ml portions) was added, and the mixture was distilled until 800 ml of distillate had been collected. The distillate was extracted with three portions of ether. The ether extracts were washed three times with water and twice with brine, dried ($MgSO_4$), and concentrated to leave 2.85 g (60%) of tan solid, mp 88–92°. This solid was dissolved in a minimum amount of benzene and chromatographed on a 1.58 × 28.5 cm column packed with unactivated Alcoa F-20 alumina. Elution with 1 l. of hexane followed by concentration left 2.06 g of white solid, mp 90–92°. Recrystallization of a small sample from methanol afforded an analytical sample: mp 92–93°; uv max (95% C_2H_5OH) 230 mμ (ε 5630), 238 (8300), 264.5 (16,000), 273 (16,700) 280 (sh, 7100), 287 (8,600), and 299 (13,410); nmr ($CDCl_3$) τ 2.30–3.05 (m, 6, $C_{10}H_6S$) and 6.30 (s, 2, $C_6H_4CH_2C_4H_2S$).

Anal. Calcd for $C_{11}H_8S$: C, 76.69; H, 4.68; S, 18.62. Found: C, 76.53; H, 4.62; S, 18.78.

8H-Indeno[1,2-*c*]thiophene-3-carboxylic Acid (16).—A 100-ml, three-necked flask fitted with a calcium chloride drying tube, reflux condenser, and pressure-equalizing addition funnel was flame dried under a stream of nitrogen. To a solution of **3** (0.50 g, 2.90 mmol, homogeneous by tlc) dissolved in anhydrous ether (30 ml) was added ethereal 1.26 *M* *n*-butyllithium[15] (2.30 ml, 2.90 mmol). The solution turned dark red immediately upon addition of the *n*-butyllithium and was refluxed for 30 min. Refluxing was stopped and the reaction was quenched with *ca.* 10 g of freshly chipped Dry Ice. Several minutes after the vigorous reaction had subsided, water (20 ml) was added and the layers were separated. The aqueous layer was washed with four portions of ether and the ether solutions were back washed with one portion of water. The aqueous layers were combined, cooled, acidified with 1 *M* hydrochloric acid, and extracted with three portions of ether. The ether solution was washed with two portions of water and two portions of brine, dried ($MgSO_4$), and evaporated to leave 0.28 g (45%) of acidic material.

The neutral ether solution was evaporated to yield 0.10 g of unchanged starting material.

An analytical sample of **16** was obtained by recrystallization from benzene–hexane of a sample obtained in a similar experiment: mp 209–210° dec; ir (KBr) 1640 cm^{-1} (acid C=O); nmr (acetone-*d*) τ 1.25 (m, 1, H-4), 2.20–2.65 (m, 4, $C_{10}H_4S$), and 6.30 (s, 2, $C_6H_3CH_2C_4HS$).

Anal. Calcd for $C_{12}H_8O_2S$: C, 66.65; H, 3.73; S, 14.83. Found: C, 66.79; H, 3.78; S, 14.68.

Fluorene-4-carboxylic Acid (17).—Fluorenone-4-carboxylic acid (5 g) was reduced in the manner described by Weisburger and Weisburger:[16] yield 57%; mp 192–193° (lit.[16] mp 191–192°); ir (KBr) 1680 cm^{-1} (acid C=O); nmr ($CDCl_3$) τ −3.2 (s, 1, CO_2H), 1.5 (m, 1, H-4), 2.0–2.7 (m, 6, $C_{12}H_6$), and 6.10 (s, $C_{12}H_6CH_2$).

Anal. Calcd for $C_{14}H_{10}O_2$: C, 79.61; H, 4.77. Found: C, 79.82; H, 4.83.

Registry No.—**2**, 7260-71-1; **3**, 7260-70-0; **8**, 5706-08-1; **9**, 23062-40-0; **10**, 23062-41-1; **11**, 23062-42-2; **12**, 23062-43-3; **13**, 23062-44-4; **13** methyl ester, 23062-45-5; **16**, 23062-46-6; **17**, 6954-55-8.

Acknowledgment.—The authors wish to thank Mr. Robert Smith, Mr. Donald Wieland, and Kiyoshi Yamauchi for recording the nmr spectra.

(16) E. K. Weisburger and J. H. Weisburger, *J. Org. Chem.*, **20**, 1396 (1955).

Azepinoindoles. IV.[1] 1,2,3,4,5,10-Hexahydroazepino[3,4-*b*]indole and 1,2,3,4,5,10-Hexahydroazepino[2,3-*b*]indole

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The selective preparation of both 3,4,5,10-tetrahydroazepino[3,4-*b*]indol-1(2H)-one (**5**) and 3,4,5,10-tetrahydroazepino[2,3-*b*]indol-2(1H)-one (**14**) from 1,2,3,4-tetrahydrocarbazol-1-one *via* the Beckmann rearrangement is described. Rapid air oxidation of the initial product derived from the lithium aluminum hydride reduction of **14** gave 2,3,4,5-tetrahydroazepino[2,3-*b*]indol-5a(1H)-ol (**17**). The proof of structure **17** and some of its interesting chemistry is discussed.

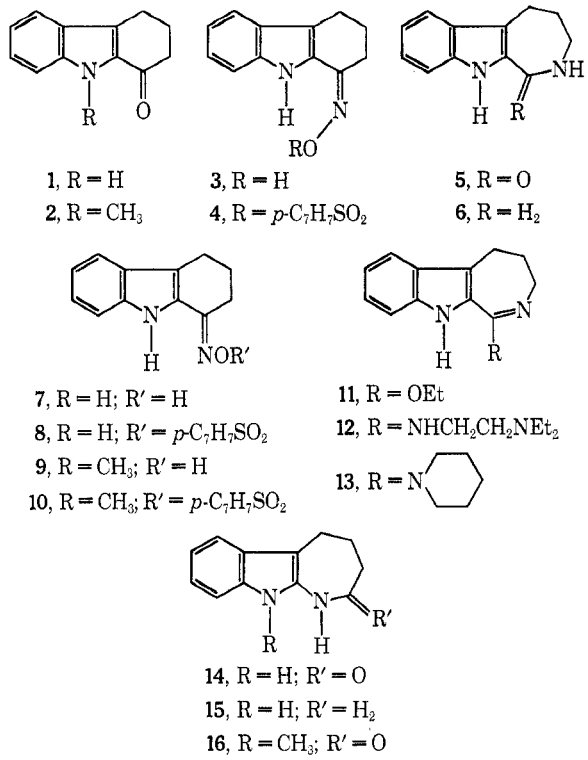
Recently,[2] we reported the selective preparation of 3,4,5,6-tetrahydroazepino[4,3-*b*]indol-1(2H)-one and 3,4,5,6-tetrahydroazepino[3,2-*b*]indol-2(1H)-one *via* the Beckmann rearrangements of the oxime and tosyloxy oxime of 1,2,3,4-tetrahydrocarbazol-4-one with polyphosphoric acid and deactivated alumina, respectively. Concurrent with this study we investigated the preparation and chemistry of 3,4,5,10-tetrahydroazepino[3,4-*b*]indol-1(2H)-one (**5**) and 3,4,5,10-tetrahydroazepino-[2,3-*b*]indol-2(1H)-one (**14**). The latter investigation is the subject of the present discussion.

The reaction of 1,2,3,4-tetrahydrocarbazol-1-one (**1**)[3] with hydroxylamine (Chart I) gave a mixture of oximes **3** and **7** which could be separated by silica gel chromatography. Both oximes underwent a facile rearrangement in polyphosphoric acid to give the same lactam **5** in 73–85% yield.[4] This compound **5** was also obtained by the reaction of **1** with sodium azide in polyphosphoric acid.[5] Positive identification of **5** was supplied by its characteristic uv spectrum and by its lithium aluminum hydride reduction to **6**, which had previously been reported in the literature[6] and had an nmr singlet at δ 4.00 for the C-1 protons. Alkylation of **5** with triethyloxonium fluoroborate[7] gave the expected imino ether **11**, which reacted with amines to give amidines such as **12** and **13**.[8]

Since it was apparent that in polyphosphoric acid, analogous to our previous results,[2] oxime **7** was undergoing a facile isomerization to **3** prior to Beckmann rearrangement, we employed the method of Craig and Naik[9] for the preparation of **14**. Oximes **3** and **7** were converted into the corresponding tosyloxy derivatives **4** and **8** with *p*-toluenesulfonyl chloride in pyridine. Rearrangement of **4** with neutral alumina, which had been deactivated with 1% water, gave **5** in 81% yield. The analogous rearrangement of **8** on alumina which had been deactivated with 0.5% water gave the iso-

(1) Part III: J. B. Hester, Jr., *J. Org. Chem.*, **32**, 4095 (1967).
(2) J. B. Hester, Jr., *ibid.*, **32**, 3804 (1967).
(3) S. Coffee, *Rec. Trav. Chim. Pays-Bas*, **42**, 528 (1923).
(4) H.-J. Teuber, D. Cornelius, and U. Wolcke, *Justus Liebigs Ann. Chem.*, **696**, 116 (1966), have reported the preparation of **5** by the Beckmann rearrangement of **1** oxime in polyphosphoric acid under conditions similar to ours.
(5) N. J. Doorenbos and R. E. Havranek, *J. Org. Chem.*, **30**, 2474 (1965).
(6) S. Morosawa, *Bull. Soc. Chem. Jap.*, **33**, 1113 (1960).
(7) H. Meerwein, *Org. Syn.*, **46**, 113 (1966).
(8) R. E. Benson and T. L. Cairns, *J. Amer. Chem. Soc.*, **70**, 2115 (1948).
(9) J. C. Craig and A. R. Naik, *ibid.*, **84**, 3410 (1962).

