A Study of Some Octahydroimidazo[1,5-*a*]pyridines. A New Example of Ring-Chain Tautomerism.

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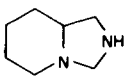
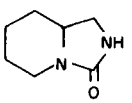
A series of 3-substituted octahydroimidazo[1,5-*a*]pyridines has been prepared. An nmr study at several temperatures showed that 3-phenyloctahydroimidazo[1,5-*a*]pyridine (XIII) and 3-*t*-butyloctahydroimidazo[1,5-*a*]pyridine (XIV) exhibited ring-chain tautomerism. The *n*-propyl (X), isopropyl (XI) and benzyl (XII) derivatives did not show this form of isomerism. It has also been shown that Crabb and Newton's statement (3) that Freed and Day (1) had failed to obtain the parent compound, octahydroimidazo[1,5-*a*]pyridine (1), is incorrect.

Octahydroimidazo[1,5-*a*]pyridine (I) was prepared by Freed and Day in 1960 (1). The synthesis of the ring system by another route was reported by Winterfeld in the same year (2). Winterfeld and co-workers investigated primarily the oxo forms (II and III) of the ring system. They did prepare compound I by another method, however, which will be discussed later.



I



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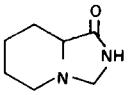
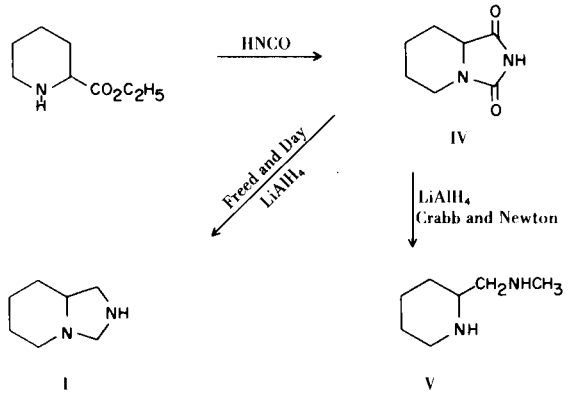


III

Originally it had been our plan to prepare a number of alkylated derivatives of I and study their ring-chain tautomeric nature. While this work was in progress Crabb and Newton (3) challenged the synthesis of octahydroimidazo-[1,5-*a*]pyridine by the method originated by Freed and Day. They repeated the work of Freed and Day, reacting ethyl 2-piperidinecarboxylate with isocyanic acid to obtain the octahydroimidazo[1,5-*a*]pyridine-1,3-dione (IV) reported in reference (1). They claimed, however, that the product of reduction with lithium aluminum hydride was not octahydroimidazo[1,5-*a*]pyridine but 2-methylaminomethylpiperidine (V) (See Scheme 1).

Scheme I



I V

The evidence presented by Crabb and Newton for 2-methylaminomethylpiperidine was convincing:

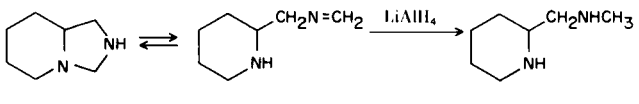
(a) correct analytical data.

(b) an N–CH_3 peak in the nmr spectrum at 7.59 τ (δ 2.43).

(c) the nmr and ir spectra were identical with those of an authentic sample of V.

(d) lack of depression of the melting point when the phenylurea derivatives of the reaction product and an authentic sample of 2-methylaminomethylpiperidine were mixed together.

In spite of the convincing nature of these data, we felt that the earlier data (1) were also convincing. At this point it seemed obvious to us that Crabb and Newton had overlooked the theoretically possible ring-chain tautomeric nature of octahydroimidazo[1,5-*a*]pyridine which could be activated by the lithium aluminum hydride.



I V

It would appear that either I or V, or both, could be obtained from IV by reduction with lithium aluminum hydride and the relative amounts should depend on reduction time and other reaction conditions.

