CHART III

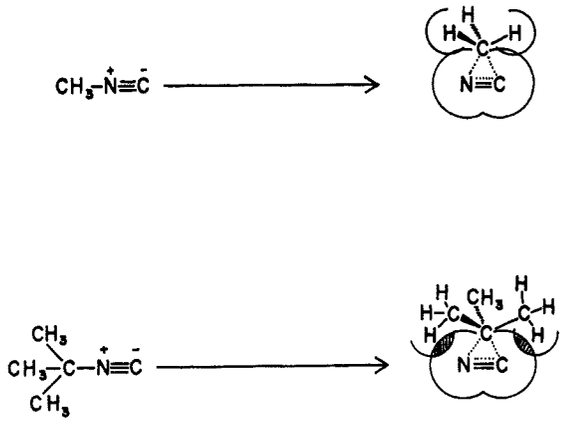
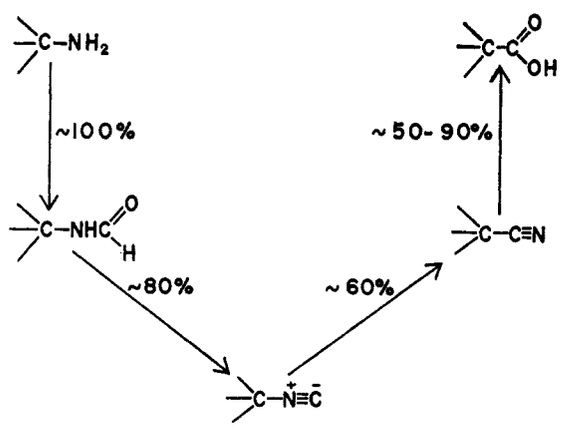


CHART IV



The conversion of optically active amines stereospecifically into optically active carboxylic acids is a desirable but heretofor difficult transformation. The present work suggests that a synthetic route which utilizes the isonitrile–nitrile rearrangement for such a sequence, shown in Chart IV, is a practical method to accomplish this objective. Subject to the obvious limitation of partial racemization in compounds which possess an α-hydrogen atom, and to the additional disadvantage of manipulation of a vile-smelling substance, this sequence of reactions nevertheless represents a potentially useful method of accomplishing an otherwise difficult transformation. Thus, it constitutes a process which compliments the many reactions known for the conversion of optically active carboxylic acids into optically active amines.[7]

Acknowledgment.—The work described in this paper was financially supported by a grant from the National Institutes of Health (CA-6369) and from the National Science Foundation (Undergraduate Research Participation Program), for which the authors are grateful. J. C. is particularly indebted to the Chemistry Department of Indiana University for an appointment during the academic year 1965–1966, during which period this manuscript was prepared, and to several members of that department for stimulating discussions.

The Solvolysis of Derivatives of 3-Azabicyclo[3.3.1]nonane[1]

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The solvolyses of the amino alcohol *p*-nitrobenzoate esters **8–13** have been studied in aqueous dioxane. The relative rates of reaction of each of the pairs of epimers are similar, suggesting that in none of the cases does the nonbonded electron pair on nitrogen provide substantial aid to ionization of the C–O bond. The products from the secondary alcohol derivatives **8** and **11** correspond to simple ester hydrolysis while the products from the tertiary phenylcarbinol derivatives **10** and **13** correspond to ionization followed by fragmentation. The tertiary methylcarbinol derivatives **9** and **12** are intermediate in behavior, giving products expected of ester hydrolysis and ionization. One epimer (**12**) also undergoes a competing elimination reaction to form the bicyclic olefin **49**. The results of these and earlier studies are interpreted as evidence for the existence of these bicyclic molecules primarily in chair–chair conformation **14a** with a lesser contribution from chair–boat conformation **14d**.

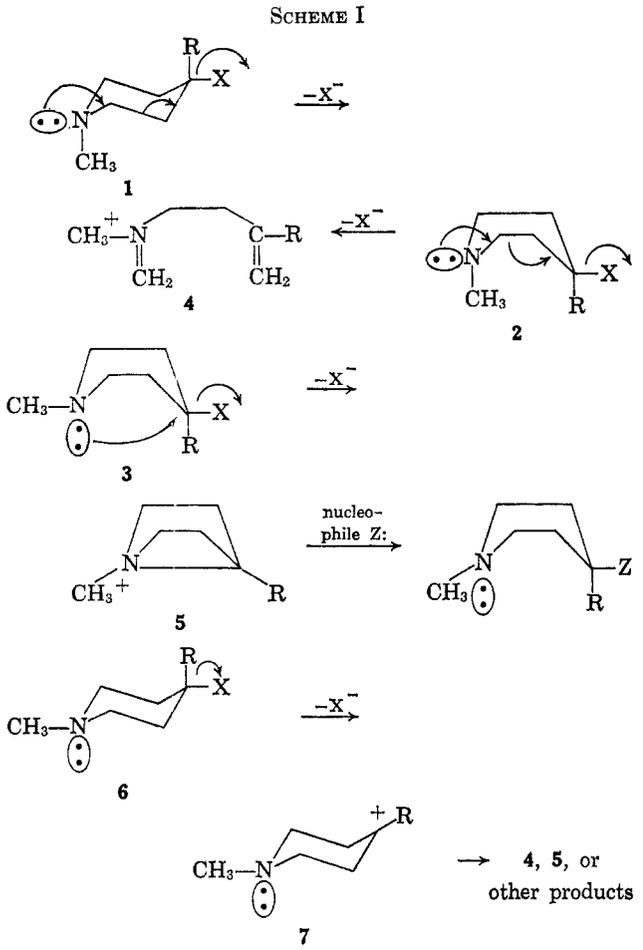
Extensive studies of the solvolytic ionization of various γ-amino alkyl halides (or esters) by Grob and co-workers[2] have demonstrated that the amino function may assist ionization of the alkyl halide when certain geometrical requirements are met. The most common manifestation of this assisted ionization is the synchronous fragmentation reaction which may occur when the nonbonded electron pair on nitrogen and the C–X bond bear one of the geometrical relationships illustrated in structures **1** and **2**. A less common (and apparently energetically less favorable) type of assistance is the backside displacement process (as in **3**) which can lead to nucleophilic displacement of the halogen atom with over-all retention of configuration.[2,3] When one of the above processes is not geometrically favorable, then ionization of the alkyl halide is not significantly aided by the amino function. The initially formed carbonium ion intermediate **7** may undergo subsequent fragmentation (to form **4**), ring closure (to form **5**), loss of a proton (elimination), or reaction with a nucleophile (substitution). (See Scheme I.)

(1) This research has been supported by research grants from (a) the National Institutes of Health (Grant No. GM-08761), and (b) the Directorate of Chemical Sciences, Air Force Office of Scienific Research (Grant No. AF-AFOSR-573).

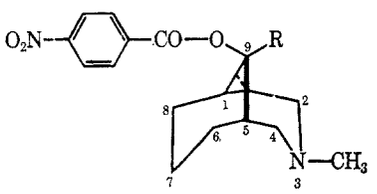
(2) (a) C. A Grob, *Experientia*, **13**, 126 (1957); (b) C. A. Grob in "Theoretical Organic Chemistry, Papers Presented to the Kekulé Symposium," Butterworth and Co. (Publishers) Ltd., London, 1959, pp 114–126; (c) C. A. Grob, *Bull. Soc. Chim. France*, 1360 (1960); (d) C. A. Grob, *Gazz. Chim. Ital.*, **92**, 902 (1962); (e) R. D'Arcy, C. A. Grob, T. Kaffenberger, and V. Krasnobajew, *Helv. Chim. Acta*, **49**, 185 (1966); (f) C. A. Grob, R. M. Hoegerle, and M. Ohta, *ibid.*, **45**, 1823 (1962).

