The Nuclear Magnetic Resonance Spectra of Some 1-Alkyl-2-phenyl-3-aroylazetidines and Related Compounds. Dispersion Effects and Conformational Analysis[1a]

EARL DOOMES AND NORMAN H. CROMWELL[1b]

Avery Laboratory of Chemistry, The University of Nebraska, Lincoln, Nebraska 68508

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Chemical shifts and coupling constants for geminal and vicinal protons of the azetidine ring have been determined for several *cis*-1-alkyl-2-phenyl-3-aroylazetidines (IVa–f). Similarly, the chemical shifts of azetidine ring protons at C-2 and C-4 have been determined for the corresponding *trans*-3-deuterioazetidines (V′a–f). The geminal coupling, $J_{a'b'}$, from the spectra of V′ and the vicinal coupling, $J_{c'd'}$, from the spectra of V were also determined. The observed trend in the chemical shifts is rationalized in terms of a large contribution from intramolecular van der Waals dispersion effects. On the basis of the nmr spectral data of IVa–f, we suggest that the conformation of the azetidine ring is a function of the steric requirement of the N-alkyl substituent, and that the azetidines bearing the smaller N substituents are puckered to a greater extent. Even in the open-chain compounds, 2-[α-(N-triethylcarbinylamino)benzyl]-4′-phenylacrylophenone (IIIa) and the *t*-butylamino analog (IIIb), deshielding due to van der Waals interactions is apparently important. The preparations and characterizations of 12 new azetidines are described.

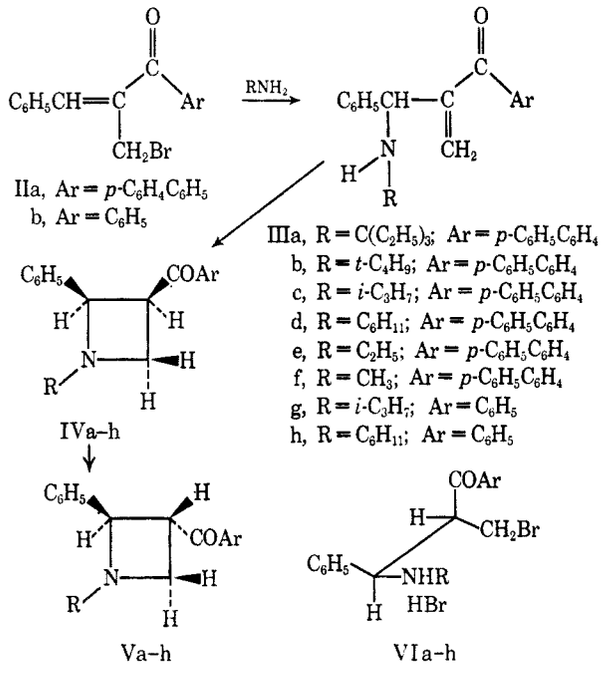
In previous communications[2] we reported on the synthesis, epimerization, and configurational assignment of several N-*t*-butylazetidines. The magnitude of vicinal proton–proton couplings was then used as an aid in configurational assignment along with infrared (ir), ultraviolet (uv), and chemical data. More recently, additional support for the original assignments was obtained through mass spectral studies.[3] As a continuation of our studies we have examined the effect of the nature of the N-alkyl substituent on the course of these cyclizations leading to various N-substituted azetidinyl ketones. Therefore, a large number of these compounds have been prepared and their spectra determined.

We felt that a detailed analysis of the pmr spectra of these cyclic compounds would give some insight into the probable conformation of the four-membered ring. This has been attempted for *cis* compounds by comparison of various ring proton couplings and the relative magnitudes of intramolecular van der Waals dispersion effects exerted upon ring protons by large N-alkyl substituents.

Preparation of Materials.—The reaction of α-(bromomethyl)chalcones (IIa and b) with 2 equiv of primary amines gave [α-(N-alkylamino)benzyl]acrylophenones (IIIa–h) in high yield[4] (Scheme I). Much shorter reaction times were required for reactions involving the less bulky amines. Thus, the reaction of IIa with 2 equiv of triethylcarbinylamine at room temperature required at least 24 hr for completion, whereas the reaction of IIa with 2 equiv of ethylamine under identical conditions required only 1.5 hr. In each case, the reaction time and amine concentration were controlled to minimize rearrangement of the first formed 2-[α-(N-alkylamino)benzyl]acrylophenones (III).

The reaction of the 2-[α-(N-alkylamino)benzyl]-acrylophenones with hydrogen bromide gave α-phenyl-

SCHEME I



β-aroyl-γ-bromopropylamine hydrobromides of type VI which upon treatment with base produced the new *cis*-C-aroylazetidines (IVa and c and IVe–h) in good yield[2] (Scheme I). Thus, the cyclization of these γ-bromopropylamines appears to be general with respect to the N-alkyl group, although the yield of azetidine drops sharply as the steric requirement of the N-alkyl group is reduced (*i.e.*, isolated yields ranged from 92% when R is *t*-butyl to 38% when R is methyl). These results are consistent with the suggestion by Vaughan[5] that in a given series a bulky N substituent favors cyclization and increases the stability of the azetidine ring. In all cases studied very high stereoselectivity toward formation of the *cis*-3-aroylazetidine (IV) was observed. However, in several instances the nmr spectrum of the crude mixture was taken after the bulk of the *cis* compound had been removed by

(1) (a) Presented in part at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968, Organic Chemistry Abstracts, p 72. (b) To whom inquiries should be addressed.

(2) (a) N. H. Cromwell and E. Doomes, *Tetrahedron Lett.*, 4037 (1966); (b) J.-L. Imbach, E. Doomes, R. P. Rebman, and N. H. Cromwell, *J. Org. Chem.*, **32**, 78 (1967).

(3) J.-L. Imbach, E. Doomes, N. H. Cromwell, H. E. Baumgarten, and R. G. Parker, *ibid.*, **32**, 3123 (1967).

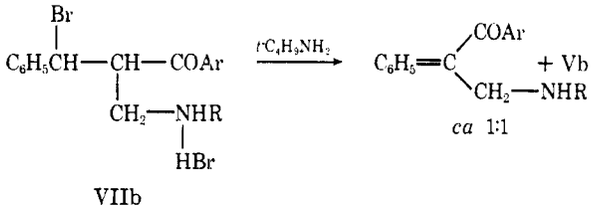
(4) See N. H. Cromwell and R. P. Rebman, *ibid.*, **32**, 3830 (1967), for previous paper.

(5) W. R. Vaughan, R. S. Klonowski, R. S. McElhinnery, and B. B. Millward, *ibid.*, **26**, 138 (1961).

crystallization and it indicated the presence of small amounts (<5%) of *trans* isomer, the origin of which was not determined with certainty. In view of the facile epimerization of the *cis* compounds, these small amounts of *trans* compounds might arise by epimerization of the former during crystallization.

