Aromatic Substitution. Part XXIV.[1] The Emmert Reaction: Effects of Substituents on Orientation

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The reactions of pyridine and 3-picoline with cyclohexanone and 2-methylcyclohexanone, and of pyridine with 4-t-butylcyclohexanone, in the presence of magnesium amalgam have been studied quantitatively. In the latter case the conformations of the products have been established. The *cis–trans*-isomer ratio was 54·2 : 45·8. With 3-picoline, attack took place predominantly at C-6. The results are thought to fit a 1,3-dipolar cycloaddition or a co-ordination of $R_2\overset{-}{C}\cdot O\overset{+}{M}$ at nitrogen followed by nucleophilic cyclisation mechanism.

THE Emmert reaction involves the condensation of a pyridine with a ketone in the presence of magnesium or aluminium amalgam to give a pyridyl alcohol.[2-5] With magnesium it is reported that attack only takes place at the α-position of the pyridine ring, whereas with aluminium attack at both the α- and the γ-position occurs. Two mechanisms have been proposed to account for the formation of the products as well as the pinacols that are occasionally obtained. Bachman and his co-workers [5a] suggested a mechanism involving nucleophilic attack upon the pyridine ring (Scheme 1). An alternative, free-radical process has also been put forward (Scheme 2).[6]

We were interested in the mechanism of this reaction and in the orientation imposed by a 3-substituent in the pyridine ring upon the attacking group. A 3-methyl group generally directs an entering nucleophile [1,7] or free radical [8] predominantly to the 2-position unless the nucleophile is large and relatively non-selective.[1] For example, 3-picoline and phenyl-lithium give 3-methyl-2-phenylpyridine and 5-methyl-2-phenylpyridine in the ratio of 19 : 1,[7] and homolytic phenylation of 3-picoline gives mainly 3-methyl-2-phenylpyridine.[8] On the other hand, the Emmert reaction between 3-picoline and cyclopentanone in the presence of magnesium and

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[2] B. Emmert and E. Asendorf, *Ber.*, 1939, **72**B, 1188.

[3] B. Emmert and E. Pirot, *Ber.*, 1941, **74**B, 714.

[4] C. H. Tilford, R. S. Shelton, and M. G. Van Campen, jun., *J. Amer. Chem. Soc.*, 1948, **70**, 4001.

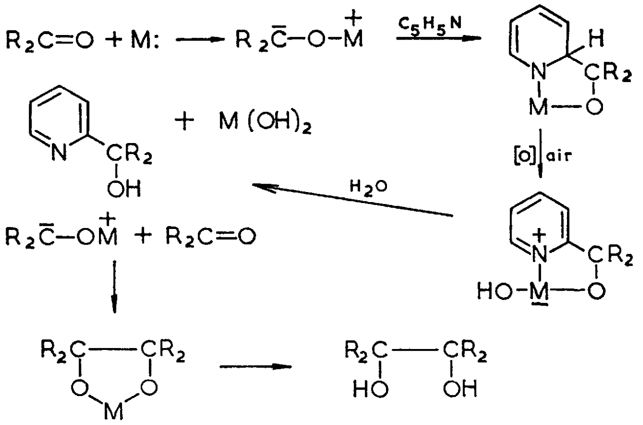
[5] (*a*) G. B. Bachman, M. Hamer, E. Dunning, and R. M. Schisla, *J. Org. Chem.*, 1957, **22**, 1296; (*b*) G. B. Bachman and R. M. Schisla, *ibid.*, p. 1302; (*c*) G. B. Bachman and D. D. Micucci, *J. Amer. Chem. Soc.*, 1948, **70**, 2381.

[6] R. A. Barnes, in 'Pyridine and its Derivatives,' ed. E. Klingsberg, Part 1, Interscience, New York, 1960, ch. 1.