(3) (a) S. Archer, M. R. Bell, T. R. Lewis, J. W. Schulenberg, and M. J. Unser, *J. Am. Chem. Soc.*, **79**, 6337 (1957); **80**, 4677 (1958); (b) also see S. Archer, T. R. Lewis, M. R. Bell, and J. W. Schulenberg, *ibid.* **83**, 2386 (1961).

SCHEME I

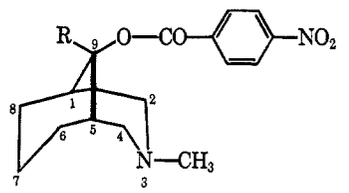


After completing the synthesis and characterization of the epimeric amino esters **8–13**,[4] we wished to learn the behavior of these substances on solvolysis. Only the α-acyloxy derivatives **8–10** possess the appropriate



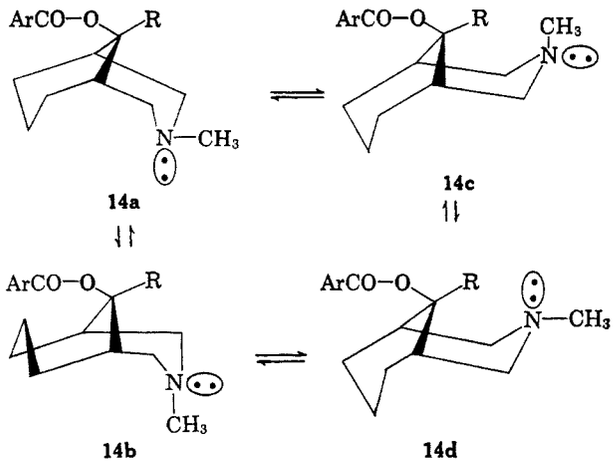
α-acyloxy derivatives
8, R = H
9, R = CH_3
10, R = C_6H_5

stereochemistry at C-9 to undergo either a synchronous fragmentation (*e.g.*, **1** or **2**) or a concerted backside displacement (*e.g.*, **3**). Since this type of assistance to ionization has been found to enhance the ionization rate in piperidine derivatives by factors of 50–100 or more,[2] we are led to expect that a synchronous participation by nitrogen in the ionization of the α-*p*-nitrobenzoates **8–10** would cause them to react substantially faster than their β epimers **11–13**. In previous papers,[4,5] we have

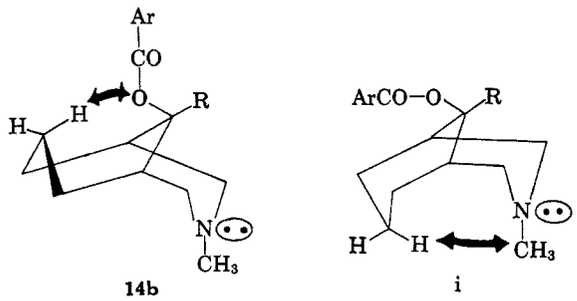


β-acyloxy derivatives
11, R = H
12, R = CH_3
13, R = C_6H_5

cited a substantial body of circumstantial evidence indicating the most stable conformation of the α-acyloxyl derivatives **8–10** to be **14a**. Other reasonable conformations for these materials are **14b**,[6] **14c**, and **14d**. By reference to structures **1–3**, it is apparent that one of the conformations **14b** (analogous to **1**) or **14c** (analogous to **2**) would be required for a synchronous fragmentation, and that conformation **14d** (analogous to **3**) would be required for a concerted backside displacement. Therefore, it seemed possible that solvolysis studies with amino esters **8–13** would provide additional information about the relative populations of the conformations **14**.



Each of the amino esters **8–13** was solvolyzed at 89° in dioxane–water (60:40 by volume) containing 1 molar equiv of triethylamine to neutralize the acid produced (*cf.* ref 2).[7] The relative reaction rates and products

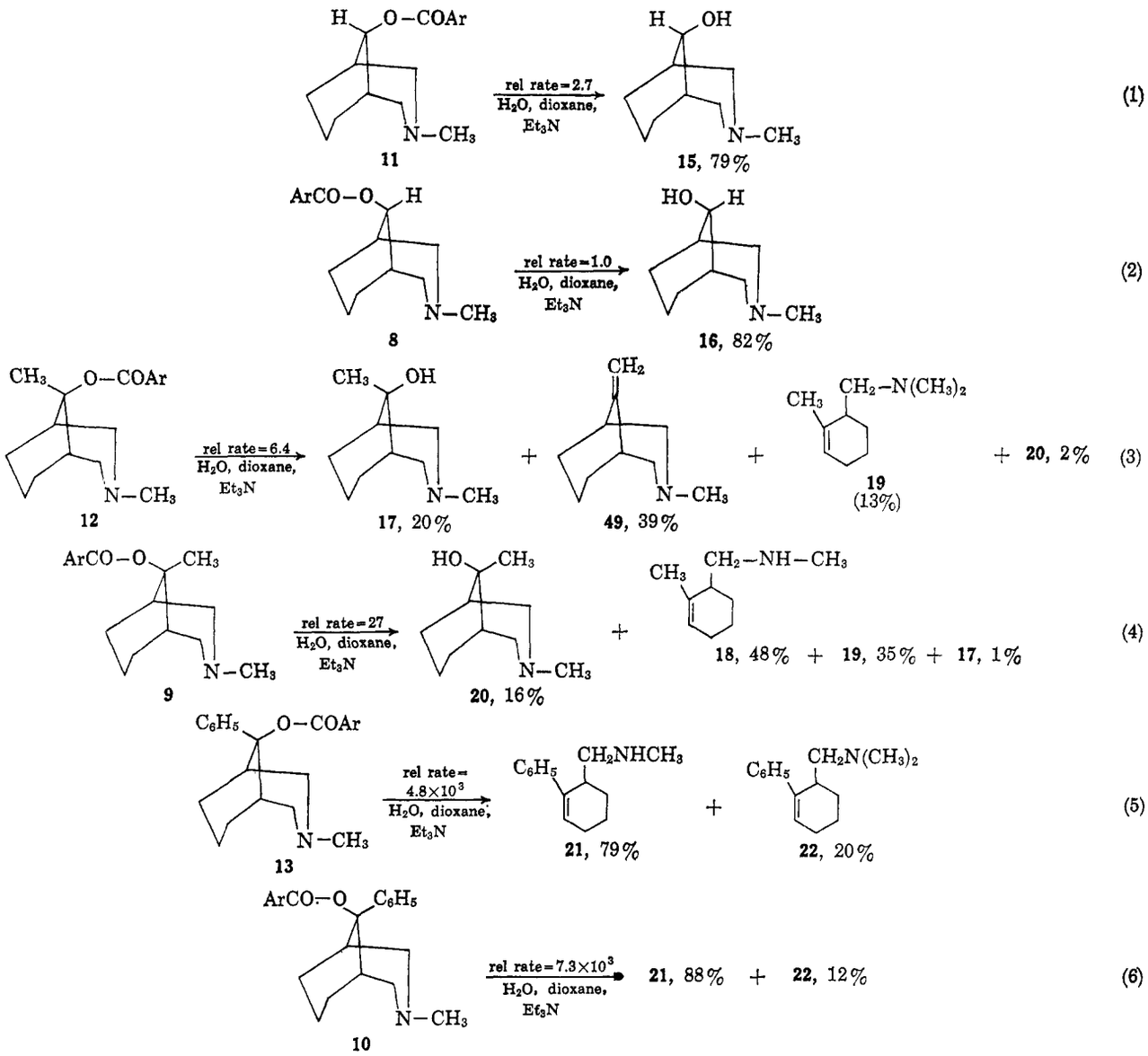


(4) (a) H. O. House, H. C. Müller, C. G. Pitt, and P. P. Wickham, *J. Org. Chem.*, **28**, 2407 (1963); (b) H. O. House and W. M. Bryant, *ibid.*, **30**, 3634 (1965); (c) W. M. Bryant, A. L. Burlingame, H. O. House, C. G. Pitt, and B. A. Tefertiller, *ibid.*, **31**, 3120 (1966).