The *cis*-1-alkyl-2-phenyl-3-aroylazetidines (IVa–h) were readily epimerized to the thermodynamically more stable *trans* isomers in high yield (>95%). Epimerization was achieved by warming *cis* compounds IV in methanol which contained a catalytic amount of sodium methoxide[2] or simply by refluxing IV in methanol without added catalyst for 14 hr. Thus, the steric requirement of the N-alkyl substituent seems to have little effect upon the position of the *cis–trans* equilibrium. Although reasonably stable in hydrocarbons, compound IVb partially isomerized when heated at 88–98° for 14 hr, whereas compound IVd was stable under these conditions. The isomerization of IVb in hydrocarbons and in methanol without added catalyst is probably induced by intermolecular catalysis due to the weakly basic azetidine ring nitrogen.

erythro-β-phenyl-β-N-*t*-butylamino-α-(bromomethyl)-4-phenylpropiophenone hydrobromide (VIb), from the addition of HBr to IIIb, was isolated and characterized. When VIb was allowed to react with an excess (>2 equiv) of *t*-butylamine in chloroform solution a quantitative yield of IVb was obtained, with no detectable amount of elimination product (IIIb). The isolation of VIb and its reaction with base were of considerable importance in connection with the mechanism of the reaction of primary alkylamines with the β-aroylallyl system (IIa and b) since under identical conditions β-aroylallylbromides (IIa and b) yielded only the corresponding β-aroylallylamines with no detectable amount of cyclic product.[4] This rules out the intermediacy of the free base of compounds such as VI for the latter type of reaction, implying that the reaction proceeds in one step. Although γ-bromopropylamine hydrobromide VIIb was not obtained in pure form, the fact that 2 equiv of hydrogen bromide/mol was generated when crude VIIb was treated with excess *t*-butylamine indicates, as was previously suggested,[2b] that there is indeed competition between cyclization and elimination. The products of the reaction were *trans*-azetidine Vb and α-(N-*t*-butylaminomethyl)-4′-phenylchalcone.[2a]



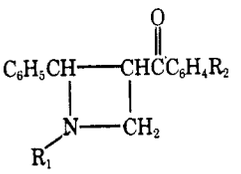
VIIb

R = *t*-C_4H_9; Ar = *p*-$C_6H_5C_6H_4$

As was pointed out previously,[2] spectral methods may be employed in determining the gross structure and the configurations of these azetidinyl ketones. We have now studied a large number of isomeric aroylazetidines and have observed differences in the uv and ir spectra which parallel those previously found in studies involving isomeric pairs of substituted aroylaziridines.[6] Thus the *trans* isomers (V) (see Table I) show uv λ_{max} with increased molar extinction coefficients (ε) compared with those of the parent saturated ketones,[7] $C_6H_5CH_2CH_2COC_6H_4C_6H_4$-*p* and $C_6H_5CH_2CH_2COC_6H_5$. The *cis* isomers IV also show uv spectra with increased λ_{max} (nearly identical with the values for the *trans* isomer) but with ε values less than those of the parent ketones. The polarization effects in these structures are of a lower order than in the aziridines and a full theoretical treatment must await further studies. Nevertheless, these *cis*- and *trans*-arylaroylazetidines are readily distinguished from each other by careful comparison of the extinction coefficients of the aroyl bands resulting from the $\pi \rightarrow \pi^*$ transitions. The lowered extinction coefficient for the *cis* isomers IV results from steric crowding between the 2-phenyl and 3-aroyl groups causing carbonyl–aryl[8] (and possibly carbonyl four-ring[2a]) interactions to have a lower probability than in the parent ketones (and *trans* isomers V).

TABLE I

SUMMARY OF SPECTRAL DATA FOR



Compd	R_1	R_2	Confign	λ_{max}, mμ (ε × 10^{-3})	$\nu_{C=O}$, cm^{-1}
IVa	$(C_2H_5)_3C$	*p*-C_6H_5	*cis*	282 (23.1)	1683
Va	$(C_2H_5)_3C$	*p*-C_6H_5	*trans*	282 (26.8)	1680
IVb	*t*-C_4H_9[a]	*p*-C_6H_5	*cis*	282 (22.8)	1683
Vb	*t*-C_4H_9[a]	*p*-C_6H_5	*trans*	282 (26.2)	1680
IVc	C_6H_{11}[b]	*p*-C_6H_5	*cis*	282 (23.2)	1684
Vc	C_6H_{11}[b]	*p*-C_6H_5	*trans*	282 (26.1)	1680
IVd	*i*-C_3H_7	*p*-C_6H_5	*cis*	282 (23.0)	1683
Vd	*i*-C_3H_7	*p*-C_6H_5	*trans*	282 (26.3)	1680
IVe	C_2H_5	*p*-C_6H_5	*cis*	282 (22.7)	1683
Ve	C_2H_5	*p*-C_6H_5	*trans*	282 (26.1)	1680
IVf	CH_3	*p*-C_6H_5	*cis*	282 (22.7)	1685
Vf	CH_3	*p*-C_6H_5	*trans*	282 (26.2)	1680
IVg	*i*-C_3H_7	H	*cis*	240 (10.5)	1688
Vg	*i*-C_3H_7	H	*trans*	241 (15.4)	1682
IVh	C_6H_{11}	H	*cis*	240 (10.5)	1688
Vh	C_6H_{11}	H	*trans*	242 (15.0)	1682
IVi	*t*-C_4H_9[c]	H	*cis*	240 (10.9)	1688
Vi	*t*-C_4H_9[c]	H	*trans*	242 (15.5)	1680

[a] See ref 2a. [b] See ref 3. [c] See ref 2b.

The stretching vibrations of the carbonyl groups in both the *cis*- (IV) and *trans*-arylaroylazetidines (V) lead to ir absorption bands of lower frequency than those of the parent ketones. The *trans* isomers show lower frequencies than the *cis* compounds and thus again the effect of steric crowding is observed with the

(6) N. H. Cromwell, R. E. Bambury, and J. L. Adelfang, *J. Amer. Chem. Soc.*, **82**, 4241 (1960).

(7) See, for example, N. H. Cromwell and R. J. Mohrbacher, *ibid.*, **79**, 401 (1957); note that, for $C_6H_5CH_2CH_2COC_6H_4C_6H_5$-*p*, λ_{max} is 276 mμ (ε 25,100) and $\nu_{C=O}$ is 1690 cm^{-1}, and, for $C_6H_5CH_2CH_2COC_6H_5$, λ_{max} is 238 mμ (ε 12,400) and $\nu_{C=O}$ is 1694 cm^{-1}.[6]

(8) The intensity of the benzoyl band ($\pi \rightarrow \pi^*$) in the uv for α-substituted acetophenones decreases as the steric requirement of the α substituent is increased; see G. D. Hedden and W. G. Brown, *ibid.*, **75**, 3744 (1953). On the other hand such substitution was found to shift the ir carbonyl bands to lower wave numbers; see J. L. Adelfang, P. H. Hess, and N. H. Cromwell, *J. Org. Chem.*, **26**, 1402 (1961).

latter. A full theoretical discussion of these mild ground-state effects must also await further experimental results.

Proton Magnetic Resonance Spectra.[9]—For each *cis* isomer (IVa–h) studied one ring proton appears upfield with respect to the remainder of the azetidine ring protons. The upfield proton (designated as H_a) for compounds IVa–e appears as either a triplet or a doublet of doublets depending upon the magnitude of couplings with H_b and H_c (see structure IV). However, for compound IVf, H_a appears as a triplet of doublets which collapsed into a well-defined triplet for IV′f (where H_d is replaced by deuterium). Thus, by a first-order graphical analysis it was found that H_a apparently couples with H_d through four σ bonds by 1.9 Hz. The proton at C-4 which is *trans* to the aroyl group would be expected to absorb at the highest field of the ring protons since the major deshielding experienced by this proton is due to the nearby nitrogen atom and the N-alkyl substituents. Thus, H_a is assigned as shown in structure IV.

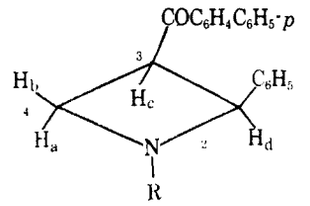
When H_d was replaced by deuterium, simple first-order AMX or ABX spectra resulted for ring protons which could be analyzed by the graphical method (structure IV′). From the coupling constants and chemical shifts obtained in this manner, a theoretical spectrum was calculated. The calculated and the observed spectra were in excellent agreement. In the spectra of 2-deuterioazetidines (IV′a–f) the downfield doublet for what would be H_d was absent and therefore confirmed the assignment of this proton. Thus, both the chemical shift of H_d and the spin–spin coupling constant (J_{cd}) were obtained from the spectra of IVa–f. The proton assignment at C-3 of the azetidine ring was based upon broadening of this resonance band due to the expected vicinal coupling of this proton with the deuterium atom at C-2 in IV′. Thus, H_c was assigned to the slightly broadened doublet of doublets. The proton at C-4 which is *cis* to the 3-aroyl group was assigned to the well-defined doublet of doublets which appeared immediately upfield from the slightly broaden multiplet due to H_c. A combination of the spectra of IV and IV′ allows the assignment of resonance frequencies and the various coupling constants for ring protons (Tables II and III).

