Addition Reactions of Conjugated Double Bonds. Part V.[1] Stereochemistry of Pyrazoline Ring Formation from αβ-Unsaturated Phenylhydrazones

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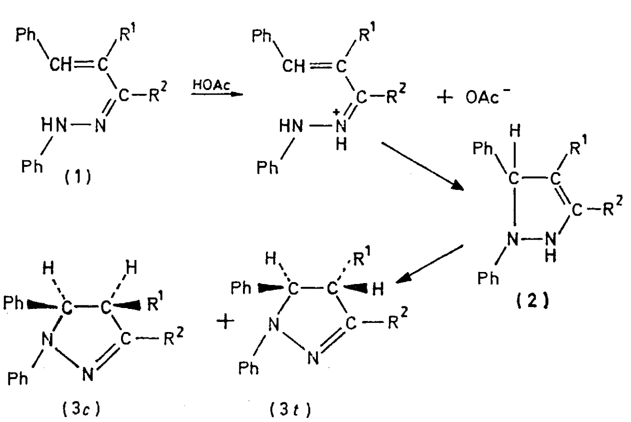
The stereochemistry of cyclisation of the phenylhydrazones of some αβ-unsaturated ketones is discussed in terms of a stereoselective enamine–imine tautomerism step. Cyclisation of the phenylhydrazone of 1-acetyl-4-t-butylcyclohexene results in an initial axial attack of the nitrogen nucleophile on the six-membered ring.

THE mechanism of cyclisation of αβ-unsaturated ketone phenylhydrazones has been the subject of recent investigations [2-4] and the currently accepted mechanism is summarised below. Under conditions of kinetic control the product stereochemistry is determined by the stereochemistry of the step (2) ⟶ (3). This enamine–imine tautomerism is the nitrogen analogue of keto–enol tautomerism which is known to be stereoselective in some cases.[5] Cyclisation of 4-phenylbut-3-en-2-one phenylhydrazone (1; $R^1 = H$, $R^2 = Me$) in deuterioacetic acid gave a stereoselective preference for the *trans*-compound (3*t*; $R^1 = D$, $R^2 = Me$).[2] We have extended this earlier work by studying the stereochemistry of cyclisation of 2-methyl-1,3-diphenylprop-2-en-1-one phenylhydrazone (1; $R^1 = Me$, $R^2 = Ph$). A mixture of *cis*- and *trans*-pyrazolines (3*c* and *t*; $R^1 = Me$, $R^2 = Ph$) was formed, together with varying amounts of the corresponding pyrazole. Stereochemical assignments were again made on the basis of n.m.r. spectroscopy.[6,7] The isomer ratio varied with the reaction conditions; cyclisations in acetic acid solution for seven days at 60 °C gave almost exclusively the *trans*-isomer whereas solutions heated under reflux for six hours gave isomers in *cis* : *trans* ratio *ca.* 1 : 4. The individual isomers were shown to equilibrate on heating in boiling acetic acid solution and the equilibrium ratio of 1 : 4 was approached from both sides. The ratio did not vary with the amount of pyrazole formed. A thermodynamic preference for the *trans*-isomer has been established for other 4,5-disubstituted-2-pyrazolines.[4,8]



Elguero and his co-workers have reported that in equilibration of the isomeric 3,4-dimethyl-1-*p*-nitrophenyl-5-phenyl-2-pyrazolines in deuterioacetic acid, some epimerisation occurred at C-4 without deuterium incorporation.[9] When the *cis*-pyrazoline (3*c*; $R^1 = Me$, $R^2 = Ph$) was heated in deuterioacetic acid, equilibration occurred. No evidence for equilibration without deuterium incorporation could be found.