CHART I

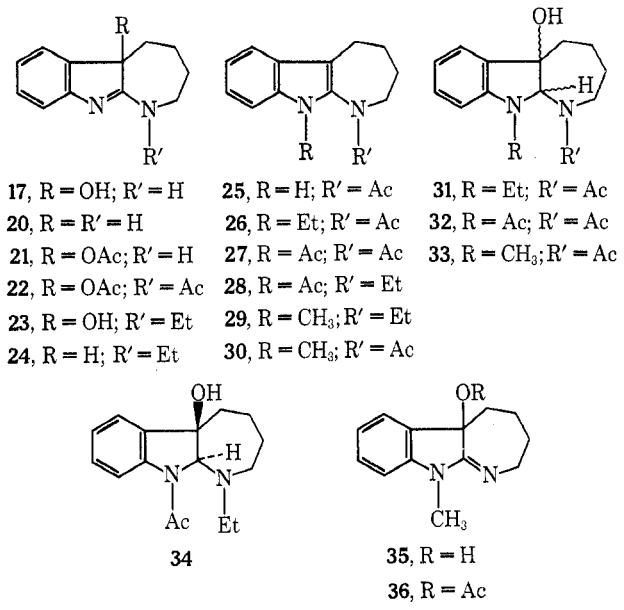


1, R = H
2, R = CH_3
3, R = H
4, R = p-$C_7H_7SO_2$
5, R = O
6, R = H_2
7, R = H; R′ = H
8, R = H; R′ = p-$C_7H_7SO_2$
9, R = CH_3; R′ = H
10, R = CH_3; R′ = p-$C_7H_7SO_2$
11, R = OEt
12, R = $NHCH_2CH_2NEt_2$
13, R = N⟨ ⟩
14, R = H; R′ = O
15, R = H; R′ = H_2
16, R = CH_3; R′ = O

meric lactam **14**, uncontaminated by **5**, in 25% yield. In this reaction, the low yield of **14** compared with that of **5** and the necessity of using a more active alumina catalyst for the rearrangement of **8** than for **4** are consistent with the view[2,10] that aryl migration in this case is more difficult than alkyl migration. The probable explanation for this phenomenon assumes that a highly strained intermediate would be required for aryl migration; however, the electronic interaction of the oxime with the indole nucleus is undoubtedly a contributing factor.

Lithium aluminum hydride reduction of **14** followed by isolation of the product by crystallization from methanol resulted in a 71% yield of the alcohol **17** (Chart II). Strong support for structure **17** was provided by the similarity of its uv absorption with that of an analogous product [λ_{max} (EtOH) 224 mμ (ϵ 20,000), 280 (13,800), 289 (13,500), and 317 (6600)] obtained by air oxidation of 3-methyl-2-piperidinoindole.[11] The presence of an alcohol function was suggested by the ir and mass spectra. Compound **17** formed stable, crystalline salts with both hydrochloric and hydrobromic acids. The nmr spectrum of these salts was interesting in that the C-2 protons were strongly deshielded by the amidine system and formed the AB portion of an ABXY spin system.[12] For the hydrochloride, assignment of the axial configuration to the downfield (δ 4.12) proton was based on its apparent ($J \cong 10$ Hz) coupling with the C-3 axial proton; the C-2 equatorial proton was found at δ 3.49 and had an apparent coupling ($J \cong 5$ Hz) with the

CHART II



17, R = OH; R′ = H
20, R = R′ = H
21, R = OAc; R′ = H
22, R = OAc; R′ = Ac
23, R = OH; R′ = Et
24, R = H; R′ = Et
25, R = H; R′ = Ac
26, R = Et; R′ = Ac
27, R = Ac; R′ = Ac
28, R = Ac; R′ = Et
29, R = CH_3; R′ = Et
30, R = CH_3; R′ = Ac
31, R = Et; R′ = Ac
32, R = Ac; R′ = Ac
33, R = CH_3; R′ = Ac

34
35, R = H
36, R = Ac

C-3 equatorial proton. When the C-2 protons were replaced by deuterium, the assigned nmr peaks were absent.[13] Confirmation of structure **17** was accomplished by an X-ray crystallographic study[14] of **17** hydrobromide using the heavy atom method with least-squares refinement of the initial trial structure. The final R factor was 0.169.

Support for the view that **17** was formed by air oxidation of an initially formed amine **15** was provided by the isolation of a stable hydrochloride salt **20** and acetamide **25**[15a] from the reactions of the lithium aluminum hydride reduction product of **14** with hydrogen chloride and acetic anhydride, respectively, before exposure to air. Assignment of structure **20** rather than the double-bond tautomer (1,2,3,4,5,10-hexahydroazepino[2,3-b]indole hydrochloride) to the hydrochloride was based on the ir spectrum which had the characteristic C=N$^+$ band at 1680 cm^{-1} and analogy to a similar product obtained from 3-methyl-2-piperidinoindole.[11,15b]

The reaction of **17** with acetic anhydride in pyridine yielded a mixture of the mono- and diacetyl derivatives **21** and **22**, which was separated by silica gel chromatography. Structure **21** was supported by the ester band at 1750 cm^{-1} in the ir, the C-methyl peak at δ 2.10 in the nmr, and peaks in the mass spectrum corresponding to the loss of CH_3CO (m/e 201), CH_3COO (m/e 185), and CH_3OOH (m/e 184) from the molecular ion (m/e 244); peaks in the mass spectrum corresponding to loss of 17 or 18 mass units from the molecular ion were not observed. Compound **22** had ir bands at 1745 and 1670 cm^{-1} for the ester and amide functions. In the mass spectrum the major fragmen-

(10) See R. Huisgen, J. Witte, and I. Ugi, *Chem. Ber.*, **90**, 1844 (1957); P. A. S. Smith in "Molecular Rearrangements," Part I, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, Chapter 8.

(11) T. Hino, M. Nakagawa, T. Wakatsuki, K. Ogawa, and S. Yamada, *Tetrahedron*, **23**, 1441 (1967).

(12) The chemical shifts presented for this discussion are based on first-order approximations.

(13) These and subsequent nmr assignments are consistent with the molecular configuration in which the azepine ring assumes a chair conformation with N-1 and C-2, -5a and -10a approximately coplanar. Support for this conformation in solution is provided by the uv spectrum, which suggests a high degree of π-orbital overlap in the amidine system; in the crystalline hydrobromide salt this conformation was demonstrated by X-ray diffraction studies.

(14) D. J. Duchamp, unpublished results.

(15) (a) Contrast this result to the work of J. Kebrle and K. Hoffmann, *Helv. Chim. Acta*, **39**, 116 (1956), which suggests that the reaction of 2-aminoindole with acetic anhydride to give 1-acetyl-2-acetamidoindole occurs *via* initial acylation of the indole nitrogen. (b) See A. R. Katritzky and J. M. Lagowski, *Advan. Heterocycl. Chem.*, **2**, 23 (1963).

tation corresponded to loss of ketene (*m/e* 244) from the molecular ion (*m/e* 286) with further fragmentation being similar to that of **21**; minor peaks of *m/e* 226 and 227 corresponded to loss of CH_3COOH and CH_3COO from the molecular ion. The nmr spectrum of **22** had singlets at δ 2.59 and 2.08 which were assigned to the amide and ester acetyl groups, respectively. In addition this spectrum offered an interesting example of the strong deshielding exerted by an amide on the adjacent equatorial proton.[2,16] The quartet at δ 4.95 was assigned to the C-2 equatorial proton based on its apparent coupling ($J \cong 7$ Hz) with the C-3 equatorial proton; the quartet at δ 3.21 had an apparent coupling ($J \cong 10$ Hz) with the C-3 axial proton and was thus assigned to the C-2 axial proton. Both C-2 proton absorptions had the expected geminal coupling constant ($J = -15$ Hz). This assignment was supported by a spin-decoupling experiment. Substitution of deuterium for the C-2 protons of **22** to give **18** was effected by acylating the product **19** derived from the lithium aluminum deuteride reduction of **14**. The nmr peaks assigned to the C-2 protons of **22** were absent in the spectrum of **18**.

Brief treatment with 1 equiv of sodium hydroxide in ethanol at ambient temperature converted **22** into the original alcohol **17**. Lithium aluminum hydride reduction of **22** gave a mixture of **17** and a new alcohol **23**. The latter compound **23** was also obtained in 75% yield from the lithium aluminum hydride reduction of **25**. The uv spectrum of **23** was similar to that of **17**; the presence of the hydroxyl and ethyl moieties was demonstrated by the nmr and mass spectra.

Catalytic hydrogenation of **21** with a palladium catalyst in acetic anhydride gave **25** as the only isolable product. An explanation for this transformation assumes either (a) initial reduction of the amidine double bond followed by elimination of acetic acid and acylation of the resulting amine **15** or (b) hydrogenolysis of the acetoxy moiety to give **15**, which could subsequently undergo acylation by the acetic anhydride. This transformation thus offers strong chemical support for the gross structure of oxidation product **17**.

Catalytic hydrogenation of **17** in acetic anhydride with a palladium catalyst gave a complex mixture of products from which four crystalline materials, **26**, **31**, **32**, and **34**, were isolated by silica gel chromatography. Compound **26** was characterized by its typical indole chromophore in the uv, the amide band at 1675 cm^{-1}, and the absence of NH and OH absorption in the ir and the characteristic N–Et and $CH_3(C{=}O)N$ absorptions in the nmr. The nmr hextet at δ 4.73, assigned to the C-2 equatorial proton, was characteristic of the deshielding effect of an adjacent amide and thus established the location of the acetamide function (N-1).

The alcohol **31** was characterized by its OH and amide carbonyl bands in the ir, its typical indoline chromophore in the uv, and the peak at *m/e* 256 in the mass spectrum, which represented loss of water from the molecular ion (*m/e* 274). The nmr demonstrated that **31** was a mixture of *cis* and *trans* epimers. In particular the C-10a proton was represented by two singlets at δ 6.09 and 5.34 which had an area ratio of 6:5. The exchangeable hydroxyl protons were represented by singlets at δ 3.83 and δ 3.48. This interpretation was justified by the clean, acid-catalyzed conversion of **31** into **26** in 78% yield.

Assignment of structure **32** was based on the uv spectrum, which suggested an oxindole-type chromophore, the ir spectrum, which had OH and amide carbonyl absorption, and the mass spectrum, which had peaks corresponding to the successive loss of water (*m/e* 270) and two molecules of ketene (*m/e* 229 and 186) from the molecular ion (*m/e* 288). The nmr spectrum had singlets at δ 6.69 and 5.98 with an area ratio of 5:2, which were assigned to the C-10a proton, and thus indicated that this material was also a mixture of *cis* and *trans* isomers. Singlets at δ 2.03 and 2.18 were assigned to the acetamide moieties of the major isomer. Assignment of the downfield multiplet, δ 8.17, to the C-9 aromatic proton was based on the reported deshielding of the *ortho* proton by the amide carbonyl of *ortho*-monosubstituted N-phenylamides.[17] The acid-catalyzed dehydration of **32** gave the new diacetyl indole **27** in 92% yield. Support for structure **27** was derived from spectral data and from its facile conversion into **25** with sodium in ethanol.