An additional interesting characteristic of the nmr spectra of the *cis*-2-phenyl-3-aroylazetidines is found in the aromatic region. In the spectrum of each *cis* isomer studied there is an upfield multiplet (with respect to the remainder of the aromatic protons) which corresponds to two (or three) protons. This upfield multiplet is almost identical for both the *p*-phenylbenzoyl and benzoyl compounds (although overlap is more severe in the spectra of the latter) suggesting that this multiplet is due to protons contained in the 2-phenyl group. The spectra of the *trans* isomers show only complex multiplets for the aromatic protons with no apparent separation. This difference in the aromatic region alone aids in differentiating isomers in this series of azetidines.

(9) The proton magnetic resonance (pmr) spectra were determined as *ca.* 15% deuteriochloroform solutions at 60 MHz and the chemical shifts are reported in hertz relative to internal tetramethylsilane (0.0 Hz). The pertinent coupling constants were determined on either 100- or 250-Hz sweep width. The sweep width was calibrated before and after each spectrum with a chloroform (437 Hz) in deuteriochloroform solution relative to tetramethylsilane (0.0 Hz) as internal standard.

TABLE II

CHEMICAL SHIFTS OF RING PROTONS OF SOME *cis*-1-ALKYL-2-PHENYL-3-AROYLAZETIDINES[a]



IV (H_d = D)

Compd	R	Hz			
		H_a	H_b	H_d	H_c
IVa	$(C_2H_5)_3C$	216	239	321	263
IVb	*t*-C_4H_9	201	237	297	256
IVc	*i*-C_3H_7	183	*ca.* 249	276	*ca.* 259
IVd	C_6H_{11}	184	251	278	263
IVe	C_2H_5	181	249	275	263
IVf	CH_3	182	249	272	263

[a] Chemical shifts of H_d were obtained from spectra of IVa–f and those of H_a, H_b, and H_c by analysis of the spectra IV′a–f. These chemical shifts are reproducible and accurate within ±1 Hz.

TABLE III

COUPLING CONSTANTS FOR RING PROTONS OF SOME *cis*-1-ALKYL-2-PHENYL-3-AROYLAZETIDINES[a]

Compd	Hz			
	$\lvert J_{ab}\rvert$[b]	J_{ac}[b]	J_{bc}[b]	J_{cd}[c]
IVa	6.8[a]	7.8	3.5	9.5
IVb	6.9	8.0	3.4	9.5
IVc	*ca.* 7	*ca.* 7	3.0	9.0
IVd	6.8	7.4	3.0	9.0
IVe	6.5	7.5	2.8	8.5
IVf	6.6	7.4	2.8	*ca.* 7.5

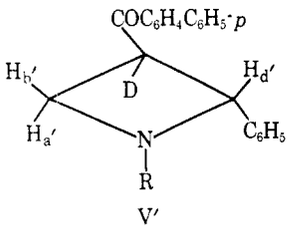
[a] These coupling constants are reproducible within ±0.2 Hz. [b] Obtained by analysis of the AMX or ABX spectra of IV′a–f. [c] Obtained from the spectra of IVa–f.

Since the spectra (for azetidine ring protons) of *trans* compounds were more complex and could not be reliably analyzed by the first-order graphical method, the spectra were not analyzed as explicitly for the proton–proton couplings as in the case of *cis* compounds. For each *trans* compound at least two coupling constants were determined, $J_{c'd'}$ and $J_{a'b'}$ (Table IV). However, the nmr spectra of *trans*-3-deuterioazetidines V′a–f were determined in order to obtain chemical shifts of ring protons $H_{a'}$, $H_{b'}$, and $H_{d'}$ (Table IV). In general, $H_{a'}$ and $H_{b'}$ appeared as an AB spectrum from which the chemical shifts of these protons and the geminal coupling ($J_{a'b'}$) were obtained by simple analysis. Resonance frequency assignments are based on arguments similar to those presented above for assignments in the *cis* compounds. $H_{a'}$ is assigned to the upfield doublet, $H_{b'}$ to the second doublet, and $H_{d'}$ to the singlet at lowest field of the azetidine ring protons. For *trans*-3-deuterio-N-*t*-butylazetidines $H_{a'}$ and $H_{b'}$ appear as a singlet,[2] the chemical shifts of these protons being equal. The nmr spectrum of *trans*-N-triethylcarbinylazetidine (V′a) again shows a pair of doublets for $H_{a'}$ and $H_{b'}$, but the reverse assignment is made; $H_{b'}$ is assigned to the upfield doublet for reasons given below.

The N-isopropyl methyl groups of azetidines IVc and g and Vc and g were magnetically nonequivalent, ap-

TABLE IV

CHEMICAL SHIFTS OF RING PROTONS OF SOME *trans*-2-PHENYL-3-DEUTERIO-3-AROYLAZETIDINES[a]



V'

V, D = H_c'

Compd	R	$H_{a'}$	$H_{b'}$	Hz $H_{d'}$	Hz $\lvert J_{a'b'}\rvert$[b]	Hz $J_{c'd'}$[c]
V'a	$C(C_2H_5)_3$	231	214	303	6.0	5.2
V'b	*t*-C_4H_9	213	213	282		6.5
V'c	*i*-C_3H_7	191.5	226	264	6.8	7.0
V'd	C_6H_{11}	192	226	264.5	6.8	7.2
V'e	C_2H_5	193	230	262	6.5	7.3
V'f	CH_3	192.5	230.5	258	6.8	7.3

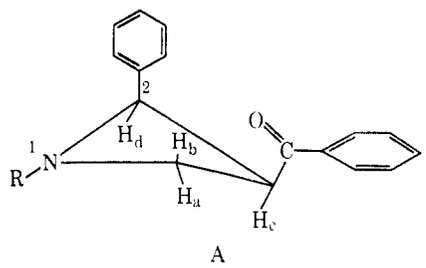
[a] These chemical shifts are reproducible and accurate within ±1 Hz and the coupling constants are reproducible and accurate within ±0.2 Hz. [b] From the AB spectra of V'a–f. [c] $J_{c'd'}$ of V (nondeuteriated).

pearing as two doublets. The degree of nonequivalence of the methyl groups in compound IVg was relatively independent of both temperature (in the range −45–50°) and solvent polarity, $\Delta\gamma$ for the methyl groups equaling 22 ± 2 Hz. The methylene protons of the N-ethyl group in Ve are magnetically nonequivalent, giving rise to a multiplet of at least 10 lines, whereas the analogous *cis* compound IVe shows a well-defined quartet for these protons.

In all isomeric pairs studied, except for N-methyl compounds (IVf and Vf), the *cis*-vicinal coupling (J_{cd}) is larger than the corresponding *trans*-vicinal coupling ($J_{c'd'}$). For compounds IVf and Vf, J_{cd} is equal to $J_{c'd'}$ within experimental error. Thus, the magnitude of proton–proton couplings alone is not sufficient grounds for configurational assignment of diastereoisomers in this type of compound.

Discussion of the Proton Magnetic Resonance Spectra.—The establishment of the configurations of these isomeric azetidines by chemical and other spectral methods allows several conclusions to be drawn from the nmr data.[10] As expected, this study shows that *cis*-vicinal couplings in this ring system are generally larger than corresponding *trans*-vicinal couplings. For example, $J_{ac} \simeq 7.5$ Hz $> J_{bc} = 2.8$–3.5 Hz for *cis* compounds IVa–f (Table III). Also, a comparison of J_{cd} and J_{ac} for these compounds illustrates the effect of substituent on the magnitude of these couplings. The increased coupling exhibited by *cis* protons across the C-2–C-3 bond when compared with *cis* proton coupling across the C-3–C-4 bond is probably a result of phenyl substitution for hydrogen at C-2 and/or a reflection of the dihedral angles between the protons involved. In substituted aziridines[10] and other related compounds,[11] the electronegativity of substituents have been shown to affect the magnitude of proton–proton couplings, and it seems reasonable the couplings in this system might be affected in a similar manner. However, the large differences in the size of some of these couplings might be best explained in terms of differences in dihedral angles which in turn would be indicative of the conformation of the azetidine ring. Dihedral angles for ring protons of *cis* structures were approximated from the values of the observed couplings.[12] The calculated values so obtained were compared with the dihedral angles obtained by inspection of Dreiding models for these compounds and good qualitative agreement was found.

