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# Synthesis of 1,2,3,4,5,6-Hexahydro-1,5-methano-2-methylpyrido[2,3-*c*]azocine[1]

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Synthesis of benzomorphan analog of which aromatic ring is heterocyclic was investigated. The key compounds of this synthetic route, 2-benzoyl-2-azabicyclo[3.3.1]-nonan-8-one derivatives (X, and XII), were prepared starting from ethyl 4-pyridinepropionate (I). 1,2,3,4,5,6-Hexahydro-1,5-methanopyrido[2,3-*c*]azocine derivative (XV) was synthesized by condensation of XII with 3-aminoacrolein. Furthermore, the pyrazolone derivative (XI) was also prepared from X by treatment with hydrazine, and the pyrimidine derivative (XIV) was obtained from XII *via* the β-diketone (XIII).

It is well known that benzomorphan derivatives show analgetic activity. In connection with our studies on structure-activity relationship of analgetics, we were interested in synthesis and pharmacological effect of benzomorphan analogs of which aromatic ring is heterocyclic. To our knowledge, these compounds have not been reported except the synthesis of uleine and epiuleine.[3] This paper deals with the synthesis of 1,2,3,4,5,6-hexahydro-1,5-methanopyrido[2,3-*c*]azocine derivative.

4-Pyridineacrylic acid was prepared by the condensation of chloral with 4-picoline and the subsequent hydrolysis with alcoholic potassium hydroxide according to the procedure of King, *et al.*[4] for 2-pyridineacrylic acid. This acid was esterified with ethanol and sulfuric acid and followed by catalytic hydrogenation over palladium catalyst to give ethyl 4-pyridinepropionate (I). 2-Cyano- and 4-cyanopyridine derivatives are obtainable from alkoxypyridinium salt and aqueous alkali cyanide.[5] Okamoto and Tani[5a] reported that 2-cyanopyridine formed in high yield when aqueous ethanol was used as solvent at low temperature in the above reaction. Ethyl 4-pyridinepropionate 1-oxide (II) was prepared by heating of I with 30% hydrogen peroxide in acetic acid. In this reaction it was found that using of a mixture of acetic acid and acetic anhydride as solvent shortened markedly the reaction period. The compound (II) was then treated with dimethyl sulfate to afford the methoxypyridinium salt (III). Treatment of III with sodium cyanide in 80% ethanol at 0—20° gave a mixture of 2-cyanopyridine derivative (IV) and I. On thin-layer chromatography (TLC) the reaction product showed two spots in approximately ratio of 1:1. Distillation afforded two materials (A), bp 102—104° (0.9 mmHg) and (B), bp 149—153° (0.9 mmHg). Material (A) was identical with I by comparison of infrared (IR) and nuclear magnetic resonance (NMR) spectra. IR spectrum of material (B) showed an absorption of nitrile at 2250 $cm^{-1}$, and in NMR spectrum of it three pyridine ring protons appeared as ABX pattern.

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3) L.J. Dolby and H. Biere, *J. Am. Chem. Soc.*, **90**, 2699 (1968); N.D.V. Wilson, A.J. Gaskell, and J.A. Joule, *J. Chem. Soc.* (*C*), **1969**, 2738; G. Büchi, S.J. Gould, and F. Näf, *J. Am. Chem. Soc.*, **93**, 2492 (1971).

4) J.A. King, V. Hofmann, and F.H. McMillan, *J. Org. Chem.*, **16**, 1100 (1951).

5) *a*) T. Okamoto and H. Tani, *Chem. Pharm. Bull.* (Tokyo), **7**, 925 (1959); H. Tani, *ibid.*, **7**, 930 (1959); *b*) W.E. Feely and E.M. Beavers, *J. Am. Chem. Soc.*, **81**, 4004 (1959); *c*) R. Tan and A. Taurins, *Tetrahedron Letters*, **1965**, 2737.

