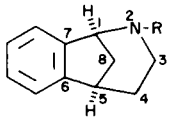
Azabicyclo Chemistry II. Synthesis of 1,5-Methano-2,3,4,5-Tetrahydro-1*H*-2-Benzazepines. B-Norbenzomorphans (1)

Michael Mokotoff and Arthur E. Jacobson

Department of Medicinal Chemistry, School of Pharmacy, University of Pittsburgh
and Laboratory of Chemistry, National Institutes of Health

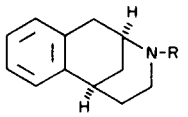
The syntheses of the B-norbenzomorphans, 1,5-methano-2,3,4,5-tetrahydro-1*H*-2-benzazepine (Ia) and its *N*-methyl derivative (Ib) were accomplished. Phenylsuccinic anhydride (III) was cyclized to 3-carboxy-1-indanone (IVa), which was converted by the Arndt-Eistert method to the homologous methyl indanone-3-acetate (V). One experiment in the synthesis of V led to the by-products 3-carboxamido-1-indanone (IVd) and 3-(*N*-methylcarboxamido)-1-indanone (IVe), identified by physical and chemical means. Methyl 1-aminoindan-3-acetate (VII) was prepared by catalytic reduction of methyl indanone-3-acetate oxime (VI). Hydrolysis of VII afforded 1-aminoindan-3-acetic acid (VIII), which was cyclized with dicyclohexylcarbodiimide to 1,5-methano-2,3,4,5-tetrahydro-1*H*-2-benzazepin-3-one (IX). Reduction (lithium aluminum hydride) of IX gave amine Ia which was then methylated to Ib. The mass spectral fragmentation patterns of IX and Ia are discussed.

The significant analgetic activity (1a) of the 7-methoxy B-norbenzomorphans, a new heterocyclic ring system, prompted the synthesis of the parent molecule of the series, 1,5-methano-2,3,4-5-tetrahydro-1*H*-2-benzazepine (Ia) and its *N*-methyl derivative (Ib). We desired to compare their analgetic activities with those of the parent 6,7-benzomorphan molecule (IIa) and its *N*-methyl derivative (IIb) (2).



I

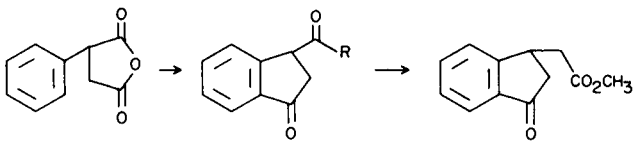
a) R = H
b) R = CH_3



II

The starting material, phenyl succinic anhydride (III), was readily prepared from commercial phenyl succinic acid. Anhydride III was cyclized (3) to the known (4) indanone-3-carboxylic acid (IVa). Chain elongation according to the method of Arndt and Eistert (5) involved conversion of IVa to its acid chloride IVb, reaction of the latter with excess diazomethane and rearrangement of the resulting diazoketone IVc with silver oxide in methanol, thus affording the keto-ester V. Initial experiments of this procedure always gave two by-products on addition of IVb to the ethereal diazomethane, but only when the diazomethane precursor was *N*-methyl-*N*-nitroso-*N'*-nitroguanidine. The by-products were separated (preparative tlc) and identified as the amide IVd and *N*-methylamide IVe. The structures of IVd and IVe were deduced by both physical and chemical means. Treatment of IVb with ammonia and methylamine gave IVd and IVe, respectively, identical in all respects with the by-products separated by chromatography.

Arndt (6) has reported that diazomethane prepared from nitrosomethylurea does not contain ammonia but does contain traces of methylamine. No doubt the source of contaminating ammonia and methylamine came from the diazomethane precursor, because when the precursor was changed to *N,N'*-dinitroso-*N,N'*-dimethyl terephthalamide no evidence of IVd or IVe was observed, and a 50% yield (from IVa) or desired keto-ester V was obtained.



