Conformational Isomerism of 2-Carboazetidines (1)

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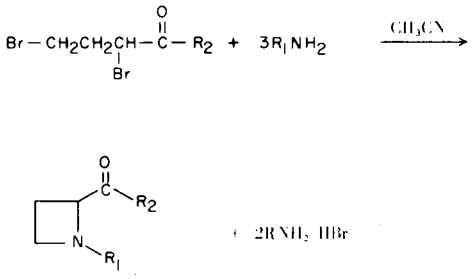
A number of 1-alkyl-2-carboazetidines have been prepared from the reaction of primary amines with α,γ-dibromocarbonyl compounds. Several of these new azetidines exhibit doublet carbonyl stretching absorptions in their infrared spectra. A possible explanation of this phenomenon is offered in terms of three rotational conformers which represent various degrees of dipole-dipole and steric interactions. The *cis* and *trans* forms of 1-*t*-butyl-2-carbomethoxy-4-methylazetidine have been obtained from the reaction of *t*-butylamine with methyl α,γ-dibromovalerate. A detailed examination indicates that the ir and nmr spectra of these epimers are in agreement with the foregoing conformational postulates.

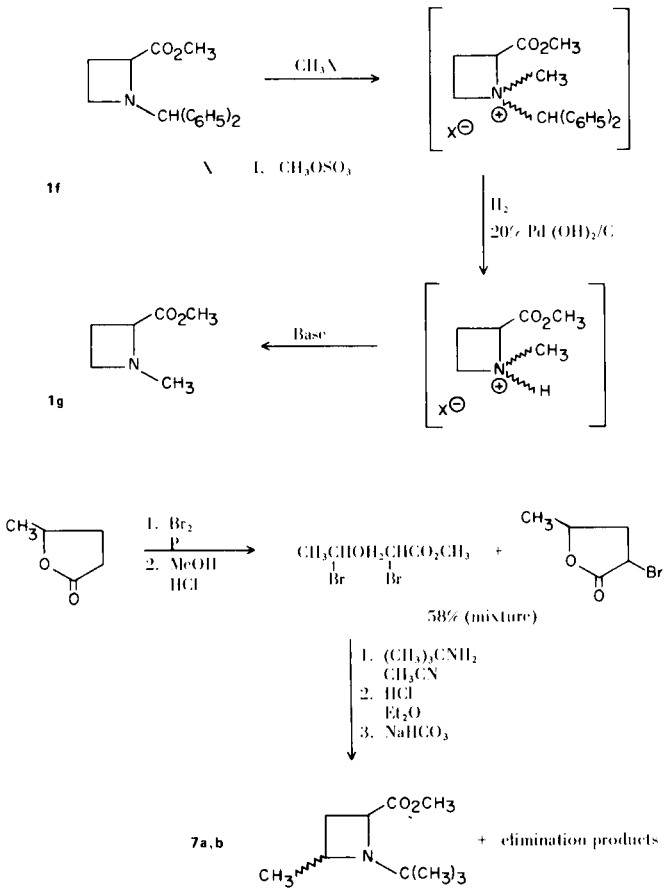
Results and Discussion.

In previous publications (4) we reported that several primary amines react with α,γ-dibromo carbonyl compounds to afford, in useful yields, various 2-carboazetidines.



The reaction is general when R_1 is any alkyl group other than methyl and a number of azetidines of this type have been prepared (Table I). As expected, when R_1 is very small a complex mixture of products is obtained. Since an *N*-methyl azetidine was of particular interest in this investigation this compound **1g** was prepared (in low yield) by quaternerizing 1-benzhydryl-2-carbomethoxy-azetidine (**1f**) with dimethyl sulfate followed by hydrogenolysis of the benzhydryl group. The epimeric pair of azetidinyl esters (**7a-b**) was obtained by condensation of methyl α,γ-dibromovalerate with *t*-butylamine, the isomers being separated by preparative vpc. The configurations of **7a,b** were assigned by detailed examination of their ir and nmr spectra and application of conformational postulates derived from spectral data of the simpler di-substituted ring systems.

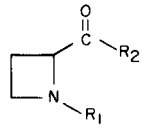
A majority of the compounds investigated exhibit doublet carbonyl stretching absorptions in their infrared spectra



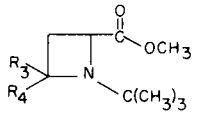
(Table I). That Fermi resonance is not likely the cause of these doublet absorptions is indicated by the fact that several closely analogous compounds (*i.e.*, **1g**) show only a single symmetrical carbonyl band.

TABLE I

Infrared Data for 1-Alkyl-2-Carboazetidines (a)



Compound	R_1	R_2	ν C=O (cm^{-1})/% abs
1a (4a)	$C(CH_3)_3$	OCH_3	1756/64; 1729/58
1b (4a)	C_6H_{11}	OCH_3	1755/72; 1730/69
1c	$C(CH_3)_2CH_2C(CH_3)_3$	OCH_3	1755/67; 1730/57
1d	$CH(CH_3)_2$	OCH_3	1757/76; 1731/76
1e (4a)	$CH_2C_6H_5$	OCH_3	1747/79
1f	$CH(C_6H_5)_2$	OCH_3	1746/96
1g	CH_3	OCH_3	1745/79
2a	$C(CH_3)_3$	$OCH_2C_6H_5$	1753/57; 1727/46
2b	C_6H_{11}	$OCH_2C_6H_5$	1752/70; 1727/61
2d	$CH(CH_3)_2$	$OCH_2C_6H_5$	1749/55; 1725/48
2f (4b)	$CH(C_6H_5)_2$	$OCH_2C_6H_5$	1745/86
3 (4c)	$C(CH_3)_3$	C_6H_5	1697/85; 1668/71
4	$CH(CH_3)_2$	C_6H_5	1699/52; 1669/41
5	$C(CH_3)_3$	p-$C_6H_5C_6H_4$	1695/87; 1666/77
6	CH_3	p-$C_6H_5C_6H_4$	1692/55



	R_3	R_4	
7a	H	CH_3	1751/70; 1725/63
7b	CH_3	H	1751/57; 1738/82

Model Compounds

methyl acetate	1740 (14)
methyl propionate	1740 (14)
methyl butyrate	1735 (14)
acetophenone	1690 (7)
p-phenylacetophenone	1682 (6)
p-phenylpropiophenone	1687 (15)
cylcohexyl phenyl ketone	1682 (16)

(a) All spectra were recorded in carbon tetrachloride solutions. See experimental section for further details.