Bicyclic Pyrazolines.—Cyclisation of the phenylhydrazones of benzoylcyclohexene, acetylcyclohexene, and benzoylcyclopentene gave *cis*-pyrazolines together with varying amounts of gummy materials and, in the case of acetylcyclohexene, significant amounts of the corresponding pyrazole. *cis*-Pyrazoline has previously been obtained from a reaction of acetylcyclohexene with hydrazine hydrate.[10] The *cis*-isomers did not equilibrate when heated in boiling acetic acid showing that they are thermodynamically preferred. Other bicyclo-[3.3.0] and -[4.3.0] ring systems containing sp^2 carbon atoms shows a preferred *cis*-bridgehead stereochemistry.[11,12] The *cis*-isomers also appear to be kinetically controlled but the possibility that the *trans*-products are formed and subsequently selectively converted into gummy material or pyrazole by oxidation during the isolation–separation procedure cannot be eliminated.

Cyclisation of 1-acetyl-4-t-butylcyclohexene phenylhydrazone led to the isolation of a single pyrazoline identified as the *cis*-8-t-butyl-*cis*-bicyclo-isomer by n.m.r. spectroscopy. This compound is the product of initial axial attack of the nitrogen nucleophile on the ring, a

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result in agreement with the suggestions of Abramovitch and his co-workers.[13]

EXPERIMENTAL

General.—General conditions were as described previously.[3] Acetic acid was of AnalaR grade. All cyclisations were carried out under an atmosphere of N_2. N.m.r. decoupling experiments were performed by Mr. R. Spratt.

Cyclisation of 4-*Phenylbut*-3-*en*-2-*one Phenylhydrazone in Deuterioacetic Acid.*—The hydrazone (1; R^1 = H, R^2 = Me) (3·0 g), m.p. 155—156 °C (lit.,[14] 156—157°) was dissolved in deuterioacetic acid (40 cm^3) and the solution kept at 70° for 5 min. During this time the colour changed from orange to dark green. The mixture was cooled and was allowed to stand for 12 h at 20°. Large green crystals of 1,5-diphenyl-3-methyl-2-pyrazoline were precipitated and had m.p. 112—113° (lit.,[7] 115—115·5°) after one recrystallisation from ethanol (Found: C, 80·8; H + D, 6·5. Calc. for $C_{16}H_{15}DN_2$: C, 81·0; H + D, 6·5%), $\nu_{max.}$ (KBr) 1608, 1508, 1389, 1121, 870, 748, and 698 cm^{-1}, τ 3·0 (m, Ar), 5·0 (5-H), 6·5 (4-H, integrating for 0·3H), 7·3 (4-H, integrating for 0·66H), 7·9 (s, Me). An undeuteriated sample of the pyrazoline had the absorptions at τ 5·0, 6·5, and 7·3 as an AMX system with J_{AM} 12·25, J_{AX} 8·25, and J_{MX} 17·5 Hz.

A solution of the hydrazone (3·0 g) in acetic acid (40 cm^3) was kept for 2 h at 0° and the product (2·8 g) was isolated in dichloromethane. One recrystallisation from ethanol gave the pyrazoline, m.p. 110—112°, whose i.r. and n.m.r. spectra were identical with those of the above sample.

Reactions of 3-*Methyl*-1,5-*diphenyl*-2-*pyrazoline with Deuterioacetic Acid.*—(a) The pyrazoline (1·5 g) was dissolved in deuterioacetic acid (20 cm^3) and the solution was heated for 5 min at 70°. The product was isolated in dichloromethane and i.r. and n.m.r. showed no deuterium incorporation had occurred.

(b) A solution of the pyrazoline (3·0 g) in deuterioacetic acid (40 cm^3) was heated under reflux for 2 h. The solution was cooled to 0° for 12 h and the pyrazoline (2·5 g) was recrystallised from ethanol to give a product, m.p. 110—111°, τ 3·0 (10H), 5·0 (1H), 6·5 (0·75H), 7·3 (0·75H), and 7·9 (2H).