To categorically state (3) that the previous workers (1) had not obtained octahydroimidazo[1,5-*a*]pyridine

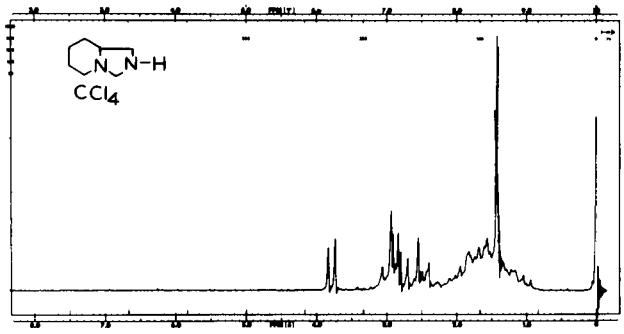


Figure 1

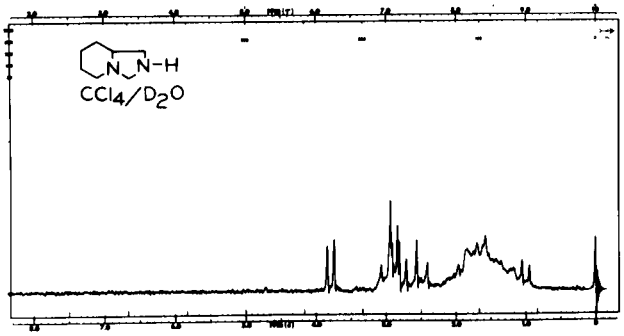


Figure 2

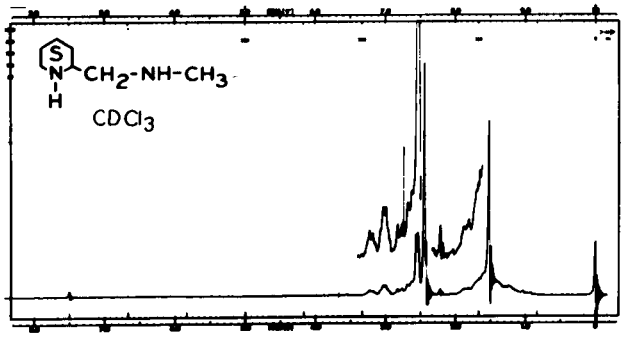


Figure 3

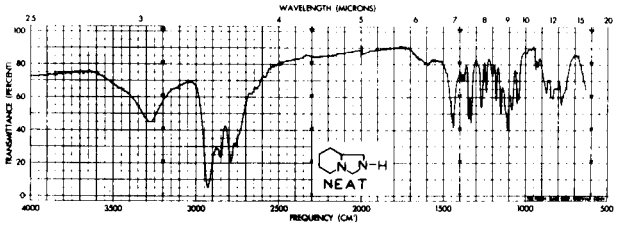


Figure 4

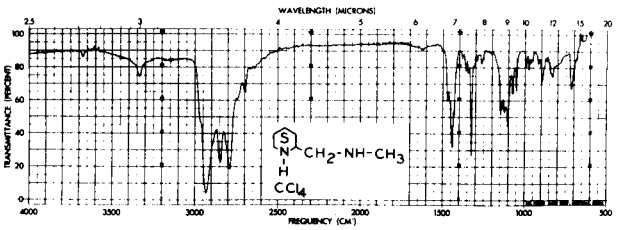


Figure 5

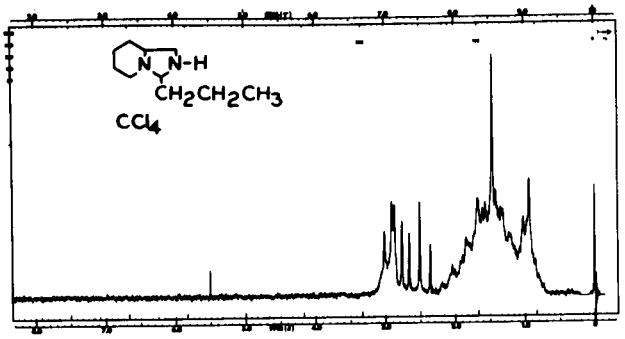


Figure 6

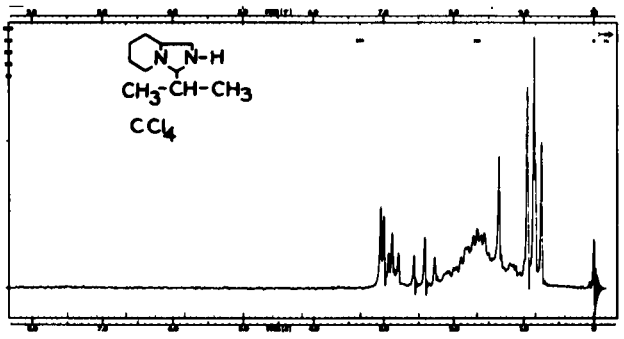


Figure 7

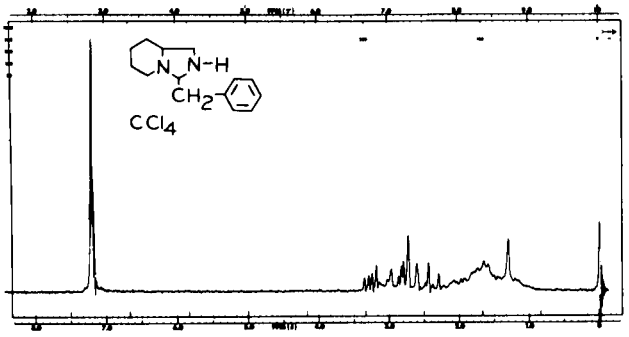


Figure 8

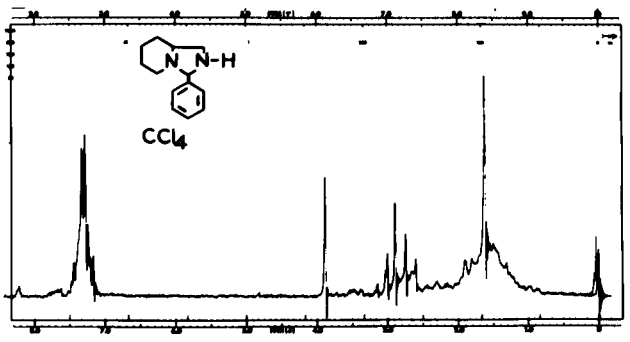


Figure 9

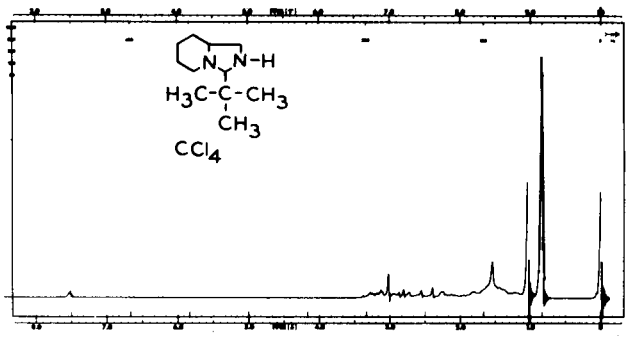
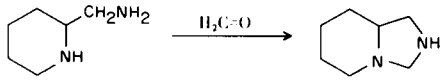


Figure 10

appeared to us to be unreasonable. Therefore, it was decided to repeat the synthesis of octahydroimidazo[1,5-*a*]pyridine by Freed and Day's method (1) and by Winterfeld's method (2) using a formaldehyde condensation (Scheme 2).

Scheme 2



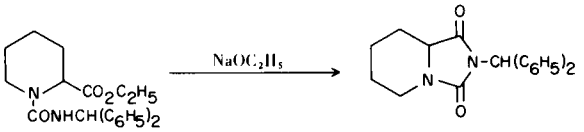
The products of these two reactions were compared with each other and with an authentic sample of 2-methylaminomethylpiperidine. Incidentally, Crabb and Newton (3) claimed that the condensation of 2-aminomethylpiperidine with formaldehyde gave only polymeric material. They did not refer to Winterfeld's article which reported the successful synthesis of octahydroimidazo[1,5-*a*]pyridine by this condensation.