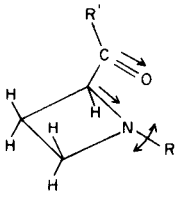
Reports of doublet infrared carbonyl stretching absorptions which have been ascribed to conformational isomerism are numerous in the literature (5-13).

Other reports from this laboratory have described various classes of compounds which exhibit this same general phenomenon (7). The doublet carbonyl bands observed for several isomeric aziridinyl ketones were considered to be due in part to the presence of three-ring carbonyl hyperconjugation and conformational isomerism. Several acyclic α-amino ketones were also studied (8), the

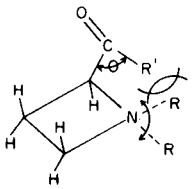
observed doublet bands apparently resulting from dipole-dipole interactions of the type suggested in the work of Bellamy (10), as well as from three-ring electrostatic factors (7).

In connection with our continuing interest in azetidine chemistry we now report our observation of anomalous infrared spectral characteristics of a number of 2-carboazetidine derivatives.

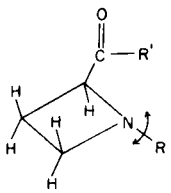
The frequency difference ν_1-ν_2 for compounds in Table I showing doublet peaks is in general larger than that observed in most previous studies. It will be noted that for all compounds displaying two carbonyl absorption maxima (except **7b**) one of the peaks is at a somewhat higher frequency than that in the corresponding model compounds while the other is found at a significantly lower frequency than that in the models. This suggests that both dipole-dipole and steric interactions are important in these systems, thus implying that rotation of the carbonyl moiety is partially hindered. We suggest that three conformers, *C*, *D*, and *E* may be of varying importance in these systems.



C (*syn*)



D (*anti*)



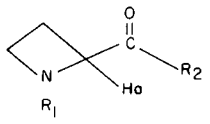
E (*gauche*)

In the *syn* conformer (*C*) the ring nitrogen and carbonyl oxygen are eclipsed (or nearly so). The resulting intramolecular dipole-dipole interaction would be expected to produce an increase in the carbonyl stretching frequency thus tentatively accounting for the high band. Other studies (10) have shown that such eclipsed conformers involving a dipole-dipole interaction often represent the most stable arrangement for functional groups in the molecule and this seems to be indicated here by the predominance in intensity of the high frequency band for several of the azetidines.

Conformer *D*, denoted *anti*, may arise from *C* by a 180° bond rotation of the carbonyl moiety. In accordance with the work of Bottini and Roberts (17) it may be assumed that the pyrimidal nitrogen inversion in this ring system is reasonably rapid. Thus at any moment in time when the *N*-substituent is oriented in a position *cis* to the carbonyl moiety in the *anti* conformer *D*, nonbonded repulsive interactions may occur between R_1 and R_2. One mode of relieving such compression would be an increase in the angle θ which would result in increased *s*-character in the C-C bonds and increased *p*-character in the C-O bond with a consequent carbonyl stretching frequency lower than that observed in the model compounds. Dreiding models indicate that such a steric interaction is indeed to be expected when the *N*-alkyl group is bulky but that no such interaction should occur with small R_1 groups. The data is in agreement with this concept since the compounds in which R_1 is methyl, benzyl, etc. (**1e**, **1f**, **1g** and **6**) show no low frequency absorption. An alternative

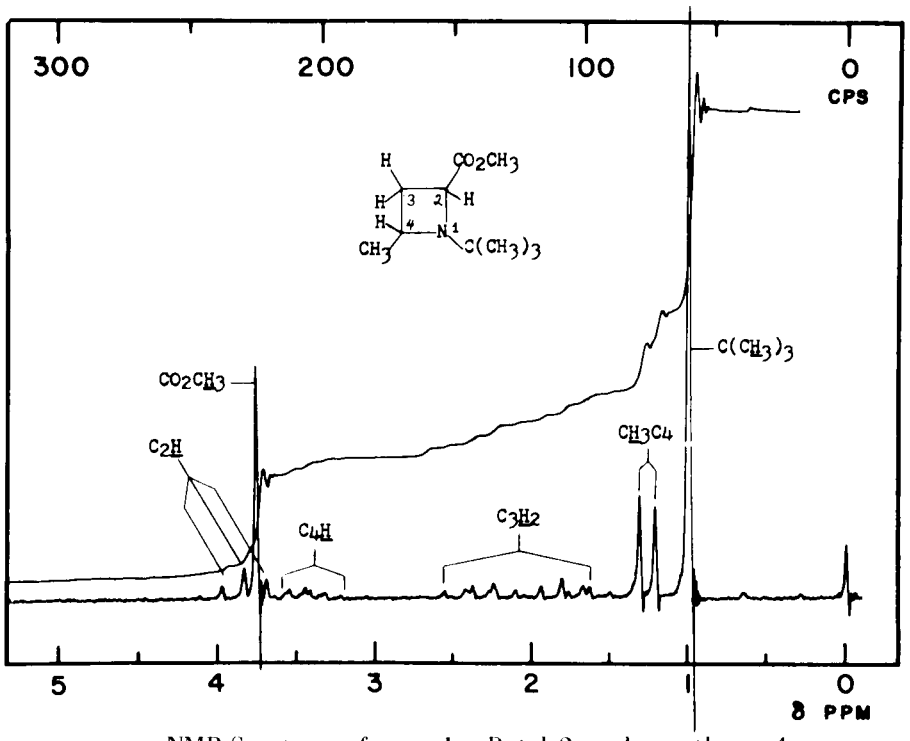
TABLE II

Chemical Shifts of the C_2 Proton (Ha) in 2-Carboazetidine Derivatives (a)