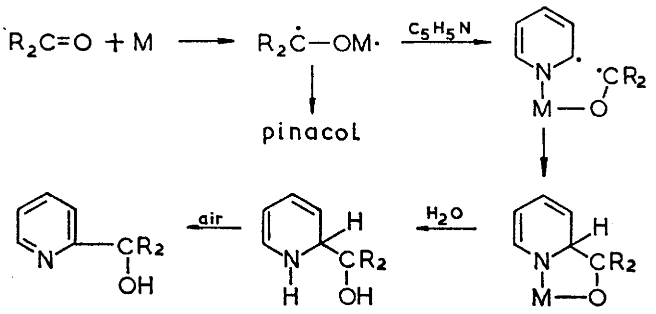
[7] R. A. Abramovitch and C. S. Giam, *Canad. J. Chem.*, 1964, **42**, 1627.

[8] R. A. Abramovitch and M. Saha, *Canad. J. Chem.*, 1966, **44**, 1765.

mercuric chloride was reported[9] to give the 2,3- and 2,5-isomers in the ratio of 25 : 75, similar to the ratio obtained from isopropyl-lithium and 3-picoline. We have investigated the reaction of a number of cyclohexanones with pyridine and 3-picoline. It was hoped the results would point to one of the alternative mechanisms. It was also of interest to determine whether any hitherto undetected substitution had taken place at C-3, particularly when aluminium was used.



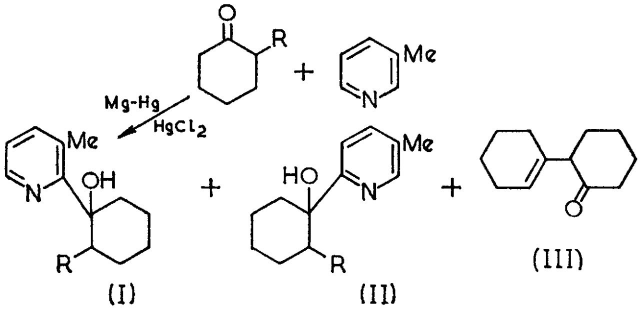
SCHEME 1



SCHEME 2

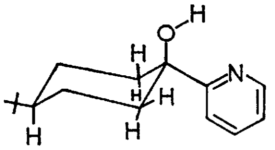
The reaction between pyridine, cyclohexanone, and magnesium amalgam[3] was repeated with the reagents in the molar ratio of 2 : 1 : 0·5. Only 1-(2-pyridyl)-cyclohexanol was obtained, whereas Emmert and Pirot, using a molar ratio of 1·26 : 1·0 : 0·41 reported the formation of 1,1′-dihydroxybicyclohexyl as well.[3] The latter is undoubtedly formed because of the higher proportion of cyclohexanone present. When aluminium was used instead of magnesium[9] both the 1-(2-pyridyl) and the 1-(4-pyridyl) derivatives were obtained in the ratio of 79·2 : 20·8. Again, only 2-methyl-1-(2-pyridyl) cyclohexanol was obtained (8·4%) from pyridine and 2-methylcyclohexanone in the presence of magnesium in air. The yield of product was not appreciably increased (9·6%) by carrying out the reaction under dry, oxygen-free nitrogen. In no case was any product of attack at C-3 detected by g.l.c.

When treated with 3-picoline in the presence of magnesium, cyclohexanone gave a mixture of 1-(3-methyl-2-pyridyl)- and 1-(5-methyl-2-pyridyl)-cyclohexanol (I and II; R = H) in the ratio of 29·1 : 70·9. A neutral by-product isolated in this case was characterised as 2-cyclohex-1-enylcyclohexanone (III), an aldol condensation product. No such by-product was formed when 2-methylcyclohexanone was used and the ratio of (I) to (II) (R = Me) was 24·6 : 75·4, showing evidence of some steric hindrance by the 3-methyl group.