From the above result, it was confirmed that the cyano compound (IV) was formed. However, distillation of the crude product of cyanation reaction was accompanied with considerable decomposition, so the mixture of products was directly submitted to hydrolysis and the subsequent esterification without separation and purification. Fractional distillation of the above esterified product gave I and the diester (V) in 28% and 29% yield (from I), respectively. Catalytic hydrogenation of V over platinum oxide in acetic acid afforded the piperidine derivative (VI) in 63% yield. It would be possible that the presence of two diastereomers due to *cis* and *trans* relationship between two substituents of piperidine ring of VI, whereas TLC and gas chromatography of VI gave only one spot and only one peak, respectively. NMR spectrum of VI also suggested the formation of a sole product, but we could not determine whether VI is *cis* or *trans* isomer. Acylation of the secondary amine (VI) with formic acetic anhydride[6] and benzoyl chloride gave the formamide (VII) and the benzamide (VIII), respectively. Dieckmann condensation of the diester (VII) with sodium hydride yielded the $\beta$-keto ester (IX) in 64% yield, and in a similar condition VIII gave X in 85% yield. Although the compound (X) reacted with hydrazine to give pyrazolone derivative (XI) in high yield, the following reactions of X did not proceed; Knoevenagel condensation with ethyl cyanoacetate, Reformatsky reaction with ethyl bromoacetate, and Michael condensation with acrylonitrile and methyl vinyl ketone. These reactions resulted in recovery and/or cleavage of $\beta$-keto ester. Taking into account steric effect of benzamido group of X, the formamide (IX) was submitted to similar reactions as above. These attempts were also unsuccessful. It was considered that in rigid structure of IX and X enol form would probably be stable on account of a strong hydrogen bonding between carbonyl of amido group and hydroxyl of enol, and reactivity of carbonyl of keto ester would decrease. Therefore we attemped to investigate reactions of the corresponding ketones. The $\beta$-keto esters (IX and X) were submitted to acid-catalyzed hydrolysis in order to obtain ketones. These reaction products showed many spots on TLC. On hydrolysis with methanolic potassium hydroxide, although IX gave unidentified mixture as in the case of above, X afforded the desired ketone (XII) in 78% yield. Treatment of XII with ethyl formate in the presence of sodium hydride gave the $\beta$-diketone

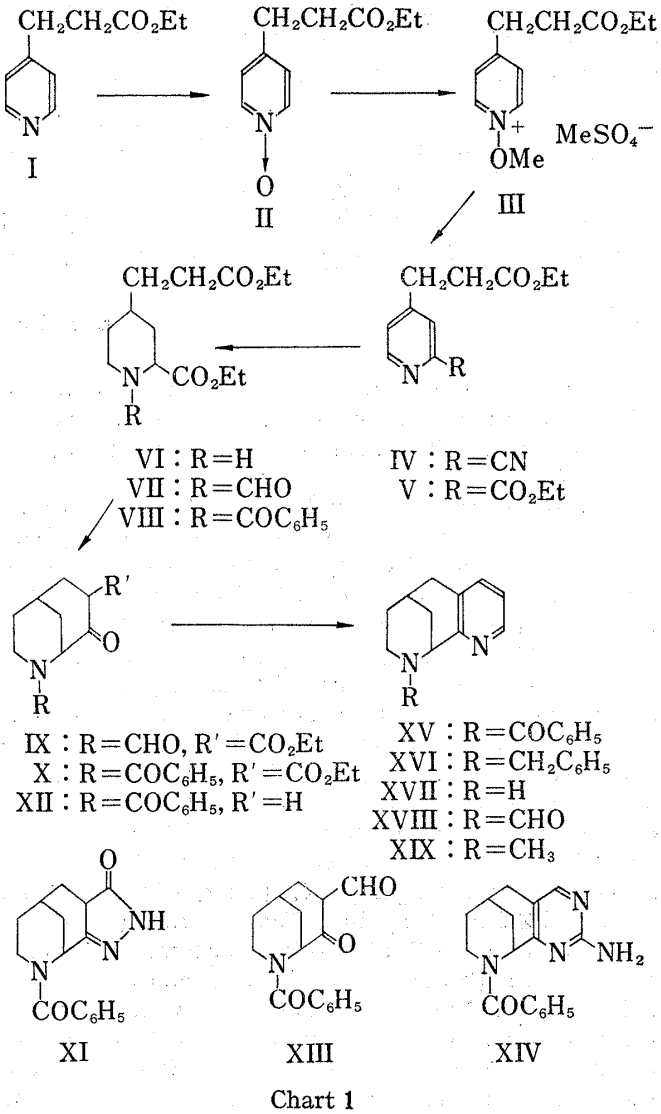


Chart 1

6) C.W. Huffman, *J. Org. Chem.*, **23**, 727 (1958).

(XIII) in a low yield, which was followed by condensation with guanidine to yield amino pyrimidine derivative (XIV).

