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MOBILE KETO ALLYL SYSTEMS. III. CONVERSION OF β-KETOALLYLAMINES TO AZETIDINYL KETONES AND THEIR EPIMERIZATION.

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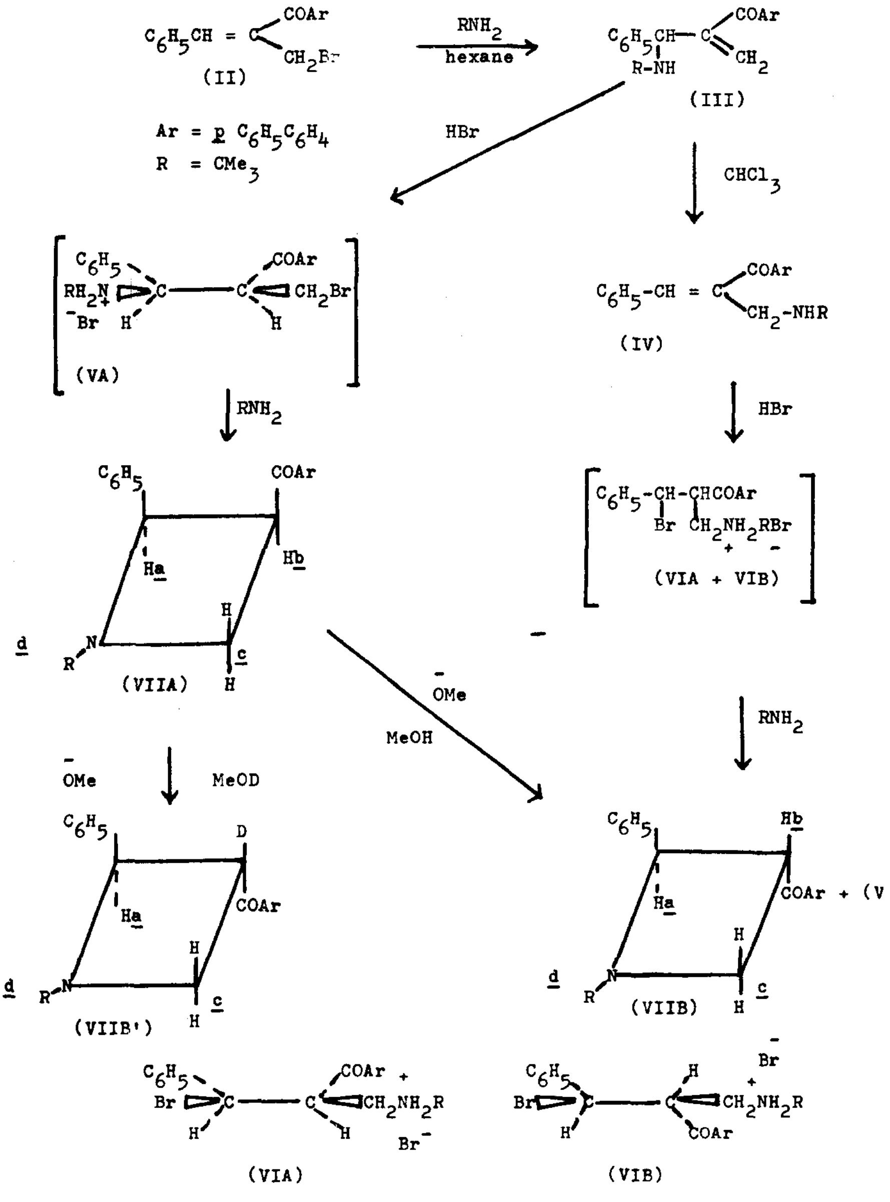
Originally we had considered it possible that a C-aroylazetidine (an azetidinyl ketone) might result from the reaction of α-bromomethylchalcone with primary amines, or from the rearrangement of the α-[N-alkylaminobenzyl]-acrylophenone which was actually obtained in the initial reaction; however, this latter type of structure was found to readily rearrange to an α-[N-alkylaminomethyl]-chalcone and no evidence for an azetidinyl ketone was observed (1).