Using the Karplus relationship,[13] the small values (2.8–3.5 Hz) for the *trans* couplings across the C-3–C-4 bond suggest dihedral angles on the order of 125–130° for the protons in question (H_b and H_c, A). The relatively large values for *cis* couplings (J_{cd} = 8.5–9.5 Hz) across the C-2–C-3 bond in compounds IVa–e suggest that H_c and H_d are fully eclipsed, or nearly so, and that staggering of the *cis*-phenyl and -aroyl groups is minimal. For N-methylazetidine (IVf) this same coupling is relatively small (J_{cd} = *ca.* 7.5 Hz), indicating that there is considerable staggering of H_d and H_c. The vicinal couplings along with the small geminal couplings ($|J_{gem}| \simeq 7$ Hz) are consistent with a nonplanar azetidine ring (A). However, the major contribution



A

to the magnitude of these geminal couplings is probably due to the overlap of the C–H bonds with the lone pair on the adjacent nitrogen atom.[14]

The fact that the apparent long-range coupling (J_{ad}) is 1.9 Hz for N-methylazetidine IVf, whereas this same coupling is less than 0.5 Hz for compounds IVa–e suggests that the four-membered ring of the former is more puckered than those of compounds containing the larger N-alkyl substituents. Since the apparent necessary geometrical requirement for long-range coupling[15] is that the protons in question form a "W" with the three carbon atoms involved (H_d–C-2–C-3–C-4–H_a) the above suggestion seems reasonable. The gradual decrease in the magnitude of the vicinal coupling (J_{cd}) as the steric requirement of the N-alkyl group is increased also supports this view (Table III). There is also an increase in the coupling $J_{c'd'}$ for *trans*-azetidines V when the steric requirement of the N-alkyl group is decreased. We suggest that as puckering of the four-ring is increased $H_{c'}$ and $H_{d'}$ become closer to *trans* pseudodiaxial and thus the increase in $J_{c'd'}$ is observed.

(10) Although the pmr data were used previously[2] in establishing configurations, the other data seems sufficient for this purpose.

(11) S. J. Brois and G. P. Beardsley, *Tetrahedron Lett.*, 5113 (1966).

(12) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); *J. Amer. Chem. Soc.*, **85**, 2870 (1963).

(13) A. D. Cohen and T. Schaefer, *Mol. Phys.*, **10**, 209 (1966).

(14) See, for example, T. A. Crabb and R. F. Newton, *Chem. Ind.* (London), 339 (1966), and references cited therein.

(15) J. Meinwald and Y. C. Meinwald, *J. Amer. Chem. Soc.*, **85**, 2514 (1963).

This conformational variation in both V and IV can be rationalized in terms of greater 1,3 interactions in cases involving large substituents.

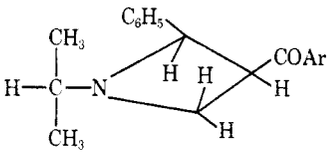
The chemical shifts of azetidine ring protons at C-2 and C-4 are sensitive functions of the steric requirement of the N-alkyl substituent, especially when the N-alkyl group is bulky.[16] Any shielding or deshielding exerted upon ring protons at C-2 and C-4 by the N-alkyl group as reflected in their chemical shifts is a combination of the anistropy of the C–C and C–H single bonds[17] and intramolecular van der Waals dispersion effects.[18] Depending upon the magnitude of each of these shielding effects a net shielding or a net deshielding might result. In the present investigation by varying the N-alkyl group it was found that N-triethylcarbinyl and N-*t*-butyl groups deshield ring protons (H_a and H_d, structure IV) by *ca.* 40 and *ca.* 18 Hz, respectively, with regard to smaller N-alkyl groups (Table II). The downfield shifts observed for H_a and H_d upon increasing the size of the N-alkyl substituent should be due primarily to the effect of this substituent since the aroyl and phenyl groups are situated on the opposite side of the azetidine ring. These results indicate that in the case of large N-alkyl groups increased deshielding resulting from intramolecular van der Waals interactions is much greater than the shielding which results from the anisotropy of the increased number of C–C and C–H single bonds when compared with smaller N-alkyl groups. However, the small observed differences in the chemical shifts in varying the N-alkyl group in the sequence, isopropyl to cyclohexyl to ethyl to methyl, indicate that the van der Waals contribution is, as expected, rather small.[16] For *trans* compounds V'a–f the situation is much more complex since $H_{b'}$ and $H_{d'}$ are *cis* to the aroyl group. Thus, the effect of the aroyl group on the chemical shifts of these protons obscures the effect of the N-alkyl substituent. The fact that opposite trends in the chemical shifts of $H_{d'}$ and $H_{b'}$ were observed, although both of these protons are *cis* to the aroyl group, suggests that the conformational orientation of the latter with respect to $H_{d'}$ is different from that with respect to $H_{b'}$.

The ring protons, H_d and H_a, are deshielded by 43 and 33 Hz, respectively, in going from an N-triethylcarbinyl to the less bulky N-isopropyl group. This difference in deshielding might reflect the relative conformational orientations of H_d and H_a with regard to the N-alkyl substituent. If H_d is pseudoaxial deshielding due to steric crowding might be expected to be greater for this proton than for the less axial H_a, in agreement with the experimental facts.

The increased shielding of the C-4 proton (H_b, IV), which is *cis* to the aroyl substituent, as the steric requirement of the N-alkyl substituent is increased, cannot be explained on the basis of intramolecular van der Waals dispersion effects and single-bond anisotropy alone and is probably a result of a large contribution from the ring-current effect of the phenyl portion of the aroyl group.[11] For example, H_b in N-*t*-butylazetidine IVb is shielded by *ca.* 13 Hz when compared with compounds bearing smaller N-alkyl substituents (Table II). Apparently, the deshielding due to the aroyl group offsets the effect of the N-alkyl substituent; otherwise an opposite trend in the chemical shift of Hb would be expected.

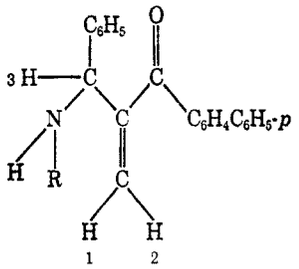
The upfield shift of two aromatic protons in the *cis* compounds is tentatively rationalized on the basis of intramolecular shielding of the *ortho* protons of the 2-phenyl group by the π cloud of the carbonyl function.

The large degree of magnetic nonequivalence of the N-isopropyl methyl groups of these N-isopropylazetidines (B) is apparently a result of the intrinsic molecular asymmetry of the relatively rigid system. A major portion of the nonequivalence is ascribed to the phenyl group at the C-2 asymmetric center.[19]



B

Deshielding due to van der Waals interactions is also prevalent in some acylic structures. The chemical shift of one of the vinyl protons of 2-[α-(N-alkylamino)-benzyl]acrylophenone derivative (C) is a function of the steric requirement of the N-alkyl group. Thus, H-1 for IIIa, IIIb, and IIIc appears at 388, 374, and 365 Hz, respectively, whereas the chemical shifts of H-2 and H-3 are relatively constant, appearing at 343 ± 2 and 306 ± 3 Hz, respectively. We suggest that H-1 is *cis* to the α-(N-alkylamino)benzyl group and its chemical shift is governed by van der Waals dispersion effects due to the steric requirements of the N-alkyl group.



