the proton being transferred and symmetrically located at the transition state (chlorine considered to have not changed), and 4.2 for complete proton transfer (chloride not changed). For the reaction with hydroxide ion they were 0.64 for a transition state like 4-chlorobutoxide ion and 2.54 for one with the proton being

transferred and symmetrically located (chlorine not changed). Thus the conclusion from these more detailed calculations agrees with the one earlier in this paper that the observed isotope effects (1.28 with water and 0.93 with hydroxide) are inconsistent with proton transfer during the rate-determining step.

Transannular Cyclizations in Medium-Sized Unsaturated Lactams. Apparent Dependence of Transannular Interaction upon Conformational Factors[1,2]

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Contribution from the Evans Chemistry Laboratory, The Ohio State University, Columbus, Ohio 43210. Received October 30, 1964

A series of azabicyclic amides of varying ring size (eight to ten members) are shown to be readily transformed to α,β-unsaturated lactams by the Hofmann elimination procedure. These unsaturated secondary lactams of the azacyclooctane and azacyclononane series undergo transannular cyclization when treated with acids. The related N-methylamides, as well as the azacyclodecane example, merely undergo protonation of the dimethylamino group under identical conditions. These results are discussed in terms of conformational factors.

Of the number of features exhibited by medium ring compounds which do not relate to other cyclic and acyclic structures, the phenomenon of transannular reaction is perhaps the most remarkable. Numerous examples of such reaction pathways in carbocyclic rings of eight to ten members can be found, most notably in the work of Cope[4] and Prelog.[5] In medium-sized rings containing nitrogen,[6] sulfur,[7] and phosphorus[8] atoms, the demonstration of transannular interaction of the heteroatom (properly substituted in some cases, e.g., sulfoxide) with the carbon atom of a ketone group placed diametrically across the ring[9] has been thoroughly elucidated by Leonard and his co-workers. We have observed an additional type of transannular reaction in a heterocyclic system and the present paper reports the results of our investigation.

Results

In a previous communication,[10] the Hofmann degradation of 9-methyl-3,9-diazabicyclo[4.2.1]nonan-4-one methiodide (Ia) was shown to give rise exclusively to the α,β-unsaturated amide II. Treatment of an ethereal solution of II with ethanolic perchloric acid has now afforded in quantitative yield a perchlorate

Ia, X = I
b, X = ClO₄
c, X = Cl
d, X = Br

salt. The n.m.r. spectrum of this material was superimposable on that of methiodide Ia and was therefore confirmatory for the bridged perchlorate structure Ib. An authentic sample of Ib prepared directly from Ia showed the two samples to be identical.

Careful re-examination of the perchlorate salt formation revealed that the product of kinetic control was actually the salt III (n.m.r. similar to II),[11,12] which

(1) Unsaturated Heterocyclic Systems. XIII. For paper XII in this series, see L. A. Paquette, J. Org. Chem., 30, 228 (1965).
(2) We gratefully acknowledge the partial support of this research by the National Science Foundation.
(3) Taken in part from the M.S. thesis submitted by L. D. W., 1964.
(4) A. C. Cope and D. M. Gale, J. Am. Chem. Soc., 85, 3747 (1963), and earlier papers in this series.
(5) V. Prelog and V. Boarland, Helv. Chim. Acta, 38, 1776 (1955), and other papers in this series; see also V. Prelog, Record Chem. Progr. (Kresge-Hooker Sci. Lib.), 18, 247 (1957).
(6) N. J. Leonard and M. Oki, J. Am. Chem. Soc., 77, 6245 (1955), and earlier papers in this series; see also N. J. Leonard, Record Chem. Progr. (Kresge-Hooker Sci. Lib.), 17, 243 (1956).
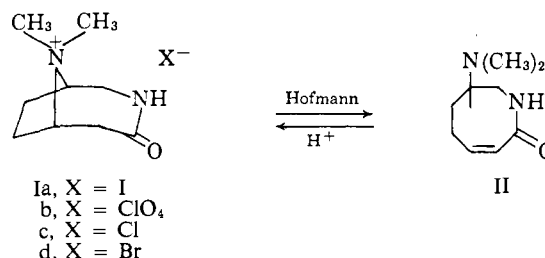(7) N. J. Leonard and W. L. Rippie, J. Org. Chem., 28, 1957 (1963), and other pertinent references cited therein.
(8) N. J. Leonard, S. E. Cremer, and A. L. Ternay, Jr., Abstracts, 146th National Meeting of the American Chemical Society, Denver, Colo., Jan. 20–22, 1964, p. 21C.
(9) Transannular reactions in heterocyclic systems were first recognized more than 50 years ago; for example, F. L. Pyman [J. Chem.

