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THE STRUCTURES OF THE HYDROGEN HALIDE SALTS OF GLUTARONITRILE AND RELATED COMPOUNDS, AND THEIR CONVERSION TO DIHYDROPYRIDINES

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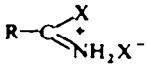
Abstract— The constitutions of the hydrogen halide salts of glutaronitrile are shown by NMR analysis, to be 2,2-dihalo-6-amino-2,3,4,5-tetrahydropyridinium halides (VIII). A simple procedure for converting these materials to 2-amino-6-halo-3,4-dihydropyridines is described. The latter, which are reasonably stable, represent a new and reactive class of functionally substituted dihydropyridines.

Salts derived from several other substituted glutaronitriles have also been examined and proof of their structures is presented.

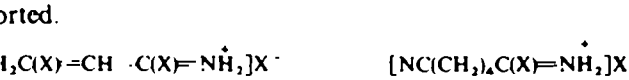
INTRODUCTION

THE constitution of the salts derived from simple nitriles and hydrogen halides has been the subject of a number of investigations. In particular, those of Hantzsch,[1] Janz,[2] Klages[3] and Zil'berman[4] are noteworthy. However, only recently has their constitution been clarified and this largely by the elegant IR spectral studies of Allenstein *et al.*[5-9] They concluded that the salts of the simplest type are best represented by the structure I. Recent neutron-diffraction studies[10] have confirmed this in the case where R = Me.



I

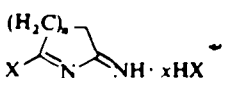
Despite the fact that hydrohalides of both malononitrile[11] and adiponitrile[12] have been investigated in depth, the former having structure II (X = Br) and the latter structure III (X = Cl), no detailed work on the salts of succinonitrile or glutaronitrile has been reported.



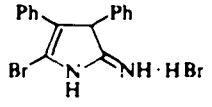
II III

[1] A. Hantzsch, *Ber. Dtsch. Chem. Ges* **64**, 667 (1931).
[2] G. J. Janz and S. S. Danyluk, *J. Am. Chem. Soc.* **81**, 3846, 3850, 3854 (1959); *Ibid*; *Chem. Rev.* 209 (1960).
[3] F. Klages and W. Grill, *Liebigs Ann.* **594**, 21 (1956)
[4] For a summary see E. N. Zil'berman, *Russ. Chem. Rev.* **31**, 615 (1962).
[5] E. Allenstein, *Ber. Dtsch. Chem. Ges.* **96**, 3230 (1963).
[6] E. Allenstein, *Z. Anorg. Allg. Chem.* **322**, 265, 276 (1963).
[7] E. Allenstein and P. Quis, *Ber. Dtsch. Chem. Ges.* **96**, 1035 (1963).
[8] E. Allenstein and A. Schmidt, *Spectrochimica Acta* **20**, 1451 (1964).
[9] E. Allenstein and P. Quis, *Ber. Dtsch. Chem. Ges.* **97**, 3162 (1964).
[10] S. W. Peterson and J. M. Williams, *J. Am. Chem. Soc.* **88**, 2866 (1966).
[11] E. Allenstein and P. Quis, *Ber. Dtsch. Chem. Ges.* **97**, 1857 (1964).
[12] E. N. Zil'berman and A. E. Kulikova, *Zh. Obshch. Khim.* **29**, 1694 (1959).

The first recorded example of the reaction of one of these dinitriles with a halogen acid to give a non-oxygenated product appears to be that of Blitz.[13] From 50% hydrodic acid and succinonitrile he obtained a substance to which he assigned the formula $(CH_2Cl_2NH_2)_2$. However, as we noted in a previous publication[14] his analytical figures agree better with the composition $(CH_2CN)_2 \cdot 3HI$. More recently, compositions of matter derived from succinonitriles or glutaronitriles and halogen acids have been the subject of a patent disclosure by Howard.[15] He assigned to these substances, structure IV (n = 1 or 2 respectively; X = Br or I) in which x varied capriciously from 1·25 to 2 depending on the nature of the starting dinitrile. No physical data were provided to substantiate this formulation, but shortly after the issuance of this patent, a thesis by Osborn[16] appeared in which the constitutions of the adducts of hydrogen bromide with succinonitrile and with 2,3-diphenylsuccinonitrile, were discussed at length. The results of his elemental and IR spectral analyses



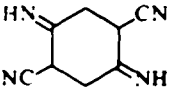
IV



V

led Osborn to concur with Howard in regard to the constitution of the former salt, and he assigned structure V to the latter salt, a substance not prepared previously.

In contrast, Décombe and Verry[17] have recently claimed that treatment of succinonitrile or glutaronitrile with hydrogen chloride in ether leads to VI or VII respectively; conclusions that were based on the nature of the hydrolysis products.



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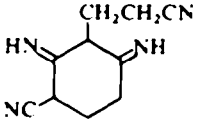


VII

These claims have been disputed by Zil'berman and Pyryalova[18] who repeated the work. By chemical and physical methods they purported to show that the compounds in question both were salts, having the constitution IV (X = Cl; x = 1; n = 2 or 3 respectively).

In view of the uncertainty surrounding the structure of these hydrogen halide adducts, we undertook a complete reinvestigation of their constitution, and of the nature of their hydrolysis products. These results, which show that all previous structures proposed for these salts are incorrect, form the basis for this and the succeeding paper.

Because the salts derived from glutaronitrile and certain of its derivatives yielded the most interesting chemistry, these will be discussed first.

[13] H. Blitz, *Ber. Dtsch. Chem. Ges.* **25**, 2533 (1892).
[14] F. Johnson, J. P. Panella, A. A. Carlson and D. H. Hunneman, *J. Org. Chem.* **27**, 2473 (1962).
[15] E. G. Howard, Jr., U.S. Patent 2,810,726 (October 22, 1957).
[16] J. H. Osborn, Ph D. Thesis, University of Minnesota 1958; *Diss. Abstr.* **19**, 2475 (1959).
[17] J. Décombe and C. Verry, *C.R. Acad. Sci., Paris* **256**, 5156 (1963).
[18] E. N. Zil'berman and P. S. Pyryalova, *Zh Org. Khim.* **1**, 983 (1965).

Glutaronitrile-hydrogen halide adducts

The adducts of the halogen acids and glutaronitrile were prepared in an inert medium, usually ether, under anhydrous conditions. A special reactor (described in the experimental section) was devised to ensure complete exclusion of moisture and also to facilitate the handling of the products. The hydrogen bromide and hydrogen iodide salts precipitated almost as soon as the hydrogen halide gas was introduced. The reactivity of hydrogen chloride, however, appears to be at least two orders of magnitude less than that of its higher homologs since very high concentrations of the gas in ether were required together with up to 24 hr of reaction time to produce good yields of the desired salts.

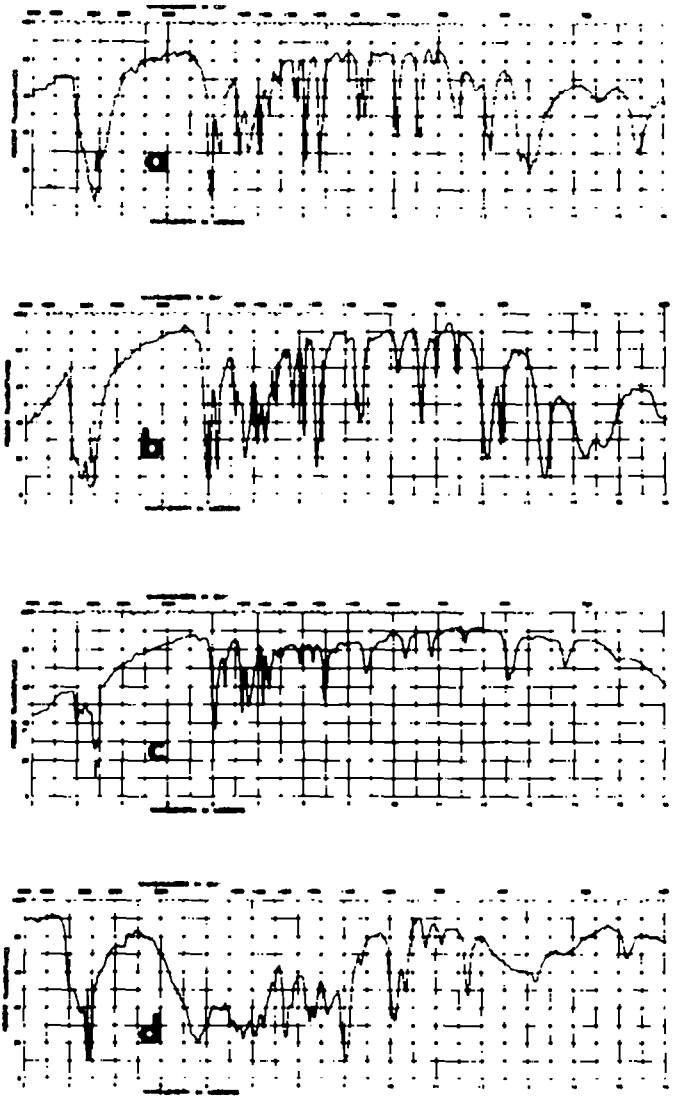
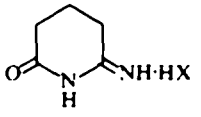


FIG. 1. IR spectra of (a) VIIIa, (b) VIIIb, (c) VIIIc and (d) XII in Nujol mull.

