The Dow Chemical Company, Eastern Research Laboratory

Polyfunctional Aliphatic Compounds VI.

The Cyclization of Dinitriles to Benzazepines

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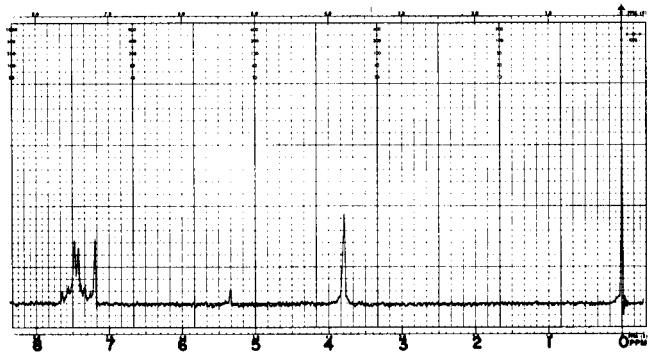
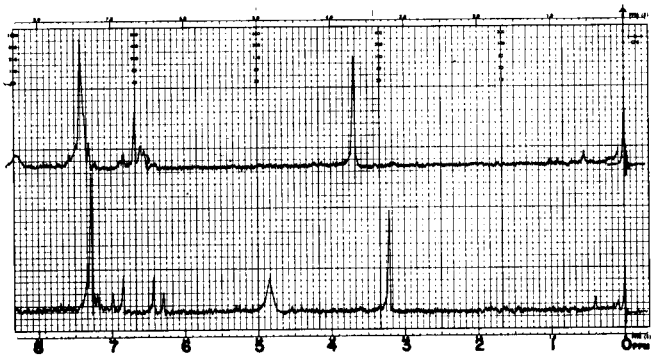
The action of hydrogen bromide or iodide on aryl-*o*-diacetonitriles has been studied and found to give condensed azepine derivatives. This constitutes a new and interesting synthesis of seven-membered ring nitrogen heterocycles. The structure of the parent substance has been shown by physical and chemical means to be 2-amino-4-halo-1H-3-benzazepine. Several related compounds have been prepared and assigned similar structures by analogy. A number of reactions of 2-amino-4-bromo-1H-3-benzazepine (III) have been examined. It is concluded that the reactivity of the bromo group is similar to that of 2-bromopyridine. In its reactions, 2-amino-1H-3-benzazepine not only has some of the character of 2-aminopyridine but resembles the simple amidines also.

In previous papers (1) we have demonstrated that the halogen acid-induced cyclization of α,ω-dinitriles (Fig. 1) may be used for the synthesis of a variety of previously inaccessible derivatives of five- and six-membered nitrogen heterocycles. The facility of this ring closure raised the intriguing possibility that it might be applied to the synthesis of seven-membered rings. Not only would the products of such a cyclization be of intrinsic interest but the reaction itself would add a new method to a rather limited roster (2a-i) of reactions available for the synthesis of azepine derivatives.



N. m. r. spectrum of III in deuteriochloroform-trifluoroacetic acid.

Fig. 2a



N.m.r. spectrum of VI (a) in trifluoroacetic acid (upper) (b) in deuteriochloroform (lower).

Fig. 2b

SYNTHESIS

Because succinonitrile and glutaronitrile are cyclized by hydrogen bromide (3) [hydrogen chloride leads to entirely different types of compounds (4)], we first examined the action of this acid on adiponitrile in benzene. This led to a highly crystalline solid, but after removal of the solvent and excess hydrogen bromide, the product rapidly became sticky and in twelve hours had liquified with the liberation of hydrogen bromide even in the total absence of air and oxygen (5). In fact the material appeared to be stable only in the presence of an excess of hydrogen bromide. Interestingly the presence of a nitrile group was not apparent in its infrared spectrum. However, addition of the initial solid material, to sodium hydrogen carbonate solution, surprisingly, led to a good recovery of adiponitrile. The reaction of 1,4-dicyanobutene-2 (6) with gaseous hydrogen bromide also led to a similar, highly crystalline material, again very sensitive to moisture. However the delicate nature of these products (7) was discouraging from the point of view of using simple adiponitriles for the synthesis of azepine derivatives. Thus we turned to an examination of systems where the two nitrile groups are locked in close proximity to one another by the geometry of the molecule, in the hope that more stable products would be obtained. A likely candidate appeared to be *o*-phenylenediacetonitrile (I).

When this compound was treated with hydrogen bromide in acetic acid, a highly crystalline salt rapidly separated from solution. Contrary to the

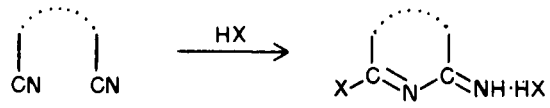
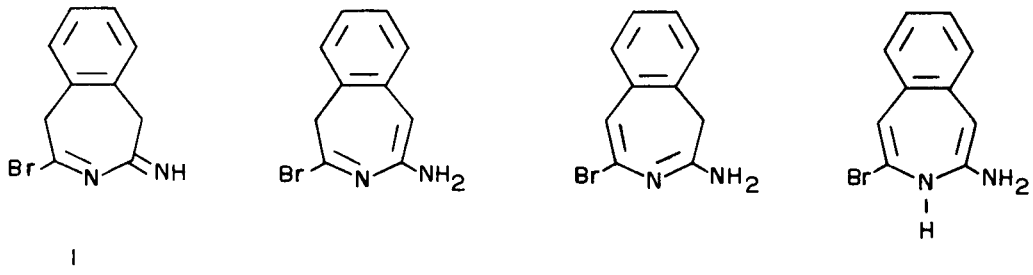
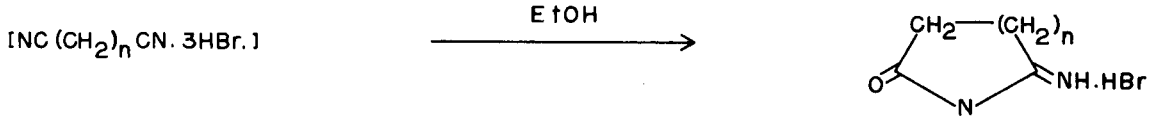


Figure I

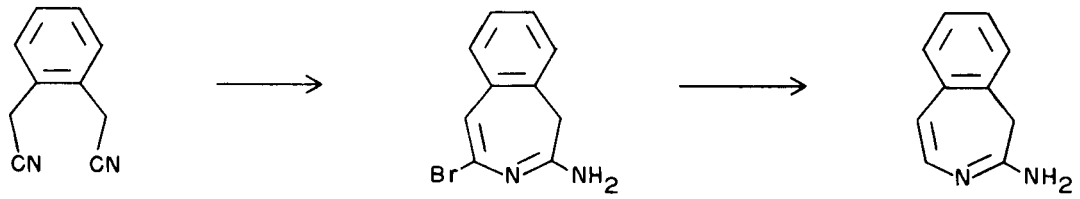


I

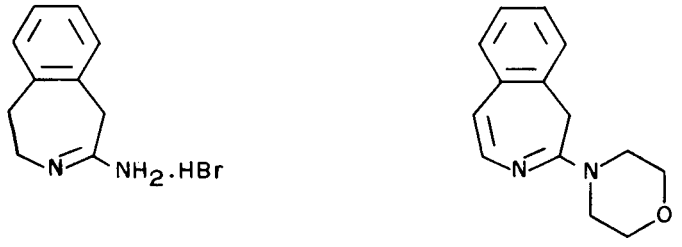
III a III b III c III d



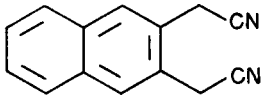
IV n = 1 or 2 V



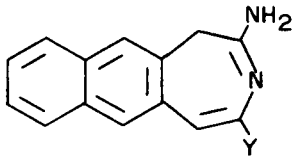
I III VI



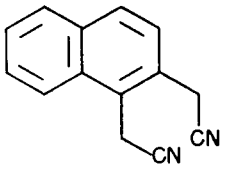
VIII VII



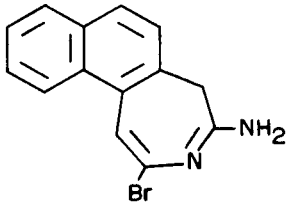
IX



X

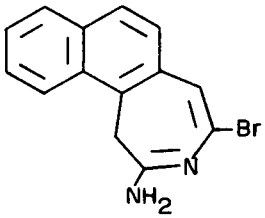


XI



XII

or



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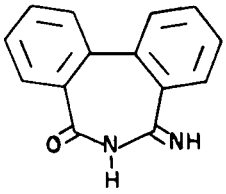

