# Synthesis and Rearrangements of 2,3,4,5-Tetrahydro-3-benzazocin-6(1*H*)ones (I)

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The preparation of 3-benzenesulfonyl- and 3-benzoyl-2,3,4,5-tetrahydro-3-benzazocin-6(1*H*)-ones by intramolecular acylation is described. Acid catalyzed rearrangements of these 3-benzazocin-6-ones occurs by 3,4-bond cleavage, which is followed by intramolecular or intermolecular alkylation, to produce indanones (*i.e.* XIV) or a 3,4-dihydroisoquinoline (II), respectively. In addition to spectral support for these structures, an independent synthesis of II is described from a known 3,4-dihydroisoquinoline. Two rearrangements of 3-benzazocin-6-ones under alkaline conditions are also described, and the products are again evidence for 3,4-bond cleavage to vinylphenones. These benzazocine rearrangements have been observed only with the 6-keto compounds.

During our investigation of the synthesis of hexahydro-3-benzazocines as analgesic agents *via* tetrahydro-3-benzazocin-6(1*H*)ones, we observed some anomalous products which result from a facile ring cleavage of the 3,4-bond. The observation of these rearrangements has so far been limited to 3-benzazocines containing the 6-keto function. The preparation of related hexahydro-3-benzazocines by different routes has been reported recently (2-5), but none of these involve the benzazocin-6-ones.

The 3-benzenesulfonyl-2,3,4,5-tetrahydro-3-benzazocin-6(1*H*)one (I) has been synthesized by a high dilution cyclization of the acid chloride of *N*-(benzenesulfonyl)-*N*-phenethyl-β-alanine (6). Several reagents cleave tertiary benzenesulfonamides, including 48% hydrobromic acid with phenol as a bromine scavanger (7); this latter reagent is one which would not also react with the ketone function. In the reaction of I with 48% hydrobromic acid and phenol, instead of the expected benzazocin-6-one an amphoteric product was isolated along with diphenyl disulfide. The amphoteric product was assigned structure II on the basis of spectral evidence, and this has been confirmed by subsequent chemical reactions and an independent synthesis.

The ir spectrum of II (nujol, potassium bromide pellet or chloroform solution) shows a strong peak at 1627 $cm^{-1}$ which is characteristic of the C=N stretching vibration as seen for 1-ethyl-3,4-dihydroisoquinoline (8). The 100 MHz nmr spectrum shows one N-$CH_2$ group at 3.57 ppm (9) in deuteriochloroform. In trifluoroacetic acid, the $NCH_2$ is shifted downfield to 3.89 ppm and further split due to protonation of the nitrogen. The uv shows λ max 277 and 218 nm in 0.1*N* HCl or absolute ethanol, but 290 and 242 nm in 0.1*N* sodium hydroxide. These data are consistent for a K-band from a dihydroisoquinoline (8) and a phenolic group, respectively. In 95% ethanol, the bands at 279 and 250 nm are indicative of a zwitterion. The mass spectrum showed $M^+$ at m/e 251, and its base peak at m/e 130 would accommodate the dihydroisoquinoline cation.

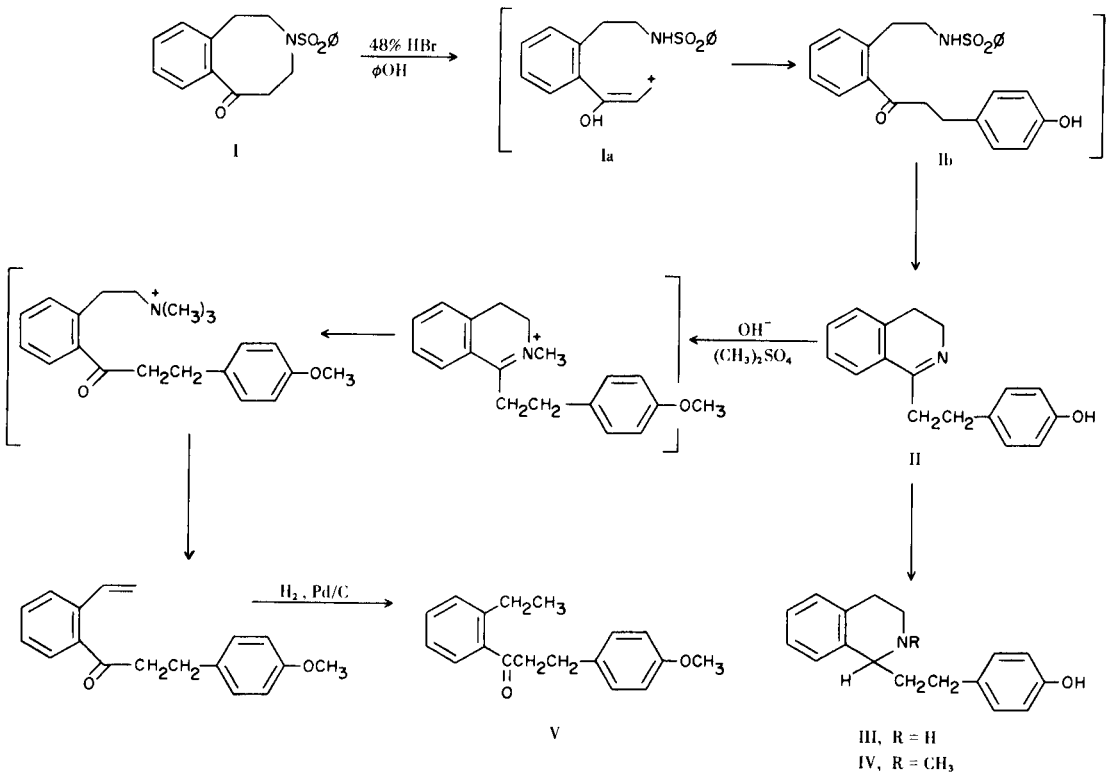
Methylation of II with excess dimethyl sulfate in aqueous base, followed by catalytic hydrogenation of a crude olefin, yielded V, as outlined in Scheme 1. The formation of this deaminated material can be rationalized as outlined, and can be taken as support for structure II.

