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THE MICHAEL REACTION OF ENAMINES WITH NITROOLEFINS

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Abstract—Several Michael reactions of enamines with nitroolefins (or their cogeners, the β-nitroalkyl acetates) are described. Reduction of the products with amalgamated aluminum leads to heterocyclic compounds, e.g. from 2-(β-nitro-α-phenylethyl)cyclohexanone (IV) to a partially hydrogenated 3-phenylindole (VII).

RECENTLY,[2–5] the Michael reaction of certain enamines with nitroolefins or their congeners, the β-nitroalkyl acetates,[6,7] has been reported. As the β-nitroalkylketones obtained in this reaction, lead by reduction and subsequent dehydration between the amino and carbonyl groups to heterocyclic systems,[8–12] we wish to report on additional Michael reactions in this series, and on the behaviour of the products on reduction and cyclodehydration. The condensations carried out are summarized in Table 1.

Systematic reduction experiments were carried out with compound IV. Palladium–charcoal gave a N-free product by hydrogenolysis, a reaction which has been observed in similar cases[13,14] while LAH led to the crystalline 2-(β-amino-α-phenylethyl)cyclohexanol (VII). It easily gave a N-benzoyl derivative and showed the IR absorptions characteristic of the amino and secondary hydroxyl group. The most interesting results were obtained with aluminum amalgam which afforded a compound of the formula $C_{14}H_{17}N$. This was, obviously, a product of the desired self-condensation between the carbonyl and the amino group. It does not contain a C═N double bond, the absorption of which is absent from the IR spectrum, but shows the band characteristics of enamines (222 mμ) in the UV,[15] while absorption related to a vinylbenzene system is absent. Thus, the product can only be the partially hydrogenated 3-phenylindole derivative VIII; indeed, dehydrogenation with Pd–C gives the known 3-phenylindole (IX).

Analogous, though not equally conclusive observations were made in the reduction of 2-(β-nitroethyl)*cycloheptanone* with LAH. A colorless liquid was formed, to which we ascribe, on the basis of its properties and in analogy to VIII, the tentative structure X of a cyclohepta [*b*] pyrroline or 3-phenyl-octahydro-1-azaazulene. Dehydrogenation in the gas phase converted X into a red oil as indicated in the literature for 3-phenyl-1-azaazulene (XI).[16] For lack of material this could not be purified completely, but showed the spectrum reported for 1-azaazulenes by Nozoe *et al.*[17]

When 2-(β-nitroethyl)*cyclopentanone* was subjected to reduction with aluminum amalgam, a solid product was obtained; we have failed to elucidate its structure.

TABLE 1. CONDENSATION OF

(At 15° in dioxan soln. Generally, water was

Enamine	Acceptor	B.p. (°/mm) or m.p. (°)	Product Formula	Yield (%)
1-N-Pyrrolidino-cyclohexene	2-Nitro-1-butyl acetate[a]	80–90/0·3	$C_{10}H_{17}NO_3$[b] (I)	72
1-N-Morpholino-cyclohexene	2-Nitro-1-butyl acetate		$C_{10}H_{17}NO_3$ (I)	68
1-N-Pyrrolidino-cyclopentene	2-Nitro-1-butyl acetate	90/0·3	$C_9H_{15}NO_3$ (II)	55
1-N-Morpholino-cyclopentene	2-Nitro-1-butyl acetate		$C_9H_{15}NO_3$ (II)	91
1-N-Morpholino-cycloheptene	2-Nitro-1-butyl acetate	85–94/0·25	$C_{11}H_{19}NO_3$ (III)	82
1-N-Pyrrolidino-cyclohexene	2-Nitroethyl acetate	127/3·5	$C_8H_{13}NO_3$[f]	80[g]
1-N-Pyrrolidino-cyclohexene	ω-Nitrostyrene	108 (EtOH)	$C_{14}H_{17}NO_3$[h] (IV)	84
1-N-Pyrrolidino-cyclohexene	1-Acetoxy-2-nitro 1-phenylethane		$C_{14}H_{17}NO_3$ (IV)	94
1-N-Morpholino-cyclohexene	ω-Nitrostyrene		$C_{14}H_{17}NO_3$ (IV)	71–83
1-N-Pyrrolidino-cyclopentene	ω-Nitrostyrene	78–79 (EtOH)	$C_{13}H_{15}NO_3$[k] (IVA)	73
1-N-Morpholino-cyclopentene	ω-Nitrostyrene		$C_{13}H_{15}NO_3$ (IVA)	78
1-N-Pyrrolidino-cycloheptene	ω-Nitrostyrene	78–79 (EtOH)	$C_{15}H_{19}NO_3$ (IVB)	87
2-N-Pyrrolidino-2-pentene (V)	2-Nitro-1-butyl acetate	90–92/2	$C_9H_{17}NO_3$ (VI)	88

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[a] With 2-nitro-1-butene, this product was obtained in 10% yield.

