

Azetidinyl Ketones.
Synthesis of 1-Alkyl-2,4-diphenyl-3-benzoylazetidines (1)

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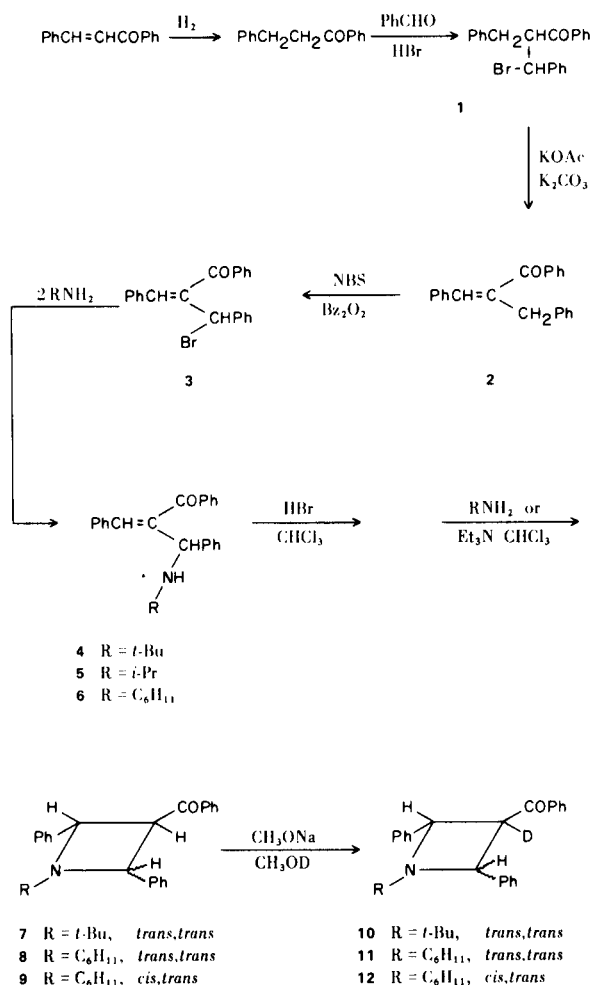
α -(α' -Bromobenzyl)chalcone (**3**) reacts with primary amines (*t*-butyl, isopropyl, cyclohexyl) to give α -(α' -alkylaminobenzyl)chalcones (**4**, **5** and **6**). When these allylic amines are treated with hydrogen bromide followed by reaction with base, they produce 1-alkyl-2,4-diphenyl-3-benzoylazetidines (**7**, **8** and **9**). These azetidines were readily converted to their 3-deuterio derivatives (**10**, **11** and **12**) by treatment with sodium methoxide in deuteriomethanol. The configurations were assigned primarily by pmr spectra and mass spectra in reference to analogous compounds.

Introduction.

We have previously reported from this laboratory the syntheses of several azetidinyl ketones (**3** and **4**) and the mass spectral studies of some of those compounds (**5**). These earlier studies produced the important basic chemical shift and mass ion data by which the configurations of the current series of 1-alkyl-2,4-diphenyl-3-benzoylazetidines could be assigned. This new series of symmetrical azetidines was synthesized both for spectral reasons and to further determine the utility of this ring closure technique.

Results.

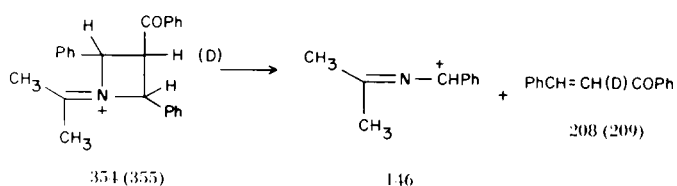
The treatment of dihydrochalcone with benzaldehyde in the presence of hydrogen bromide led to α -(α' -bromobenzyl)dihydrochalcone (**1**). This compound was subsequently dehydrohalogenated with potassium acetate and potassium carbonate to α -benzylchalcone (**2**). The major starting material α -(α' -bromobenzyl)chalcone (**3**) was then prepared by reacting **2** with *N*-bromosuccinimide in the presence of benzoyl peroxide. The treatment of **3** with two equivalents of various primary amines led to the α -(α' -alkylaminobenzyl)chalcones **4**, **5** and **6**. The azetidines **7**, **8** and **9** were synthesized by reacting **4** and **6** first with hydrogen bromide in chloroform and then with a suitable amine base in chloroform. The yields in general were low and small amounts of regenerated α -(α' -alkyl-aminobenzyl)chalcone were found. These azetidinyl ketones **7**, **8** and **9** could not be isomerized with base, but did undergo deuterium exchange at the C-3 position to form the 1-alkyl-2,4-diphenyl-3-deuterio-3-benzoylazetidines **10**, **11** and **12** when treated with sodium methoxide in deuteriomethanol. The deuterations require nearly a week to go to completion at room temperature.