IIIa, R = $C(C_2H_5)_3$
b, R = t-C_4H_9
c, R = i-C_3H_7

In a recent paper Goldberg and coworkers[20] reported some apparent anomalies in the nmr spectra of some N-neopentyl-N-methylamines and neopentylmethyl ether, the methylene protons appearing at higher field than the N- and O-methyl groups, respectively. In view of our findings and those of others,[16,18] these results can be rationalized in terms of van der Waals interactions of the *t*-butyl portion of the neopentyl group with the N-methyl or O-methyl groups which result in deshielding

(16) For a somewhat analogous result in aziridines, see S. J. Brois, *J. Amer. Chem. Soc.*, **87**, 4242 (1967); Abstracts of papers, the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, No. 0-72.

(17) J. W. Apsimon, W. G. Craig, P. V. DeMarco, D. W. Mathieson, L. Saunders, and W. B. Whally, *Tetrahedron*, **19**, 2339 (1967).

(18) For discussion of this deshielding mechanism, see A. D. Buckingham, T. Schaefer, and W. G. Schneider, *J. Chem. Phys.*, **32**, 1227 (1960); T. Schaefer, W. F. Reynolds, and T. Yonemoto, *Can. J. Chem.*, **41**, 2969 (1963); V. M. S. Gil and W. A. Gibbons, *Mol. Phys.*, **8**, 199 (1964).

(19) G. M. Whitesides, D. Holtz, and J. D. Roberts, *J. Amer. Chem. Soc.*, **86**, 2628 (1964).

(20) S. I. Goldberg, F.-L. Lam, and J. E. Davis, *J. Org. Chem.*, **32**, 1658 (1967).

of the latter. Owing to the spatial arrangement of the different groups in the molecules, interactions of this type with the methylene group are very unlikely as indicated by Dreiding models. Thus, the methyl groups are deshielded while the methylene groups are unaffected by the bulky *t*-butyl group and the reversal in chemical shift is observed.

Experimental Section[21]

α-Methyl-4′-phenylchalcone (I).—A 63-g (0.30 mol) sample of 4-phenyl-propiophenone[22] was suspended in 100 ml (an excess) of benzaldehyde and the mixture was saturated with dry hydrogen chloride until it turned dark brown. The solution became homogeneous and then solidified while kept at 0°. The tightly stoppered mixture was allowed to stand at room temperature for 48 hr. Excess hydrogen chloride and water were removed under reduced pressure at *ca.* 40°. Potassium carbonate (42 g, 0.30 mol), potassium acetate (30 g, 0.30 mol), and 800 ml of ethanol were added and the mixture was kept at reflux temperature for 96 hr. The hot solution was filtered to remove the precipitated inorganic salts, concentrated, and cooled to induce crystallization. Recrystallization and decolorization of the solid which resulted from ethanol yielded 70 g (78%) of white plates, mp 98–99° (lit.[2a] mp 99°).

2-Methyl-3-deuterio-3-phenyl-4′-phenylacrylophenone (I′).—Compound I′ was obtained when the above-described procedure was repeated using 1-deuteriobenzaldehyde[23] instead of benzaldehyde, mp 98–99°. The nmr spectra of I and I′ were identical except for the absence of the benzal proton in the spectrum of I′.

α-(Bromomethyl)-4′-phenylchalcone (IIa).—A 29.8-g (0.10 mol) sample of I was dissolved in 300 ml of carbon tetrachloride to which was added N-bromosuccinimide (18.0 g, 0.10 mol) and the mixture was heated to a gentle reflux. To the vigorously stirred refluxing mixture was added benzoyl peroxide (0.50 g, 0.002 mol) in 100 ml of the same solvent over a period of 1 hr. The reaction mixture was kept at reflux temperature with continuous stirring for an additional 3 hr. After the mixture was allowed to cool, the succinimide was removed by filtration and the solvent was removed under reduced pressure. The yellow oil which resulted was crystallized from 200 ml of a 2:1 ethyl ether–ethanol mixture. Recrystallization (decolorization with charcoal) of the yellow solid from ethyl ether yielded 29.6 g (79%) of slightly yellow crystals, mp 106–107° (lit.[2a] mp 107°).

2-[α-(N-Triethylcarbinylamino)benzyl]-4′-phenylacrylophenone (IIIa).—A 3.77-g (0.010 mol) sample of IIa and 2.30 g (0.020 mol) of triethylcarbinylamine[24] dissolved in 500 ml of *n*-hexane were allowed to react at room temperature for 30 hr. The usual work-up[4] gave 2.43 g (59%) of white crystals: mp 80–82° (methanol); ir $\nu_{C=O}$ at 1655 cm^{-1}; nmr peaks at *ca.* 445 (m, 14 H, aromatic protons), 388 and 341 (s, 1 H, each, vinyl protons), 303 (s, 1 H, benzyl proton), and *ca.* 79 and *ca.* 44 Hz (q and t, respectively, J = 7 Hz, 15 H, 3 CH_2CH_3).

Anal. Calcd for $C_{29}H_{33}NO$: C, 84.63; H, 8.08; N, 3.40. Found: C, 84.50; H, 7.97; N, 3.45.

2-[α-(N-t-Butylamino)benzyl]-4′-phenylacrylophenone (IIIb).—A 7.54-g (0.020 mol) sample of IIa was dissolved in 900 ml of *n*-hexane, *t*-butylamine (3.0 g, 0.041 mol) was added, and the mixture was allowed to react at room temperature for 24 hr. The usual work-up[4] yielded 6.21 g (84%) of white crystals, mp 89–90° (pentane) (lit.[2a] mp 90°).

2-[α-(N-Isopropylamino)benzyl]-4′-phenylacrylophenone (IIIc).—A 3.77-g (0.010 mol) sample of IIa and isopropylamine (1.2 g, 0.020 mol) dissolved in 500 ml of *n*-hexene were allowed to react at room temperature with stirring for 15 hr. The usual work-up[4] afforded 3.05 g (86%) of white crystals: mp 88–89° (petroleum ether, bp 60–69°); ir $\nu_{C=O}$ at 1655 cm^{-1}; nmr peaks at *ca.* 450 (m, 14 H, aromatic protons), 365 and 344 (s, 1 H each, vinyl protons), 305 (s, 1 H, benzyl proton), 169 (h, J = 6 Hz, 1 H, methine), 106 (s, 1 H, NH), and 66 Hz (d, 6 H, 2 CH_3).

Anal. Calcd for $C_{25}H_{25}NO$: C, 84.47; H, 7.39; N, 3.94. Found: C, 84.50; H, 7.21 N; 4.07.

2-[α-(N-Cyclohexylamino)benzyl]-4′-phenylacrylophenone (IIId).—A 3.77-g (0.010 mol) sample of IIa and cyclohexylamine (2.0 g, 0.020 mol) dissolved in 500 ml of *n*-hexane was allowed to react at room temperature for 15 hr. The usual work-up[4] yielded 2.73 g (69%) of white crystals, mp 90–91°.[25]

2-[α-(N-Ethylamino)benzyl]-4′-phenylacrylophenone (IIIe).—A 1.89-g (0.0050 mol) sample of IIa and ethylamine (*ca.* 0.65 ml, *ca.* 0.01 mol) was added and the mixture was allowed to react at room temperature for 1.5 hr. (The ethylamine was added *via* a pipet, while both were kept at 0°.) The usual work-up[4] yielded 1.23 g (72%) of white crystals: mp 63–64° (*n*-hexane); ir $\nu_{C=O}$ at 1656 cm^{-1}; nmr peaks at *ca.* 455 (m, 14 H, aromatic protons), 367 and 345 (s, 1 H each, vinyl protons), 299 (s, 1 H, benzyl proton), 158 (q, J = 7 Hz, 2 H, methylene protons), *ca.* 144 (s, 1 H, NH), and 67 Hz (t, J = 7 Hz, 3 H, CH_3).