The analysis for the products, obtained from both methods, agreed with the values calculated for octahydroimidazo[1,5-*a*]pyridine. The nmr spectrum of the compound from the method of Freed and Day did not show a N–CH_3 peak at 7.57 τ (δ 2.43) as reported by Crabb and Newton (See Figure 1). It did show a N–H singlet at δ 1.14 (1H). The spectrum integrated for the correct number of protons. The nmr spectrum with deuterium oxide (Figure 2) showed the loss of only one N–H which eliminates 2-methylaminomethylpiperidine as the product since it contains two N–H bonds. The nmr spectrum of the product obtained by Winterfeld's method was identical with that obtained from Freed and Day's method. The nmr spectrum for an authentic sample of 2-methylaminomethylpiperidine integrated correctly and exhibited a N–CH_3 peak at 7.56 τ (δ 2.44) as reported by Crabb and Newton (Figure 3). The two samples of octahydroimidazo[1,5-*a*]pyridine had identical infrared spectra (Figure 4) which were clearly different from the infrared spectrum of 2-methylaminomethylpiperidine (Figure 5).

Work in this laboratory indicated that the length of time that the reaction mixture was heated with lithium aluminum hydride was important. When the reflux time was increased from the eight hours, used by Freed and Day, to twenty-four hours, no significant change in yield (approximately 26%) was noted. When the reflux time was changed to seventeen hours, the yield was increased to 50%. Obviously, even better yields of primary product (I) might be possible if the optimum time of refluxing had been determined. In no case was starting material recovered. Under our reaction conditions compound V was not isolated. Crabb and Newton's failure to repeat Winterfeld's synthesis remains unexplained. In our hands it worked.

Attempts to prepare *N*-alkyl derivatives of I, by direct alkylation methods, failed. However, starting material was not recovered. It has been previously demonstrated that compound I is rapidly cleaved by acids to yield 2-aminomethylpiperidine (1). Alkylating agents would form similar onium intermediates and probably induce the same type of cleavage. Consequently we turned to other methods.

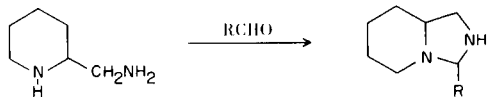
It had been demonstrated earlier (1) that ethyl-2-piperidinecarboxylate reacted with ethyl and butyl isocyanates to form the corresponding 2-ethyl and 2-butyl octahydroimidazo[1,5-*a*]pyridine-1,3-diones. The latter were reduced with lithium aluminum hydride to form 2-ethyl and 2-butyloctahydroimidazo[1,5-*a*]pyridines, respectively (VI and VII). When this procedure was carried out with diphenylmethyl isocyanate, the reaction stopped with the formation of the open-chain urea derivative (VIII). Compound VIII was cyclized to 2-diphenylmethyloctahydroimidazo[1,5-*a*]pyridine-1,3-dione (IX) by heating with sodium ethoxide in ethanol.



VIII IX

The ir and nmr spectra clearly distinguished these compounds (see experimental). All attempts to reduce IX with lithium aluminum hydride failed. Because of this failure to reduce IX we decided to extend Winterfeld's procedure in order to obtain a number of 3-substituted octahydroimidazo[1,5-*a*]pyridines for our study.

2-Aminomethylpiperidine was reacted with the following aldehydes: ethanal, butanal, 2-methylpropanal, phenylethanal, benzaldehyde and 2,2-dimethylpropanal. Only ethanal failed to give the desired product. It yielded a complex mixture of compounds which could neither be separated nor identified.

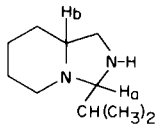


(R $CH_3CH_2CH_2$ (X), $(CH_3)_2CH$ (XI), $C_6H_5CH_2$ (XII), C_6H_5 (XIII) and $(CH_3)_3C$ (XIV).

3-Butyloctahydroimidazo[1,5-*a*]pyridine and 3-phenyloctahydroimidazo[1,5-*a*]pyridine exhibited ring-chain tautomerism whereas the 3-propyl, 3-isopropyl and 3-benzyl derivatives did not. This was determined largely through a study of the nmr spectra of these compounds (Figures 6,7,8,9 and 10, respectively).