Soc., 817 (1913)] observed and studied the conversion of the des-base of l-canadine (i) to the quaternary of dl-canadine (ii).

i   ii
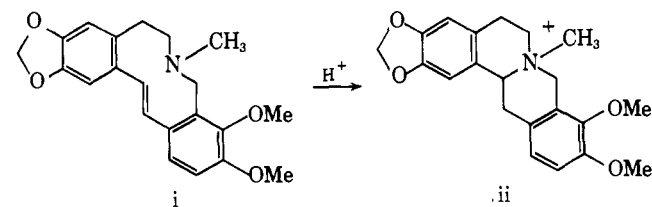
(10) L. A. Paquette and L. D. Wise, J. Org. Chem., 30, 228 (1965).
(11) This material melted at ca. 140° when rapidly heated. With slow heating, the solid softened at 140–150°, resolidified, and melted with decomposition at 327° (pure Ib melts at 334° dec.). The bridging reaction therefore can proceed under purely thermal conditions.
(12) Although III was the major component, the various samples prepared in this manner were always contaminated with varying minor quantities of the bridged salt Ib.

HN(CH₃)₂⁺ ClO₄⁻

III
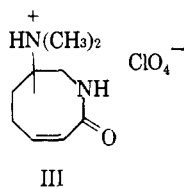
rapidly was converted quantitatively during the recrystallization process to the thermodynamically more stable bridged structure.

Further, the transannular ring closure of the type II → 1 was found to be general for strong acids. Thus, the reaction of II with slightly more than 1 equiv. of ethanolic solutions of hydrochloric, hydrobromic, and hydriodic acids readily gave rise to the azabicyclic amides Ic, Id, and Ia, respectively.
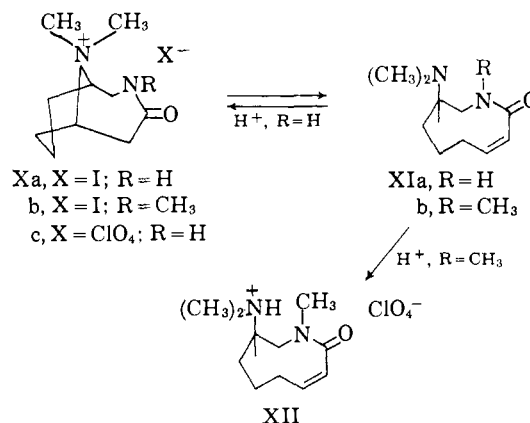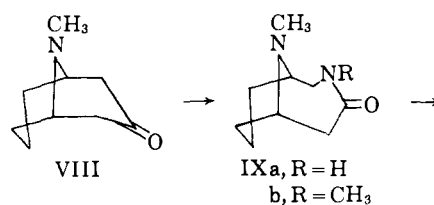
A similar sequence of reactions was repeated with the N-methyl homolog. The synthesis of the required 1-methyl-7-dimethylamino-5,6,7,8-tetrahydro-2(1H)-azocinone (VI) was accomplished by careful methylation of 9-methyl-3,9-diazabicyclo[4.2.1]nonan-4-one (IVa), followed by reaction of IVb with methyl iodide and subsequent Hofmann elimination of the quaternary salt V. A comparison of the spectral

IVa, R = H
b, R = CH₃

V

HN(CH₃)₂⁺ ClO₄⁻ ⟵ HClO₄ ⟵ N(CH₃)₂

VII   VI
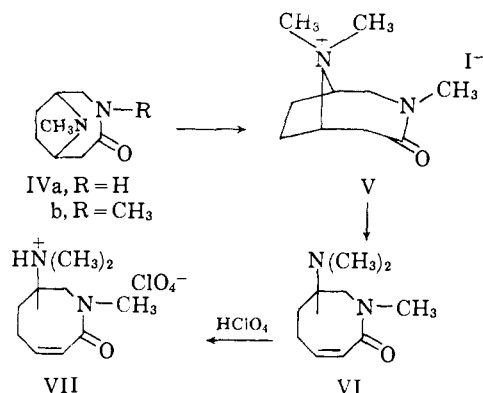
properties of the Hofmann product VI (see Experimental) with those for the related II[10] permitted the firm structural assignment to be made. Upon admixture of VI with ethanolic perchloric acid, there resulted a crystalline perchlorate salt which was found *not* to be the product of a transannular reaction. That its structure was simply that derived from the mere protonation of VI was evident from its n.m.r. spectrum (see Experimental). Attempts to induce the bridging reaction by refluxing VII for several hours (up to 12) in ethanol gave no evidence for the formation of a quaternary salt of type V.

Because of the somewhat unprecedented contrasts in the reactions of II and VI, it became of interest to extend our study to include the nine- and ten-membered ring congeners. Accordingly, the Schmidt ring expansion of pseudopelletierine (VIII) afforded the amide IXa[13] in 91% yield. Compound IXa was methylated to give IXb. These azabicyclic amides were converted to the quaternary salts Xa and Xb by the usual procedure. Hofmann elimination of the corresponding hydroxides led to XIa and Xlb, respectively. Both unsaturated amides displayed only terminal end absorption in the ultraviolet. In addition, their n.m.r. spectra (see Experimental) were quite similar to that

(13) The structures of the bicyclic compounds given in the text are in no way meant to imply the preferred conformations of these molecules.