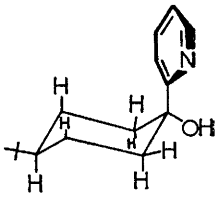


When 3-picoline and pyridine were allowed to compete for a small amount of cyclohexanone in the presence of magnesium amalgam it was found that $^{\mathrm{Me}}{}_{\mathrm{H}}K$ was 0·28. This, together with the formation of an aldol condensation product (III) in one case, the observed orientation, and the absence of any influence of atmospheric oxygen, is best interpreted in terms of either a 1,3-dipolar cycloaddition mechanism or a two-step process involving co-ordination of the metal cation at nitrogen followed by rate-determining nucleophilic cyclisation, rather than a free-radical mechanism.

It was of interest to determine whether there was any stereospecificity in the reaction with cyclic ketones, and the reaction of pyridine with 4-t-butylcyclohexanone in the presence of magnesium was studied. Two alcohols, C and D, were obtained in the ratio of 54·2 : 45·8. The same two alcohols were obtained in the ratio of 59·1 : 40·9 from the reaction of 2-pyridyl-lithium with 4-t-butylcyclohexanone. Compound C was identified as 1-(2-pyridyl)-*cis*-4-t-butylcyclohexanol (IV) and D as the corresponding *trans*-isomer (V) on the basis of the following considerations. The reaction of 4-t-butylcyclohexanone with methyl-lithium gives a *cis*–*trans* ratio of 65 : 35,[10] while with phenylmagnesium bromide about equal amounts of the two isomers are formed.[11] It was argued[11] that with the latter two compounds, when the 1-phenyl group was axial the protons at C-2 and C-6 were deshielded by the diamagnetic anisotropy



(IV)



(V)

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[9] H. L. Lochte, P. F. Kruse, jun., and E. N. Wheeler, *J. Amer. Chem. Soc.*, 1953, **75**, 4477.

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of the benzene ring, the equatorial proton signals being downfield from those of the axial protons (τ 7·48 and 8·3, respectively). When the phenyl was equatorial the cyclohexane protons absorbed at τ 8·36. Compound D similarly gave rise to a 2-proton doublet at τ 7·69 but a broad 3-proton signal at τ 8·3. A four-proton signal at τ 8·89 in the spectrum of D was assigned to the protons at C-3 and C-5, which would be expected to be shielded by the axial pyridine ring. In contrast, compound C gave rise to a nine-proton doublet at τ 8·36. Another important difference between the n.m.r. spectra of C and D is in the position of the hydroxy-absorptions (exchangeable with deuterium oxide). In the spectrum of C, the axial hydroxy-group resonates at τ 5·53, while the equatorial hydroxy-group in D resonates at τ 7·16. This is the reverse of what is usually expected for epimeric hydroxy-groups.[11] A likely explanation is based on the preferred rotational configuration of the pyridyl group in each of the conformations. By analogy with the configuration of axial and equatorial carboxy-groups [12] it may be expected (and Dreiding models confirm this) that an equatorial pyridine ring would adopt a configuration perpendicular to the cyclohexane ring rather than parallel to it, and that an axial pyridine would prefer a tangential configuration (V). Hydrogen bonding of the axial hydroxy-group with the pyridine nitrogen lone pair would then be sterically reasonable in (IV) but unlikely in (V), thus accounting for the reversal. As expected on this basis, C is less polar than D and is adsorbed less strongly on alumina.

The stereoselectivities of the organolithium and Emmert reactions—which proceed by diametrically opposite mechanisms—are about the same, suggesting that the transition states have similar geometries.