The nmr spectrum of 3-propyloctahydroimidazo[1,5-*a*]pyridine (X) (Figure 6) showed a singlet at δ 1.46 (1H) for the N–H group. This was determined by a deuterium exchange experiment which showed only one N–H bond to be present.

The nmr spectrum of 3-isopropyloctahydroimidazo-[1,5-*a*]pyridine (XI) (Figure 7)

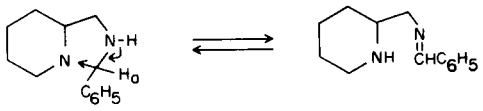


XI

showed a singlet at δ 1.35 (1H) for the N–H group. The "a" proton gave a multiplet centered at δ 3.02 (1H) and the "b" proton gave a triplet at δ 2.41 (1H, J = 9.0 Hz). The methyl groups gave a pair of doublets at δ 0.90 and δ 0.79 (6H, J = 5.4 Hz). The methyl groups were split by the asymmetric center to which the isopropyl group is attached. An nmr spectrum in dichlorobenzene at 140° showed no change which indicated that the splitting was due to the asymmetric center and not to conformational isomerism. Temperatures greater than 140° could not be used because of decomposition of the compound. Splitting caused by asymmetric centers has been reported frequently in the literature (4).

The nmr spectrum of 3-benzyloctahydroimidazo[1,5-*a*]-pyridine (XII) (Figure 8) showed a singlet at δ 1.30 (1H) for the N–H group. The "a" proton appeared to give the X part (centered at δ 3.26) of an ABX pattern. This is probably due to the fact that the asymmetric center, to which the benzyl group is attached, caused the benzyl protons (CH_2) to be non-equivalent.

The nmr spectrum of 3-phenyloctahydroimidazo[1,5-*a*]-pyridine (XIII) (Figure 9) showed a singlet at δ 1.62 (1H) for the N–H group. The "a" proton gave a singlet at δ 3.88 (1H). The phenyl protons gave two multiplets centered at δ 7.33 and δ 7.71 (5H). Another multiplet centered at δ 8.23 was observed. It integrated for less than one proton but its small size prevented accurate measurement. The nmr spectrum of the phenyl derivative was then measured at 43°, 80°, 100° and 120° (higher temperatures caused decomposition). The phenyl multiplet at δ 7.33 progressively grew smaller as the temperature increased while the phenyl multiplet at δ 7.71 grew larger. The ratio of the larger phenyl multiplet to the smaller one changed from 21.9:1 at 43° to 5.33:1 at 120°. At 120° the phenyl multiplets had not moved towards each other but remained fixed. On cooling from 120° to 43° the ratio returned to 21.9:1. These data rule out two of three possible explanations. The splitting was not caused by the asymmetric center since the ratio changed with the temperature. Furthermore it was not caused by conformational isomerism since the peaks did not move at all with increasing temperature. A third explanation of the data would be that a chemical change was taking place. The fact that the ratios of the multiplets returned to their original values, after cooling, required that the chemical change be reversible. This is satisfied by the following equilibrium:



XIII

Further study of the nmr spectrum of XIII gave more evidence for this suggestion. The small multiplet at δ 8.23 occurred in the region where the C–H of Schiff bases is known to absorb. Furthermore the data showed that the ratio of the larger phenyl multiplet (δ 7.33) to the Schiff base C–H multiplet at δ 8.23 changed from 49.8:1 at 43° to 14.8:1 at 120°. The percent of cyclic structure decreases with increase in temperature and the percent of Schiff base increases. The multiplet at δ 7.33, therefore, was assigned to the phenyl group of the cyclic form and the multiplet at δ 7.71 was assigned to the phenyl group

of the open-chain structure. The ratio of the open-chain phenyl group to the Schiff base (C—H) would be expected to remain constant at 5:1 and this was observed.

Further evidence for the ring-chain tautomerism of XIII is supplied by the absorption of the "a" proton at δ 3.88. This decreased, as the temperature was increased, by the same percentage as the ring phenyl group (phenyl 15%, "a" proton 18%). The ir spectrum of XIII gave an additional bit of evidence. A small but definite Schiff base peak was observed at 1644 cm^{-1}. The ratio of the open-chain phenyl multiplet to the ring phenyl multiplet, in dimethyl sulfoxide at 43°, indicated that the open-chain isomer existed in equilibrium with the ring isomer in a 5:95% ratio.