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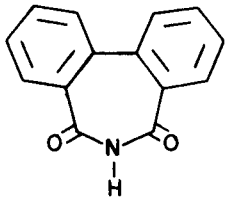

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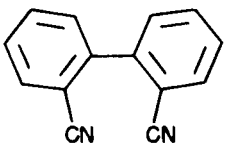

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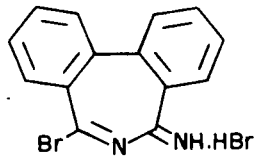
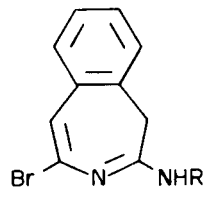
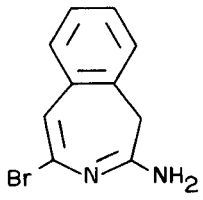


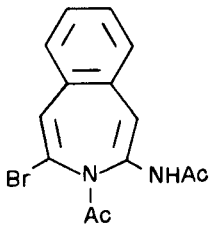
XVI



XVIII



III



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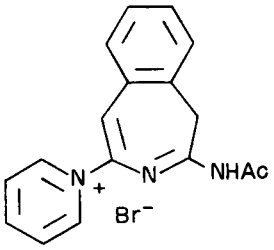

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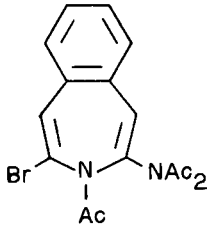

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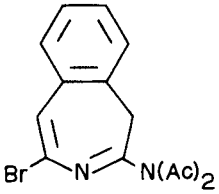

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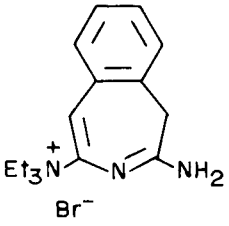

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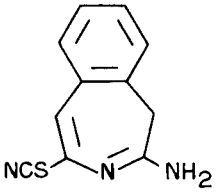

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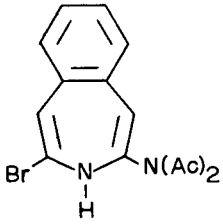
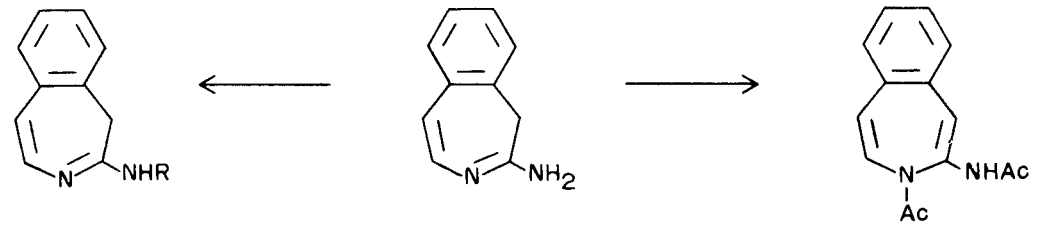
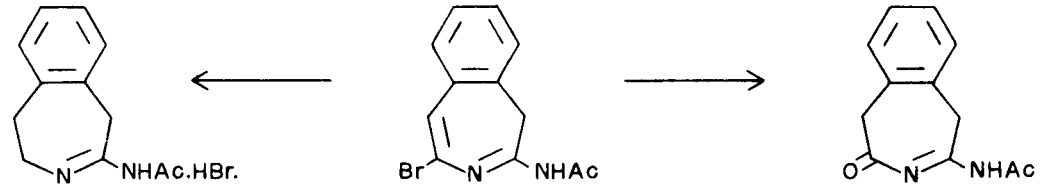


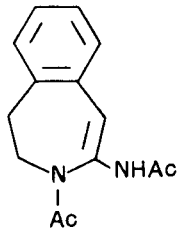
XXI



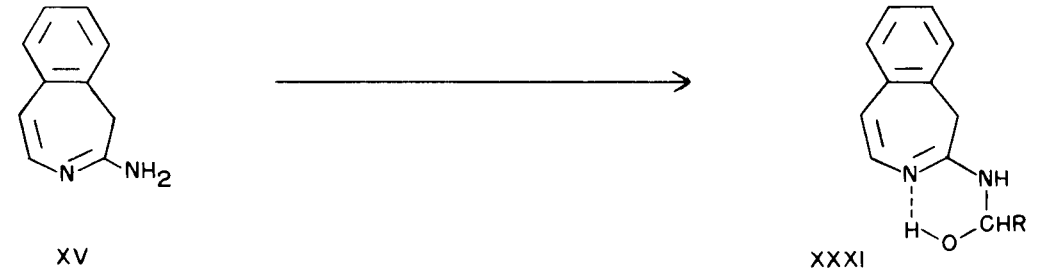
XXVI VI XXVII



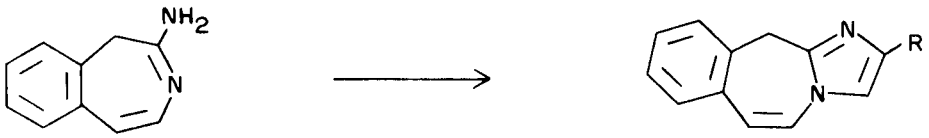
XXVIII XXVIII XXIX



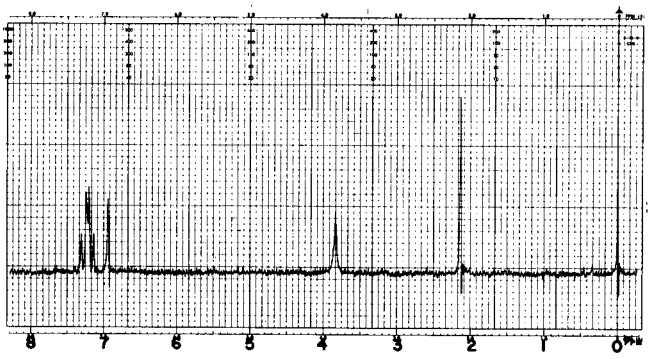
XXX



XV XXXI

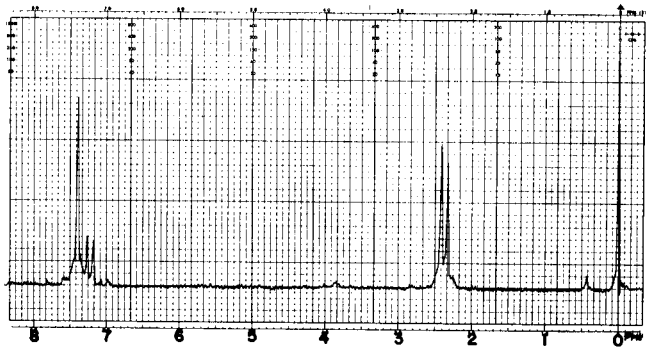


VI XXXII



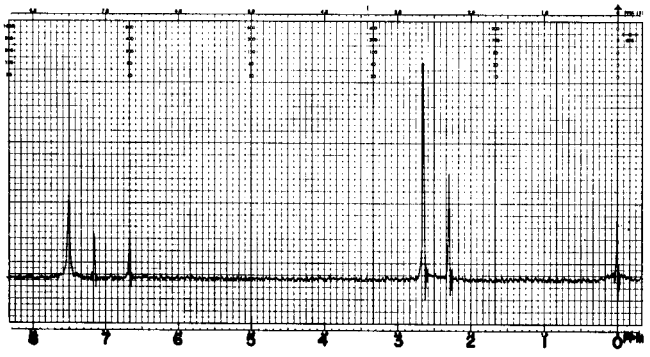
N.m.r. spectrum of XVIII in deuteriochloroform.