VIII   IXa, R = H
              b, R = CH₃

Xa, X = I; R = H
b, X = I; R = CH₃
c, X = ClO₄; R = H

XIa, R = H
b, R = CH₃

(CH₃)₂NH⁺ CH₃ ClO₄⁻

XII

reported earlier for II.[10] Accordingly, we have assigned to XIa and XIb the α,β-unsaturated amide fomulas depicted in the text; the presence of a *cis*-olefinic bond can be logically assumed from the relatively weak coupling constant of the olefinic protons[14] (see Experimental) and from the known greater stability of the *cis* relative to the *trans* isomer in the cyclononene ring system.[15,16]

Addition of ethanolic perchloric acid to an ethereal solution of XIa afforded initially a gummy material which, after heating for 5 min. to complete the reaction, gave rise to a crystalline perchlorate salt in 81.5% yield. Evidence that the reaction product was indeed the bicyclic quaternary perchlorate Xc resulting from the intervention of a transannular ring closure was found in the superimposability of its n.m.r. spectrum on that of the bicyclic methiodide Xa.

The N-methylamide XIb likewise gave a crystalline perchlorate, and again a striking difference in the mode of reaction was observed. The infrared spectrum of the product displayed strong C=C absorption at 1600 cm.⁻¹; its n.m.r. spectrum was very similar to that of XIa and XIb in the olefinic hydrogen region. Thus, whereas XIa did undergo the transannular reaction, XIb, which differs simply by an N-methyl substituent, merely underwent protonation to give XII.

A similar series of reactions transformed homopseudopelletierine (XIII) *via* the azabicyclic amide XIV to XVI. The n.m.r. signals of the vinyl protons of this crystalline α,β-unsaturated amide, because of their complexity, were not instructive in establishing the presence of cisoid a or transoid b configuration.

(14) For an excellent compilation of coupling constants to be found in medium-sized cycloalkenes, see G. V. Smith and H. Kriloff, *J. Am. Chem. Soc.*, **85**, 2016 (1963).

(15) For various studies in this area, see A. C. Cope, P. T. Moore, and W. R. Moore, *ibid.*, **82**, 1744 (1960); A. C. Cope, D. C. McLean, and N. A. Nelson, *ibid.*, **77**, 1628 (1955); R. B. Turner and W. R. Meador, *ibid.*, **79**, 4133 (1957); A. T. Blomquist, L. H. Liu, and J. C. Bohrer, *ibid.*, **74**, 3643 (1952).

(16) The significance of placing a *trans* double bond α,β to a carbonyl group in a medium-sized ring (specifically, in this instance, *trans*-2-cyclooctenone) in terms of increased reactivity has recently been demonstrated: P. E. Eaton and K. Lin, *ibid.*, **86**, 2087 (1964). Neither XIa nor XIb possess the remarkable properties associated with this type of species.

XIII → XIV →

XV → XVI →

XVII (CH₃)₂ṄH ... ClO₄⁻

(CH₃)₂N ... a   XVI   b
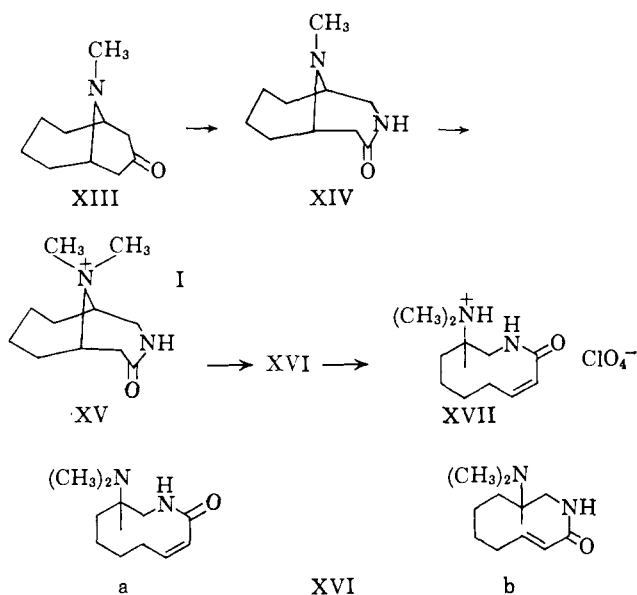
However, the reaction of XVI with perchloric acid to provide only the product of protonation (i.e., XVII) and conformational rationalization of this behavior (see below) support the belief that XVIa represents the true structure of this molecule.[17]

Discussion

It has been shown that the eight- and nine-membered cyclic α,β-unsaturated secondary amides II and XIa readily undergo a transannular bridging reaction in the presence of acids.[18] However, the related tertiary amides VI and XIb were resistant to such a cyclization process; the ten-membered system XVI likewise is not transformed to a bicyclic quaternary salt. An explanation of these phenomena may lie in the strong dependence of the transannular reaction upon the preferred conformational orientations of these medium-sized heterocyclic rings.

