Stereochemistry of the N-Alkylation of 4-*t*-Butylpiperidine Derivatives[1a]

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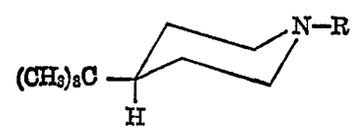
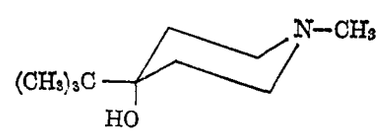
The reactions of the 4-*t*-butylpiperidine derivatives **1–4** with alkyl *p*-toluenesulfonates have been studied to determine the degree of stereoselectivity with which the alkyl groups are introduced to form quaternary ammonium salts. The preferred direction of attack resulted in introduction of the alkyl group *cis* to the 4-*t*-butyl substituent (*i.e.*, axial with respect to the 4-*t*-butylpiperidine ring).

To supplement our study of the stereochemistry of N-alkylation of azabicyclic systems,[2] we have examined the N-alkylation of the 4-*t*-butylpiperidine derivatives **1–4**.[3] These tertiary amines are expected



1, R = CH_3
2, R = C_2H_5
3, R = $CH_2C_6H_5$



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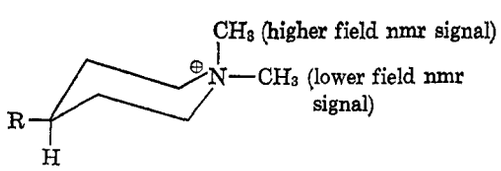
to exist very largely in conformations which allow the large *t*-butyl group to remain equatorial to the piperidine ring. Since these systems lack any serious opposing steric interactions (1,3-diaxial interactions involving two groups larger than hydrogen) which would be relieved in a boat conformation, they can also be expected to exist predominantly in the indicated chair conformations.[4] The N-alkyl groups of these amines, being substantially greater in steric requirements than the nonbonded electron pair of the nitrogen atom,[5] are expected to exist predominantly in the indicated equatorial conformations. Evidence for this latter expectation is found in the presence of intense infrared absorption in region 2700–2800 cm^{-1} for each of the amines **1–4**. Such absorption is characteristic of amines which exist, at least partially, in conformations wherein the nonbonded electron pair on nitrogen and at least two α C–H bonds are arranged in a *trans* coplanar manner.[6,7]

The N-alkylation reactions studied with the amines **1–4** are summarized in the following equations. Our assignments of nmr signals for the N-alkyl groups of the quaternary ammonium salts are indicated in parentheses beside the appropriate structural formulas. As in previous cases,[2a,3,7] the proportions of stereoisomeric quaternary ammonium salts in the alkylated products were estimated from the relative intensities of these N-alkyl nmr signals. These estimates are indicated in Scheme I. Comparison of the data for amines **1** and **4** indicates that the presence or absence of a hydroxyl group at C-4 has little effect on the stereochemical course of these N-alkylation reactions, a feature noted earlier in the N-alkylation of certain azabicyclic alcohols.[2a] The various quaternary ammonium salts **5–12** formed in these reactions are presumed to exist predominantly in the indicated chair conformations since there is no apparent reason why the usual order of stability (chair > boat)[4a] should be reversed in these salts. Furthermore, the X-ray crystallographic data presently available[3,8] for related quaternary ammonium salts is consistent with this conclusion.

The nmr assignments (and, consequently, the stereochemical assignments) presented in Scheme I are in agreement with earlier studies[3,7] of simple piperidine derivatives and related compounds in that the diastereoisomer with the nmr N-methyl signal at higher field is assigned the configuration in which the N-methyl group is axial (*i.e.*, structure **13**). Furthermore, the predominant stereochemical course for N-alkylation[3,7] of such piperidine derivatives and relatives was the introduction of the entering N-alkyl group in an axial position.[3,7] This general rule was followed provided that introduction of the new N-alkyl did not produce any new 1,3-diaxial interaction between two groups, each larger than hydrogen.



13

Although a variety of physical measurements[3,7] supported these nmr and stereochemical assignments, we considered that the addition of classical evidence

(1) (a) This research has been supported by research grants from the McNeil Laboratories and from the National Institutes of Health (Grant No. GM-08761). (b) National Institutes of Health Predoctoral Fellow, 1963–1965.

(2) (a) H. O. House and C. G. Pitt, *J. Org. Chem.*, **31**, 1062 (1966); (b) H. O. House and B. A. Tefertiller, *ibid.*, **31**, 1068 (1966).

(3) For other recent studies of the N-alkylation of piperidine derivatives, see (a) J. McKenna, J. M. McKenna, J. White, and A. Tulley, *J. Chem. Soc.*, 1711 (1965); (b) J. K. Becconsall, R. A. Y. Jones, and J. McKenna, *ibid.*, 1726 (1965); (c) J. McKenna, B. C. Hutley, and J. White, *ibid.*, 1729 (1965); (d) J. McKenna, J. M. McKenna, and J. White, *ibid.*, 1733 (1965); (e) R. Bognar and S. Szabo, *Tetrahedron Letters*, **No. 39**, 2867 (1964). For references to earlier studies, see ref 2a.

(4) (a) M. Balasubramanian, *Chem. Rev.*, **62**, 591 (1962); (b) M. Balasubramanian and N. Padma, *Tetrahedron*, **19**, 2135 (1963); (c) C.-Y. Chen and R. J. W. LeFevre, *J. Chem. Soc.*, 3467 (1965).