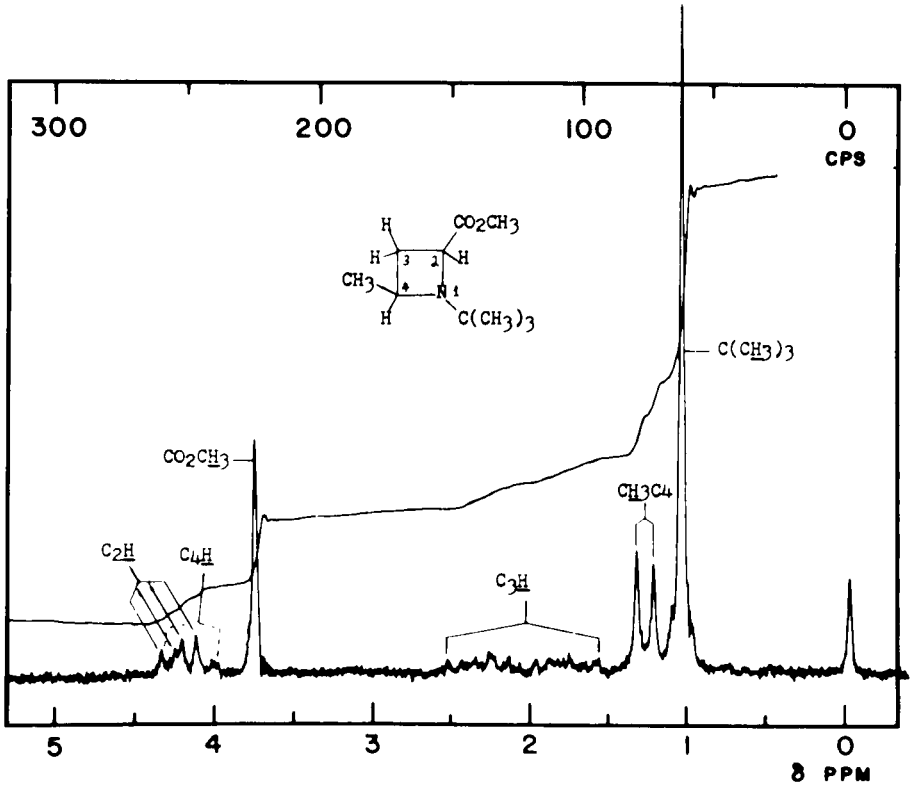


R_1	$R_2 = OCH_3$	$R_2 = OCH_2C_6H_5$	$R_2 = C_6H_5$	$R_2 = p\text{-}C_6H_5C_6H_4$
		Hz		
$C(CH_3)_2CH_2C(CH_3)_3$	236			
$C(CH_3)_3$	237	236	285	288
$CH(CH_3)_2$	217	221	275	
C_6H_{11}	215	220		
CH_3	206			255

(a) All spectra were obtained in deuteriochloroform solution.



NMR Spectrum of *trans*-1-*t*-Butyl-2-carbomethoxy-4-methylazetidine (**7a**) in $CDCl_3$.



NMR Spectrum of *cis*-1-*t*-Butyl-2-carbomethoxy-4-methylazetidine (**7b**) in $CDCl_3$.

TABLE III

Variation of Carbonyl Bands with Solvent Polarity

Compound	ν C=O/% abs	ratio ν_1/ν_2	Solvent
1a	1756/64; 1729/58	1.10	CCl_4
	1749/77; 1725/61	1.26	CH_3CN
1b	1755/72; 1730/69	1.04	CCl_4
	1749/78; 1726/64	1.22	CH_3CN
1d	1757/76; 1731/76	1.0	CCl_4
	1749/86; 1726/75	1.3	CH_3CN
3	1697/85; 1668/71	1.20	CCl_4
	1692/95; 1666/48	1.98	CH_3CN
5	1695/87; 1666/77	1.13	CCl_4
	1691/94; 1665/57	1.65	CH_3CN

mode of relieving the nonbonded repulsions between R_1 and R_2 would be a twisting of R_2 such that it is out of the plane of the carbonyl group (*i.e.*, compounds **3**, **4** and **5**). That this does not occur significantly, at least in the excited state, is indicated by the normal uv spectra observed for these compounds. The steric strain may also be diminished by (1) inversion of the nitrogen leading to the form of the *anti* conformer *D* in which the R_1 group and the carbonyl moiety are *trans* to each other, which should give a carbonyl band in the same region as the model compounds, and (2) rotation of the carbonyl moiety into rotamer *C* or *E*.

Neither dipole-dipole nor significant steric interactions are expected to be present in the *gauche* conformer *E* in which the carbonyl bond axis is perpendicular to the plane of the ring. The nitrogen atom would be expected to have little effect upon the position of the absorption maximum since through-bond inductive effects of other electronegative groups have been shown to be nearly negligible (5). Thus conformer *E* should give rise to carbonyl stretching frequencies near those found in the model compounds.

For compounds listed in Table I exhibiting doublet carbonyl absorptions (except **7b**, *vide infra*), the *syn* conformer (*C*) and *anti* conformer (*D*) seem to be preferred with the *syn* predominating slightly. It is likely that the *gauche* conformer (*E*) is also significantly populated (though less so than the other two) but the absorption band arising from it would be masked by the major portion of the other two bands. With the *N*-methyl, *N*-benzyl and *N*-benzhydryl azetidines (**1e**, **1f**, **1g** and **6**), the *gauche* conformer is apparently more important although it may be slightly perturbed in the direction of the *syn* conformer as indicated by the position of the absorption maxima.

In accord with other studies (8,9,11) the relative intensities of the doublet carbonyl bands are dependent on solvent polarity (Table III). The intensity increase in the high frequency band at the expense of the low frequency band would correspond, in terms of previous postulates, to an increased preference for the *syn* conformers (*C*), which is reasonable since the more polar solvent should favor the conformer of highest dipole moment. The fact that the intensity variation with solvent polarity is much greater in the azetidinyl ketones than in the esters is by the above reasoning to be expected. In the ester moiety a dipole exists along both the carbonyl and singly bonded C-O bonds and a preference for the *syn* over the *anti* conformer in a polar solvent would not be as great as with the ketone wherein the only possible strong dipole-dipole interaction involves the carbonyl and ring C-N bonds (the *syn* conformer).