Breitmaier, *et al.*[7] reported that pyridine derivatives were obtained by condensation of 3-aminoacroleins with alicyclic ketones and aliphatic 1,3-dicarbonyl compounds. It was considered that their method was applicable to our compound. The 2,3-cycloalkenopyridine derivative (XV) was obtained in about 57% yield by treatment of XII with 3-aminoacrolein[7d] in triethylamine in the presence of catalytic amount of ammonium acetate at 100—110°.[7c] The structure of XV was confirmed by means of IR, NMR, and mass spectra. Reduction of XV with lithium aluminum hydride in ether gave the benzylamine derivative (XVI), of which reductive debenzylation using palladium catalyst in acetic acid did not proceed. On the other hand, hydrolysis of the amido group of XV with dilute sulfuric acid was achieved to afford the secondary amine (XVII). Formylation of crude XVII with formic acetic anhydride gave the formamide (XVIII) in 58% yield based on XV. NMR spectrum of XVIII revealed the presence of two discrete species due to restricted rotation about the carbon nitrogen bond of amido function.[8] Ratio of the two rotamors was determined 3:1 by measurement of integration of formyl proton (8.3 and 8.05 ppm) and methine proton (4.75 and 4.25 ppm). Reduction of XVIII with lithium aluminum hydride yielded the desired compound (XIX) in 62% yield.

Further investigations of synthesis of another related compound and pharmacological testing of the above compounds are now under progress.

## Experimental

All melting points were taken with a Yanagimoto Micro Melting Point Apparatus and uncorrected. NMR spectra were taken on a JNM-C-60H spectrometer using TMS as an internal standard. The abbreviation used are as follows: s, singlet; d, doublet; d.d, double doublet; t, triplet; q, quartet; m, multiplet; br, broad.

**Ethyl 4-Pyridinepropionate (I)**——According to the procedure of King, *et al.*[4] for 2-pyridineacrylic acid, 4-pyridineacrylic acid was obtained in 25% yield by condensation of 4-picoline with chloral hydrate and the subsequent hydrolysis with ethanolic KOH, mp 249—250.5° (lit.[9] mp 289—291°). The above carboxylic acid was esterified with EtOH and concd. $H_2SO_4$ to afford ethyl 4-pyridineacrylate in 80% yield, mp 65.5—67° (lit.[9] mp 64.5—66°), which was hydrogenated over 10% Pd-C in AcOEt to give I in 95% yield, bp 114—115° (3 mmHg) (lit.[9] bp 133° (9 mmHg)).

**Ethyl 4-Pyridinepropionate 1-Oxide (II)**——A mixture of I (50 g), 30% $H_2O_2$ (31 ml), AcOH (200 ml) and $Ac_2O$ (76.5 ml) was heated on an oil bath at 55—60°. After 22 hr a further 30% $H_2O_2$ (31 ml) was added and the mixture was maintained at the same temperature for an additional 24 hr. The mixture was concentrated to about 100 ml *in vacuo*, diluted with 100 ml of water and then ceoncentrated *in vacuo* as far as possible. The residue was made alkaline with anhyd. $Na_2CO_3$, shaken with $CHCl_3$ and filtered. The filtrate was dried over $Na_2SO_4$, and concentrated to give 50 g of a pale yellow oil of II. This product was used in the next step without purification. IR $\nu_{max}^{film}$ $cm^{-1}$: 1730 (C=O), 1230 (N→O). NMR ($CCl_4$) $\delta$: 1.25 (3H, t, $-OCH_2\underline{CH_3}$), 2.4—3.1 (4H, m, $-CH_2\underline{CH_2}-$), 4.1 (2H, q, $-O\underline{CH_2}CH_3$), 7.1 (2H, d, $J$=7 Hz, arH), 8.0 (2H, d, $J$=7 Hz, arH).