EXPERIMENTAL

1-(2-Pyridyl)- and 1-(4-pyridyl)-cyclohexanol were prepared by the method of Wiley and his co-workers.[13] The preparation of 2-methyl-1-(5-methyl-2-pyridyl)cyclohexanol has already been described.[14]

2-*Methyl*-1-(2-*pyridyl*)*cyclohexanol*.—A solution of n-butyl-lithium (2·1 g.) in hexane (14·2 ml.) and ether (15 ml.) was stirred under dry nitrogen at −65° and treated with 2-bromopyridine (5 g.) in dry ether (10 ml.) during 15 min. The mixture was stirred for another 15 min. then 2-methylcyclohexanone (3·6 g.) in dry ether (10 ml.) was added dropwise at the same temperature. Stirring was continued for 30 min., and then for a further 3 hr. while the mixture warmed to room temperature. Crushed ice (50 g.) was added and starting materials were removed by steam-distillation. The residue was extracted with ether and the extract was dried (KOH) and evaporated; the residue was distilled *in vacuo* to give 2-*methyl*-1-(2-*pyridyl*)*cyclohexanol* (4 g., 72·1%), b.p. 112—114°/15 mm. $\nu_{max.}$ (film) 3390s, 2930s, 1585w, 1390s, 990s, 765s, and 740s cm.$^{-1}$. The *picrate* (from benzene) had m.p. 131° (Found: C, 51·8; H, 5·0. $C_{12}H_{17}NO,C_6H_3N_3O_7$ requires C, 51·4; H, 4·8%).

1-(3-*Methyl*-2-*pyridyl*)*cyclohexanol*.—Prepared (24%) from 2-bromo-3-methylpyridine and cyclohexanone it had b.p. 110—114°/4 mm., m.p. 74°, $\nu_{max.}$ (KBr) 3270s, 2930s, 1580w, 965s, 790s, and 755s cm.$^{-1}$. The *picrate* (from benzene) had m.p. 111·5° (Found: C, 51·6; H, 4·7. $C_{12}H_{17}NO,C_6H_3N_3O_7$ requires C, 51·4; H, 4·8%).

1-(5-*Methyl*-2-*pyridyl*)*cyclohexanol*.—Prepared from 2-bromo-5-methylpyridine and cyclohexanone, this *alcohol* (39%) had m.p. 36° [from light petroleum (b.p. 60—80°)], $\nu_{max.}$ (KBr) 3400s, 2925s, 1605w, 980s, and 820s cm.$^{-1}$. The *picrate* (from benzene) had m.p. 126·5° (Found: C, 51·3; H, 4·5%).

2-*Methyl*-1-(3-*methyl*-2-*pyridyl*)*cyclohexanol*.—This alcohol was obtained (25·3%) from 2-bromo-3-methylpyridine and 2-methylcyclohexanone; m.p. 94° [from light petroleum (b.p. 60—80°)], $\nu_{max.}$ (KBr) 3270s, 2940s, 1590w, 1085s, 990s, 805s, and 765s cm.$^{-1}$. The *picrate* (from benzene) had m.p. 162·5° (Found: C, 52·7; H, 5·3. $C_{13}H_{19}NO,C_6H_3N_3O_7$ requires C, 52·5; H, 5·1%).

1-(2-*Pyridyl*)-cis- *and* trans-4-*t*-*butylcyclohexanol*.—A mixture of the two isomers (1·06 g.) was obtained from 2-bromopyridine (1·03 g.), n-butyl-lithium (0·41 g.), and 4-t-butylcyclohexanone (1·0 g.). The product was dissolved in benzene and chromatographed on neutral alumina (3·5 × 30 cm.). Elution with benzene–chloroform (1 : 2) gave first 1-(2-*pyridyl*)-cis-4-*t*-*butylcyclohexanol*, m.p. 58—60° [from light petroleum (b.p. 60—80°)] (Found: C, 77·0; H, 9·5. $C_{15}H_{23}NO$ requires C, 77·25; H, 9·9%), $\nu_{max.}$ (KBr) 3390s,br, 2950s, 1582s, 1360s, 1110w, 1020w, 950s, 780s, and 743s cm.$^{-1}$; τ (CCl_4; 100 Mc./sec.) 1·56 (1H, d, $J_{5,6} = J_{4,6} =$ 6·5 c./sec.), 2·20 (1H, t, $J_{4,5} = J_{3,4} =$ 7 c./sec.), 2·73 (1H, d, $J_{3,4}$ 7 c./sec.), 2·94 (1H, t, $J_{5,6}$ 6·5, $J_{4,5}$ 7 c./sec.), 5·53 (OH), 8·36 (9H, d), and 9·07 (9H, s). 1-(2-*Pyridyl*-trans-4-*t*-*butylcyclohexanol*, m.p. 98—100° (from n-hexane), was eluted with the same solvent (Found: C, 77·2, H, 9·6%), $\nu_{max.}$ (KBr) 3320s,br, 2950s, 1585w, 1360s, 1055s, 970w, 778s, and 725s cm.$^{-1}$; τ (CCl_4; 100 Mc./sec.) 1·54 (1H, s), 2·45 (1H, t, $J_{3,4} = J_{4,5} =$ 7·5 c./sec.), 2·55 (1H, m), 2·94 (1H, m), 7·16 (OH), 7·69 (2H, d, J 7 c./sec.), 8·30 (3H, s), 8·89 (4H, m), and 9·18 (9H, s).