The reaction product II absorbed one mole of hydrogen to yield a compound which has no C=N according to its ir and uv spectra. In the nmr spectra of this reduced material, a triplet at 4.13 ppm is observed for a methine proton in deuteriochloroform, but appears as a broad triplet at 4.98 ppm in trifluoroacetic acid, which is consistent with structure III.

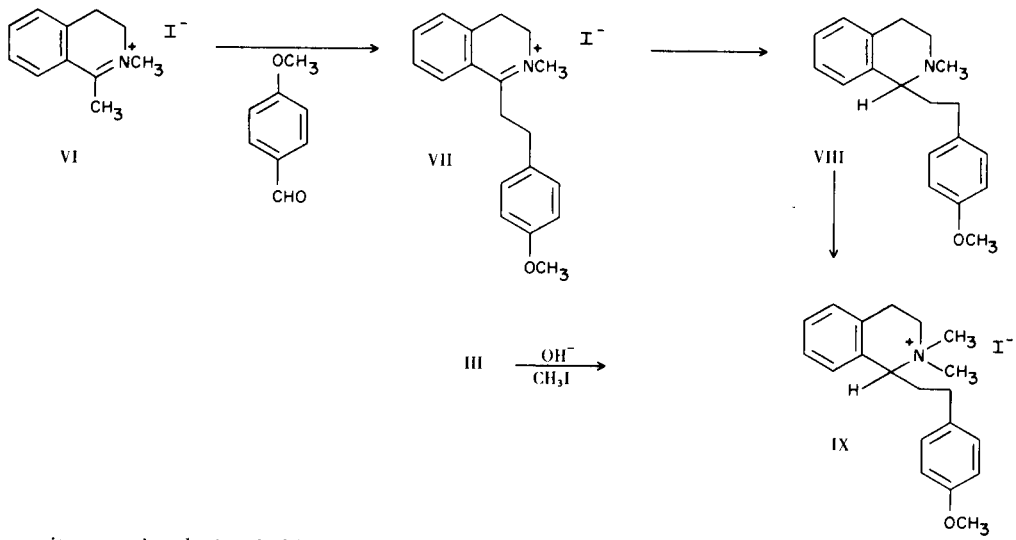
Compound III was methylated with equimolar methyl iodide in aqueous base to yield the $NCH_3$ product, IV. When an excess of methyl iodide was used in aqueous base the $OCH_3$ quaternary salt IX was obtained. Compound IX was also prepared by condensing 3,4-dihydro-1,2-dimethylisoquinolinium iodide, VI (10), with *p*-anisaldehyde to form the 1-styryl dihydroisoquinoline, VII (Scheme 2).

Kametani reduced 3,4-dihydro-1-styrylisoquinolines and dihydroisoquinoline methiodides with sodium borohydride, followed by hydrogenation over Pt, to 1-phenethyltetrahydroisoquinolines (11,12). Sodium borohydride reduces VII to a mixture of compounds which appear to have structure X (*trans*) and XI (1:1 *cis-trans*). This mixture was not completely hydrogenated to VIII since

SCHEME 1

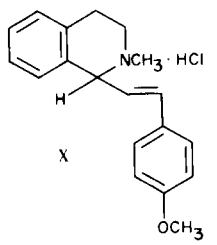


SCHEME 2

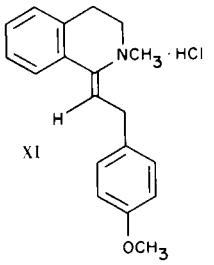


an olefinic impurity persisted (probably XI). Some 1-alkylidene tetrahydroisoquinolines have been reported (13-16), but they were not prepared by a reduction. Polarographic evidence and a selective C=C hydrogenation of a 3,4-dihydro-1-styrylisoquinoline with Pd/C demonstrate the initial reduction of C=C (17). Hydrogenation of VII over platinum oxide produces a sample of VIII, which was directly methylated with methyl iodide in aqueous base to form IX. Both samples of IX showed identical spectral properties and an undepressed mixed melting point.

This chemical and spectral evidence supports structure II for the hydrobromic acid reaction product. The dihydroisoquinoline product is formed from I by azocine ring opening, sulfonamide cleavage, alkylation of phenol, and cyclodehydration, but the order to these events is not




X




XI

clear. We suggest the azocine ring opening as an initial step, perhaps forming an enol-stabilized (18) protonated vinylphenone, Ia, followed by a rapid alkylation of phenol. Cyclodehydration could take place before or after sulfonamide cleavage. The formation of Ia as the initial step is supported by some related benzazocin-6-one rearrangements described below.