The data for the epimeric azetidines (**7a,b**) in conjunction with the aforementioned postulates concerning *syn*, *anti* and *gauche* conformers *C*, *D* and *E* enable one to make tentative configurational assignments which are substantiated by nmr spectroscopy. The mass spectra (see experimental section) of these epimers were nearly identical except for some slight peak intensity differences. However, the infrered (Table I) as well as the nmr spectra proved to be significantly different. Bottini and Roberts (17) have suggested that attachment of substituents to aziridine ring carbons leads to greater nitrogen inversion rates but that such groups if affixed in a *cis* orientation to one another tend to make the molecules assume preferred conformations with the *N*-substituent *trans* to the ring substituents. It has been found in this laboratory (18) that the *cis* compounds do assume a preferred conformation as suggested above. If a similar situation is assumed to apply in the azetidines (**7a,b**) then the *t*-butyl group should have no preferred orientation on either side of the ring in the *trans* epimer (**7a**) and the infrared spectrum should be similar to that observed for **1a**, *i.e.* the carbonyl bands resulting from a predominance of conformers *C* and *D* should be evident. On the other hand, the *cis* azetidine (**7b**) should exist in a preferred conformation with the carbomethoxy and *t*-butyl groups *trans* to each other. Significant nonbonded interactions between these two groups would not be expected to occur and the low frequency carbonyl band resulting from conformer *D* would thus not be observed. On this basis epimer **7a** was tentatively assigned the *trans* configuration and epimer **7b** the *cis* configuration.

The nmr spectra (Figures 1,2) are in agreement with these assignments and they also reveal additional information concerning the conformations of these compounds. There are two major distinguishing features. The spectrum of the *trans* isomer (**7a**) (Figure 1) is similar to that of **1a** (4a) in terms of the ring proton chemical shifts and in the appearance of the C_2 methine proton as a triplet (col-

lapsed quartet), $J_{2,3}$ = 8.2 Hz. On the other hand the corresponding proton in the *cis* isomer (**7b**) appears as a quartet, J_{cis} = 7.6 Hz, J_{trans} = 5.0 Hz, the larger coupling constant being assigned to the *cis* vicinal protons by analogy with other small ring compounds (19) and in agreement with the Karplus relationship (20). Of the compounds reported in this investigation, the observation of the C_2 methine proton as a quartet is unique. The quartet indicates that the conformation of the ring is indeed different in the *cis* isomer (**7b**) than in the *trans* isomer (**7a**), and since the *t*-butyl group in the *cis* epimer apparently has a preferred conformation on one side of the nitrogen atom (see below for further evidence of this) the nitrogen pyramid would in effect be less flat and the ring more puckered in the *cis* than in the *trans* case. The observed decrease in both the *cis* and *trans* vicinal coupling constants with a change in ring conformation cannot be rationalized solely on the basis of a change in dihedral angles. However, a similar situation was noticed for one set of vicinal protons (C_3-C_4) in the 2-aryl-3-aroylazetidines. As the amount of ring puckering increased both the *cis* and *trans* vicinal coupling constants decreased (21). In addition, a significant difference in the chemical shifts of the C_2 and C_4 ring protons of the two isomers exists which is explicable on the basis of the suggested configurational assignments. The C_2 proton in the *cis* isomer is shifted 25 Hz downfield relative to the corresponding proton in the *trans* isomer and the chemical shift difference in the C_4 protons in the two isomers is approximately 45-50 Hz in the same direction. The paramagnetic shifts of these protons in the *cis* isomer almost certainly arises from Van der Waals dispersion effects. The results of these effects in the 2-aryl-3-aroylazetidines have been reported previously (21) wherein it was shown that the chemical shifts of the C_2 and C_4 ring protons are sensitive functions of the steric requirement of the *N*-substituent. These same effects are noticeable (Table II) in the spectra of the 2-carboazetidines, the C_2 proton (22) being increasingly deshielded by *N*-substituents of greater size. These dispersion effects are expected to be more prevalent in the *cis* compound (**7b**) than in the *trans* isomer (**7a**) since the *t*-butyl group in the *cis* isomer has a preferred orientation *cis* to the adjacent C_2 and C_4 protons thus accounting for the observed chemical shifts.

That the conformational isomerism of 2-carboazetidines suggested by their ir spectra is very likely of a dynamic nature is indicated by an nmr experiment in which the spectrum of **1a** in a temperature range of +40° to -52° was recorded. The sharp triplet signal of the C_2 methine proton was observed at an expanded sweep width to undergo no change whatsoever. Thus, due to the relatively slow time scale of the nmr phenomenon, the conformational isomerism in these compounds is not detected and only the time-average magnetic environment of the C_2 proton is seen. Also negated is the notion that the doublet infrared carbonyl bands can be explained simply by the existence of two stable isomers in solution (one in which the *N*-substituent and carbonyl moiety are *cis* to each other and one in which they are *trans*), since due to the aforementioned dispersion effects, a chemical shift difference for the C_2 proton in such isomers would be expected.

EXPERIMENTAL

Melting points were determined with a Mel-temp capillary tube melting point apparatus and are uncorrected. Boiling points were determined at pressures recorded on a standard McCleod gage and are uncorrected. Elemental analyses were preformed by Micro Tech Laboratories, Skokie, Illinois. The infrared spectra were recorded on a Perkin-Elmer Model 621 Grating Infrared Spectrophotometer using carbon tetrachloride solutions in matched 0.1 mm sodium chloride cells. Band assignments are reporducible within ± 1 cm^{-1} and absorption intensities (% abs) within ± 0.5%. Ultraviolet spectra were obtained on a Cary Model 14 instrument. The nmr spectra were recorded on a Varian A-60 spectrometer and the chemical shifts are reported in hertz with tetramethylsilane as an internal standard. The mass spectra were determined on a Hitachi RMU-6D spectrometer by Mr. D. L. Von Minden. Gas chromatography was carried out on a Varian Aerograph Model 90P-3 chromatograph or a Varian Autoprep Model A-700 instrument. Types of columns and conditions utilized are specified for individual compounds.

The preparation of compounds **1a**, **1b**, **1e** (4a), **2f** (4b) and **3** (4c) have been reported previously.

General Procedure for the Preparation of 1-Alkyl-2-carbomethoxyazetidines (**1c-f**).