The infrared and ultraviolet spectra of these azetidiny ketones is not varied enough to be of help in assigning configurations. The values recorded are reasonable with respect to similar compounds, but do not offer enough diversity between *cis* and *trans* configurations to aid in the assignments (3). The configurations of these azetidiny ketones were primarily assigned on the basis of their pmr spectra and corroborated by their mass spectra which are reported in the experimental section.

Deuteration of these compounds at the C-3 position led to the disappearance of the C-3 proton and collapsed the C-2,4 proton doublets to singlets with no change in their respective chemical shifts.

The mass spectra of all the azetidines were determined and found to support the other analytical results by showing the correct molecular ions for each of these compounds. The M-17 peaks for the two *t*-butyl azetidines **7** and **10** were very weak (approximately 0.1 and 0.4% respectively of their base peaks). This would seem to argue against their having *trans,trans* configurations (5). However, the *t*-butyl compounds appear to be unique from the other azetidines in this series. They both exhibit a large M-15 peak (loss of methyl from the *t*-butyl substituent) and their base peaks come at 146 rather than 105 (loss of benzoyl) as the other azetidines do.



This loss of methyl leading to ring cleavage appears to be dominant over loss of hydroxyl (M-17) in the case of the *N*-*t*-butyl azetidines **7** and **10** and has been observed for other azetidines recently (5).

The *cis,trans* azetidine **9** and its deuterated analogue **12** show more normal M-17 peaks (~10% of their base peaks). The other *trans,trans* azetidine **8** shows a larger M-17 peak (26% of the base peak) than its *cis,trans* analogue **9**. This is good evidence that this azetidine **8** is indeed *trans,trans*.

Discussion.

Ring closure of γ -haloamines is expected to lead to the most stable azetidine configurations. In a previously reported series of very similar azetidines (3), the *cis* isomers were found to be the kinetically favored isomers but were easily transformed to the thermodynamically more stable *trans* isomers. In this series, the azetidines have three possible configurations: *cis,cis*; *cis,trans*; and *trans,trans*. Since these compounds isomerize at the benzoyl or 3-

position, it is not possible to transform the *cis,trans* isomer to either of the other two isomers or vice versa. However, if the *cis,cis* isomer were formed it is highly probable that base catalyzed epimerization would convert it to the *trans,trans* isomer. The chemical shifts of the 2,4-hydrogens should be upfield and have a larger coupling constant in the *cis,cis* isomer relative to the *trans,trans* isomer (3). Indeed in the *cis,trans* azetidine **9**, the *cis* hydrogen is upfield of the *trans* hydrogen in the 2,4-hydrogen pair and the *cis* coupling constant is 9.0 Hz as compared with the *trans* coupling constant of 7.0 Hz. The deuteration to give azetidines **10** through **12** are all base catalyzed exchanges. The chemical shifts of the 2,4-hydrogens did not change in any of these deuterated azetidines. This is evidence that the symmetrical azetidines **7** and **8** have the *trans,trans* configuration. The large M-17 peak in the mass spectrum of **8** is also good evidence that this compound is *trans,trans* (5).

As a further check, the chemical shift and coupling constant data for **8** were calculated by means of a NMR-SIM program (9). The computer plotted spectrum for the 2,4-hydrogens and the 3-hydrogen exactly matched the experimental pmr spectra of *trans,trans* azetidine **8**.

EXPERIMENTAL (10)

α -(α' -Bromobenzyl)dihydrochalcone (**1**).