Cyclization of the acid chloride of XII (Scheme 3) with aluminum chloride affords good yields of XIII, the 8,9-dimethoxy analog of I, but prolonged reaction with excess aluminum chloride results in selective cleavage of the 9-methoxy group. During cyclization studies with polyphosphoric acid, we recognized a rearrangement of the benzazocin-6-ones to XIV and XVII when the reaction was conducted above 80°. Furthermore, the homolog prepared from methyl methacrylate (XVIII) yields the 5-methyl benzazocine XIX which rearranges to XX. The indanones, although isomeric to the benzazocin-6-ones, were readily differentiated by their spectral properties. We propose that the indanones form in a similar manner to the isoquinoline II by scission of the 3,4-bond in the benzazocin-6-ones to an enol-stabilized carbonium ion, which in turn alkylates the activated benzenoid ring. A similar cleavage of amides in polyphosphoric acid has been reported (19).

The benzazocin-6-ones are stable to aqueous acid, and refluxing XIII in dilute hydrochloric acid afforded hydrolysis of the benzamide to XXI. Indanone formation has only been observed in hot polyphosphoric acid.

A benzazocine ring cleavage has also been observed under basic conditions. Compound XIII reacts with dimethyloxosulfonium methylide in dimethyl sulfoxide to yield the cyclopropylphenone XXII. This reaction presumably proceeds by proton abstraction at the 5-position, followed by $\beta$-elimination of the amide (20) to produce a vinylphenone which then reacts rapidly with the ylide (21) to yield XXII.

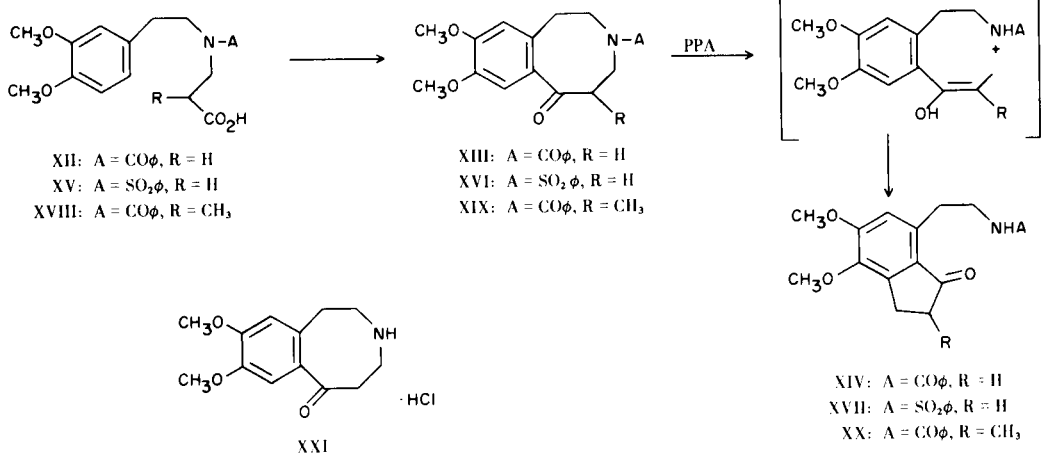
D2

Finally, the basic aminoketone XXIII forms a ring-opened oxime XXIV, even though the normal oxime of XIII is formed under the same conditions. As in the previous rearrangement, we assume a facile base-catalyzed formation of the vinylphenone (20), and methyl ketoximes can form by the reaction of vinyl ketones with hydroxylamine (22). No mechanism has been advanced for this latter reaction, but we conclude that isolation of XXIV is further evidence for benzazocine ring cleavage to the reactive vinylphenones. This evidence for vinylphenone intermediates from benzazocin-6-ones under basic conditions can be compared to the proposed formation of protonated vinylphenones (Ia) under acidic conditions.

## EXPERIMENTAL

Ir, uv, nmr and mass spectra were obtained with Beckman IR-18A, Cary 14, Varian XL-100 or Varian A60A (TMS as internal standard), and Varian MAT 311 spectrometers, respectively. Melting points were determined on a Thomas-Hoover capillary apparatus according to USP Class 1 and are corrected. Elemental analyses were determined with an F & M 185 analyzer.

SCHEME 3

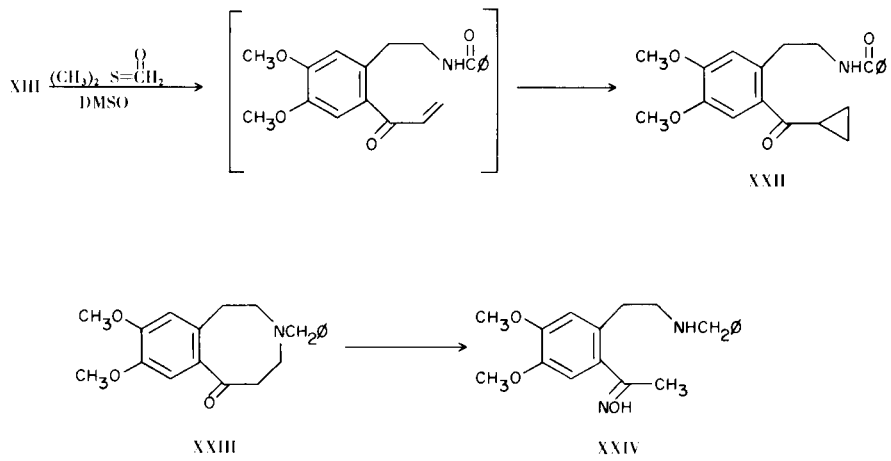



XII: A = COφ, R = H
XV: A = SO2φ, R = H
XVIII: A = COφ, R = CH3

XIII: A = COφ, R = H
XVI: A = SO2φ, R = H
XIX: A = COφ, R = CH3

XIV: A = COφ, R = H
XVII: A = SO2φ, R = H
XX: A = COφ, R = CH3

XXI



XXII



XXIII XXIV

3-Benzenesulfonyl-2,3,4,5-tetrahydro-3-benzazocin-6(1*H*)one (I).