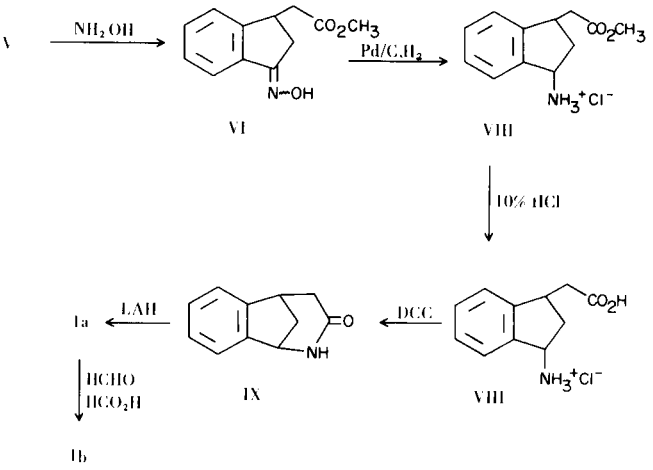
III IV V

a) R = OH
b) R = Cl
c) R = CHN_2
d) R = NH_2
e) R = $NHCH_3$

Keto-ester V was converted to its oxime VI, no attempt being made to separate possible isomers, and hydrogenated over 10% palladium-charcoal in ethanolic hydrogen chloride to give a 53% yield of amino-ester hydrochloride VII. Expected thermal cyclization of the free amine of VII was not satisfactory and thus VII was hydrolyzed in acid to

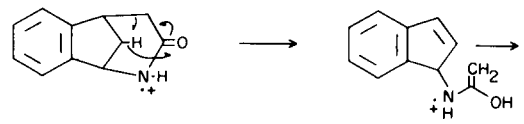
indanamine-3-acetic acid hydrochloride (VIII). Cyclization of VIII to the lactam IX was effected using dicyclohexylcarbodiimide in pyridine-water, in a yield of 61%. The nmr spectrum of IX in deuteriochloroform showed three single-proton multiplets at δ 3.46 (benzylic C-5), 4.45 (benzylic C-1), and 8.03 (lactam N-H) (7).

Reduction of the lactam IX with ethereal lithium aluminum hydride led to the formation of the desired parent B-norbenzomorphan Ia. Methylation of amine Ia with formaldehyde-formic acid gave the *N*-methyl derivative Ib. Both structures Ia and Ib were substantiated by physical data.

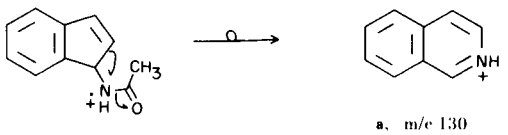


Inasmuch as the lactam IX and its reduction product Ia represent a new ring system, it was of interest to investigate the mass spectral fragmentation patterns that these compounds undergo upon electron bombardment. The following structures are only postulated, not proven, and their merit lies in rationalizing the decompositions that take place.

The mass spectrum of 1,5-methano-3-oxo-2,3,4,5-tetrahydro-1*H*-2-benzazepine (IX) has as its base peak the ion at m/e 130, formed directly from the molecular ion, as evidenced by an appropriate metastable ion at m/e 97.6



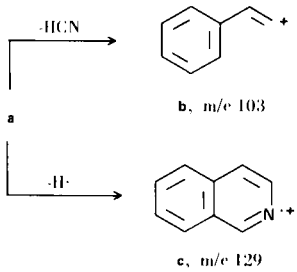
M^+, m/e 173



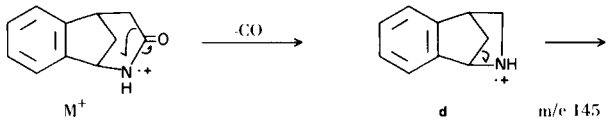
a, m/e 130

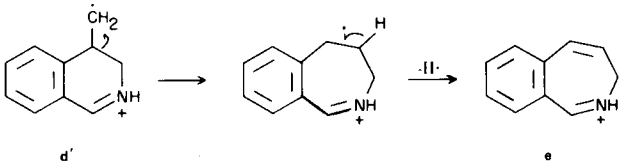
(calcd. 97.7). The accurate mass to charge ratio of this ion is 130.0664, which compares favorably with the value 130.0659 calculated for $C_9H_8N^+$. One rationalization for the formation of this ion is invisaged as the transfer of a hydrogen atom through a McLafferty rearrangement (8), followed by cleavage and rearrangement ot the isoquinolinium ion **a**.

The ion **a** might be expected to expel hydrogen cyanide with transfer of a hydrogen atom to the aromatic ring to give ion **b**, relative intensity 13% (9). For this transformation a metastable ion was observed at m/e 81.6. Loss of a hydrogen atom from ion **a** gives the isoquinoline ion **c**, m/e 129, of relative intensity 52%.



Another major ion observed (relative intensity 30%) in the electron bombardment of IX has been shown by accurate mass measurement to have m/e 144.0810 ($C_{10}H_{10}N^+$ requires 144.0814). This would be satisfied by the loss of CO from the molecular ion (10), to give species **d**, m/e 145 (relative intensity 13%), a relationship established by recognition of a metastable ion at m/e 121.5, ring cleavage to **d′** followed by ring expansion and expulsion of a hydrogen atom to ion **e**.