A 5.25-g. (0.025 mole) sample of dihydrochalcone (6) and 2.65 g. (0.025 mole) of benzaldehyde dissolved in 20 ml. of benzene were cooled to 0° and subjected to hydrogen bromide gas. After one hour, the solution solidified. The reaction mixture was allowed to stand overnight at room temperature and the solvent removed with a rotary evaporator. The product was recrystallized from ethanol to give 9.5 g. (100%) of white crystals, m.p. 119-124°; λ max 243 m μ (ϵ , 14,900); ν C=O 1678 cm⁻¹ (CH₂Cl₂).

The pmr spectrum of **1** showed a complex multiplet (15 H) in the range 419 to 482 Hz (aromatic), a doublet of doublets (1 H, J = 11.0, 4.0 Hz) at 326 Hz (-CHBrPh), a broad multiplet (1 H) in the range 270 to 300 Hz (methine), and a very broad multiplet (2 H) in the range 157 to 221 Hz (methylene).

Anal. Calcd. for C₂₂H₁₉BrO: C, 69.65; H, 5.06; Br, 21.07. Found: C, 69.78; H, 5.13; Br, 21.35.

α -Benzylchalcone (**2**).

A 37.93-g. (0.1 mole) sample of α -(α' -bromobenzyl)dihydrochalcone (**1**), 9.81 g. (0.1 mole) of potassium acetate, and 27.64 g. (0.2 mole) of potassium carbonate added to 400 ml. of ethyl alcohol were refluxed for five days. The mixture was allowed to stand overnight, filtered, the filtrate washed with ether, and the combined solvents removed with a rotary evaporator. The resultant slurry was placed in ether, filtered to remove the last of the salts, and the solvent removed with a rotary evaporator. The product was a light orange colored oil, weighed 29.88 g. (100%) and had a boiling range of 240 to 260° @ 4.5 to 6.0 mm (lit. (7) b.p. 238 to 250° @ 6 mm.). Eventual crystallization from methanol afforded white crystals, m.p. 47.5-49° (lit. (7) m.p. 48°), whose pmr spectrum suggested a 50:50 mixture of *cis:trans* isomers; λ max 246 m μ (ϵ , 16,800), λ max 280 m μ (ϵ , 9,900); ν C=O 1657 cm⁻¹; the pmr spectrum of **2** showed a complex multiplet (15.5

H) in the range 417 to 468 Hz (aromatic and *trans* vinyl), a triplet (0.5 H, $J = 1.5$ Hz) at 394 Hz (*cis* vinyl), a singlet (1 H) at 246 Hz (*trans* methylene), and a doublet (1 H, $J = 1.5$ Hz) at 224 Hz (*cis* methylene).

Anal. Calcd. for $C_{22}H_{18}O$: C, 88.55; H, 6.09. Found: C, 88.62; H, 6.07.

α -(α' -Bromobenzyl)chalcone (**3**).

A 7.59-g. (0.025 mole) sample of α -benzylchalcone **2** and 4.63 g. (0.026 mole) of fresh *N*-bromosuccinimide (**8**) in 200 ml. of carbon tetrachloride was heated to reflux with stirring and treated slowly with a solution of 0.25 g. (catalytic amount) of benzoyl peroxide in 50 ml. of carbon tetrachloride. Reflux was continued overnight, then the solution was cooled, filtered, and the solvent removed with a rotary evaporator. The resultant orange oil was crystallized from ethyl ether to give 6.18 g. (64.5%) of yellow crystals, m.p. 87.5-91.5° (T.L.C. showed 3-4 spots); λ max 253 μ (ϵ , 22,100); ν C=O 1657 cm^{-1} .

The pmr spectrum of **3** showed a complex multiplet (15 H) in the range 430 to 481 Hz (aromatic), a singlet (1 H) (impurity), a doublet (1 H, $J = 1.5$ Hz) at 409 Hz (vinyl), and a doublet (1 H, $J = 1.5$ Hz) at 376 Hz (methine).

Anal. Calcd. for $C_{22}H_{17}BrO$: C, 70.03; H, 4.55; Br, 21.18. Found: C, 70.02; H, 4.56; Br, 21.37.

α -(α' -*t*-Butylaminobenzyl)chalcone (**4**).

