Oxidative Cleavage of Ozonide. Silver Oxide Method.[39]—The ethyl bromide solution of the ozonide was hydrolyzed with 70 ml. of water by refluxing 30 minutes. To the cooled mixture were added double molar quantities of freshly prepared silver oxide and sodium hydroxide. After a three-hour reflux period, the alkaline solution was filtered to remove silver and evaporated *in vacuo* on the steam-bath. The solid residue was taken up in a minimum amount of water, acidified with dilute sulfuric acid and thoroughly extracted with ether. Removal of the solvent from the dried ether extracts left a dark yellow, semi-solid residue of acids. A positive ferric chloride test indicated the presence of *o*-cresotinic acid.[40] The latter was cleanly removed from the dibasic acid by sublimation *in vacuo* at 90–95°. The unsublimed crude 2-carboxy-6-methylphenoxyacetic acid (XII) was purified by treatment with Norite and repeated recrystallization from acetonitrile, m.p. 200–203°, undepressed on admixture with an authentic sample. The dibasic acid XII was obtained in very poor yield (6–9%) by this method from samples II, XIII and the α-ether preparation.

Hydrogen Peroxide–Acetic Acid Method.[41]—In a typical case, a 0.6-g. sample of ether was ozonized and hydrolyzed in the presence of zinc. After removal of the zinc by filtration, the ethyl bromide was evaporated *in vacuo* and the remaining oil and water mixture treated with equal volumes (8 ml. each) of 20% hydrogen peroxide and 25% acetic acid. The oxidizing mixture was refluxed 3 hours. Cloudiness and an oily layer appeared on cooling. The cooled solution was thoroughly extracted with ether. Evaporation of the ether left a pale yellow liquid which was heated with excess 30% methanolic potassium hydroxide for 5 minutes in a water-bath to hydrolyze the ester. The cooled yellow solution was treated with an equal volume of water, extracted once with ether and acidified with 6 *N* sulfuric acid. The yellow-white solids which separated were taken up in ether and the ethereal solution was filtered through anhydrous sodium sulfate and dried over anhydrous magnesium sulfate. Removal of the ether left a yellow solid which was freed of cresotinic acid by sublimation as described above. The unsublimed material was of sufficient purity that recrystallization was generally not necessary. The m.p. of unrecrystallized XII ranged from 195 to 204°. XII was obtained in yields of 25–38% from samples of II, XIII and the α-ether preparation. No evidence for the more soluble, lower melting α-(2-carboxy-6-methylphenoxy)-butyric acid (see below), the expected oxidation product of I, could be found.

2-Carboxy-6-methylphenoxyacetic Acid (XII).—Alkylation of V with ethyl bromoacetate was accomplished with sodium methoxide in methyl alcohol using conventional alkylation methods. Unreacted starting materials were removed by distillation *in vacuo*. The residue was evaporatively distilled at a bath temperature of 150–180° and pressure of 0.08 mm. to give a 30% yield of ethyl 2-carbomethoxy-6-methylphenoxyacetate. The diester was directly hydrolyzed with methanolic potassium hydroxide to give XII, fine short needles from acetonitrile, m.p. 205–206.5° (reported 203–204°[42]).

Anal. Calcd. for $C_{10}H_{10}O_5$: neut. equiv., 105. Found: neut. equiv., 106.

α-(2-Carboxy-6-methylphenoxy)-butyric Acid.—This acid was prepared by saponification of the diester, ethyl α-(2-carbomethoxy-6-methylphenoxy)-butyrate, formed from V and ethyl α-bromo-*n*-butyrate in a manner analogous to that described for the diester of XII. Recrystallized from ethyl acetate the acid melted at 127.5–128.5°.

Anal. Calcd. for $C_{12}H_{14}O_5$: C, 60.5; H, 5.9; neut. equiv., 119. Found: C, 60.4; H, 5.9; neut. equiv., 120.

Stability of α-Ethylallyl Chloride (IV).—A 10-g. sample of α-ethylallyl chloride protected from atmospheric moisture was heated for 45 hours at 80°. Fractionation through a 3-foot Podbielniak column at 195 mm. gave 85.3% recovery, n^{20}_{D} 1.4254. The residual material was a brown polymer. No γ-ethylallyl chloride could be detected.

Infrared Spectra.—The infrared spectra were secured with a Perkin–Elmer Model 12C spectrophotometer, using sodium chloride cells of 0.025 mm. and 0.005 ± 0.001 mm. thickness.