Furthermore, **d′** could lose a methyl radical, thereby also contributing to the base peak, isoquinolinium ion **a**. These fragmentations are summarized in Figure 1.

d' a, m/e 130

The mass spectrum of 1,5-methano-2,3,4,5-tetrahydro-1*H*-2-benzazepine (Ia) showed all the major fragments that the lactam IX showed and in addition a strong (relative intensity 33%) M^+-1 ion at m/e 158. The M^+-1 peak, based on analogy with other azabicyclo compounds (11), is formulated as the ion **f**.

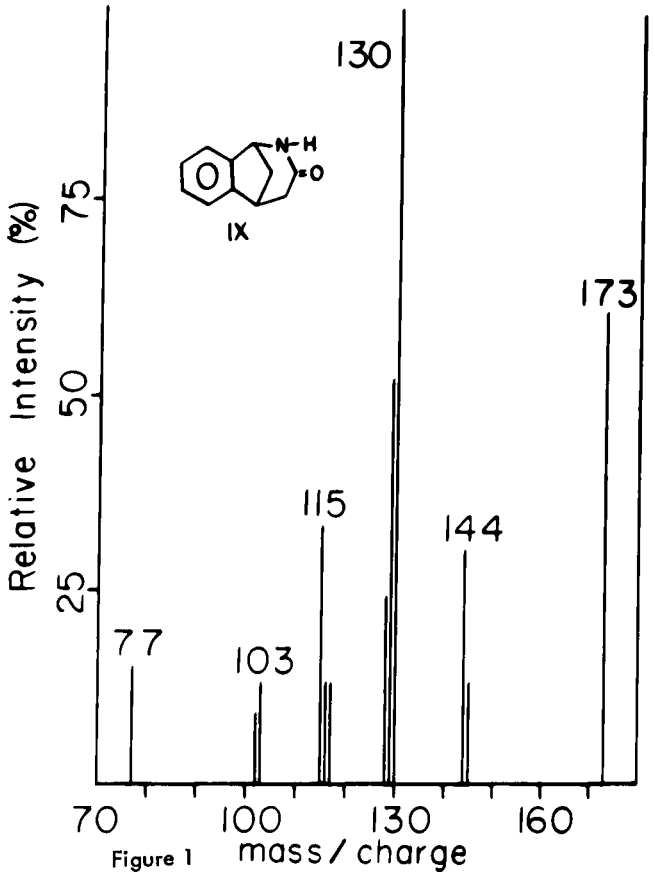
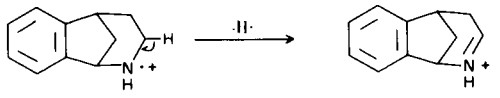
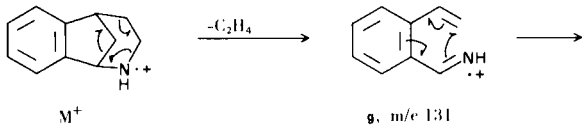


Figure 1

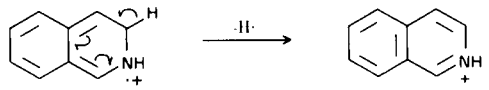


M^+, m/e 159 f, m/e 158

The base peak for Ia is identical with the base peak for IX. The accurate mass to charge ratio for this ion **a** is 130.0666, which compares favorably with the value of 130.0659 calculated for $C_9H_8N^+$. The route to **a** may be viewed as proceeding *via* a retro-Diels-Alder fragmentation, similar to that reported for morphinan derivatives (12), giving ion **g**, m/e 131 (relative intensity 35%), cyclization to **g'** followed by loss of a hydrogen atom.



M^+ g, m/e 131



g' a, m/e 130

The loss of 15 mass units from the molecular ion to give the species **e** has been confirmed by accurate mass measurement, m/e 144.0809 ($C_{10}H_{10}N^+$ requires 144.0814). Simple α-cleavage followed by loss of a methyl radical would satisfy this observation. The other major peaks observed in the fragmentation of Ia are summarized in Figure 2.