A 1.81-g. (0.005 mole) sample of α -(α' -bromobenzyl)chalcone **3** and 2 ml. (0.019 mole) of *t*-butylamine dissolved in 45 ml. of chloroform was stirred for one day, the solvent removed with a rotary evaporator and the resultant material worked up in ethyl ether. The amine salt was removed by filtration and the solution cooled to yield several fractions of white crystals for a total of 0.50 g. (27%), m.p. 88-89.5° after vacuum drying; λ max 239 μ (ϵ , 15,000); ν C=O 1651 cm^{-1} .

The pmr spectrum of **4** showed a complex multiplet (16 H) in the range 419 to 464 Hz (aromatic and vinyl), a singlet (1 H) at 295 Hz (methine), a broad singlet (1 H) at 97 Hz (hydrogen on nitrogen), and a singlet (9 H) at 63 Hz (*t*-butyl).

Anal. Calcd. for $C_{26}H_{27}NO$: C, 84.50; H, 7.38; N, 3.79. Found: C, 84.43; H, 7.47; N, 3.63.

α -(α' -Isopropylaminobenzyl)chalcone (**5**).

A 3.77-g. (0.01 mole) sample of α -(α' -bromobenzyl)chalcone (**3**) dissolved in 500 ml. of *n*-hexane had added to it 1.8 ml. (0.02 mole) of isopropylamine and was stirred overnight. The solution was filtered, but since only 0.40 g. (28.6%) of amine salt was isolated, another 0.5 ml. of isopropylamine was added and stirring resumed for five days. The solution was filtered, the solvent partially removed with a rotary evaporator, and the solution cooled. Several portions of product were isolated for a total of 2.33 g. (65.6%) of white crystals, m.p. 131.5-132.5° after vacuum drying; λ max 252 μ (ϵ , 15,070); ν C=O 1655 cm^{-1} .

The pmr spectrum of **5** showed a complex multiplet (16 H) in the range 417 to 471 Hz (aromatic and vinyl), a singlet (1 H) at 319 Hz (methine) geminal to phenyl, a broad multiplet (2 H) in the range 155 to 184 Hz (methine and hydrogen on nitrogen), and doublets (3 H each, $J = 6.5$ Hz) at 62 and 54 Hz (two non-equivalent methyls).

Anal. Calcd. for $C_{25}H_{25}NO$: C, 84.49; H, 7.09; N, 3.96. Found: C, 84.42; H, 7.10; N, 4.03.

α -(α' -Cyclohexylaminobenzyl)chalcone (**6**).

A 3.77-g. (0.01 mole) sample of α -(α' -bromobenzyl)chalcone (**3**) and 2.4 ml. (0.02 mole) of cyclohexylamine in 100 ml. of

chloroform was stirred three days. The solvent was removed with a rotary evaporator, the oil dissolved in anhydrous ethyl ether, and the solution filtered to yield 1.5 g. (82.2%) of amine salt. The solvent was reduced to 50 ml. and cooled. Three crops of product were collected to give a total of 1.7 g. (43.7%) of white cotton-like crystals, m.p. 109-119°, after recrystallization from CH_2Cl_2 -*n*-hexane and drying; λ max 246 μ (ϵ , 43,050); ν C=O 1653 cm^{-1} .

The pmr spectrum of **6** showed a complex multiplet (16 H) in the range 408 to 460 Hz (aromatic and vinyl), a doublet (1 H, $J = 1.0$ Hz) at 292 Hz (methine), a broad multiplet (1 H) in the range 133 to 161 Hz (methine on cyclohexyl), and a complex multiplet (11 H) in the range 37 to 127 Hz (hydrogen on nitrogen and methylenes on cyclohexyl).

Anal. Calcd. for $C_{28}H_{29}NO$: C, 85.02; H, 7.39; N, 3.54. Found: C, 84.79; H, 7.60; N, 3.63.

trans,trans-1-*t*-Butyl-2,4-diphenyl-3-benzoylazetidide (**7**).