(5) (a) H. O. House and C. G. Pitt, *ibid.*, **31**, 1062 (1966); (b) H. O. House and B. A. Tefertiller, *ibid.*, **31**, 1068 (1966); (c) H. O. House, B. A. Tefertiller, and C. G. Pitt, *ibid.*, **31**, 1073 (1966).

(6) Both the boat–chair conformation (**14b**) and the related chair–chair conformation (i) possess the indicated serious nonbonded interactions. Examination of molecular models suggests that this destabilizing interaction can be relieved (by twisting) more easily in conformation **14b** than in conformation i. It appears that the chair–chair conformation i is favored only in cases where neither of the two groups involved in the indicated nonbonded interaction is larger than hydrogen.

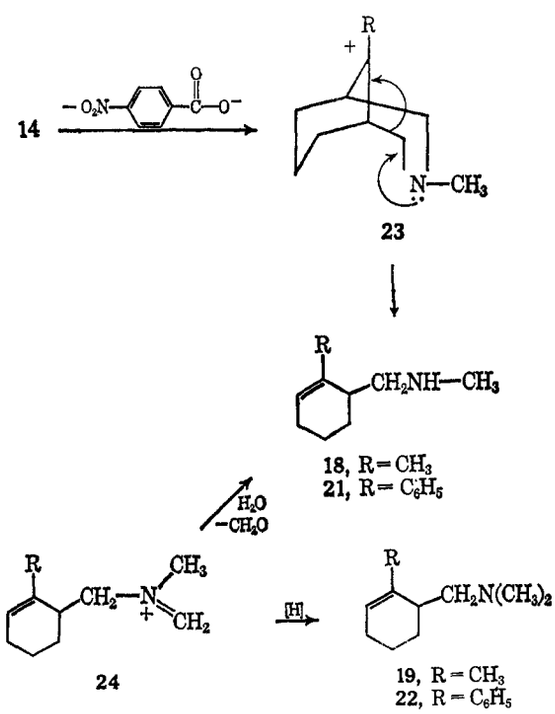
(7) The rate constants obtained (2.8–12 × 10^{-6} sec^{-1} for the methylcarbinols **9** and **12** and 2.1–3.2 × 10^{-3} sec^{-1} for the phenylcarbinols **10** and **13**) are similar to the values determined in dioxane–water (60:40) at 60° for the *p*-nitrobenzoates of 1-methylcyclopentanol (*ca.* 0.5 × 10^{-6}) and 1-phenylcyclopentanol (*ca.* 0.3 × 10^{-3}): H. C. Brown, F. J. Chloupek, and M. H. Rei, *J. Am. Chem. Soc.*, **86**, 1247 (1964).



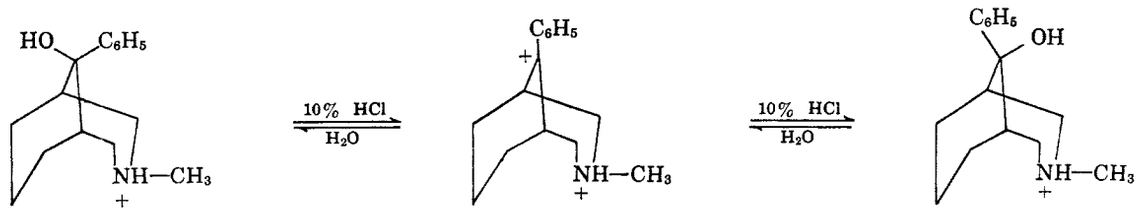
formed are summarized in eq 1–6 in which Ar = *p*-nitrophenyl and the yields of products are also indicated.

Since with every pair of epimers the relative rates of solvolysis differed by less than a factor of 5, we have concluded that in no case does the nitrogen atom substantially assist the rate-limiting ionization step in the solvolysis reaction. In those reactions (eq 1–4) where the bicyclic amino alcohols **15**–**17** and **20** constitute a substantial fraction of the reaction products, we presume that acyl-oxygen fission (*i.e.*, normal ester hydrolysis) of the *p*-nitrobenzoate is either faster than (reactions 1 and 2) or competitive with (reactions 3 and 4) ionization of the O–C-9 bond. The monocyclic unsaturated amines **18**, **19**, **21**, and **22** are believed to arise by ionization of the O–C-9 bond to form the carbonium ion intermediate **23** which undergoes subsequent fragmentation to the immonium salt **24**. Subsequent hydrolysis or reduction of the immonium salt would lead to the observed products **18** or **21** and **19** or **22**.

The identity of the reducing agent(s) for the intermediate iminium salts (*e.g.*, **24** → **19**) is unclear. Grob and co-workers[2f] have observed similar reduction products in solvolysis reactions conducted in solutions of sodium hydroxide in aqueous ethanol. These workers

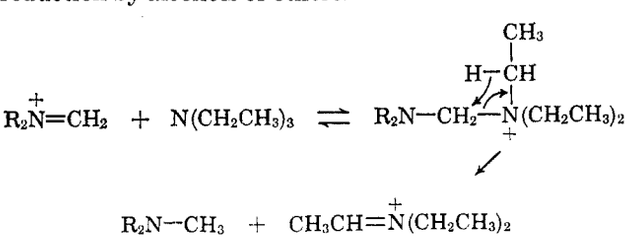


SCHEME II

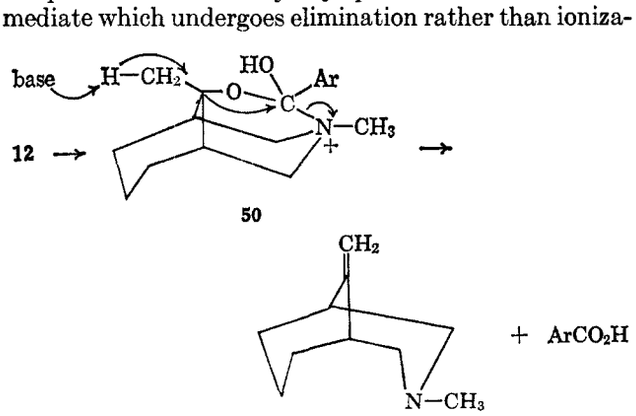


29

have suggested that the formaldehyde liberated in the reaction mixture is slowly oxidized by air to formate ion which reduces the imminium salt in a reaction analogous to the Leuckart reaction. Several features suggest that this is not the correct explanation for the reductions we have observed. In particular, all of our solvolysis experiments were run under nitrogen atmosphere and still the amount of reduction was substantial even for the relatively rapid reactions 5 and 6 which were complete in 1 hr. Also, analysis of aliquots removed throughout the course of reactions 3 and 4 indicated that the relative proportions of products were not changing substantially as the reactions progressed. Finally, we observed that the ratio of tertiary to secondary amine (**19**/**18**) obtained from the ester **9** increased from a value of about 0.8 to about 1.2 when the molar concentration of triethylamine in the reaction mixture was increased by a factor of 3. These observations prompt us to suspect that immonium salts such as **24** may be exceptionally reactive hydride ion acceptors in reactions similar to the Meerwein–Pondorf–Verley reduction. The following equation indicates a possible reaction path for hydride transfer from triethylamine to an immonium salt; similar pathways can be envisaged for reduction by alcohols or ethers.