**Ethyl 2-Carbethoxy-4-pyridinepropionate (V)**——A mixture of crude II (50 g) and $Me_2SO_4$ (33 g) was heated on an oil bath at 90—100° for 2 hr. After cooling, the mixture was washed with ether, dissolved in 80% EtOH (300 ml) and cooled to 0° on ice–salt bath. To this solution was added dropwise a suspension of NaCN (29.4 g) in 80% EtOH (150 ml) with stirring at 0—5° over a 1.5 hr period. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirring was maintained for an additional 7 hr. EtOH was removed *in vacuo*, and the residue was extracted with $CHCl_3$. The extract was worked up in usual manner to give 43 g of an oil, which was then heated together 20% HCl (200 ml) on a steam bath for 6 hr. The mixture was concentrated under reduced pressure to dryness. The residue was dissolved in abs. EtOH (1.3 liters) and conc. $H_2SO_4$ (70 ml), and refluxed for 7 hr. After removal of EtOH *in vacuo*, the residue was poured into ice–water, neutralized with $K_2CO_3$, and extracted with $CHCl_3$. The

7) *a*) E. Breitmaier and E. Bayer, *Angew. Chem.*, **81**, 785 (1969); *b*) E. Breitmaier, and E. Bayer, *Tetrahedron Letters*, **1970**, 3291; *c*) E. Breitmaier, S. Gassenmann, and E. Bayer, *Tetrahedron*, **26**, 5907 (1970); *d*) E. Breitmaier and S. Gassenmann, *Chem. Ber.*, **104**, 665 (1971).
8) H. Paulsen and K. Todt, *Chem. Ber.*, **100**, 3385 (1967).
9) A.R. Katritzky, *J. Chem. Soc.*, **1955**, 2581.

extract was washed with water, dried over $K_2CO_3$, and concentrated. Distillation of the residue gave 13.9 g (27.8% recovery) of I, bp 88—92° (0.2 mmHg), and 20.3 g (29% based on I) of a colorless oil of V, bp 135—141° (0.2 mmHg). IR $\nu_{max}^{film}$ $cm^{-1}$: 1730 (C=O). NMR ($CDCl_3$) $\delta$: 1.25 (3H, t, $-OCH_2C\underline{H}_3$), 1.35 (3H, t, $-OCH_2C\underline{H}_3$), 2.6—3.3 (4H, m), 4.15 (2H, q, $-OC\underline{H}_2CH_3$), 4.45 (2H, q, $-OC\underline{H}_2CH_3$), 7.35 (1H, br.d, $J$=5 Hz, arH), 7.96 (1H, br.s, arH), 8.6 (1H, d, $J$=5 Hz, arH). *Anal.* Calcd. for $C_{13}H_{17}O_4N$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.06; H, 6.79; N, 5.57.

**Ethyl 2-Carbethoxy-4-piperidinepropionate (VI)**——A solution of V (10.7 g) in AcOH (150 ml) was shaken with Adams $PtO_2$ (350 mg) in $H_2$ atmosphere at room temperature. After up-take of 2.8 liters of $H_2$, the catalyst and the solvent were removed. The residue was dissolved in $CHCl_3$, washed with saturated aq. $NaHCO_3$ solution, and dried over $K_2CO_3$. Evaporation of the solvent and distillation gave 6.9 g (63%) of VI as a colorless oil, bp 127—135° (0.4 mmHg). IR $\nu_{max}^{film}$ $cm^{-1}$: 3300 (NH), 1735 (C=O). NMR ($CDCl_3$) $\delta$: 1.3 (6H, br. t, 2×$-OCH_2C\underline{H}_3$), 2.15 (1H, s, disappeared with addition of $D_2O$, –NH), 4.25 (2H, q, $-OC\underline{H}_2CH_3$), 4.3 (2H, q, $-OC\underline{H}_2CH_3$). *Anal.* Calcd. for $C_{13}H_{23}O_4N$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.62; H, 9.06; N, 5.50.

**Ethyl 2-Carbethoxy-1-formyl-4-piperidinepropionate (VII)**——A mixture of $Ac_2O$ (22.4 g) and $HCO_2H$ (10.1 g) was heated at 50° on an oil bath for 2 hr. After cooling the mixture was diluted with ether (100 ml), and to this solution was added dropwise a solution of VI (10.9 g) in ether (150 ml) with stirring at room temperature over 1 hr period. The mixture was stirred for an addition 4 hr at the same temperature. After concentration *in vacuo*, the residue was neutralized with saturated $NaHCO_3$ solution, and extracted with benzene. The extract was washed with brine and dried over $Na_2SO_4$. Evaporation of the solvent gave an oily material, which was distilled to give 9.6 g (79.4%) of colorless oil of VII, bp 165—170° (0.5 mmHg). IR $\nu_{max}^{film}$ $cm^{-1}$: 1735, 1675 (C=O). NMR ($CDCl_3$) $\delta$: 1.2 (3H, t, $-OCH_2C\underline{H}_3$), 1.3 (3H, t, $-OCH_2C\underline{H}_3$), 1.3—2.5 (9H, m), 3.3—3.65 (2H, m, >N–$CH_2$–), 4.1 (4H, q, 2×$-OC\underline{H}_2CH_3$), 4.75 (1H, t, >N–CH<), 8.1 (1H, s, –CHO). *Anal.* Calcd. for $C_{14}H_{23}O_5N$: C, 58.93; H, 8.13; N, 4.91. Found: C 58.74; H, 8.10; N, 5.07.