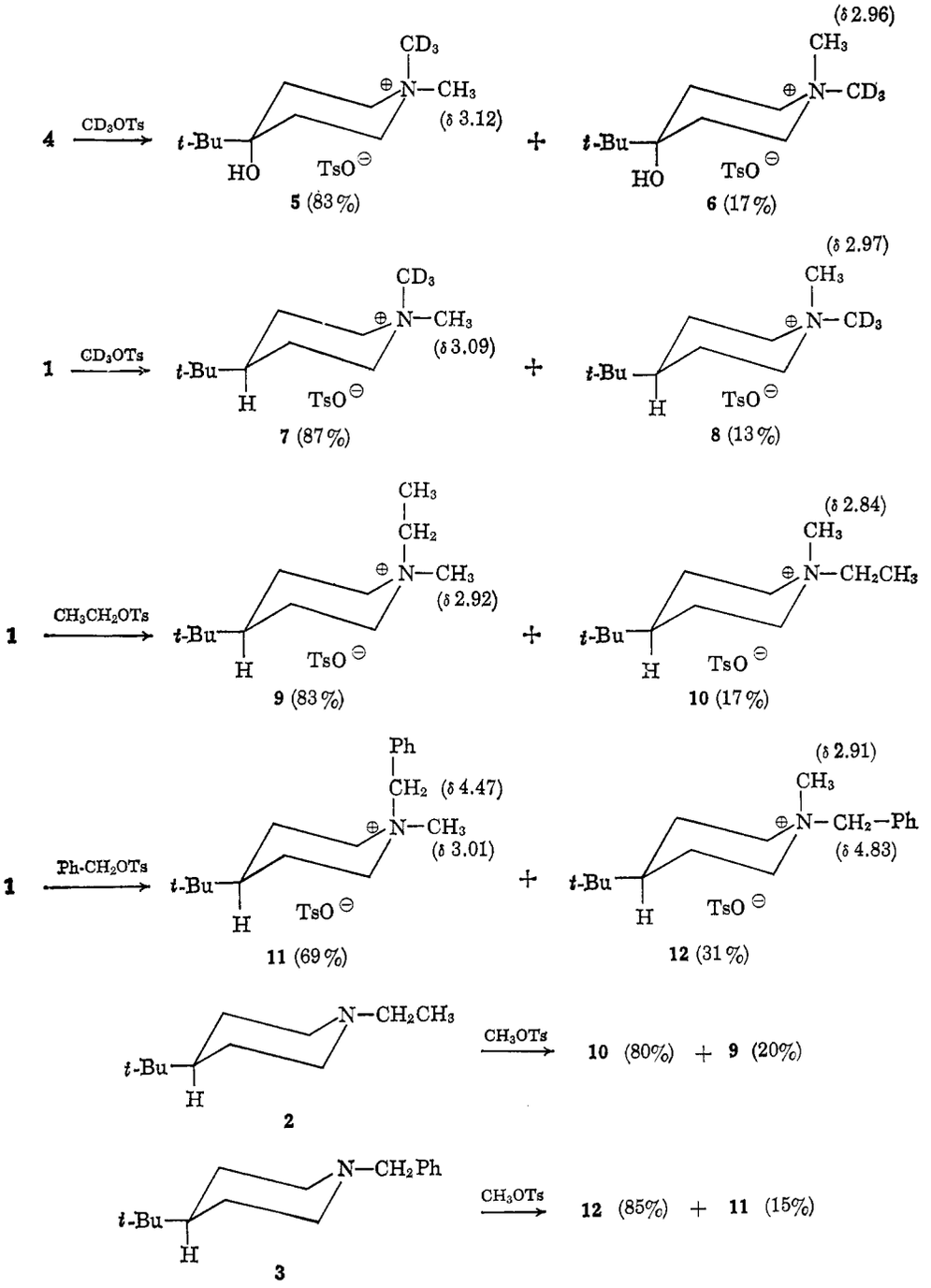
(5) (a) N. L. Allinger and J. C. Tai, *J. Am. Chem. Soc.*, **87**, 1227 (1965); (b) N. L. Allinger, J. G. D. Carpenter, and F. M. Karkowski, *ibid.*, **87**, 1232 (1965); (c) R. J. Bishop, L. E. Sutton, D. Dineen, R. A. Y. Jones, and A. R. Katritzky, *Proc. Chem. Soc.*, 257 (1964); (d) K. Brown, A. R. Katritzky, and A. J. Waring, *ibid.*, 257 (1964).

(6) (a) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958); (b) C.-Y. Chen and R. J. W. LeFevre, *Tetrahedron Letters*, **No. 21**, 1611 (1965).

(7) (a) A. R. Katritzky, *Rec. Chem. Progr.* (Kresge-Hooker Sci. Lib.), **23**, 223 (1962); (b) T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 2637 (1962); (c) M. Shamma and J. M. Richey, *J. Am. Chem. Soc.*, **85**, 2507 (1963); (d) W. L. Meyer and N. Sapianchiay, *ibid.*, **86**, 3343 (1964).

(8) C. H. MacGillavry and G. Fodor, *J. Chem. Soc.*, 597 (1964).

SCHEME I



for the stereochemistry of one of these quaternary ammonium salts would not be without merit. Accordingly, the amino alcohol **4** was treated with methyl bromoacetate to form the quaternary ammonium salts **14** and **15**. Our plan to cyclize the quaternary salt **15** to the lactone **17**, a procedure which has been used in other cases,[2b,9] was not successful. However, the alternative procedure[2b,10] *via* the crude bromoacetate **16** yielded a sample of the lactone **17** (Scheme II). Conversion of this lactone **17** to the quaternary salt **15** established the stereochemistry of this salt. It will be noted that the previously discussed correlation of stereochemistry with the position of the N-methyl nmr signal (*i.e.*, structure **13**) is fully consistent with the nmr data for salts **14** and **15**. It will also be noted that the N-alkylation of the amine **4** with methyl bromoacetate exhibits no significant stereoselectivity.

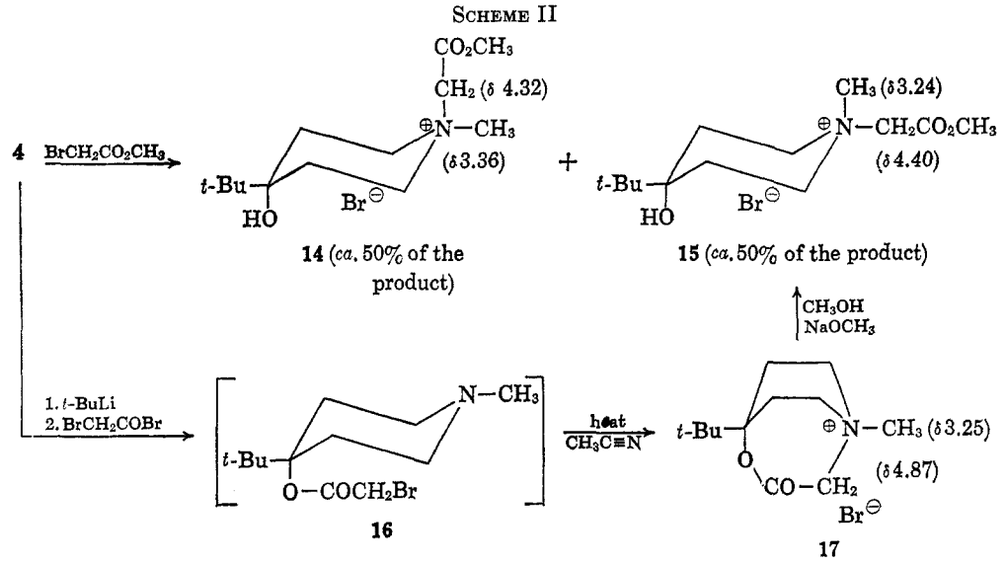
Thus, our data for the N-alkylation of 4-*t*-butylpiperidine derivatives and related azabicyclic compounds leads to the conclusion that both reactions are normally partially stereoselective[11] leading to an excess of one diastereoisomeric quaternary ammonium salt. The preferred stereochemical pathways for these two series of amines are summarized in

(9) For a recent review of the N-alkylation of tropane derivatives, see G. Fodor, "The Alkaloids," Vol. 6, R. H. F. Manske, Ed., Academic Press Inc., New York, N. Y., 1960, pp 145–177.

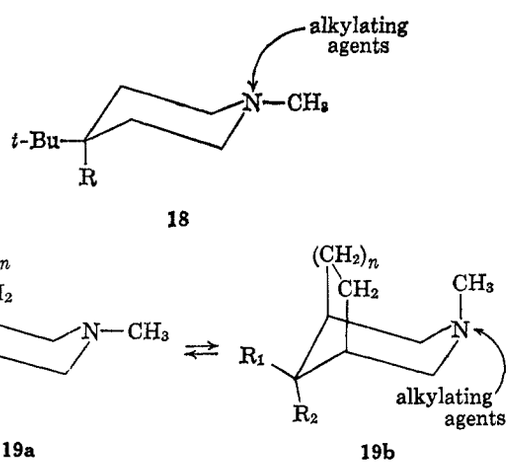
(10) G. Fodor, F. Uresch, F. Dutka, and T. Szell, *Collection Czech. Chem. Commun.*, **29**, 274 (1964).