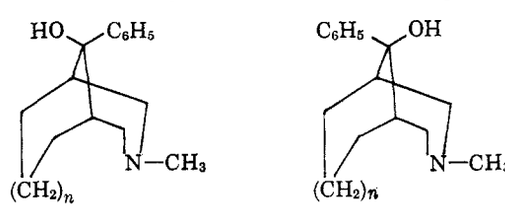
The substantial amounts of elimination product **49** formed at the expense of fragmentation products **18** and **19** from the β-acyloxyamine **12** suggests that in a fraction of the molecules the nitrogen function is participating in early stages of this reaction in a way which is not possible for the α-acyloxy epimer **9** to form an intermediate which undergoes elimination rather than ionization and subsequent fragmentation. One possibility is the formation of the cyclic intermediate **50**. This intermediate **50**, which carries a full positive charge and lacks a free electron pair on the nitrogen atom, would not be expected to undergo readily either a concerted fragmentation or an unassisted ionization of the O–C-9 bond. However, the concerted elimination process (leading to olefin **49**) which is illustrated in structure **50** seems reasonable. The same type of cyclic intermediate has already been suggested[4] to account for the ready O acylation of β-alcohol **17** under conditions where α-isomer **20** fails to react. The fact that β-ester **11** is hydrolyzed more rapidly than α-epimer **8** is also explicable in terms of a comparable intermediate.



50

49

As indicated above, we believe that the carbonium ion intermediates **23** undergo the indicated fragmentation unaccompanied by any significant attack by water to form alcohols. Since largely the bicyclic alcohol **17** was obtained from the ester **12** and primarily the epimeric alcohol **20** was obtained from ester **9**, the presence of the common intermediate **23** (R = CH_3) for both alcohols is precluded. Furthermore, when formation of the carbonium ion intermediate was favored by the presence of a phenyl substituent (*i.e.*, **23**, R = C_6H_5), only fragmentation products **21** and **22** were observed. A study of the equilibration of the phenyl alcohols **25**–**28** in aqueous mineral acid[4b,c,8] provides an



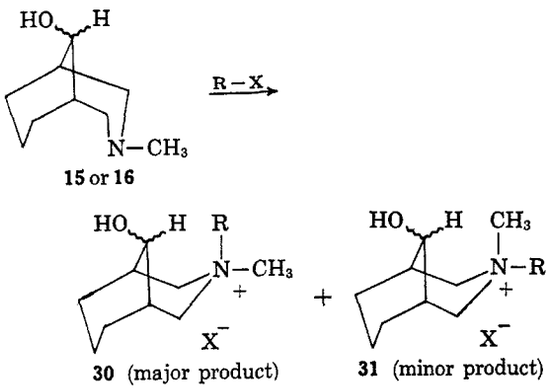
25, $n=1$ **26**, $n=1$
27, $n=2$ **28**, $n=2$

illustration of the reaction of a related carbonium ion **29** when fragmentation is prevented by protonation of nitrogen. In this case, the carbonium ion intermediate is trapped by reaction with water to give an equilibrium mixture of the salts of the bicyclic alcohols in which the β-alcohol **26** or **28** predominates. (See Scheme II.)

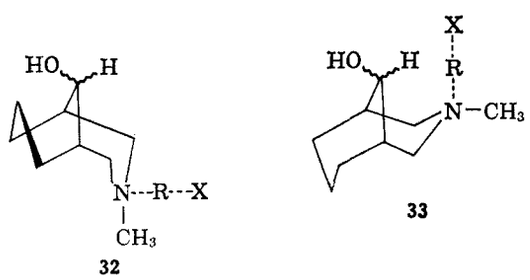
The foregoing data suggest that the transition states which would be derived from conformations **14b** and **14c** for the synchronous fragmentation of these bicyclic amino esters must be unfavorable; presumably the populations of conformations **14b** and **14c** are very low. Even 1-*t*-butyl-4-chloropiperidine has been observed to undergo synchronous fragmentation[2e] in spite of the fact that conformations analogous to **1** and **2** would certainly not be favorable for this substrate. Studies[5] of the N alkylation of amino alcohols **15** and **16** have

(8) Sankyo Co., Ltd., British Patent 952,137 (March 11, 1964); *Chem. Abstr.*, **61**, 5614 (1964).

demonstrated a moderate preference for the formation of the salt **30** rather than the stereoisomer **31**. (We

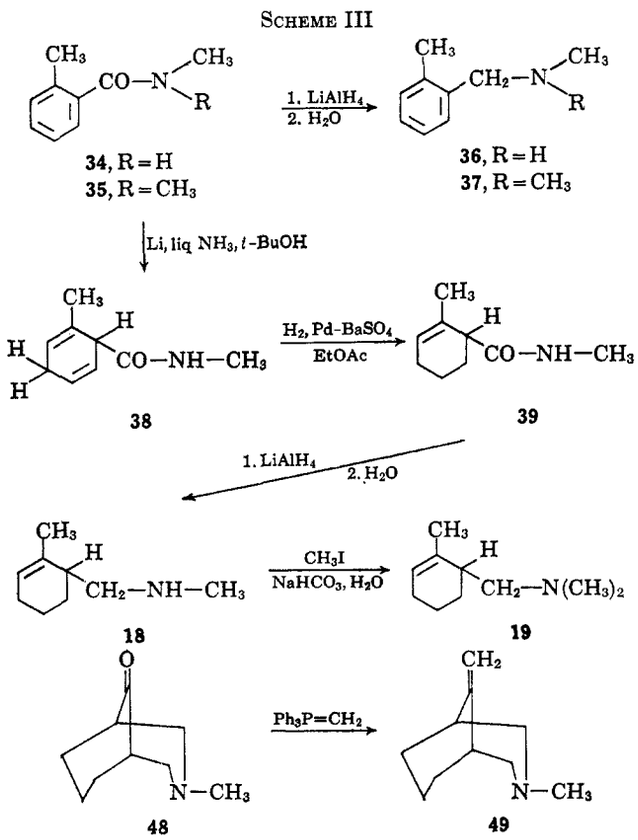


believe the most probable conformations of products **30** and **31** to be those indicated.[6]) Thus, one of the transition states **32** (related to conformation **14b**) or **33**



(related to conformation **14d**) is apparently preferred in the N-alkylation reaction. The present solvolysis studies, indicating that transition states derived from conformations **14b** and **14c** are not favorable, would suggest that the preferred transition state for the N-alkylation reaction is represented by structure **33** rather

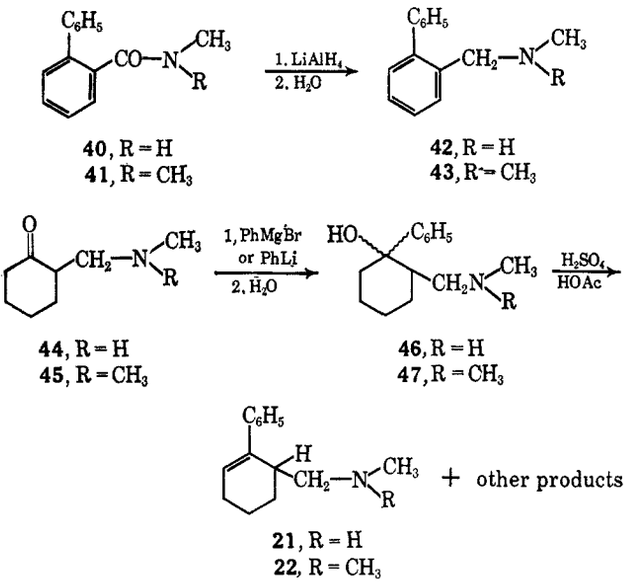
SCHEME III



than structure **32**. In view of these results and earlier studies[4,5] the favored conformation of the various amino alcohol derivatives appears to be **14a** with conformation **14d** being the next most favorable arrangement.

Schemes III and IV summarize the reactions used to obtain authentic samples of the fragmentation products **18**, **19**, **21**, **22**, and **49**, as well as certain other products whose absence in the solvolysis mixtures was demonstrated by gas chromatography.