Thus, an examination of Dreiding models of II and XIa in conformations which possess a minimum of nonbonded interactions has clearly demonstrated that the dimethylamino group is situated within proximate bonding distance to the β-carbon of the unsaturated linkage (see XVIII). The net result of introducing a methyl substituent onto the amide nitrogen is to effec-

(17) Earlier studies of the equilibrium between *cis*- and *trans*-cyclodecene have made abundantly clear the greater stability of the *cis* relative to the *trans* isomer: (a)Cope, Moore, and Moore, ref. 15a; (b) N. L. Allinger, *J. Am. Chem. Soc.*, **79**, 3443 (1957); (c) Cope, McLean, and Nelson, ref. 15b; (d) A. T. Blomquist and A. Goldstein, *J. Am. Chem. Soc.*, **77**, 1001 (1955); (e) A. T. Blomquist, R. E. Burge, Jr., and A. C. Sucsy, *ibid.*, **74**, 3636 (1952). Further, although cyclodecyltrimethylammonium iodide affords, on Hofmann elimination, *trans*-cyclodecene in 90% yield,[17e] presumably *via* the simple *trans* E2 elimination process, XV most likely undergoes elimination by means of the two-step β-carbanion (Elcb) mechanism.[10] The net effect of this change in reaction pathway is to permit the formation of the isomer which has the lower free energy. In addition, since the normal planar sp² hybridization of the unsaturated carbons undoubtedly receives a contribution of type iii endowing it with some sp³ character, the preferred formation of the *cis* isomer (XVIa) would *a*

iii
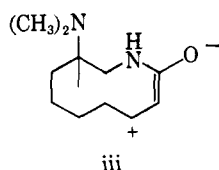
priori be anticipated.
(18) A related type of cyclization, but in a seven-membered ring, has

tively twist the –N(CH₃)–CO– bond from its normally planar configuration because of the newly generated steric interference between N-methyl and carbonyl oxygen. Any degree of rotation about the bond in question to offset this steric factor is sufficient to cause


XVIII   XIX
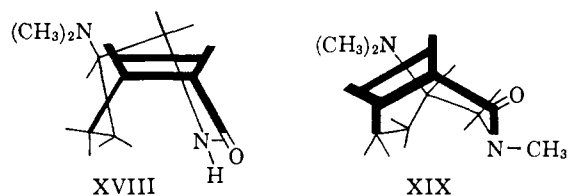
the dimethylamino group to be disposed in a more remote position with respect to the β-olefinic carbon atom (see XIX).[19] The manifestation of these non-bonded repulsions is probably reflected in the inability of VI and XIb to cyclize in acid medium.

Huisgen and Walz[20] have observed on the basis of physical measurements that in simple lactams the eight-membered ring system possesses a *cis*-amide function and the ten-membered mesocycle is endowed with *trans* geometry, while the nine-membered ring represents a borderline case. More recently, Moriarty[21] has examined the n.m.r. spectra of N-methylcaprolactam, N-methylcapryllactam, and N-methyllauryllactam and has concluded that the seven- and nine-membered heterocycles exist with the N-methyl *cis* to oxygen, while the thirteen-membered ring apparently is a mixture of *cis–trans* isomers. The effect of introducing a site of unsaturation into such lactams has not been examined. However, the contribution of this factor to added ring strain, minimization of nonbonded interactions, and development of π-orbital overlap between the double bond and the carbonyl group would seem to suggest that increase in the –N(CH₃)–CO– bond angle at the C₈ and C₉ ring sizes is probably unprohibited.

Manipulation of a Dreiding model of XVIa indicates clearly that the potential nitrogen bridge in strainless conformations is far removed from the β-olefinic carbon.[22] XVIa is in many ways similar to XXI; whereas the amino ketone XX readily undergoes transannular bond formation between the diametrical 1,6-positions on protonation (creating effectively two six-membered rings), XXI which possesses segmental 1,5-positions does not exhibit transannular cyclization (to a 5,7-system).[23] Reaction of XVIa in the manner discussed herein would lead to a 7,7-bicyclic system.

been observed by A. Nickon [*J. Am. Chem. Soc.*, **77**, 4094 (1955)] in the conversion of iv to v.


iv   v
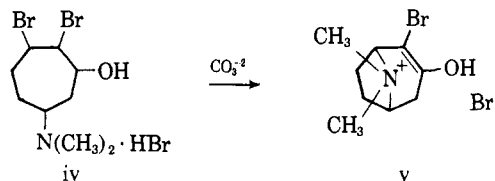
(19) Note, however, that in XIX the π-orbital overlap between C=C and amide carbonyl remains unfavorable (cf. ultraviolet data).
(20) R. Huisgen and H. Walz, *Chem. Ber.*, **89**, 2616 (1956).
(21) R. M. Moriarty, *J. Org. Chem.*, **29**, 2748 (1964).
(22) Examination of a model of the *trans* isomer XVIb revealed that the dimethylamino group in this molecule is ideally positioned for a transannular cyclization reaction. The fact that the bridging process did not occur strengthens the belief that the *cis* isomer XVIa resulted from the Hofmann elimination (see ref. 17).
(23) N. J. Leonard, M. Oki, and S. Chiavarelli, *J. Am. Chem. Soc.*, **77**, 6234 (1955).

XX   XXI
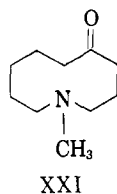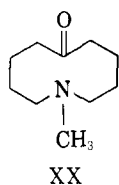
Experimental[24]

Transannular Cyclizations of 7-Dimethylamino-5,6,7,8-tetrahydro-2(1H)-azocinone (II). A. With Hydriodic Acid. A solution of 0.99 g. (5.9 mmoles) of II[10] in 5 ml. of ethanol was treated with a slight excess of an ethanolic solution of hydriodic acid (1:1) and the mixture was heated on a steam bath for 5 min. After cooling, the precipitate was filtered and dried to give 1.5 g. (85.3%) of white crystals, m.p. 270–300° dec. Three recrystallizations from ethanol raised the m.p. to 306° dec. This material proved to be identical with an authentic sample of 9,9-dimethyl-4-oxo-3-aza-9-azoniabicyclo[4.2.1]nonane iodide (Ia) (lit.[10] m.p. 306° dec.) by the usual criteria.