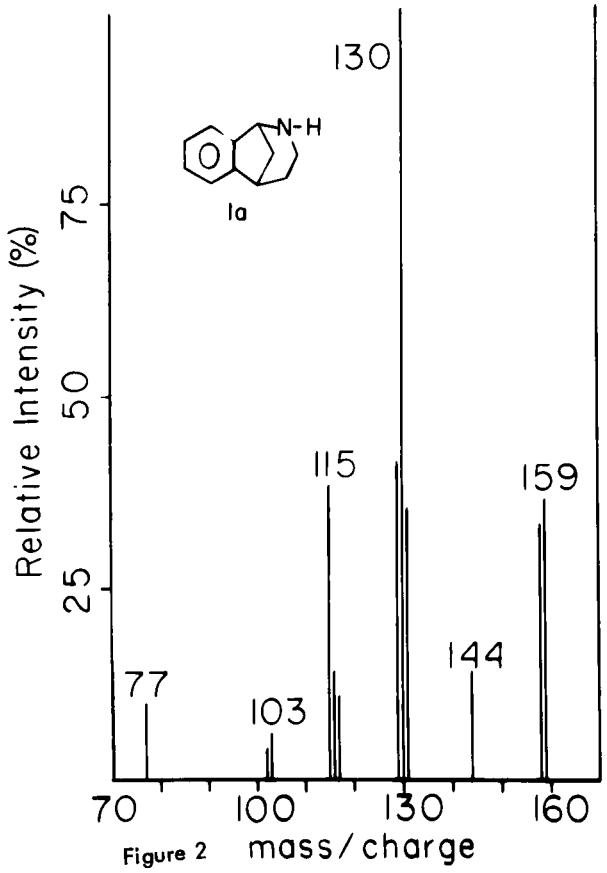
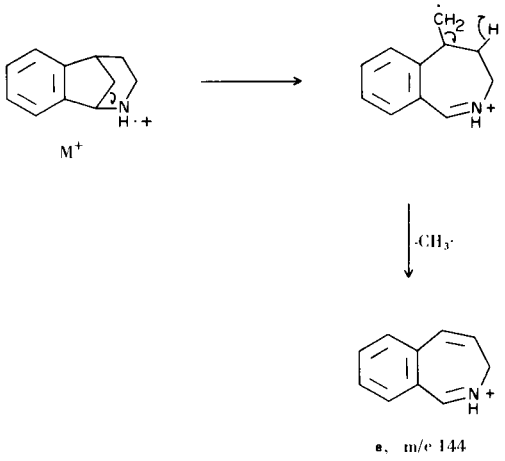


Figure 2



The analgetic activities of Ia and Ib were determined in mice by the hot-plate method (13). Compound Ia had an ED_{50} of approximately one-third that of codeine, while Ib had about one-fourth the acitvity of codeine, and was relatively toxic. In comparison, the homologous 6,7-benzomorphans, IIa and IIb, were codeine-like (2).

EXPERIMENTAL

Melting points were determined on a Fisher-Johns apparatus and are corrected. Microanalyses were performed by Spang Microanalytical Laboratory, P. O. Box 1111, Ann Arbor, Michigan 48106. Low resolution mass spectra were determined on an LKB Model 9000 spectrometer, while the high resolution mass spectral measurements were determined on a Hitachi-Perkin Elmer RMU-7 double focusing spectrometer; perfluorokerosene as standard. The nmr spectra were determined on a Varian A-60 spectrometer as solutions in deuteriochloroform, unless otherwise stated, with TMS as internal standard. Chemical shifts are recorded as δ values in ppm. Infrared spectra were recorded on a Perkin-Elmer Infracord spectrophotometer. Thin layer chromatography (tlc) and preparative tlc (1 mm thick) were performed on plates of silica gel GF obtained from analtech, Inc. The spots on tlc were located by spraying the plates with a solution of 3% ceric sulfate in 3 *N* sulfuric acid and then heating. All concentrations were performed under reduced pressure, except for recrystallization experiments. Ultraviolet spectra were recorded on a Beckman DB-G grating spectrophotometer. Vapor phase chromatography (vpc) was performed isothermally on either a 3 ft. by ¼ inch glass column packed with 3% SE 30 on chrom WAW 60/80 (column A) or a 5 ft by ¼ inch stainless steel column packed with 3% SE 30 on Varaport 30 100/120 (column B). Skellysolve B refers to petroleum ether b.p. 66-75°, while Skellysolve F refers to petroleum ether b.p. 30-60°.

3-Carboxy-1-indanone (IVa).

Phenylsuccinic anhydride (48.0 g., 0.27 mole; obtained by treatment of commercial phenylsuccinic acid with acetyl chloride) was dissolved in 350 ml. of methylene chloride, cooled in ice and treated, portionwise over 1 hour with anhydrous aluminum chloride (75.0 g., 0.56 mole). The ice was removed and stirring continued at room temperature for 3.5 hours. This mixture was then poured into a mixture of ice and 130 ml. of concentrated hydrochloric acid (about 1 l.). The resulting precipitate was collected by filtration, crystallized from benzene-Skellysolve B, thus affording 41.7 g. (87%) of IVa, m.p. 119-120° (lit. (4) m.p. 118°, 120°); ir (nujol) 5.75 ($-CO_2H$), 5.92 μ (aromatic C=O); uv (EtOH) 245 and 295 mμ (ε = 10,650, 2,460) (House, *et al.*, (3) reports similar ir and uv assignments for a substituted indanone 3-acetic acid); nmr (DMSO-d_6), δ 2.92 (d, 2, J = 6 Hz, CH_2CO), 4.35 (t, 1, J = 6 Hz, aromatic -CHCO); mass spectrum (80 ev) m/e (rel. intensity) 176 (83) M^+, 158 (56) M^+-H_2O, 131 (100) M^+-CO_2H, 130 (100), 103 (78), 77 (44).