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[39] W. G. Young, A. C. McKinnis, I. D. Webb and J. D. Roberts, THIS JOURNAL, **68**, 293 (1946).

[40] In all the ozonolyses of these compounds *o*-cresotinic acid was found in appreciable amounts in the acid fractions from oxidative cleavages. This has been established as a product of abnormal ozonolysis, which subject will be treated in a forthcoming paper. *Cf.* also ref. 39.

[41] G. Stork, E. E. van Tamelen, L. J. Friedman and A. W. Burgstahler, THIS JOURNAL, **75**, 384 (1953).

[42] R. Meyer and C. Duczmal, *Ber.*, **46**, 3374 (1913). These authors report the preparation of XII in poor yield from *o*-cresotinic acid and chloroacetic acid in concentrated sodium hydroxide solution. We were unable to obtain satisfactory results with this method.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Cyclic Aminoacyloins. II. F-Strain Limitation of Transannular Interaction between N and C_{CO}

BY NELSON J. LEONARD AND MICHINORI ŌKI

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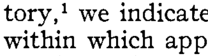
It has been demonstrated, by determination of the infrared absorption spectra and comparison of the pK'_a values in different solvents for a series of 1-alkyl-1-azacyclononan-5-ol-6-ones (II), that steric strain (F-strain) places a limitation on transannular interaction between N and C_{CO} in cyclic aminoacyloins. In the series IIa, b, c, d, as the bulk of the N-alkyl group increases, the extent of transannular N → C_{CO} bonding decreases. It has also been shown that the physical state of the compounds (solid or solution) and the nature of the solvent employed for solutions of these compounds may influence the extent to which steric interference prevents transannular bonding.

In a previous communication from this Laboratory,[1] we indicated the probable limits of ring size within which appreciable transannular interaction,  $\mathrm{R{-}\overset{|\delta+}{\underset{|}{N}}{:}\curvearrowright\overset{|}{\underset{|}{C}}{=}\overset{\curvearrowright\delta-}{O}}$,[2] will occur in cyclic aminoketones and aminoacyloins. It seemed reasonable to expect that an additional limitation of transannular interaction would be found in steric hindrance.

Accordingly, we have extended our synthesis of nine-membered ring aminoacyloins (II) to include the N-isopropyl (IIc) and N-*t*-butyl (IId) derivatives. Together with the N-methyl (IIa) and N-ethyl (IIb) compounds previously reported,[1] these constitute an excellent series in which to compare progressive changes in properties with increasing bulk of the alkyl group attached to nitrogen. As

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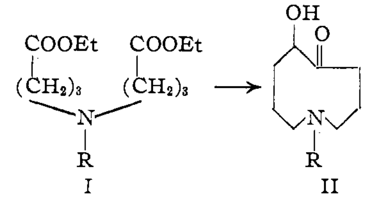
[1] N. J. Leonard, R. C. Fox, M. Ōki and S. Chiavarelli, THIS JOURNAL, **76**, 630 (1954).

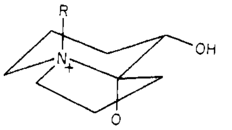
[2] (a) F. A. L. Anet, A. S. Bailey and Sir Robert Robinson, *Chemistry and Industry*, 944 (1953); (b) E. H. Mottus, H. Schwarz and L. Marion, *Can. J. Chem.*, **31**, 1144 (1953); (c) R. Huisgen, H. Wieland and H. Eder, *Ann.*, **561**, 193 (1949); (d) see also H. C. Brown and E. A. Fletcher, THIS JOURNAL, **73**, 2808 (1951).



I II

	R
a	CH_3
b	C_2H_5
c	$CH(CH_3)_2$
d	$C(CH_3)_3$

the size of this group increases, bicyclic formulations (*e.g.*, III) involving a full transannular bond between N and C_{CO} become less possible due to increasing steric interference (F-strain)[3] between the N-alkyl group (along with the N-alkylene groups) on one side of the nine-membered ring and the alkylene (and CHOH) groups attached to CO on the other side of the ring. Thus, scale molecular models indicate that whereas a bicyclic structure III is readily possible for 1-methyl-1-azacyclononan-5-ol-6-one (IIa), conformations of the monocyclic structure are much preferred over those of the bicyclic structure for 1-*t*-butyl-1-azacyclononan-5-ol-6-one (IId).