Fig. 3a



N.m.r. spectrum of XIX in trifluoroacetic acid.

Fig. 3b



N.m.r. spectrum of XXII in deuteriochloroform.

Fig. 3c

results obtained with adiponitrile, this substance proved to be stable in moist air and could be recrystallized unchanged from ethanol-ether mixtures. It analyzed well for $C_{10}H_{10}Br_2N_2$ (II) and had an infrared spectrum which showed complex absorption in the 3.1-3.3 μ region and a strong band at 5.96 μ, but no absorption around 4.4 μ. Treatment of this substance with cold sodium hydrogen carbonate solution afforded the free base, a stable, faintly yellow, very crystalline compound $C_{10}H_9BrN_2$ (III). That cyclization had definitely taken place became obvious when it was found that simply boiling III with water led to *o*-phenylenediacetimide in good yield (8), but whether or not III should be represented by IIIa or by one of its more probable tautomers (IIIb-d) was not clear at this point. Nevertheless the lack of hydrolysis of both II and III in cold hydroxylic solvents was in marked contrast to the behavior of the corresponding salts (IV) prepared (9) from succinonitrile and glutaronitrile (n = 2 or 3). The latter on dissolution in ethanol for instance, suffer a very fast hydrolysis to salts of the type represented by V. In addition it had also been observed previously (10) that many hydrogen bromide adducts of simple nitriles, such as the salt $(CH_3CN\cdot HBr)_2$ undergo immediate hydrolysis to the corresponding imide. Thus on the basis of chemical behavior it appeared that III must be one of the tautomers IIIb-d.

At this point in our investigation a publication (11) came to our attention describing the isolation of II during an attempted bromination of I in ether. The author, who also obtained this substance from I and hydrogen bromide alone, presented considerable infrared evidence that the structure of the base III was represented by the tautomer IIIa, the hydrobromide salt having the same structure.

An examination of the n.m.r. spectrum of III (Fig. 2a) resolved the problem and it is obvious from the peaks (12) at 7.20, (one vinyl hydrogen) and 3.80 ppm ($-CH_2-$ group) that III must be represented by IIIb or IIIc. Final evidence that III is in fact IIIc was obtained by hydrogenation of this material in a basic medium to a bromide-free compound VI, (the omission of base in this reduction led to good yields of VIII) whose n.m.r. spectrum (Fig. 2b) in deuteriochloroform revealed two vinyl protons splitting one another and the methylene group still intact. The single peak for amino hydrogen in the latter spectrum at 4.84 ppm corresponding to two protons also suggests that the tautomeric form of the amidine shown, is the preferred one for VI. This undoubtedly applies to III also, since the infrared spectra of III and VI bear a remarkable similarity over the 3-10 μ region. In addition the ultraviolet spectra of both III and VI very closely resemble that of VII each of the three compounds having a single maximum at approximately 300 mμ. The latter compound was obtained in mediocre yield by refluxing VI with morpholine for a short period and its n.m.r. spectrum is completely in agreement with this structure. The above data in a self-consistent way, preclude the possibility that bond migration could have taken place during the preparation of VI or VII. That the preferred tautomeric forms of III and VI correspond to IIIc rather than IIId is not surprising since Hafner (2e) has shown that azepine itself exhibits similar behavior.

The cyclization of I could also be effected with hydrogen iodide and this led, after neutralization of the salt, to the iodo compound corresponding to III. The dinitrile IX, prepared by the action of potassium cyanide on the corresponding dibromide (13), also underwent ring closure when treated with hydrogen bromide or iodide. The products X (Y = Br or I)

were obtained in excellent yield, again after neutralization of the initially formed salts. However when hydrogen bromide reacted with the unsymmetrical dinitrile XI a mixture of salts was obtained from which, after neutralization, only one of the expected products could be isolated and then in poor yield. Whether this product is XII or XIII has not been ascertained.

An attempt was also made to cyclize 2,2'-dicyanobiphenyl (XIV) with hydrogen bromide in acetic acid. After stirring overnight a salt precipitated which analyzed well for the incorporation of one mole of water (14) and one of hydrogen bromide. Neutralization of the product with mild base led to a bromine-free substance. From its elemental analysis and infrared spectrum it is assigned structure XV; the initial salt is regarded as the hydrobromide of XV. However, when XIV was treated with hydrogen bromide in benzene, there was obtained a moisture-sensitive crystalline compound quite different from XV.HBr. It analyzed for XIV with incorporation of two moles of hydrogen bromide, and its infrared spectrum did not exhibit nitrile absorption. Hydrolysis in aqueous acetic acid led to XVII and on this basis it is thought to have structure XVI.

REACTIONS

Because functionally substituted benzazepines such as III and VI have not been available before, a preliminary investigation of some of their chemistry has been made. This has consisted largely of a study of (a) their acetylation and (b) their condensation with carbonyl compounds. A few substitution reactions of the bromine atom in III were studied, and some other ancillary experiments made in connection with the above topics.

When III was stirred with acetic anhydride in the cold, a moderate yield of a monoacetyl compound was obtained whose n.m.r. spectrum (Fig. 3a) indicated its structure to be XVIII (R = Ac). Similarly phenyl isocyanate reacted with III to give the mixed urea XVIII (R = $CONHC_6H_5$). When, however, III was boiled briefly with acetic anhydride, the product obtained had structure XIX. This assignment is based on the fact that its n.m.r. spectrum (Fig. 3b) in trifluoroacetic acid (15) shows two types of absorption for acetyl hydrogen at 2.33 and 2.42 ppm as well as two vinyl proton absorptions in the 7.25 ppm region. These data, together with the absence of methylene absorption in the 3 to 4 ppm region, rules out the possibility of its having structure XX or XXI. Interestingly, it did not prove possible to convert XVIII (R = Ac) to XIX with boiling acetic anhydride unless a trace of acetic acid were present, indicating the acetylation of the ring nitrogen to be acid-catalyzed. Although XIX is stable in the absence of moisture, it very slowly decomposes with deliquisence, on standing in air.

A triacetylated compound XXII was also obtained on one occasion when the hydrobromide salt of III was boiled with acetic anhydride. The yield was very small and the product decomposed easily in air to XIX with the evolution of acetic acid. Thus poor analytical data were obtained for this compound but its n.m.r. spectrum (Fig. 3c) in deuteriochloroform, again, left little doubt that the structure assigned to it is correct.