Elemental analyses of these adducts (VIIIa, VIIIb and VIIIc; X = Cl, Br, I, respectively) indicated that contrary to previous work[15, 17, 18] they all had the empirical formula $CH_2(CH_2CN)_2 \cdot 3HX$, while their IR spectra (Fig. 1) in the 5·9–8·5 μ region were sufficiently similar to assume that they all had the same basic structure. The hydrogen bromide salt (VIIIb) being the easiest to prepare, most of the structure studies were carried out with this material.

The most urgent problem requiring solution at the outset, was that of determining how much of the hydrogen halide in the compound was intrinsically bound and how much was present in the salt form. This question arose of course only because of the extreme sensitivity of these adducts to moisture, whereby the usual method of titrating to the neutral point with base failed completely. In contact with moisture VIIIb almost instantaneously was hydrolyzed (as were its homologs) to a hydrohalide, whose structure may be assigned loosely as IX (X = Br). This compound was much more easily obtained by treating glutaronitrile in acetic acid with hydrogen bromide without moderating the reaction by cooling. IX (X = Br) crystallized spontaneously from solution under these conditions. On longer stirring in the same medium, IX gave rise to N,N-bis(acetyl) glutarimide (X), identified by elemental analysis and its



IX

$CH_2(CH_2CONHCOCH_3)_2$

X

spectral properties.[19] In water, on long standing, IX afforded glutarimide as could be expected.

When VIIIb was treated with sodium bicarbonate solution, the bulk of the product proved to be insoluble free base of IX, but methylene chloride extraction of the aqueous phase did afford a small amount of a highly crystalline compound XI which analyzed for $C_5H_6N_2 \cdot HBr$. Although this substance was reconverted to VIIIb by dry hydrogen bromide, further work proved that it was not the true free base of VIIIb and a discussion of its structure is deferred until later.

The problem concerning the distribution of halogen in VIIIb was solved by carrying out a halogen exchange reaction with liquid hydrogen fluoride. The latter material is known to cause substitution of fluorine for organically bound higher halogen on a *one for one basis* when the latter is very reactive. On the other hand, provided the hydrogen fluoride was present in excess, it should exchange inorganic halide on a *two for one basis* since under these conditions the bifluoride ion is the more stable. Thus it was felt that *the arithmetic difference between the number of equivalents of bromine in* VIIIb *and the number of equivalents of fluorine in the product from the exchange, should represent the number of bromines present as hydrobromide in* VIIIb. An unequivocal answer would only result here, provided it could be demonstrated that no fundamental structural change occurred during the exchange.

Treatment of VIIIb with liquid hydrogen fluoride at 0° caused an immediate

[19] It now appears that the previously unidentified compound $C_5H_{11}N_3O_4$ isolated from the reaction of HBr/HOAC on a crude sample of NCNHCH$_2$CN [F. Johnson and W. A. Nasutavicus, *J. Org Chem.* **29**, 153 (1964)] must have the analogous structure $CH_3CONHCONHCH_2CONHCOCH_3$. All of the physical data are in agreement with this formulation

evolution of hydrogen bromide gas. The product XII of the reaction, again a very moisture sensitive compound, crystallized on trituration with ether and elemental analysis revealed the empirical formula $C_5H_6N_2 \cdot 4HF$. Thus, tentatively at least, it could be concluded that the original compound (VIIIb) must have *two bromine atoms organically bound and one present in the hydrobromide form*. In support of this conclusion it was found that treatment of VIIIb with a large excess of liquid hydrogen chloride gave rise to a salt which analyzed well for $C_5H_6N_2 \cdot 2HBr \cdot HCl$, while

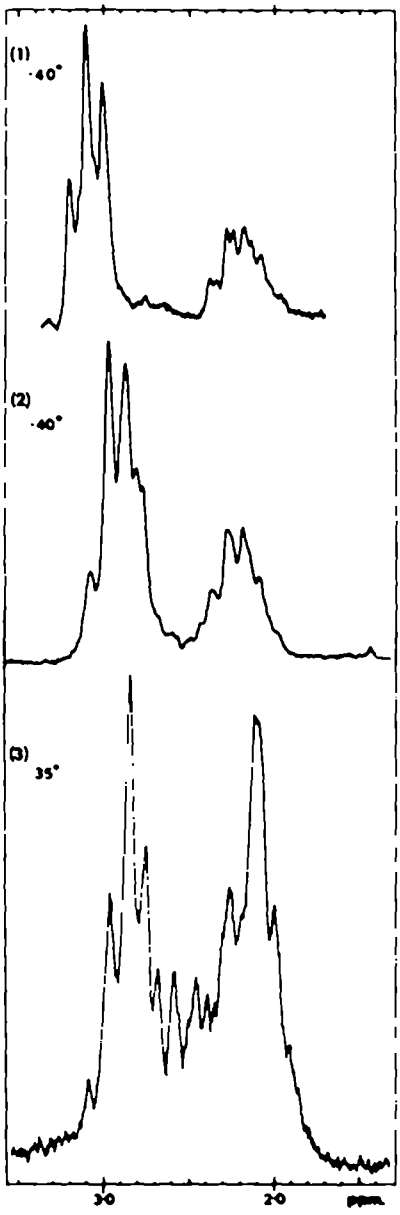


FIG. 2. CH proton resonance spectra of (1) VIIIb, (2) VIIIa and (3) XII

liquid hydrogen iodide afforded the corresponding $C_5H_6N_2 \cdot 2HBr \cdot HI$ salt. In contrast to hydrogen fluoride, neither of the latter hydrogen halides could be expected to exchange halogen with active organically-bound bromine since their conjugate bases have little or no basic character.

It still remained, however, to show that VIIIb and XII were essentially homologous. Unfortunately, a good comparison of their solid state infrared spectra was not possible, because the 4·5–7·5 μ region of the fluoro compound was almost completely blanked out, presumably by the HF_2^- ion absorption. In addition it was difficult to find solvents for solution spectral studies, with which these materials would not react. Fortunately VIIIa, VIIIb and XII, but not VIIIc, proved to be very soluble in liquid SO_2 even at $-60°$, and while this medium precluded infrared studies, it was possible to conduct an NMR investigation of their structures. Even so, this solvent was not without its difficulties; for example above $-25°$, VIIIb in particular rapidly underwent a quite remarkable reaction affording thionyl bromide and the highly insoluble salt IX (X = Br) previously obtained by hydrolysis of VIIIb. Such an exchange of organically bound bromine for one of the oxygen atoms of sulfur dioxide seems without precedent. Despite this difficulty, acceptable spectra were obtained in the range $-60°$ to $-30°$ in the cases of VIIIa and VIIIb and up to $\sim 20°$ for XII.

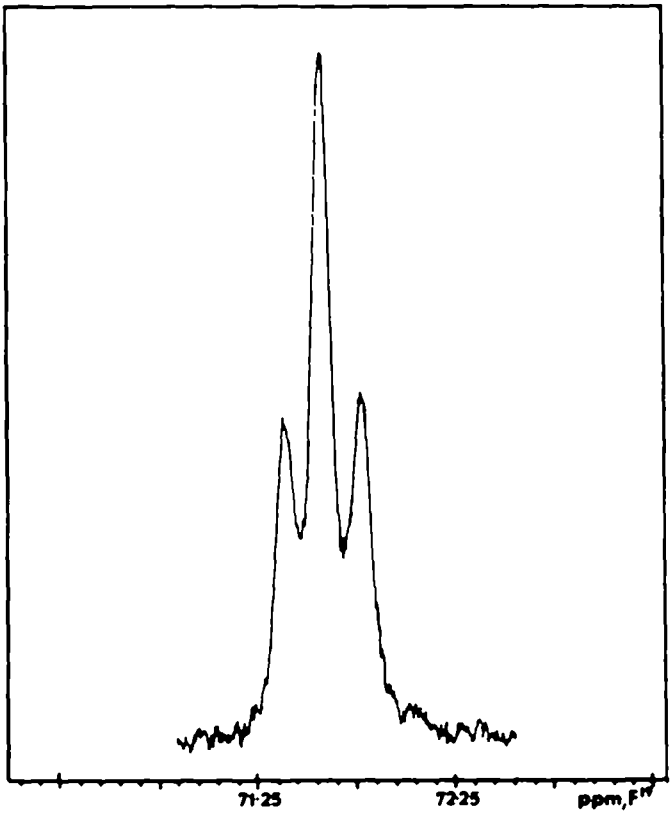


FIG. 3. CF resonance spectrum of XII in liquid SO_2 at $-20°$.