III

A comparison of the infrared absorption maxima in the 6μ region exhibited by the aminoacyloins II (Table I) indicates that as the bulk of the N-alkyl group increases, the carbonyl band is shifted to higher frequency, a trend which is indicative of decreasing transannular interaction between N and C_{CO}. Our findings are consistent with those of Brown[6] on the formation of an intermolecular N → B bond. He showed that the tendency of representative tertiary amines to add boron trimethyl decreases in the order: quinuclidine > trimethylamine > triethylamine, and attributed the position of triethylamine in this sequence to the projection of the third ethyl group into the region usually assigned to the unshared electron pair on nitrogen (F-strain). An analogous steric situation is encountered in system II, wherein N-alkyl groups larger than methyl necessarily project over the face of the ring nitrogen which could bond to transannular carbonyl.[6a]

TABLE I

II	Infrared absorption maxima,[4] cm.$^{-1}$ Base	Perchlorate	pK'_a[5] 66% DMF	Water	Δ pK'_a
a	1666, 3410	3440	10.6	9.2	−1.4
b	1671, 3428	3425	10.2	9.2	−1.0
c	1691, 3465	3435, 3245	6.9	8.1	+1.2
d	1698, 3480	1706, 3335	6.4	7.6	+1.2

The fact that the perchlorates of the methyl, ethyl and isopropyl compounds II are transparent in the 6 μ region indicates that these salts exist in the transannular quaternary form, $R-\overset{|}{\underset{|}{N}}{}^{+}-\overset{|}{\underset{|}{C}}-OH$ (IV), in the mull. By contrast, the salt of the *t*-butylaminoacyloin (IId) exhibits normal ketone carbonyl absorption (in addition to the expected hydroxyl band) and therefore cannot exist wholly in the transannular quaternary form IV in the solid state.[7] The spectrum of IId perchlorate is similar to that of 1-methyl-1-azacyclohendecan-6-ol-7-one perchlorate,[1] in which no appreciable transannular ring.

The pK'_a values observed for both IIa and IIb decrease in changing solvent from 66% dimethylformamide to water, and since this is a behavior typical of enols and acids,[8,9] it is clear that the proton is attached to the oxygen (IV) in the conjugate acids of this pair in 66% dimethylformamide solution. In marked contrast, the increase in pK'_a observed for both IIc and IId in making the same change from the mixed solvent to water is consistent with the attachment of the proton to the nitrogen in the conjugate acids of these bases,[10] and this increase is probably a result of steric hindrance to solvation of the $-\overset{|}{\underset{|}{N}}{}^{+}-H$ by the dimethylformamide. The abrupt decrease in pK'_a between the N-ethyl and N-isopropyl compounds in the series measured in 66% dimethylformamide is further indication of a difference in kind between these two aminoacyloins. The decreasing pK'_a values of the cyclic aminoacyloins in aqueous solution represent an order: R_2NCH_3, $R_2NCH_2CH_3$ > R_2N-$CH(CH_3)_2$ > $R_2NC(CH_3)_3$, which is indicative of increasing steric strain with increasing steric requirements of the alkyl substituents. This decrease can be attributed to F-strain or to increasing restriction to solvation of $-\overset{|}{\underset{|}{N}}{}^{+}-H$.[10a]

While this investigation has demonstrated that

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[3] H. C. Brown, H. Bartholomay, Jr., and M. D. Taylor, THIS JOURNAL, **66**, 435 (1944).

[4] We wish to thank Miss Helen Miklas, Mrs. Rosemary F. Hill and Mr. James Brader for determination of the infrared absorption spectra. The bases were determined in 10% carbon tetrachloride solution; the salts, in Nujol mull, using a Perkin-Elmer Recording Spectrophotometer, Model 21.

[5] We are indebted to Mrs. Helen Arndt for the electrometric titrations and to Dr. Harold E. Boaz, both of Eli Lilly and Company, Indianapolis, Ind., for aid in the interpretation.

[6] H. C. Brown, *ibid.*, **70**, 2878 (1948); see also H. C. Brown and M. D. Taylor, *ibid.*, **69**, 1332 (1947).

[6a] It seems much less likely that the physical data accumulated for the cyclic aminoacyloins (II) could be accounted for by an expression involving variation in the extent of internal O—H—N bonding between the enediol grouping, in the tautomer, and the nitrogen atom.