A similar ring-chain tautomerism was observed for 3-*t*-butyloctahydroimidazo[1,5-*a*]pyridine (XIV). The nmr spectrum for XIV (Figure 10) showed a singlet at δ 1.54 (1H) for the N—H group. The methyl groups, of the *t*-butyl group gave two singlets at δ 1.05 and δ 0.85. Heating the compound to 140° in 1,2-dichlorobenzene and examining its nmr spectrum showed that the ratio of the peak at δ 0.85 to the peak δ 1.05 had changed from 2:1 to 1:2. The peaks did not move towards each other nor did they broaden. Upon cooling the original ratio was restored. In this spectrum the Schiff base multiplet was observed at δ 7.53. As in the previous nmr spectra, the spectrum integrated correctly for the total number of protons present. Finally the ir spectrum showed a Schiff base peak at 1665 cm^{-1}. The ratio of the open-chain butyl peak to the ring butyl peak indicated that the open-chain isomer was in equilibrium with the ring isomer in a 33:67% ratio at 43°.

The fact that only the 3-phenyl and 3-*t*-butyl derivatives exhibited ring-chain tautomerism may be explained by the presence of greater electron-release forces which facilitate the ring opening, *i.e.* $C_6H_5-\overset{|}{C}H\rightarrow\overset{|}{N}-$ and $(CH_3)_3C-\overset{|}{C}H\rightarrow\overset{|}{N}-$.

An nmr study of the unsubstituted octahydroimidazo-[1,5-*a*]pyridine (I) gave no evidence for ring-chain tautomerism when carried out below decomposition temperatures

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 521 double beam spectrophotometer NMR spectra were mesaured on a Varian Associates A-60A spectrometer and chemical shifts are expressed in parts per million downfield from tetramethylsilane as a standard. Mass spectra were obtained on a Consolidated Electrodynamics Corporation 32-130 spectrometer.

Octahydroimidazo[1,5-*a*]pyridine (I).

Method A- from ethyl 2-piperidinecarboxylate and cyanic acid followed by reduction with lithium aluminum hydride (1), yield 50%, b.p. 59-61° (3mm), n_D^{25} 1.4700. The nmr and ir spectra are shown in Figures 1 and 4, respectively.

Anal. Calcd. for $C_7H_{14}N_2$: C, 66.62; H, 11.18; N, 22.20; mol. wt. 126. Found: C, 66.46; H, 11.14; N, 22.36; mol. wt. 126 (mass spectrum).

Method B- from 2-aminomethylpiperidine and formaldehyde (2), yield 63%, b.p. 60° (3mm), n_D^{25} 1.4702. The nmr and ir spectra were identical with those shown in Figures 1 and 4.

Anal. Calcd. for $C_7H_{14}N_2$: C, 66.62; H, 11.18; N, 22.20; mol. wt. 126. Found: C, 66.42; H, 11.37; N, 22.00; mol. wt. 126.

2-Methylaminomethylpiperidine (V).

2-Methylaminomethylpyridine (5) (12.11 g., 0.1 mole) in 40 ml. of acetic acid was hydrogenated over platinum oxide at 5 atmospheres (20 hours). After removing the catalyst, the acetic acid was removed under reduced pressure. The residue was dissolved in 15 ml. of water and cooled to 5°. The solution was adjusted to *p*H 8 with 40% potassium hydroxide while keeping the temperature below 10°. The aqueous solution was extracted with five 20 ml. portions of chloroform. The solution was then adjusted to *p*H 11 and extracted again and the combined extracts dried (sodium sulfate). The chloroform was removed under reduced pressure. The residual oil was fractionated at 4.1 mm. and the fraction boiling at 66-66.5° was collected, yield 67%. A vapor phase chromatogram showed only one peak. The vpca were carried out on a F and M Model 700 chromatograph with thermal conductivity detector. The helium gas had a flow rate of 60 ml./min. The 8 ft. long, ¼ in. OD column was packed with 10% silicone F6-1265 on 60-80 W. 700. The nmr and ir spectra are shown in Figures 3 and 5, respectively.