A 1.94-g. (0.005 mole) sample of α -(α' -*t*-butylaminobenzyl)chalcone (**4**) was dissolved in 100 ml. of chloroform which had previously been saturated with hydrogen bromide gas and allowed to stand overnight. The solvent was removed with a rotary evaporator and the orange oil placed in 75 ml. of ethyl ether. To this solution, 0.71 ml. (0.007 mole) of *t*-butylamine and 3 ml. of chloroform were added to give a clear solution. The solution was chilled, filtered and the solvent removed with a rotary evaporator. The orange oil was boiled in *n*-pentane and cooled overnight. This solution was filtered to yield 0.44 g. (22.9%) of white crystals, m.p. 104.5-107° after vacuum drying; λ max 243 μ (ϵ , 14,150); ν C=O 1680 cm^{-1} .

The pmr spectrum of **7** showed a complex multiplet (15 H) in the range 423 to 472 Hz (aromatic), a doublet (2 H, $J = 7.5$ Hz) at 282 Hz (2,4-hydrogens), a triplet (1 H, $J = 7.5$ Hz) at 217 Hz (3-hydrogen), and a singlet (9 H) at 55 Hz (*t*-butyl).

The mass spectrum of **7** showed a molecular ion at 369 (calcd. 369), a M-17 peak at 352 (0.1% of base peak), and the base peak appeared at 146.

Anal. Calcd. for $C_{26}H_{27}NO$: C, 84.50; H, 7.38; N, 3.79. Found: C, 84.48; H, 7.70; N, 3.84.

trans,trans-1-Cyclohexyl-2,4-diphenyl-3-benzoylazetidide (**8**) and *cis,trans*-1-Cyclohexyl-2,4-diphenyl-3-benzoylazetidide (**9**).

A 0.80-g. (0.002 mole) sample of α -(α' -cyclohexylaminobenzyl)chalcone (**6**) was dissolved in 10 ml. of chloroform and added to 100 ml. of chloroform which had previously been saturated with hydrogen bromide gas while cooled in an ice bath. The solvent was removed with a rotary evaporator. The solid residue was dissolved in 100 ml. of chloroform, 1 ml. (0.007 mole) of triethylamine was added, and the solution cooled for 12 hours. The solvent was removed with a rotary evaporator employing no heat. The solid residue was dissolved in anhydrous ethyl ether, filtered to remove 0.61 g. (83.3%) of amine salt, and the solvent removed with a rotary evaporator. The solid was recrystallized from methanol to give 0.43 g. (53.5%) of white platelets, whose pmr spectrum indicated a 50:50 ratio of **8** to **9**. The pure isomers were separated by careful leaching with methanol at room temperature. The purest crystals were the ones which did not go into the solution. The m.p. of **8** was 114.5-119°; λ max 242 μ (ϵ , 14,500); ν C=O 1677 cm^{-1} .

The pmr spectrum of **8** showed a complex multiplet (15 H) in the range 403 to 464 Hz (aromatic), a doublet (2 H, $J = 7.5$ Hz) at 257 Hz (2,4-hydrogens), a triplet (1 H, $J = 7.5$ Hz) at 213 Hz (3-hydrogen), a broad multiplet (1 H) in the range 125 to 162 Hz (methine on cyclohexyl), and a complex multiplet (10 H) in the

range 33 to 112 Hz (methylenes on cyclohexyl).

The 2,4-hydrogens' doublet and the 3-hydrogens' triplet were duplicated precisely by a computer simulation. The calculated peaks were at identically the same position and the same size and shape as the experimental pmr spectrum peaks (9).

The mass spectrum of **8** showed a molecular ion at 395 (calcd. 395), a M-17 peak at 378 (26% of base peak), and the base peak appeared at 105.

Anal. Calcd. for $C_{28}H_{29}NO$: C, 85.02; H, 7.39; N, 3.54. Found: C, 85.08; H, 7.49; N, 3.56.

The m.p. of **9** was 157-160°; λ max 240 m μ (ϵ , 14,600); ν C=O 1680 cm^{-1} .

The pmr spectrum of **9** showed a complex multiplet (15 H) in the range 390 to 463 Hz (aromatic), a doublet (1 H, $J = 7.0$ Hz) at 326 Hz and another doublet (1 H, $J = 9.0$ Hz) at 315 Hz (2,4-hydrogens), a doublet (0.5 H, $J = 7.0$ Hz) at 257 Hz and another doublet (0.5 H, $J = 7.0$ Hz) at 248 Hz (3-hydrogen), a broad multiplet (1 H) in the range 130 to 165 Hz (methine on cyclohexyl), and a complex multiplet (10 H) in the range 28 to 100 Hz (methylenes on cyclohexyl).