Interesting results were obtained when acetylation of III was attempted using a hot mixture of acetic anhydride and pyridine. This quickly caused the precipitation of a highly crystalline yellow salt. From its elemental analysis, n.m.r. and infrared spectra we have assumed it to be the quaternary salt XXIII. Quaternization of III without acetylation appears easy to accomplish because simply stirring it with triethylamine in methanol overnight led to XXIV in reasonable yield. The behavior of the bromine atom in III is thus reminiscent of the reactivity of the halogen in 2-bromo or 2-chloropyridine (16).

Several other displacement reactions of the bromine atom of III were examined. Although tertiary bases reacted with III to give nicely crystalline products, secondary or primary bases such as pyrrolidine, morpholine or allylamine afforded only intractable tarry mixtures. The bromine atom could not be displaced by azide ion in either ethanol or dimethylformamide solution and the reaction of sodium thiophenoxide with III, in the former solvent, led to no definite product. However, III did react with sodium thiocyanate in dimethylformamide to give a 40% yield of XXV. The n.m.r. of the latter very closely resembled that of III.

The reaction of VI with either phenyl isocyanate or isothiocyanate led, as expected, to the urea (XXVI; R = $CONHC_6H_5$) and the thiourea (XXVI; R = $CSNHC_6H_5$) respectively.

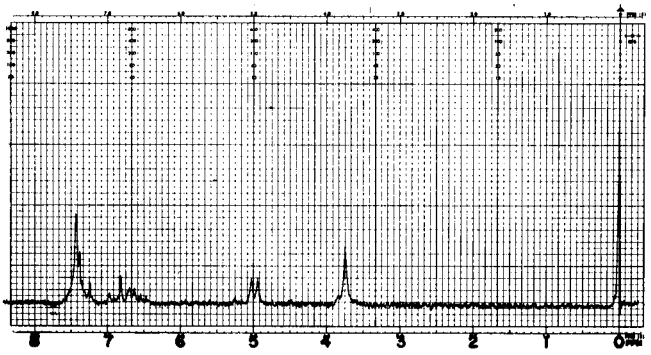
However the acetylation of VI occurred with such great ease in pyridine-acetic anhydride at room temperature that only complex mixtures were obtained. Nevertheless when acetic anhydride was used alone the diacetylated compound XXVII could be isolated in fair yield. An attempt was made to prepare a monoacetyl derivative of VI by reductive debromination of XVIII (R = Ac). The approach proved unsuccessful because palladium-catalyzed hydrogenation of this compound in the absence of base led to XXVII whereas in the presence of base ($KHCO_3$) only hydrolysis occurred, affording XXIX. In this connection it is interesting to note that hydrogenation of the diacetyl derivative XIX in the absence of base also afforded a product (XXX) in which complete reduction of the bromoethene group had taken place. It is worth noting that although III and VI have the formal appearance of being enamines we have not observed any C-acylation at the 5-position in these molecules.

Turning now to carbonyl condensation reactions, initial efforts were directed towards obtaining Schiffs' bases by the condensation of III with aldehydes. However neither benzaldehyde, formaldehyde, acetaldehyde nor isobutyraldehyde could be made to react with III even under azeotroping conditions. Generally it did not prove possible to effect such condensations with VI either. In fact we have found that only the

very active aldehydes, formaldehyde and trichloroacetaldehyde react with VI. Both give compounds having structure XXXI (R = H or CCl_3 respectively). The structure in non-acidic media of the formaldehyde condensation product (XXXI; R = H) was assigned on the basis of spectroscopic evidence. Its ultraviolet spectrum is essentially identical with that of the parent compound VI, and the presence of a hydrogen bonded hydroxyl group is evident from the broad absorption in the 3 μ region of its infrared spectrum. More convincing is the n.m.r. evidence. The spectrum of XXXI (R = H) (Fig. 4) taken in trifluoroacetic acid shows a doublet at -4.99 ppm (J = 6 cps) which can be assigned to the $-NH-CH_2-$ group. In dimethylsulfoxide, however, this absorption appears as a single line at -4.61 ppm the lack of splitting being due to rapid proton exchange on the exocyclic nitrogen in this medium. It is interesting to note that the spectra of VI (see Fig. 2b) and XXXI (R = H) in trifluoroacetic acid, show that protonation occurs on the nitrogen atom of the seven-membered ring. For the latter compound the ring NH proton occurs at -9.6 ppm whereas the exocyclic NH absorption appears at -8.8 ppm. Both are broad lines in this medium.

VI is also capable of undergoing condensation reactions with α-haloketones in much the same way as 2-aminopyridine. For instance with 2-bromoacetophenone, VI yields XXXII (R = C_6H_5) whereas chloroacetone leads to XXXII (R = CH_3). The structures of these products have been assigned by analogy with the products obtained using 2-aminopyridine (17). Reactions of this type could not be accomplished using III and the lack of reactivity of the amidine group in this molecule can only be ascribed to the deactivating influence of the bromine atom.

Attempts to diazotize III or VI failed. This, perhaps, is not surprising, since it is well-known that amidines can form reasonably stable salts with nitrous acid, and undergo diazotization with difficulty (18).



N.m.r. spectrum of XXXI in trifluoroacetic acid.

Fig. 4

Lastly whereas acid hydrolysis of III led ultimately to *o*-benzenediacetic acid, boiling VI with hydrochloric acid effected no reaction except that of salt formation. This, on the other hand, is more typical of the behavior of 2-aminopyridine than that of a simple amidine (18).

Further work on the reactions of these interesting compounds will be reported later. Presently, efforts are being made to extend this dinitrile cyclization procedure to the synthesis of the simple azepine ring system itself.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point block and are not corrected. Infrared spectra were recorded using a Baird spectrophotometer Model No. 4-55 as films or as Nujol Mulls and ultraviolet spectra were obtained in ethanol using a Carey spectrophotometer Model No. 14. N.m.r. data were taken using a Varian A-60 instrument. Hydrogen bromide in acetic acid was used as supplied by Eastman-Kodak.

2-Amino-4-bromo-1H-3-benzazepine (III) and its Hydrobromide.

(a) A solution of *o*-phenylenediacetonitrile (1.0 g., 6.4 mmoles) in dry ethyl ether (35 ml.) was treated with a slow stream of anhydrous hydrogen bromide for 1.5 hours. The salt which had precipitated was removed by filtration and dried (1.5 g., 74%) m.p. 256-257° (softening at 235°). Its infrared spectrum showed bands at 3.13-3.29 μ (-NH) and a doublet at 5.96-6.02 μ.

Anal. Calcd. for $C_{10}H_{10}Br_2N_2$: C, 37.8; H, 3.2; Br, 50.3; N, 8.8. Found: C, 37.3; H, 3.1; Br, 50.2; N, 8.7.

The salt obtained above (4.7mmoles) was stirred vigorously with excess sodium bicarbonate solution and the product filtered off to give 2-amino-4-bromo-1H-3-benzazepine (1.0 g., 89%). Recrystallization from methylene chloride afforded the pure material (0.78 g.) m.p. 194-196° dec.

Its infrared spectrum showed peaks at 2.93, 3.05, 3.21 (NH) and 6.08 μ.

U.V. λ max: 296 mμ (ϵ, 11,360).

Anal. Calcd. for $C_{10}H_9BrN_2$: C, 50.7; H, 3.8; Br, 33.7; N, 11.8. Found: C, 50.8; H, 3.8; Br, 33.5; N, 12.1.

(b) The following procedure was found to be more suitable for large scale preparations.

A solution of *o*-phenylenediacetonitrile (18 g., 0.115 mole) in acetic acid (30 ml.) was added dropwise to a stirred 30% solution (72 g.) of hydrogen bromide in acetic acid. After two hours the precipitated solid was removed by filtration, washed with a little acetic acid, then ether and dried. The product (28 g.) was dissolved in dimethylformamide (100 ml.) and the solution added dropwise with stirring to saturated sodium bicarbonate solution (500 ml.). The precipitate was removed by filtration, washed thoroughly with water and dried. One crystallization from ethyl acetate afforded the pure product (16.0 g., 61.4%) m.p. 193-195°.

o-Phenylenediacetimide.