Compound **34** was an isomer of **31** which had an oxindole chromophore in the uv spectrum and bands corresponding to OH and amide carbonyl absorption in the ir spectrum. In the mass spectrum the major fragmentation pathway was represented by peaks at *m/e* 245 and 203 which corresponded to successive loss of ethyl and ketene from the molecular ion (*m/e* 274). Minor peaks at *m/e* 259 and 256 corresponded to loss of methyl and water from the molecular ion. The nmr spectrum confirmed the presence of N-ethyl and N-acetyl groups; it had a sharp singlet at δ 4.85 for the C-10a proton and a broad singlet at δ 3.3 for the exchangeable hydroxyl proton. There was no indication of an isomer mixture, as had been observed for **31** and **32**. The low-field multiplet at δ 8.21, assigned to the C-9 proton, supported the N-10 acetamide assignment. Acid-catalyzed dehydration of **34** gave the noncrystalline indole **28**, which had an ir ($CHCl_3$) band at 1685 cm^{-1} for the amide carbonyl but no absorption attributable to a hydroxyl group. Further characterization of this compound was not attempted. Ethanolysis of **28** with sodium ethoxide in ethanol followed by isolation of the product by crystallization from methanol–ethyl acetate gave the alcohol **23**, presumably by air oxidation of the initially formed product. Acidification of **28** with anhydrous hydrogen chloride followed by crystallization of the salt from methanol–ethyl acetate gave **24**. This compound had the characteristic $C{=}N^+$ absorption at 1675 cm^{-1} in the ir; in the nmr spectrum the C-5a proton was represented by a quartet at δ 4.17.

The facile autoxidations of **15** and its N-1 alkyl derivatives (*viz.* **25**(**28**) → **23**) and the unusual behavior of the oxidation product **17** toward catalytic hydrogenation in acetic anhydride made it of interest to investigate the effect of alkylation at N-10 on these reactions. For this purpose **1** was alkylated with

(16) Numerous examples of this effect have now been reported, *e.g.*, (a) H. Paulsen and K. Todt, *Chem. Ber.*, **100**, 3385 (1967); (b) R. A. Johnson, *J. Org. Chem.*, **33**, 3627 (1968); (c) D. M. Lynch and W. Cole, *ibid.*, **31**, 3337 (1966).

(17) (a) R. F. C. Brown, L. Radom, S. Sternhell, and I. D. Rae, *Can. J. Chem.*, **46**, 2577 (1968); (b) M. Zanger, W. W. Simons, and A. R. Gennaro, *J. Org. Chem.*, **33**, 3673 (1968); (c) A. Ribera and M. Rico, *Tetrahedron Lett.*, 535 (1968); (d) K. Nagarajan, M. D. Nair, and P. M. Pillai, *Tetrahedron*, **23**, 1683 (1967).

dimethyl sulfate to give **2**, which was subsequently converted into the oxime **9**[18] and tosyloxy oxime **10**. Beckmann rearrangement of **10** on neutral alumina which had been deactivated with 0.4% water gave a 23% yield of **16**, which was uncontaminated by the isomeric lactam. Lithium aluminum hydride reduction of **16** followed by the usual work-up in air gave a 71% yield of the autoxidation product **35**. Support for structure **35** was obtained from the ir spectrum, which had bands at 3180 and 1665 cm^{-1} for OH and C=N, respectively, and the nmr spectrum, which had a broad singlet at δ 5.82 for the exchangeable hydroxyl proton and quartets at δ 3.39 and 4.14, assigned to the C-2 equatorial and axial protons, respectively.

Catalytic reduction of **35** in acetic anhydride with a 10% palladium on carbon catalyst gave a mixture of four compounds, **29**, **30**, **33**, and **36**, which was separated by chromatography. Compound **29** was an oil which had no NH or OH absorption in the ir spectrum; it was characterized as its crystalline hydrochloride salt. Support for structure **29** was provided by the mass spectrum, which had peaks at *m/e* 213 and 199 corresponding to loss of methyl and ethyl radicals from the molecular ion of the free base (*m/e* 228) and by the nmr spectrum of the salt, which had peaks attributable to the N-methyl and N-ethyl groups. The ir spectrum of the hydrochloride had a strong band at 1640 cm^{-1} ($C{=}N^+$) and no absorption attributable to ^+NH, which suggests that salt formation occurs by protonation at C-5a rather than on nitrogen. It should also be noted that **29**, a 1,10-dialkyl derivative of **15**, was relatively stable to autoxidation and could be handled in air without appreciable degradation.

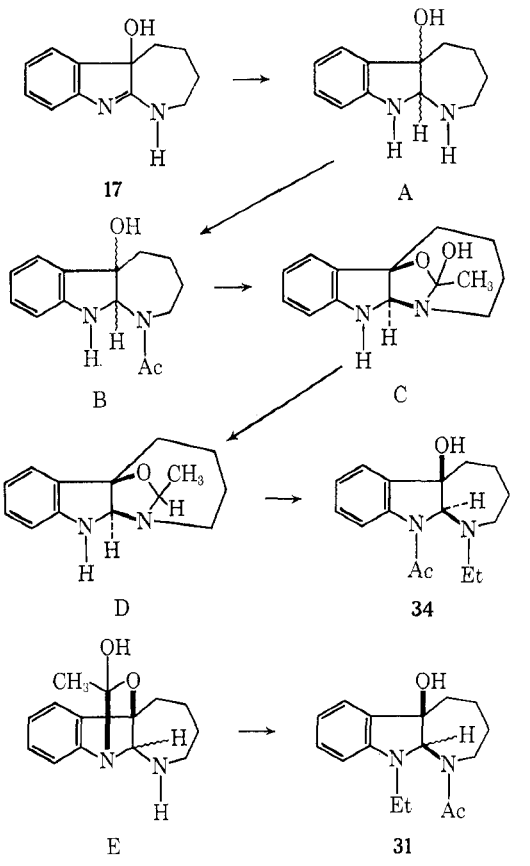
Structure **33** was suggested by the high-resolution mass spectrum, which had a peak at *m/e* 242.1429 corresponding to loss of water from the molecular ion (*m/e* 260.1514). The hydroxyl and amide assignments were supported by ir bands at 3280 and 1615 cm^{-1}; the indoline chromophore appeared in the uv spectrum. The nmr spectrum had a pair of singlets at δ 5.85 and 5.20 with an area ratio of 8.5:6 which were assigned to the C-10a proton; the N-methyl and acetamide moieties were also represented by pairs of singlets which suggested that **33** was a mixture of *cis* and *trans* isomers. This view was confirmed by the facile, acid-catalyzed conversion of **33** into the indole **30**, which had also been isolated from the hydrogenation mixture. Support for the latter structure (**30**) was derived from the typical indole chromophore in the uv spectrum, the peak corresponding to loss of CH_3CO (*m/e* 199) from the molecular ion (*m/e* 242) in the mass spectrum, the amide band at 1670 cm^{-1} in the ir spectrum, and the C-methyl and N-methyl singlets as well as the characteristic hextet at δ 4.56 for the C-2 equatorial proton in the nmr spectrum.

Assignment of structure **36** was based on the ester and C=N bands at 1740 and 1675 cm^{-1} in the ir spectrum, the characteristic uv chromophore, the C-methyl and N-methyl singlets at δ 2.04 and 3.13 in the nmr spectrum, and the molecular ion at *m/e* 258.1369 in the high-resolution mass spectrum.

With regard to the autoxidation of **15** and its N-monoalkylated derivatives, we suggest that, analogous to other known samples,[2,19] the reaction proceeds *via* a radical mechanism, initiated by homolytic cleavage of the N–H bond of the amine. The resulting allylic radical could react with oxygen or hydroperoxide radical at C-5a to give a hydroperoxide intermediate. Further reaction of this hydroperoxide with a second molecule of the amine (*viz.*, **15**) would give the observed product, **17**. Support for this mechanism is derived from the fact that the N,N′-dialkyl derivative **29** is stable to this type of autoxidation.

A mechanistic interpretation of the products obtained from the catalytic reduction of **17** and **35** in acetic anhydride is illustrated in Scheme I for compound **17**.

SCHEME I



We suggest that the reaction is initiated by reduction of the amidine double bond to give a *cis–trans* mixture of alcohols (A). Acylation of A can then occur at either or both nitrogens; monoacylation at N-1 would give B. In this case, when the hydroxyl and acetamide groups are *cis* to each other (*trans* ring junction), an interaction can occur to give the oxazolidine intermediate C. This type of interaction is general for molecules containing similarly positioned functional groups[20] and has been specifically invoked to explain the N → O acyl-transfer reaction.[21] Of importance to this discussion is the fact that the formation of C would destroy the resonance stabilization of the amide function and would thus make it susceptible to catalytic reduction. Precedent for the reduction of C

(18) V. I. Shvedov, L. B. Altukhova, E. K. Komissarova, and A. N. Grenev, *Chem. Heterocycl. Compounds*, **1**, 241 (1965).

(19) (a) H. I. X. Mager and W. B. Bevends, *Rec. Trav. Chim. Pays-Bas*, **84**, 1329 (1965). (b) See A. G. Davies, "Organic Peroxides," Butterworth and Co. Ltd., London, 1961, p 27–31.

(20) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, Inc., New York, N. Y., 1966, Chapter 1.

(21) E. E. vanTamelen, *J. Amer. Chem. Soc.*, **73**, 5773 (1951).

to oxazolidine D may be found in the catalytic reduction of rhetsinine to rhetsine,[22] which undoubtedly proceeds by way of a similar intermediate; catalytic reduction of oxazolidines such as D to amino alcohols has been reported.[23] In this case the reduction of D followed by acylation of the remaining nitrogen would give **34**, which, if this mechanism is correct, must have the stereochemistry shown. Monoacylation of A at N-10 followed by the acyl–alcohol interaction just described would give the oxazolidine intermediate E. In this case, however, formation of the oxazolidine would not be dictated by the stereochemistry of the ring junction; both isomers could be formed. Reduction of E could thus lead to a mixture of the *cis* and *trans* isomers of **31**, which was the observed result. Both diacetylation of A and monoacetylation of *cis*-B could give **32**, which would therefore be expected to be a *cis–trans* mixture. The observed predominance of one isomer in this case suggests that the latter route may be more important. In view of the observed facile dehydration of the C-5a alcohols, it is probable that the indoles (*viz.*, **26**) obtained from the hydrogenation reaction mixtures are the result of dehydration of the corresponding alcohol either during the reaction or during the work-up procedure.