**Ethyl 1-Benzoyl-2-carbethoxy-4-piperidinepropionate (VIII)**——To a stirred solution of VI (4.49 g) in pyridine (10 ml) was added dropwise benzoyl chloride (2.53 g) in pyridine (10 ml) at 0—5°. The mixture was then allowed to stand at room temperature overnight. After removal of the solvent *in vacuo*, the residue was dissolved in $CHCl_3$, washed with 10% HCl and water. The $CHCl_3$ solution was worked up as usual to give an oily material. Distillation gave 5.51 g (87.4%) of VIII as a colorless syrup, bp 190—210° (0.1 mmHg, bath temp.). IR $\nu_{max}^{film}$ $cm^{-1}$: 1735, 1640 (C=O). NMR ($CCl_4$) $\delta$: 1.25 (3H, t, $-OCH_2C\underline{H}_3$), 1.3 (3H, t, $-OCH_2C\underline{H}_3$), 1.4—2.5 (9H, m), 3.3—3.7 (2H, m), 4.15 (4H, q, 2×$-OC\underline{H}_2CH_3$), 4.7 (1H, t, >N–CH<), 7.35 (5H, s, arH). *Anal.* Calcd. for $C_{20}H_{27}O_5N$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.48; H, 7.58; N, 4.08.

**7-Carbethoxy-2-formyl-2-azabicyclo[3.3.1]nonan-8-one (IX)**——To a suspension of NaH (1.5 g) in toluene (40 ml) was added a solution of VII (3.55 g) in toluene (30 ml) at room temperature. After refluxing for 1.5 hr, the reaction mixture was acidified with 30% AcOH, and the toluene layer was separated. The aqueous layer was extracted with benzene. The organic solutions were combined, washed with brine, and dried over $Na_2SO_4$. Removal of the solvent gave an oily residue, which was distilled to afford 1.9 g (64.2%) of IX as a colorless oil, bp 160—180° (0.1 mmHg, bath temp.). This product crystallized on standing, mp 76—81°. IR $\nu_{max}^{film}$ $cm^{-1}$: 3400—3000 (broad, OH), 1675 (broad, C=O). NMR ($CDCl_3$) $\delta$: 1.3(3H, t, $-OCH_2C\underline{H}_3$), 1.5—3.5 (9H, m), 4.2 (2H, q, $-OC\underline{H}_2CH_3$), 5.0 (1H, br. t, >N-CH<), 8.05 (1H, s, -CHO), 11.7 (1H, br. peak, disappeared with addition of $D_2O$, -OH). *Anal.* Calcd. for $C_{12}H_{17}O_4N$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.44; H, 7.01; N, 5.75.

**2-Benzoyl-7-carbethoxy-2-azabicyclo[3.3.1]nonan-8-one (X)**——To a stirred suspension of NaH (1.8 g) in toluene (40 ml) was added dropwise a solution of VIII (5.5 g) in toluene (60 ml). The mixture was refluxed for 8 hr. After cooling, the mixture was worked up in a similar manner as above to give 4.1 g (85%) of colorless cubes of X, mp 124—126° (ether). IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3400—3000 (broad, OH), 1660, 1625 (C=O). NMR ($CDCl_3$) $\delta$: 1.32 (3H, t, $-OCH_2C\underline{H}_3$), 4.27 (2H, q, $-OC\underline{H}_2CH_3$). 5.3—5.5 (1/2H, br. peak), 7.45 (5H, s, arH), 12.2 (1/2H, s, disappeared with addition of $D_2O$, -OH). *Anal.* Calcd for $C_{18}H_{21}O_4N$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.44; H, 6.92; N, 4.60.