2-*Methyl*-1,3-*diphenylprop*-2-*en*-1-*one Phenylhydrazone* (1; R^1 = Me; R^2 = Ph).—The ketone was prepared as a light yellow oil, b.p. 130—133° at 0·6 mmHg, n_D^{25} 1·6200 (lit.,[15] b.p. 154—159° at 0·3 mmHg, n_D^{26} 1·6163). The phenylhydrazone after five recrystallisations from ethanol had m.p. 123—125° (lit.,[15] 128°), τ 2·3—3·3 (m, Ar), 3·8 (s, 3-H), and 7·6 (s, Me).

trans-4-*Methyl*-1,3,5-*triphenyl*-2-*pyrazoline* (3*t*; R^1 = Me, R^2 = Ph).—The phenylhydrazone (1; R^1 = Me; R^2 = Ph) (2·1 g) was dissolved in acetic acid (50 cm^3) and the solution was allowed to stand for 7 days at 60°. The mixture was cooled and neutralised with a saturated solution of sodium carbonate. The product was extracted into ether, the ether layer washed with water, dried ($MgSO_4$), and the ether was evaporated to give a crude product (2·0 g). N.m.r. spectroscopy showed that only a small amount (2—5%) of *cis*-isomer was present and two recrystallisations from light petroleum gave trans-4-*methyl*-1,3,5-*triphenyl*-2-*pyrazoline*, m.p. 111—112·5° (Found: C, 84·8; H, 6·6; N, 8·9. $C_{22}H_{20}N_2$ requires C, 84·6; H, 6·4; N, 9·0%), τ 2·2—3·0 (m, Ar), 5·26 (d, 5-H), 6·67 (m, 4-H), and 8·68 (d, Me) with $J_{4,5}$ 5·4 and $J_{4,Me}$ 6·1 Hz.

cis-4-*Methyl*-1,3,5-*triphenyl*-2-*pyrazoline* (3*c*; R^1 = Me, R^2 = Ph).—The phenylhydrazone (2·1 g) was dissolved in acetic acid (50 cm^3) and the solution was heated under reflux for 6 h. Isolation as above gave a product (2·0 g) which was chromatographed on alumina. Elution with light petroleum gave a faintly yellow solid (1·4 g, 70%), m.p. 45—60°, where n.m.r. spectrum indicated that it was a mixture of *cis*- and *trans*-isomers in the ratio *ca.* 1 : 3. Further elution with light petroleum gave cis-4-*methyl*-1,3,5-*triphenyl*-2-*pyrazoline* (0·2 g, 10%), m.p. 142—144° (from light petroleum) (Found: C, 84·9; H, 6·6; N, 9·0%), τ 2·2—2·9 (m, Ar), 4·7 (d, 5-H), 6·1 (m, 4-H), 9·2 (d, Me) with $J_{4,5}$ 11 and $J_{4,Me}$ 6 Hz. Elution with light petroleum–benzene (1 : 3) gave 4-*methyl*-1,3,5-*triphenylpyrazole* (0·1 g, 5%), m.p. 123—124° (Found: C, 85·4; H, 5·9; N, 9·1. $C_{22}H_{18}N_2$ requires C, 85·2; H, 5·8; N, 9·0%), τ 2·04—2·8 (m, Ar) and 7·75 (s, Me). The n.m.r. spectrum of the original reaction mixture indicated that the *cis* : *trans* ratio was 3 : 7. Further cyclisations under similar conditions in both acetic and deuterioacetic acid gave similar isomer ratios with *ca.* 10—20% of pyrazole (by n.m.r.).

Equilibrations of cis- *and* trans-4-*Methyl*-1,3,5-*triphenyl*-2-*pyrazolines.*—Samples of the individual isomers (100 mg) in acetic acid (10 cm^3) were heated under reflux for the periods given in the Table. The product (85—96 mg) was isolated in dichloromethane and the composition determined by n.m.r. Equilibration of the *trans*-isomer (100 mg) in deuterioacetic acid (10 cm^3) for 12 h gave a product (92 mg) which was shown to contain *cis*- and *trans*-isomers in the ratio *ca.* 3 : 7 together with pyrazole (*ca.* 35%). The *cis*-isomer showed τ 9·2 (s, Me) but no doublet centred on τ 9·2 was detected.