Experimental Section[24]

***syn*-3,4-Dihydrocarbazol-1(2H)-one Oxime (3) and *anti*-3,4-Dihydrocarbazol-1(2H)-one Oxime (7).**—A mixture of **1** (330.0 g, 1.783 mol), hydroxylamine hydrochloride (187 g), NaOAc (242 g), EtOH (6.5 l.), and water (1.62 l.) was refluxed under N_2 for 7 hr, cooled, and allowed to stand at ambient temperature for 18 hr. Concentration of the solution *in vacuo* gave a solid residue which was collected by filtration, washed with water, and dried. Chromatography of this solid on silica gel (16 kg) with 30% EtOAc–70% Skellysolve B separated the isomers. The first material eluted from the column was crystallized from ether–Skellysolve B to give 157.4 g of **7**, mp 134–143°. An analytical sample was obtained: mp 129–136°; uv (EtOH) λ_{max} 205 mμ (ε 22,900), 244 (13,750), 304 (22,850), and 311 (inflection, 22,300); ir (Nujol) 3440, 3320, 3200 (NH and OH), and 1630 cm^{-1} (C=N).

Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.24; H, 6.19; N, 14.16.

The second material eluted from the column was crystallized from EtOAc–Skellysolve B to give 145 g of **3**, mp 155–165°. An analytical sample was obtained: mp 175.5–176.5°; uv (EtOH) λ_{max} 206 mμ (ε 21,650), 244 (16,600), 306 (21,750), and 313 (inflection, 21,350); ir (Nujol) 3460, 3420, 3120, 3010 (NH and OH), and 1635 cm^{-1} (C=N).

Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.58; H, 5.98; N, 14.12.

3,4,5,10-Tetrahydroazepino[3,4-*b*]indol-1(2H)-one (5). A.—A stirred mixture of **7** (9.95 g, 0.0497 mol) and polyphosphoric acid (300 g) was heated under N_2 at 110–120° for 10 min, cooled, and poured into a mixture of crushed ice and water. The resulting solid was collected by filtration, washed with water, dried, and recrystallized from CH_2Cl_2–MeOH to give 7.22 g (72.5%) of **5**, mp 222–228°. An analytical sample was obtained: mp 228–229° [lit.[4] mp 224–227°]; uv (EtOH) end absorption, λ_{max} 229 mμ (ε 25,550) and 298 (17,250); ir (Nujol) 3270, 3200 (NH), and 1625 cm^{-1} (C=O).

Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.72; H, 6.22; N, 13.96.

B.—In the manner described in A, the reaction of compound **3** (14.1 g, 0.0704 mol) with polyphosphoric acid (424 g) gave 12.0 g (85%) of **5**, mp 221–224°.

C.—A stirred mixture of **1** (6.5 g, 0.0351 mol) in polyphosphoric acid (200 g) was warmed to 50–60° and treated during 20 min with sodium azide (2.97 g, 0.0457 mol). Heating was continued for 3 hr, after which the mixture was poured into ice-water. The product was extracted with CH_2Cl_2; the extract was washed with water, dried ($MgSO_4$), and concentrated. Chromatography of the residue on silica gel (500 g) with EtOAc gave 1.73 g of recovered **1**, mp 168–169.5° (lit.[3] mp 169–170°), and 1.47 g (21%) of **5**, mp 222–230°.

D.—A solution of **3** (10.0 g, 0.05 mol) in pyridine (250 ml) was cooled in an ice bath, treated with *p*-toluenesulfonyl chloride (10.5 g, 0.0552 mol), and allowed to stand at ambient temperature for 18 hr. It was then treated with water and concentrated *in vacuo*. The resulting crystalline product was collected by filtration, washed with water, and dried to give 17.3 g of **4**, mp 132–135° dec. A solution of **4** (9.00 g) in benzene was adsorbed on a column of neutral alumina (600 g) which had been deactivated with 1% water. The column was treated successively with benzene (1 l.), 50% benzene–50% $CHCl_3$ (2 l.), and $CHCl_3$ (1.5 l.); the product was eluted with 20% MeOH–80% $CHCl_3$ and crystallized from CH_2Cl_2–MeOH to give 3.01 g, mp 228–229.5°, and 1.21 g, mp 220–224°, of **5**. In these experiments **5** was identified at least by ir ($CHCl_3$) comparison with the authentic sample. The melting-point discrepancies were due to the appearance of two polymorphic crystalline forms.

1,2,3,4,5,10-Hexahydroazepino[3,4-*b*]indole (6).—Compound **5** (2.00 g, 0.01 mol) was added under N_2 to a stirred, ice-cold suspension of $LiAlH_4$ (2.0 g) in tetrahydrofuran (150 ml). The resulting mixture was warmed to ambient temperature during 5 hr and refluxed for 10.75 hr. It was then cooled in an ice bath and treated successively with water (2 ml), 15% NaOH (2 ml), and water (6 ml). This mixture was filtered and the filtrate was concentrated to give a solid which was recrystallized from MeOH–EtOAc to yield 1.35 g (72.5%) of **6**, mp 212–214°. An analytical sample was obtained: mp 212.5–214.5°; uv (EtOH) λ_{max} 225 mμ (ε 33,850), 284 (7500), 291 (6900), and 276 (inflection, 6650); nmr [$(CD_3)_2NCDO$] δ 4.00 (s, 2, C-1).

Anal. Calcd for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04. Found: C, 76.98; H, 7.84; N, 14.96.

1-Ethoxy-3,4,5,10-tetrahydroazepino[3,4-*b*]indole (11).—A solution of triethyloxonium fluoroborate, prepared from boron trifluoride etherate (4.06 ml) and epichlorohydrin (1.88 ml), in CH_2Cl_2 (10 ml), was added to a stirred suspension of **5** (3.00 g, 0.015 mol) in CH_2Cl_2 (250 ml) at 10–15°. This mixture was allowed to stand at ambient temperature for 18 hr and the solid complex was collected by filtration and treated with cold, dilute K_2CO_3. The product was extracted with CH_2Cl_2; the extract was washed with water, dried (K_2CO_3), and concentrated. Crystallization of the residue from EtOAc–Skellysolve B gave 1.65 g (48.3%) of **11**: mp 122.5–124°; uv (EtOH) λ_{max} 208 mμ (ε 20,750), 231 (24,500), and 300 (17,950); ir (Nujol) 3130, 3070 (NH), and 1650 cm^{-1} (C=N).

Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.85; H, 7.27; N, 12.26.

1-{[2-(Diethylamino)ethyl]amino}-3,4,5,10-tetrahydroazepino-[3,4-*b*]indole (12).—A mixture of **11** (4.56 g, 0.02 mol), N,N-diethylethylenediamine (14 g), *p*-toluenesulfonic acid (800 mg), and benzene (200 ml) was refluxed under N_2 for 15 hr. During the inital stages of the reaction the ethanol–water azeotrope was distilled from the mixture through a small, helix-packed column. The cooled reaction mixture was poured into water and the product was extracted with ether. The ether extract was washed with water and brine, dried (K_2CO_3), and concentrated. Crystallization of the residue from EtOAc–Skellysolve B yielded 4.37 g, mp 143.5–145°, and 0.848 g, mp 141.5–143.5° (87.7%), of **12**. An analytical sample was obtained: mp 144.5–145.5°;

(22) I. J. Pachter and G. Suld, *J. Org. Chem.*, **25**, 1680 (1960).

(23) (a) E. Gil-Av, *J. Amer. Chem. Soc.*, **74**, 1346 (1952); (b) A. C. Cope and E. M. Hancock, *ibid.*, **64**, 1503 (1942); (c) M. Senkus, *ibid.*, **67**, 1515 (1945).

(24) Melting points were taken in capillary tubes and are corrected. Ultraviolet spectra were determined on a Cary Model 14 spectrophotometer, ir spectra on a Perkin-Elmer Model 421 spectrophotometer, mass spectra at 70 eV on an Atlas Model CH-4 spectrometer, high-resolution mass spectra on a Consolidated Electronics Model 21-110 spectrometer, and nmr spectra on a Varian Model A-60A spectrometer. Nmr peaks are recorded in parts per million downfield from tetramethylsilane. In general, only those nmr peaks which are either necessary for the structure proof or are readily assignable to a specific proton or group of protons are reported; the integrated spectra are, however, in all cases in agreement with the assigned structures. Skellysolve B is a commercial hexane, bp 60–70°, made by Skelly Oil Co., Kansas City, Mo. Darco G-60 is an activated carbon prepared by Atlas Chemical Industries, Inc., Wilmington 99, Del. Celite is a filter aid manufactured by Johns–Manville, New York, N. Y. The alumina used for chromatography was obtained from M. Woelm, Eschwege, Germany, and the silica gel from E. Merck AG, Darmstadt, Germany.

uv (EtOH) λ_{max} 207 mμ (ϵ 22,850), 238 (21,100), and 307.5 (20,450).

Anal. Calcd for $C_{18}H_{26}N_4$: C, 72.44; H, 8.78; N, 18.78. Found: C, 72.45; H, 9.00; N, 18.61.

3,4,5,10-Tetrahydro-1-piperidinoazepino[3,4-*b*]indole Hydrochloride Dihydrate (13).—Compound **11** (5.75 g, 0.0252 mol) was added to a cold, stirred mixture of sulfuric acid (0.63 ml) and piperidine (63 ml) and the resulting mixture was refluxed under N_2 for 36 hr and poured into ice–water. The resulting mixture was treated with 1.5 ml of 50% aqueous NaOH and extracted with ether; the ether extract was washed with brine, dried (K_2CO_3), and concentrated. The residue was chromatographed on silica gel (1.1 kg); the product was eluted with 2% acetic acid–methanol as the acetic acid salt. A solution of this material in water was made alkaline with 50% aqueous NaOH, and the solid which precipitated was collected by filtration, washed with water, and dried. A suspension of this material in EtOAc was acidified with methanolic hydrogen chloride. The resulting salt was recrystallized from water to give 2.04 g, mp 225–237° (softening at 136°), and 0.285 g, mp 230–239° (softening at 130°), of **13**. An analytical sample was obtained: mp 150–153° dec; uv (EtOH) λ_{max} 208 mμ (ϵ 25,750), 241 (15,340), and 315 (20,750).