B. With Perchloric Acid (Ib). A solution of 1.7 g. (0.01 mole) of II in 20 ml. of anhydrous ether was treated dropwise with a slight excess of an 1:1 ethanolic perchloric acid solution. When the addition was completed, the contents were cooled and the supernatant solution was decanted from the gummy white salt. A fresh 10 ml. of ethanol was added and the mixture was warmed on a steam bath for 30 sec. when crystallization could be induced with scratching. This material was filtered, washed well with ether, and dried to give 2.63 g. (97.5%) of a white solid, m.p. *ca.* 140° (rapid heating). With slow heating, the solid softens at 140–150° and melts with decomposition at 327°. Two recrystallizations of this material from 95% ethanol afforded 2.5 g. of white platelets, m.p. 334° dec.; ν^{Nujol} 3360 (NH) and 1655 cm.$^{-1}$ (amide carbonyl). The ultraviolet spectrum showed only end absorption.

Anal. Calcd. for $C_9H_{17}ClN_2O_5$: C, 40.22; H, 6.38; N, 10.43. Found: C, 40.47; H, 6.36; N, 10.32.

C. With Hydrochloric Acid (Ic). A solution of 1.01 g. (5.95 mmoles) of II in 5 ml. of absolute ethanol was treated with a slight excess of a 1:1 ethanol-hydrochloric acid solution as described above. There was obtained 0.65 g. (57.6%) of Ic as white crystals, m.p. 294–295° dec. (from ethanol); ν^{Nujol} 3150 (NH) and 1640 cm.$^{-1}$ (amide carbonyl).

Anal. Calcd. for $C_9H_{17}ClN_2O$: C, 52.80; H, 8.37; N, 13.69. Found: C, 52.40; H, 8.50; N, 13.97.

D. With Hydrobromic Acid (Id). A solution of 1.01 g. (5.95 mmoles) of II was treated with ethanolic hydrobromic acid (1:1) and the resulting bromide salt was isolated. There was obtained 0.79 g. (53.4%) of Id as white crystals, m.p. 311–312° dec. (from ethanol); ν^{Nujol} 3250 (NH) and 1640 cm.$^{-1}$ (amide carbonyl).

Anal. Calcd. for $C_9H_{17}BrN_2O$: C, 43.38; H, 6.88; N, 11.25. Found: C, 43.78; H, 7.00; N, 11.14.

Direct Synthesis of Ib from Ia. A small sample of Ib was dissolved in ethanol and treated with excess 70%

perchloric acid. Addition of a small amount of ether caused the separation of the perchlorate. This salt (Ib) was purified by recrystallization from ethanol, m.p. 335° dec. The infrared spectrum of this sample was superimposable on the spectrum of Ib prepared above by the transannular pathway.

3,9-Dimethyl-3,9-diazabicyclo[4.2.1]nonan-4-one (IVb). To a stirred suspension of 0.20 mole of sodium hydride in 250 ml. of dry dimethylformamide was added 30.8 g. (0.20 mole) of IVa[25] and the mixture was stirred at 50° for 1 hr. while hydrogen was evolved. The solution was cooled to 0°, and a solution of 31.3 g. (0.22 mole) of methyl iodide in 25 ml. of ether was added at 5–15°. Stirring was continued for an additional 30 min. and to the solution was added 150 ml. of ether. The precipitated sodium iodide was filtered and washed well with ether. The combined filtrates were evaporated under reduced pressure and the residue was distilled under nitrogen to give 25.0 g. (74.3%) of colorless liquid, b.p. 152–157° (13 mm.), $n^{27}D$ 1.5082. A sample of the base was converted to its perchlorate salt which on recrystallization from 95% ethanol afforded white prisms, m.p. 220–221°; ν^{Nujol} 1615 cm.$^{-1}$ (amide carbonyl).

Anal. Calcd. for $C_9H_{17}ClN_2O_5$: C, 40.22; H, 6.38; N, 10.43. Found: C, 40.49; H, 6.66; N, 10.23.

3,9,9-Trimethyl-4-oxo-3-aza-9-azoniabicyclo[4.2.1]-nonane Iodide (V). A solution of 8.4 g. (0.05 mole) of IVb and 10.7 g. (0.075 mole) of methyl iodide in 75 ml. of absolute ethanol was refluxed for 1 hr., cooled somewhat, and ether added to precipitate 15.0 g. (96.8%) of very pale yellow solid, m.p. 200–205°. Recrystallization from 95% ethanol gave pure V as white prisms, m.p. 205–206°.

Anal. Calcd. for $C_{10}H_{19}IN_2O$: C, 38.72; H, 6.17; N, 9.03. Found: C, 38.59; H, 6.47; N, 9.00.