Anal. Calcd. for $C_7H_{16}N$: C, 73.61; H, 14.12; N, 12.25. Found: C, 73.52; H, 14.30; N, 12.20.

Attempted Alkylation of Octahydroimidazo[1,5-*a*]pyridine (I) with Benzhydryl Bromide.

A variety of conditions were tried: (a) benzhydryl bromide in liquid ammonia (6); (b) sodium hydride and benzhydryl bromide in tetrahydrofuran; and (c) benzhydryl bromide and triethylamine in acetone. Only resinous material was obtained.

Reactions of Ethyl 2-Piperidinecarboxylate (7,8) with Isocyanates. Ethyl 1-[(Diphenylmethyl)carbamoyl]-2-piperidinecarboxylate (VIII).

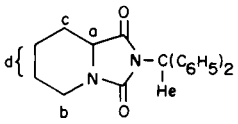
Ethyl 2-piperidinecarboxylate (3.14 g., 0.02 mole) was dissolved in 40 ml. of petroleum ether (100-115°). Diphenylmethyl isocyanate (9) (4.18 g., 0.02 mole) dissolved in 30 ml. of petroleum ether, was added to the solution of the ester dropwise over a 90 minute period. The colorless precipitate which formed was collected and recrystallized from ethanol, yield 7 g. (94%), m.p. 171.5-173°. The ir spectrum (potassium bromide) showed absorptions at 3350 cm^{-1} (N—H); 1625 cm^{-1} (amide C=O); and 1720 cm^{-1} (ester C=O). The nmr spectrum showed the following absorptions: singlet at δ 7.29 (10H, phenyl); quartet at δ 4.16 (2H, J = 7.3 Hz, ester CH_2); triplet at δ 1.22 (3H, J = 7.3 Hz, ester CH_3); doublet at δ 5.17 (1H, J = 7.3 Hz, N—H); doublet at δ 6.20 (1H, J = 7.3 Hz, benzhydryl C—H). The benzhydryl proton was established by running the nmr in deuterated trifluoroacetic acid. The benzhydryl proton moved downfield.

Anal. Calcd. for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64.

Found: C, 72.22; H, 7.13; N, 7.65.

2-Diphenylmethyloctahydroimidazo[1,5-*a*]pyridine-1,3-dione (IX).

Sodium (0.2 g.) was dissolved in 5 ml. of ethanol. Five drops of this solution were added to 5 g. (0.0136 mole) of ethyl 1-[(diphenylmethyl)carbamoyl]-2-piperidinecarboxylate refluxing in 100 ml. of ethanol. Refluxing was continued for one hour. The solid which formed was removed and recrystallized from ethanol, yield 98% (4.3 g.), m.p. 183-184°. The ir spectrum showed no N–H absorption and showed two imide bands at 1700 cm^{-1} and 1760 cm^{-1}. The nmr spectrum for IX



showed the following absorptions: multiplet at δ 7.33 (10H, phenyl); singlet at δ 6.29 (1H, "e" proton); multiplet at δ 4.54 (1H, "a" proton); 2 multiplets at δ 4.05 (1H) and δ 3.26 (1H) for the "b" protons; multiplet at δ 2.67 (2H, "c" protons); and a multiplet at δ 1.53 (4H, "d" protons).

Anal. Calcd. for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 75.08; H, 6.38; N, 8.54.

Attempted Reductions of IX with Lithium Aluminum Hydride.

Although various ethers, diethyl ether, tetrahydrofuran and dioxane were used and reaction times were widely varied, only starting material was recovered.

2-Aminomethylpiperidine.

2-Aminomethylpiperidine was prepared by hydrogenating 2-aminomethylpyridine in acetic acid solution over platinum oxide (10), yields 60-70%. The product boiled at 80-81° as stated in reference 10.

Reactions of 2-Aminomethylpiperidine with Aldehydes.

Preparation of 3-Propyloctahydroimidazo[1,5-*a*]pyridine (X).