Anal. Calcd for $C_{17}H_{21}N_3 \cdot HCl \cdot 2H_2O$: C, 60.08; H, 7.71; N, 12.36; Cl, 10.43; H_2O, 10.60. Found: C, 60.46; H, 7.83; N, 12.43; Cl, 10.53; H_2O, 10.46.

3,4,5,10-Tetrahydroazepino[2,3-*b*]indol-2(1H)-one (14).—A solution of **7** (157.4 g, 0.788 mol) in pyridine (3.5 l.) was cooled in an ice bath under N_2 and treated with *p*-toluenesulfonyl chloride (172 g). This mixture was kept at ambient temperature for 18 hr and poured into ice–water. The resulting crystalline product was collected by filtration, washed with water, dried, and recrystallized from benzene to give 258.2 g of **8**, mp 165.5–167° dec. A solution of this material in benzene was absorbed on a column of neutral alumina (16 kg) which had been deactivated with 0.5% water. The column was then treated successively with benzene (20 l.), 20% $CHCl_3$–80% benzene (28 l.), and $CHCl_3$ (63 l.). During this procedure some unreacted **8** was eluted from the column. The product was eluted from the column with mixtures of MeOH (20–40%) and $CHCl_3$; it was crystallized from CH_2Cl_2–MeOH to give 39.6 g (25.2%) of **14**, mp 200–206° dec. The analytical sample was crystallized from MeOH–EtOAc: mp 205.5–206.5°; uv (EtOH) end absorption, λ_{max} 321 mμ (ϵ 28,400) and 299 (13,850) and inflections at 218 (21,550), 273 (7100), and 285, (11,000); ir (Nujol) 3410, 3370, 3270, 3170 (NH), and 1680 cm^{-1} (C=O); nmr [$(CD_3)_2NCDO$] δ 2.1 (m, 2, C-4) and 2.7 (m, 4, C-3, C-5); mass spectrum *m/e* (rel intensity) 200 (100) and 145 (90.7).

Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.90; H, 5.61; N, 14.28.

2,3,4,5-Tetrahydroazepino[2,3-*b*]indol-5a(1H)-ol (17). A.—Compound **14** (12.7 g, 0.0634 mol) was added under N_2 to an ice-cold, stirred suspension of $LiAlH_4$ (13 g) in tetrahydrofuran (1300 ml). The resulting mixture was refluxed for 15 hr, cooled in an ice bath, and treated successively with water (13 ml), 15% aqueous NaOH (13 ml), and water (39 ml). This mixture was stirred for a few minutes and filtered. The filtrate was concentrated *in vacuo*. A solution of the residue in MeOH was stored at 0° for 2 days and crystallized to give 4.80 g, mp 252.5–253.5° dec, 2.99 g, mp 248.5–250° dec, and 1.30 g, mp 247–248.5° dec (70.8%), of **17**. An analytical sample was obtained: mp 255–259.5°; uv (EtOH) λ_{max} 223 mμ (ϵ 23,060), 280 (10,030), 290 (9270), and 319 (4300); ir (Nujol) 3270, 3230, 3180, 3120 (NH and OH), and 1640 cm^{-1} (C=N); mass spectrum *m/e* (rel intensity) 202 (100), 185 (7), 173 (44), 146 (13), and 145 (12); pK_a' (60% EtOH) 6.9.

Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 70.82; H, 6.99; N, 13.64.

B.—A stirred mixture of **22** (100 mg, 0.350 mmol) and absolute ethanol (10 ml), under N_2, was treated with 0.320 ml of 1.113 *N* NaOH, and the resulting solution was kept at ambient temperature for 50 min and poured into ice water. This mixture was extracted with CH_2Cl_2. The extract was dried (K_2CO_3) and concentrated *in vacuo*. Crystallization of the residue from MeOH gave 28 mg of **17**, mp 250.5–254.5° dec. Recrystallization from MeOH gave material, mp 252–253.5° dec, which was identical with authentic **17** by comparison of the ir and uv spectra.

The hydrochloride of **17** was prepared by acidifying a solution of **17** in MeOH with methanolic hydrogen chloride. The analytical sample was crystallized from MeOH: mp 229.5–230.5° dec; uv (EtOH) λ_{max} 221 mμ (ϵ 19,650), 224 (19,700), 269 (5700), 278 (5550), 299 (4200), and 293 (inflection, 4150); ir (Nujol) 3170, 3060, 3010 (NH and OH) and 1685 cm^{-1} (C=N$^+$); nmr (D_2O) δ 4.12 (q, 1, $J_{gem} \cong -14$ Hz, $J_{a,e} \cong 10$ Hz, C-2 axial) and 3.49 (q, 1, $J_{gem} = -14$ Hz, $J_{e,e} = 5$ Hz, C-2 equatorial).

Anal. Calcd for $C_{12}H_{15}ClN_2O$: C, 60.37; H, 6.33; Cl, 14.86; N, 11.74. Found: C, 60.44; H, 6.63; Cl, 15.00; N, 11.52.

The hydrobromide of **17** was prepared by acidifying a methanolic solution of **17** with methanolic hydrogenbromide. The salt was crystallized from MeOH–EtOAc, mp 205.5–206.5° dec.

Anal. Calcd for $C_{12}H_{15}BrN_2O$: C, 50.89; H, 5.34; Br, 28.22; N, 9.90. Found: C, 50.82; H, 5.47; Br, 28.23; N, 10.14.

1-Acetyl-1,2,3,4,5,10-hexahydroazepino[2,3-*b*]indole (25). A.—Compound **14** (5.05 g, 0.0252 mol) was added under N_2 to an ice-cold, stirred suspension of $LiAlH_4$ (5.0 g) in tetrahydrofuran (350 ml). The resulting mixture was refluxed for 18 hr, cooled in an ice bath, and treated successively with water (5 ml), 15% aqueous NaOH (5 ml), and water (15 ml). This mixture was stirred under N_2 for 1 hr and filtered. The filtrate was treated with pyridine (100 ml) and acetic anhydride (10 ml) and concentrated to a volume of 100 ml *in vacuo*. This solution was treated with additional acetic anhydride (10 ml), kept under N_2 at ambient temperature for 18 hr, and concentrated *in vacuo*. The residue was stirred with water for several hours, and the crystalline product was collected by filtration, washed with water, dried, and recrystallized from EtOAc to give 1.55 g (26.9%) of **25**, mp 194.5–196.5°. A small second crop, 0.121 g, mp 193.5–194.5°, was obtained by concentrating the mother liquor. An analytical sample was obtained: mp 193°; uv (EtOH) λ_{max} 223 mμ (ϵ 37,050), 285 (8800), 289.5 (8400), and 275 (inflection, 9350); ir (Nujol) 3180 (NH) and 1640 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity) 228 (100), 186 (65.7), 185 (64.5), 158 (17.8), 157 (35.3), and 130 (28); nmr [$(CD_3)_2SO$] δ 1.72 (m, 4, C-3,4), 1.98 (s, 3, CH_3CO), 2.74 (m, 2, C-5), 3.65 (m, 2, C-2), 7.25 (m, 4, C-6–9), and 11.2 (s, 1, NH).

Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.39; H, 7.14; N, 12.37.

B.—A mixture of **21** (1.00 g, 4.09 mmol), 10% palladium on carbon (0.5 g), and acetic anhydride (100 ml) was hydrogenated at an intial pressure of 30 psi for 8 hr and filtered through Celite. The filtrate was concentrated *in vacuo*. A solution of the residue in xylene was concentrated *in vacuo* to remove last traces of acetic anhydride. This residue was crystallized from EtOAc to give 0.362 g of **25**, mp 192–193.5°.

C.—Compound **27** (81 mg, 0.30 mmol) was added under N_2 to a solution of sodium (10 mg) in absolute ethanol (3 ml). The resulting solution was stirred for 44 min at ambient temperature and poured into water. The solid product was collected by filtration, washed with water, dried, and recrystallized from EtOAc to give 53 mg (77%) of **25**, mp 192–193.5°.

The products from B and C were identified by mixture melting point and ir, uv, and nmr comparison with the authentic sample.

1,2,3,4,5,5a-Hexahydroazepino[2,3-*b*]indole Hydrochloride (20).—Compound **14** (1.00 g, 5.00 mmol) was added under N_2 to an ice-cold, stirred suspension of $LiAlH_4$ (1.0 g) in tetrahydrofuran (100 ml). The resulting mixture was refluxed for 18 hr, cooled in an ice bath, and treated successively with water (1 ml), 15% aqueous NaOH (1 ml), and water (3 ml). This mixture was filtered into a flask containing methanolic hydrogen chloride. The resulting solution was concentrated *in vacuo*. A solution of the residue in water was decolorized with Darco G-60 and concentrated *in vacuo*. Water was removed from the resulting material by the addition of absolute ethanol twice with concentration after each addition. The resulting crystalline product was recrystallized from EtOH–EtOAc and then from MeOH–EtOAc to give 0.362 g (32.5%) of **20**, mp 254–257° dec. An analytical sample was obtained: mp 253.5–255.5°; uv (EtOH) λ_{max} 215 mμ (ϵ 18,000) and 273 (10,150) and inflections at 265 (9550), 269 (9900), and 280 (7400); ir (Nujol) 3000, 2780, 2720 (NH), and 1680 cm^{-1} (C=N$^+$); nmr (D_2O) δ 3.68 (m, 2, C-2), and 7.38 (m, 4, C-6–9).

Anal. Calcd for $C_{12}H_{13}ClN_2$: C, 64.71; H, 6.79; Cl, 15.92; N, 12.58. Found: C, 64.65; H, 6.90; Cl, 16.08; N, 12.54.

1-Acetyl-2,3,4,5-tetrahydroazepino[2,3-*b*]indol-5a(1H)-ol Acetate Ester (22) and 2,3,4,5-Tetrahydroazepino[2,3-*b*]indol-5a-(1H)-ol Acetate Ester (21).—A stirred mixture of **17** (1.02 g, 5.05 mmol), acetic anhydride (3 ml), and pyridine (50 ml) was kept at ambient temperature in the dark under N_2 for 18 hr and concentrated *in vacuo*. A solution of the residue in xylene was

concentrated *in vacuo* to remove last traces of pyridine and acetic anhydride. The residue was chromatographed on silica gel (50 g). The first compound was eluted with 40% EtOAc–60% cyclohexane and was crystallized from EtOAc–Skellysolve B to give 0.377 g (26.1%) of **22**, mp 127.5–128.5°. An analytical sample was obtained: mp 127.5–129°; uv (CH_2Cl_2) $\lambda_{max} \sim 230$ mμ (ε 20,100), 287 (8310), 297 (9720), and 309 (9410); ir (Nujol) 1745 [CH_3(C=O)O] and 1670 cm^{-1} [CH_3(C=O)N]; mass spectrum *m/e* (rel intensity) 286 (51), 244 (100), 227 (1.7), 226 (2.4), 201 (63), 185 (50), 184 (32), and 157 (24); nmr ($CDCl_3$) δ 2.07 [s, 3, CH_3(C=O)O], 2.58 [s, 3, CH_3(C=O)N], 3.21 (q, 1, $J_{gem} \cong 15$ Hz, $J_{a,a} \cong 10$ Hz, C-2 axial), 4.95 (q, 1, $J_{gem} \cong -15$ Hz, $J_{e,e} \cong 7$ Hz, C-2 equatorial), and 7.25 (m, 4, C-6–9).

Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.11; H, 6.34; N, 9.78. Found: C, 67.29; H, 6.79; N, 9.57.

The second compound was eluted from the column with 50% pyridine–50% EtOAc and was crystallized from CH_2Cl_2–EtOAc to give 0.308 g (25%) of **21**, mp 172–173° dec. An analytical sample was obtained: mp 176° dec; uv (CH_2Cl_2) λ_{max} 282 mμ (ε 10,200), 292 (9190), and 320 (3990); ir (Nujol) 1750 [CH_3(C=O)O], and 1650 cm^{-1} (C=N); mass spectrum *m/e* (rel intensity) 244 (78), 201 (100), 185 (95), 184 (54), and 157 (88); nmr [$CDCl_3$ + $(CD_3)CDO$] δ 2.10 [s, 3, CH_3(C=O)O].

Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.16; H, 6.67; N, 11.43.

2,2-Dideuterio-2,3,4,5-tetrahydroazepino[2,3-*b*]indol-5a(1H)-ol (19) Hydrochloride.—Compound **14** (1.18 g, 5.90 mmol) was added under N_2 to an ice-cold, stirred suspension of $LiAlD_4$ (1.0 g) in tetrahydrofuran (100 ml) and the resulting mixture was refluxed for 10 hr, allowed to stand at ambient temperature for 18 hr, cooled in an ice bath, and treated successively with water (1.0 ml), 15% aqueous NaOH (1.0 ml), and water (3 ml). This mixture was stirred for a few minutes and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in MeOH and allowed to crystallize during 18 hr to give 0.867 g (72%) of **19**, mp 246–250° dec. A sample of this material was suspended in MeOH and acidified with methanolic hydrogen chloride. The salt was crystallized from MeOH–EtOAc to give **19** hydrochloride: mp 231–232.5°; uv (EtOH) λ_{max} 221 mμ (ε 20,900), 224 (20,950), 278 (7150), and 290 (5850) and inflections at 272 (6350) and 305 (3800); ir (Nujol) 3180, 3060, 3020 (OH and N^+H) and 1690 cm^{-1} ($C=N^+$); mass spectrum *m/e* (rel intensity) 204 (85), 187 (7), 175 (19), 174 (14), 173 (16), 147 (12), 146 (18), 145 (23), 103 (61), 90 (42), 85 (48), 57 (50), 43 (83), 42 (74), 41 (100), and 29 (100); nmr (D_2O) δ 1.2–2.45 (m, 6, C-3–5), and 7.22 (m, 4, C-6–9).

Anal. Calcd for $C_{12}H_{13}D_2ClN_2O$: C, 59.88; H, 5.44; D, 1.66. Found: C, 59.77; H, 5.26; D, 1.61.

1-Acetyl-2,2-dideuterio-2,3,4,5-tetrahydroazepino[2,3-*b*]indol-5a-(1H)-ol Acetate Ester (18).—Compound **19** (0.759 g, 3.72 mmol) was added to a stirred solution of acetic anhydride (3 ml) in pyridine (50 ml) and the resulting mixture was kept in the dark under N_2 for 17 hr and concentrated *in vacuo*. A solution of the residue in xylene was concentrated to dryness to remove last traces of pyridine. A solution of this residue in benzene was washed successively with ice-cold, dilute $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on silica gel (50 g) with 40% EtOAc–60% cyclohexane. The first compound eluted from the column was crystallized from EtOAc–Skellysolve B to give 0.157 g, mp 126–127.5°, and 0.031 g, mp 121–127°, of **18**. An analytical sample was obtained: mp 120.5–121.5°; uv (CH_2Cl_2) λ_{max} 288 mμ (ε 8100), 297 (9550), and 308 (9150); ir (Nujol) 1745 [CH_3(C=O)O], and 1675 cm^{-1} [CH_3(C=O)N]; mass spectrum *m/e* (rel intensity) 288 (42), 246 (100), 203 (57), 187 (42), 185 (30), and 159 (18); nmr ($CDCl_3$) δ1.14–2.5 (m, 6, C-3–5), 2.08 [s, 3, CH_3(C=O)O], 2.59 [s, 3, CH_3(C=O)N], and 7.22 (m, 4, C-6–9).

Anal. Calcd for $C_{16}H_{16}D_2N_2O_3$: C, 66.65; H, 6.98. Found: C, 66.94; H, 6.72.

1-Ethyl-2,3,4,5-tetrahydroazepino[2,3-*b*]indol-5a(1H)-ol (23).

A.—Compound **25** (0.500 g, 2.19 mmol) was added under N_2 to an ice-cold, stirred suspension of $LiAlH_4$ (0.500 g) in tetrahydrofuran (50 ml). The resulting mixture was refluxed for 17 hr, cooled in an ice bath, and treated successively with water (0.5 ml) 15% aqueous NaOH (0.5 ml), and water 1.5 ml. The mixture was stirred for a few minutes and filtered. The filtrate was concentrated under reduced pressure. The residue was dissolved in MeOH, filtered to remove a small amount of flocculent solid, and crystallized from MeOH–EtOAc to give 0.279 g, mp 250–252° dec, and 0.100 g, mp 248.5–251.5° dec (75.2%), of **23**. The analytical sample was crystallized from methanol: mp 251.5–252.5° dec; uv (EtOH) end absorption, λ_{max} 224 mμ (ε 21,400), 282 (11,400), 291 (11,150), and 320 (5370); ir (Nujol) 3120 (OH) and 1615 cm^{-1} (C=N); mass spectrum *m/e* (rel intensity) 230 (100), 213 (51), 202 (23), 174 (41), and 146 (20); nmr (C_5D_5N) δ 1.10 (t, 3, J = 7 Hz, CH_3CH_2N), 2.96 (q, 1, $J_{gem} \cong 14$ Hz, $J_{e,e} \cong 5$ Hz, C-2 equatorial), 3.65 (q, 2, J = 7 Hz, CH_3CH_2N), 4.64 (q, 1, $J_{gem} \cong -14$ Hz, $J_{a,a} \cong 10$ Hz, C-2 axial), and 8.72 (s, 1, OH).

Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17. Found: C, 73.08; H, 7.67; N, 12.20.

B.—A solution of **34** (100 mg, 0.365 mmol) and *p*-toluenesulfonic acid (10 mg) in benzene (10 ml) was refluxed under nitrogen for 1.5 hr. The cooled solution was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to give a noncrystalline oil. A solution of this oil in absolute ethanol (1 ml) was added under N_2 to a stirred solution of sodium (17 mg) in ethanol (2 ml), and the resulting solution was kept at ambient temperature for 35 min and poured into water. This mixture was extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated. Crystallization of the residue from MeOH–EtOAc gave 43 mg (51%) of **23**, mp 245–251° dec. This material was identical with the authentic sample by ir and uv comparison.

C.—Compound **22** was added, under N_2, to an ice-cold, stirred suspension of $LiAlH_4$ (300 mg) in tetrahydrofuran (30 ml) and the mixture was refluxed for 18 hr, cooled in an ice bath, and treated successively with water (0.3 ml), 15% aqueous NaOH (0.3 ml), and water (0.9 ml). This mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel (15 g) with 2% Et_2NH–3% MeOH–95% EtOAc. The first compound eluted from the column was crystallized from MeOH–EtOAc to give **23**, mp 252.5–253.5° dec, which was identical with the authentic sample by comparison of the ir (Nujol) and uv spectra. The second compound eluted from the column was crystallized from MeOH to give **17**, mp 248.5–251.5° dec, which was identical with the authentic sample by comparison of the ir and uv spectra.

1-Acetyl-10-ethyl-1,2,3,4,5,10-hexahydroazepino[2,3-*b*]indole (26), 10-Acetyl-1-ethyl-2,3,4,5,10,10a-hexahydroazepino[2,3-*b*]-indol-5a(1H)-ol (34), 1-Acetyl-10-ethyl-2,3,4,5,10,10a-hexahydroazepino[2,3-*b*]indol-5a(1H)-ol (31), and 1,10-Diacetyl-2,3,4,-5,10,10a-hexahydroazepino[2,3-*b*]indol-5a(1H)-ol (32).—A mixture of **17** (7.00 g, 0.0346 mol), 10% palladium on carbon (3.5 g), and acetic anhydride (700 ml) was hydrogenated at an initial pressure of 30 psi for 8 hr and allowed to stand under hydrogen for an additional 16 hr. It was then filtered through Celite and the filtrate was concentrated *in vacuo*. A solution of the residue in xylene was concentrated *in vacuo* to remove last traces of acetic anhydride; the residual oil was chromatographed on silica gel (400 g). Compounds **26** and **34** were eluted with 30% EtOAc–70% Skellysolve B and compounds **31** and **32** were eluted with EtOAc. The first compound eluted from the column was crystallized from EtOAc–Skellysolve B to give 0.658 g, mp 141–142.5°, 0.183 g, mp 140–142°, and 0.053 g, mp 138.5–140.5° (10.8%), of **26**. An analytical sample was obtained: mp 140.5–141.5°; uv (EtOH) λ_{max} 226 mμ (ε 39,750), 284 (9230), 293 (7870), and 278 (inflection, 8520); ir (Nujol) 1675 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity) 256 (100), 241 (3.2), 288 (4.1), 227 (2.6), 214 (35), and 213 (60); nmr ($CDCl_3$) δ 1.29 (t, 3, J = 7 Hz, CH_3CH_2N), 1.91 [s, 3, CH_3(C=O)N], 4.06 (octet, 2, J = 7 and 2.5 Hz, CH_3CH_2N), 4.73 (sextet, 1, $J_{gem} \cong -13$ Hz, $J_{e,e} \cong 3$ Hz, C-2 equatorial), and 7.34 (m, 4, C-6–9).