A solution of 66.6 g. (0.2 mole) of 3-(*N*-benzenesulfonyl)-*N*-phenethyl-β-alanine (6) in 500 ml. of dry methylene chloride was refluxed wtih 100 ml. of thionyl chloride for 40 minutes, then the solvent and excess thionyl chloride evaporated at reduced pressure. The brown oily acid chloride in 200 ml. of dry methylene chloride was added dropwise over 2 hours through two condenseres into a stirred refluxing suspension of 53.3 g. (0.4 mole of anhydrous aluminum chloride in 3 l. of dry methylene chloride. Reflux was continued 2 hours, then the mixture treated with 500 ml. water. The organic layer was twice washed with water and dried (magnesium sulfate), then evaporated at reduced pressure to a brown solid, which was recrystallized from isopropyl acetate to afford I in 76% yield, m.p. 158.5-159.5°; nmr (deuteriochloroform): δ 2.93 (m, 2, $CCH_2$), 2.97 (m, 2, $CCH_2$), 3.44 (m, 2, $NCH_2$), 3.50 (m, 2, $NCH_2$); ir ν (potassium bromide): 1675 $cm^{-1}$ (C=O).

*Anal.* Calcd. for $C_{17}H_{17}NO_3S$: C, 64.74; H, 5.43; N, 4.44; S, 10.17. Found: C, 64.86; H, 5.70; N, 4.59; S, 10.26.

3,4-Dihydro-1-(4-hydroxyphenethyl)isoquinoline (II).

A mixture of 6.3 g. (0.02 mole) of I, 100 ml. of freshly distilled 48% hydrobromic acid, and 20 g. of phenol was stirred under reflux (nitrogen) for an hour, cooled and diluted to 350 ml. with water. The mixture was extracted three times with 100 ml. of ether, the aqueous layers made basic with sodium hydroxide then acidified to *p*H 6 with dry ice, and the solid collected by filtration. After rubbing the solid in acetonitrile, it crystallized from ethanol-water (1:1) to afford near-white crystals (1.85 g., 37%), m.p. 186-189°; ir ν (chloroform): 1627 $cm^{-1}$ (C=N); nmr (deuteriochloroform): δ 2.60 (t, 2, 4-$CH_2$), 2.83 (m, 2, β-$CH_2$), 3.08 (m, 2, α-$CH_2$), 3.57 (t, 2, 3-$CH_2$, $J_{3,4}$ = 7.1 Hz), 6.45 (m, 2, ArH), 6.79 (m, 2, ArH), 7.3 (m, 3, ArH), 7.56 (m, 1, ArH), 8.26 (s, 1, OH); δ (trifluoroacetic acid): 3.16 (m, 4, $CH_2$), 3.52 (t, 2, α-$CH_2$), 3.89 (dt, 2, 3-$CH_2$, $J_{3,4}$ t = 7.5 Hz, $J_{3,NH}$ + d = 3.5 Hz), 6.99 (m, 4, ArH), 7.8 (m, 4, ArH); uv λ max (0.1*N* hydrochloric acid): 277 (ε 13,500) and 218 (ε 16,500); λ max (0.1*N* sodium hydroxide): 290 (ε 4300) and 242 (ε 17,900); λ max (95% ethanol): 279 (ε 4100) and 250 (ε 10,100); mass m/e 251, $M^+$, 158 (M-93)$^+$ and 130 (M-121)$^+$.

*Anal.* Calcd. for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.56; H, 6.84; N, 5.41.

1,2,3,4-Tetrahydro-1-(4-hydroxyphenethyl)isoquinoline (III).

A solution of 5 g. (0.02 mole) of II in 175 ml. of 95% ethanol was hydrogenated wtih 10% Pd/C on a Parr apparatus. After removing the catalyst, the filtrate was evaporated at reduced pressure and the residue crystallized from ethanol, then recrystallized from acetonitrile to yield white crystals (4.0 g., 80%), m.p. 162.5-163.5°; ir ν (potassium bromide): no peak at 1627 $cm^{-1}$, 3210 $cm^{-1}$ (NH), 3430 $cm^{-1}$ (OH); uv λ max (0.1*N* hydrochloric acid or 95% ethanol): 275 (ε 1600); λ max (0.1*N* sodium hydroxide): 295 (ε 2500) and 238 (ε 12,900); nmr (deuteriochloroform): δ 4.13 (t, 1, CH), 2.27 (m, 2, $CH_2$), 2.5-3.5 (m, 6, $CH_2$), 4.6 (bs, 2, OH and NH); (trifluoroacetic acid): δ 4.98 (bt, 1, CH), 2.58 (m, 2, $CH_2$), 2.9 (m, 2, $CH_2$), 3.3 (m, 2, $CH_2$), 3.82 (m, 2, $CH_2$).

*Anal.* Calcd. for $C_{17}H_{19}NO$: C, 80.57; H, 7.56; N, 5.53. Found: C, 80.54; H, 7.66; N, 5.52.

1,2,3,4-Tetrahydro-1-(4-hydroxyphenethyl)-2-methylisoquinoline Hydrochloride (IV).