Methyl Indanone-3-acetate (V), 3-Carboxamido-1-indanone (IVd), and 3-(*N*-methylcarboxamido)-1-indanone (IVe).

Compound IVa (6.0 g., 34 mmoles) was dissolved in 130 ml. of refluxing benzene and treated dropwise, during 2.5 minutes with a solution of oxalyl chloride (50 g., 0.40 mole) in 20 ml. of benzene. The bright red solution was refluxed for 30 minutes, allowed to remain at room temperature for 1 hour and then concentrated to dryness. The resulting oil was dissolved in benzene and re-concentrated (3 times) to remove traces of oxalyl chloride. The red oily residue was dissolved in anhydrous ether, insoluble meterial removed by filtration through glass wool, and added portionwise to an ice-cold ethereal solution (235 ml.) of diazomethane (titrated (6) for 69 mmoles). The diazomethane was prepared from *N*-methyl-*N*-nitroso-*N'*-nitroguanidine (20 g., 0.13 mole), according to the procedures of Arndt (6) and McKay (14). Addition of the acid chloride (IVb) to the diazomethane solution resulted in the immediate formation of ppt A. After remaining at room temperature for 1 hour, the ppt A was collected by filtration (weight = 0.70 g.) and the filtrate concentrated to a reddish gum (IVc)-ir, 4.70 μ for diazoketone. Crude IVc was dissolved in 100 ml. of methanol and, while stirring and warming, treated portionwise with a methanolic slurry of silver oxide (Fisher Chemical Co.). The mixture was refluxed for 1 hour, the inorganic material removed by filtration and the filtrate concentrated to a dark oil. The product was distilled at 200°/0.2 mm and gave 3.3 g. of an amber colored oil, whose vpc on column A (190°) showed evidence of a major and minor peak. Further distillation of this amber oil using a Nessler-Faust spinning band column effected a somewhat better separation of the desired product. Fractions containing purer material spontaneously crystallized. Crystallization of these fractions from isopropyl ether gave almost colorless crystals, (2.47 g., 35%), m.p. 59-60° (lit. (15) m.p. 54° from benzene-petroleum ether), of keto-ester V; nmr δ 3.72 (s, 3, $-OCH_3$); mass spectrum (80 ev) m/e (rel. intensity) 204 (65) M^+, 173 (13) M^+-OCH_3, 145 (90), 144 (91), 131 (100), 130 (29), 115 (48), 103 (52), 91 (18), 77 (48).

The precipitate A was crystallized from acetone-Skellysolve B to give, in 2 crops, 0.4 g. of gold-colored crystals, m.p. 179-182° (crystals B). The mother liquor from B was concentrated to a brown residue which was sublimed at 130°/0.2 mm, giving 0.14 g. of a tan sublimate C. This sublimate showed 2 spots on tlc (10% methanol-chloroform), the spot of lower R_f corresponded to crystalline B. Sublimate C was purified by preparative tlc (15% methanol-chloroform). The product from the lower band was combined with crystalline B and sublimed at 140°. The sublimate was crystallized from acetone and gave 0.29 g. of IVd as colorless crystals, m.p. 184.5-185.5° (lit. (16) m.p. 177-178° from water); ir (Nujol) 2.95, 3.11 (NH_2), 5.85 (aromatic C=O), and 5.97 μ ($-\overset{O}{\overset{\|}{C}}-NH_2$); uv (ethanol), 244 and 288 mμ (ε = 10,630, 1700); nmr (DMSO-d_6), δ 2.95 (d, 2, J = 5 Hz, CH_2CO), 4.22 (t, 1,

J = 5 Hz, aromatic-CHCO), 7.20, 7.92 (1 proton each, -C-NH_2) (17); mass spectrum (80 ev) m/e 175.064, M^+ (calcd. 175.063).

A portion of IVa was converted to IVb, as above, and treated with an ethereal solution of dry ammonia. The crude product was separated from starting material by preparative tlc (15% methanol-chloroform) and crystallized from acetone-ether. It was identical in ir and m.p. to IVd isolated above (mixed m.p. 184.5-185.5°).