[b] Prepared (by a different route) by N. S. Gill, K. B. James, F. Lions and K. T. Potts, *J. Am. Chem. Soc.* **74**, 4923 (1952).

[c] Found: C, 50·8; H, 5·7. Calc. for $C_{16}H_{21}N_5O_6$: C, 50·7; H, 5·6%.

[d] Found: C, 49·4; H, 7·2. Calc. for $C_{10}H_{18}N_4O_3$: C, 49·6; H, 7·5%.

[e] Found: C, 53·9; H, 8·9. Calc. for $C_{12}H_{22}N_4O_3$: C, 53·3; H, 8·2%.

[f] Described before by B. Reichert and H. Posemann, *Arch. Pharm.* **275**, 61 (1931), and by F. E. King, D. M. Bovey, K. G. Mason and R. L. St. D. Whitehead, *J. Chem. Soc.* 250 (1953). B. Belleau, *Canad. J. Chem.* **35**, 651 (1957). Cf. Ref. 5.

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added to the reaction product after 24 hr.)

Anal., calc'd.			Anal., fd.			Remarks
%C	%H	%N	%C	%H	%N	
60·3	8·6	7·0	60·8	8·7	7·2	$\tilde{\nu}_{\text{liq.}}$ 2940, 1725, 1475, 1390, 1358, 1140, 827 cm^{-1}. n_D^{24} 1·4720. Semicarbazone, m.p. 138°, from benzene,[b] D.N.P., m.p. 142°, from EtOH[c]
58·4	8·2		59·7	8·9		$\tilde{\nu}_{\text{liq.}}$ 2960, 1755, 1570, 1470, 1400, 1370, 1172, 855, 830 cm^{-1}. n_D^{24} 1·4728. Semicarbazone, from EtOH, m.p. 178–179°[c,d]
62·0	9·0		61·5	9·3		$\tilde{\nu}_{\text{liq.}}$ 2885, 1718, 1534, 1478, 1398, 1355, 1318, 1162, 1132 cm^{-1}. n_D^{24} 1·4728. Semicarbazone, m.p. 83–85°, from cyclohexane[e]
56·1	7·7	8·2	56·4	7·6	8·1	n_D^{26} 1·4783. Semicarbazone, m.p. 151–152°[f]
68·0	6·9	5·7	67·6	6·9	5·4	$\tilde{\nu}_{\max}^{\text{KBr}}$ 2920, 1775, 1475, 1400, 1338, 1318, 1260, 1238, 1150, 1080, 995, 900, 810 cm^{-1}. Semicarbazone, unsharp m.p. 174–184°, from benzene[i]
66·9	6·5	6·0	66·9	6·7	5·9	Semicarbazone, m.p. 135°, from aqueous EtOH[l]
68·9	7·3	5·4	68·9	7·2	5·1	$\tilde{\nu}_{\max}^{\text{KBr}}$ 3450, 3050, 2950, 1710, 1520, 1460, 1400, 1380, 1150, 1095, 1045, 985, 945, 900, 865, 815, 780, 710 cm^{-1}. D.N.P., m.p. 178–180°, from benzene–hexane[m]
57·7	9·2		58·5	9·6		$\tilde{\nu}_{\text{liq.}}$ 3000, 1735, 1575, 1485, 1395, 1300, 1110, 1045, 995, 870, 815 cm^{-1}. n_D^{24} 1·4438. Semicarbazone, m.p. 103–105°, from benzene–hexane

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[g] The product was purified by VPC.

[h] Cf. Ref. 3, 4 and 5.

[i] Found: C, 58·9; H, 6·8. Calc. for $C_{15}H_{20}N_4O_3$: C, 59·2; H, 6·6%.

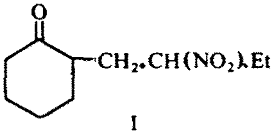
[k] Cf. Ref. 4.