(11) The term "stereoselective" is used in the sense defined by E. L. Eliel ("Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 436) and does not mean partially stereospecific.

SCHEME II



structures **18** and **19**. Comparison of our data with earlier studies of piperidine derivatives[3] and, especially,

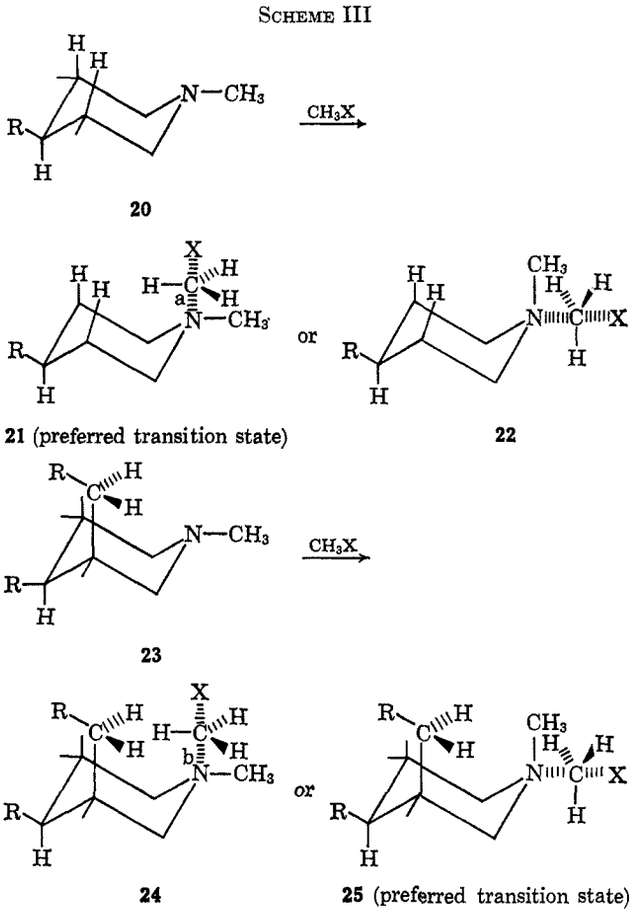


with an earlier thorough study[7a,b] of quinalizidine derivatives leads to the generalizations expressed in Scheme III. In other words, when the starting amine (*e.g.*, **20**) possesses no large groups which will bear a 1,3-diaxial relationship to entering alkyl group (as in **24**), a transition state (*e.g.*, **21**) leading to alkylation from an axial direction is of slightly lower energy than the transition state (*e.g.*, **22**) leading to introduction of an equatorial alkyl group. However, when the starting amine does possess an axial substituent at the 3-position (as in **23**) then a transition state (*e.g.*, **25**) leading to introduction of the alkyl group from an equatorial position is of slightly lower energy than the alternative **24**.

If the relative energies of transition states *21* and *22* are considered, one is led to the conclusion that the steric interactions between the axial hydrogen atoms at C-3 and C-5 and the entering dicoordinated methyl group (as in **21**)[12] are less than the interactions between

(12) Although our studies employed a trideuteriomethyl group, we have assumed that the steric differences between a methyl group and the corresponding trideuteriomethyl group are sufficiently small that they are not primarily responsible for the differences observed. This assumption is consistent with the analogous selectivity observed when the entering group is ethyl or benzyl which is certainly not smaller than a methyl group. For evidence indicating that a trideuteriomethyl group is slightly smaller than a methyl group, see K. Mislow, R. Graeve, A. J. Gordon, and G. H. Wahl, Jr., *J. Am. Chem. Soc.*, **86**, 1733 (1964); A. Horeau, A. Nonaille, and K. Mislow, *ibid.*, **87**, 4957 (1965).

SCHEME III



the corresponding hydrogen atoms and a methyl group fully bonded to nitrogen (as in **22**).[3d] Since the planar array of carbon and three hydrogen atoms in the dicoordinated methyl group is almost certainly larger than the corresponding array of atoms in a fully bound N-methyl group, one is forced to the conclusion that it is the increased length of the forming C–N bond (bond a in structure **21**) which allows steric interaction to be less with the entering methyl group than with the methyl group which is already fully bonded.[3d]

At first glance the situation with amines having 3-alkyl substituents (*e.g.*, **23**) appears anomalous because here steric destabilization is greater with the

entering methyl group (as in **24**) rather than with the fully bonded methyl group (as in **25**). However, this anomaly is avoided if one assumes that the lengths of the forming C–N bonds (bond a in **21** and bond b in **24**) are different in the two cases. In particular, bond b (in **24**) would be expected to be more fully formed (and hence shorter) than bond a (in **21**) since the rate of alkylation of amines such as **23** is slower than the rate of alkylation of unhindered amines such as **20**.[13,14]

Although we have not measured the relative rates of alkylation for amines of the types **18** and **19**, it is apparent from qualitative observation that the half-life for N-alkylation of the monocyclic amines **18** is of the order of minutes, whereas the half-life for N-alkylation of the bicyclic amines is several days. In view of this rate difference, we believe that the foregoing argument will serve to explain the stereochemical preferences summarized in structures **18** and **19**; the same considerations would appear to be valid in other N-alkylations[3,7] as well.

Experimental Section[15]

Quaternary Ammonium Salts Derived from 4-*t*-Butyl-4-hydroxy-1-methylpiperidine (4).—A solution of 520 mg (3.04 mmoles) of the amino alcohol **4**[16] and 1.0 ml of methyl iodide in 5 ml of acetone was allowed to stand at room temperature for 15 hr. The initial crop of crystalline methiodide was collected and the mother liquor was diluted with ethyl acetate to precipitate an additional portion of the salt (total yield 864 mg, 90.8%), mp 184–185.5° dec. Recrystallization from a methanol–ethyl acetate mixture afforded the pure **methiodide of 4** as white needles, mp 186–186.5° dec. The sample has broad infrared absorption[17,18] in the region 3300–3500 cm^{-1} (associated O–H) with nmr[19] singlets at δ 3.25 (3 H, N–CH_3), 3.12 (3 H, N–CH_3), and 0.97 [9 H, $(CH_3)_3C$–] as well as complex absorption in the regions δ 3.3–3.8 (4 H, –CH_2–N) and 1.7–2.3 (4 H, aliphatic C–H).

Anal. Calcd for $C_{11}H_{24}INO$: C, 42.18; H, 7.72; N, 4.47. Found: C, 41.91; H, 7.71; N, 4.08.