The NMR spectra[20] of VIIIa and VIIIb (Fig. 2) each show two sets of CH peaks in the ratio of 1 : 2, in the range 1·7- 3·3 ppm. The set at higher field is obviously due to a

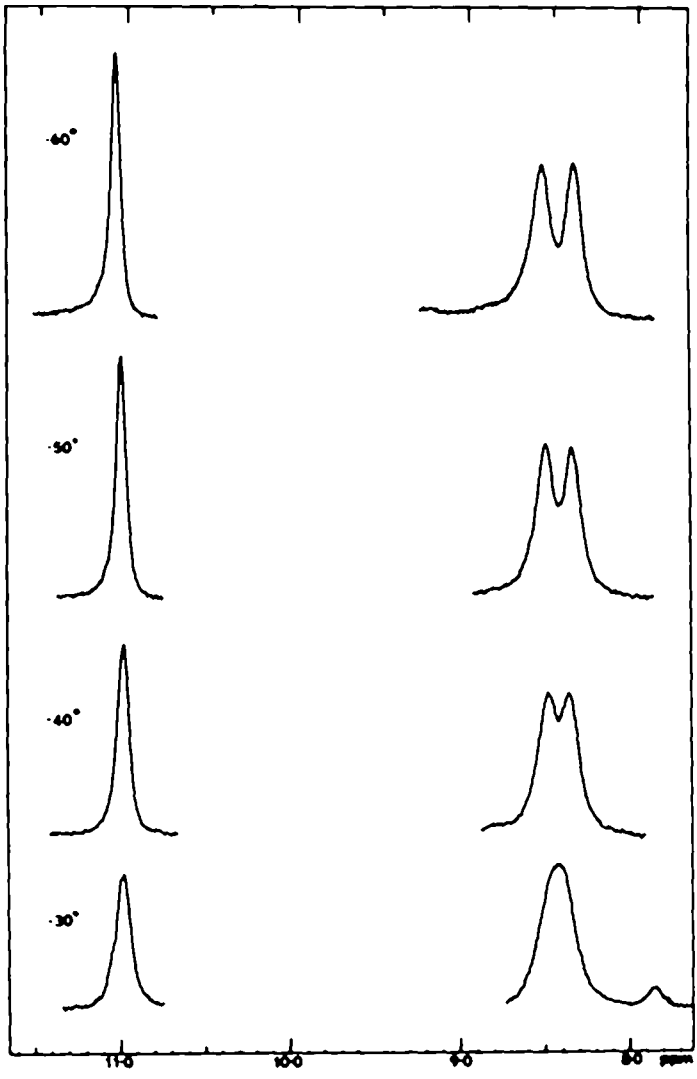
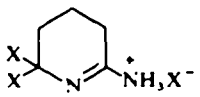


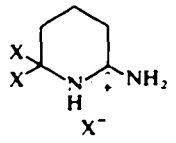
FIG. 4 NH proton resonance spectra of VIIIa in liquid SO_2.

[20] Chemical shifts are reported to the estimated center of the peaks or multiplets at 60 Mc in the case of proton spectra and at 56·4 Mc for fluorine spectra. TMS was used as the reference standard (at 0·0 ppm) in measuring the proton spectra of compounds XI, XII, XX and XXI. This standard was unsuitable for the more reactive salts because it reacted with them. Therefore, in all other cases, proton spectra were measured using tetramethylammonium fluoroborate as an internal standard (taken at 3·28 ppm relative of TMS at 0·00 ppm in liquid sulfur dioxide) to locate the exact positions of the CH resonance peaks. The latter which did not vary with temperature were then used as reference points for the NH proton peaks in the absence of an added internal standard. This was necessary because the NH resonance positions were susceptible to added fluoroborate ion, the anion exchange averaging in this case causing upfield shifts. Fluorotrichloromethane was used as the standard (taken at 0 ppm) for the measurement of F^{19} spectra.

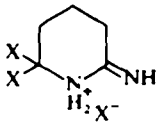
$-C\underline{H}_2-$ split by two pairs of adjacent methylene hydrogens having almost the same chemical shifts. The latter appear as two sets of superimposed multiplets at slightly lower field. In the spectrum of the chloro compound VIIIa one of these multiplets appears at higher field than the corresponding multiplet of the bromo compound VIIIb, and this would be logical if the methylene group producing this signal were



VIII-I



VIII-II



VIII-III

adjacent to carbon bearing halogen, because chlorine deshields vicinal hydrogen less than bromine.[21] Since no ethylenic absorption appears in the spectra, logical structures for VIII are VIII-I, VIII-II, or VIII-III.

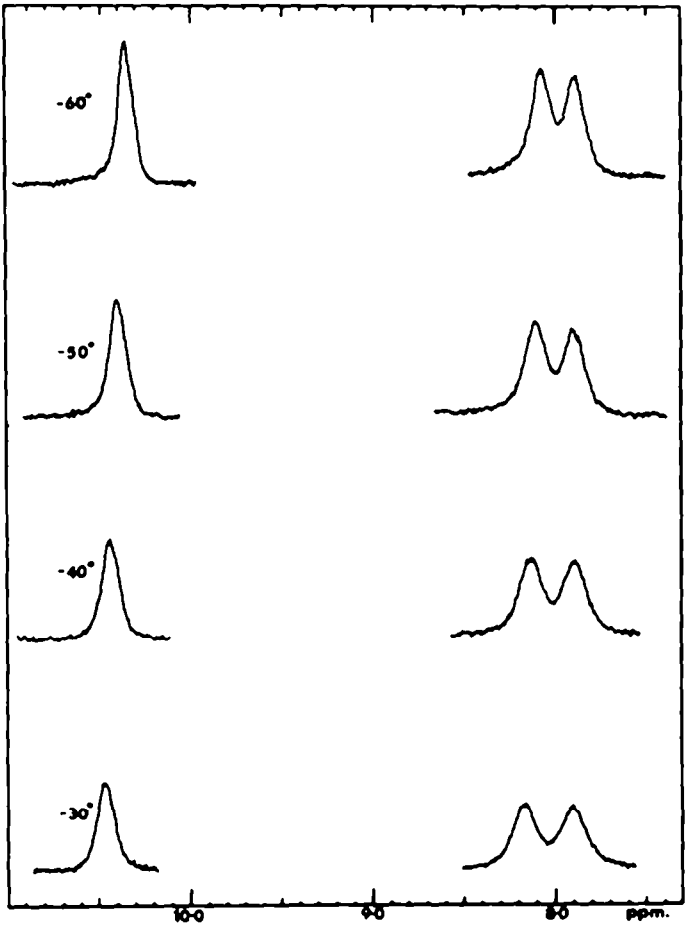


FIG. 5 $N\underline{H}$ proton resonance spectra of VIIIb in liquid SO_2.

[21] cf. spectra No. 10, 11 and 13 of the Varian NMR Spectra Catalog (1962)

If XII is simply a homolog of VIII then it could be expected that the PMR absorption of the methylene hydrogens adjacent to the CF_2 group should appear at even higher field than those of the corresponding protons in VIIIa and VIIIb. The PMR spectrum (Fig. 2) of XII at room temperature shows precisely this behavior there being a multiplet having its most intense peak at 2·13 ppm (four protons) due to the protons

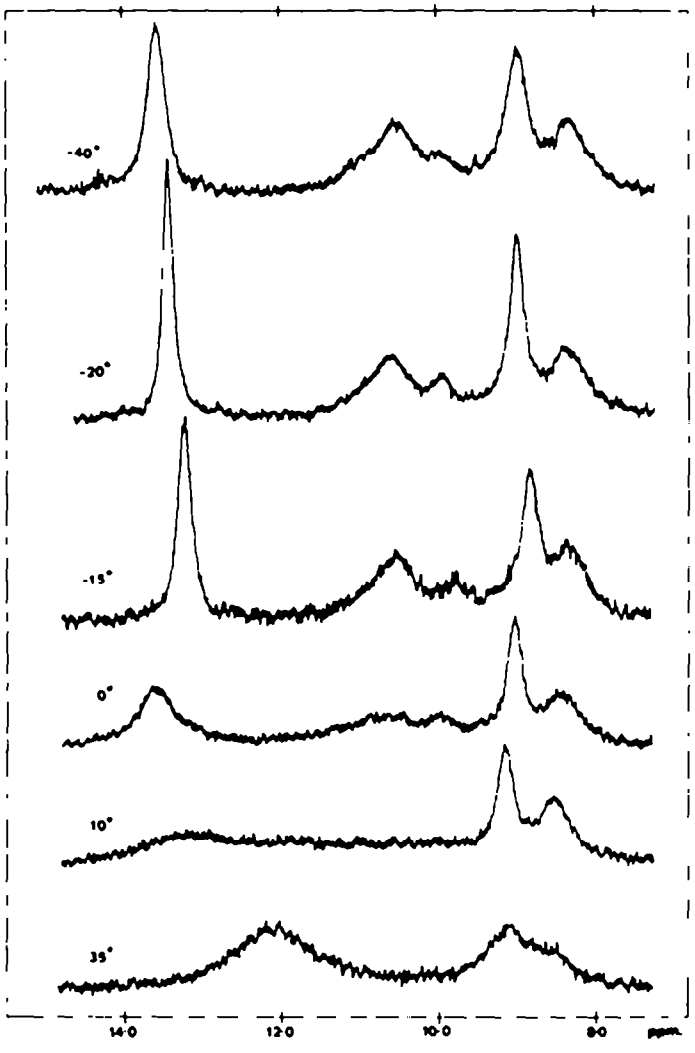


FIG. 6 NH proton resonance spectra of XII in liquid SO_2

in question being superimposed on the signal of the C-4 hydrogen atoms. The remaining methylene protons appear as a multiplet centered at 2·85 ppm (two protons). Much more convincing is the fluorine resonance spectrum of XII. This exhibits two bands of equal area, the first being a symmetrical triplet (Fig. 3) at +71·59 ppm. (J = 11 c/s), which is what might be anticipated for a $-CH_2CF_2-$ group and the