Anal. Calcd for $C_{24}H_{23}NO$: C, 84.42; H, 6.79; N, 4.10. Found: C, 84.62; H, 6.72; N, 3.91.

2-[α-(N-Isopropylamino)benzyl]acrylophenone (IIIg).—A 3.01-g (0.010 mol) sample of α-(bromomethyl)chalcone (IIb)[4] and isopropylamine (1.20 g, 0.20 mol) were allowed to react at room temperature while being stirred magnetically for 15 hr. The usual work-up[4] afforded 2.19 g (78%) of flaky white crystals: mp 92–93° (*n*-hexane); ir $\nu_{C=O}$ at 1658 cm^{-1}; nmr peaks at *ca.* 455 (m, 10 H, aromatic protons), 364 and 343 (s, 1 H each, vinyl protons), 306 (s, 1 H, benzyl proton), 168 (h, 1 H, methine proton), *ca.* 128 (s, 1 H, NH), and 65 Hz (d, 6 H, CH_3).

Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.90; H, 7.59; N, 5.24.

2-[α-(N-Methylamino)benzyl]-3-bromo-4′-phenylpropiophenone Hydrobromide (VIf).—A 1.89-g (0.0050 mol) sample of IIa and *ca.* 0.5 ml (*ca.* 0.01 mol) of methylamine (added *via* a Dry Ice–acetone trap) were allowed to react at room temperature while being stirred magnetically for 0.5 hr. The solution was filtered to remove the precipitated methylamine hydrobromide and the filtrate was subjected to reduced pressure to remove any unreacted methylamine. The clear *n*-hexane solution was then subjected to a stream of dry hydrogen bromide for 0.25 hr while the mixture was stirred magnetically. Stirring was continued for 0.5 hr and then the solution was filtered to remove the slightly yellow solid which separated. Recrystallization of this material from a methanol–ethyl ether mixture yielded 0.87 g (33%) of IVf as white needles: mp 184–185°; characteristic ir peaks ($CHCl_3$) at 3400, 3100, 2950, 2850, 2500, and 2300 ($\overset{+}{N}H_2$ and CH stretching) and 1680 cm^{-1} (C=O).

Anal. Calcd for $C_{23}H_{23}NOBr_2$: C, 56.44; H, 4.67; N, 2.86; Br, 32.66. Found: C, 56.34; H, 4.82; N, 3.18; Br, 32.54.

General Procedure for the Preparation of *cis*-1-Alkyl-2-phenyl-3-aroylazetidines (IVa–h).—A sample of the appropriate 2-[α-(alkylamino)benzyl]acrylophenone derivative was dissolved in chloroform (100 ml) which had been previously saturated with dry hydrogen bromide gas, while the solution was kept at 0°. The reaction flask was tightly stoppered and kept overnight. After removal of excess hydrogen bromide under reduced pressure, the cold solution was neutralized with triethylamine (excess). The solution was then allowed to stand at room temperature for 6 hr. The solvent was evaporated under reduced pressure (without heat), the resulting residue was extracted with dry ethyl ether (200 ml), and the mixture was filtered to remove the suspended triethylamine hydrobromide. The residue which resulted upon evaporation of the ethyl ether was recrystallized from the appropriate solvent.

(21) The melting points are corrected. Their measurements were made on a Perkin-Elmer Model 21 instrument employing carbon tetrachloride solutions unless otherwise indicated. The uv spectra were obtained with a Cary Model 11 instrument employing *ca.* 10^{-4} *M* isooctane solutions. The nmr spectra were determined on a Varian A-60 spectrometer equipped with a V-6040 variable-temperature probe and controller, the spectra being determined as dilute deuteriochloroform solutions with tetramethylsilane as internal standard unless otherwise indicated. Chemical shifts are listed in hertz. For variable-temperature nmr spectra the temperature controller was calibrated by measuring resonance peak separations for methanol or ethylene glycol. The following notations are used for pmr data: s, singlet; d, doublet; t, triplet; q, quartet; h, heptet; and m, multiplet. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.

(22) L. M. Long and H. R. Henze, *J. Amer. Chem. Soc.*, **63**, 1939 (1941).

(23) D. Seebach, B. W. Erickson, and G. Singh, *J. Org. Chem.*, **31**, 4303 (1966).

(24) E. H. White, M. C. Chen, and L. A. Dolak, *ibid.*, **31**, 3038 (1966).

(25) The peaks in the nmr spectrum corresponding to the two vinyl protons and the benzyl proton appear at 363, 343, and 308 Hz, respectively. These peaks were erroneously reported in ref 3.

cis-1-**Triethylcarbinyl-2-phenyl-3-(*p*-phenylbenzoyl)azetidine** (**IVa**).—From a 2.06-g (0.0050 mol) sample of IIIa was obtained 1.56 g (74%) of IVa as white needles from methanol: mp 109–110°; nmr peaks at *ca.* 445 and *ca.* 416 (m, 14 H, aromatic protons), 321 (d, J = 9.5 Hz, 1 H, C-2 proton), 263 (octet, 1 H, C-3 proton), 239 (d of d, J = 6.8, J = 3.5 Hz, 1 H, C-4 proton), 216 (d of d, J = 6.8, J = 7.8 Hz), and *ca.* 78 and 54 Hz (distorted q and t, respectively, 15 H, 3 CH_2CH_3). See Table I for uv and ir data for compounds IVa–h and Va–h.

Anal. Calcd for $C_{29}H_{33}NO$: C, 84.63; H, 8.08; N, 3.40. Found: C, 84.46; H, 8.14; N, 3.43.

cis-1-*t*-**Butyl-2-phenyl-3-(*p*-phenylbenzoyl)azetidine** (**IVb**).—From a 1.85-g (0.0050 mol) sample of IIIb was obtained 1.70 g (92%) of IVb as a flaky white solid from petroleum ether (bp 60–69°), mp 165–166° (lit.[2a] mp 165°).

cis-1-**Isopropyl-2-phenyl-3-(*p*-phenylbenzoyl)azetidine** (**IVc**).—From a 1.78-g (0.0050 mol) sample of IIIc was obtained 1.41 g (79%) of IVc as a white crystalline solid from petroleum ether: mp 141–142°; nmr peaks at *ca.* 445 and *ca.* 417 (m, 14 H, aromatic protons), 276 (d, J = 9.0 Hz, 1 H, C-2 proton), 242–272 (m, 2 H, C-3 and one C-4 protons), 182 (t, J = 7.0 Hz, 1 H, C-4 proton), 152 (h, J = 6 Hz, 1 H, methine), and 62 and 40 Hz (d, J = 6 Hz, 3 H each, two nonequivalent CH_3's).

Anal. Calcd for $C_{25}H_{25}NO$: C, 84.47; H, 7.39; N, 3.94. Found: C, 84.30; H, 7.05; N, 3.94.

cis-1-**Cyclohexyl-2-phenyl-3-(*p*-phenylbenzoyl)azetidine** (**IVd**).—From a 1.98-g (0.005 mol) sample of IIId was obtained 1.46 g (74%) of IVd as white platlets from methanol:[26] mp 172–173° (lit.[3] mp 172–173°).

cis-1-**Ethyl-2-phenyl-3-(*p*-phenylbenzoyl)azetidine** (**IVe**).—From a 0.50-g (0.0015 mol) sample of IIIe was obtained 0.29 g (58%) of IVe as a flaky white solid from petroleum ether: mp 137–138°; nmr peaks at *ca.* 419 and *ca.* 446 (m, 14 H, aromatic protons), 274 (d, J = 8.5 Hz, 1 H, C-2 protons), 243–270 (m, 2 H, C-3 and one C-4 proton), 182 (t, J = 7.0 Hz, C-4 proton), 154 (d, J = 7 Hz, 2 H, methylene), and 54.5 Hz (t, J = 7 Hz, 3 H, CH_3).