To a solution of 4.0 g. (0.016 mole) of III in 50 ml. of water with 0.8 g. (0.02 mole) of sodium hydroxide was added 2.24 g. (0.016 mole) of methyl iodide with stirring. The solution was stirred at 40° for three days, then neutralized with dilute hydrochloric acid and the gummy material extracted into chloroform. The organic layer was dried over magnesium sulfate and evaporated to an orange oil, which was dissolved in methylene chloride-ether (1:1) and treated with ethanolic hydrogen chloride. An insoluble orange gum separated that was rubbed in hot acetonitrile to yield a beige-colored solid, which crystallized from 2-methoxyethanol-ether (1:1) to afford near-white solid (1.0 g., 21%), m.p. 231.5-240.5° dec.; ir ν (potassium bromide): 3350 $cm^{-1}$ (OH), 2620 and 2700 $cm^{-1}$ ($R_3\overset{+}{N}H$); nmr (deuterium oxide and trifluoroacetic acid): δ 2.88 (s, 3, $NCH_3$), 4.32 (m, 1, CH), 2.27 (m, 2, $CH_2$), 2.5-3.7 (m, 6, $CH_2$).

*Anal.* Calcd. for $C_{18}H_{21}NO \cdot HCl$: C, 71.15; H, 7.30; N, 4.61; Cl, 11.67. Found: C, 70.79; H, 7.57; N, 4.47; Cl, 11.35.

2-Ethyl-3-(4-methoxyphenyl)propiophenone (V).

A 4.1 g. (0.016 mole) sample of II was dissolved in 50 ml. of 10% aqueous sodium hydroxide and stirred with 20 ml. of dimethyl sulfate at 50° for two hours. The dark oil which separated was extracted into methylene chloride, the organic layer dried over magnesium sulfate and evaporated to a red oil. The oil dissolved in dry ethanol, was filtered from insolubles and hydrogenated with 10% Pd/C for 5 minutes on a Parr

apparatus. The reaction mixture was filtered from catalyst and evaporated to an oil which was slurried in 100 ml. of benzene and filtered from an amine salt. The benzene solution was eluted from a basic alumina column and the eluates evaporated to a yellow oil (1.8 g.); ir $\nu$ (film): 1700 $cm^{-1}$ (C=O); nmr (carbon tetrachloride): $\delta$ 1.17 (t, 3, $CCH_3$, J = 7.5 Hz), 2.82 (q, 2, 2′-$CH_2$, J = 7.5 Hz), 3.04 (m, 4, 2- and 3-$CH_2$), 3.72 (s, 3, $OCH_3$).

*Anal.* Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51; O, 11.93. Found: C, 80.31; H, 7.45; O, 11.76.

3,4-Dihydro-1-(4-methoxystyryl)-2-methylisoquinolinium Iodide (VII).

A 5.0 g. (0.017 mole) sample of VI (10) and 4.8 g. (0.035 mole) of *p*-anisaldehyde were refluxed in 100 ml. of dry ethanol with two drops of piperidine for one day. The dark solution was evaporated and the residue warmed in 200 ml. ethyl acetate to afford a yellow solid. The solid was dissolved in warm acetonitrile and reprecipitated with ether, then recrystallized from water to yield yellow needles (6.5 g., 94%), m.p. 190.5-191.5° dec.; ir $\nu$ (nujol): 980 $cm^{-1}$ (*trans* CH=CH); uv $\lambda$ max (ethanol): 253, 276, 295, 385 ($\epsilon$ 11450, 11250, 11200, 24000); nmr (deuteriochloroform): $\delta$ 3.86 (s, 3, $NCH_3$), 4.08 (s, 3, $OCH_3$), 3.33 (t, 2, $NCH_2$), 4.22 (t, 2, $ArCH_2$), 7.20 (dd, 2, CH=CH), 7.3-7.4 (m, 8, ArH).

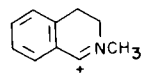
*Anal.* Calcd. for $C_{19}H_{20}NO\cdot I$: C, 56.31; H, 4.97; N, 3,46. Found: C, 56.29; H, 4.97; N, 3.52.

1,2,3,4-Tetrahydro-1-(4-methoxyphenethyl)-2,2-dimethylisoquinolinium Iodide (IX).

From VII: A 4.6 g. (0.011 mole) sample of VII dissolved in 50 ml. of glacial acetic acid with warming and was hydrogenated with 0.2 g. of platinum oxide on a Parr apparatus. The theoretical uptake of hydrogen was achieved in 30 minutes, then the catalyst was filtered and the solution evaporated. The residue dissolved in water, was filtered from insolubles, the solution made alkaline and twice extracted with chloroform. The organic layer was dried over potassium carbonate and evaporated to a yellow oil, VIII; nmr (deuteriochloroform) no olefinic absorption, $\delta$ 2.47 (s, 3, $NCH_3$). The oil dissolved in dry ether, was filtered from insolubles, and stirred with 3 ml. of methyl iodide for two days as 2.7 g. of orange solid separated. Rubbing this material in ethyl acetate with a trace of acetone afforded straw-colored solid, m.p. 165-167° dec.

From III.

A 1.0 g. sample of III dissolved in 25 ml. of *N* aqueous sodium hydroxide was stirred with 3 ml. of methyl iodide for 60 hours. The heavy organic layer was extracted into chloroform, washed with water, dried over magnesium sulfate and evaporated to a yellow glass. Rubbing the residue in ethyl acetate afforded a straw-colored solid, 1.5 g., m.p. 168-171° dec.; ir $\nu$ (potassium bromide): 1250 and 1040 $cm^{-1}$ ($ArOCH_3$); nmr (deuteriochloroform): $\delta$ 3.63 (s, 3, $OCH_3$), 3.30 (s, 3, $NCH_3$), 3.54 (s, 3, $NCH_3$), 4.90 (m, 1, CH); mass m/e 281 ($M^+$-$CH_3I$) and 146 (

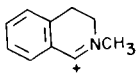


). A m.p. on admixture of above two samples of IX, 164-168° dec.