second a broad singlet at +106·1 ppm which can be assigned to the HF_2^- ion. Thus we may conclude that VIII and XII have the same basic skeleton.

The only point now in contention concerns the exact nature of the protonated amidine function in these molecules or stating it more broadly—what is the nature of the hypothetical free base of such a salt as VIII and on which nitrogen atom does it protonate? An examination of the NH proton resonances (Figs 4 and 5) narrowed the structural possibilities to VIII-II and VIII-III since in the spectrum of a substance having structure VIII-I the signal to be expected for protons bonded to N^{14} should be a broad singlet or a triplet (J = 60 c/s) depending on whether quadrupole relaxation of the nitrogen nucleus is rapid or not.[22]

What is observed for both VIIIa and VIIIb at low temperatures is the presence of a low field singlet integrating for one hydrogen and a pair of peaks at higher field corresponding to two hydrogens. In the case of VIIIa an increase in temperature leads to coalescence of the high field peaks; a process that reverses itself when the temperature is lowered again.[23] The bromo compound VIIIb exhibits a similar spectral pattern. Here however, complete coalescence of the upfield pair of peaks could not be observed because the material reacted with the solvent, before this occurred. The NH proton signals (Fig. 6) of the fluoro compound XII are roughly in agreement with those of VIIIa over the same temperature range,[24] although here the ratio of low field to high field hydrogen is in the ratio of 1:3, two of the NH protons and the HF_2^- proton apparently absorbing in the same region. The upfield pattern in the NH absorption region of XII is also more complicated than that of VIIIa, probably because of differences in hydrogen exchange and hydrogen bonding phenomena, and the relative positions of the respective anions.

The simplest interpretation of these data is that the upfield peaks are due to $>C-NH_2$ with restricted rotation about the C–N bond[25] and that the low field peak is due to a highly acidic proton on nitrogen. The only formulation in agreement with these results is VIII-II, since VIII-III, while it might conceivably give the same pattern, would be expected to show a downfield to upfield NH peak area ratio of 2:1.

The above argument in favor of VIII-II is not unequivocal, but some very convincing evidence comes from a comparison of our results with the work of Becker *et al.*,[26]

[22] J. D. Roberts, *J. Am. Chem. Soc.* **78**, 4495 (1956); see also R. J. Gillespie and T. Birchall, *Canad. J. Chem.* **41**, 148 (1963)

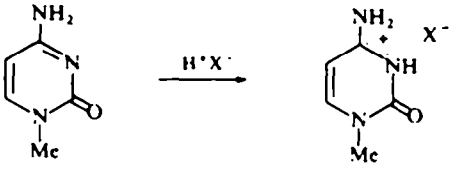
[23] It is important to note that suitable spectra showing this coalescence were obtained only when working with reasonably dilute solutions of the approximate concentration 0·7 moles/l. At high concentrations it appears that aggregation of the molecules operates to prevent rotation around the C–N bond of the amino group and no coalescence could be observed

[24] The poorer resolution at −40° as compared with that at −20° is undoubtedly due to the higher degree of solution viscosity at the lower temperature because the TMS reference signal showed corresponding line broadening

[25] A detailed discussion of the relationship of broadening and coalescence of resonance lines to the ratio of processes such as these rotations is given by J. A. Pople, W. G. Schneider, and H. J. Bernstein in "High Resolution Nuclear Magnetic Resonance", McGraw-Hill Book Co. Inc., New York, N.Y. (1959) Chapter 10

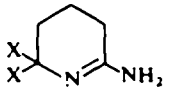
[26] H. T. Miles, R. B. Bradley and E. D. Becker, *Science*, **142**, 1569 (1963); E. D. Becker, H. T. Miles and R. B. Bradley, *J. Amer. Chem. Soc.* **87**, 5575 (1965); see also O. Jardetzky, P. Pappas and N. G. Wade, *J. Amer. Chem. Soc.* **85**, 1657 (1963) and B. W. Roberts, J. B. Lambert and J. D. Roberts, *J. Amer. Chem. Soc.* **87**, 5439 (1965)

on the site of protonation of N-methylcytosine (XIII). These workers were able to show unequivocally by some very elegant N^{15} studies that XIII protonates on the ring nitrogen atom at the 3-position and that salts of XIII have structure XIV.



XIII XIV

In liquid sulfur dioxide at $-60°$, XIV (X = Cl) displays rather broad peaks in the NMR spectrum at 7·45 and 7·83 and at ~11·44 ppm corresponding to the 4-amino and ring NH proton absorptions respectively. The shapes and positions of these peaks correspond well with those of VIIIa [8·38, 8·57 and 11·07 ppm at $-60°$] considering the structural differences in the two molecules. Again in the case of XIV the two NH peaks at higher field coalesce as the temperature is raised and when the anion X is changed from chloride to iodide all of the NH proton resonances then appear at higher field. Similar effects are to be noted in the spectra (at $-60°$) of VIIIa and VIIIb, the latter showing NH proton peaks at 7·90, 8·08 and 10·36 ppm at the same temperature[27] (cf. the values for VIIIa noted immediately above). Thus it seems fair to conclude that VIIIa, VIIIb, VIIIc and XII must be represented by VIII-II (X = Cl, B, I or F respectively) and that the so-far hypothetical free bases of these salts can be considered to have structure XV (X = Cl, Br, I, or F respectively) which by analogy with 1-methylcytosine, protonate on the ring nitrogen.



XV

It is very interesting to note that Allenstein *et al.*,[28] have shown very recently by IR analysis that the sesquihalides of hydrogen cyanide have the structure $[X_2CHNHCH{=}\overset{+}{N}H_2]X^-$ and are in reality the parent substances of a general class of compounds prepared by Jentzsch[29] as shown below.

$$2RNHCHO \xrightarrow[-CO_2]{COCl_2} [X_2CHN(R)CH{=}\overset{+}{N}HR]X^- \qquad (R = \text{alkyl or aryl})$$

Thus apart from the proposed location of the positive site and the extent of the double bond character associated with the terminal nitrogen atom of the amidine portion of the molecule, these salts correspond closely to VIII.

[27] It is interesting to note that the NH proton resonance at lowest field shows the unusual effect of moving to lower field (~8 c·s) as the temperature is raised (-60 to $-30°$) in the case of VIIIb but not in the case of VIIIa. A similar downfield shift of the NH protons was noted by Becker *et al.*,[26] with the N-methylcytosine salts XIV.

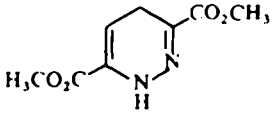
[28] E. Allenstein and A. Schmidt, *Ber. Dtsch. Chem Ges.* **97**, 1863 (1964); E. Allenstein, A. Schmidt and V. Beyl, *Ibid* **99**, 431 (1966).

[29] W. Jentzsch, *Ber. Dtsch. Chim. Ges.* **97**, 1361 (1964).

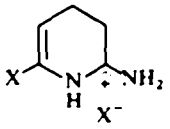
The structure of the compound XI, obtained as a by-product from the neutralization of VIII, now commanded our attention. Although it was available by this route, the yield was very small and it was fortunate that we were able to find an alternate preparation. This occurred when we attempted to acetylate VIIIb with acetic anhydride in the hope that its N-acetyl derivative would be more stable to moisture than VIIIb itself, as had proved to be the case[30] with 4-amino-2-bromothiazoles and -imidazoles. However, elemental analysis of the product (XVIb) showed it to contain simply one less equivalent of hydrogen bromide than VIIIb, while its IR spectrum suggested that it was still a salt (NH bands at 3·10 and 3·22 μ). In addition, it was much less sensitive to moisture and mild base than VIIIb, for on treatment with cold sodium bicarbonate solution, XI could be isolated in good yield. The homologs of the salt XVIb where the halogen involved is chlorine (XVIa) or iodine (XVIc) were readily obtained from VIIIa and VIIIc respectively, by the same procedures. Only in the case of the fluorine compound, XII, did the method fail. In this instance the only substance that could be isolated was a crude sample of X.