[l] Found: C, 58·1; H, 6·3. Calc. for $C_{14}H_{18}N_4O_3$: C, 57·9; H, 6·3%.

[m] Found: C, 57·0; H, 5·4. Calc. for $C_{21}H_{23}N_5O_6$: C, 57·1; H, 5·3%.

[n] Found: C, 49·4; H, 8·1. Calc. for $C_{10}H_{20}N_4O_3$: C, 49·2; H, 8·3%.

Finally, the nitroketone VI was treated with aluminum amalgam. A strongly basic oil was formed, which gave a crystalline picrate and showed in the IR the peak (1630 cm^{-1}) characteristic of the azomethine grouping. It is, therefore, assumed to be 2,5-diethyl-3-methyl-Δ^1-pyrroline (XII).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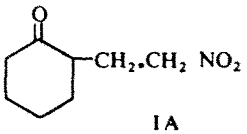
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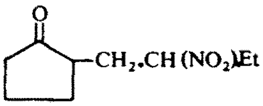
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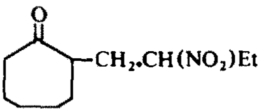
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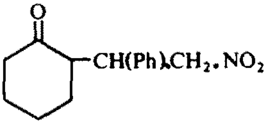
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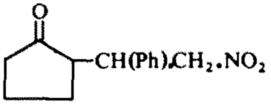
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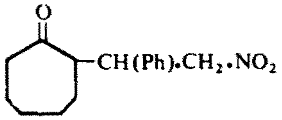
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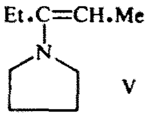
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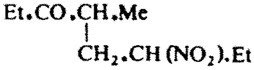
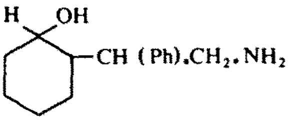


$$\begin{array}{l}\mathrm{Et.CO.CH.Me}\\ \qquad\quad|\\ \qquad\quad\mathrm{CH_2.CH(NO_2).Et}\end{array}$$

VI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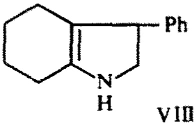
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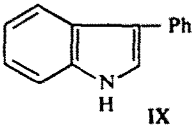
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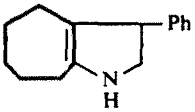
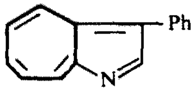

X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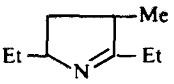
XII

EXPERIMENTAL*

Materials. 1-(N-Pyrrolidino)cyclohexene, b.p. 110–112° (12 mm) was prepared in 80% yield according to Terrell.[18] 1-(N-morpholino)cyclohexene, b.p. 118–120° (10 mm); n_D^{23} 1·5133, in 75% yield according to Huenig *et al.*[19] 1-(N-Pyrrolidino)cyclopentene and 1-(N-morpholino)cyclopentene, b.p. 80° (8·5 mm), n_D^{25} 1·5133, and b.p. 93° (7 mm), n_D^{27} 1·5088, respectively, have been obtained according to Bergmann and Ikan[20] in 81 and 60% yield, while 1-(N-morpholino)cycloheptene, b.p. 108° (4 mm), n_D^{24} 1·5083, and V, b.p. 64° (6·5 mm); n_D^{24} 1·4843, were prepared according to Stork *et al.*[15]

2-*Nitro*-1-*butene*,[21] b.p. 35–44° (20 mm); ω-*nitrostyrene*,[22] m.p. 58°.

2-*Nitro*-1-*butyl acetate*, b.p. 101° (2·5 mm); n_D^{22} 1·4285, was prepared according to Hass[23] in 63% yield. 1-*acetoxy*-2-*nitro*-1-*phenylethane*, b.p. 108–114° (0·4 mm); n_D^{23} 1·5135, according to Bordwell and Garbisch.[24]

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* All m.ps are uncorrected.

2-*Nitroethyl acetate* was prepared according to the lit.[25,26]

2-(β-*Amino-α-phenylethyl*)*cyclohexanol* (VII). In a Soxhlet apparatus, 13 g of IV was gradually extracted into a boiling suspension of 8 g LAH in 300 ml anhyd ether. After 30 more min at reflux temp, the excess reducing agent was destroyed by addition of AcOEt and 250 ml 10% NaOH aq. The layers were separated and the aqueous phase was extracted repeatedly with ether. Distillation (145–165°, 0·3 mm) gave a viscous oil which solidified quickly and crystallized from cyclohexane, m.p. 102°. (Found: C, 76·8; H, 9·9; N, 6·7. Calc. for $C_{14}H_{21}NO$: C, 76·7; H, 9·7; N, 6·4%.)