As a continuation of these studies of the chemistry of β-ketoallyl systems trans α-(bromomethyl)-*p*'-phenylchalcone (II) (from the reaction of N-bromosuccinimide with trans α-methyl-*p*'-phenylchalcone (I) has been found to react with *t*-butylamine in solvent hexane to give a high yield of the rearrangement-substitution product, α-(N-*t*-butylaminobenzyl)-*p*-phenylacrylophenone (III). The aminoketone III rearranged quantitatively to the thermodynamically more stable isomer IV on refluxing in the more polar solvent chloroform. N.m.r. studies of these reaction mixtures gave no evidence for the presence of other products such as the desired arylaroylazetidines. A simple method of synthesis producing these four-membered ring ketones in high yield has now been developed.


(II)
RNH2
hexane
(III)
Ar = p C6H5C6H4
R = CMe3
HBr
CHCl3
(VA)
(IV)
RNH2
HBr
(VIA + VIB)
(VIIA)
Ha
Hb
c
d
OMe
MeOH
RNH2
OMe
MeOD
(VIIB')
(VIIB)
+ (V
(VIA)
(VIB)

The amino ketone III was dissolved in chloroform previously saturated with dry HBr and allowed to stand six hours at room temperature, to allow for the formation of the bromoaminoketone hydrobromide VA. Cooling this reaction mixture to 0° and neutralization with *t*-butylamine produced a 78% yield of the *cis* 1-*t*-butyl-2-phenyl-3-*p*-phenylbenzoylazetidine (VIIA). The addition of HBr to III appears to have produced only the more stable *erythro* racemate VA which would be expected to ring-close to give exclusively the *cis*-azetidine VIIA. A similar series carried out with the aminoketone IV appears to have produced a mixture of the *erythro* racemate VIA and the *threo* isomer VIB in a ratio of the order of 2:1. Treatment of the isomeric mixture of VIA + VIB with *t*-butylamine produced the *cis* VIIA and *trans* VIIB in a 2:1 ratio (total yield, 84%).

The assignment of the configurations of VIIA and VIIB is based upon absorption spectral studies. The *trans* isomer VIIB shows a u.v. λmax. with an increased extinction coefficient ε compared with that of VIIA. We suggest this indicates an expected increased four-ring hyperconjugation effect for the *trans* isomer similar to that previously established for three-ring carbonyl compounds (2). The n.m.r. spectra were especially useful in that the *cis* isomer VIIA showed the expected (3) larger coupling constant for the benzylproton, [Ha, 5.06τ(J, 9.5)] as compared with the value for the *trans* isomer VIIB [Ha, 4.65τ(J, 6.5)].

The *cis* arylaroylazetidine VIIA was readily epimerized in 75% yield to the thermodynamically more stable *trans* isomer VIIB with sodium methoxide on refluxing in methanol solution; and when CH_3OD was used, the deuterated *trans* azetidine VIIB' resulted. The n.m.r.

spectrum of VIIB' was simpler and helped to establish the location of the Ha, Hb and Hc bands for isomers VIIA and VIIB.

α-Methyl-p'-phenylchalcone (I), m.p. 99°C, from the HBr catalyzed condensation of benzaldehyde with p-phenylpropiophenone showed a u.v. spectrum (isooctane) λmax, 284 mμ (ε , 27,100) and an infrared spectrum (CCl_4), γc=o, 1653cm^{-1}. The n.m.r. spectrum (CCl_4) showed a multiplet (14H) at 2.1-2.8τ (aromatic), a singlet (1H) at 2.85τ (vinyl proton), and a singlet (3H) at 7.77τ (methyl protons).

<u>Anal</u>. Calcd. for $C_{22}H_{18}O$: C, 88.56; H, 6.08. Found: C, 88.48; H, 6.00.

The u.v. spectrum (isooctane) of II, m.p. 107°C, showed a λmax. at 285 mμ (ε 34,800) and the infrared spectrum (CCl_4) γc=o at 1660cm^{-1}. The n.m.r. spectrum (CCl_4) showed a multiplet (15H) at 2.0-3.0τ (aromatic + benzal proton), a singlet (2H) at 5.48τ (α-bromomethyl protons).

<u>Anal</u>. Calcd. for $C_{22}H_{17}BrO$: C, 70.03; H, 4.54; Br, 21.15. Found: C, 69.92; H, 4.61; Br, 20.93.