1-Methyl-7-dimethylamino-5,6,7,8-tetrahydro-2-(1H)-azocinone (VI). A 12.8-g. (0.041 mole) sample of V was eluted through a column of Amberlite IRA-400 in its basic form. The alkaline fractions were combined and evaporated under reduced pressure. The residue was pyrolyzed under reduced pressure with elimination beginning at *ca.* 140–150°. A colorless oil distilled, b.p. 121–122° (0.04 mm.), 5.7 g. (76.0%), $n^{26}D$ 1.5140. Redistillation afforded a center fraction, b.p. 110° (0.2 mm.), $n^{26}D$ 1.5140, which was analyzed; ν^{CHCl_3} 1655 (amide carbonyl) and 1610 cm.$^{-1}$ (C=C—C=O). The ultraviolet spectrum showed only end absorption.

Anal. Calcd. for $C_{10}H_{18}N_2O$: C, 65.89; H, 9.96; N, 15.37. Found: C, 65.80; H, 10.18; N, 15.29.

Reaction of VI with Perchloric Acid. VII. A solution of 500 mg. of VI in ether was treated with ethanolic perchloric acid as above to give a perchlorate salt (VII), m.p. 184–185° (from 95% ethanol–ether). Heating of this material in ethanol for several hours did not produce any change; ν^{Nujol} 1650 (amide carbonyl) and 1595 cm.$^{-1}$ (C=C—C=O). The ultraviolet spectrum showed only end absorption (see Table I for n.m.r. data).

Anal. Calcd. for $C_{10}H_{19}ClN_2O_5$: C, 42.48; H, 6.77; N, 9.91. Found: C, 41.73; H, 6.77; N, 9.43.

(24) Melting points were obtained with a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were obtained with a Perkin-Elmer Infracord spectrophotometer, Model 137.

(25) R. J. Michaels and H. E. Zaugg, *J. Org. Chem.*, 25, 637 (1960).

Compd.	Solvent[b]	(CH3)2N-	$\overset{\mid}{-CH_2-NR}$	Vinyl protons
II	CDCl3	2.29	3.43[c]	6.11[c]
				5.70[c] (J = 12.5 c.p.s.)
VI	CDCl3	2.27	3.50	6.08[c]
				5.72[c] (J = 13 c.p.s.)
XIa	CDCl3	2.18	3.33	5.83[d]
XIb	CDCl3	2.25	3.33[c]	5.93[c]
XVIa	CDCl3	2.27	3.41	5.75[c]
VII	D2O	2.90	3.50[c]	6.15[c]
XII	D2O	3.00	3.50[c]	6.18[c]
XVII	D2O	3.02	3.45[c]	6.13[c]

[a] Spectra were determined as dilute solutions on a Varian A-60 spectrophotometer; in δ-units. [b] The CDCl3 solutions were calibrated from internal TMS, while the D2O solutions were calibrated from external TMS. [c] Represents center of a multiplet pattern. [d] Width at half-height = 7 c.p.s.

10-Methyl-3,10-diazabicyclo[4.3.1]decan-4-one (IXa). A solution of 16.7 g. (0.109 mole) of pseudopelletierine (VIII)[26] in 175 ml. of chloroform, cooled to −5° in an ice–salt mixture, was treated dropwise with 63 ml. of concentrated sulfuric acid below 15°. Sodium azide (13 g., 0.20 mole) was added in 1-g. portions over a 2-hr. period below 30°. The reaction was stirred for an additional 2 hr. at 50°. The mixture was diluted with 500 ml. of ice and was neutralized portionwise with solid potassium carbonate. The mixture was made strongly alkaline by the addition of 75 ml. of 50% potassium hydroxide solution. The alkaline solution was filtered to remove inorganic salts, and the filtrate was extracted with three 500-ml. portions of chloroform. The combined organic layers were dried, filtered, and evaporated to yield 15.3 g. (91%) of white crystals, m.p. 158–162°. Recrystallization from ethyl acetate–hexane, with the aid of Darco G-60, succeeded in producing white prisms, m.p. 164–166°.

Anal. Calcd. for C9H16N2O: C, 64.25; H, 9.59; N, 16.65. Found: C, 64.15; H, 9.44; N, 16.88.

10,10-Dimethyl-4-oxo-3-aza-10-azoniabicyclo[4.3.1]-decane Iodide (Xa). A solution of 45.0 g. (0.27 mole) of IXa and 76.0 g. (0.54 mole) of iodomethane in 450 ml. of absolute ethanol was refluxed for 1.5 hr. and cooled, and the precipitate was filtered and dried to give 81.0 g. (97.5%) of crude methiodide, m.p. 300–301° dec. Recrystallization of this material from aqueous ethanol–ether raised the m.p. to 304–305° dec.; ν^{Nujol} 3230 (NH) and 1660 cm.$^{-1}$ (amide carbonyl).

Anal. Calcd. for C10H19IN2O: C, 38.72; H, 6.17; N, 9.03. Found: C, 38.66; H, 6.21; N, 8.84.

Hofmann Elimination of Xa. A solution of 15.5 g. of Xa in water was passed through a column of Amberite IRA-400 in its basic form. The 800 ml. of solution collected was concentrated under reduced pressure and the residue was distilled (with elimination commencing at *ca.* 160°) to give 6.43 g. (70.4%) of crystalline distillate, b.p. 140–143° (0.1 mm.), m.p. 110–113°. Three recrystallizations of this material from ethyl acetate–hexane gave pure white crystals of XIa, m.p. 112–113°; ν^{Nujol} 3220 (NH) and 1660 cm.$^{-1}$ (amide carbonyl). The ultraviolet spectrum showed only end absorption.