A two-tenths molar solution of methyl α,γ-dibromobutyrate (23) and three molar equivalents of the appropriate primary amine in acetonitrile was refluxed for 12 to 24 hours. The reaction mixture was cooled, diluted with ethyl ether and the precipitated amine hydrobromide removed by filtration. The filtrate was evaporated to dryness and the residue taken up in ethyl ether. After filtration the ethereal solution was exposed to a stream of dry hydrogen chloride gas for 5 minutes. The ether was decanted and the syrupy precipitate (in some cases a filterable solid) was washed with ether, dissolved in chloroform and treated with an excess of triethylamine. After evaporation of the chloroform and excess triethylamine the residue was extracted with ether, the extract filtered and the ether evaporated from the filtrate under reduced pressure. The resulting crude product was purified by vacuum fractional distillation, column chromatography or gas chromatography.

1-(1,1,3,3-Tetramethylbutyl)-2-carbomethoxyazetidine (**1c**).

From 26.00 g. (0.10 mole) of methyl α,γ-dibromobutyrate and 38.70 g. (0.30 mole) of 1,1,3,3-tetramethylbutylamine was obtained 14.10 g. (61.8%) of **1c**, isolated by distillation as a colorless oil (24), b.p. 83-85° (0.7 mm); ir (carbon tetrachloride), 1755/67 (ester ν_1 C=O/% abs) and 1730 cm^{-1}/57 (ester ν_2 C=O/% abs); nmr (deuteriochloroform), 236 (t, 1H, J = 8.1 Hz, C_2 proton), 220 (S, 3H, methoxy), 180-198 (m, 2H, C_4 protons), 112-141 (m, 2H, C_3 protons), 75 (s, 2H, *t*-octyl methylene), and 59 Hz (s, 15H, *t*-octyl methyls).

Anal. Calcd. for $C_{13}H_{25}NO_2$: C, 68.68; H, 11.08; N, 6.16. Found: C, 68.84; H, 11.19; N, 6.09.

1-Isopropyl-2-carbomethyoxyazetidine (**1d**).

From 5.20 g. (0.02 mole) of methyl α,γ-dibromobutyrate and 4.00 g. (0.07 mole) of isopropylamine was obtained 3.14 g. (61.5%) of **1d**, isolated by distillation as a colorless oil (24), b.p. 40-42° (0.6 mm); ir (carbon tetrachloride), 1757/76 (ester ν_1 C=O/% abs) and 1731 cm^{-1}/76 (ester ν_2 C=O/% abs); nmr (deuteriochloroform), 223 (s, 3H, methoxy), 217 (t, 1H, J = 8.6 Hz, C_2 proton), 116-210 (m, 5H, C_3 protons, C_4 protons and isopropyl methine), and 54.5 Hz (d, 6H, J = 6.7 Hz, isopropyl methyls). The analytical sample was obtained by vpc on a 5-ft. x 1/8-in. column of Carbowax 20 M (15%) on Chromasorb W (60/80 mesh) with column temperature, 125°; detector, 265°; injection port, 250° and flow rate, 40 ml./minute.

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 60.98; H, 9.44; N, 8.77.

1-Benzhydryl-2-carbomethoxyazetidine (**1f**).

From 13.60 g. (0.05 mole) of methyl α,γ-dibromobutyrate and 27.5 g. (0.15 mole) of benzhydrylamine was obtained 10.0 g. (72.2%) of **1f**, isolated as a viscous light yellow oil by column chromatography on 400 g. of florisil (benzene elution). High vacuum distillation of a small portion of the eluent gave the analytical sample, b.p. 142-144° (0.25 mm); ir (carbon tetrachloride), 1746 cm^{-1}/96 (ester ν C=O/% abs); nmr (carbon tetrachloride), 421-453 (m, 10H, aromatic), 269 (s, 1H, benzhydryl methine), 220 (t, 1H, J = 8.0 Hz, C_2 proton), 198 (s, 3H, methoxy), 152-217 (m, 2H, C_4 protons), and 115-147 (m, 2H, C_3 protons); mass spectrum (70 eV) m/e (rel. intensity): 281 (2), 222 (12), 195 (15), 168 (17), 167 (100), 165 (25), 152 (13).

Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.67; H, 6.91; N, 5.01.

1-Methyl-2-carbomethoxyazetidine (**1g**).

A 28.1-g. sample (0.10 mole) of 1-benzhydryl-2-carbomethoxyazetidine (**1f**) was heated with 25 g. of dimethyl sulfate to 100° with magnetic stirring. After 10 minutes, the dark red mixture was allowed to cool. The resulting viscous oil was dissolved in a minimum amount of methanol and ethyl ether added precipitating a red syrup. The solvent was decanted and the residue dissolved in 400 ml. of methanol containing 1.0 g. of 20% palladium hydroxide on charcoal (25), and the solution was hydrogenolyzed at 45 psi and room temperature. After 1 hour the mixture was filtered, 0.5 g. of fresh catalyst was added to the filtrate and the mixture hydrogenolyzed for an additional 2 hours. Filtration and addition of fresh catalyst, as before, followed by hydrogenation for an additional hour resulted in a total uptake of 95% of the theoretical amount of hydrogen. After filtration to remove the catalyst the methanol was evaporated from the filtrate under reduced pressure, the residual syrup was dissolved in 20 ml. water and the by-product diphenylmethane was extracted with several portions of ether. After addition of 200 ml. of ether, solid sodium bicarbonate was added to neutrality. The ethereal layer was decanted and the aqueous layer extracted with three additional 200-ml. portions of ether. The combined extract was dried over magnesium sulfate and the solvent evaporated leaving 1.5 g. (*ca.* 10%) of a residual oil. Vacuum fractional distillation through an 8-cm Vigreaux column yielded 1.0 g. (8%) of **1g** as a colorless oil, b.p. 70-72° (40 mm); ir (carbon tetrachloride), 1745 cm^{-1}/79 (ester ν C=O/% abs); nmr (deuteriochloroform), 226 (s, 3H, methoxy), 206 (t, 1H, J = 7.6 Hz, C_2 proton), 157-210 (m, 2H, C_4 protons), 145 (s, 3H, *N*-methyl), and 121-152 Hz (m, 2H, C_3 protons); mass spectrum (80 eV) m/e (rel. intensity); 129 (7), 72 (6), 71 (6), 70 (100), 58 (7), 44 (7), 43 (9), 42 (45), 41 (91), 32 (10), 28 (33). The analytical sample was obtained by vpc on the column used for **1d** with column temperature, 115°; detector, 225°, injection port, 170° and flow rate 55 ml./minute.