Anal. Calcd for $C_{24}H_{23}NO$: C, 84.42; H, 6.79; N, 4.10. Found: C, 84.12; H, 6.83; N, 4.12.

cis-1-**Methyl-2-phenyl-3-(*p*-phenylbenzoyl)azetidine** (**IVf**).—To a 1.89-g (0.0050 mol) sample of IIa dissolved in 250 ml of *n*-hexane was added 9 drops of methylamine (*via* a Dry Ice–acetone trap) and the mixture was allowed to react at room temperature for 0.30 hr. The precipitated methylamine hydrobromide was removed by filtration and the clear filtrate was subjected to a stream of hydrogen bromide while being stirred. (The reaction vessel was equipped with a drying tube to exclude moisture.) Stirring was continued for 2 hr and the solution was then filtered to remove the slightly hygroscopic solid. Upon removal of the amine hydrobromide from the hexane solution this salt immediately absorbed moisture and attempts to dry it failed. The amine hydrobromide was dissolved in 150 ml of chloroform which was then saturated with hydrogen bromide at 0° and allowed to stand at room temperature for 6 hr. Excess hydrogen bromide was removed under reduced pressure and the resulting cold solution was neutralized with triethylamine. The solution was worked up exactly as was done in the general procedure for preparation of *cis* compounds. Recrystallization of the solid from ethyl ether yielded 0.52 g (32%) of white crystals: mp 142–143°; nmr peaks at *ca.* 445 and 420 (m, 14 H, aromatic protons), 240–280 (m, 3 H, C-2, C-3, and one C-4 proton), 182 (t of d, J = 7 and J = 1.9 Hz, respectively, 1 H, C-4 proton), and 142.5 Hz (s, 3 H, CH_3).

Anal. Calcd for $C_{23}H_{21}NO$: C, 84.37; H, 6.47; N, 4.28. Found: C, 84.52; H, 6.71; N, 4.39.

The yield of N-methylazetidine IVf was not significantly improved when pure VIf was used. Thus, treatment of a 0.40-g sample of pure VIf hydrobromide with triethylamine gave upon work-up 0.12 g (38%) of the desired product.

cis-1-**Isopropyl-2-phenyl-3-benzoylazetidine** (**IVg**).—From a 1.40-g (0.0050 mol) sample of IIIg was obtained 1.04 g (76%) of IVg as white crystals from pentane: mp 84–85°; nmr peaks at *ca.* 436 and *ca.* 415 (m, 10 H, aromatic protons), 277 (d, J = 9.0 Hz, 1 H, C-2 proton), 241–272 (m, 2 H, C-3 and one C-4 proton), 182 (t, J = 6.5 Hz, 1 H, C-4 proton), 152 (h, J = 6 Hz, 1 H, methine proton), and 62 and 40 Hz (d, J = 6 Hz, 3 H each, two nonequivalent CH_3's).

Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.53; H, 7.61; N, 5.04.

cis-1-**Cyclohexyl-2-phenyl-3-benzoylazetidine** (**IVh**).—From a 1.60-g (0.0050 mol) sample of 2-[α-(N-cyclohexylamino)benzyl]-acrylophenone[4] was obtained 0.98 g (61%) of IVh as a white crystalline solid from pentane: mp 102–103°; nmr peaks at *ca.* 436 and *ca.* 416 (m, 10 H, aromatic protons), 278 (d, J = 9 Hz, 1 H, C-2 proton), 240–273 (m, 2 H, C-3 and one C-4 proton), 183 (t, J = 7 Hz, 1 H, C-4 proton), and 30–150 Hz (m, 11 H, cyclohexyl protons).

Anal. Calcd for $C_{22}H_{25}NO$: C, 82.72; H, 7.89; N, 4.38. Found: C, 82.83; H, 7.95; N, 4.48.

cis-1-**Alkyl-2-deuterio-2-phenyl-3-aroylazetidines** (**IV'a–f**).—When the above scheme was carried out starting with deuterated chalcone (I') instead of α-methyl-*p*-phenylchalcone, these compounds (IV'a–f) were obtained. These were identified by mixture melting points with the corresponding nondeuterated compounds and the identity of ir spectra.

General Procedure for the Preparation of *trans*-**1-Alkyl-2-phenyl-3-aroylazetidines** (**Va–h**).—The appropriate *cis* compound was dissolved in methanol which contained a catalytic amount of sodium methoxide (*ca.* 0.05 g); the mixture was warmed for *ca.* 1 hr and then allowed to stand at room temperature for 3 hr. The methanol was evaporated under reduced pressure and the resulting residue was extracted with dry ethyl ether. The ether was evaporated and the nmr spectrum of the residue was obtained. The products were crystallized and recrystallized from the appropriate solvent. Comparison of the spectra of the gross products with those of the corresponding crystalline products indicated that the *cis* into *trans* conversion was quantitative and occurred without detectable amounts of decomposition as determined by nmr techniques.

When deuterated methanol (CH_3OD) was used instead of methanol the *trans*-3-deuterio compounds (V') were obtained.

trans-1-**Triethylcarbinyl-2-phenyl-3-(*p*-phenylbenzoyl)azetidine** (**Va**).—From a 0.50-g sample of IVa was obtained 0.40 g (80%) of Va as a white solid from a minimum amount of methanol: mp 75–76°; nmr peaks at 420–480 (m, 14 H, aromatic protons), 303 (d, J = 5.2 Hz, 1 H, C-2 proton), 200–250 (m, 3 H, C-3 and C-4 protons), and 76 and 52 Hz (q and t, respectively, 15 H, 3 CH_2CH_3).

Anal. Calcd for $C_{29}H_{33}NO$: C, 84.63; H, 8.08; N, 3.40. Found: C, 84.89; H, 8.19; N, 3.26.

trans-1-*t*-**Butyl-2-phenyl-3-(*p*-phenylbenzoyl)azetidine** (**Vb**).—From a 1.00-g sample of IVb was obtained 0.91 g (91%) of Vb as white needles from methanol: mp 127–128° (lit.[2a] mp 128°).

trans-1-**Isopropyl-2-phenyl-3-(*p*-phenylbenzoyl)azetidine** (**Vc**).—From a 0.50-g sample of IVc was obtained 0.46 g (92%) of Vc as a white crystalline solid from methanol: mp 109–110°; nmr peaks at 425–480 (m, 14 H, aromatic protons), 264 (d, J = 7.0 Hz, 1 H, C-2 proton), 180-250 (m, 3 H, C-3 and C-4 protons), 151 (h, 1 H, methine proton), and 59 and 44 Hz (d, J = 6 Hz, 3 H each, two nonequivalent CH_3's).

Anal. Calcd for $C_{25}H_{25}NO$: C, 84.47; H, 7.39; N, 3.94. Found: C, 85.01; H, 7.16; N, 4.17.

trans-1-**Cyclohexyl-2-phenyl-3-(*p*-phenylbenzoyl)azetidine** (**Vd**).—From a 1.28-g sample of IVd was obtained 1.11 g (87%) of Vd as a white crystalline solid from methanol: mp 142–143° (lit.[3] mp 142–143°).

trans-1-**Ethyl-2-phenyl-3-(*p*-phenylbenzoyl)azetidine** (**Ve**).—From a 0.20-g sample of IVe was obtained 0.13 g (65%) of Ve as a white crystalline solid from *n*-pentane: mp 70–71°; nmr peaks at 425–485 (m, 14 H, aromatic protons), 262 (d, J = 7 Hz, 1 H, C-2 proton), 218–254 (m, 2 H, C-3 and one C-4 proton), 181–202 (m, 1 H, C-4 proton), 135–175 (m, 2 H, CCH_2), and 56 Hz (t, J = 6.5 Hz, 3 H, CH_3).