As will be shown below XVIb is simply the hydrobromide of XI, and the homologs of these substances containing chlorine or iodine are similarly related. They are stable indefinitely at room temperature in sealed tubes and react with moisture only slowly. On the other hand, the free bases XVI, if they are to be kept for any extended period must be stored at ~ −20°. At room temperature they are stable for a few weeks when kept in sealed tubes but decompose to red gums when exposed to air for several days. In its behavior with sulfur dioxide, XVIb was similar to the salt (VIIIb) from which it was derived, in that above −25° it reacted to produce IX (X = Br).

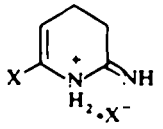
At the high field end, the NMR spectra of both XVIa and XVIb are very similar in overall pattern (Figs 7 and 8). Both display two multiplets each of which integrates for two protons. The most significant feature however, is the presence of a triplet ($J \sim 4{\cdot}5$ c/s) at 5·86 ppm in the spectrum of XVIb (5·63 ppm at −30° in the case of XVIa) which must be assigned to a vinylic proton adjacent to a $C\underline{H}_2$ group. The fine splitting ($J = 1{\cdot}65$ c/s) that can be observed in this triplet suggests allylic coupling. These values are of the same order of magnitude found by Avram *et al.*,[31] for XVII where the vinylic proton absorbs in the NMR spectrum at 5·80 ppm and has J values of 4·2 and 2·3 c/s by virtue of its coupling with the ring $C\underline{H}_2$ and $N\underline{H}$ protons respectively.[32] Thus by analogy a reasonable structure for XVI would be XVI-I.



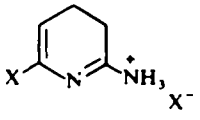
XVII



XVI-I



XVI-II



XVI-III

Support for this formulation comes from a temperature study of the low field end of the NMR spectra (Fig. 6) of XVIa and XVIb. Both show absorption characteristics

[30] F. Johnson and W. A. Nastuavicus, *J. Org. Chem* **28**, 1877 (1963); *Ibid.* **29**, 153 (1964)

[31] M. Avram, G. R. Bedford and A. R. Katritzky, *Rec. Trav. Chim* **82**, 1053 (1963).

[32] It can be seen that one of the methylene signals of XVIb also shows fine splitting ($J = 1{\cdot}3$ c/s). This may be due to long range coupling of the $N\underline{H}$ proton of the ring with the C-4 hydrogen. Unfortunately good resolution of the signals for the saturated methylenes of the free base of XVIb (*vide infra*) could not be obtained, so that we were unable to test this idea.

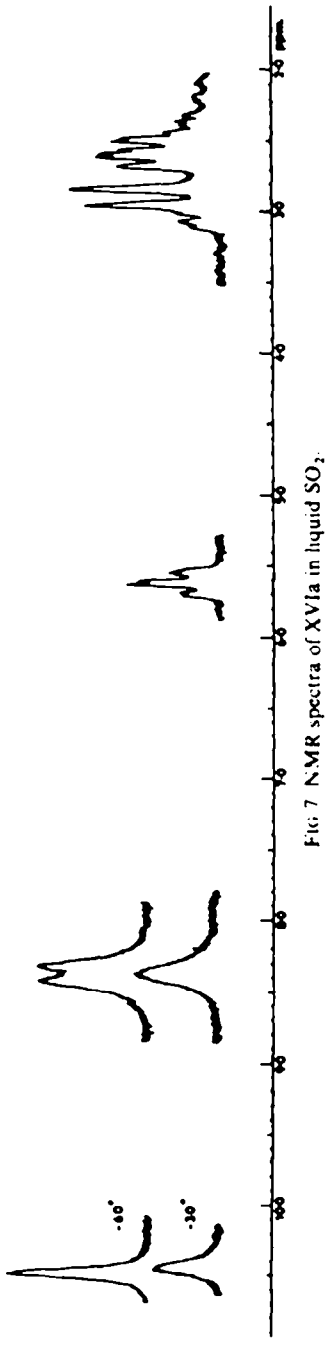


FIG. 7. NMR spectra of XVIa in liquid SO_2.

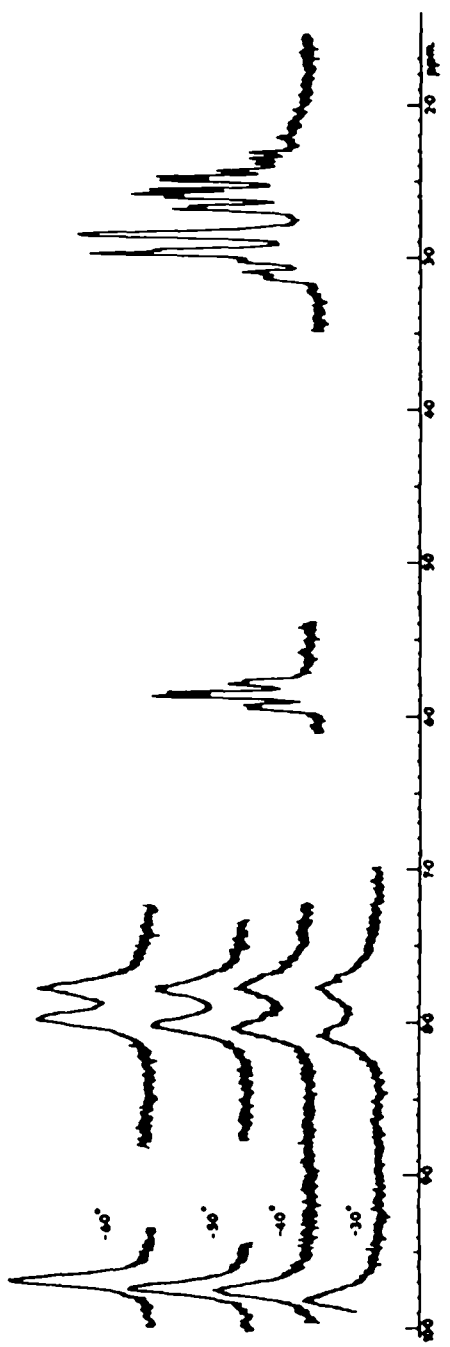
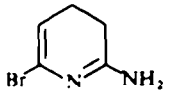


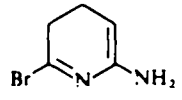
FIG. 8. NMR spectra of XVIb in liquid SO_2.

which are clearly very similar in pattern and behavior to those of VIIIa and VIIIb in that (a) at $-60°$ they comprise three peaks, at 8·32, 8·42 and 10·52 ppm for XVIa and at 7·78, 7·98 and 9·70 ppm for XVIb, each of which has an area corresponding to one proton, (b) one of the peaks is at considerably lower field than the other two and (c) an increase in temperature leads to coalescence of the upfield pair of peaks, once again in the case of the chloro compound XVIa, and to partial coalescence in the case of the bromo compound XVIb over the range -60 to $-30°$. Arguments similar to those used with the $C_5H_6N_2 \cdot 3HX$ adducts above can also be used to exclude such formulations as XVI-II and XVI-III as possibilities for XVI, and will not be reiterated.

Two points still remain; these concern (a) the exact nature of the hydrolysis product IX and (b) the structure of the compound XI which at an earlier point, we mentioned was the free base of XVIb. If this latter is true than XI, in the light of the above argument, concerning XVI, should be formulated as XI-I and its vinylic proton should



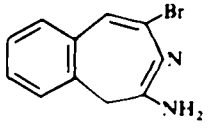
XI-I



XI-II

show a simple triplet pattern with no fine splitting in the NMR spectrum. This proved to be the case the triplet (J = 4·3 c/s) in question appearing at 4·61 ppm. In addition the spectrum, which was run in $(CD_3)_2SO$ because of the insolubility of XVI in liquid sulfur dioxide, showed a broad singlet characteristic of an $N\underline{H}_2$ resonance at 8·5 ppm.

An alternate structure XI-II for XI can be ruled out on the basis of a comparison of the IR spectra of XI and XVIII.