Anal. Calcd. for $C_6H_{11}NO_2$: C, 55.79; H, 8.58; N, 10.85. Found: C, 55.50; H, 8.88; N, 10.68.

General Procedure for the Preparation of 1-Alkyl-2-carbobenzoxyazetidines (**2a-d**).

A two-tenths molar solution of benzyl α,γ-dibromobutyrate (4) and three molar equivalents of the appropriate primary amine in acetonitrile was refluxed 18 hours. The work up was the same as that described in the general procedure for the preparation of compounds **1c-f**. Infrared spectra of the crude products in some cases revealed the presence of amides as well as the desired material. Purification was accomplished by column chromatography and/or distillation.

1-*t*-Butyl-2-carbobenzoxyazetidine (**2a**).

From 13.46 g. (0.04 mole) of benzyl α,γ-dibromobutyrate and 8.78 g. (0.12 mole) of *t*-butylamine was obtained 7.20 g. (72.8%) of **2a**, isolated by vacuum distillation as a colorless oil (24), b.p. 118-119° (0.65 mm); ir (carbon tetrachloride), 1753/57 (ester ν_1 C=O/% abs) and 1727 cm^{-1}/46 (ester ν_2 C=O/% abs); nmr (deuteriochloroform), 445 (s, 5H, aromatic), 309 (s, 2H, benzylic), 236 (*t*, 1H, J = 8.1 Hz, C_2 proton), 182-199 (m, 2H, C_4 protons), 112-136 (m, 2H, C_3 protons), and 56 Hz (s, 9H, *t*-butyl).

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.70; H, 8.55; N, 5.85.

1-Cyclohexyl-2-carbobenzoxyazetidine (**2b**).

From 6.73 g. (0.02 mole) of benzyl α,γ-dibromobutyrate and 5.95 g. (0.06 mole) of cyclohexylamine was obtained 3.07 g. (56.4%) of **2b**, isolated by chromatography on 130 g. of silica gel (eluted with ether-hexane, 1:1) as a light yellow oil. The analytical sample was obtained by distillation of a portion of the eluent as a colorless oil (24), b.p. 141-142° (0.5 mm); ir (carbon tetrachloride), 1752/70 (ester ν_1 C=O/% abs) and 1727 cm^{-1}/61 (ester ν_2 C=O/% abs); nmr (deuteriochloroform), 441 (s, 5H, aromatic), 310 (s, 2H, benzylic), 220 (t, 1H, J = 8.2 Hz, C_2 proton), 194-209 and 153-185 (two m, 2H, C_4 protons), 118-149 (m, 3H, C_3 protons and cyclohexyl methine), and 45-110 Hz (m, 10H, cyclohexyl methylenes).

Anal. Calcd. for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.80; H, 8.36; N, 5.15.

1-Isopropyl-2-carbobenzoxyazetidine (**2d**).

From 6.73 g. (0.02 mole) of benzyl α,γ-dibromobutyrate and 3.55 g. (0.06 mole) of isopropylamine was obtained 2.52 g. (54.2%) of **2d**, isolated as a light yellow oil by chromatography on 100 g. of silica gel (eluted with ethyl ether). The analytical sample was obtained by distillation of a portion of the eluent as a colorless oil (24), b.p. 113-115° (0.9 mm); ir (carbon tetrachloride), 1749/55 (ester ν_1 C=O/% abs) and 1725 cm^{-1}/48 (ester ν_2 C=O/% abs); nmr (deuteriochloroform), 441 (s, 5H, aromatic), 310 (s, 2H, benzylic), 221 (t, 1H, J = 8.2 Hz, C_2 proton), 194-210 and 159-184 (two m, 2H, C_4 protons), 118-152 (m, 3H, C_3 protons and isopropyl methine), 53 and 56 Hz (two d, 6H, J = 6.2 Hz, nonequivalent isopropyl methyls).

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.04; H, 8.21; N, 6.00. Found: C, 71.82; H, 8.19; N, 5.74.

1-Isopropyl-2-benzoylazetidine (**4**).

A solution of 12.26 g. (0.04 mole) of α,γ-dibromobutyrophenone (4c) and 7.10 g. (0.12 mole) of isopropylamine in 100 ml. of acetonitrile was stirred magnetically in a tightly stoppered flask at room temperature for 2 days. The acetonitrile was evaporated from the reaction mixture under reduced pressure. The resulting dark green tarry residue was extracted with dry ethyl ether, the extract filtered through magnesium sulfate and the resulting yellow filtrate exposed to a stream of dry hydrogen chloride gas for 5 minutes. The ether was decanted and the syrupy residue dissolved in 25 ml. of water. The aqueous solution was washed three times with 100-ml. portions of ether, the washings being discarded. After the addition of 150 ml. of ether to the aqueous solution, solid sodium bicarbonate was added portionwise to neutrality. The ether layer was decanted, the aqueous layer being washed three times with 100 ml. of ether and the washes combined with the original decantant. The ethereal solution was dried over magnesium sulfate and the ether evaporated under reduced pressure. Vacuum distillation of the resulting dark red oil gave 1.05 g. (13%) of **4** as a very unstable yellow oil (24), b.p. 100-102° (0.6 mm); ir (carbon tetrachloride), 1699/52 (ketone ν_1 C=O/% abs) and 1669 cm^{-1}/41 (ketone ν_2 C=O/% abs); nmr (deuteriochloroform), 445-496 (m, 5H, aromatic), 275 (t, 1H, J = 8.5 Hz, C_2 proton), 171-227 (m, 3H, C_4 protons and isopropyl methine), 126-167 (m, 2H, C_3 protons), 56 and 64 Hz (two d, 6H, J = 6.1 Hz, nonequivalent isopropyl methyls). Ketone **4** was analyzed as its picrate salt, m.p. 177-178°.

Anal. Calcd. for $C_{19}H_{20}N_4O_8$: C, 52.78; H, 4.66; N, 12.96. Found: C, 52.78; H, 4.71; N, 13.04.

α,γ-Dibromo-*p*-phenylbutyrophenone.