A solution of 342 mg (2.00 mmoles) of the amine **4** and 446 mg (2.40 mmoles) of methyl *p*-toluenesulfonate in 10 ml of benzene was refluxed for 3 days. The **metho-*p*-toluenesulfonate of 4** separated as 703 mg (99%) of white plates, mp 164.5–165°. The material, whose melting point was unchanged by recrystallization from a methanol–ethyl acetate mixture, was dried at 100° for 1 week. The material has broad infrared absorption[17,18] in the region 3200–3500 cm^{-1} (associated OH) with an ultraviolet maximum[20] at 222 mμ (ϵ 11,300) and nmr[19] singlets at δ 3.12 (3 H, N–CH_3), 2.96 (3 H, N–CH_3), 2.39 (3 H, aryl CH_3–C), and 0.89 [9 H, $(CH_3)_3C$–] as well as multiplets in the regions δ 7.2–7.9 (4 H, aryl C–H), 3.2–3.5 (4 H, –CH_2–N), and 1.4–2.2 (4 H, aliphatic C–H).

Anal. Calcd for $C_{18}H_{31}NO_4S$: C, 60.48; H, 8.74; N, 3.92. Found: C, 60.41; H, 8.86; N, 3.98.

A solution of 171 mg (1.00 mmole) of the amine **4** and 208 mg (1.10 mmoles) of trideuteriomethyl *p*-toluenesulfonate[2a] in 5 ml of acetone was allowed to stand at 25–30° for 7 days. After the resulting mixture had been concentrated, the residue was washed with ethyl acetate and recrystallized from a methanol–ethyl acetate mixture to separate 356.5 mg (99%) of the mixture of quaternary salts **5** and **6**, mp 165–165.5°. From the relative heights of the nmr[19] N-methyl peaks in this sample, its composition is estimated to be 83% of salt **5** (N–Me peak at δ 3.12) and 17% of salt **6** (N-Me peak at δ 2.96).

Preparation of the 1-Alkyl-4-*t*-butylpiperidines. A. The N-Methyl Derivative 1.—A solution of 3.08 g (23 mmoles) of 4-*t*-butylpyridine[21] and 5.062 g (27 mmoles) of methyl *p*-toluenesulfonate in 80 ml of benzene was refluxed for 24 hr. The crude salt which had separated during the reaction crystallized on cooling. This crude material was collected and recrystallized from chloroform–ether mixtures to separate 4.236 g (54.8%) of the crude **metho-*p*-toluenesulfonate of 4-*t*-butylpyridine** as white plates, mp 100–101°. A solution of 1.237 g (3.96 mmoles) of this pyridium salt in 10 ml of acetic acid was hydrogenated at room temperature and atmospheric pressure over the catalyst from 2.25 g of platinum oxide. After 5 hr the hydrogen uptake (270 cc or 1.04 equiv) ceased, and the reaction mixture was filtered, made basic with aqueous sodium hydroxide, and extracted with ether. Distillation of the ethereal extract afforded 154 mg of the **N-methylamine 1** as a colorless liquid, bp 58–59° (9 mm), $n^{25}D$ 1.4498. In a larger run, 84.0 g (0.261 mole) of the pyridinium salt in 200 ml of acetic acid was hydrogenated at 25° and 30 psi over the catalyst from 15 g of platinum oxide. The amine **1**, bp 58–59° (9 mm), $n^{25}D$ 1.4498, amounted to 31.4 g (77.5%). The product has no infrared absorption[22] in the 3- or 6-μ regions attributable to O—H, C=O, or C=C functions and has nmr[23] singlets at δ 2.25 (3 H, N–CH_3) and 0.86 [9 H, $(CH_3)_3C$–] superimposed on complex absorption in the region δ 0.8–3.2 (9 H, aliphatic C–H). In acid solution,[24] the nmr singlets occur at δ 2.82 (3 H, CH_3–N) and 0.89 [9 H, $(CH_3)_3C$–] and are accompanied by multiplets in the regions δ 2.5–4.0 (4 H, –CH_2–N) and 1.1–2.3 (5 H, aliphatic C–H). The mass spectrum of the material has a molecular ion peak at *m/e* 155 with abundant fragment peaks at *m/e* 154, 140, 98, 70, 44, 43, 42, and 41.

Anal. Calcd for $C_{10}H_{21}N$: C, 77.35; H, 13.63; N, 9.02. Found: C, 77.45; H, 13.62; N, 8.92.

A solution of 297.8 mg (1.92 mmoles) of the amine **1** and 312.7 mg (2.21 mmoles) of methyl iodide in 3 ml of acetone was allowed to stand at 25° for 5 hr. The crude salt which separated was collected and recrystallized from methylene chloride–ether mixtures to separate 325.7 mg (57%) of the **methiodide of amine 1** as white plates, mp 208.5–210° dec. This salt has nmr singlets[19] at δ 3.22 (3 H, N–CH_3), 3.13 (3 H, N–CH_3), and 0.93 [9 H, $(CH_3)_3C$–] with multiplets in the regions δ 3.0–3.8 (4 H, –CH_2–N) and 1.2–2.2 (5 H, aliphatic C–H).

Anal. Calcd for $C_{11}H_{24}IN$: C, 44.44; H, 8.08; N, 4.71. Found: C, 44.46; H, 8.13; N, 4.73.

A solution of 1.045 g (6.84 mmoles) of the amine **1** and 1.534 g (8.25 mmoles) of methyl *p*-toluenesulfonate in 50 ml of benzene was refluxed with stirring for 24 hr. The salt which separated was collected and recrystallized from chloroform–ether mixtures to afford 2.097 g (93%) of the **metho-*p*-toluenesulfonate of amine 1** as white plates, mp 183.5–185° dec. The product has an ultraviolet maximum[20] at 222 mμ (ϵ 11,800) with a series of weak maxima (ϵ 345) in the region 250–270 mμ and nmr[19] singlets at δ 3.09 (3 H, N–CH_3), 2.97 (3 H, N–CH_3), 2.39 (3 H, aryl C–CH_3), and 0.85 [9 H, $(CH_3)_3C$–] as well as multiplets in the regions δ

(13) In accordance with Hammond's postulate, the transition state for alkylation of the unhindered amine **20** should lie closer to the starting materials (*i.e.*, less bond formation): G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

(14) In studies of the N-alkylation of aziridine derivatives, Bottini and co-workers have noted that the effect of solvents on the stereoselectivity of N-alkylation may be interpreted as reflecting differing lengths of the forming C–N bond in the transition state: (a) A. T. Bottini and R. L. Van Etten, *J. Org. Chem.*, **30**, 575 (1965); (b) A. T. Bottini, B. F. Dowden, and L. Sousa, *J. Am. Chem. Soc.*, **87**, 3249 (1965); (c) A. T. Bottini, B. F. Dowden, and R. L. Van Etten, *ibid.*, **87**, 3250 (1965).

(15) 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. 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.

(16) H. O. House, H. C. Müller, C. G. Pitt, and P. P. Wickham, *J. Org. Chem.*, **28**, 2407 (1963).

(17) Determined as a Nujol mull.

(18) Determined as a suspension in a potassium bromide pellet.

(19) Determined as a solution in deuterium oxide.

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

(21) (a) This pyridine derivative, bp 71–73° (8 mm), was prepared as previously described [H. C. Brown and W. A. Murphy, *J. Am. Chem. Soc.*, **73**, 3308 (1951)] and was also purchased from the Reilly Tar and Chemical Co. (b) The hydrogenation of 4-*t*-butylpyridine has been described by K. J. Rorig, U. S. Patent 3,101,340 (Aug 20, 1963); *Chem. Abstr.*, **60**, 1713 (1964).