XVIII

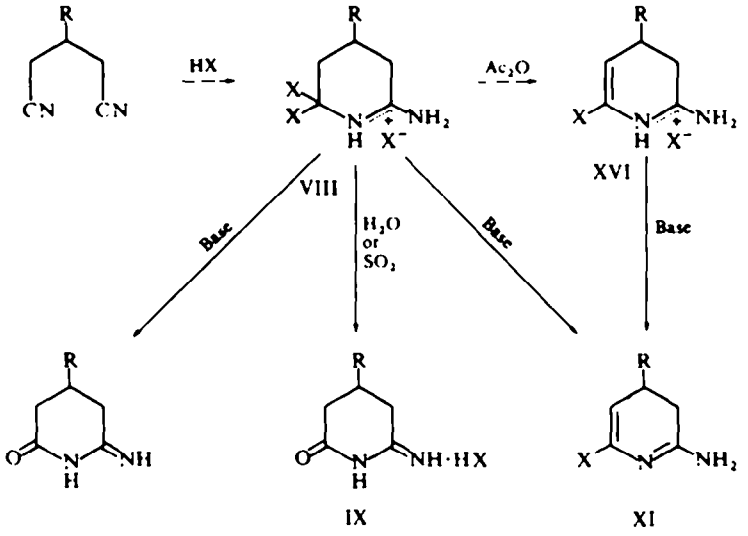
The $N\underline{H}_2$ absorption patterns in the IR spectra of these substances are absolutely identical both in the solid and liquid state. Not only this but bands which seem to be characteristic of the $>C{=}C(Br)N{=}C{-}NH_2$ chromophore appear in both spectra at approximately 6·05, 6·20, 6·35–6·42, 7·70 and 8·50 μ. Since the structure of XVIII has previously been established[33] unequivocally by a combination of physical and chemical means, there can be little doubt that XI must be represented by XI-I and not by XI-II.

Finally structural work on IX proved to be disappointing for the material had little solubility in any of the usual solvents suitable for NMR work with the exception of trifluoroacetic acid. In the latter medium, IX showed two partially superimposed peaks for N$\underline{H}$ resonances at 9·10 and 9·23 ppm which combined, integrated for two protons. The other N$\underline{H}$ proton absorption appears to be under the trifluoroacetic acid signal. Thus an analysis of this system was not feasible and the exact structure of IX remains an open question.

[33] F. Johnson and W. A. Nasutavicus, *J. Heterocyclic Chem.* **2**, 26 (1965).

The complete series of transformations described above now can be represented as shown in Chart I. (R = H).

CHART I

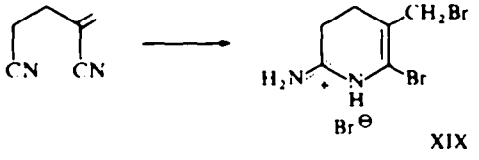


X = Cl, Br or I

Substituted glutaronitrile-hydrogen halide adducts

The reactions of several other derivatives of glutaronitrile with hydrogen bromide were also examined. In particular 3-phenyl-, and 3-(2-nitrophenyl) glutaronitrile were examined and found to behave in exactly the same way as glutaronitrile itself. They provided the same set of compounds shown in Chart I where R = Ph or 2-$NO_2C_6H_4$ respectively, and X = Br. This is mentioned only in passing and a fuller description of this work will be the subject of a separate paper.

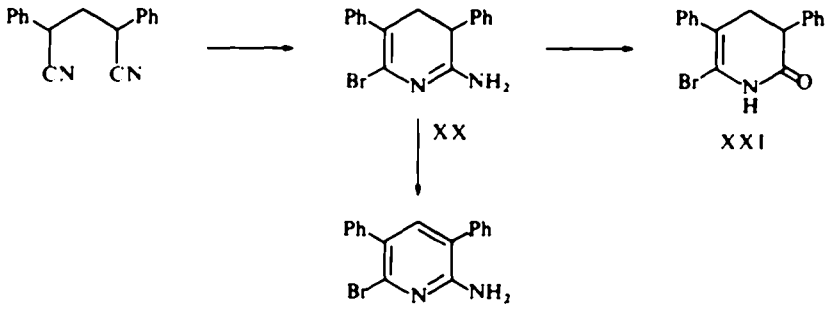
Of greater interest was the action of hydrogen bromide on 2-methyleneglutaronitrile. This afforded XIX in good yield. The assignment of this structure follows unambiguously from its NMR spectrum (in liquid sulfur dioxide at $-40°$) and its elemental analysis.



XIX

The former again shows an NH proton pattern typical of this form of a protonated amidine having singlet peaks at 10·03, 8·22 and 8·02 ppm. In addition there is a peak at 4·30 ppm which exhibits some fine splitting (< 1 c/s) and which can be assigned to the CH_2Br group. The methylene hydrogens on the ring show what appears to be partially superimposed quartets at 3·04 and 2·77 c/s ($J \sim 6$ c/s).

Finally 2,4-diphenylglutaronitrile was treated with hydrogen bromide in acetic acid. The hydrobromide salt obtained, when neutralized with mild base, afford XX.



XXII

The assignment of this structure to the compound rests on an analysis of both its NMR and infrared spectra. The former, taken in a mixture of $CDCl_3$ and CF_3CO_2H, shows a doublet at 3·12 ppm (J = 9 c/s) and a triplet at 4·29 ppm (J = 9 c/s) whose areas are in the ratio of 2:1. These obviously must be associated with the $-CH_2-CH<$ moiety of the ring. In the IR spectrum, the 3 μ region was almost identical with that of the benzazepine XVIII.

On the chemical side, treatment of the hydrobromide of XX with hot aqueous dimethylformamide led to the precipitation of a compound XXI whose NMR spectrum and elemental analysis are unequivocal in terms of the proposed structure. The NMR spectrum taken in $(CD_3)_2SO$ shows the typical $-CH_2-CH<$ doublet and triplet at 2·90 and 3·88 ppm. (J = 4 c/s) respectively, while a signal at 7·20 ppm appears to represent both the phenyl and NH proton signals since it integrated for eleven hydrogen atoms. Finally oxidation of XX with dichlorodicyanoquinone in benzene afforded a poor yield of 2-amino-6-bromo-3,5-diphenylpyridine (XXII). Further investigations with the very reactive compounds described in this paper will be discussed in future papers.

EXPERIMENTAL

M.ps were determined on a Fisher-Johns m.p. block and are uncorrected.

IR spectra were measured as Nujol mulls on a Baird spectrophotometer Model No 4 55.

NMR spectra were recorded using a Varian A56-60 spectrometer.

Cyclization of the dinitriles

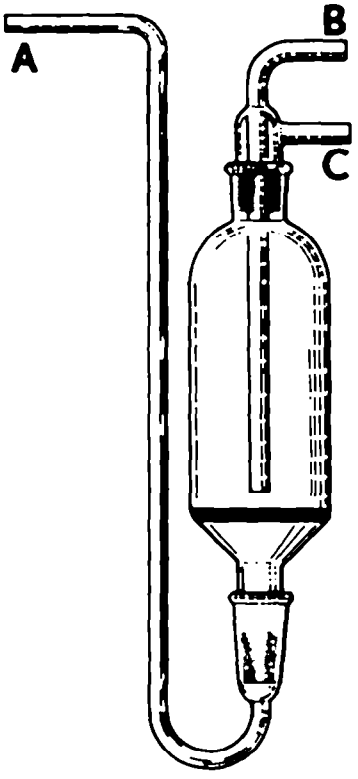
The cyclization procedure for a considerable number of the dinitriles of both this and the succeeding paper is illustrated by the preparation of 2,2-dibromo-6-amino-2,3,4,5-tetrahydropyridinium bromide described below

Where HBr or HCl was the cyclizing agent, benzene or ether or mixtures of the latter with CH_2Cl_2 were satisfactory solvents In the cases of cyclization with HI, benzene gave the best results.

2,2-Dibromo-6-amino-2,3,4,5-tetrahydropyridinium bromide (VIIIb)

Glutaronitrile (20 g; 0·212 mole) in dry ether (400 ml) was placed in the apparatus shown in the inset figure and a slow stream of dry N_2 was passed upwards through the sintered (medium porosity) glass disc via inlet A. This served not only to support the solution above the disc but also very effectively stirred the mixture during reaction. The vessel was then immersed in a mixture of ice and water and a slow flow of HBr was admitted through inlet B. After precipitation of the salt appeared complete (20–60 min) the HBr source was disconnected, inlet C was closed and the flow of N_2 shifted from inlet A to B. The filtrate from the reaction emerged from A and was discarded. The solid in the vessel was then washed twice with the

reaction solvent again using N_2 pressure to force the latter through the solid cake of product. Finally traces of solvent were removed by allowing the N_2 to flow through the solid at room temp for ~24 hr. In this manner analytically pure 2,2-dibromo-6-amino-2,3,4,5-tetrahydropyridinium bromide (60 g;



0·178 mole; 84%) was obtained: m.p. 157–160° with decomposition setting in at 148° (Found: C, 18·0; H, 2·7; Br, 71·0; N, 8·3. Calc. for $C_5H_6Br_3N_2$: C, 17·8; H, 2·7; Br, 71·2; N, 8·3%.)