SCHEME IV



Experimental Section[9]

Preparation of the Epimeric *p*-Nitrobenzoates 8–13.—The esters **9**, **10**, **12**, and **13** were prepared as previously described;[4] the ester of the phenylcarbinol **10** was obtained as yellow prisms, mp 157–158° (lit.[4b] mp 154–155°). An aqueous solution of 2.01 g of the previously described[4a] hydrochloride of amino ester **11** was made basic with aqueous sodium hydroxide and extracted with ether. The ethereal extract was dried and concentrated to leave 1.497 g of the *p*-nitrobenzoate **11**, mp 126–127.5°. Recrystallization from an ether–hexane mixture afforded the pure amino ester **11** as yellow prisms, mp 127–128°. This product has infrared absorption[10] at 2700, 2740 (shoulder), and 2780 (CH bonds α to nitrogen and oriented *trans* to the free electron pair) and at 1720 cm^{-1} (conjugated ester C=O) with an ultraviolet maximum[11] at 259 mμ (ϵ 13,500). The sample has nmr singlets[12] at δ 8.31 (4 H, aryl CH) and 2.19 (3 H, NCH_3) with a triplet (J = 3 cps) at 5.04 (1 H, >CHO) and multiplets in the regions 2.3–2.9 (4 H, CH_2N) and 1.3–2.3 (8 H, aliphatic CH).

Anal. Calcd for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62; N, 9.21. Found: C, 63.29; H, 6.71; N, 9.16.

A solution of 3.39 g (21.8 mmoles) of the amino alcohol **16** in 30 ml of pyridine was treated with 4.45 g (24.0 mmoles) of *p*-nitrobenzoyl chloride and then allowed to stand at room temperature for 20 hr. Dilution with ether precipitated 7.957 g of the crude hydrochloride of the amino ester **8** as beige prisms, mp 232–235° dec (lit.[4a] mp 239.5–240°). This hydrochloride

(9) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated magnesium sulfate was employed as a drying agent. The infrared spectra were determined with a Perkin-Elmer, Model 237, infrared recording spectrophotometer fitted with a grating. The ultraviolet spectra were determined with a Cary recording spectrophotometer, Model 14. The nmr spectra were determined at 60 Mc with a Varian, Model A-60, nmr spectrometer and tetramethylsilane was used as an internal standard. The mass spectra were obtained with a CEC, Model 21-130, mass spectrometer. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory.

(10) Determined as a solution in chloroform.

(11) Determined as a solution in 95% ethanol.

(12) Determined as a solution in deuteriochloroform.

was treated with a mixture of aqueous sodium hydroxide and ether and the ethereal solution of the free base was separated, dried, and concentrated to leave 5.90 g (89%) of the amino ester **8**, mp 125–127°. Recrystallization from ether–hexane mixtures afforded the pure amino ester **8** as yellow prisms, mp 129–130°.[13] The product has infrared peaks[10] at 2760, 2740 (shoulder), and 2700 (CH bonds α to nitrogen and oriented *trans* to the free electron pair) and at 1720 cm^{-1} (conjugated ester C=O) with an ultraviolet maximum[11] at 259 mμ (ϵ 13,800). The material has nmr peaks[12] at δ 8.31 (4 H, aryl CH), 5.07 (1 H triplet, J = 3 cps, >CHO), and 2.19 (3 H, NCH_3), as well as broad multiplets in the region 1.2–3.2 (aliphatic CH).

Anal. Calcd for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62; N, 9.21. Found: C, 63.22; H, 6.71; N, 9.24.

Preparation of the *o*-Methylbenzylamines 36 and 37.—The toluamides **34** and **35** were prepared by reaction of ether or benzene solutions of *o*-toluyl chloride with the appropriate amines. The N-methylamide **34**, obtained as white needles melting at 75.5–76.5° (lit.[14] mp 75°), has infrared absorption[10] at 3440 (NH), 3300 (associated NH), 1660 (amide C=O), and 1520 cm^{-1} (NH bending) with an ultraviolet maximum[11] at 269 mμ (ϵ 623) as well as intense end absorption. The nmr spectrum[12] has a multiplet in the region δ 6.6–7.5 (5 H, NH and aryl CH) with peaks at 2.67 (3 H doublet with J = 5 cps, NCH_3) and 2.23 (3 H, aryl CH_3). The N,N-dimethylamide **35** was obtained as a liquid, bp 115–118° (4.8 mm), $n^{25}D$ 1.5329 [lit.[14] bp 147° (18 mm)], with infrared absorption[10] at 1655 cm^{-1} (amide C=O) and ultraviolet maxima[11] at 271 mμ (ϵ 385) and 264 mμ (ϵ 450), as well as intense end absorption. The nmr spectrum[12] has a multiplet in the region δ 6.9–7.4 (4 H, aryl CH) with singlets at 3.03 (NCH_3), 2.72 (NCH_3), and 2.23 (aryl CH_3). Each of the amides **34** and **35** was reduced with excess ethereal lithium aluminum hydride; the amines **36** and **37** were initially isolated as their crystalline hydrochloride salts and then converted to the free bases and distilled. The N-methylamine **36**, bp 82–97° (5 mm), $n^{25}D$ 1.5221 [lit.[15] bp 100–102° (11 mm)], has ultraviolet maxima[11] at 262 mμ (ϵ 285) and 271 mμ (ϵ 222) with intense end absorption and abundant peaks in its mass spectrum at *m/e* 135, 134, 118, 105, 104, 91, 77, 67, 65, 51, 44, 42, and 39. The nmr spectrum[12] has a multiplet in the region δ 6.9–7.4 (4 H, aryl CH) with peaks at 3.62 (2 H, broad, NCH_2), 2.39 (3 H, broad, NCH_3), 2.26 (3 H, aryl CH_3), and 1.18 (1.H, broad, NH). The N,N-dimethylamine **37**, bp 68–69° (6 mm), $n^{25}D$ 1.5025 [lit.[16] bp 80–80.2° (14 mm)], has ultraviolet maxima[11] at 263.5 mμ (ϵ 250) and 271.5 mμ (ϵ 205), as well as intense end absorption and abundant mass spectral peaks at *m/e* 149, 105, 104, 91, 77, 58, 44, 42, and 39. The nmr spectrum[12] has a multiplet in the region δ 6.9–7.3 (4 H, aryl CH) with peaks at 3.29 (2 H, CH_2N), 2.30 (3 H, aryl CH_3), and 2.15 (6 H, NCH_3).

Preparation of the Unsaturated Amines 18 and 19.—To a solution of 11.2 g (75 mmoles) of N-methyl-*o*-toluamide (**34**) and 20 ml of *t*-butyl alcohol in 250 ml of liquid ammonia was added, portionwise over a 5-min period, 1.1 g (150 mg-atom) of lithium wire. After a period of 30 min, the reaction solution became colorless and was diluted with ether. After the ammonia had been allowed to evaporate, the residual material was partitioned between ether and water and the ethereal phase was dried and concentrated. The residual white solid (15.9 g, mp 76–87°) was fractionally crystallized from ether to separate 3.07 g (27%) of the dihydroamide **38**, mp 122–124°. Recrystallization from ether afforded the pure dihydroamide **38** as white needles, mp 127–128°, with infrared absorption[10] at 3420 (NH), 1660 (amide C=O), and 1520 cm^{-1} (NH bending) and end absorption in the ultraviolet at 220 mμ (ϵ 680).[11] The nmr spectrum[12] has multiplets in the regions δ 5.3–6.0 (4 H, vinyl CH and NH) and 1.5–1.8 (3 H, CH_3C) with a doublet (J = 4.5 cps) at 2.73 (3 H, CH_3N) superimposed on a complex multiplet in the region 2.5–3.7 (3 H, allylic CH).

Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.38; H, 8.56; N, 9.33.