The mass spectrum of **9** showed a molecular ion at 395 (calcd. 395), a M-17 peak at 378 (7.4% of base peak), and the base peak appeared at 105.

Anal. Calcd. for $C_{28}H_{29}NO$: C, 85.02; H, 7.39; N, 3.54. Found: C, 85.05; H, 7.45; N, 3.49.

trans,trans-1-*t*-Butyl-2,4-diphenyl-3-deuterio-3-benzoylazetidene (**10**).

A 0.10-g. (3×10^{-4} mole) sample of *trans,trans*-1-*t*-butyl-2,4-diphenyl-3-benzoylazetidene (**7**) was dissolved in 5 ml. of deuterio-methanol which had previously been treated with 0.05 g. of clean sodium to generate a trace of sodium methoxide. All glassware and the azetidene sample had been previously dried in an oven at 105° to remove any traces of water. The solution was tightly stoppered and stirred for one week. The solvent was removed with a rotary evaporator using no heat. The oil was dissolved in sodium-dried ethyl ether and filtered to remove the sodium methoxide. The solvent was removed with a rotary evaporator without using heat and the process repeated with carbon tetrachloride. The oil was dissolved in deuteriochloroform and its pmr spectrum determined.

The pmr spectrum of **10** showed a complex multiplet (15 H) in the range 423 to 470 Hz (aromatic), a singlet (2 H) at 282 Hz (2,4-hydrogens), and a singlet (9 H) at 56 Hz (*t*-butyl).

The mass spectrum of **10** showed a molecular ion at 370 (calcd. 370), a M-17 peak at 353 (0.4% of base peak), and the base peak appeared at 146.

trans,trans-1-Cyclohexyl-2,4-diphenyl-3-deuterio-3-benzoylazetidene (**11**).

A 0.10-g. (2.54×10^{-4} mole) sample of *trans,trans*-1-cyclohexyl-2,4-diphenyl-3-benzoylazetidene **8** with some *cis,trans*-azetidene **9** as an impurity, was added to 6 ml. of deuteriomethanol which had previously had a small piece of sodium reacted with it. The solution was stirred for three days, but not all the azetidene had dissolved. Therefore, 2 ml. of sodium-dried benzene was added to the solution and all of the solid immediately dissolved. The solution was stirred for six more days. The solvent was removed with a rotary evaporator using no heat, and the solid dissolved in lithium-dried ethyl ether. The solution was filtered to remove the sodium salts, the solvent removed, carbon tetrachloride added, then removed, then the oil was dissolved in deuteriochloroform. The pmr spectrum of this oil indicated that both isomers **9** and **8** had been completely deuterated. The solvent was removed and

methanol was allowed to stand over the solid for several hours. The undissolved white crystals were dried and their pmr spectrum showed them to be mainly *trans,trans* (**11**).

The pmr spectrum of **11** showed a complex multiplet (15 H) in the range 399 to 462 Hz (aromatic), a singlet (2 H) at 257.5 Hz (2,4-hydrogens), a broad multiplet (1 H) in the range 129 to 162 Hz (methine on cyclohexyl), and a complex multiplet (10 H) in the range 25 to 109 Hz (methylenes on cyclohexyl).

The mass spectrum of **11** showed a molecular ion at 396 (calcd. 396), a M-17 peak at 379 (9.8% of base peak), and the base peak appeared at 105.

cis,trans-1-Cyclohexyl-2,4-diphenyl-3-deuterio-3-benzoylazetidene (**12**).

Following the above described procedure for **11** compound **12** was obtained from **9**.

The pmr spectrum of **12** showed a complex multiplet (15 H) in the range 406 to 463 Hz (aromatic), a singlet (1 H) at 326 Hz and another singlet (1 H) at 315 Hz (2,4-hydrogens), a broad multiplet (1 H) in the range 134 to 164 Hz (methine on cyclohexyl), and a complex multiplet (10 H) in the range 24 to 113 Hz (methylenes on cyclohexyl).

The mass spectrum of **12** showed a molecular ion at 396 (calcd. 396), a M-17 peak at 379 (11% of base peak), and the base peak appeared at 105.

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