2,2-*Dichloro*-6-*amino*-2,3,4,5-*tetrahydropyridinium chloride* (VIIIa)

The method described above was used but no solid ppt appeared even when the ether soln was saturated with HCl. The reaction mixture was then stored at −5 to −10° for 24 hr during which time the product slowly crystallized as large colorless cubes, m.p. 175°, dec. setting in at 155°, yield 88%. (Found: C, 29·5; H, 4·6; Cl, 52·2; N, 13·6. Calc. for $C_5H_9Cl_3N$: C, 29·5; H, 4·5; Cl, 52·3; N, 13·8%.)

2,2-*Diiodo*-6-*amino*-2,3,4,5-*tetrahydropyridinium iodide* (VIIIc)

From glutaronitrile (10 g; 0·106 mole) this salt was obtained in 68% yield (34·5 g; 0·072 mole) as a mustard colored solid m.p. ~190° (dec). This substance undergoes slow decomposition at room temp (dry atm) but specimens have been kept intact as long as 2 years by storing in tightly capped bottle at −10°. (Found: C, 12·7; H, 1·5; I, 80·2; N, 5·9. Calc. for $C_5H_9I_3N_2$: C, 12·6; H, 1·9; I, 79·7; N, 5·9%.)

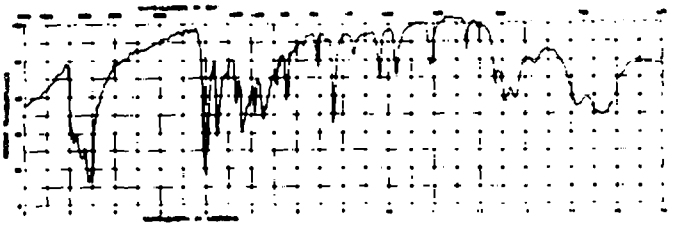
6-*Halo*-2-*amino*-3,4-*dihydropyridinium halides* (XVI)

The general method for preparing these compounds is exemplified by the preparation of the bromide XVIb. The succeeding homologs XVIa and XVIc were prepared in the same manner.

6-*Bromo*-2-*amino*-3,4-*dihydropyridinium bromide* (XVIb)

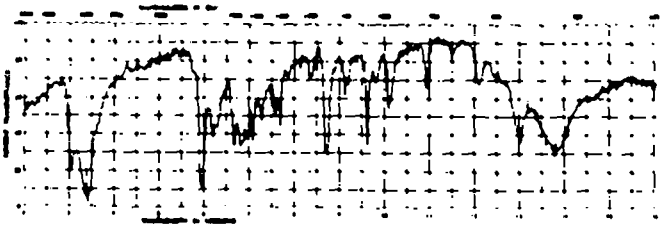
2,2-Dibromo-6-amino-2,3,4,5-tetrahydropyridinium bromide (14 g; 4·12 mmole) was added to Ac_2O (170 ml) and the mixture was stirred for 5·5 hr. The suspended solid was then removed by filtration from

the lilac-colored liquid phase, washed with a little Ac_2O, then ether and finally air-dried. The analytically pure material (9·65 g; 3·77 mmole; 91·5% yield) thus obtained had m.p. 155–157°. (Found: C, 23·4; H, 2·9; Br, 62·2; N, 10·9. Calc for $C_5H_8Br_2N_2$: C, 23·5; H, 3·15; Br, 62·4; N, 11·0%.)



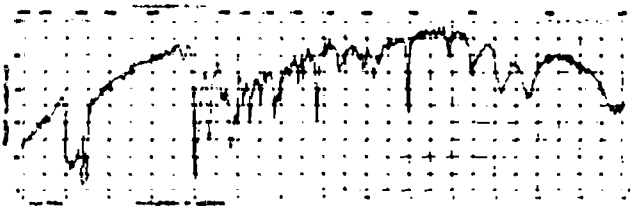
6-*Chloro*-2-*amino*-3,4-*dihydropyridinium chloride* (XVIa)

This compound was obtained in 50% yield and had m.p. 155°. (Found: C, 36·1; H, 5·0; Cl, 42·2; N, 16·7. Calc for $C_5H_8Cl_2N_2$: C, 36·0; H, 4·8; Cl, 42·5; N, 16·8%.)



6-*Iodo*-2-*amino*-3,4-*dihydropyridinium iodide* (XVIc)

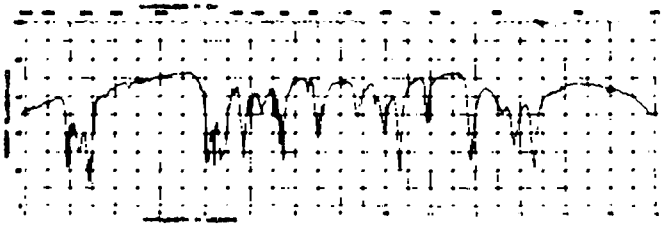
This compound was isolated in 99% yield using the standard procedure, the reaction being allowed to proceed for only 45 min. The pale yellow crystalline compound had no definite m.p. It becomes deep yellow at 100° and assumes a reddish color at 120°, finally liquifying to a dark liquid over the range 133–150°. (Found: C, 16·9; H, 2·2; I, 72·9. Calc for $C_5H_8I_2N_2$: C, 17·2; H, 2·3; I, 72·5%.)



2-*Amino*-6-*halo*-3,4-*dihydropyridines*

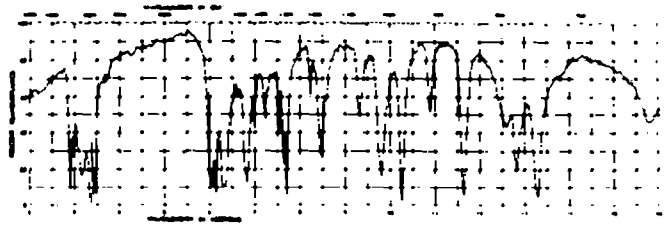
These compounds were prepared by neutralizing the appropriate XVI with cold sat $NaHCO_3$ aq followed by rapidly extracting the product with AcOEt or CH_2Cl_2. The latter soln was dried over $MgSO_4$ and the solvent was then removed under reduced press at < 15°. The highly crystalline residue although usually faintly yellow was quite pure. Recrystallization could be accomplished by redissolving the material in AcOEt or CH_2Cl_2 concentrating by evaporation under reduced press and then adding ether or pet. ether (b.p. 30–60°) until spontaneous crystallization occurred. In this manner the 3 compounds described immediately below were prepared.

2-*Amino*-6-*bromo*-3,4-*dihydropyridine* (XI) was isolated in 57% yield and crystallized in thin nacreous plates m.p. 80° decomposing to a red viscous liquid. (Found: C, 34·3; H, 4·0; Br, 46·0; N, 15·8. Calc. for $C_5H_7BrN_2$: C, 34·3; H, 4·0; Br, 45·7; N, 16·0%.)

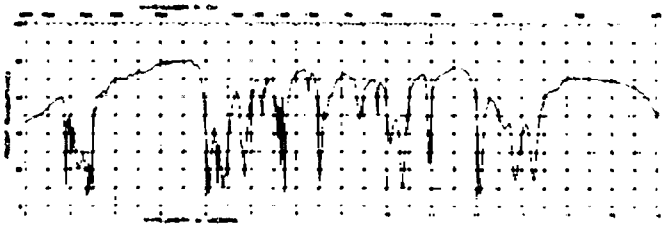


This compound could also be obtained in 4% yield by neutralizing VIIIb with $NaHCO_3$aq and isolating the product as described above. The major product of this reaction was insoluble in the extraction solvents used and proved to be 6-imino-2-piperidone.

2-*Amino-6-chloro-3,4-dihydropyridine* was obtained by the above method in 45% yield m.p. 75°. (Found: C, 45·9; H, 5·6; Cl, 27·2; N, 21·3. Calc. for $C_5H_7ClN_2$: C, 46·0; H, 5·4; Cl, 27·2; N, 21·5%.)



2-*Amino-6-iodo-3,4-dihydropyridine* was isolated in 46% yield using the above procedure. It crystallized in yellow plates m.p. 95–97° with dec. (Found: C, 27·1; H, 3·3; I, 57·4. Calc. for $C_5H_7IN_2$: C, 27·1; H, 3·2; I, 57·2%.)



2,2-*Difluoro-6-amino-2,3,4,5-tetrahydropyridinium bifluoride* (XII)

2,2-Dibromo-6-amino-2,3,4,5-tetrahydropyridinium bromide (9·3 g; 0·0276 mole) in a polyethylene bottle (500 ml) was treated with excess dry liquid HF (~40 ml) at 0°. Gas evolution occurred rapidly and subsided after a few min. After 45 min the excess HF was removed in a stream of dry N_2 and the glassy residue was then triturated with dry ether. The resulting white crystalline product, XII (3·23 g; 0·0126 mole), melted at 62–65° to an opalescent liquid which resolidified at 79–80° becoming yellow at 185°. At 208–210° gas evolution occurred and at ~290° the material changed to an orange-red solid. (Found: C, 34·9; H, 6·1; F, 43·0; N, 15·8. Calc. for $C_5H_{10}F_4N_2$: C, 34·5; H, 5·8; F, 43·6; N, 16·1%.)