[7] Similarly, the largest increment of decrease in bonding ability, N → B, was found to lie between isopropyl- and *t*-butylamine in saturation pressure measurements on the boron trimethyl complexes of a series of amines at 25° (H. C. Brown and H. Pearsall, *ibid.*, **67**, 1765 (1945) and in the standard free energies of dissociation of these complexes at 100° (H. C. Brown and G. K. Barbaras, *ibid.*, **75**, 6 (1953)).

[8] L. Michaelis and M. Mitzutani, *Z. physik. Chem.*, **116**, 135 (1925), found that the pK'_a's of carboxylic acids in varying ethanol-water mixtures decrease with decreasing ethanol content.

[9] J. C. Speakman, *J. Chem. Soc.*, 270 (1943), found that the pK's of benzoic, adipic and succinic acids decrease with decreasing organic solvent content in 30% dioxane, 50% ethanol, 25% ethanol and water solutions.

[10] M. Mitzutani, *Z. physik. Chem.*, **116**, 350 (1925), showed that organic bases exhibit a marked increase in pK'_a with decreasing ethanol content in ethanol-water solutions.

[10a] If Brown's viewpoint were to be adopted that the small steric requirements of the proton make F-strain effects involving the proton relatively small, the decrease could be ascribed to increasing "B-strain"[3] in the system.

F-strain places a limitation on transannular interaction between N and C_{CO} in cyclic aminoacyloins, it has also shown that the physical state of the compounds (solid or solution) and the nature of the solvent employed for solutions of these compounds may influence the extent to which steric interference prevents transannular bonding. In carbon tetrachloride solution (by infrared), the greatest apparent decrease in transannular interaction within series II occurs between the N-ethyl and N-isopropyl bases, and in 66% dimethylformamide (pK'_a), the same is true. In the solid state (by infrared, mull), the perchlorates of II exhibit the sharpest difference between N-isopropyl and N-*t*-butyl. In aqueous solution, all of the base-conjugate acids appear to be in the monocyclic —$\overset{|}{\underset{|}{\text{N}}}{}^{+}$—H form, since the pK'_a values for IIa and IIb are about the same as that for an eleven-member ring aminoacyloin,[1] in which there is no evidence of appreciable transannular bonding.

Although the absence of intermolecular bonding between N and C_{CO} has been demonstrated by Anet, Bailey and Robinson[2a] in their finding that the infrared maximum for acetone in chloroform is not affected by the addition of triethylamine, nor that of cyclopentanone by the addition of N-methylpiperidine, it was considered that a different amine–ketone combination could be selected to offer more convincing evidence, in the light of our present results and those of Brown.[6] Accordingly, we determined the infrared spectra of 5% solutions of cyclohexanone[11] in carbon tetrachloride and of cyclohexanone plus a 1.2-molar proportion of quinuclidine[6] in the same solvent. The fact that the maxima of the two solutions (1718 ± 2 cm.$^{-1}$ and 1719 ± 2 cm.$^{-1}$) were identical within experimental limits is a clear indication that intermolecular N–C_{CO} interaction does not occur even between tertiary amine and ketone molecules which offer the minimum of steric hindrance to such bonding.

Experimental[12]

Diethyl γ,γ'-Isopropylimino-bis-butyrate (Ic).—A mixture of 32 g. (0.55 mole) of isopropylamine, 132 g. (0.95 mole) of potassium carbonate, 242 g. (1.0 mole) of ethyl γ-iodobutyrate and 1 l. of absolute ethanol was heated under reflux with stirring for 24 hours. The solid was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was treated with 200 ml. of water, and the mixture was extracted with ether. The ethereal extracts were dried, the ether was removed and the residue was distilled. The first distillation gave 34 g. of forerun, b.p. 80–90° (1 mm.) and 60 g. of material, b.p. 110–120° (0.3 mm.), which was redistilled at 116° (0.3 mm.) as a colorless oil, n^{20}_D 1.4448; d^{30}_4 0.9695; yield 55 g. (39%). The infrared spectrum of the pure liquid exhibited peaks at 1737 cm.$^{-1}$ (ester C═O) and other bands including those at 1472, 1455, 1426, 1379, 1257, 1190 and 1165 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{29}NO_4$: C, 62.68; H, 10.17; N, 4.88. Found: C, 62.97; H, 9.95; N, 5.06.