A solution of 680 mg (4.5 mmoles) of the dihydroamide **38** in 20 ml of ethyl acetate was hydrogenated over 94 mg of a 5% palladium-on-barium sulfate catalyst[17] at room temperature and atmospheric pressure. After 3 hr (hydrogen uptake 100 ml or 4.1 mmoles) the reaction was stopped and the solution was filtered from the catalyst and concentrated. The residual solid (710 mg, mp 91–93°) was recrystallized from ether to separate 397 mg (58%) of the tetrahydroamide **39** as white prisms, mp 95–96.5°. The product has infrared absorption[10] at 3450, 3425, and 3320 (NH stretching), at 1650 and 1665 (shoulder, amide C=O and nonconjugated C=C), and at 1520 cm^{-1} (NH bending) with only end absorption in the ultraviolet.[11] The nmr spectrum[18] has a broad multiplet in the region δ 7.1–7.9 (1 H, NH) with a broad peak at 5.55 (1 H, vinyl CH), a doublet (J = 4.5 cps) at 2.73 (NCH_3) superimposed on a multiplet in the region 2.5–3.0 (allylic >CH), and a broad but unresolved peak at 1.63 (allylic CCH_3) superimposed on a broad multiplet in the region 1.2–2.2 (CH_2).

Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14; mol wt, 153. Found: C, 70.75; H, 9.56; N, 9.08; mol wt, 153 (mass spectrum).

A solution of 459 mg (3.0 mmoles) of the tetrahydroamide **39** and 456 mg (12.0 mmoles) of lithium aluminum hydride in 30 ml of ether was stirred at room temperature for 44 hr and then treated with sufficient aqueous sodium hydroxide to precipitate the lithium and aluminum salts. After filtration, the residue was washed with ether and the combined ether filtrates were dried and concentrated. The residual pale yellow liquid (386 mg) exhibited one major peak on gas chromatography[19] accompanied by five minor peaks. Samples of the major component, the unsaturated amine **18**, were collected[19] for spectra and analysis. The infrared spectrum[10] has a very weak peak at 1655 cm^{-1} (C=C) with no absorption corresponding to a carbonyl function and the ultraviolet spectrum[11] shows only end absorption. The nmr spectrum[12] has a broad peak at δ 5.48 (1 H, vinyl CH) with a partially resolved multiplet at 1.69 (allylic CH_3C) superimposed on a complex multiplet in the region 1.1–3.0 (aliphatic CH and NH).

Anal. Calcd for $C_9H_{17}N$: C, 77.63; H, 12.31; N, 10.06; mol wt, 139. Found: C, 77.42; H, 12.28; N, 10.14; mol wt, 139 (mass spectrum).

A solution of 269 mg (1.93 mmoles) of the N-methylamine **18** and 282 mg (2.0 mmoles) of methyl iodide in 20 ml of ether was stirred at room temperature for 42 hr. The hydroiodide of the starting amine **18** which had separated (202 mg, mp 139–140°) was collected and reconverted to the starting material by treatment with aqueous alkali. The ethereal filtrate was washed with aqueous sodium hydroxide, dried, and concentrated to leave a pale yellow oil which contained[19] mainly the dimethylamine **19** accompanied by lesser amounts of the starting amine **18** and other minor components. A collected sample of the N,N-dimethylamine **19** has weak infrared absorption[10] at 1645 cm^{-1} (C=C) with only end absorption in the ultraviolet.[11] The nmr spectrum[12] has peaks at δ 5.42 (1 H, broad, vinyl CH) and 2.20 (6 H, singlet, NCH_3) with a partially resolved multiplet centered at 1.67 (3 H, allylic CCH_3) and a complex multiplet in the region 1.3–2.6 (9 H, aliphatic CH). The mass spectrum has a weak molecular ion peak at *m/e* 153 with abundant fragment peaks at *m/e* 91, 79, 77, 67, 59, 58, 57, 55, 53, 44, 43, 42, 41, and 39.

Anal. Calcd for $C_{10}H_{19}N$: C, 78.36; H, 12.50; N, 9.14. Found: C, 78.45; H, 12.52; N, 9.09.

Preparation of the *o*-Phenylbenzylamines 42 and 43.—The N-methylamide **40**[20] was reduced with excess lithium aluminum hydride in ether solution. After following the previously described isolation procedure, the crude amine **42** was converted to its hydrochloride salt which crystallized from acetone as white platelets, mp 152–154° (lit.[21] mp 152–154°), yield 49%. Treatment of this hydrochloride with a mixture of ether and aqueous sodium hydroxide afforded an ether solution of the free base which was dried, concentrated, and distilled in a short-path

(13) A mixture of the two amino esters **8** and **11** melted at 96–104°.

(14) M. L. Van Scherpenzeel, *Rec. Trav. Chim.*, **20**, 149 (1901).

(15) J. v. Braun and R. Michaelis, *Ann.*, **507**, 1 (1933).

(16) S. W. Kantor and C. R. Hauser, *J. Am. Chem. Soc.*, **73**, 4122 (1951).

(17) Attempts to catalytically hydrogenate dihydrobenzene derivatives have frequently been reported to result in initial disproportionation of the diene to the corresponding benzene derivatives and cyclohexene derivatives. M. E. Kuehne and B. F. Lambert [*ibid.*, **81**, 4278 (1959)] observed this difficulty in the hydrogenation of dihydrobenzamide over a palladium-on-carbon catalyst. Our preliminary experiments with platinum- and palladium-on-carbon catalysts suggested that we were encountering similar difficulties. However, the use of the 5% palladium-on-barium sulfate catalyst purchased from Engelhard Industries Inc. apparently avoids this problem.

(18) Determined as a solution in carbon tetrachloride.

(19) A gas chromatography column packed with Carbowax 20M suspended on Chromosorb W was employed for this analysis.

(20) T. Mukai, *Bull. Chem. Soc. Japan*, **32**, 272 (1959).

(21) St. Goldschmidt and W. L. C. Veer, *Rec. Trav. Chim.*, **67**, 489 (1948).

still. The amine **42**, collected at 155–167° (5 mm), exhibits a single peak on gas chromatography[19] and has ultraviolet maxima[11] at 232 and 234 mμ (ε 10,100). The nmr spectrum[12] of the sample exhibits nmr peaks at δ 2.50 (3 H, CH_3N) and 4.21 (2 H, CH_2N) with a multiplet in the region 6.8–7.9 (10 H, aryl CH and NH). The mass spectrum exhibits a molecular ion peak at *m/e* 197 with abundant fragment peaks at *m/e* 196, 182, 166, 165, 44, 42, and 39.

Anal. Calcd for $C_{14}H_{15}N$: C, 85.23; H, 7.66; N. 7.10. Found: C, 85.03; H, 7.63; N, 7.14.

After reaction of 50 g (0.23 mole) of *o*-phenylbenzoyl chloride[22] with 100 g (2.2 moles) of dimethylamine in 1 l. of benzene for 3 hr, the mixture was washed with water and the organic phase was decolorized with Norit, dried, and concentrated to leave the crude amide (35.3 g) as a brown oil. On standing, this oil deposited 15.74 g of the crude amide **41**, mp 51–54°, which was separated and recrystallized from an ether–petroleum ether (bp 30–60°) mixture. The pure amide **41** separated as pale yellow prisms, mp 58–60°. The sample has infrared absorption[10] at 1630 cm^{-1} (conjugated amide C=O) with ultraviolet maxima[11] at 227 mμ (ε 17,200), 296 (55), and 307 (75). The nmr spectrum[23] has peaks at δ 2.41 and 2.75 (3 H each, NCH_3) with a multiplet in the region 7.1–7.7 (9 H, aryl CH).

Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22; mol wt, 225. Found: C, 79.92; H, 6.75; N, 6.17; mol wt, 225 (mass spectrum).

Reduction of the N,N-dimethylamide **41** with excess lithium aluminum hydride in ether as previously described yielded the dimethylamine **43** as a colorless liquid after a short-path distillation [bath temperature 157–166° (5 mm), lit.[21] bp 154–155° (18 mm)], $n^{25}D$ 1.5740. The product, which shows a single peak on gas chromatography,[19] has an ultraviolet maximum[11] at 232 mμ (ε 10,500). The nmr spectrum[12] has peaks at δ 2.09 (6 H, NCH_3) and 3.30 (2 H, CH_2N) with a multiplet in the region 6.9–7.7 (9 H, aryl C–H). The mass spectrum has a molecular ion peak at *m/e* 211 with abundant fragment peaks at *m/e* 210, 196, 167, 166, 165, 58, 44, and 42.