$\tilde{\nu}_{max}^{KBr}$ 3500, 3175, 3050, 3010, 2920, 2850, 1600, 1498, 1475, 1430, 1350, 1140, 1020, 970, 755, 700 cm^{-1}.

A *monobenzoyl* derivative was prepared, m.p. 185° from EtOH. (Found: C, 77·7; H, 7·5; N, 4·5. Calc. for $C_{21}H_{25}NO_2$: C, 78·0; H, 7·8; N, 4·3%.)

3-*Phenyl*-2,3,4,5,6,7-*hexahydroindole* (VIII). A mixture of 6 g amalgamated[27] Al turnings, 300 ml 96% EtOH and 24·7 g IV was refluxed until all the Al had disappeared; this was accelerated by adding gradually 30 ml water to the refluxing mixture. The alcohol was removed *in vacuo* and the viscous residue treated with water and chloroform. Vacuum distillation of the organic layer gave 12 g (60%) of VIII, b.p. 102° (0·3 mm); n_D^{23} 1·5611. (Found: C, 84·7; H, 8·3; N, 6·9. Calc. for $C_{14}H_{17}N$: C, 84·4; H, 8·6; N, 7·0%.)

$\tilde{\nu}_{liq.}$ 3425, 3060, 2940, 1690, 1635, 1520, 1470, 1400, 1378, 1370, 1340, 1318, 1200, 1170, 1005, 900, 850 cm^{-1}.

3-*Phenylindole* (IX). A mixture of 2·5 g of VIII and a little Pd–C (5%) was heated for 3 hr at 210–220°. The product was dissolved in benzene and the soln distilled *in vacuo*. The oil, which boiled at 140° (0·2 mm), solidified on cooling; the product was recrystallized from pet. ether (b.p. 60–80°), m.p. 85° (lit.[28,29] m.p. 87–88°). (Found: N, 7·2. Calc. for $C_{14}H_{11}N$: 7·3%.)

$\tilde{\nu}_{max}^{KBr}$ 3340, 3050, 2940, 2860, 1630, 1470, 1357, 1240, 1110, 1020, 1010 cm^{-1}.

2-*Phenyloctahydro*-1-*azaazulene* (X). The reduction of 2-(β-nitro-α-phenylethyl)cycloheptanone was carried out as described for IV. The product (yield, 55%) was a colorless oil of b.p. 120–130° (0·4 mm); n_D^{24} 1·5630, and was purified by VPC. It then had n_D^{23} 1·5555. (Found: C, 84·3; H, 9·2; N, 6·4. Calc. for $C_{15}H_{19}N$: C, 84·5; H, 9·0; N, 6·6%.)

$\tilde{\nu}_{liq.}$ 3060, 2940, 1655, 1628, 1545, 1520, 1480, 1375, 1320, 1255, 1200 cm^{-1}.

Dehydrogenation. Following the method of Plattner,[30] 1 g of X was introduced slowly into a tube heated at 330° and filled with 450 mg of 5% Pd–C catalyst. The operation was carried out in an atmosphere of N_2. The product was collected in a dry ice–acetone trap; it formed a red oil which showed the characteristic absorption of XI at 470 mμ.

2,5-*Diethyl*-3-*methyl*-Δ^1-*pyrroline* (XII). Similarly, XII was prepared by reduction of VI with amalgamated aluminum. The product (yield, 50%) which boiled at 64° (2·5 mm), could not be obtained in analytical purity. (Found: C, 76·2; H, 11·9; N, 9·5. Calc. for $C_9H_{17}N$: C, 77·6; H, 12·3; N, 10·1%.)

The IR spectrum was extremely rich in absorption bands.

$\tilde{\nu}_{liq.}$ 3705, 2970, 2935, 1630, 1560, 1498, 1360, 1310, 1280, 1105, 945, 915, 775, 745, 725, 710 cm^{-1}.

The *picrate* of the base melted at 126–127° after recrystallization from EtOH. (Found: C, 49·5; H, 5·6. Calc. for $C_{15}H_{20}N_4O_7$: C, 48·9; H, 5·5%.)

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