Isomer distribution on thermal equilibrations

Isomer	Time	Ratio		Pyrazole
(3; R^1 = Me, R^2 = Ph)	(h)	3*c* :	3*t*	(%)
cis	3	60	40	20
cis	6	35	65	15
trans	3	20	80	5
trans	6	30	70	10

Cyclisation of 1-*Benzoylcyclohexene Phenylhydrazone.*—1-Benzylcyclohexene (3·72 g), b.p. 138—140° at 2 mmHg (lit.,[16] b.p. 135° at 2 mmHg), was added to an aqueous alcoholic solution of phenylhydrazine hydrochloride (5·58 g) and crystalline sodium acetate (6 g). The oily, air-sensitive phenylhydrazone (3·8 g, 70%) was induced to crystallise with difficulty, m.p. 55—65° (from ethanol). Further crystallisation of a portion of this product did not lead to a rise in m.p. The hydrazone (2·75 g) was dissolved in acetic acid (40 cm^3) and the solution was heated under reflux for 6 h. The crude product (2·7 g) was chromatographed on alumina and eluted with light petroleum. The early fractions (1·7 g, 63%) gave *cis*-2,3-diaza-2,4-diphenylbicyclo-[4.3.0]non-3-ene, m.p. 74—75° (from methanol) (lit.,[6] 75—76°) as long needles. Mixed m.p. with a sample prepared by the method of Huisgen *et al.*,[6] 74—75°, τ 2·1—2·8 (m, Ar), 5·92 (m, 1-H), 6·45 (m, 5-H), 7—8 (complex CH_2 groups) with $J_{1,5}$ 9·6 and $J_{1,9}$ 4·7 Hz. The latter fractions consisted of gummy material (0·6 g) which showed no absorption at τ 5—7.

Cyclisation of 1-*Benzoylcyclopentene Phenylhydrazone.*—1-Benzoylcyclopentene, b.p. 112—116° at 0·8 mmHg (lit.,[17]

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143° at 12 mmHg), was converted into an air-sensitive phenylhydrazone, m.p. 47—61°. A solution of the phenylhydrazone (2·62 g) in acetic acid (40 cm^3) was heated under reflux for 6 h. The product (2·6 g) was isolated in ether and chromatographed on alumina. Elution with light petroleum gave *cis*-2,3-diaza-2,4-diphenylbicyclo[3.3.0]-oct-3-ene (0·93 g, 36%), m.p. 130—136 raised to 136—137° after sublimation at 148° and 1 mmHg. Mixed m.p. with an authentic sample[6] 135—136° (lit.,[6] 136—137°), τ 2·2—3·1 (m, Ar), 5·38 (m, 1-H), 5·98 (m, 5-H) with $J_{1,5}$ 10·0, $J_{1,8}$ 5·4 and 2·6, and $J_{5,6}$ 6·0 Hz. Elution with light petroleum–ether (1 : 1) gave gummy material (0·7 g) which showed no absorption at τ 5—7.