2,2-*Dibromo-6-amino-2,3,4,5-tetrahydropyridinium chloride and iodide*

Dry HCl was passed through a trap containing solid 2,2-dibromo-6-amino-2,3,4,5-tetrahydropyridinium bromide (4·29 g; 0·0127 mole) at a temp of −100° (liquid N_2 bath). The salt dissolved and after 2 hr the soln (~10 ml) was allowed to evaporate to dryness in a stream of dry N_2. The resulting salt had (3·59 g; 0·0123 mole) m.p. 174–175° (softening at 160–162°). (Found: C, 20·4; H, 3·2; Br, 54·5; Cl, 12·1; N, 9·6. Calc. for $C_5H_9Br_2ClN_2$: C, 20·5; H, 3·1; Br, 54·7; Cl, 12·1; N, 9·6%.) The IR spectrum of this material was indistinguishable from that of VIIIb.

When the above experiment was carried out using HI at −80° (solid CO_2–perchloroethylene bath) VIIIb (4·82 g; 0·0143 mole) afforded the corresponding iodide (4·92 g; 0·0128 mole) as a yellow crystalline material. (Found: C, 15·0; H, 2·7; Halogen, 74·9; N, 7·3. Calc for $C_5H_9Br_2IN_2$: C, 15·6; H, 2·4; Halogen, 74·7; N, 7·3%.) Its IR spectrum showed bands at 2·98, 3·11, 3·16, 3·25, 3·27, 6·00, 6·26, 6·65, 7·10, 7·92, 8·45, 9·37, 10·24, 10·72, 10·85, 12·50, 12·60 and 13·36 μ.

6-Imino-α-piperidinone hydrobromide (IX; X = Br)

(a) A soln of glutaronitrile (9·4 g; 0·1 mole) in AcOH (30 ml) was added dropwise to a soln (100 ml) of 30% HBr (0·3 mole) in the same solvent. Upon completion of the addition a highly crystalline white solid precipitated and 30 min later this was removed by filtration, washed twice with ether and air dried. The combined filtrate and ether washings on standing yielded a further 4 g of material as pure as the first crop. Total yield of IX (X = Br) amounted to 18 g (0·093 mole; 93%) m.p. 200–202°. A sample recrystallized from MeOH–ether showed no improvement in m.p. Its IR spectrum showed bands at 3·05, 3·30, 3·56, 5·73, 5·90, 6·95, 7·08, 7·40, 7·90, 8·59, 9·42, 10·88, 11·20, 11·49, 11·75, 12·59 and 13·12 μ. (Found: C, 31·1; H, 4·5; Br, 41·4; N, 14·2. Calc for $C_5H_9BrN_2O$: C, 31·1; H, 4·7; Br, 41·4; N, 14·5%.)

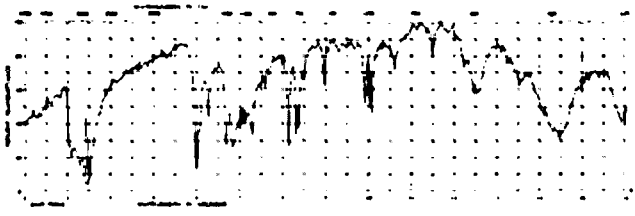
(b) A sample of VIIIb (2·13 g) was treated with liquid SO_2 (10 ml) at −30°. The clear soln slowly became yellow and a crystalline ppt appeared. The SO_2 was then allowed to evaporate and the solid residue washed with ether. The product (2·47 gm) had m.p. 198–200° after recrystallization and did not depress the m.p. of a sample prepared according to method (a) above.

N,N'-Diacetylglutaramide (X)

Glutaronitrile (3·0 g; 0·032 mole) in AcOH (10 ml) was added dropwise to a cooled and stirred soln (8·7 ml) of 15% HI (0·096 mole) in AcOH. After stirring for 96 hr the heavy white ppt (5·05 g) was washed with ether air-dried then recrystallized from dimethylformamide–ether to give pure X m.p. 224–226° (1·71 g; 0·8 mmole; yield 25%). (Found: C, 50·3; H, 6·3; N, 13·1. Calc for $C_9H_{14}N_2O_4$: C, 50·5; H, 6·6; N, 13·1%.)

2-Amino-6-bromo-5-bromomethyl-3,4-dihydropyridinium bromide (XIX)

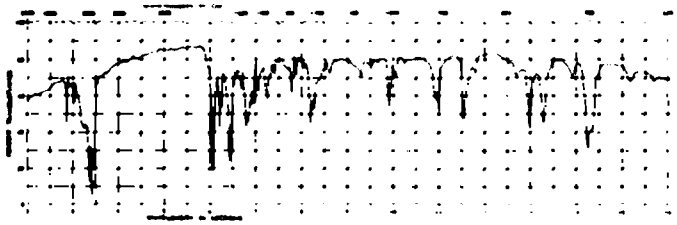
A slow stream of dry HBr was passed through a soln of 2-methylene-glutaronitrile (1·0 g; 9·43 mmole) in dry ether (75 ml). After 20 min the white crystalline ppt (2·04 g; 5·85 mmole; 62% yield) was removed by filtration, m.p. 167°. (Found: C, 20·8; H, 2·7; Br, 68·6; N, 8·2. Calc for $C_6H_9Br_3N_2$: C, 20·7; H, 2·6; Br, 68·7; N, 8·0%.)



The use of AcOH as a solvent in this reaction did not affect the nature of the product.

2-Amino-6-bromo-3,5-diphenyl-3,4-dihydropyridine (XX)

A soln of 2,4-diphenylglutaronitrile (2 g; 8·13 mmole) in dry ether (200 ml) was treated with a stream of dry HBr. After 45 min the solvent was partially removed under reduced press. The product, a white crystalline material (2·85 g; 6·98 mole; 86% yield) had m.p. 237–238°. (Found: C, 50·1; H, 3·8; Br, 39·1; N, 7·0. Calc for $C_{17}H_{16}Br_2N_2$: C, 50·0; H, 4·0; Br, 39·2; N, 6·9%.) Its IR spectrum showed bands at 3·10, 3·25, 3·56, 6·00, 6·27, 6·70, 8·42, 9·15, 9·61, 9·85, 10·75, 10·88, 12·26, 12·42, 12·68, 12·99, 13·14 and 14·25 μ. A sample (0·63 g) of this salt was dissolved in N,N-dimethylformamide (25 ml) and the soln then added slowly with rapid stirring to sat $NaHCO_3$ aq (25 ml). The white ppt was removed by filtration washed with hot water and dried; (0·43 g) m.p. 196–198°. Recrystallization from MeOH afforded the pure material. (Found: C, 62·2; H, 4·7; Br, 24·3; N, 8·5. Calc for $C_{17}H_{15}BrN_2$: C, 62·4; H, 4·6; Br, 24·4; N, 8·6%.)



6-Bromo-3,5-diphenyl-3,4-dihydropyridone-2. (XXI)

Compound XX (1·0 g; 2·45 mmole) was dissolved in a mixture of water (10 ml) and N,N-dimethylformamide (5 ml) and heated on a steam bath for 2 hr. On cooling the product crystallized as white needles (0·62 g; 1·90 mmole). One crystallization from MeOH afforded the pure material m.p. 190–192°. (Found: C, 61·8; H, 4·6; Br, 24·0; N, 4·3. Calc. for $C_{17}H_{14}BrNO$: C, 62·2; H, 4·3; Br, 24·4; N, 4·3%.) Its IR spectrum showed bands at 3·15, 3·23, 5·96, 6·07, 6·13, 6·70, 7·35, 8·02, 8·10, 8·48, 9·94, 10·82, 13·18, 13·90 and 14·44 μ.

2-Amino-6-bromo-3,5-diphenylpyridine

2-Amino-6-bromo-3,5-diphenyl-3,4-dihydropyridine (0·5 g; 1·5 mmole) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0·5 g) were dispersed in dry benzene (25 ml) and refluxed for 18 hr. The benzene was then drawn off under reduced press leaving a brown-orange, semi-crystalline mass which was chromatographed on a silica gel column. Mixtures of AcOEt and CH_2Cl were used as eluants. Fractions obtained from 8% AcOEt in CH_2Cl_2 afforded 0·373 g (1·15 mmole) of crude product. After two recrystallizations from CH_2Cl_2 ether a light brown crystalline solid was obtained m.p. 170–172°. (Found: C, 63·6; H, 4·1; Br, 24·2; N, 8·3. Calc. for $C_{17}H_{13}BrN_2$: C, 62·8; H, 4·0; Br, 24·6; N, 8·6%.) Its IR spectrum showed bands at 2·88, 3·05, 3·16, 6·14, 6·51, 6·94, 7·53, 8·00, 8·92, 9·30, 9·68, 9·89, 10·94, 12·86, 13·10, 13·29 and 14·20–14·36 μ.

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