Anal. Calcd for $C_{16}H_{20}N_2O$: C, 74.96; H, 7.86. Found: C, 74.89; H, 7.83.

The second compound eluted from the column was crystallized from EtOAc–Skellysolve B to give 2.30 g, mp 162.5–164°, and 0.185 g, mp 161.5–162.5° (26.2%), of **34**. The analytical sample was crystallized from EtOAc: mp 164–165°; uv (EtOH) end absorption, λ_{max} 248 mμ (ε 13,900) and inflections at 278 (2460) and 286 (1685); ir (Nujol) 3330 (OH) and 1650 cm^{-1} [CH_3(C=O)-N]; mass spectrum *m/e* (rel intensity) 274 (74), 259 (13), 257 (8), 256 (11), 245 (100), 231 (10), 203 (44), 186 (11), 185 (18), 146 (25), 120 (26), and 112 (24); nmr ($CDCl_3$) δ 0.91 (t, 3, J = 7 Hz, CH_3CH_2N), 2.08 [s, 3, CH_3(C=O)N], 2.54 (q, 2, J = 7 Hz, CH_3CH_2N), 3.3 (br s, 1, OH), 4.87 (s, 1, C-10a), 7.22 (m, 3, C-6–8), and 8.2 (m, 1, C-9).

Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.98; H, 8.21; N, 10.19.

The third compound eluted from the column was crystallized from EtOAc-Skellysolve B to give 0.261 g, mp 124–125°, and 0.094 g, mp 117.5–119° (3.74%), of **31**. An analytical sample was obtained: mp 111.5–112.5°; uv (EtOH) λ_{max} 208 mμ (ε 34,200), 251 (13,840), and 309 (2670); ir (Nujol) 3310 (OH) and 1620 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity) 274 (9.1), 256 (100), 215 (54), 214 (60), 213 (85), 185 (13.6), 174 (11.9), 160 (7.2), 158 (7.8), 146 (8.7), 144 (9.1), and 130 (9.1); nmr ($CDCl_3$)[25] δ 1.13, 1.10 (t, 3, J = 7 Hz, CH_3CH_2N), 2.19, 2.26 [s, 3, $CH_3(C=O)N$], 2.92–3.54 (m, 2, CH_3CH_2N), 3.48, 3.83 (s, 1, OH), 6.09, and 5.34 (s, 1, C-10a).

Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.12; H, 8.22; N, 10.31.

The fourth compound eluted from the column was crystallized from MeOH–EtOAc to give 2.58 g (25.8%) of **32**, mp 199–201°. An analytical sample was obtained: mp 200–201°; uv (EtOH) end absorption, λ_{max} 246 mμ (ε 14,150), 278 (2040), and 287 (1600); ir (Nujol) 3370 (OH) and 1645 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity) 288 (4.6), 270 (28), 228 (100), and 186 (53); nmr [$(CD_3)_2SO$][26] δ 2.03 [s, 3, $CH_3(C=O)N$], 2.18 [s, 3, $CH_3(C=O)N$], 3.57 (br d, 1, $J \cong -16$ Hz, C-2 equatorial), 5.75 [5.89] (s, 1, OH), 6.69 [5.98] (s, 1, C-10a), 7.28 (m, 3, C-6–8), and 8.17 (m, 1, C-9).

Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.64; H, 6.99; N, 9.72. Found: C, 66.31; H, 6.96; N, 9.55.

1-Acetyl-10-ethyl-1,2,3,4,5,10-hexahydroazepino[2,3-*b*]indole (26).—A stirred mixture of **31** (81 mg, 0.295 mmol), *p*-toluenesulfonic acid (5 mg), and benzene (10 ml) was warmed under N_2 to 80° during 20 min, cooled, and poured into ice water. This mixture was extracted with ether. The extract was dried ($MgSO_4$) and concentrated *in vacuo*. Crystallization of the residue from EtOAc–Skellysolve B gave 59 mg (78%) of **26**, mp 140–141°. The mixture melting point with authentic **26** was undepressed. It was identical with the authentic sample by comparison of the ir and nmr spectra.

1-Ethyl-1,2,3,4,5,5a-hexahydroazepino[2,3-*b*]indole Hydrochloride (24).—A mixture of **34** (250 mg), *p*-toluenesulfonic acid (20 mg), and benzene (25 ml) was refluxed under N_2 for 1.5 hr. The resulting solution was cooled, washed with cold water, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was dissolved in petroleum ether, filtered through a little silica gel, and concentrated; no crystalline material was obtained. The oil was acidified with ethereal hydrogen chloride and the resulting salt was crystallized from MeOH–EtOAc to give 94 mg of **24**, mp 226–228° dec. An analytical sample was obtained: mp 226.5–228° dec; uv (EtOH) λ_{max} 216 mμ (ε 18,640) and 274 (12,720) and inflections at 265 (10,640), 269 (11,760), and 283 (10,550); ir (Nujol) 2620 (N^+H) and 1675 cm^{-1} ($C=N^+$); nmr (D_2O) δ 1.30 (t, 3, J = 7 Hz, CH_3CH_2N), 3.59 (q, 2, J = 7 Hz, CH_3CH_2N), *ca.* 3.71 (m, 2, C-2), 4.17 (q, 1, $J \cong 12$ and 3 Hz, C-5a), and 7.24 (m, 4, C-6–9).

Anal. Calcd for $C_{14}H_{19}ClN_2$: C, 67.05; H, 7.64; Cl, 14.14; N, 11.17. Found: C, 66.59; H, 7.70; Cl, 13.86; N, 10.96.

1,10-Diacetyl-1,2,3,4,5,10-hexahydroazepino[2,3-*b*]indole (27).—A mixture of **32** (200 mg, 0.694 mmol), *p*-toluenesulfonic acid (20 mg), and benzene (30 ml) was refluxed under N_2 for 30 min. The cooled solution was washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo*. Crystallization of the residue from ether gave 172 mg (91.7%) of **27**, mp 112–115.5°. An analytical sample was obtained: mp 113.5–115.5°; uv (EtOH) end absorption, λ_{max} 243 mμ (ε 15,950), 273 (10,150), 293 (7000), and 302 (6450); ir (Nujol) 1705, 1695, and 1675 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity) 270 (37), 228 (100), 186 (53), ad 185 (33); nmr ($CDCl_3$) δ 1.90 [s, 3, $CH_3(C=O)$-N-1], 2.50 [s, 3, $CH_3(C=O)$-N-10], 4.69 (sextet, 1, $J_{gem} \cong -13$ Hz, $J_{e,e} \cong$ 3 Hz, C-2 equatorial), 7.39 (m, 3, C-6–8), and 8.42 (m, 1, C-9).

Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.98; H, 6.58; N, 10.54.

3,4-Dihydro-9-methylcarbazol-1(2H)-one Oxime (9).—A mixture of **2**[18] (112.2 g, 0.563 mol), hydroxylamine hydrochloride (59.4 g), anhydrous sodium acetate (76.6 g), water (510 ml), and ethanol (2100 ml) was refluxed under N_2 for 18 hr and cooled in an ice bath. The crystalline product was collected by filtration, washed with water, and dried to give 106.3 g (87.9%) of **9**, mp 183–185° (lit.[18] mp 185–186°).

3,4-Dihydro-9-methylcarbazol-1(2H)-one Oxime *p*-Toluenesulfonate (10).—A solution of **9** (112.2 g, 0.524 mol) and *p*-toluenesulfonyl chloride (198 g, 1.05 mol) in pyridine (6 l.) was prepared at 0°, stored under N_2 at ambient temperature in the dark for 98 hr, and poured into ice-water (12 l.). This mixture was stirred for *ca.* 1 hr and the crystalline product was collected by filtration, washed with water, dried, and recrystallized from EtOAc–Skellysolve B to give 161.8 g (84.1%) of **10**, mp 119.5–121.5°. An analytical sample was obtained: mp 120–121.5°; uv (EtOH) end absorption, λ_{max} 207 mμ (ε 29,600), 226 (26,350), and 310 (26,050), and inflections at 243 (16,700), 274 (3450), and 345 (6500).

Anal. Calcd for $C_{20}H_{20}N_2O_3S$: C, 65.19; H, 5.47; N, 7.60; S, 8.70. Found: C, 65.15; H, 5.39; N, 7.64; S, 8.53.

3,4,5,10-Tetrahydro-10-methylazepino[2,3-*b*]indol-2(1H)-one (16).—A solution of **10** (153.7 g, 0.417 mol) in benzene (1.5 l.) was adsorbed on a column of neutral alumina (15 kg) which had been deactivated with 0.4% water. The column was developed with 32 l. of benzene and eluted with 10 l. of $CHCl_3$ followed by 25 l. of 20% MeOH–80% $CHCl_3$. The combined product was chromatographed on silica gel (4.5 kg) with 60% EtOAc–40% cyclohexane. The product obtained from this column was dissolved in MeOH–EtOAc, decolorized with Darco G-60, and crystallized from EtOAc to give 20.6 g (23.1%) of **16**, mp 189–191°. An analytical sample was obtained: mp 193–194.5°; uv (EtOH) λ_{max} 232 mμ (ε 30,500) and 297 (13,800) and inflections at 211 (29,250) and 292 (12,700); ir (Nujol) 3200, 3110 (NH), and 1670 cm^{-1} (C=O); nmr [$(CD_3)_2SO$] δ 3.6 (s, 3, CH_3N), 7.21 (m, 4, C-6–9), and 9.7 (s, 1, NH).

Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.89; H, 6.58; N, 13.22.

3,4,5,10-Tetrahydro-10-methylazepino[2,3-*b*]indol-5a(2H)-ol (35).—Compound **16** (17.7 g, 0.0824 mol) was added under N_2 to an ice-cold, stirred suspension of $LiAlH_4$ (18 g) in tetrahydrofuran. The resulting mixture was refluxed for 18 hr, cooled in an ice bath, and treated successively with water (18 ml), 15% aqueous NaOH (18 ml), and water (54 ml). This mixture was stirred for 1.5 hr and filtered. The filtrate was concentrated under reduced pressure. An EtOAc solution of the residue was allowed to stand at ambient temperature for 3 hr and was then cooled in an ice bath and acidified with methanolic hydrogen chloride. The precipitate was collected by filtration and dried to give 14.7 g (70.6%) of **35** hydrochloride, mp 268–269°. An analytical sample was obtained: mp 264.5–265°; uv (EtOH) λ_{max} 219 mμ (ε 20,550), 271 (5930), 278 (5810), 296 (4120) and 222 (inflection, 20,000); ir (Nujol) 3120, 3000 (OH and N^+H), and 1675 cm^{-1} ($C=N^+$); mass spectrum *m/e* (rel intensity) 216 (100), 199 (7.1), 188 (69), and 160 (34); nmr (D_2O) δ 3.64 (s, 3, CH_3N), 3.82 (q, 1, $J \cong -13$ and 4 Hz, C-2 equatorial), 4.40 (q, 1, $J \cong -13$ and 10 Hz, C-2 axial), and 7.60 (m, 4, C-6–9).