Freshly distilled butanal (1.23 g., 0.0170 mole) was added dropwise to 2 g. (0.0175 mole) of 2-aminomethylpiperidine in 50 ml. of benzene at 0°. The solution was allowed to come to room temperature and solid potassium carbonate was added. The mixture was stirred for 24 hours and filtered. The benzene was removed from the filtrate under reduced pressure and the residual oil fractionated under reduced pressure, yield 65%, b.p. 49-50° (0.25 mm). A vapor phase chromatogram showed only one peak. See Figure 6 for nmr spectrum.

Anal. Calcd. for $C_{10}H_{20}N_2$: C, 71.37; H, 11.98; N, 16.65. Found: C, 71.51; H, 12.02; N, 16.57.

Preparation of 3-Isopropyloctahydroimidazo[1,5-*a*]pyridine (XI).

In this preparation the addition of 2-methylpropanal to 2-aminomethylpiperidine (in benzene) was carried out at 25°. Otherwise the steps were the same as for compound X. Yield 81%, b.p. 58-60° (0.20 mm). A vapor phase chromatogram showed only one peak. The nmr spectrum is shown in Figure 7.

Anal. Calcd. for $C_{10}H_{20}N_2$: C, 71.37; H, 11.98; N, 16.65. Found: C, 71.24; H, 12.04; N, 16.80.

Preparation of 3-Benzyloctahydroimidazo[1,5-*a*]pyridine (XII).

The procedure here was the same as that used for the preparation of the isopropyl derivative (XI) except phenylethanal was used. After removing the benzene a solid was obtained which was purified by sublimation at 73° (4 mm). Yield 50%, m.p. 61-63°. A vapor phase chromatogram showed only one peak. The nmr spectrum is shown in Figure 8.

Anal. Calcd. for $C_{14}H_{20}N_2$: C, 77.73; H, 9.32; N, 12.95. Found: C, 77.71; H, 9.14; N, 12.75.

Preparation of 3-Phenyloctahydroimidazo[1,5-*a*]pyridine (XIII).

The procedure was the same as that used for compound XI except that benzaldehyde was used. Yield 73%, b.p. 143° (0.27 mm). A vapor phase chromatogram showed only one peak. The nmr spectrum is shown in Figure 9.

Anal. Calcd. for $C_{13}H_{18}N_2$: C, 77.19; H, 8.97; N, 13.84. Found: C, 77.10; H, 8.91; N, 13.97.

Preparation of *t*-Butyloctahydroimidazo[1,5-*a*]pyridine (XIV).

Compound XIV was prepared by the procedure used for making the propyl derivative (X) except that 2,2-dimethylpropanal was used. Yield 84%, b.p. 57-59° (0.55 mm). A vapor phase chromatogram showed only one peak. The nmr spectrum is shown in Figure 10.

Anal. Calcd. for $C_{11}H_{22}N_2$: C, 72.47; H, 12.16; N, 15.37. Found: C, 72.47; H, 12.17; N, 15.60.

REFERENCES

(1) M. E. Freed and A. R. Day, *J. Org. Chem.*, **25**, 2108 (1960).

(2) K. Winterfeld and H. Schüler, *Arch. Pharm.*, **293**, 203 (1960); K. Winterfeld and G. B Singh, *ibid.*, **294**, 404 (1961).

(3) T. A. Crabb and R. F. Newton, *Tetrahedron*, **24**, 6327 (1968).

(4) G. Maar, R. E. Moore and B. W. Rockett, *Tetrahedron Letters*,, 2521 (1960).

(5) Obtained from the Aldrich Chemical Co.

(6) K. T. Potts and J. E. Saxton, *Org. Syn.*, **40**, 68 (1960).

(7) S. M. McElvain and R. Adams, *J. Am. Chem. Soc.*, **45**, 2745 (1923).

(8) W. Reckhow and D. S. Tarbell, *ibid.*, **74**, 4961 (1952).

(9) J. Donleavy and J. English, Jr., *ibid.*, **62**, 218 (1940).

(10) T. R. Norton, A. A. Benson, R. A. Seibert and F. W. Bergstrom, *ibid.*, **68**, 1330 (1946).

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