Cyclisation of 1-*Acetylcyclohexene Phenylhydrazone*.—1-Acetylcyclohexene, b.p. 79—83° at 13 mmHg, n_D^{25} 1·4870 (lit.,[18] b.p. 63—64° at 6 mmHg, n_D^{20} 1·4881) gave a crystalline *phenylhydrazone*, m.p. 76—78° (from aqueous alcohol) (Found: C, 78·2; H, 8·4; N, 12·1. $C_{14}H_{18}N_2$ requires C, 78·5; H, 8·4; N, 13·1%). The phenylhydrazone (2·15 g) was dissolved in acetic acid (30 cm^3) and the solution was heated under reflux for 3 h. The product (2·1 g) was isolated in ether and chromatographed on alumina. Elution with benzene–light petroleum (1 : 1) gave a pale yellow sample of cis-2,3-*diaza*-4-*methyl*-2-*phenylbicyclo*[4.3.0]*non*-3-*ene* (0·79 g, 38%), m.p. 47—48° after sublimation at 100° at 0·2 mmHg (Found: C, 78·3; H, 8·8; N, 13·4. $C_{14}H_{18}N_2$ requires C, 78·5; H, 8·4; N, 13·1%), τ 2·6—3·3 (m, Ar), 5·87 (m, 1-H), 7·05 (m, 5-H), 7·95 (s, Me), and 8—8·8 (m, CH_2 groups) with $J_{1,5}$ 10·1, and $J_{1,9}$ 5·0 Hz. Further elution with the same solvent system gave the 1(9),3-*diene* (0·8 g, 38%), m.p. 52—53° (from ether–light petroleum) (Found: C, 79·0; H, 7·4. $C_{14}H_{16}N_2$ requires C, 79·2; H, 7·6%), τ 2·5—2·85 (m, Ar), 7·0—7·8 (m, CH_2), 8·27 (s, Me). Elution with benzene–ether (1 : 3) gave acetanilide (0·19 g, 9%), m.p. and mixed m.p. 114—115°.

Cyclisation of 1-*Acetyl*-4-*t*-*butylcyclohexene Phenylhydrazone*.—1-Acetyl-4-t-butylcyclohexene, b.p. 134—136° at 14 mmHg (lit.,[19] 135—137° at 14 mmHg), gave a *phenylhydrazone*, m.p. 80—82° (Found: C, 79·5; H, 9·0; N, 10·2. $C_{18}H_{26}N_2$ requires C, 80·0; H, 9·6; N, 10·4%). A solution of the phenylhydrazone (2·7 g) in acetic acid (40 cm^3) was heated under reflux for 3 h and the product (2·3 g) was isolated in ether as a pale yellow solid. Elution from an alumina column with light petroleum gave cis-2,3-*diaza*-4-*methyl*-2-*phenyl*-8-*t*-*butylbicyclo*[4.3.0]*non*-3-*ene* (1·25 g, 48%), m.p. 46—48° after sublimation at 90° and 0·5 mmHg (Found: C, 80·0; H, 9·7; N, 10·4. $C_{18}H_{26}N_2$ requires C, 80·0; H, 9·6; N, 10·4%), τ 2·5—3·1 (m, Ar), 6·1 (m, 1-H), 7·1 (m, 5-H), 7·5—8·9 (m, CH_2 groups), 8·0 (s, Me), and 9·2 (s, CMe_3). Double irradiation experiments gave $J_{1,5}$ 10·0 and $J_{1,9}$ 3·4 Hz. Elution with benzene–light petroleum (3 : 1) gave yellow crystals of the 1(9),3-*diene* (0·34 g, 13%), m.p. 106—108° (from ether–light petroleum) (Found: C, 80·2; H, 8·6; N, 10·6. $C_{18}H_{24}N_2$ requires C, 80·6; H, 8·9; N, 10·4%), τ 2·5—2·8 (m, Ar), 7·4—8·1 (m, CH_2 groups), 7·75 (s, Me), and 9·1 (s, CMe_3).

Equilibration Experiments.—A solution of the pyrazoline from 1-benzoylcyclohexene phenylhydrazone (100 mg), m.p. 74—75°, in acetic acid (19 cm^3) was heated under reflux for 3 h. The product (94 mg) was isolated in ether. It had identical spectral properties to the starting material and after one recrystallisation had m.p. 74—75°. A solution was heated for 6 h and gave product (86 mg) of lower m.p. 68—74°. The n.m.r. spectrum of this sample showed a decrease in intensity of the absorptions at τ 5·92 and 6·45 but no new absorptions in this region suggesting some pyrazole formation had occurred.

Attempted equilibrations of the pyrazolines from benzoylcyclopentene and acetylcyclohexene gave recovered starting materials in 91 and 85% yields.

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