Amino ketone III, m.p. 90°C, showed a u.v. spectrum (isooctane) λmax, 284 mμ (ε , 29,300) and an infrared spectrum (CCl_4) γc=o, 1658cm^{-1}. The n.m.r. spectrum ($CDCl_3$) showed a multiplet (14H) at 2.1-3.0τ (aromatic protons) two singlets (1H each) at 3.74τ and 4.28τ (vinyl protons), a singlet (1H) at 4.85τ (benzyl proton), a singlet (1H) at 8.68τ (NH proton) and a singlet (9H) at 8.92τ (t-butyl protons).

<u>Anal</u>. Calcd. for $C_{26}H_{27}NO$: C, 84.51; H, 7.37; N, 3.79. Found: C, 84.52; H, 7.25; N, 3.84.

Amino ketone IV, m.p. 92°C, showed a u.v. spectrum (isooctane) λmax, 284 mμ (ε , 20,500) and an infrared spectrum (CCl_4) γc=o,

$1647cm^{-1}$. The n.m.r. spectrum ($CDCl_3$) showed a multiplet (15H) at 2.00-2.83τ (aromatic + benzal proton), a singlet (2H) at 6.26τ (methylene protons), a singlet (1H) at 8.03τ (NH proton) and a singlet (9H) at 8.82τ (t-butyl protons).

Anal. Found: C, 84.45; H, 7.43; N, 3.66.

The u.v. spectrum of the cis isomer VIIA (isooctane), m.p. 165°C, showed a λmax at 282 mμ (ε, 22,800) and an infrared spectrum (CCl_4) γc=o at $1683cm^{-1}$. The n.m.r. spectrum ($CDCl_3$) showed a doublet (1H) at 5.06τ(J, 9.5) (Ha proton), a multiplet (3H) at 5.30-6.68τ (Hb + Hc protons), and a singlet (9H) at 9.07τ (Hd protons).

Anal. Found: C, 84.40; H, 7.45; N, 3.76.

The trans isomer VIIB, m.p. 128°C, showed a u.v. spectrum (isooctane)λmax, 282 mμ (ε, 26,100) and an infrared spectrum (CCl_4) γc=o, $1680cm^{-1}$. The n.m.r. spectrum ($CDCl_3$) showed a doublet (1H) at 4.65τ(J, 6.5) (Ha proton), a multiplet (3H) at 6.06-6.64τ (Hb + Hc protons) and a singlet (9H) at 9.07τ (Hd protons).

Anal. Found: C, 84.38; H, 7.39; N, 4.09.

The deuterated trans isomer VIIB', m.p. 128°C, showed a u.v. spectrum (isooctane)λmax, 282 mμ (ε, 26,200) and an infrared spectrum (CCl_4), γc=o, $1680cm^{-1}$. The n.m.r. spectrum showed a singlet (1H) at 4.65τ (Ha proton), a singlet (2H) at 6.48τ (Hc protons) and a singlet (9H) at 9.07τ (Hd protons).

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1. R. P. Rebman and N. H. Cromwell, Tetrahedron Letters, No. 52, 4833 (1965).
2. See for example: N. H. Cromwell, R. Bambury, and J. L. Adelfang, J. Am. Chem. Soc. 82, 4241 (1960); N. H. Cromwell, F. H. Schumacker and J. L. Adelfang, ibid. 83, 974 (1961); R. J. Mohrbacher and N. H. Cromwell, ibid. 79, 401 (1957), note that for $C_6H_5CH_2CH_2COC_6H_4$-C_6H_5-p, λmax = 276 (ε, 25,100), $\nu_{C=O}$ = 1690cm^{-1}.
3. The cis hydrogen coupling constants are expected to be larger for the azetidines as they have been shown to be for the analogous cis hydrogens of the arylaroylaziridines, see for example: A. E. Pohland, R. C. Badger and N. H. Cromwell, Tetrahedron Letters, No. 48, 4369 (1965); N. J. Leonard, R. Y. Ning and R. L. Booth, J. Org. Chem., 30, 4357 (1965); and, N. J. Leonard, Rec. Chem. Prog. 26, No. 4, 211 (1965).