The upper band from the purification of sublimate C was crystallized from acetone-Skellysolve B and gave 21 mg. of colorless IVe, m.p. 197-198°; ir (Nujol), 3.04 (NH), 5.84 (aromatic C=O), and 6.09 μ (-C-$NHCH_3$); uv (ethanol) 244 and 290 mμ (ϵ = 6180, 1030); nmr (DMSO-d_6), δ 2.67 (d, 3, J = 4.5 Hz, $NHCH_3$) 2.78 (d, 2, J = 5 Hz, CH_2CO), 4.18 (t, 1, J = 5 Hz, aromatic-CHCO), and 8.37 (m, 1, $NHCH_3$; mass spectrum (80 ev) m/e 189.077, M^+ (calcd. 189.079).

Similarly, a portion of IVa was converted to IVb and treated with an ethereal solution of dry methylamine. The crude product was purified by preparative tlc (15% methanol-chloroform), and crystallization from acetone-Skellysolve F gave pure IVe, m.p. 197.5-198.5°. This was identical (ir and mixed m.p.) with IVe isolated above.

Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86. Found: 69.77; H, 5.80.

When the acid chloride IVb (from 10.7 g., 61 mmoles of IVa) was treated with an ethereal solution of diazomethane (0.16 mole by titration) that had been prepared from *N,N'*-dinitroso-*N,N'*-dimethylterephthalamide (18), no by-product was formed. Upon refluxing the resulting diazoketone with methanolic silver oxide (freshly prepared from 10% silver nitrate and 10% sodium hydroxide), and workup including one distillation followed by crystallization, a total yield of 6.24 g. (50%) of V was obtained.

Methyl Indanone-3-acetate Oxime (VI).

Keto-ester V (7.00 g., 34 mmoles) was dissolved in 60 ml. of ethanol and mixed with a solution of anhydrous sodium acetate (8.20 g., 0.10 mole) and hydroxylamine hydrochloride (6.95 g. 0.10 mole) in 50 ml. of water. The mixture was refluxed for 1 hour, concentrated until all the ethanol was removed and the product extracted into chloroform. The organic layer was washed twice with water, dried (sodium sulfate), and concentrated to an amber-colored gum. Crystallization of the gum from benzene-Skellysolve F gave a colorless first crop of oxime VI (4.93 g.), m.p. 78-79°. Further concentration afforded, in 2 crops, another 1.16 g., for a total yield of 6.09 g. or 82%. The analytical sample, obtained by repeated crystallization from isopropyl ether, had a m.p. 79-79.5°; ir (chloroform) 5.85 (ester - C=O), 6.02 weak (C = N), and 10.7 μ (broad, N-O); nmr δ 3.69 (s, 3, -OCH_3), 7.17-7.42 (m, 3, C-4, 5, 6 arom H) 7.75 (m, 1, C-7 arom H); 10.12 (broad, 1, N-OH); mass spectrum (80 ev) m/e 219 (M^+), 202 (M^+-OH), 146, 145 (base peak, M^+–H_2C=C(OH)-OCH_3).

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.69; H, 5.90; N, 6.28.

Methyl 1-Aminoindan-3-acetate Hydrochloride (VII).

A solution of the oxime VI (5.30 g., 24 mmoles) in 70 ml. of absolute ethanol was placed in a 500 ml. Parr hydrogenation flask, the air displaced with nitrogen, 0.8 g. of 10% palladium-charcoal catalyst added followed by 25 ml. of dry ethanolic hydrogen chloride (1M). The mixture was hydrogenated overnight (all the hydrogen uptake was observed after 3 hours), the catalyst removed by filtration and the filtrate concentrated to a solid mass. The solid was crystallized from methanol-ether and in 3 crops afforded 3.08 g. (53%) of colorless crystalline VII. Recrystallization gave the analytical sample, m.p. 177-178°; mass spectrum (80 ev) m/e 205 M^+ (free base).

Anal. Calcd. for $C_{12}H_{16}ClNO_2$: C, 59.62; H, 6.67; N, 5.80. Found: C, 59.43; H, 6.71; N, 5.69.

1-Aminoindan-3-acetic acid Hydrochloride (VIII).