**Reaction of X with Hydrazine**——A mixture of X (1.0 g), 80% $NH_2NH_2 \cdot H_2O$ (2.4 g) and water (4 ml) was refluxed on an oil bath for 1 hr. The mixture was then concentrated *in vacuo* to dryness. Recrystallization of the residue from EtOH gave 801 mg (89%) of colorless fine needles of XI, mp 256—260°. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3300—3000 (broad, OH), 1600 (C=O). *Anal.* Calcd. for $C_{16}H_{17}O_2N_3$: C, 67.82; H, 6.05; N, 14.83. Found: C, 67.92; H, 6.04; N, 14.98.

**2-Benzoyl-2-azabicyclo[3.3.1]nonan-8-one (XII)**——A mixture of X (2.0 g), 5% KOH (14 ml) and MeOH (56 ml) was refluxed for 24 hr. After removal of the solvent under reduced pressure, the residue was extracted with benzene. The extract was worked up as usual to give a viscous oil. Distillation afforded 1.21 g (78%) of a colorless syrup of XII, bp 160—180° (0.05 mmHg, bath temp.), which crystallized on standing, mp 72—77°. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1710, 1630 (C=O). NMR ($CDCl_3$) $\delta$: 1.2—2.8 (11H, m), 4.5 (1H, br. peak >N–CH<), 7.4 (5H, s, arH).

Oxime of XII: Colorless sticks, mp 178—180° (ether). *Anal.* Calcd. for $C_{15}H_{18}O_2N_2$: C, 69.74; H, 7.02; N, 10.85. Found: C, 69.77; H, 6.96; N, 11.06.

**2-Benzoyl-1,2,3,4,5,6-hexahydro-1,5-methano(2-aminopyrimido)-[4,5-*c*]azocine (XIV)**——To a mixture of XII (560 mg) and ethyl formate (340 mg) in benzene (10 ml) was added a suspension of NaH (60 mg) in benzene (10 ml), and the mixture was stirred at room temperature in a stream of $N_2$ for 30 hr. The mixture was thoroughly extracted with water, and aq. extract was made acidic with 10% HCl. Extraction with benzene and usual working up of the extract gave 96 mg of XIII, which gave purple color with $FeCl_3$. A mixture of crude XIII (95 mg) and guanidine carbonate (126 mg) in toluene (10 ml) was refluxed for 14 hr. After addition of water, the mixture was extracted with $CHCl_3$. The extract was worked up as usual, and the resulting crystalline product was chromatographed on alumina. Elution with $CHCl_3$ afforded 41 mg (6% based on XII) of XIV. For analysis recrystallization from EtOH gave colorless plates of XIV, mp 237—239°. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3300, 3200 ($NH_2$), 1610 (C=O). NMR ($CDCl_3$) $\delta$: 1.5—3.2 (9H, m), 2.8 (2H, br.s, disappeared with addition of $D_2O$, $-NH_2$), 4.85 (1H, m, >N–CH<), 7.5 (5H, s, arH), 8.25 (1H, s, arH). *Anal.* Calcd. for $C_{17}H_{18}ON_4$: C, 69.37; H, 6.16; N, 19.04. Found: C, 69.23; H, 6.13; N, 19.03.

**2-Benzoyl-1,2,3,4,5,6-hexahydro-1,5-methanopyrido[2,3-*c*]azocine (XV)**——A mixture of XII (615 mg), 3-aminoacrolein[7d] (270 mg), $Et_3N$ (20 ml) and catalytic amount of $NH_4OAc$ was heated on an oil bath at 100—110° for 35 hr. After concentration *in vacuo*, the residue was dissolved in $CHCl_3$, and extracted with 5% HCl. From the $CHCl_3$ solution 93 mg of unchanged XII was obtained. The aqueous extract was basified with $K_2CO_3$, extracted with $CHCl_3$. The extract was washed with brine, dried over $Na_2SO_4$, and concentrated. Distillation of the residue gave 400 mg (56.9%) of XV, bp 150—160° (0.05 mmHg, bath temp.). IR $\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1615 (C=O), 1585, 1430. NMR ($CDCl_3$) $\delta$: 1.6—3.2 (9H, m), 4.2—4.6 (1H, m, >N–CH<), 7.0—7.8 (7H, m, arH), 8.4 (1H, br. d, $J$=5 Hz, arH). Mass Spectrum *m/e*: 278 ($M^+$), 173 ($M-COC_6H_5$). *Anal.* Calcd. for $C_{18}H_{18}ON_2$: C, 77.67; H, 6.52; N, 10.07. Found: C, 77.53; H, 6.50; N, 9.92.