2-Amino-4-bromo-1H-3-benzazepine (0.3 g., 1.27 mmoles) in 90% aqueous ethanol (10 ml.) was refluxed for 4 hours. When cooled, the reaction mixture afforded the product in quantitative yield. Recrystallization from hot water afforded the pure compound m.p. 193° [lit. (8) 191-192°].

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.6; H, 5.1; N, 8.0. Found: C, 68.7; H, 5.1; N, 8.1.

2-Amino-4-iodo-1H-3-benzazepine.

To a cooled solution of *o*-phenylenediacetonitrile (13 g., 0.0833 mole) in acetic acid (50 ml.) there was added dropwise with stirring a solution (330 ml.) of 12% hydrogen iodide in acetic acid. After standing overnight, the precipitated yellow solid was removed by filtration and stirred with sodium bicarbonate solution until effervescence ceased. The pale yellow solid (8.4 g., 35.5%) was recrystallized from methanol and led to the pure product m.p. 191-193°.

Anal. Calcd. for $C_{10}H_9IN_2$: C, 42.3; H, 3.2; I, 44.7; N, 9.9. Found: C, 42.4; H, 3.1; I, 44.7; N, 9.8.

2-Amino-1H-3-benzazepine (VI).

A solution of 2-amino-4-bromo-1H-3-benzazepine (III; 1.2 g., 5.0 mmoles) in ethanol (150 ml.) containing potassium bicarbonate (1.0 g.) was stirred in an atmosphere of hydrogen at normal pressure, with a 10% palladium-on-charcoal catalyst (150 mg.). After three hours hydrogen uptake (100% of theory) ceased. The reaction solution was filtered through diatomaceous earth and the solvent removed *in vacuo*, at less than 40° (19). The crystalline residue was recrystallized from methylene chloride giving the product (0.51 g., 63%) m.p. 165°

(some decomposition was evident at 150°). The infrared spectrum of this compound showed bands at 2.99, 3.19 (-NH) 6.00 and 6.37 μ.

U.V. λ max: 295 mμ (ε, 14,000).

Anal. Calcd. for $C_{10}H_{10}N_2$: C, 75.9; H, 6.4; N, 17.7. Found: C, 76.0; H, 6.5; N, 17.6.

2-(N-morpholino)-1H-3-benzazepine (VII).

A solution of 2-amino-1H-3-benzazepine (0.8 g., 5.0 mmoles) in morpholine (25 ml.) was refluxed under an atmosphere of nitrogen for one hour. The excess morpholine was then removed *in vacuo* and the residual dark gum dissolved in methylene chloride. The solution was percolated through a column of silica gel and the column eluted with a methylene chloride-ethyl acetate mixture (1:3). Evaporation of this eluate afforded the crude product (0.43 g., 36.8%). A sample prepared for analysis by crystallization from ether-petroleum ether (b.p. 30-60°) had m.p. 70-71°. Its n.m.r. spectrum is deuteriochloroform showed a single peak at 3.31 ppm ($-CH_2-$), two doublets at 6.33 and 7.7 ppm for vinyl hydrogens splitting one another and a peak at 3.61 ppm for the hydrogen atoms of the morpholine group. The infrared spectrum showed no absorption for N-H in the 3 μ region.

U.V. λ max: 307 mμ (ε, 11,450).

Anal. Calcd. for $C_{14}H_{16}N_2O$: C, 73.7; H, 7.1; N, 12.3. Found: C, 73.5; H, 7.1; N, 12.3.

2-Amino-4,5-dihydro-1H-3-benzazepine Hydrobromide (VIII).

A solution of 2-amino-4-bromo-1H-3-benzazepine (2.35 g., 10.0 mmoles) in ethanol (50 ml.) containing acetic acid (4 ml.) was stirred in an atmosphere of hydrogen at 42 lbs./sq. in. with a 10% palladium-on-charcoal catalyst (0.1 g.). After 45 minutes the pressure had dropped to 24 lbs./sq. in. and no further diminution in pressure occurred thereafter. The reaction mixture was warmed to effect solution of precipitated solid, filtered and taken to dryness under reduced pressure. The residue was crystallized from methanol-ethyl ether to give the product (2.2 g., 92%) as long thin blades m.p. 207-208°.

Anal. Calcd. for $C_{10}H_{13}BrN_2$: C, 49.8; H, 5.4; Br, 33.1; N, 11.6. Found: C, 49.8; H, 5.2; Br, 33.0; N, 11.7.

2-Amino-4-bromo-1H-naphtho[2,3-d]azepine (X; Y = Br).

A suspension of 2,3-bis(cyanomethyl)naphthalene (1.0 g., 4.85 mmoles) in glacial acetic acid (10 ml.) was treated with a 30% solution (20 ml.) of hydrogen bromide in acetic acid. After three hours the suspended salt was removed by filtration and triturated with a saturated solution of sodium bicarbonate. The insoluble solid (1.1 g., 79%) was removed by filtration washed with water and dried in air. Recrystallization of this material from dimethylformamide afforded the pure product m.p. 240-242° dec. Its infrared spectrum showed significant bands at 2.92, 3.05, 3.21 and 6.08 μ.

Anal. Calcd. for $C_{14}H_{11}BrN_2$: C, 58.6; H, 3.9; Br, 27.8; N, 9.8. Found: C, 58.6; H, 4.0; Br, 27.6; N, 9.5.

2-Amino-4-iodo-1H-naphtho[2,3-d]azepine (X; Y = I).

This compound (1.4 g., 86.6%) was prepared from 2,3-bis(cyanomethyl)naphthalene (1.0 g., 4.85 mmoles) and 13% hydrogen iodide in glacial acetic acid in the same way as described for the anlogous bromo compound above. Recrystallization from dioxane led to the pure compound m.p. 240-242°.

Anal. Calcd. for $C_{14}H_{11}IN_2$: C, 50.3; H, 3.3; I, 38.0; N, 8.4. Found: C, 50.3; H, 3.5; I, 38.2; N, 8.2.

Cyclization of 1,2-Bis(cyanomethyl)naphthalene with Hydrogen Bromide.

1,2-Bis(cyanomethyl)naphthalene (0.5 g., 2.43 mmoles) was cyclized with hydrogen bromide using the same procedure as was used for the 2,3-isomer. The crude product (0.7 g.) was recrystallized several times from dimethylformamide and afforded pure XII or XIII m.p. 232-238° dec., in poor yield (0.22 g., 31.6%).

Anal. Calcd. for $C_{14}H_{11}BrN_2$: C, 58.6; H, 3.9; N, 9.8. Found: C, 58.7; H, 3.9; N, 9.6.

2,2'-Dicyanobiphenyl.

2,2'-Dibromobiphenyl (10 g., 0.032 mole) and cuprous cyanide (6.5 g., 0.0725 mole) were added to dimethylformanide (30 ml.) and the mixture refluxed for three hours. The hot solution was then added to 20% potassium cyanide solution (400 ml.) and stirred for 2 hours. The product was removed by filtration and, after drying, crystallized from ethyl acetate to give pure 2,2'-dicyanobiphenyl (4.5 g., 69%) m.p. 179-180° [lit. (20) 172°].

6,7-Dihydro-5-imino-5H-dibenz[c,e]azepine-7-one (XV) and its Hydrobromide.