(22) Determined as a solution in chloroform.

(23) Determined as a solution in deuteriochloroform.

(24) Determined as a solution in deuterium oxide containing 15–20% (by weight) of deuterium chloride.

7.2–8.0 (4 H, aryl C–H), 3.0–3.5 (4 H, $-CH_2-N$), and 1.1–2.1 (5 H, aliphatic C–H).

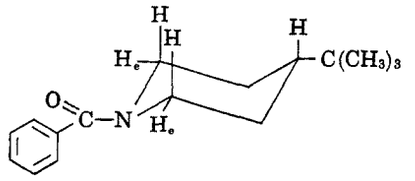
Anal. Calcd for $C_{18}H_{31}NO_3S$: C, 63.31; H, 9.15; N, 4.10. Found: C, 63.18; H, 9.19; N, 4.06.

A solution of 79.3 mg (0.51 mmole) of the amine **1** and 106 mg (0.56 mmole) of trideuteriomethyl *p*-toluenesulfonate[24a] in 2.5 ml of acetone was allowed to stand at room temperature for 3 days. After the reaction mixture had been concentrated, the residue was washed with ethyl acetate and recrystallized from methanol–ethyl acetate mixtures to separate 116.6 mg (66.3%) of the mixture of salts **7** and **8** as white plates, mp 182–183° dec. From the relative heights of the nmr[19] N-methyl peaks, this mixture was estimated to contain 87% of the salt **7** (N–Me peak at δ 3.09) and 13% of the salt **8** (N–Me peak at δ 2.97).

B. The N-Ethyl Derivative 2.—A solution of 8.400 g (62.2 mmoles) of 4-*t*-butylpyridine and 18.42 g (92 mmoles) of ethyl *p*-toluenesulfonate[25] in 80 ml of benzene was refluxed overnight and then concentrated. The residual white solid was recrystallized from chloroform–ether mixtures to separate 17.83 g (84.4%) of the crude **etho-*p*-toluenesulfonate of 4-*t*-butylpyridine** as white plates, mp 82–83°. A solution of 16.68 g (49.5 mmoles) of this salt in 100 ml of acetic acid was hydrogenated at room temperature and a pressure of 30 psi over the catalyst from 3.0 g of platinum oxide. After the rapid uptake of hydrogen (130 mmoles) ceased, the mixture was filtered, made basic with aqueous sodium hydroxide, and extracted with ether. The ethereal extract was dried, concentrated, and distilled to separate 6.032 g (71.8%) of the N-ethylamine **2** as a colorless liquid, bp 95° (19 mm), $n^{25}D$ 1.4532. The sample lacks infrared absorption[22] in the 3- or 6-μ region attributable to OH, NH, C=O, or C=C functions and has an nmr[23] singlet at δ 0.92 [9 H, $(CH_3)_3C-$] with a triplet (J = 7.5 cps) centered at δ 1.14 (3 H, methyl group of CH_3CH_2-N), a quartet (J = 7.5 cps) centered at δ 2.51 (2 H, methylene group of CH_3CH_2-N), and multiplets in the regions δ 2.9–3.5 (2 H) and 1.3–2.3 (7 H) attributable to the remaining aliphatic protons. The mass spectrum has a molecular ion peak at *m/e* 169 with abundant fragment peaks at *m/e* 168, 154, 112, 84, 70, 55, 42, and 41.

Anal. Calcd for $C_{11}H_{23}N$: C, 78.03; H, 13.69; N, 8.27. Found: C, 77.84; H, 13.63; N, 8.35.

C. The N-Benzyl Derivative 3.—A solution of 42.43 g (0.314 mole) of 4-*t*-butylpyridine in 150 ml of acetic acid was hydrogenated at 75° and a pressure of *ca.* 30 psi over 40 g of 5% palladium-on-carbon catalyst. After the hydrogen uptake ceased, the mixture was filtered, made basic with aqueous sodium hydroxide, and extracted with ether. The ethereal extract was dried, concentrated, and distilled to afford 11.29 g (25.4%) of 4-*t*-butylpiperidine as a colorless liquid, bp 83° (31 mm), $n^{25}D$ 1.4578 [lit.[21b] bp 70–75° (17 mm)]. This piperidine derivative has broad infrared absorption[22] in the region 3100–3400 cm^{-1} (associated N–H) with a molecular ion peak in the mass spectrum at *m/e* 141 accompanied by abundant fragment peaks at *m/e* 140, 126, 85, 57, 56, 55, 44, 43, 42, and 41. Because this amine reacted very rapidly on exposure to air (presumably with carbon dioxide), it was converted to the N-benzoyl derivative for further characterization. To a cold (0°) mixture of 11.005 g (81.7 mmoles) of 4-*t*-butylpiperidine and a solution of 14 g (350 mmoles) of sodium hydroxide in 30 ml of water was added, dropwise and with stirring over a 1-hr period and under a nitrogen atmosphere, 16.5 g (120 mmoles) of benzoyl chloride. The resulting mixture was stirred for 1 hr at room temperature and then filtered. The residual white solid was washed with water, taken up in ether, and combined with the ethereal extract of the aqueous phase. After the resulting ethereal solution had been dried and concentrated, the residual oil was subjected to a short-path distillation under reduced pressure. A solution of the distillate in 150 ml of concentrated hydrochloric acid was washed with ether and then made basic with aqueous sodium hydroxide and again extracted with ether. The latter ethereal extract was dried and concentrated to leave 11.005 g of the **1-benzoyl-4-*t*-butylpiperidine** which crystallized on standing: mp 51–52.5°. Recrystallization from pentane afforded the pure amide as white prisms, mp 50–51.5°. The amide has broad infrared absorption[22] at 1620 cm^{-1} (conjugated amide C=O) with nmr[23] singlets at δ 7.39 (5 H, aryl C–H) and 0.84 [9, H, $(CH_3)_3C-$] as well as a complex multiplet in the region δ 1.0–2.0 (5 H, aliphatic C–H), a broad complex multiplet (half-band width *ca.* 25 cps) centered at δ 2.79 (2 H, $-CH_2-N$), and a very broad peak (half-band width *ca.* 55 cps) centered at δ 4.26. This latter peak sharpened (half-band width *ca.* 35 cps) when the sample was warmed to 44°. When the sample was cooled to −20°, the lower field broad peak separated into two broad doublets (each with J = 13 cps and further coupling apparent but not resolved) centered at δ 4.80 and 3.82; the higher field broad multiplet (in the region δ 2.4–3.2) became more complex. These peaks are attributable to the methylene groups adjacent to nitrogen with the lower field absorption presumably arising from the two equatorial protons (H_e in structure **26**). At lower temperatures (*i.e.*, −20°) rotation about the C–N bond of the amide is



26

sufficiently slow that the two equatorial protons are shielded to different extents.

Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.47; H, 9.48; N, 5.63.