**2-Benzyl-1,2,3,4,5,6-hexahydro-1,5-methanopyrido[2,3-*c*]azocine (XVI)**——A mixture of XV (275 mg), $LiAlH_4$ (190 mg) and ether (15 ml) was refluxed for 3.5 hr. After cooling, to the mixture was added saturated aq. potassium sodium tartrate solution, and extracted with ether. The extract was washed with brine, and dried over $Na_2SO_4$. Removal of the solvent and the subsequent distillation afforded 140 mg (53.6%) of XVI as a pale yellow oil, bp 140—160° (0.04 mmHg, bath temp.). NMR ($CCl_4$) $\delta$: 1.2—3.1 (9H, m), 3.8 (2H, s, >N–$CH_2C_6H_5$), 3.8—4.1 (1H, br, >N–CH<), 6.9—7.5 (7H, m, arH), 8.35 (1H, br. d, $J$=5 Hz, arH). *Anal.* Calcd. for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60. Found: C, 81.76; H, 7.70; N, 10.43.

**2-Formyl-1,2,3,4,5,6-hexahydro-1,5-methanopyrido[2,3-*c*]azocine (XVIII)**——A mixture of XV (310 mg) and 10% $H_2SO_4$ (10 ml) was refluxed on an oil bath for 18 hr. After cooling, the mixture was neutrallized with $K_2CO_3$, and extracted with $CHCl_3$. The extract was worked up as usual to give 140 mg of crude XVII. This product was dissolved in benzene (10 ml) and added dropwise to a solution of formic acetic anhydride (prepared from 510 mg of $Ac_2O$ and 230 mg of $HCO_2H$ by heating at 50° for 2 hr and cooled) in benzene (10 ml). The mixture was stirred at room temperature for 1 hr. After concentration *in vacuo*, to the residue was added saturated $NaHCO_3$ solution, and extracted with $CHCl_3$. The extract was washed with brine, and dried over $Na_2SO_4$. Evaporation of the solvent gave an oily residue, which was then chromatographed on silica gel. Elution with $CHCl_3$ afforded 130 mg (58%) of XVIII. An analytical sample was sublimed at 115—125° (0.04 mmHg, bath temp.), mp 151—154°. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1650 (C=O). NMR ($CDCl_3$) $\delta$: 1.5—3.6 (9H,m), 4.25 (1/4H, br) and 4.75 (3/4H, br, >N–CH<), 7.15 (1H, d.d, $J$=7.5, 5 Hz, arH), 7.45 (1H, d, $J$=7.5 Hz, arH), 8.05 (1/4H, s) and 8.3 (3/4H, s, –CHO), 8.4 (1H, d, $J$=5 Hz, arH). *Anal.* Calcd. for $C_{12}H_{14}ON_2$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.47; H, 6.76; N, 13.84.

**1,2,3,4,5,6-Hexahydro-1,5-methano-2-methylpyrido[2,3-*c*]azocine (XIX)**——To a suspension of $LiAlH_4$ (95 mg) in tetrahydrofuran (5 ml) was added a solution of XVIII (100 mg) in tetrahydrofuran (5 ml), and the mixture was refluxed with stirring for 40 min. To the mixture was added saturated aq. potassium sodium tartrate solution, and extracted with $CHCl_3$. The extract was washed with brine, dried over $Na_2SO_4$, and concentrated. Distillation gave 58 mg (62%) of a colorless oil of XIX, bp 60—70° (0.04 mmHg, bath temp.). IR $\nu_{max}^{film}$ $cm^{-1}$: 2800 (N-Me). NMR ($CCl_4$) $\delta$: 1.3—2.95 (9H, m), 2.1 (3H, s, N-$CH_3$), 3.65 (1H, d.d, $J$=7, 3 Hz, >N–CH<), 7.0 (1H, d.d, $J$=7.5, 4.5 Hz, arH), 7.3 (1H, d, $J$=7.5 Hz, arH), 8.25 (1H, d, $J$=4.5 Hz, arH).

Dipicrate of XIX: Yellow cubes, mp 205—209° (acetone). *Anal.* Calcd. for $C_{12}H_{16}N_2 \cdot 2C_6H_3O_7N_3$: C, 44.66; H, 3.44; N, 17.33. Found: C, 44.58; H, 3.32; N, 17.20.

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