1-Isopropyl-1-azacyclononan-5-ol-6-one (IIc).—The acyloin ring closure of Ic was run under purified nitrogen and high dilution conditions,[13] using a Morton high speed stirrer assembly,[14] and taking precautions to keep the reaction anhydrous. To 11.0 g. (0.48 gram atom) of sodium in 1 l. of refluxing xylene was added 26.3 g. (0.092 mole) of diethyl γ,γ'-isopropylimino-bis-butyrate (Ic) in 100 ml. of xylene during a 5-hour period. When the addition was complete, the refluxing and stirring was continued for an additional 30 minutes. The flask and contents were cooled slowly, while increasing the input of purified nitrogen. Finally the flask was cooled in an ice-bath and glacial acetic acid was added cautiously to the moderately stirred mixture until it became slightly acidic. Water was added to dissolve the sodium acetate, and potassium carbonate was added to saturation. The two layers were separated, and the aqueous layer was extracted with ether. The combined organic portions were dried, the solvent was removed, and the residue was distilled *in vacuo* as a pale yellow oil, b.p. 85–87° (0.9 mm.); n^{20}_D 1.4986, yield 11.0 g. (60%).

Anal. Calcd. for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.64; N, 7.03. Found: C, 66.73; H, 10.53; N, 7.28.

The acyloin changed color very quickly at room temperature and reduced Fehling solution within 5 minutes at 25°.

The perchlorate crystallized as colorless prisms, m.p. 134–135°, from ethanol–ether.

Anal. Calcd. for $C_{11}H_{22}ClNO_6$: C, 44.08; H, 7.40. Found: C, 44.15; H, 7.32.

Diethyl γ,γ'-*t*-Butylimino-bis-butyrate (Id).—A mixture of 36 g. (0.49 mole) of *t*-butylamine, 242 g. of ethyl γ-iodobutyrate (1.0 mole), 138 g. (1.0 mole) of potassium carbonate and 750 ml. of absolute ethanol was treated as described for the isopropyl conpound. Twenty-four hour heating resulted in 12 g. of oil, b.p. 127–130° (0.6 mm.). The forerun was heated again with 100 g. of potassium carbonate and 500 ml. of ethanol for 72 hours and 20 g. of oil, b.p. 115–120° (0.25 mm.), was obtained. The two portions were combined and redistilled; n^{20}_D 1.4484, d^{28}_4 0.9702, yield 30 g. (20%). The infrared spectrum of the pure liquid exhibited peaks at 1738 cm.$^{-1}$ (ester C═O) and at 1396, 1368 cm.$^{-1}$, among other bands.

Anal. Calcd. for $C_{16}H_{31}NO_4$: C, 63.76; H, 10.37; N, 4.65. Found: C, 63.72; H, 10.40; N, 4.85.

1-*t*-Butyl-1-azacyclononan-5-ol-6-one (IId).—The acyloin ring closure of Id was run under the same conditions as described above, using 29.9 g. (0.099 mole) of diethyl γ,γ'-*t*-butylimino-bis-butyrate and 11.0 g. (0.48 gram atom) of sodium and an addition time of 4.5 hours. The product was distilled as a colorless oil; b.p. 101° (0.7 mm.), n^{30}_D 1.4908.

Anal. Calcd. for $C_{12}H_{23}NO_2$: C, 67.57; H, 10.88; N, 6.57. Found: C, 67.97; H, 10.66; N, 6.82.

The acyloin reduced Fehling solution within 5 minutes at 25°, but was apparently more stable than the N-isopropyl homolog.

The perchlorate crystallized from ethanol–ether as colorless plates, m.p. 136–137° dec.

Anal. Calcd. for $C_{12}H_{24}ClNO_6$: C, 45.93; H, 7.71. Found: C, 46.21; H, 7.61.

The *p*-toluenesulfonate salt, formed in acetone, crystallized from ethanol–ether as small colorless prisms, m.p. 138–139°. The compound was transparent in the 6μ region, both in the mull and in 1.5% chloroform solution.

Anal. Calcd. for $C_{16}H_{25}NO_5S$: C, 55.95; H, 7.34; N, 4.08. Found: C, 56.12; H, 7.15; N, 3.95.

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[11] H. C. Brown, R. S. Fletcher and R. B. Johannesen, THIS JOURNAL, **73**, 212 (1951).

[12] Microanalyses were performed by Mrs. Lucy Chang, Mrs. Esther Fett and Mr. Joseph Nemeth.

[13] N. J. Leonard and R. C. Sentz, THIS JOURNAL, **74**, 1704 (1952), and references therein.

[14] A. A. Morton, B. Darling and J. Davidson, *Ind. Eng. Chem.*, **14**, 734 (1942).