The methyl ester VII (2.79 g., 11.5 mmoles) was refluxed for 3 hours in 10% aqueous hydrochloric acid and then concentrated to dryness. The crystalline residue was triturated with 3 portions of acetone and the acetone removed by decantation. The remaining crystalline product was recrystallized from methanol-ether and in 2 crops gave 2.09 g. of VIII. The crude product from the mother liquor was re-cycled for another 3 hours reflux period with 10% hydrochloric acid and above workup afforded another 0.23 g. of product; total yield 2.32 g. (89%). Repeated crystallizations from methanol-ether gave the analytical sample, m.p. 225-229° dec.; mass spectrum (70 ev) m/e (rel. intensity) 191 (9) M^+, 190 (10), 144 (4), 131 (62), 130 (100), 117 (8), 115 (9).

Anal. Calcd. for $C_{11}H_{14}ClNO_2$: C, 58.02; H, 6.20. Found: C, 58.03; H, 6.24.

1,5-Methano-2,3,4,5-tetrahydro-1*H*-2-benzazepin-3-one (IX).

The amino acid hydrochloride VIII (1.12 g., 4.95 mmoles) was dissolved in 25 ml. of water. Pyridine (50 ml.) was added and this caused the precipitation of the free amino acid. More pyridine (20 ml.) was added, the mixture heated to boiling and enough water added (about 50 ml.) to bring the amino acid into solution. The solution was cooled to 60° and treated with a solution of dicyclohexylcarbodiimide in 5 ml. of pyridine, and the resulting mixture (immediate precipitation of dicyclohexylurea occurred) stirred at room temperature for 4 days. Filtration of the dicyclohexylurea and removal of the solvent *in vacuo* gave a residue which was dissolved in chloroform, washed successively with 10% hydrochloric acid (twice), saturated sodium bicarbonate solution (twice), and water (once), dried (sodium sulfate) and concentrated to a crude product, wt 0.69 g. This crude lactam was sublimed at 100° (0.15 mm Hg) and the sublimate (0.66 g.) crystallized from acetone-Skellysolve F, affording 0.52 g. (61% yield, in 2 crops) of desired lactam IX, m.p. 160-162°. The analytical sample had a m.p. 160-160.5°; ir (chloroform) 6.02 μ (C=O).

Anal. Calcd. for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.36; H, 6.49; N, 8.09.

1,5-Methano-2,3,4,5-tetrahydro-1*H*-2-benzazepine Hydrobromide (Ia).

The lactam IX (0.52 g., 3.0 mmoles) was dissolved in 11 ml. of hot tetrahydrofuran (purified by distillation from lithium aluminum hydride) and added to a stirred suspension of lithium aluminum hydride (0.23 g., 6.0 mmoles) in purified tetrahydrofuran (19 ml.). The mixture was refluxed, under a slight positive pressure of nitrogen for 1 day. A tlc (30% methanol-chloroform) examination of an aliquot still indicated the presence of some lactam and therefore 3 ml. of an ethereal solution of lithium aluminum hydride (about 1 *M*) was added and the mixture refluxed another day. The mixture was cooled in ice, the excess lithium aluminum hydride destroyed by dropwise addition of 10% sodium hydroxide solution, followed by the addition of chloroform. The inorganic salts were removed by filtration and boiled in chloroform. Combination of the chloroform solution and concentration gave a brown oil, whose tlc still indicated some lactam. The oil

was therefore re-dissolved in 20 ml. of purified tetrahydrofuran, treated with 7 ml. of the above ethereal lithium aluminum hydride solution and refluxed for another 2 days. Above workup gave an oil (0.35 g.) which on distillation (bath temperature 80°, 0.2 mm Hg) afforded a colorless oil (one peak in vpc on column B at 150°, one spot tlc). The latter was immediately converted to its hydrobromide salt, crystallized from acetone, and in 3 crops gave 0.30 g. (42%) of colorless crystalline Ia-hydrobromide, m.p. 174-177°. Recrystallizations from acetone-ether gave the analytical sample, m.p. 176-178°; nmr (free base) δ 3.15 (m, 1, C-5), 4.18 (m, 1, C-1).

Anal. Calcd. for $C_{11}H_{14}BrN$: C, 55.01; H, 5.88; N, 5.83. Found: C, 55.14; H, 5.86; N, 5.70.

1-5-Methano-2-methyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine Hydrobromide (Ib).