Anal. Calcd for $C_{24}H_{23}NO$: C, 84.42; H, 6.79; N, 4.10. Found: C, 84.92; H, 6.87; N, 4.17.

trans-1-**Methyl-2-phenyl-3-(*p*-phenylbenzoyl)azetidine** (**Vf**).—From a 0.30-g sample of IVf was obtained 0.12 g (40%) of Vf as a white solid from *n*-pentane: mp 63–64°; nmr peaks at 420–460 (m, 14 H, aromatic protons), 258 (d, J = 7.5 Hz, 1 H, C-2 proton), 218–253 (m, 2 H, C-3 and one C-4 proton), 190 (m, 1 H, C-4 proton), and 142 Hz (s, 3 H, CH_3).

Anal. Calcd for $C_{23}H_{21}NO$: C, 84.37; H, 6.47; N, 4.28. Found: C, 84.31; H, 6.54; N, 4.18.

trans-1-**Isopropyl-2-phenyl-3-benzoylazetidine** (**Vg**).—From a

(26) Recrystallization of this compound from methanol sometimes leads to a small amount of epimerization.

0.25-g sample of IVg was obtained 0.20 g (80%) of Vg as a white solid from *n*-pentane: mp 42–43°; nmr peaks at 425–480 (m, 10 H, aromatic protons), 265 (d, J = 7 Hz, 1 H, C-2 protons), 180–250 (m, 3 H, C-3 and C-4 protons), 151 (h, J = 6 Hz, 1 H, methine), and 59 and 44 Hz (two d, J = 6 Hz, 3 H each, two nonequivalent CH_3's).

Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.88; H, 7.64; N, 5.16.

trans-**1-Cyclohexyl-2-phenyl-3-benzoylazetidine (Vh).**—From a 0.30-g sample of IVh was obtained 0.24 g (80%) of Vh as white needles from methanol: mp 96–97°; nmr peaks at 420–475 (m, 10 H, aromatic protons), 266 (d, J = 7.0 Hz, 1 H, C-2 proton), 150–180 (m, 3 H, C-3 and C-4 protons), and 30–150 Hz (m, 11 H, cyclohexyl protons).

Anal. Calcd for $C_{22}H_{25}NO$: C, 82.72; H, 7.84; N, 4.38. Found: C, 82.60, H, 7.93; N, 4.48.

erythro-**2-[α-(N-*t*-Butylamino)benzyl]-3-bromo-4′-phenylpropiophenone Hydrobromide (VIb).**—A 1.50-g sample (0.004 mol) of IIIb was dissolved in 100 ml of chloroform which had been previously saturated with dry hydrogen bromide at 0°. The solution was allowed to stand at room temperature for 4 days. Excess hydrogen bromide and chloroform were removed under reduced pressure. The light brown solid which resulted was recrystallized by being dissolved in a minimum amount of dry methanol and then addition of about 100 ml of dry ethyl ether. Several crops of white crystals were collected: 1.51 g (70%); mp 175–176°; characteristic ir bands ($CHCl_3$) at 3380, 3140, 2870, 2610, 2480, 2350 ($>\overset{+}{N}H_2$), 1668 (broad and unsymmetrical, >C=O), and 1605 cm^{-1} (aromatic C=C); nmr peaks at 425–495 (m, 14 H, aromatic protons), 120–365 (broad m, 6 H, $>\overset{+}{N}H_2$ and aliphatic protons other than *t*-C_4H_9), and 80 Hz (s, 9 H, *t*-C_4H_9).

Anal. Calcd for $C_{26}H_{29}NOBr_2$: C, 58.75; H, 5.51; N, 2.64; Br, 30.01. Found: C, 58.98; H, 5.65; N, 2.60; Br, 30.08.

Reaction of γ-Bromopropylamino Ketone Hydrobromide (VIb) with Excess *t*-Butylamine.—A 0.531-g sample (0.001 mol) of VIb was dissolved in 15 ml of chloroform and the solution was slowly made basic with *t*-butylamine while the reaction mixture was kept at room temperature. The solution was allowed to stand at room temperature for 3 hr, 25 ml of dry ethyl ether was added, and the precipitated *t*-butylamine hydrobromide was removed by filtration. Evaporation of the solvent without heat, extraction of the resulting residue with dry ethyl ether, removal of the remainder of the amine salt, and evaporation of the solvent yielded a white solid. The nmr spectrum of the gross product indicated the presence of only compound IVb. Recrystallization of the product from petroleum ether (bp 60–69°) yielded flaky white crystals of IVb, 0.336 g (91%), mp 165–166° (lit.[2a] mp 165°).

trans-**1-*t*-Butyl-2-phenyl-3-(*p*-phenylbenzoyl)azetidine** *via* **2-(N-*t*-Butylaminomethyl-3-bromo-3-phenyl-4′-phenylpropiophenone Hydrobromide (VIIb).**—A 2.00-g sample (0.0054 mol) of α-(N-*t*-butylaminomethyl)-4′-phenylchalcone dissolved in 15 ml of chloroform was added to 100 ml of chloroform which had been previously saturated with dry hydrogen bromide while being kept at 0°. The solution was allowed to stand at room temperature for 4 days to ensure completion of the addition of hydrogen bromide. The excess hydrogen bromide and chloroform were removed under reduced pressure to yield a light brown solid. Several attempts to crystallize the solid from various solvent systems failed. An ether–chloroform solution (100 ml) of the product(s) was made basic with *t*-butylamine and was allowed to stand for 3 hr. Removal of the *t*-butylamine hydrobromide (1.61 g, 98% of theoretical yield was obtained assuming 2 equiv/molecule) as described above and recrystallization of the residue from methanol yielded 1.09 g (54%) of white crystals of Vb, mp 127–128° (lit.[2a] mp 128°). The spectrum of the crude mixture (after removal of amine salts and solvent) indicated the presence of only Vb and α-(N-*t*-butylaminomethyl)-4′-phenylchalcone.[2a]

Thermal Stability of *cis*-1-Alkyl-2-phenyl-3-aroylazetidines (IVb and IVd). A. In Petroleum Ether (Bp 88–89°).—A 0.20-g sample of IVd was heated in 25 ml of this solvent at reflux temperature for 14 hr, and IVd was recovered unchanged. However, the similar treatment of a 0.20-g sample of IVb lead to partial isomerization. The nmr spectrum of the gross product in the latter case indicated the presence of a 1:1 mixture of IVb and its *trans* isomer Vb by integration of the C-2 ring-proton bands.

B. In Methanol.—A 0.20-g sample of the *cis* compound was heated in 25 ml of this solvent at reflux temperature for 14 hr. The solution was concentrated and cooled at 0° to induce crystallization. The solution was filtered to remove a high yield (>90%) of the *trans* compound. Compound IVb gave Vb, mp 127–128°, while IVd gave Vd, mp 142–143°.

α-(N-*t*-Butylaminomethyl)-4′-phenylchalcone (VIII).—A 1.89-g (0.0050 mol) sample of IIa dissolved in 50 ml of chloroform was allowed to react with *t*-butylamine (1.1 g, 0.015 mol) for 24 hr. Removal of the solvent, extraction with dry ether, removal of the suspended *t*-butylamine hydrobromide by filtration, and evaporation of the solvent yielded a yellow solid. The nmr spectrum of the crude mixture indicated the presence of a quantitative yield of VIII. The product was crystallized from ethyl ether: mp 91–92° (lit.[2a] mp 92°).

Registry No.—IIIa, 18588-35-7; IIIc, 18621-07-3; IIIe, 18621-08-4; IIIg, 18588-36-8; IVa, 18599-78-5; IVb, 13871-55-1; IVc, 18599-80-9; IVd, 13970-36-0; IVe, 18599-82-1; IVf, 18599-83-2; IVg, 18599-84-3; IVh, 18599-85-4; Va, 18599-86-5; Vb, 13871-53-9; Vc, 18599-88-7; Vd, 18599-89-8; Ve, 18599-90-1; Vf, 18599-91-2; Vg, 18599-92-3; Vh, 18599-93-4; V′a, 18599-96-7; V′b, 13871-54-0; V′c, 18599-98-9; V′d, 13871-57-3; V′e, 18600-00-5; V′f, 18600-01-6; VIb, 18599-94-5; VIf, 18599-95-6.

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