Preparation of the Unsaturated Amines 21 and 22.—A solution of 6.46 g (41.6 mmoles) of 2-(dimethylaminomethyl)cyclohexanone (**45**)[24] in 30 ml of ether was added dropwise and with stirring to 28 ml of an ethereal solution containing 53 mmoles of phenylmagnesium bromide and the resulting mixture (containing a precipitate) was stirred at room temperature and under a nitrogen atmosphere for 30 min. After the magnesium salts had been hydrolyzed by the addition of an aqueous solution (pH 7.5) of ammonia and ammonium chloride, the ether layer was separated and the aqueous phase was made basic with sodium hydroxide and extracted with ether. The combined ether solutions were dried and concentrated to leave 8.10 g of a mixture of stereoisomeric amino alcohols **47** as a pale yellow liquid. A 1.182-g aliquot of this liquid was distilled in a short-path still [80–150° (0.1 mm)] to separate 1.078 g of colorless liquid which contained[19] two components (presumably the stereoisomeric amino alcohols **47**) in the approximate proportions 4 (first peak eluted) to 1 (second peak eluted). A solution of 523 mg (2.3 mmoles) of this crude amine in 10 ml of acetic acid was treated with 1.0 ml of concentrated sulfuric acid and the resulting solution was stirred at room temperature for 25 min and then poured into cold (0°), aqueous sodium hydroxide. The ether extract of this mixture was dried and concentrated to leave 470 mg of yellow liquid which contained[19] primarily the unsaturated amine **22** accompanied by several minor components. A collected[19] sample has weak infrared absorption[10] at 1630 cm^{-1} (C=C) with no absorption in the 3- or 6-μ regions attributable to OH, NH, or C=O functions, and an ultraviolet maximum[11] at 242.5 mμ (ε 10,700). The nmr spectrum[12] has peaks at δ 7.27 (5 H, aryl CH), 5.94 (1 H triplet, J = 4 cps, of doublets, J = 1 cps, vinyl CH), and 2.16 (6 H singlet, NCH_3); this latter peak is superimposed on a complex multiplet in the region δ 1.4–3.1 (9 H, aliphatic CH). The mass spectrum has a molecular ion peak at *m/e* 215 with abundant fragment peaks at *m/e* 115, 91, 77, 59, 58, 42, and 39.

Anal. Calcd for $C_{15}H_{21}N$: C, 83.66; H, 9.83; N, 6.51. Found: C, 83.59; H, 9.80; N, 6.31.

To a solution containing 37.8 mmoles of phenylmagnesium bromide in 270 ml of ether was added 778.4 mg (4.38 mmoles) of the hydrochloride of 2-(N-methylaminomethyl)cyclohexanone (hydrochloride of **44**, mp 98–99°, lit.[24] mp 100–101°). The resulting mixture was stirred for 30 hr and then partitioned between aqueous ammonium chloride solution and ether. The resulting ether solution was extracted with aqueous 10% hydrochloric acid. This acidic, aqueous extract was made basic with aqueous sodium hydroxide and extracted with ether. After this ethereal extract had been dried and concentrated, the remaining pale yellow oil amounted to 520 mg. The infrared spectrum[10] of this liquid is consistent with the assumption that it is composed of a mixture of the stereoisomeric amino alcohols **46**. A solution of 6.08 g (27.7 mmoles) of this crude amino alcohol **46** in a mixture of 50 ml of acetic acid and 4 ml of concentrated sulfuric acid was stirred at room temperature for 2 hr and then poured into excess cold aqueous sodium hydroxide. After the ethereal extract of this mixture had been dried and concentrated, the residual oil (5.47 g) was distilled in a short-path still to separate 2.784 g (50%) of colorless liquid, bp 92–93° (0.08 mm), which contained[19] the unsaturated amine **21**. The amine **21** has infrared absorption[10] at 3340 cm^{-1} (weak, NH) with an ultraviolet maximum[11] at 241 mμ (ε 10,000). The nmr spectrum[10] has peaks at δ 7.12 (5 H, multiplet, aryl CH) and 5.80 (1 H multiplet, vinyl CH) with broad, complex absorption in the region 1.3–3.0 (13 H, NH and aliphatic CH). In a second measurement, a sample of the amine **21** was allowed to stand in perdeuteriodimethyl sulfoxide for 30 hr to effect exchange of deuterium for hydrogen at the NH function. The nmr spectrum of the resulting solution has peaks at δ 7.18 (5 H multiplet, aryl CH) and 5.83 (1 H triplet, J = 4 cps, with further coupling apparent but not resolved, vinyl CH) as well as a singlet at 2.09 (3 H, NCH_3) superimposed on complex absorption in the region 1.4–3.0 (aliphatic CH).

Anal. Calcd for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96; mol wt, 201. Found: C, 83.61; H, 9.47; N, 6.93; mol wt, 201 (mass spectrum).

Preparation of the Unsaturated Amine 49.—To a solution of triphenylphosphine methylene, prepared under a nitrogen atmosphere from 3.25 g (9.1 mmoles) of methyltriphenylphosphonium bromide, 6 ml of a hexane solution containing 9.7 mmoles of butyllithium, and 40 ml of tetrahydrofuran, was added a solution of 1.66 g (10.8 mmoles) of the amino ketone **48** in 10 ml of tetrahydrofuran. The resulting solution was refluxed with stirring for 16 hr and then concentrated and extracted with a hexane–methylene chloride mixture. After this mixture had been filtered to remove the triphenylphosphine oxide and salts, the filtrate was concentrated and distilled to separate 1.332 g of colorless liquid, bp 120–122° (21 mm), which contained[19] primarily the unsaturated amine **49**. Samples of the pure amine **49** were collected from the gas chromatograph[19] for characterization. The material has infrared absorption[10] at 2660, 2700, and 2770 cm^{-1} (CH α to N atom and *trans* and coplanar to the unshared electron pair) as well as peaks at 1660 (C=C) and 880 cm^{-1} ($C=CH_2$). The mass spectrum has a molecular ion peak at *m/e* 151 with abundant fragment peaks at *m/e* 150, 93, 79, 58, 57, 44, 42, 41, and 39. The nmr spectrum[12] has singlets at δ 4.46 (2 H, vinyl CH) and 2.04 (3 H, NCH_3) with a complex multiplet in the region 1.2–3.2 (12 H, aliphatic CH).

Anal. Calcd for $C_{10}H_{17}N$: C, 79.40; H, 11.34; N, 9.26. Found: C, 79.67; H, 11.44; N, 9.07.

Solvolyses and Kinetic Measurements. A. General Procedure.—Solutions which were 0.0100 *M* in the *p*-nitrobenzoate and 0.0101–0.011 *M* in freshly distilled triethylamine were prepared in a dioxane[25] (6 volumes)–water (4 volumes) mixture. These solutions were heated to reflux (89°) under a nitrogen atmosphere. Aliquots (1.00 ml) were removed from the solutions and quenched in 50 ml of 1 *M* aqueous sodium carbonate. After the resulting mixtures had been extracted with three 80-ml portions of ether, the ether extracts were washed with 40 ml of aqueous 1 *M* sodium carbonate and the combined aqueous sodium carbonate solutions were diluted to 100.0 ml. The optical densities of these aqueous solutions were measured at 268 mμ with a Beckman spectrometer, Model DU, to determine the concentrations of the *p*-nitrobenzoate anion. Appropriate blank experiments demonstrated that this procedure did not hydrolyze significant amounts of the starting *p*-nitrobenzoate esters and

(22) F. D. Greene, G. R. van Norman, J. C. Cantrill, and R. D. Gilliom, *J. Org. Chem.*, **25**, 1790 (1960).