Hydrobromide Ia (0.147 g., 0.61 mmole) was dissolved in water and converted to its free base with 10% sodium hydroxide solution. The free base was extracted into chloroform, washed with water, dried (sodium sulfate) and concentrated to an oil. The oil was dissolved in a mixture of formic acid (0.60 ml., Mallinckrodt 88%) and formaldehyde (0.60 ml., Mallinckrodt 37% solution) and heated at 100° for 3 hours. The cooled solution was made basic with a 10% sodium hydroxide solution, and the oily product extracted into chloroform. The chloroform solution was washed with water, dried (sodium sulfate) and concentrated. The resulting oily amine was distilled (bath temperature 95°, 0.15 mm Hg), giving 78 mg. (74%) of colorless amine Ib (one peak on vpc, column B, 150°). The free base was converted to its hydrobromide salt, crystallized from acetone-ether, and in 2 crops gave 79 mg. (51%) of crystalline Ib-hydrobromide, m.p. 165-167°. The analytical sample had m.p. 165-165.5°; nmr (free base) δ 2.13 (s, 3, N-CH_3), 3.08 (m, 1, C-5), 3.77 (m, 1, C-1); mass spectrum m/e (rel. intensity) 173.1191 (36) M^+ (calcd. m/e 173.1201), 172 (33), 158 (10) M^+-CH_3, 144 (48), 129 (40) M^+-C_2H_6N, 115 (52), 44 (100) CH_3-$\overset{H}{N}$=CH_2.

Anal. Calcd. for $C_{12}H_{16}BrN$: N, 5.51. Found: N, 5.35.

Acknowledgment.

The authors wish to thank Mr. William R. Landis, National Institutes of Health, for recording the high resolution mass spectra, and Mr. John Naworal, University of Pittsburgh, for the low resolution spectra (the latter performed under Grant FR-00273 from the National Institutes of Health). The authors also thank Dr. Donald J. Abraham, University of Pittsburgh, for helpful discussions concerning interpretation of some of the mass spectral data.

REFERENCES

(1a) Part I: A. E. Jacobson and M. Mokotoff, *J. Med. Chem.*, 13, 7 (1970). (b) This work was supported in part by Grant FRO5455-06 from the National Institutes of Health, Bethesda, Md. (c) Presented in part at the 158th National Meeting of the American Chemical Society, Division of Medicinal Chemistry, New York, N. Y., September, 1969, 28 Medi.

(2) K. Kanematsu, M. Takeda, A. E. Jacobson and E. L. May, *J. Med. Chem.*, 12, 405 (1969).

(3) H. O. House, F. J. Sauter, W. G. Kenyon and J. J. Riehl, *J. Org. Chem.*, 33, 957 (1968).

(4) E. A. Speight, A. Stevenson and F. Thorpe, *J. Chem. Soc.*, 2185 (1924); M. Donbrow, *ibid.*, 1963 (1959).

(4) W. E. Bachmann and W. S. Struve, *Org. Reactions*, 1, 38 (1942).

(6) F. Arndt, "Organic Syntheses," Coll. Vol. II, 165 (1943).

(7) K. Mitsuhashi, S. Shiotani, R. Oh-Uchi and K. Shiraki, *Chem. Pharm. Bull. (Tokyo)*, 17, 434 (1969). A homologous 1,5-methano benzazocine derivative (XXVII) showed single-proton multiplets at δ 4.40 (benzylic C-1) and 7.73 (lactam N-H).

(8) A. M. Duffield, C. Djerassi, L. Wise and L. A. Paquette, *J. Org. Chem.*, 31, 1599 (1966).

(9a) H. Budzikiewicz, C. Djerassi and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967, p. 573; (b) Catalog of Mass Spectral Data, American Petroleum Institute Research Project 44, Carnegie Institute of Technology, Pittsburgh, Pa., Spectra Nos. 625 and 626.

(10a) Ref. 9a, p. 353; (b) A. M. Duffield, H. B. Budzikiewicz and C. Djerassi, *J. Am. Chem. Soc.*, 87, 2913 (1965).

(11) W. M. Bryant, III, A. L. Burlingame, H. O. House, C. G. Pitt and B. A. Tefertiller, *J. Org. Chem.*, 31, 3120 (1966).

(12) H. Nakata, Y. Hirata and A. Tatematsu, *Tetrahedron Letters*, 829 (1965).

(13) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exp. Ther.*, 107, 385 (1953). We are indebted to Mrs. L. Atwell, NIH, for these data.

(14) A. F. McKay, *J. Am. Chem. Soc.*, 70, 1974 (1948).

(15) R. A. Manske, *ibid.*, 53, 1104 (1931).

(16) W. Baker and W. G. Leeks, *J. Chem. Soc.*, 974 (1948).

(17) R. H. Bible, "Guide to the NMR Empirical Method. A Workbook," Plenum Press, New York 1967, p. 225. Amide protons are split due to double bonded character of -$\overset{O^-}{\underset{\|}{C}}$=$NH_2^+$.

(18) J. A. Moore and D. E. Reed, "Organic Syntheses," 41, 16 (1961).

Received March 30, 1970

Pittsburgh, Pa. 15213
Bethesda, Md. 20014