*Anal.* Calcd. for $C_{20}H_{26}NO\cdot I$: C, 56.74; H, 6.19; N, 3.31; I, 29.98. Found: C, 56.43; H, 6.29; N, 3.04; I, 29.77.

1,2,3,4-Tetrahydro-1-(4-methoxystyryl)-2-methylisoquinoline Hydrochloride (X) and 1,2,3,4-Tetrahydro-1-(4-methoxyphenethylidene)-2-methylisoquinoline Hydrochloride (XI).

To a solution of 32.2 g. (0.08 mole) of VII in 100 ml. of methanol with 6 g. of sodium hydroxide was added slowly 12 g. of sodium borohydride as the color disappeared. After stirring 15 hours, the mixture was filtered, the solution evaporated, and the residue partitioned with water and chloroform. The organic layer was dried over potassium carbonate and evaporated to a residue which was stirred in ethanolic hydrogen chloride with 50 g. of Dowex 2-X8 resin (chloride), filtered and the solution evaporated to a yellow glass. The glass dissolved in methanol and was allowed to stand several days as white solid separated, 2.7 g., recrystallized from ethanol-ether (1:1), m.p. after drying at 1 mm. 232-235° dec.; XI: ir $\nu$ (nujol): 825 $cm^{-1}$ (C=CH); uv $\lambda$ max (ethanol): 225 ($\epsilon$ 9000); nmr (deuterium oxide): $\delta$ 6.4 (m, 1, C=CH), 2.84 (s, 1.5, $NCH_3$), 2.90 (s, 1.5, $NCH_3$); mass m/e 146 (



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By evaporating the above methanol filtrates and rubbing the residue in ethyl acetate, a yellow solid was obtained, which crystallized from methanol-isopropyl ether (1:1) to afford 15 g. of white solid, m.p. 213-215°; X: ir $\nu$ (nujol): 975 and 1300 $cm^{-1}$ (*trans* CH=CH); uv $\lambda$ max (ethanol): 270 ($\epsilon$ 25000); nmr (trifluoroacetic acid): $\delta$ 3.31 (d, 3, $NCH_3$, J = 5.0 Hz), 5.22 (m, 1, CH), 6.48 (dd, 1, C=CH, J = 8.8, 15.0 Hz), 7.14 (d, 1, C=CH, J = 15.0 Hz).

*Anal.* Calcd. for $C_{19}H_{21}NO\cdot HCl\cdot\frac{1}{2}H_2O$: C, 70.25; H, 7.14; N, 4.31; $H_2O$, 2.77. Found: C, 70.44; H, 7.17; N, 4.41; $H_2O$, 1.7 (TGA).

Compounds X and XI are differentiated by tlc on silica (chloroform with ammonia).

3-(*N*-Benzoyl-3,4-dimethoxyphenethylamino)propionic Acid (XII).

To a solution of 100 g. (0.55 mole) of 3,4-dimethoxyphenethylamine in 150 ml. of dry ethanol was added 60 g. (0.6 mole) of ethyl acrylate, and the mixture was stirred 16 hours at room temperature. After evaporating the solvent, the residual oil was dissolved in 330 ml. of pyridine, cooled to 10°, and 89 g. (0.63 mole) of benzoyl chloride added below 20°. After stirring 1.5 hours, the mixture was poured into 360 ml. of 12*N* hydrochloric acid and 500 g. of ice. The mixture was twice extracted with methylene chloirde, dried over magnesium sulfate, and evaporated to an oil. The oil in 650 ml. of acetone was refluxed with 33 g. (0.82 mole) of sodium hydroxide in 250 ml. of water for 1.5 hours, the solution concentrated at reduced pressure and washed with ether, then the aqueous solution acidified with 12*N* hydrochloric acid. The precipitated solid was extracted into methylene chloride, the organic layer dried over magnesium sulfate and evaporated to a crude solid which was rubbed in ether then crystallized from 2-propanol to afford near-white solid (157 g., 80%), m.p. 147.5-149.5°; nmr (deuteriochloroform): $\delta$ 2.76 (m, 4, $CCH_2$), 3.67 (m, 4, $NCH_2$), 3.80 (s, 3, $OCH_3$), 3.86 (s, 3, $OCH_3$), 6.63 (m, 3, ArH), 7.35 (m, 5, ArH), 9.92 (bs, 1, $CO_2H$).

*Anal.* Calcd. for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.12; H, 6.53; N, 2.86.

3-(*N*-Benzoyl-3,4-dimethoxyphenethylamino)-2-methylpropionic Acid (XVIII).

Prepared as XII above, except that methyl methacrylate was used in place of ethyl acrylate, white solid, m.p. 120-122.5°;

nmr (deuteriochloroform): δ 1.17 (d, 3, $CCH_3$, J = 6.6 Hz), 2.5-4.0 (m, 7, $CH_2$ and CH), 3.78 (s, 3, $OCH_3$), 3.88 (s, 3, $OCH_3$), 6.3-7.7 (m, 8, ArH), 10.08 (bs, 1, $CO_2H$).