To a suspension of 2.6 g (68 mmoles) of lithium aluminum hydride in 40 ml of anhydrous ether was added, dropwise and with stirring over a 1-hr period and under a nitrogen atmosphere, a solution of 10.36 g (42.8 mmoles) of 1-benzoyl-4-*t*-butylpiperidine in 40 ml of ether. After the resulting mixture had been refluxed with stirring for 15 hr, it was cooled to 0° and 10 ml of water was added dropwise with stirring. The resulting mixture was made basic with aqueous sodium hydroxide and steam distilled. The distillate was acidified with hydrochloric acid, concentrated, made basic with sodium hydroxide, and extracted with ether. After the ethereal extract had been dried and concentrated, distillation of the residue afforded 6.033 g (61.1%) of the **N-benzylamine 3** as a colorless liquid, bp 175–180° (19 mm), $n^{25}D$ 1.5112. The product lacks infrared absorption[22] in the 3- or 6-μ regions attributable to OH, NH, or C=O functions and has a series of weak ultraviolet maxima[20] (ϵ 259 or less) in the region 250–270 mμ with intense end absorption. The nmr spectrum[23] has singlets at δ 3.45 (2 H, $N-CH_2-Ph$) and 0.80 [9 H, $(CH_3)_3C-$] with a peak centered at δ 7.32 (5 H, aryl C–H) and complex multiplets in the regions δ 2.7–3.2 (2 H) and 1.0–2.2 (7 H) attributable to aliphatic protons. The mass spectrum has a molecular ion peak at *m/e* 231 with abundant fragment peaks at *m/e* 230, 216, 154, 140, 92, 91, 55, 42, and 41.

Anal. Calcd for $C_{16}H_{25}N$: C, 83.05; H, 10.89; N, 6.05. Found: C, 83.14; H, 10.95; N, 6.04.

Preparation of the 1-Ethyl-1-methyl-4-*t*-butylpiperidinium Salts 9 and 10. A. From the N-Methylamine 1.—A solution of 508 mg (3.28 mmoles) of the amine **1** and 669.8 mg (3.35 mmoles) of ethyl *p*-toluenesulfonate in 2.83 g of acetone was allowed to stand for 3 days at 25° and then concentrated. The crude mixture of quaternary ammonium salts[26] which remained was estimated from the peak heights of the nmr N-methyl peaks to contain 83% of the salt **9** (N–Me peak at δ 2.92) and 17% of the salt **10** (N–Me peak at δ 2.84). From a comparable reaction of 1.434 g (9.26 mmoles) of the amine **1** with 1.987 g (9.91 mmoles) of ethyl *p*-toluenesulfonate, the crude product was washed with ethyl acetate to leave 1.679 g (50.8%) of the mixture of quaternary salts. Fractional recrystallization of this mixture from chloroform–ether mixtures separated 423.8 mg of the pure major component, **quaternary salt 9**, as white plates, mp 158–159° dec; the composition of this material indicated that it crystallized as a stable hemihydrate. The sample has broad infrared absorption[22] at 3400 cm^{-1} (OH from water of hydration) with nmr singlets[19] at δ 2.92 (3 H, $N-CH_3$), 2.36 (3 H, aryl CH_3-C), and 0.85 [9 H, $(CH_3)_3C-$] as well as multiplets in the regions δ 7.2–8.0 (4 H, aryl C–H), 2.9–3.7 (6 H, $-CH_2-N$), and 1.0–2.2 (8 H, aliphatic C–H).

Anal. Calcd for $C_{19}H_{33}NO_3S \cdot 0.5H_2O$: C, 62.63; H, 9.34; N, 3.83. Found: C, 62.61; H, 9.35; N, 3.78.

(25) The ethyl *p*-toluenesulfonate, mp 31–32° (lit. mp 32°), was prepared as previously described: R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).

(26) Analysis by thin layer chromatography with a silicic acid adsorbent and a chloroform–methanol mixture as an eluent demonstrated the absence of the starting amine in this crude product.

B. From the N-Ethylamine 2.—A solution of 5.741 g (23.9 mmoles) of the N-ethylamine **2** and 9.443 g (50.8 mmoles) of methyl *p*-toluenesulfonate in 40 ml of acetone was stirred at 25° for 15 hr and then concentrated. From the nmr spectrum[19] of the crude crystalline product (11.116 g),[26] the composition was estimated to be 20% of the salt **9** (N-Me peak at δ 2.92) and 80% of the salt **10** (N-Me peak at δ 2.84). Fractional recrystallization of this mixture of salts from chloroform–ether mixtures separated 932.8 mg of the major product, the pure **quaternary salt 10**, as white plates, mp 201–202° dec. This product has nmr[19] singlets at δ 2.84 (3 H, N-CH_3), 2.40 (3 H, aryl CH_3-C), and 0.85 [9 H, $(CH_3)_3$C-] with multiplets in the regions δ 7.2–8.0 (4 H, aryl C-H), 2.9–3.6 (6 H, N-CH_2-), and 1.0–2.0 (8 H, aliphatic C-H).

Anal. Calcd for $C_{19}H_{33}NO_3S$: C, 64.20; H, 9.36; N, 3.94. Found: C, 64.13; H, 9.31; N, 3.81.

Preparation of the 1-Benzyl-1-methyl-4-*t*-butylpiperidinium Salts 11 and 12. A. From the N-Methylamine 1.—A solution of 507.8 mg (3.27 mmoles) of the amine **1** and 1.0 g (3.8 mmoles) of benzyl *p*-toluenesulfonate[27] in 2.71 g of acetone was allowed to stand at 25° for 3 days and then concentrated. From the relative heights of the nmr[23] N-methyl peaks and *t*-butyl peaks, the the crude product[26] was estimated to contain 69% of the salt **11** (N-Me peak at δ 3.01 and *t*-Bu peak at δ 0.80) and 31% of the salt **12** (N-Me peak at δ 2.91 and *t*-Bu peak at δ 0.72). From a comparable reaction employing 554.4 mg (3.57 mmoles) of the amine **1** and 1.056 g (4.0 mmoles) of benzyl *p*-toluenesulfonate, the crude product was washed repeatedly with ethyl acetate to leave the pure major isomer, **quaternary salt 11**, as white plates, mp 157.5–159° dec, yield 834.9 mg (56.2%). Attempts to separate a pure sample of the minor isomer from the mother liquors were not successful. The salt **11** has a series of weak ultraviolet maxima[20] (ε 563–713) in the region 250–270 mμ with intense end absorption and nmr[23] singlets at δ 3.01 (3 H, N-CH_3), 2.25 (3 H, aryl CH_2-C), and 0.80 [9 H, $(CH_3)_3$C-] as well as a broad unsplit peak at δ 4.47 (2 H, N-CH_2-Ph) and multiplets in the regions δ 6.9–7.9 (9 H, aryl C-H), 3.2–3.7 (4 H, -CH_2-N), and 1.0–2.0 (5 H, aliphatic C-H).

Anal. Calcd for $C_{24}H_{35}NO_3S$: C, 69.03; H, 8.45; N, 3.35. Found: C, 68.75; H, 8.46; N, 3.24.