2,2'-Dicyanobiphenyl (1.0 g., 4.9 mmoles) was stirred with a 30% solution of hydrogen bromide in glacial acetic acid (25 ml.). It slowly dissolved and on stirring overnight a precipitate appeared. This was filtered under dry nitrogen, washed with acetic acid and ether, then dried (1.4 g., 98%) m.p. 230°. Its infrared showed significant bands at 5.86 and 5.98 μ but only broad absorption for N-H in the 3 μ region.

Anal. Calcd. for $C_{14}H_{11}BrNO$: C, 55.5; H, 3.7; N, 9.2. Found: C, 55.5; H, 3.7; N, 9.4.

A sample (1.4 g., 4.85 mmoles) of the above material was triturated with sodium bicarbonate solution and the resulting white powder removed by filtration. Recrystallization of the dried product (1.0 g., 92.5%) from a large volume of ethyl acetate-methanol afforded pure XV as a white powder, m.p. 247-250°.

Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.7; H, 4.5; N, 12.6. Found: C, 76.0; H, 4.5; N, 12.6.

7-Bromo-5-Imino-5H-dibenz[c,e]azepine Hydrobromide (XVI).

2,2-Dicyanobiphenyl (1.0 g., 4.9 mmoles) was dissolved in dry benzene (125 ml.) and the solution cooled in ice-water. Dry hydrogen bromide was bubbled through the solution for three hours and the precipitate was then removed by filtration. The resulting solid was washed with anhydrous ether (3 x 50 ml.) and then dried overnight in a stream of rigorously dried nitrogen. The product (1.7 g., 98%) m.p. 250-252° exhibited broad bands in its infrared spectrum in the 3.0-4.0 and 6.0-6.3 μ regions.

Anal. Calcd. for $C_{14}H_{10}Br_2N_2$: C, 45.9; H, 2.8; Br, 43.7; N, 7.7. Found: C, 45.6; H, 3.0; Br, 43.5; N, 7.9.

Diphenimide (XVII).

A sample (0.3 g., 0.84 mmole) of XVI was stirred with a mixture of glacial acetic acid (10 ml.) and water (1 ml.) overnight at room temperature. After pouring into water (150 ml.) the product was removed and dried (25 mg; 13% yield). One recrystallization from acetone afforded pure diphenimide m.p. 223-224° [lit. (21) 217-219°].

Anal. Calcd. for $C_{14}H_9NO_2$: C, 75.3; H, 4.1; N, 6.3. Found: C, 75.2; H, 4.1; N, 6.3.

2-Acetylamino-4-bromo-1H-3-benzazepine (XVIII; R = $COCH_3$).

Acetic anhydride (10 ml.) and III (0.6 g., 2.5 mmoles) were stirred at room temperature. After 45 minutes the solution became homogeneous but 15 minutes later a precipitate began to appear. After standing overnight the excess acetic anhydride was removed under reduced pressure at about 40°. The residue was recrystallized from methylene chloride-petroleum ether (b.p. 30-60°) and afforded the product (0.5 g., 72%) m.p. 172-173° (phase change at 146-148°). The infrared spectrum showed a doublet at 3.10 and 3.16 μ for N-H absorption and bands at 5.96, 6.18 and 6.27 μ.

U.V. λ max: 276 mμ (ε, 8,300).

Anal. Calcd. for $C_{12}H_{11}BrN_2O$: C, 51.6; H, 4.0; Br, 28.6; N, 10.0. Found: C, 51.9; H, 3.8; Br, 28.7; N, 10.0.

2-Acetylamino-3-acetyl-4-bromo-3H-3-benzazepine (XIX).

To acetic anhydride (60 ml.) at 100° there was added III (5 g., 0.021 mole). The mixture was stirred vigorously and heated at reflux until the reaction mixture was homogeneous (~ 15 minutes). The excess acetic anhydride was removed under reduced pressure and the residue crystallized from methylene chloride-ether. Two crops of essentially pure material were combined (4.0 g., 59%) and a sample recrystallized from a small amount of methylene chloride for analysis. The infrared spectrum of this material, m.p. 160°, showed bands at 3.03, 5.97, 6.06 and 6.13 μ.

U.V. λ max: 250 (ε, 38,800); 280 mμ (ε, 10,800).

Anal. Calcd. for $C_{14}H_{13}BrN_2O_2$: C, 52.4; H, 4.1; Br, 24.8; N, 8.7. Found: C, 52.1; H, 4.1; Br, 24.9; N, 8.4.

3-Acetyl-4-bromo-2-diacetylamino-3H-3-benzazepine (XXII).

2-Amino-4-bromo-1H-3-benzazepine (III) hydrobromide (3 g., 9.4 mmoles) was added to acetic anhydride (50 ml.) and the mixture heated at 100° until solution was effected. After standing overnight at room temperature the bulk of the acetic anhydride was removed under reduced pressure and the residue stirred with sodium acetate solution briefly. The gummy product was then crystallized from methanol and afforded only a low yield (0.2 g., 5.9%) of crude XXII. Recrystallization from the same solvent led to the pure material m.p. 149° (softening 140°). Its infrared spectrum showed the absence of any NH absorption in the 3 μ region. Carbonyl absorption was evident at 5.78, 5.84 and 5.90 μ.

Anal. Calcd. for $C_{16}H_{15}BrN_2O_3$: C, 52.9; H, 4.2; Br, 22.0; N, 7.7. Found: C, 50.9; H, 4.1; Br, 21.3; N, 7.5.

1-(4-Bromo-1H-3-benzazepin-2-yl)-3-phenylurea (XVIII; R = $CONHC_6H_5$).

A solution of 2-amino-4-bromo-1H-3-benzazepine (III; 0.8 g., 3.38 mmoles) in tetrahydrofuran (20 ml.) was treated dropwise with phenyl isocyanate (0.5 g., 4.2 mmoles) in tetrahydrofuran (5 ml.). After two hours the white precipitate (1.2 g., 100%) was removed by filtration

and recrystallized from ethyl acetate to give the pure material m.p. 245-246°.

Anal. Calcd. for $C_{17}H_{14}BrN_3O$: C, 57.3; H, 3.9; N, 11.8. Found: C, 57.5; H, 3.8; N, 12.0.

1-(1H-3-Benzazepin-2-yl)-3-phenylurea (XXVI; R = $CONHC_6H_5$).

A solution of IV (0.8 g., 5.05 mmoles) in tetrahydrofuran (10 ml.) was treated with phenyl isocyanate (0.5 g., 4.2 mmoles) in the same solvent (5 ml.). After 2 hours the precipitated solid (1.1 g., 78.5%) was removed by filtration. Recrystallization of a sample from ethyl acetate afforded the analytical specimen m.p. 202-205°.

Anal. Calcd. for $C_{17}H_{15}N_3O$: C, 73.6; H, 5.5; N, 15.2. Found: C, 73.9; H, 5.5; N, 15.3.

1-(1H-3-Benzazepin-2-yl)-3-phenyl-2-thiourea (XXVI; R = $CSNHC_6H_5$).

2-Amino-1H-3-benzazepine (0.3 g., 1.9 mmoles) in tetrahydrofuran (25 ml.) was treated with phenyl isothiocyanate (0.3 g., 2.2 mmoles). The mixture was refluxed for 0.5 hour, then cooled and scratched to induce crystallization. The product (0.5 g., 89.5%) was recrystallized from methylene chloride m.p. 173-175°.

Anal. Calcd. for $C_{17}H_{15}N_3S$: C, 69.6; H, 5.2; N, 14.3; S, 10.9. Found: C, 69.8; H, 5.2; N, 14.3; S, 10.8.

1-(2-Acetylamino-1H-3-benzazepin-4-yl)pyridinium Bromide (XXIII).