To a mechanically stirred suspension containing 24.94 g. (0.162 mole) of biphenyl and 43.30 g. (0.162 mole) of aluminum chloride in 100 ml. of carbon disulfide at 0° was added dropwise, over a period of 2 hours, 50.0 g. (0.162 mole) of α,γ-dibromobutyryl bromide (26). After the addition was completed the reaction mixture was stirred an additional hour at 0°. Carbon disulfide (200 ml.) was added and the catalyst complex was decomposed by pouring the reaction mixture over a mixture of ice and concentrated hydrochloric acid. Ethyl ether (600 ml.) was added and the organic layer was separated, washed four times with water and once with a saturated aqueous solution of sodium chloride. It was then dried over magnesium sulfate and the solvent evaporated under reduced pressure. Petroleum ether (b.p. 30-60°) (500 ml.) was added to the residual solid and the suspension filtered yielding 58.0 g. (94%) of a light yellow solid crude product, m.p. 84-87°. The crude product was dissolved in an ether-petroleum ether (b.p. 60-69°) mixture, boiled with charcoal, filtered and cooled yielding 45.5 g. (74%) of a white solid, m.p. 87.5-88.5°; ir (carbon tetrachloride), 1685 (ketone ν C=O); nmr (deuteriochloroform), 425-485 (m, 9H, aromatic), 324 (t, 1H, J = 6.6 Hz, C_2 proton), 215 (t, 2H, J = 5.7 Hz, C_4 protons), and 156 Hz (apparent q, 2H, J ≅ 6.2 Hz, C_3 protons).

Anal. Calcd. for $C_{16}H_{14}Br_2O$: C, 50.29; H, 3.69; Br, 41.83. Found: C, 50.28; H, 3.66; Br, 41.67.

1-*t*-Butyl-2-*p*-phenylbenzoylazetidine (**5**).

A solution containing 3.82 g. (0.010 mole) of α,γ-dibromo-*p*-phenylbutyrophenone and 2.19 g. (0.030 mole) of *t*-butylamine in 75 ml. of acetonitrile was stoppered tightly and stirred magnetically at room temperature for 3 days. After evaporation of the acetonitrile the residue was extracted with ether, the extract filtered and the filtrate exposed to dry hydrogen chloride gas for 5 minutes. The resulting hygroscopic, orange precipitate was collected by filtration, washed with ether and immediately dissolved in 40 ml. of water. Ether (100 ml.) was added and solid sodium bicarbonate was added portionwise to neutrality. The ether layer was decanted and the aqueous layer washed twice with 50-ml. portions of ether, the washes being combined with the original decantant. The ethereal solution was dried over magnesium sulfate and the ether evaporated leaving 1.63 g. (55.6%) of a red oily crude product which was chromatographed on 75 g. of florisil (ether elution) giving 1.17 g. (40%) of **5** as a viscous yellow oil which solidified upon standing to a waxy solid; uv (isoctane); λ max 277 mμ (ε, 22,600); ir (carbon tetrachloride), 1695/87 (ketone ν_1 C=O/% abs) and 1666 cm^{-1}/77 (ketone ν_2 C=O/% abs); nmr (deuteriochloroform), 439-493 (m, 9H, aromatic), 288 (t, 1H, J = 8.5 Hz, C_2 proton), and 61 Hz (s, 9H, *t*-butyl). Ketone **5** was analyzed as its picrate, m.p. 207-209°.

Anal. Calcd. for $C_{26}H_{26}N_4O_8$: C, 59.76; H, 5.02; N, 10.72. Found: C, 59.70; H, 5.02; N, 10.69.

1-Methyl-2-*p*-phenylbenzoylazetidine (**6**).

A suspension of 3.82 g. (0.01 mole) of α,γ-dibromo-*p*-phenylbutyrophenone in 50 ml. of acetonitrile was stirred magnetically at room temperature while a cold solution (0°) of *ca.* 1.0 g. (0.03 mole) of methylamine in 35 ml. of acetonitrile was added in 2-ml. portions every 15 minutes over a period of 4 hours. After stirring an additional 3 hours the reaction mixture was cooled to 0° and allowed to stand overnight. Workup was the same as with ketone **5**, 0.50 g. (20%) of an unstable orange, oily crude product being obtained; ir (carbon tetrachloride), 1692 cm^{-1}/55 (ketone ν C=O/% abs); nmr (deuteriochloroform), 433-483 (m, 9H, aromatic), 255 (t, 1H, J = 8.5 Hz, C_2 proton), 130-218 (m, 4H, C_3 and C_4 protons), and 145 Hz (s, 3H, *N*-methyl). Attempts to purify the crude product *via* chromatography or to form crystalline derivatives (picrates, hydrazones) gave only decomposition. A mass spectrum could not be obtained due to the rapid decomposition of **6** in the inlet system of the spectrometer.

Reduction.

A 0.9-g. sample (3.6 mmoles) of crude **6** in 10 ml. of anhydrous ethyl ether was added dropwise to a solution of 0.40 g. (10.5 mmoles) of lithium aluminum hydride in 50 ml. of ether and the mixture refluxed 20 hours. The excess hydride was hydrolyzed by the careful addition of 5 ml. of water. After addition of a quantity of magnesium sulfate the mixture was filtered and the solvent evaporated giving 0.60 g. (60%) of an unstable orange solid which could not be induced to crystallize; ir (chloroform), 3360 cm^{-1} (OH), ν C=O absent; nmr (deuteriochloroform), 426-456 Hz (m, 9H, aromatic), 280 (broad s, 1H, OH), 276 (d, 1H, J = 4.0 Hz, benzylic methine), 87-206 (complex m, 5H, azetidine ring protons), and 131 Hz (s, 3H, *N*-methyl); mass spectrum (70 eV) m/e (rel. intensity): 253 (1) (M^+), 208 (4), 131 (5), 155 (5), 153 (6), 152 (10), 115 (5), 77 (14), 71 (18), 70 (100), 51 (5).

Synthesis of *cis*- and *trans*-1-*t*-Butyl-2-carbomethoxy-4-methylazetidines (**7a,b**). Preparation of Methyl α,γ-Dibromovalerate.