B. From the N-Benzylamine 3.—A solution of 4.969 g (24.5 mmoles) of the amine **3** and 6.994 g (37.6 mmoles) of methyl *p*-toluenesulfonate in 25 ml of acetone was stirred for 12 hr at 25° and then concentrated. From the nmr spectrum[23] of the crude product (10.05 g),[26] the composition was estimated to be 85% of the salt **12** (N-Me peak at δ 2.91 and *t*-Bu peak at δ 0.72) and 15% of the salt **11** (N-Me peak at δ 3.01 and *t*-Bu peak at δ 0.80). Fractional recrystallization of this crude mixture of salts from an ether–chloroform mixture separated 1.536 g (15%) of the major isomer present, the **quaternary salt 12**, as white plates, mp 177.5–179° dec. The product has weak ultraviolet maxima[20] (ε 572–718) in the region 250–270 mμ with intense end absorption. The nmr spectrum[23] has singlets at δ 2.91 (3 H, N-CH_3), 2.25 (3 H, aryl CH_3), and 0.72 [9 H, $(CH_3)_3$C-] with a broad unsplit peak at δ 4.83 (2 H, N-CH_2-Ph) and multiplets in the regions δ 6.9–7.9 (9 H, aryl C-H), 3.2–3.7 (4 H, -CH_2-N), and 1.0–2.0 (5 H, aliphatic C-H).

Anal. Calcd for $C_{24}H_{35}NO_3S$: C, 69.03; H, 8.45; N, 3.35. Found: C, 68.72; H, 8.39; N, 3.22.

Preparation of the 1-Carbomethoxymethyl-1-methyl-4-hydroxy-4-*t*-butylpiperidinium Salts 14 and 15.—A solution of 1.003 g (6.03 mmoles) of the amine **4** and 1.00 g (6.54 mmoles) of methyl bromoacetate in 10 ml of acetone was stirred for 24 hr at 25°. At the end of this period the crystalline precipitate, which began to form immediately after the reactants were mixed, was collected and recrystallized from ethanol. The **quaternary salt 14** separated as 987.5 mg (50.7%) of white plates, mp 215–218° dec. The product has infrared absorption[18,28] at 3380 (associated O-H) and 1750 cm^{-1} (ester C=O). Attempts to examine the absorption of dilute solutions[29] of this salt **14** in the 3-μ region of the infrared were complicated by the insolubility of the substance; however, a saturated solution[29] did exhibit absorption at 3370 cm^{-1} attributable to an associated O-H function. The sample has nmr[19] singlets at δ 4.32 (2 H, N-CH_2-CO-), 3.88 (3 H, O-CH_3), 3.36 (3 H, N-CH_3), and 0.95 [9 H, $(CH_3)_3$C-] with multiplets in the regions δ 3.5–3.9 (4 H, -CH_2-N) and 1.6–2.5 (4 H, aliphatic C-H).

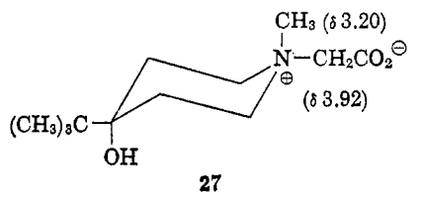
Anal. Calcd for $C_{12}H_{26}BrNO_3$: C, 48.16; H, 8.03; N, 4.32. Found: C, 47.94; H, 8.10; N, 4.11.

The mother liquors remaining after the separation of the salt **14** were concentrated and diluted with ether to precipitate 980 mg of crystalline salt. Recrystallization from ethanol afforded 826.3 mg (44%) of the **quaternary salt 15** as white plates, mp 149–151°. When the molten solid was heated, it resolidified at *ca.* 180° and then remelted at 210–220°. The material has infrared absorption[18,28] at 3425, 3360 (associated O-H), and 1750 cm^{-1} (ester C=O). A saturated solution (less than 0.005 *M*) in carbon disulfide still exhibited absorption at 3360 and 3425 cm^{-1} (associated O-H). Dilute solutions (0.009–0.0006 *M*) of this salt **15** in chloroform all have infrared bands at 3590 and 3370 cm^{-1} which appear to be attributable to unassociated and associated O-H functions. Hence, these measurements allow no clear decision as to whether one of the two salts **14** and **15** exhibits intramolecular hydrogen bonding. The product exhibits nmr[19] singlets at δ 4.40 (2 H, N-CH_2-CO-), 3.87 (3 H, OCH_3), 3.24 (3 H, N-CH_3), and 0.95 [9 H, $(CH_3)_3$C-] with multiplets in the region δ 3.5–3.9 (4 H, -CH_2-N) and 1.5–2.5 (4 H, aliphatic C-H).

Anal. Calcd for $C_{12}H_{26}BrNO_3$: C, 48.16; H, 8.03; N, 4.32. Found: C, 47.91; H, 8.14; N, 4.04.

In a comparable alkylation reaction, the solvent was distilled from the mixture, and the nmr spectrum was determined on the total crude mixture of salts. From the relative heights of the N-methyl peaks and the N-CH_2-CO peaks, the crude product was estimated to contain 54% of the salt **15** (N-Me peak at δ 3.24 and N-CH_2-CO peak at δ 4.40) and 46% of the salt **14** (N-Me peak at δ 3.36 and N-CH_2-CO peak at δ 4.32).

A variety of attempts to lactonize the ester **15** resulted either in recovery of the starting material or in conversion to a new material believed to be the betaine **27**. For example, a solution of 84 mg of the ester **15** and several milligrams of *p*-toluenesulfonic



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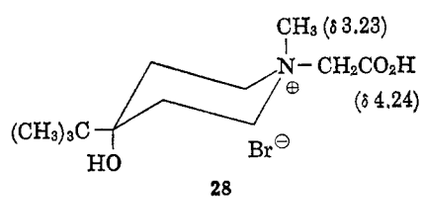

28

acid in 1,2-dimethoxyethane was refluxed for 4 hr and then concentrated and diluted with ether. The product, believed to be the betaine **27**, separated as white plates, mp 215–220° dec. This material has infrared absorption[28] at 3250 (associated O-H), 1640, and 1610 cm^{-1} (carboxylate ion) with no absorption in the region 1700–1800 cm^{-1} (ester or lactone C=O). The nmr spectrum[19] has singlets at δ 3.92 (2 H, N-CH_2-CO), 3.20 (3 H, CH_3-N), and 0.96 [9 H, $(CH_3)_3$C-] with multiplets in the regions δ 3.4–3.8 (4 H, -CH_2-N) and 1.4–2.4 (4 H, aliphatic C-H). A product, mp 215–220° dec, with comparable infrared absorption was obtained in 87% yield from reaction of the ester **15** with an aqueous suspension of silver oxide. Also, a sample of the ester **15** which had been heated to 170° for 5 min was then found to melt with decomposition in the range 215–225°; this sample had infrared absorption[28] at 1750 and at 1640 and 1610 cm^{-1} attributable to the starting ester **15** and to the betaine **27**, respectively. Treatment of a 200-mg sample of the betaine **27**, mp 215–220°, with hydrogen bromide in acetone solution followed by concentration of the solvents and recrystallization of the residue from ethanol afforded 250 mg of white crystals, which melted at 205–210° and then resolidified and remelted at 232°. This product, believed to be the acid **28**, has infrared absorption[28] at 3350 (associated O-H), 2800 (very broad, associated carboxyl O-H), and 1740 cm^{-1} (carboxyl C=O) as well as nmr[19] singlets at δ 4.24 (2 H, N-CH_2-CO), 3.23 (3 H, N-CH_3), and 0.98 [9 H, $(CH_3)_3$C-] with multiplets in the regions

(27) The benzyl *p*-toluenesulfonate, mp 53–55° (lit.[25] mp 55°), was prepared as previously described.[25]

(28) Determined as a mull in perfluorokerosene.