(26) K. Ziegler and H. Wilms, *Ann.*, **567**, 31 (1950); A. Cope, H. L. Dryden, Jr., C. G. Overberger, and A. A. D'Addieco, *J. Am. Chem. Soc.*, **73**, 3416 (1951).

Anal. Calcd. for C10H18N2O: C, 65.90; H, 9.95; N, 15.37. Found: C, 65.82; H, 9.94; N, 15.32.

Transannular Cyclization of XIa. 10,10-Dimethyl-4-oxo-3-aza-10-azoniabicyclo[4.3.1]decane Perchlorate (Xc). A solution of 0.498 g. (2.73 mmoles) of XIa in 5 ml. of anhydrous ether was treated with a slight excess of 1:1 ethanolic perchloric acid. The resulting mixture was cooled and the supernatant solution was decanted from the pale yellow oil. Ethanol (5 ml.) was added, and the contents were heated on a steam bath for 5 min. to complete the reaction. The resulting white crystals were filtered and dried to give 690 mg. (81.5%) of white crystals, m.p. 341–341.5° dec. (from 95% ethanol); ν^{Nujol} 3340 (NH) and 1660 cm.$^{-1}$ (amide carbonyl).

Anal. Calcd. for C10H19ClN2O5: C, 42.48; H, 6.77; N, 9.91. Found: C, 42.33; H, 6.83; N, 9.72.

3,10-Dimethyl-3,10-diazabicyclo[4.3.1]decan-4-one (IXb). A 13.25-g. (0.079 mole) sample of IXa was converted to its N-methyl homolog (IXb) by a process identical with that described above for IVb. There was isolated 11.3 g. (78.5%) of colorless liquid, b.p. 159–160° (6 mm.), which was converted directly to its methiodide.

3,10,10-Trimethyl-4-oxo-3-aza-10-azoniabicyclo[4.3.1]-decane Iodide (Xb). A solution of 11.0 g. (0.06 mole) of IXb and 17.1 g. (0.12 mole) of methyl iodide in 100 ml. of absolute ethanol was refluxed for 2 hr., cooled, and filtered to remove the crystalline product. There was obtained 15.85 g. (81.7%) of crude Xb, m.p. 240–255°. Repeated recrystallizations from 95% ethanol afforded white crystals, m.p. 251–253° dec.

Anal. Calcd. for C11H21IN2O: C, 40.75; H, 6.53; N, 8.32. Found: C, 40.55; H, 6.74; N, 8.67.

Hofmann Elimination of Xb. A solution of 15.45 g. (0.048 mole) of Xb in water was passed through a column of Amberlite IRA-400 (basic form). The usual work-up gave 6.25 g. (67.1%) of viscous, colorless liquid, b.p. 135° (0.3 mm.). Redistillation of this material gave an analytical sample of XIb, b.p. 108° (0.2 mm.), $n^{28}D$ 1.5098; ν^{CHCl_3} 1680 (amide carbonyl) and 1600 cm.$^{-1}$ (C=C—C=O). The ultraviolet spectrum showed only end absorption.

Anal. Calcd. for C11H20N2O: C, 67.30; H, 10.27; N, 14.27. Found: C, 67.07; H, 10.31; N, 14.03.

Reaction of XIb with Perchloric Acid. A 0.60-g. (3.0 mmoles) sample of XIb was treated with ethanolic perchloric acid as described above to give 0.93 g. (100%) of white crystals, m.p. 180–182°. Recrystallization from ethanol gave pure XII, m.p. 186–188°; ν^{Nujol} 1640 (amide carbonyl) and 1590 cm.$^{-1}$ (C=C—C=O). The ultraviolet spectrum showed only end absorption (see Table I for n.m.r. data).

Anal. Calcd. for C11H22ClN2O5: C, 44.52; H, 7.13; N, 9.44. Found: C, 44.10; H, 7.18; N, 9.59.

11-Methyl-3,11-diazabicyclo[4.4.1]undecan-4-one (XIV). A solution of 7.9 g. (0.055 mole) of homopseudopelletierine[27] in 100 ml. of chloroform, cooled to −5° in an ice–salt bath, was treated dropwise with 20 ml. of concentrated sulfuric acid below 15°. With constant stirring, 7.16 g. (0.11 mole) of sodium azide

(27) N. J. Leonard and D. F. Morrow, *ibid.*, **80**, 371 (1958).

was added in 1-g. portions over a 30-min. period below 30°. Isolation of the product by the method described above afforded 6.6 g. (66.0%) of relatively pure XIV, m.p. 110–112°. The analytical sample was obtained as white prisms from ethyl acetate–hexane, m.p. 111.5–112°.

Anal. Calcd. for $C_{10}H_{18}N_2O$: C, 65.89; H, 9.96; N, 15.37. Found: C, 66.01; H, 10.09; N, 15.18.