Anal. Calcd for $C_{13}H_{17}ClN_2O$: C, 61.77; H, 6.78; Cl, 14.03; N, 11.09. Found: C, 61.69; H, 6.91; Cl, 14.05; N, 11.12; H_2O, <0.1.

A solution of **35** hydrochloride in water was cooled in an ice bath, made alkaline with NaOH, and extracted with ether. The extract was washed with brine, dried (K_2CO_3), and concentrated *in vacuo*. The residue was crystallized from EtOAc to give **35**: mp 129–133°; uv (EtOH) λ_{max} 217 mμ (ε 24,050), 277 (13,650), and 302 (inflection, 2700); ir (Nujol) 3180 (OH) and 1665 cm^{-1} (C=N); nmr [$(CD_3)_2SO$] δ 3.00 (s, 3, CH_3N), 3.39 (q, 1, $J \cong$ −12.5 and 4 Hz, C-2 equatorial), 4.14 (q, 1, $J \cong -12.5$ and 10.5, C-2 axial), 5.82 (s, 1, OH), and *ca.* 6.91 (m, 4, C-6–9).

Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 71.83; H, 7.78; N, 12.75.

1-Ethyl-1,2,3,4,5,10-hexahydro-10-methylazepino[2,3-*b*]indole (29) Hydrochloride, 1-Acetyl-1,2,3,4,5,10-hexahydro-10-methylazepino[2,3-*b*]indole (30), 3,4,5,10-Tetrahydro-10-methylazepino[2,3-*b*]indol-5a(2H)-ol Acetate Ester (36), and 1-Acetyl-2,3,4,5,10,10a-hexahydro-10-methylazepino[2,3-*b*]indol-5a(1H)-ol (33).—A mixture of **35** (5.00 g, 0.0231 mol), 10% palladium-on-carbon catalyst (2.5 g), and acetic anhydride (500 ml) was hydrogenated at an initial pressure of 30 psi for 8 hr and allowed to stand under hydrogen without shaking for an additional 16 hr. The catalyst was removed by filtration through Celite, the solid was washed with EtOAc, and the combined filtrate was concentrated *in vacuo*. The residue was dissolved in xylene and concentrated to remove last traces of acetic anhydride. This residue was chromatographed on silica gel (250 g). The first two compounds were eluted from the column with 30% EtOAc–70% cyclohexane. A solution of the first compound in EtOAc was

(25) This material was a mixture of two isomers; the two sets of peaks are indicated.

(26) This material was a mixture of isomers; peaks assigned to the minor isomer are in brackets.

acidified with methanolic hydrogen chloride and the salt was crystallized from EtOH–EtOAc to give 1.12 g, mp 211–212° dec, and 0.344 g, mp 207.5–5–208.5° dec (23.9%), of **29** hydrochloride. An analytical sample was obtained: mp 209–210° dec; uv (EtOH) λ_{max} 219 mμ (ε 17,700), 276 (8550), 283 (8700), and 293 (inflection, 7650); ir (Nujol) 1640 cm^{-1} (C=N⁺); mass spectrum *m/e* (rel intensity) 228 (100), 213 (6.5), 200 (34), 199 (34), and 171 (16); nmr [$(CD_3)_2SO$–D_2O] δ 1.42 (t, 3, *J* = 7 Hz, CH_3CH_2N), 3.69 (s, 3, CH_3N), 3.87 (q, 2, *J* = 7 Hz, CH_3-CH_2N), and 7.39 (m, 4, C-6–9).

Anal. Calcd for $C_{15}H_{21}ClN_2$: C, 68.03; H, 7.99; Cl, 13.39; N, 10.58. Found: C, 67.73; H, 7.89; Cl, 13.46; N, 10.10.

The second compound eluted from the column was crystallized from EtOAc–Skellysolve B to give 1.42 g (25.4%) of **30**, mp 130–132.5°. The analytical sample was crystallized from EtOH–Skellysolve B: mp 125–125.5°; uv (EtOH) λ_{max} 226 mμ (ε 40,000), 285 (9290), 293 (8100), and 279 (inflection, 8560); ir (Nujol) 1670 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity) 242 (100), and 199 (77); nmr [$(CD_3)_2SO$] δ 1.81 [s, 3, CH_3-(C=O)N], 3.59 (s, 3, CH_3N), 4.56 (sextet, 1, *J* ≅ −13 and 3 Hz, C-2 equatorial), and 7.31 (m, 4, C-6–9).

Further elution of the column with EtOAc gave a mixture of two additional compounds which was rechromatographed on silica gel (150 g) with 2% Et_3N–23% cyclohexane–75% EtOAc.

The first compound eluted from this column was crystallized from EtOAc–Skellysolve B to give 0.408 g (6.87%) of **36**, mp 108.5–110°. An analytical sample was obtained: mp 105–108°; uv (EtOH) λ_{max} 217 mμ (ε 23,430), 277 (15,070), and 311 (2450); ir (Nujol) 1740 [CH_3(C=O)O] and 1675 cm^{-1} (C=N); mass spectrum (high resolution) *m/e* 258.1369; nmr ($CDCl_3$) δ 2.04 [s, 3, CH_3(C=O)O], 3.13 (s, 3, CH_3N), 3.72 (m, 2, C-2), and 6.91 (m, 4, C-6–9).

Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.85. Found: C, 69.61; H, 7.04; N, 10.36.

The second compound eluted from the column was crystallized from EtOAc–Skellysolve B (Darco) to give 0.169 g (2.81%) of **33**, mp 139–141°. An analytical sample was obtained: mp 141.5–142.5°; uv (EtOH) end absorption, λ_{max} 250 mμ (ε 12,950) and 306 (2625); ir (Nujol) 3280 (OH), and 1615 cm^{-1} (C=O); mass spectrum (high resolution) *m/e* 260.1514 (M^+) and 242.1429 ($M^+ - 18$); nmr ($CDCl_3$)[27] δ 2.18, 2.23 [s, 3, CH_3(C=O)N], 2.68, 2.72 (s, 3, CH_3N), 5.85, 5.20 (s, 1, C-10a), and 6.89 (m, 4, C-6–9).

Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 68.96; H, 7.86; N, 10.71.

1-Acetyl-1,2,3,4,5,10-hexahydro-10-methylazepino[2,3-*b*]indole (30).—A solution of **33** in benzene was treated with a few crystals of *p*-toluenesulfonic acid, stirred at ambient temperature under N_2 for 30 min, and poured into water. This mixture was extracted with ether; the extract was washed with water, dried (K_2CO_3), and concentrated. Crystallization of the residue from Et_2O–Skellysolve B gave **30**, mp 126.5–127.5°. This material was identical to the authentic sample by mixture melting point and ir and uv comparison.

(27) This material was a mixture of two isomers; the more intense peaks are listed first.

Registry No.—**3**, 23240-49-5; **5**, 14384-39-5; **6**, 23240-51-9; **7**, 23240-52-0; **10**, 23240-53-1; **11**, 23240-54-2; **12**, 23240-55-3; **13** hydrochloride, 23240-56-4; **14**, 23240-57-5; **15**, 23240-58-6; **16**, 23240-59-7; **17**, 23240-60-0; **17** hydrochloride, 23240-61-1; **17** hydrobromide, 23240-62-2; **18**, 23240-63-3; **19** hydrochloride, 23240-64-4; **20** hydrochloride, 23240-65-5; **21**, 23240-66-6; **22**, 23240-67-7; **23**, 23231-29-0; **24** hydrochloride, 23231-00-7; **25**, 23231-01-8; **26**, 23231-02-9; **27**, 23231-03-0; **29** hydrochloride, 23231-04-1; **30**, 23231-05-2; **31**, 23263-76-5; **32**, 23231-06-3; **33**, 23231-07-4; **34**, 23240-68-8; **35**, 23231-08-5; **35** hydrochloride, 23231-09-6; **36**, 23231-10-9.

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The Mannich Reaction of Imidazoles

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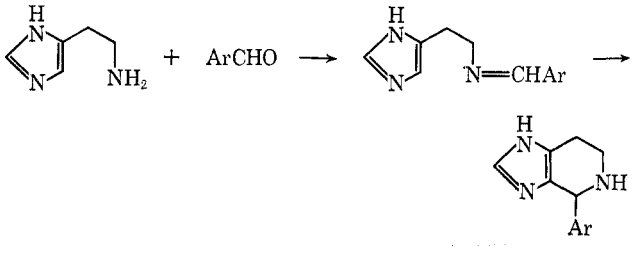
In the Mannich reaction of imidazoles, the ring is shown to be reactive at the four possible sites, the 1, 2, 4, and 5 positions. Only N-substituted imidazole Mannich bases are formed in acidic media. Both N-substituted and C-substituted products are formed in basic media. The process of N substitution is reversible in base, while C substitution is irreversible, resulting in the accumulation of C-substituted products over time in basic media. The 1 position is most reactive, with the 4 and 5 positions more reactive than the 2 position. Imidazoles having substituents at the 1 position do not react in the Mannich reaction. A mechanism is proposed which explains the behavior of the imidazole ring in the Mannich reaction.

The chemistry of imidazoles has considerable significance owing to the occurrence of this ring system in various biologically important compounds. Some 4-disubstituted aminomethyl imidazoles prepared by Turner, Huebner, and Scholz[2] in a multistep process were shown to have antihistaminic action, while others imitated histamine. It was of interest to study the Mannich reaction as a one-step method of introducing aminomethyl groups on to the imidazole ring.

Part of the rationale for studying the Mannich reaction of imidazoles grew out of our findings on the related facile base-catalyzed cyclization of histamine



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(2) R. A. Turner, C. F. Huebner, and C. R. Scholz, *J. Amer. Chem. Soc.*, **71**, 2801 (1949).