(23) Determined as a solution in perdeuteriodimethylformamide.

(24) F. F. Blicke and F. J. McCarty, *J. Org. Chem.*, **24**, 1069 (1959).

(25) The dioxane was purified by distillation from lithium aluminum hydride just prior to use.

that these manipulations served to separate quantitatively sodium *p*-nitrobenzoate and the starting *p*-nitrobenzoate esters. At the end of the kinetic runs, weighed samples of internal standards were added to the remaining reaction solutions and the mixtures were partitioned between ether and aqueous sodium carbonate. After the ether layers had been dried and concentrated, they were analyzed by gas chromatography.[19] To obtain the first-order rate constants of these solvolyses, plots of time *vs.* log of the *p*-nitrobenzoate concentration were prepared and the slopes were determined graphically. The values given are average values obtained from two different runs.

B. 9β-(4-Nitrobenzoyloxy)-3-azabicyclo[3.3.1]nonane (11).—The average first-order rate constant was $1.2 \pm 0.4 \times 10^{-6}$ sec^{-1}. The only neutral or basic product detected by gas chromatography[19] and thin layer chromatography[26] was the β-hydroxyamine **15**. The crude product from a solvolysis mixture was partitioned between ether and aqueous hydrochloric acid and then the aqueous phase was made basic with sodium hydroxide and extracted with ether. After this ethereal extract had been dried and concentrated, sublimation of the residue afforded the pure amino alcohol **15**, mp 93–93.5°, which was identified with an authentic sample by a mixture melting point determination and by comparison of infrared and mass spectra. A weighed amount of internal standard (*p*-dimethoxybenzene) was added to the crude product from a reaction which had gone to 91% of completion. The yield of amino alcohol **15** was calculated from the gas chromatograph of this mixture to be 79%.

C. 9α-(4-Nitrobenzoyloxy)-3-azabicyclo[3.3.1]nonane (8).—The average first-order rate constant was $4.4 \pm 0.9 \times 10^{-7}$ sec^{-1}. The only neutral or basic product detected by gas chromatography[19] was the α-hydroxyamine **16**; a sample of this product **16**, isolated as was described in the previous experiment, melted at 92.5–94°, and was identified with an authentic sample by a mixture melting point determination and by comparison of infrared and mass spectra. The calculated[19] yield (*p*-dimethoxybenzene internal standard) of the amino alcohol **16** from a reaction which had gone to greater than 99% completion was 82%.

D. 9α-(4-Nitrobenzoyloxy)-9β-methyl-3-azabicyclo[3.3.1]nonane (9).—The average first-order rate constant was $1.2 \pm 0.1 \times 10^{-5}$ sec^{-1}. An additional reaction was run under the exact conditions of a kinetic run except that a weighed amount of naphthalene was added as an internal standard. The crude neutral and basic materials present in the reaction mixture were analyzed by gas chromatography.[19] The calculated yields of products were dimethylamine **19** (first eluted), 35%; monomethylamine **18** (second eluted), 48%; β-hydroxyamine **17** (eluted third), 1%; and α-hydroxyamine **20** (eluted fourth), 16%. A minor unidentified component (eluted fifth) was also detected but neither of the benzylamines **36** or **37** nor unsaturated amine **49** was detected. The analogous crude product mixture from one of the kinetic runs (which did not contain an internal standard) had a similar composition,[19] namely, **19** (38%), **18** (41%), **17** (3%), and **20** (16%). Three additional unidentified minor components (total 2%) were also detected. Collected[19] samples of each of the amines **17–20** were identified with previously described authentic samples by comparison of gas chromatographic retention times and infrared and mass spectra. In a subsequent experiment to learn the effect of excess triethylamine on the amount of tertiary amine **19**, an aqueous dioxane (4:6 by volume) solution which was 0.010 *M* in the *p*-nitrobenzoate **9** and 0.030 *M* in triethylamine was heated to 89° for 117 hr at which time the solvolysis of the ester **9** was at least 98% complete. The crude mixture of basic and neutral products contained[19] 54% dimethylamine **19**, 43% monomethylamine **18**, and 3% amino alcohol **20**; the calculated yields were 34% **19**, 27% **18**, and 2% **20**.

E. 9β-(4-Nitrobenzoyloxy)-9α-methyl-3-azabicyclo[3.3.1]nonane (12).—The average first-order rate constant was $2.8 \pm 0.6 \times 10^{-6}$. After a weighed amount of naphthalene (as an internal standard) had been added to the reaction mixture from one of the kinetic runs, the crude mixture of basic and neutral products was separated and analyzed by gas chromatography.[19] The calculated yields were bicyclic amine **49** (eluted first), 39%; dimethylamine **19** (eluted second), 13%; β-hydroxyamine **17** (eluted third), 20%; and α-hydroxyamine **20** (eluted fourth), 2%. Thus, the composition[19] of the product mixture was **49**, 53%; **19**, 17%; **17**, 20%; and **20**, 3%. In another run where no internal standard was present, the composition[19] of the product mixture was **49**, 39%; **19**, 13%; **18**, 7%; **17** and **20** (not resolved), 41%. Collected samples of amines **49**, **19**, and **17** were identified with previously described authentic samples by comparison of gas chromatographic retention times and infrared and mass spectra.

F. 9β-(4-Nitrobenzoyloxy)-9α-phenyl-3-azabicyclo[3.3.1]nonane (13).—The average first-order rate constant was $2.1 \pm 0.1 \times 10^{-3}$ sec^{-1}. The crude basic and neutral product from one run contained[19] a minor unidentified component (eluted first), 1%, the dimethylamine **22** (eluted second), 20%, and the monomethylamine **21** (eluted third), 79%, but neither of the aromatic derivatives **42** or **43** was detected. The calculated yields[19] from another run containing an internal standard (biphenyl) were 20% **22** and 79% **21**. Collected[19] samples of the two unsaturated amines **21** and **22** were identified with previously described samples by comparison of gas chromatographic retention times and infrared, mass, and nmr spectra.

G. 9α-(4-Nitrobenzoyloxy)-9β-phenyl-3-azabicyclo[3.3.1]nonane (10).—The average first-order rate constant was $3.2 \pm 0.6 \times 10^{-3}$ sec^{-1}. The crude basic and neutral product from one run contained[19] 43% of the dimethylamine **22** and 52% of the monomethylamine **21** as well as 5% of two more rapidly eluted, unidentified components. As in the previous case, neither of the benzylamines **42** or **43** was detected. From another run containing an internal standard (biphenyl), the calculated[19] yields were 12% **22** and 88% **21**. Collected[19] samples of each of the amines **21** and **22** were identified with previously described authentic samples by comparison of gas chromatographic retention times and infrared and mass spectra.

(26) The thin layer chromatograms were obtained on plates coated with silicic acid and eluted with methanol–ethyl acetate mixtures.

The 1,2-Dithiolium Cation. VI.[1a] New Dithioles and No-Bond Resonance Compounds

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New evidence is presented on the condensation of dithiolium salts with carbonyl compounds. Chlorination of the products is discussed. Compound XIII may represent a new class of thiothiophthene derivative. Spectral and chemical evidence indicates a new form of no-bond resonance stabilization in the anions of XII and XIII.

An earlier paper in this series describes the condensation of 1,2-dithiolium salts with aryl methyl and aryl benzyl ketones to give acylmethylenedithioles (II) convertible to thiothiophthenes (III) by reaction with phosphorus pentasulfide. In the mechanism suggested for the condensation reaction, acylmethyldithioles (I) are formed, but not isolated, since they undergo immediate dehydrogenation to II at the expense of additional dithiolium salt.[1b] The proposed formation

(1) (a) Presented at the 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 29, 1966; paper V, E. Klingsberg, *J. Heterocyclic Chem.*, **3**, 243 (1966); (b) paper IV, E. Klingsberg, *J. Am. Chem. Soc.*, **85**, 3244 (1963).