Another reaction mixture was resolved quantitatively by gas chromatography on a column (3 ft. × ¼ in.) packed with Apiezon L (20%) on Gas Chrom P (100—120 mesh) at 192° (helium flow rate 66 ml./min.; *o*-nitromethanesulphonanilide internal standard). The *cis*–*trans* ratio was found to be 59·1 : 40·9 and the overall yield was 76%.

General Procedure for the Emmert Reaction.—The metal, mercuric chloride, and mercury were heated in an oven at 120° for 15 min.[9] The pyridine and ketone were then added and the mixture was heated at 85° for 5 hr. It was then hydrolysed with 6N-sodium hydroxide, the organic layer was extracted with 6N-hydrochloric acid and the aqueous layer was acidified and extracted with ether. The acid and neutral extracts were treated separately. The acid layers were basified with 6N-sodium hydroxide and extracted with ether to give the organic bases. The neutral layers were extracted with ether and the ether was evaporated off to give the non-basic products. Reactions were carried out in triplicate.

Reaction of Pyridine with Cyclohexanone in the Presence of Magnesium.—When the pyridine–cyclohexanone–magnesium molar ratio was 2 : 1 : 0·5 a 13·2% yield of 1-(2-pyridyl)-cyclohexanol was obtained. None was obtained when the

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[12] J. Sicher, M. Tichý, and F. Šipoš, *Tetrahedron Letters*, 1966, 1393.

[13] R. H. Wiley, P. X. Callahan, C. H. Jarboe, jun., J. T. Nielsen, and B. J. Wakefield, *J. Org. Chem.*, 1960, **25**, 366.

[14] R. A. Abramovitch and G. A. Poulton, *J. Chem. Soc.* (*B*), 1967, 267.

ratio was 25 : 1 : 0·5 and a 1·4% yield was obtained with a ratio of 25 : 1 : 7.

Reaction of Pyridine with Cyclohexanone in the Presence of Aluminium.—The procedure was the same as that described by Lochte, Kruse, and Wheeler.[9] The mixture was resolved on a column (4½ ft. × ¼ in.) packed with asphalt (10%) on Chromosorb W (60—80 mesh) at 210° (helium flow rate 66 ml./min.; coumarin internal standard). The ratio of 1-(2-pyridyl)cyclohexanol to 1-(4-pyridyl)cyclohexanol was 79·2 : 20·8 and the overall yield was 18·2%.

Reaction of Pyridine with 2-Methylcyclohexanone in the Presence of Magnesium.—The amalgam was prepared from mercuric chloride (0·18 g.), magnesium (0·39 g.), and mercury (4 drops). Pyridine (2 g.) and 2-methylcyclohexanone (3 g.) were added at 85° and after 15 min. more pyridine (2·3 g.) was added to the stirred, green solution kept at 85°. 2-Methyl-1-(2-pyridyl)cyclohexanol (0·43 g., 8·4%), identical with the authentic sample, was obtained. The reaction was repeated under an atmosphere of dry, oxygen-free nitrogen with use of degassed pyridine and 2-methylcyclohexanone. The alcohol was obtained in 9·6% yield.