11,11-Dimethyl-4-oxo-3-aza-11-azoniabicyclo[4.4.1]-undecane Iodide (XV). A solution of 10.6 g. (0.059 mole) of XIV and 19.0 g. (0.135 mole) of methyl iodide in 250 ml. of absolute ethanol was refluxed for 2 hr., cooled, and filtered to give 8.6 g. of product, m.p. 246–252°. By concentrating the mother liquor, there was obtained an additional 8.6 g. (total yield of 92.0%) of methiodide, m.p. 245–250°. Recrystallization of the combined fractions from aqueous ethanol–ether gave pure white crystals, m.p. 262–263°; ν^{Nujol} 3225 (NH) and 1660 cm.$^{-1}$ (amide carbonyl).

Anal. Calcd. for $C_{11}H_{21}IN_2O$: C, 40.69; H, 6.67; N, 8.63. Found: C, 40.65; H, 6.61; N, 8.68.

Hofmann Elimination of XV. A solution of 18.65 g. (0.058 mole) of XV in water was passed through a column of Amberlite IRA-400 (hydroxide form). One liter of eluate was collected and concentrated. The

residue was pyrolyzed to give 11.28 g. (100%) of a crystalline distillate. Three recrystallizations of this material from ethyl acetate–hexane gave an analytical sample, m.p. 128–129°; ν^{CHCl_3} 3400 (NH) and 1640 cm.$^{-1}$ (amide carbonyl). The ultraviolet spectrum showed only end absorption.

Anal. Calcd. for $C_{11}H_{20}N_2O$: C, 67.30; H, 10.27; N, 14.27. Found: C, 67.28; H, 10.40; N, 13.96.

Reaction of XVI with Perchloric Acid. A solution of 0.50 g. (2.55 mmoles) of XVI in 5 ml. of absolute ethanol was treated with an ethanolic solution of perchloric acid (1:1). The mixture was heated for 5 min. on a steam bath and cooled, and the precipitate was filtered. There was obtained 0.69 g. (91.5%) of white crystals, m.p. 158–159°; ν^{Nujol} 3350 (NH) and 1610 cm.$^{-1}$ (amide carbonyl). The ultraviolet spectrum showed only end absorption.

Anal. Calcd. for $C_{11}H_{21}ClN_2O_5$: C, 44.52; H, 7.11; N, 9.44. Found: C, 44.59; H, 7.14; N, 9.33.

Friedel–Crafts Oxygenation of Toluene with Diisopropyl Peroxydicarbonate[1]

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Cresols were prepared in about 50% yield from toluene by direct oxygenation with diisopropyl peroxydicarbonate in the presence of aluminum chloride. Several reaction variables were studied including time, temperature, ratio of reactants, and nature of the catalyst. Electrophilic oxygenation is proposed on the basis of the cresol isomer distribution (ortho, 34%; meta, 11%; para, 55%), the relative reactivity value of 9.6 for $k_{toluene}/k_{benzene}$, the necessity of a catalyst, and the absence of products which would be derived from free-radical reactions. Evidence indicates that the oxygenated product is present in the reaction mixture mainly in the form $ArO-CO_2AlCl_2$. This procedure provides the first case of direct oxygenation of toluene in reasonably good yield with essentially no undesirable side reactions.

Introduction

The literature contains numerous examples of aromatic oxygenation[3] with peroxides, *e.g.*, hydrogen peroxide, peracids, and diaroyl peroxides. In many of these cases the evidence points to participation of free-radical intermediates.[4] However, analogous reactions which proceed by an electrophilic pathway have received relatively little attention. The historical treatment will be limited largely to those investigations which apparently fall in the latter category.

Hydrogen peroxide in the presence of concentrated sulfuric acid[5] or boron trifluoride etherate[6] has been used to effect oxygenation of mesitylene, toluene, and *m*-xylene in low yields. Derbyshire and Waters postulated the involvement of hydroxonium ion.

A similar mechanism was proposed in the case of peroxy acids for both the uncatalyzed[7] and Lewis acid catalyzed reactions. Chambers, Goggin, and Musgrave,[7] who reviewed earlier work on the reaction of peracetic acid with aromatics, examined the behavior of trifluoroperacetic acid toward *m*-xylene, mesitylene, and pseudocumene. The concept of electrophilic attack is consistent with the isomer distribution observed with *m*-xylene. Phenol ethers have also been

(1) From the Ph.D. thesis (1965) of S. T. M.; presented at the symposium in honor of Sir Christopher K. Ingold, Vanderbilt University, Nashville, Tenn., Aug. 1964.

(2) Union Carbide Co. Fellow, 1963–1964.

(3) This word has been chosen to designate direct introduction of RO (R = hydrogen, alkyl, acyl, etc.) into the aromatic nucleus.

(4) *E.g.*, see J. R. L. Smith and R. O. C. Norman, *J. Chem. Soc.*, 2897 (1963); D. I. Davies, D. H. Hey, and G. H. Williams, *ibid.*, 1878 (1958).

(5) D. H. Derbyshire and W. A. Waters, *Nature*, 165, 401 (1950).

(6) J. D. McClure and P. H. Williams, *J. Org. Chem.*, 27, 24 (1962).

(7) R. D. Chambers, P. Goggin, and W. K. R. Musgrave, *J. Chem. Soc.*, 1804 (1959).