*Anal.* Calcd. for $C_{21}H_{25}NO_5$: C, 67.90; H, 6.78; N, 3.77. Found; C, 67.97; H, 7.01; N, 3.67.

3-Benzoyl-2,3,4,5-tetrahydro-8,9-dimethoxy-3-benzazocin-6(1*H*)-one (XIII).

To 3 kg. of polyphosphoric acid at 75° was added portionwise 50 g. (0.14 mole) of XII with vigorous stirring. After stirring 1.5 hours, the mixture was poured into 6 l. of ice water, the aqueous solution extracted with methylene chloride, and the organic layer washed with aqueous sodium bicarbonate (acidification of aqueous layer allowed recovery of 11.8 g. XII). The organic layer was dried over magnesium sulfate, then evaporated to a crude solid which was rubbed in isopropyl acetate to afford XIII (28.5 g., 79% conversion), crystallized from 2-propanol, m.p. 163-165°; ir ν (potassium bromide): 1652 $cm^{-1}$ (ketone), 1630 $cm^{-1}$ (amide I), 1266 $cm^{-1}$ ($ArOCH_3$); nmr (deuteriochloroform): δ 3.20 (m, 4, $CH_2$), 3.87 (m, 4, $CH_2$), 3.90 (s, 3, $OCH_3$), 3.98 (s, 3, $OCH_3$), 6.75 (m, 3, ArH), 7.32 (m, 3, ArH), 7.53 (s, 1, 7-ArH).

*Anal.* Calcd. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.92; H, 6.34; N, 3.94.

3-Benzenesulfonyl-2,3,4,5-tetrahydro-8,9-dimethoxy-3-benzazocin-6(1*H*)one (XVI).

Prepared from XV (6) according to procedure for I, crystallized from acetonitrile, 85%, m.p. 192.5-193.5°.

*Anal.* Calcd. for $C_{19}H_{21}NO_5S$: C, 60.78; H, 5.64; S, 8.54. Found: C, 60.89; H, 5.58; S, 8.47.

3-Benzoyl-2,3,4,5-tetrahydro-8,9-dimethoxy-5-methyl-3-benzazocin-6(1*H*)one (XIX).

Prepared from XVIII according to procedure for XIII except cyclization was achieved at 60°, white solid, m.p. 151-154.5°; nmr (deuteriochloroform): δ 1.22 (m, 3, $CCH_3$), 2.4-4.0 (m, 7, $CH_2$ and CH), 3.90 (s, 3, $OCH_3$), 3.98 (s, 3, $OCH_3$), 6.62 (s, 1, 10-ArH), 6.87 (m, 3, ArH), 7.37 (m, 3, ArH).

*Anal.* Calcd. for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.44; H, 6.66; N, 4.00.

7-(2-Benzoylaminoethyl)-4,5-dimethoxy-1-indanone (XIV).

To 1.4 kg. of polyphosphoric acid at 100° was added in portions 20 g. (0.056 mole) of XII and the mixture stirred vigorously at 110° for 3.5 hours. The mixture was poured into 3 l. of ice water and extracted with methylene chloride. The organic layer was washed with aqueous bicarbonate, dried over magnesium sulfate, and evaporated to afford crude solid (9 g., 48%); crystallized from 2-propanol-heptane, m.p. 164.5-165.5; ir ν (potassium bromide): 3300 $cm^{-1}$ (NH), 1700 $cm^{-1}$ (ketone), 1640 $cm^{-1}$ (amide I), 1550 $cm^{-1}$ (amide II), 1307 and 1129 $cm^{-1}$ ($ArOCH_3$); nmr (deuteriochloroform): δ 2.62 (m, 2, 3-$CH_2$), 3.06 (m, 2, 2-$CH_2$), 3.33 (m, 2, α-$CH_2$), 3.76 (m, 2, β-$CH_2$), 3.87 (s, 3, $OCH_3$), 3.91 (s, 3, $OCH_3$), 6.83 (s, 1, 6-ArH), 7.17 (bs, 1, NH).

*Anal.* Calcd. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 71.00; H, 6.30; N, 4.09.

Compound XIV was prepared in 33% by the same procedure from XIII.

7-(2-Benzenesulfonylaminoethyl)-4,5-dimethoxy-1-indanone (XVII).

This compound was prepared from XVI according to the procedure above for XIV in 5% yield, crystallized from acetonitrile, m.p. 153-155° (uncorr.); nmr (deuteriochloroform): δ 5.09 (bs, 1, NH), 6.62 (s, 1, 6-ArH), 3.83 (s, 3, $OCH_3$), 3.88 (s, 3, $OCH_3$); ir ν (potassium bromide): 1700 $cm^{-1}$ (ketone).

*Anal.* Calcd. for $C_{19}H_{21}NO_5S$: C, 60.78; H, 5.64; N, 3.73. Found: C, 60.76; H, 5.58; N, 3.93.

7-(2-Benzoylaminoethyl)-4,5-dimethoxy-2-methyl-1-indanone (XX).

This compound was prepared from XVIII or XIX according to the procedure given for XIV; m.p. 143-146°; nmr (deuteriochloroform): δ 1.25 (d, 3, $CCH_3$), 6.84 (s, 1, 6-ArH), 7.21 (bs, 1, NH); ir ν (potassium bromide) 1700 $cm^{-1}$ (ketone).

*Anal.* Calcd. for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.36; H, 6.59; N, 4.03.

2,3,4,5-Tetrahydro-8,9-dimethoxy-3-benzazocin-6(1*H*)one Hydrochloride (XXI).

