIId, 54%), m.p. 157-159° (Found: C, 72.59; H, 10.47; N, 10.21), which was converted to its methiodide  $C_{17}H_{31}N_2OI$  (IIe, 81%), m.p. 226-230° (Found: C, 50.28; H, 7.68; N, 6.28). Action of potassium hydroxide in refluxing ethylene glycol on IIe gave the displacement product  $C_{16}H_{27}NO_3$  (IIIf, 44%), m.p. 150-157°. Pyrolysis of the quaternary hydroxide from IIe gave the alcohol  $C_{14}H_{23}NO_2$  (XIV, 34%), m.p. 216-218° (sublimes), identical with that from reduction of XV (95%) with sodium borohydride, or from hydrogenation of IVa (10%)<sup>3,11</sup> at 177 atm and 230° over copper chromium oxide. Reduction of XIV with lithium aluminum hydride gave  $C_{14}H_{25}NO$  (V, 91%), m.p. 166.5-167.5°, identical<sup>12</sup> with that (71%)<sup>3</sup> from hydrogenation of XV at 170 atm<sup>12</sup> and 235° over copper chromium oxide. Methylation<sup>10</sup> of V gave the monomethyl amine Vb (81%), m.p. 75-78°, reported<sup>3</sup> 79-81°, which was converted quantitatively to its methiodide XI, m.p. 190-195°, reported<sup>3</sup> 186-187°. Pyrolysis of the quaternary hydroxide from XI gave the epoxide  $C_{16}H_{29}NO$  (XXX, 67%), colorless oil, b.p. 135-140° (0.5 mm),  $n_D^{25.5}$  1.4939. Periodic acid cleavage of XXX gave two basic products. One is the known aldehyde XXXI (11%), yellow liquid, b.p. 75-80° (2 mm),  $n_D^{30}$  1.4655, shown by infrared comparison to be identical with a synthetic<sup>13</sup> sample (32%), colorless liquid, b.p. 90° (7 mm),

<sup>10</sup> H.T. Clarke, H.B. Gillespie and S.Z. Weisshaus, J. Amer. Chem. Soc. **55**, 4571 (1933).

<sup>11</sup> We are indebted to Professor Dorothy V. Nightingale for providing an infrared spectrum of this sample of XIV for comparison.

<sup>12</sup> Donald A. Reich (with Dorothy V. Nightingale), Ph.D. thesis, University of Missouri, June 1956, pp. 36, 56.

<sup>13</sup> C. Mannich, B. Lesser and F. Silten, Ber. Dtsch. Chem. Ges. **65**, 378 (1932).

$n_D^{25}$  1.4659. The methiodides  $C_{11}H_{22}NOI$  (XXXIa, 64%), m.p. 239-240°, of the two samples were identical. The other basic product is an isomer of XXX, a saturated alcohol  $C_{16}H_{29}NO$  (XXXII, 31%) of unknown structure, m.p. 85.5-87°, or a viscous oil, b.p. 160° (2 mm),  $n_D^{25}$  1.5119; methiodide (42%),  $C_{17}H_{32}NOI$  (XXXIIa), m.p. 225-227°.

The structure of XV (and, thus, of II) has been proved by an independent synthesis. 1-Aminocyclohexanecarbonitrile (XXXIV)<sup>14</sup> was prepared<sup>15</sup> from cyclohexanone cyanohydrin (XXXIII).<sup>16</sup> Condensation of ethyl chloroformylacetate<sup>17</sup> with XXXIV gave  $C_{12}H_{18}N_2O_3$  (XXXV, 46%), yellow oil,  $n_D^{24}$  1.4839 (Found: C, 59.87; H, 7.69; N, 11.01). Cyclization of XXXV with sodium ethoxide gave  $C_{12}H_{18}N_2O_3$  (XXXVI, 68%), dimorphic forms m.p. 263-265° dec. and 269-273° dec. Alkaline saponification of XXXVI and decarboxylation gave  $C_9H_{13}NO_2$  (XXXVII, 66%), m.p. 220-222°; dibromo derivative  $C_9H_{11}NO_2Br_2$  (XXXVIIa, 71%), m.p. 246-250° dec. Sodium hydride-catalyzed cyclizative condensation of XXXVII with 1,5-dibromopentane gave XV (3%), identical with the sample derived from degradation of I. The conversion of XV to II, described above, completes the total synthesis of II.

Unless otherwise stated, elemental analyses for C, H and N of all compounds for which molecular formulas are stated were within  $\pm 0.30$  per cent of the calculated values. With all compounds the infrared spectra are consistent with the structures assigned. Cases of identity were always established by infrared and usually also by mixed melting point comparison. Melting points were determined on calibrated Kofler micro hot stages.

<sup>14</sup> R.M. Herbst and T.B. Johnson, J. Amer. Chem. Soc. **54**, 2463 (1932).

<sup>15a</sup> R.A. Jacobson, J. Amer. Chem. Soc. **67**, 1996 (1945); J.V. Dubsky and W.D. Wensink, Ber. Dtsch. Chem. Ges. **49**, 1134 (1916).

<sup>16a</sup> R.F.B. Cox and R.T. Stormont, in A.H. Blatt, Organic Syntheses, Coll. Vol. 2, p. 7. John Wiley, New York (1943); S.M. McElvain and R.E. Starn, J. Amer. Chem. Soc. **77**, 4571 (1955).

<sup>17a</sup> R.E. Strube, Org. Synth. **37**, 34 (1957); D.S. Breslow, E. Baumgarten and C.R. Hauser, J. Amer. Chem. Soc. **66**, 1286 (1944).