2-Amino-4-bromo-1H-3-benzazepine (0.5 g., 2.1 mmoles) was added to a mixture of acetic anhydride (3 ml.) and pyridine (1.5 ml.). On heating the reaction flask for 0.5 hour, a bright yellow crystalline precipitate appeared. After cooling (1 hour) the crystals were separated by filtration and washed with ether. One crystallization of this material (0.3 g., 40%) from a large volume of ethanol afforded the pure product m.p. 262-264°. Its infrared spectrum showed bands at 2.95, 3.20 and 3.26 μ (-NH) and at 5.82 (CO), 6.21 and 6.29 μ and its n.m.r. spectrum had peaks at 2.58 (CH_3CO), 4.46 (CH_2), 7.82 (phenyl H), 8.24 (vinyl H) and three sets of peaks in the 8.3-9.8 ppm region corresponding to the five hydrogens of the pyridine ring.

Anal. Calcd. for $C_{17}H_{16}BrN_3O$: C, 57.0; H, 4.5; Br, 22.3; N, 11.7. Found: C, 57.0; H, 4.7; Br, 22.0; N, 11.6.

(2-Amino-1H-3-benzazepin-4-yl) triethylammonium Bromide (XXIV).

A solution of III (1.0 g., 4.2 mmoles) in tetrahydrofuran (25 ml.) was treated with triethylamine (0.48 g., 4.8 mmoles) in one portion. The mixture was stirred overnight at room temperature and the precipitated solid then removed and dried (0.4 g.). On further standing the mother liquors yielded additional material (0.3 g.) of lesser purity (45% total yield).

A sample of the first crop was crystallized from methanol-ethyl acetate and gave (XXIV) as its methanolate. At 145-150° the crystals lost their shape and became a transparent glass but no true melting was observed. Its infrared spectrum showed bands at 2.85, 2.91, 2.99, 3.05 and 3.16 μ (-NH and -OH) and at 6.12, 6.22, 6.34 and 6.41 μ.

Anal. Calcd. for $C_{17}H_{28}BrN_3O$: C, 55.1; H, 7.6; Br, 21.6; N, 11.3. Found: C, 54.6; H, 7.8; Br, 21.7; N, 11.5.

2-Amino-1H-3-benzazepin-4-yl Thiocyanate (XXV).

2-Amino-4-bromo-1H-3-benzazepine (2.4 g., 10.0 mmoles) was dissolved in dry dimethylformamide and solid dry sodium thiocyanate (0.8 g., 10 mmoles) added to the solution. The mixture was heated at 95° for 3.5 hours and then poured into water. The precipitate was removed by filtration, dried and recrystallized from methanol (charcoal was used to remove color) to give small dense crystals (0.9 g., 41.7%) m.p. 179-181°. The infrared spectrum of this compound showed bands at 2.95 (-NH) and 4.60 μ (-SCN). Its n.m.r. spectrum very closely resembled that of the starting material, III.

Anal. Calcd. for $C_{11}H_9N_3S$: C, 61.4; H, 4.2; N, 19.5; S, 14.9. Found: C, 61.2; H, 4.3; N, 19.5; S, 15.0.

2-Acetylamino-3-acetyl-3H-3-benzazepine (XXVII).

2-Amino-3,1H-benzazepine (0.5 g., 3.16 mmoles) was added to acetic anhydride (10 ml.) and the mixture refluxed for 30 minutes. The excess anhydride was removed under reduced pressure and the gummy brown residue crystallized from methylene chloride-ether. Three crops of crystals were combined to give 0.5 g. (65.5%) of the product. A sample recrystallized from the same solvent had m.p. 154°. Its infrared spectrum showed bands at 3.04, 3.14 (NH absorptions) 5.89, 6.00 and 6.11 μ. The n.m.r. spectrum in trifluoroacetic acid had single peaks at 2.26 and 2.36 ppm for acetyl hydrogen and two doublets and a single at 6.49 (τ = 7.5), 6.79 (τ = 7.5) and 6.94 ppm respectively for three vinyl hydrogens.

U.V. λ max: 247 (ϵ, 28,600); 286 mμ (ϵ, 7,470).

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.4; H, 5.8; N, 11.6. Found: C, 68.9; H, 5.7; N, 11.6.

2-Acetylamino-4,5-dihydro-1H-3-benzazepine Hydrobromide (XXVIII).

A solution of XVIII (R = $COCH_3$; 1.9 g., 6.8 mmoles) in ethyl acetate (50 ml.) and methanol (50 ml.) was stirred in the presence of calcium carbonate (0.7 g., 7.0 mmoles) with a 10% palladium-on-charcoal catalyst under hydrogen at atmospheric pressure. Absorption of hydrogen (97% theory) ceased after 3.5 hours. The solution was filtered and the filtrate concentrated *in vacuo* until crystallization commenced. The first crop of crystals (1.0 g., 52%) was removed and recrystallized from methanol-ether to give the product m.p. 242-245°. It showed significant bands at 3.18 (-NH), 5.74 (acetyl) and 6.00 μ in the infrared spectrum.

Anal. Calcd. for $C_{12}H_{15}BrN_2O$: C, 50.9; H, 5.3; Br, 28.2; N, 9.9. Found: C, 51.0; H, 5.4; Br, 28.2; N, 9.6.

2-Acetamino-4,5-dihydro-1H-3-benzazepin-4-one. (XXIX).

To a solution of XVIII (0.28 g., 1.0 mmole) in ethanol (20 ml.), there was added potassium bicarbonate (0.11 g., 1.1 mmoles) in water (5 ml.). The mixture was heated on the steam bath for 0.5 hour and the solvents then removed under reduced pressure. The residual gum was extracted with methylene chloride and the dried extract concentrated and diluted with ether. The crystalline precipitate (50 mg., 23%) was recrystallized from ethanol to give pure XXIX m.p. 261-263°. Its infrared spectrum showed bands at 3.08, 3.14 and 3.22 μ (-NH) and at 5.91, 5.97 and 6.05 μ.

U.V. λ max: 235 (ϵ, 9,570); 294 mμ (ϵ, 12,400).

Anal. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.7; H, 5.6; N, 13.0. Found: C, 66.8; H, 5.8; N, 13.3.

2-Acetylamino-3-acetyl-4,5-dihydro-3H-3-benzazepine (XXX).

2-Acetylamino-3-acetyl-4-bromo-3H-3-benzazepine (3.2 g., 10.0 mmoles) was dissolved with heating in ethanol (75 ml.). To the cooled solution there was added potassium acetate (1.0 g.) and 10% palladium-on-charcoal catalyst (0.2 g.). The mixture was stirred with hydrogen at atmospheric pressure for 2 hours during which time the theoretical amount of gas was absorbed. The catalyst was then removed by filtration and the filtrate taken to dryness under reduced pressure. The residue was taken up in methylene chloride and the resulting solution washed with water, sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Concentration of this solution followed by the addition of ether afforded the crystalline product (1.5 g., 61.5%).

A sample crystallized from the same solvents for analysis had m.p. 142-143°. Its infrared spectrum showed bands at 3.08, 3.16 (-NH) 5.95, 6.06 and 6.12 μ.

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.8; H, 6.6; N, 11.5. Found: C, 69.1; H, 6.6; N, 11.6.

2-Hydroxymethylamino-1H-3-benzazepine (XXXI; R = H).

To a solution of VI (0.5 g., 3.17 mmoles) there was added aqueous 37% formaldehyde solution (2 g., 24.7 mmoles). After 2 hours the crystalline precipitate was removed (0.59 g., 99%) and recrystallized from methanol to give the pure product m.p. 136-139°. Its infrared spectrum showed absorption at 3.01 (-NH), 3.20 (broad -OH), 6.16, 6.30 and 6.39 μ.