A suspension of 3.8 g. (0.011 mole) of XIII in 180 ml. of 3*N* hydrochloric acid and 20 ml. of ethanol was refluxed with stirring for 6 hours. The cooled reaction mixture was extracted with methylene chloride and the aqueous solution evaporated at reduced pressure. The residue was rubbed in 2-propanol to afford white solid (1.5 g., 56%), m.p. 189-191°; ir ν (potassium bromide): 1650 $cm^{-1}$ (ketone); nmr (deuteriochloroform): δ 6.85 (s, 1, ArH), 7.15 (s, 1, ArH).

*Anal.* Calcd. for $C_{13}H_{17}NO_3 \cdot HCl$: C, 57.46; H, 6.68; N, 5.16. Found: C, 57.68; H, 6.64; N, 5.15.

*N*-[(2-Cyclopropylcarbonyl-4,5-dimethoxy)phenethyl]benzamide (XXII).

A solution of 6.8 g. (0.02 mole) of XIII in 100 ml. of dimethylsulfoxide was added dropwise to 0.022 mole of dimethyloxosulfonium methylide (20) in 100 ml. of dimethylsulfoxide with stirring. The solution was stirred 2 hours at 50°, then poured into 500 ml. of water and extracted with methylene chloride. The organic layer was dried over magnesium sulfate, then evaporated to a crude solid which was rubbed in isopropyl acetate to afford white solid (4.2 g., 55%), crystallized from benzene, m.p. 135-139.5°; ir ν (potassium bromide): 3320 $cm^{-1}$ (NH), 1660 $cm^{-1}$ (ketone), 1650 $cm^{-1}$ (amide I), 1540 $cm^{-1}$ (amide II), 1268 and 1130 $cm^{-1}$ ($ArOCH_3$); nmr (deuteriochloroform); δ 1.22 (m, 4, cyclopropyl $CH_2$), 2.49 (m, 1, cyclopropyl CH), 3.00 (m, 2, $CCH_2$), 3.72 (m, 2, $NCH_2$), 8.07 (bs, 1, NH), 3.92 (s, 6, $OCH_3$), 6.85 (s, 1, 6-ArH), 7.34 (s, 1, 3-ArH).

*Anal.* Calcd. for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.05; H, 6.31; N, 3.88.

3-Benzyl-2,3,4,5-tetrahydro-8,9-dimethoxy-3-benzazocin-6(1*H*)one Hydrochloride (XXIII).

A mixture of 17 g. (0.05 mole) of XIII and 3.1 g. (0.05 mole) of ethylene glycol was refluxed in 250 ml. benzene with 0.2 g. of *p*-toluenesulfonic acid for 3 hours. The mixture was stirred with anhydrous potassium carbonate, filtered, and the solution evaporated. The residue was rubbed in isopropyl acetate then crystallized from acetonitrile to yield 17.4 g. of pure ketal.

A mixture of 3.8 g. (0.01 mole) of the ketal and 0.2 g. (0.005 mole) of lithium aluminum hydride was refluxed 16 hours in dry tetrahydrofuran. The mixture was hydrolyzed, insolubles removed by filtration, and the solvent evaporated. The residue was stirred in warm 3*N* hydrochloric acid for 15 minutes, then the solution was made alkaline with sodium bicarbonate and extracted with ether. The organic layer was dried over potassium carbonate

then treated with ethanolic hydrogen chloride and evaporated. The gummy residue crystallized from 2-propanol and then from dry ethanol to afford white solid (2.6 g., 53%), m.p. 145.5-146°; ir $\nu$ (nujol) 1660 $cm^{-1}$ (ketone); nmr (deuteriodimethylsulfoxide) $\delta$ 4.50 (bs, 2, $NCH_2\phi$), 3.90 (s, 3, $OCH_3$), 3.97 (s, 3, $OCH_3$), 7.23 (s, 1, 10-ArH), 7.27 (s, 1, 7-ArH).

*Anal.* Calcd. for $C_{20}H_{23}NO_3 \cdot HCl$: C, 66.36; H, 6.68; N, 3.87. Found: C, 66.51; H, 6.63; N, 3.95.

2-[2-(*N*-Benzylamino)ethyl]-4,5-dimethoxyacetophenone Oxime Hydrochloride (XXIV).

A mixture of 1.8 g. (0.005 mole) of XXIII, 4 g. of pulverized potassium carbonate, and 3.6 g. of hydroxylamine hydrochloride was refluxed in 100 ml. of benzene with stirring for 16 hours. The insolubles were removed by filtration and the solvent evaporated to a crude solid, which was rubbed in 2-propanol then crystallized from ethanol to yield white solid (0.9 g., 50%), m.p. 184-185.5°; ir $\nu$ (potassium bromide): 3265 $cm^{-1}$ (NOH), 1521 $cm^{-1}$ (C=N), 1260 and 1157 $cm^{-1}$ ($ArOCH_3$); nmr (deuteriochloroform): $\delta$ 2.21 (bs, 3, $CCH_3$), 3.74 (s, 3, $OCH_3$), 3.82 (s, 3, $OCH_3$), 4.07 (d, 2, $NCH_2\phi$), 6.41 (s, 1, 3-ArH), 6.68 (s, 1, 6-ArH), 8.78 (bs, 1, NOH).

*Anal.* Calcd. for $C_{19}H_{24}N_2O_3 \cdot HCl$: C, 62.54; H, 6.99; N, 7.68. Found: C, 62.27; H, 7.16; N, 7.47.

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