Reaction of 3-Picoline with Cyclohexanone.—3-Picoline (8·7 g.), cyclohexanone (4·25 g.), magnesium (0·6 g.), mercuric chloride (0·29 g.), and mercury (4 drops) were treated as before. The fraction containing the organic bases was analysed on a column (4½ ft. × $\frac{3}{16}$ in.) packed with butanediol succinate (16%) on C-22 firebrick (60—80 mesh) at 150° (helium flow rate 62 ml./min.; bibenzyl internal standard). The ratio of 1-(3-methyl-2-pyridyl)cyclohexanol to 1-(5-methyl-2-pyridyl)cyclohexanol was 29·1 : 70·9 and the overall yield was 19·2%. The products were identical with authentic samples.

The neutral fraction (0·3 g.), b.p. 128—130°/11 mm., was 2-cyclohex-1-enylcyclohexanone, identical with an authentic sample[15] (Found: C, 80·8; H, 10·4. Calc. for $C_{12}H_{18}O$: C, 80·85; H, 10·2%), $\nu_{max.}$ (film) 3040w, 2930s, 1710s, 1620w, 1442s, 1120s, 915w, and 800w cm.$^{-1}$, τ (CCl_4) 4·74 (1H, =CH–) and 7·67br (3H, CH·CO·CH_2). The 2,4-*dinitrophenylhydrazone* had m.p. 132° (from ethanol) (Found: C, 60·7, H, 5·95; N, 15·4. $C_{18}H_{22}N_4O_4$ requires C, 60·3; H, 6·2; N, 15·6%). The semicarbazone had m.p. and mixed m.p. 172—173° (from ethanol) (lit.,[16] 178—179°).

Reaction of 3-Picoline with 2-Methylcyclohexanone.—3-Picoline (5·4 g.), 2-methylcyclohexanone (3 g.), magnesium (0·36 g.), mercuric chloride (0·18 g.) and mercury (3 drops) were treated in the usual manner. Analysis on a column (5 ft. × $\frac{3}{16}$ in.) packed with butanediol succinate (16%) on firebrick (40—60 mesh) at 170° (helium flow rate 54 ml./min.; biphenyl internal standard) gave a 2,3- to 2,5-isomer ratio of 24·6 : 75·4. The overall yield was 14·6%. The products were identical with authentic samples.

Reaction of a Mixture of Pyridine and 3-Picoline with Cyclohexanone.—3-Picoline (28·3 g., 0·3 mole), pyridine (24·2 g., 0·31 mole), and cyclohexanone (2·82 g., 0·029 mole) were added to the amalgam of magnesium (3·87 g.), mercuric chloride (0·85 g.) and mercury (10 drops). The basic fraction was resolved on a column (6½ ft. × ¼ in.) packed with Apiezon N (25%) on Chromosorb W (60—80 mesh) at 181° (helium flow rate 85 ml./min.; biphenyl internal standard). The molar ratio of 1-(2-pyridyl)cyclohexanol to the combined 1-(3-methyl-2-pyridyl)- and 1-(5-methyl-2-pyridyl)-cyclohexanol was 3·57 and the 2,3- to 2,5-isomer ratio was 29 : 71.

Reaction of Pyridine with 4-t-Butylcyclohexanone.—4-t-Butylcyclohexanone (4 g.) in dry toluene (10 ml.) and pyridine (4·7 g.) were heated with magnesium (0·23 g.), mercuric chloride (0·12 g.), and mercury (3 drops) as before. The bases were resolved on the same column as for the analysis of the authentic samples. The *cis–trans* ratio was 54·2 : 45·8 and the overall yield 25·8%. The products were identical with the authentic samples.

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[15] W. S. Rapson, *J. Chem. Soc.*, 1941, 15.

[16] O. Wallach, *Annalen*, 1911, **381**, 95.