To a stirred suspension of a catalytic quantity of red phosphorus in 57.6 g. (0.576 mole) of γ-valerolactone was added 2 ml. of bromine. After stirring for 1 hour at room temperature, the suspension was heated to 115° and 28 ml. of bromine was added dropwise through a long-stemmed dropping funnel beneath the surface of the liquid at a rate such that the reaction temperature was maintained at 115-125°. When the rate of bromine uptake decreased as evidenced by a temperature decrease, a small quantity of red phosphorus was added and the remaining bromine was

added in a dropwise manner as before. After all the bromine had been added the reaction mixture was stirred for 1 hour at 115°. It was then allowed to cool slowly to room temperature and then finally cooled to 0° in an ice bath. Methanol (240 ml.) was cooled to 5° and added to the original reaction mixture. The cooled solution was saturated with dry hydrogen chloride gas, the flask was stoppered tightly and the mixture stirred magnetically at room temperature for 36 hours. The excess methanol was evaporated under reduced pressure. The residual oil was dissolved in 200 ml. of ether, washed with 3% sodium bicarbonate solution, dried over magnesium sulfate and the ether evaporated. The residue was vacuum distilled twice through a 20-cm Vigreaux column giving 91.0 g. (58%) of a colorless, lachrymatory oil (two diastereomers of the dibromo ester plus a lactone (27), b.p. 50-52° (0.1 mm); ir (neat): 1780 (27), and 1740 cm^{-1} (ester ν C=O); nmr (deuteriochloroform), 232-282 (m, 2H, C_2 and C_4 methine protons), 228 (s, 3H, methoxy), 134-161 (m, 2H, C_3 methylene protons), 104 and 107 Hz (two d, 3H, J = 6.5 Hz, C_5 methyl protons of two diastereomers).

Anal. Calcd. for $C_6H_{10}BrO_2$: C, 26.30; H, 3.68; Br, 58.34. Found (27): C, 27.40; H, 3.85; Br, 55.81.

B. 1-*t*-Butyl-2-carbomethoxy-4-methylazetidine (*cis* and *trans*) (**7a,b**).

A solution of 55.0 g. (0.20 mole) of methyl α,γ-dibromovalerate (impure (27)) and 43.90 g. (0.60 mole) of *t*-butylamine in 600 ml. of acetonitrile was refluxed for 15 hours. The mixture was diluted with ether (300 ml.), filtered and the solvent evaporated. The residue was extracted with ether (500 ml.) and the extract exposed to a stream of hydrogen chloride gas for 5 minutes. The ether was decanted and the residual syrup was dissolved in 50 ml. of water. The aqueous solution was washed twice with ether (discarded), 300 ml. of ether added, and solid sodium bicarbonate added to neutrality. The ether layer was separated, the aqueous layer washed with three 100 ml. portions of ether, and the combined extracts dried over magnesium sulfate. Evaporation of the solvent gave 23.0 g. of a crude oily product the ir spectrum of which indicated the presence of **7a,b** plus a lactonic material (ν C=O 1770 cm^{-1}, *ca.* 50% of mixture) as well as small amounts of α,β- and β,γ-unsaturated esters (γ C=O 1720 and 1740 cm^{-1}, respectively). Careful vacuum fractional distillation of the crude product through a 20-cm Vigreaux column gave 11.63 g. (*ca.* 31.5%) of **7a,b** (plus small amounts of unsaturated esters) as a colorless oil, b.p. 49-55° (1.4 mm). Electronic integration of the C_4-methyl nmr signals (*vide infra*) indicated **7a,b** to be present in the ratio 57:43 respectively. Preparative vpc was carried out on a portion of the distillate using a 20-ft. x 3/8-in aluminum column of 20% FFAP (60/80 mesh) on Chromosorb P with column temperature, 145°; detector, 280°; injection port, 250° and flow rate 120 ml./minute. Two fractions were obtained. Fraction **1** (ret. time, 55 minutes) was a mixture of the *cis* isomer (**7b**) (*vide infra*) plus two unsaturated esters (three methoxy nmr signals). Fraction **2** (ret. time, 65 minutes) was the pure *trans* isomer (**7a**); ir (carbon tetrachloride), 1751/70 (ester ν_1 C=O/% abs) and 1725 cm^{-1}/63 (ester ν_2 C=O/% abs); nmr (deuteriochloroform), 227 (t, 1H, J = 8.2 Hz, C_2 proton), 223 (s, 3H, methoxy), 190-213 (m, 1H, C_4 methine proton), 96-153 (m, 2H, C_3 protons), 75 (d, 3H, J = 5.9 Hz, C_4-methyl), and 59 Hz (s, 9H, *t*-butyl); mass spectrum (70 eV) m/e (rel. intensity): 185 (3), 170 (39), 128 (7), 126 (31), 114 (5), 110 (4), 88 (5), 84 (6), 71 (6), 70 (100), 68 (8), 58 (12), 57 (21), 55 (9), 43 (13), 41 (10).

Anal. Calcd. for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.77; H, 10.25; N, 7.48.

Fraction **1** (*vide supra*) was rechromatographed using a 20-ft. x 3/8-in. glass column packed with 3% SE-30 on Chromosorb P operated under conditions identical to those used for **7a** above. Two fractions were obtained. The first fraction was a mixture of unsaturated esters (ν C=O 1740, 1720, ν C=C 1670 cm^{-1}). The second fraction (ret. time, 75 minutes) was the pure *cis* isomer (**7b**); ir (carbon tetrachloride), 1751/57 (shoulder-ester ν_1 C=O/% abs) and 1738 cm^{-1}/82 (ester ν_2 C=O/% abs); nmr (deuteriochloroform), 252 (q, 1H, J_{cis} = 7.6 Hz, J_{trans} = 5.0 Hz, C_2 protons), *ca.* 252 (m--partially masked by C_2H quartet, 1H, C_4 methine proton), 223 (s, 3H, methoxy), 87-152 (m, 2H, C_3 protons), 77 (d, 3H, J = 6.1 Hz, C_4-methyl), and 63 Hz (s, 9H, *t*-butyl); mass spectrum (70 eV) m/e (rel. intensity): 185 (3), 170 (18), 128 (7), 126 (24), 114 (5), 110 (5), 88 (5), 84 (8), 71 (8), 70 (100), 68 (9), 58 (11), 47 (33), 55 (10), 43 (13), 42 (14), 41 (24).

Anal. Found: C, 64.60; H, 10.26; N, 7.38.

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