(29) Determined as a solution in carbon disulfide.

δ 3.4–3.8 (4 H, $-CH_2-N$) and 1.5–2.4 (4 H, aliphatic C–H). A variety of efforts to convert this sample to the lactone **17** were unsuccessful.

Preparation of the Lactone 17.—To a solution containing 1.0 mmole of *t*-butyllithium in 58 ml of pentane was added, dropwise and with stirring over a 10-min period, a solution of 1.786 g (1.09 mmoles) of the amino alcohol **4** in 25 ml of pentane. Then a solution of 2.02 g (1.0 mmole) of bromoacetyl bromide in 25 ml of pentane was added, dropwise and with stirring over a 10-min period, to the suspension of the lithium alkoxide. The resulting mixture was diluted with pentane to 200 ml and 1.0 g of solid sodium bicarbonate was added. The reaction mixture was stirred for an additional 5 min and then filtered and the residue was washed with ether. After the combined pentane solutions had been dried and concentrated, the crude residue was heated in 200 ml of refluxing acetonitrile for 15 hr. The resulting mixture was diluted with ether to precipitate 105 mg (3.6%) of the lactone **17**, mp 235–238° dec. Recrystallization from ethanol afforded the pure **lactone 17** as white prisms, mp 239–240° dec, with infrared absorption[18,28] at 1740 cm^{-1} (δ-lactone C=O) but no absorption in the 3-μ region attributable to an O–H function. The material has nmr[30] singlets at δ 4.87 (2 H, $N-CH_2-CO$), 3.25 (3 H, $N-CH_3$), and 0.98 [9 H, $(CH_3)_3C-$] with triplets (J = 7 cps) centered at δ 3.85 (4 H, $-CH_2-N$) and 2.36 (4 H, $-CH_2-\overset{|}{C}-O$). Solutions of the lactone **17** in deuterium oxide were obtained only when this solvent was heated; the nmr spectra of these solutions corresponded to the spectrum described above except that the peak at lowest field (δ 4.87) was lacking. Consequently, the hydrogen–deuterium exchange, $N-CH_2-CO- \rightarrow N-CD_2-CO-$, must occur relatively rapidly.

(30) Determined as a solution in perdeuteriodimethyl sulfoxide.

Anal. Calcd for $C_{12}H_{22}BrNO_2$: C, 49.32; H, 7.53; Br, 27.40; N, 4.79. Found: C, 49.30; H, 7.48; Br, 27.60; N, 4.50.

Because of the low yield of the lactone **17**, the nature of the remaining products of this reaction was examined briefly. Concentration of the acetonitrile–ether mother liquors remaining after precipitation of the lactone left 920 mg of gummy solid which exhibited no infrared absorption[22] in the 1700–1800-cm^{-1} region attributable to ester or lactone functions. The water-insoluble material (678 mg) obtained from the residue left after filtration of the original reaction mixture exhibited infrared absorption[22] of medium intensity at 1740 cm^{-1} and appeared to be a mixture of a lactone or ester and some other component.

A solution of 42.3 mg (0.185 mmole) of the lactone **17** in 10 ml of methanol containing several milligrams of sodium methoxide was refluxed for 15 hr and then cooled and acidified by the addition of 1 drop of aqueous 48% hydrobromic acid. After the resulting solution had been concentrated and then diluted with ether, the gummy precipitate which separated was collected and found to contain[31] the hydroxy ester **15** but not the lactone **17**. Recrystallization of the crude product from ethanol afforded 24 mg (51%) of the hydroxy ester **15**, mp 148–150° dec, which was identified with the previously described sample by a mixture melting point determination and by comparison of infrared spectra. An appropriate control experiment demonstrated that the stereoisomeric hydroxy ester **14** (mp 215–218°) was not isomerized to ester **15** but rather recovered unchanged (70% recovery) after treatment with refluxing methanol containing several milligrams of sodium methoxide.

(31) A thin layer chromatographic plate coated with silicic acid was employed for this analysis. The eluent was a mixture of chloroform–methanol–concentrated hydrochloric acid (12:12:1 v/v).

Synthesis and Thermal Stability of 1,2-Diazetidinones. Reaction of Diphenylketene with Substituted Azobenzenes[1a]

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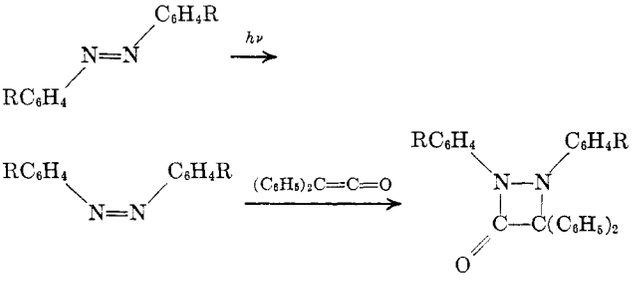
Several *cis-p,p'*-disubstituted azobenzenes have been generated *in situ* and reacted with diphenylketene to give tetraaryl-1,2-diazetidinones. Some of the problems encountered in the condensation are discussed. The decomposition of tetraphenyl-1,2-diazetidinone into phenyl isocyanate and benzophenone anil is promoted by placing strong electron-donating groups into the *para* positions of the N-1 and N-2 phenyl groups. This effect is interpreted to mean that the decomposition proceeds by initial homolytic cleavage of the N–N bond.

The formation of a 1,2-diazetidinone by reaction of a ketene with an azo compound was first reported by Ingold and Weaver.[2] They treated ethyl phenylazocarboxylate with diphenylketene and obtained a compound which was later identified by Bird[3] as ethyl 2,4,4-triphenyl-1,2-diazetidinone-1-carboxylate. Since the initial report several other workers[4–7] have studied this reaction. Cook and Jones[4] studied the reaction of diphenylketene with azobenzene and discovered that *cis*-azobenzene reacted rapidly with diphenylketene at room temperature to give tetraphenyl-1,2-diazetidinone. In contrast, *trans*-azobenzene did not react with diphenylketene at room temperature and only very slowly at 125–130°.

In order to determine what effect substituents have on the reaction of azobenzene with ketenes, a series of symmetrically substituted azobenzenes have been prepared and then allowed to react with diphenylketene. The technique used in carrying out these reactions was that developed by Cook and Jones[4] in which the *trans*-azobenzene and diphenylketene are dissolved in a suitable solvent and irradiated with ultraviolet light. In this way, the *trans*-azobenzene is converted to the *cis*-azobenzene, which then reacts with the diphenylketene. Ideally, the color of the azobenzene is discharged during the irradiation and



(1) (a) This work was supported in part by a grant from Research Corporation to Kansas State Teachers College. (b) To whom inquiries should be addressed: Southern Illinois University. (c) Undergraduate Research Assistant, 1960–1961, at Kansas State Teachers College.

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