U.V. λ max: 294 mμ (ϵ, 13,400).

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.2; H, 6.4; N, 14.9. Found: C, 70.3; H, 6.5; N, 14.5.

1H-3-Benzazepin-2-yl(1-hydroxy-2,2,2-trichloroethyl)amine (XXXI) (R = CCl_3).

2-Amino-1H-3-benzazepine (VI; 0.5 g., 3.47 mmoles) and chloral hydrate (0.6 g., 3.3 mmoles) were dissolved in ethanol (10 ml.) and allowed to stand at room temperature overnight. Concentration of the ethanol *in vacuo* afforded two crops of crystals of the pure material (0.8 g., 83%) m.p. 144-148°. Crystallization of a sample from acetone did not improve the melting point. Its infrared spectrum showed bands at 3.00, 3.10, 3.16, 6.18, 6.28 and 6.46 μ.

Anal. Calcd. for $C_{12}H_{11}Cl_3N_2O$: C, 47.2; H, 3.6; Cl, 34.8; N, 9.2. Found: C, 47.2; H, 3.4; Cl, 34.7; N, 9.2.

3-Phenyl-11H-imidazo[1,2-c]-3-benzazepine (XXXII; R = C_6H_5).

A solution of 2-amino-1H-3-benzazepine (0.5 g., 3.47 mmoles) and 2-bromoacetophenone (0.64 g., 3.47 mmoles) in ethanol (25 ml.) containing potassium bicarbonate (0.5 g.) was refluxed for 3 hours. On cooling the reaction mixture the product (0.6 g., 73.5%) crystallized. This was dissolved in methylene chloride and percolated through a column of alumina (10 g.) to remove color. Concentration of the first 50 ml. of eluate afforded the product as flat white blades m.p. 204-205°.

U.V. λ max: 262 mμ (ϵ, 28,600).

Anal. Calcd. for $C_{18}H_{14}N_2$: C, 83.7; H, 5.5; N, 10.9. Found: C, 83.5; H, 5.5; N, 10.8.

3-Methyl-11H-imidazo[1,2-c]-3-benzazepine (XXXII; R = CH_3).

To a solution of VI (1.0 g., 6.33 mole) in ethanol (50 ml.) there was added chloroacetone (1.0 g., 10.8 mmoles), sodium bicarbonate (0.84 g.) and water (15 ml.). The mixture was refluxed for 3 hours and at the end of this time the bulk of the solvents was removed under reduced pressure. The residue was worked up in the usual way using methylene chloride, and the dried extract passed through a column of silica gel (50 g.). The eluate on evaporation yielded a crystalline solid (0.23 g., 18%) which when recrystallized from ether led to pure XXXII (R = CH_3), m.p. 95-97°.

Anal. Calcd. for $C_{13}H_{12}N_2$: C, 79.6; H, 6.2; N, 14.3. Found: C, 79.8; H, 6.2; N, 13.9.

Attempted Hydrolysis of 2-Amino-1H-3-benzazepine.

A sample (0.25 g., 1.58 mmoles) of VI was dissolved in 5% hydrochloric acid (10 ml.) and the solution refluxed for 2 hours. The colorless solution was evaporated to dryness under reduced pressure and the crystalline residue recrystallized from methanol-ethyl acetate to give VI hydrochloride (0.24 g., 78%) as white needles m.p. 220° dec.

Anal. Calcd. for $C_{10}H_{11}ClN_2$: C, 61.7; H, 5.7; Cl, 18.2; N, 14.4. Found: C, 61.5; H, 5.5; Cl, 18.1; N, 14.2.

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REFERENCES

(1) F. Johnson, J. P. Panella, A. A. Carlson and D. H. Hunneman, *J. Org. Chem.*, 27, 2473 (1962); F. Johnson and W. A. Nasutavicus, *ibid.*, 27, 3953 (1962); *ibid.*, 28, 1877 (1963); *ibid.*, 29, 153 (1964).

(2a) K. Dimroth and H. Freyschlag, *Chem. Ber.*, 89, 2602 (1956); (b) R. Huisgen and M. Appl, *ibid.*, 91, 1 (1958); R. Huisgen, D. Vossius and M. Appl, *ibid.*, 91, 12 (1958); (c) H. W. Whitelock, *Tetrahedron Letters*, 593 (1961); (d) P. Craig, B. Lester, A. Saggiomo, C. Kaiser and C. Zirkle, *J. Org. Chem.*, 26, 135 (1961); J. Rigandy and P. Tardieu, *Compt. rend.*, 248, 1538 (1959); E. G. Bergmann and M. Rabinovitz, *J. Org. Chem.*, 25, 827 (1960); (e) K. Hafner and C. Konig, *Angew. Chem.*, 75, 89 (1963); R. J. Cotter and W. F. Beach, *J. Org. Chem.*, 29, 751 (1964); K. Hafner, *Angew. Chem.*, 75, 1041 (1963); (f) P. J. Brignell, E. Bullock, U. Eisner, B. Gregory and J. W. Johnson, *J. Chem. Soc.*, 4819 (1963); (g) W. Triebs and A. Lange, *J. prakt. Chem.*, 14, 208 (1961); (h) L. A. Paquette, *J. Am. Chem. Soc.*, 84, 4987 (1962); (i) E. Vogel and R. Erb, *Angew. Chem.*, 74, 76 (1962).

(3) E. G. Howard, U. S. Patent 2,810,726.

(4) J. Decombe and C. Verry, *Compt. rend.*, 256, (24) 5156 (1963).

(5) The same type of behavior has been observed with the adduct of adiponitrile and hydrogen chloride (E. N. Zil'berman and A. E. Kulikova, *Zh. Obshch. Khim.*, 29, 1694 (1959).

(6) The commercial product (Aldrich Chemical Co.) comprising mainly the *trans* isomer was used.

(7) A discussion of the structures of these salts will be published at a later date.

(8) This undoubtly represents the better way to prepare this compound since the only other method reported [J. O. Halford and B. Weissman, *J. Org. Chem.*, 17, 1646 (1952)] involves considerable experimental difficulty and low yields.

(9) Unpublished observations. See also references 4 and 12.

(10) C. Engler, *Ann.*, 149, 297 (1869).

(11) J. H. Osborn, *Disseration Abstr.*, 19, 2475 (1959).

(12) Measured downfield from internal TMS taken at 0 ppm. The solvent used in this case was deuteriochloroform containing a little trifluoroacetic acid to facilitate the solubility of III. Integrations of the peaks in this and other spectra agree with the postulated structures under discussion.

(13) W. Reid and H. Bodem, *Chem. Ber.*, 89, 708 (1956).

(14) This doubtless arises from the *in situ* conversion of acetic acid to its anhydride or acetyl bromide.

(15) In deuteriochloroform both acetyl methyls absorb in the same place, at 2.19 ppm.

(16) E. Klingsberg, "Pyridine and Derivatives Part II", Interscience Publishers, Inc., New York, 1961, p. 345 ff.

(17) K. Schilling, F. Kröhnke and B. Kickhofen, *Chem. Ber.*, 88, 1093 (1955).

(18) R. L. Shriner and F. W. Neumann, *Chem. Rev.*, 35, 351 (1944).

(19) At higher temperatures considerable loss of product occurs through decomposition.

(20) H. W. Underwood and L. A. Clough, *J. Am. Chem. Soc.*, 51, 584 (1929).

(21) C. W. Muth and W. L. Sung, *West. Va. Univ. Bull.*, Ser. 56, No. 12-15, 46 (1955); *Chem. Abstrs.*, 51, 5735 (1957).

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