Synthesis of 1-Substituted 3-Anilino-4-diethylaminomethyl-5-oxo-3,4-dehydropiperidines and 2-Substituted 1,2,3,5,6,11-Hexahydro-5-phenyl-4*H*-pyrido[3,4-*b*][1,5]benzodiazepin-4-ones

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The Synthesis of novel 1-substituted 3-anilino-4-diethylaminomethyl-5-oxo-3,4-dehydropiperidines and 2-substituted 1,2,3,5,6,11-hexahydro-5-phenyl-4*H*-pyrido[3,4-*b*][1,5]benzo diazepin-4-ones from the β-arylaminovinylketones derived from *N*-substituted piperidine-3,5-diones is described.

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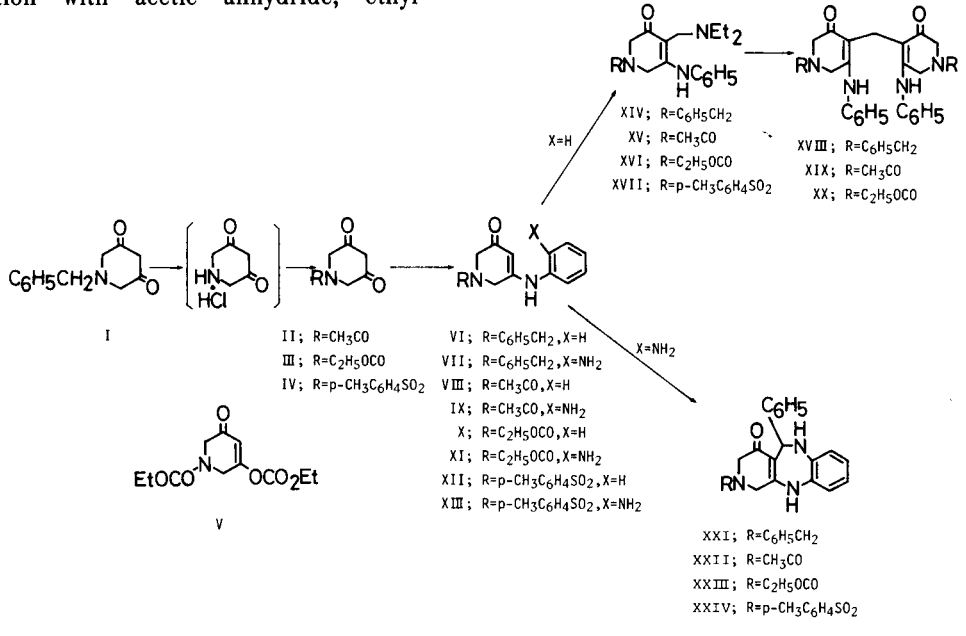
The Mannich bases and the Mannich-type cyclisation products of β-arylaminovinylketones derived from 5,5-dimethylcyclohexane-1,3-dione have strong narcotic and analgetic activities (1), but are unstable for clinical use. Hoping to obtain more practically useful agents, we are pursuing analogs in which C-5 $C(CH_3)_2$ in the cyclohexenone ring is replaced by NR (R = $C_6H_5CH_2$, CH_3CO, C_2H_5OCO, and p-$CH_3C_6H_4SO_2$). In this direction, the synthesis of 1-substituted 3-anilino-4-diethylaminomethyl-5-oxo-3,4-dehydropiperidines (Mannich bases) (XIV-XVII) and 2-substituted 1,2,3,5,6,11-hexahydro-5-phenyl-4*H*-pyrido[3,4-*b*][1,5]benzodiazepin-4-ones (Mannich-type cyclisation products) (XXI-XXIV) from the β-arylaminovinylketones derived from *N*-substituted piperidine-3,5-diones (I-IV) was undertaken and is reported herein.

The synthesis of the title compounds outlined in the Scheme was achieved from the known *N*-benzylpiperidine-3,5-dione (I) (2). Debenzylation of I hydrochloride by catalytic hydrogenation on 5% palladium-carbon and subsequent acylation with acetic anhydride, ethyl chloroformate, and *p*-toluenesulphonyl chloride gave *N*-acetyl- (II), *N*-carboethoxy- (III), and *N*-*p*-toluenesulphonylpiperidine-3,5-diones (IV), respectively, in moderate yields. Heating of I with ethyl chloroformate in the presence of triethylamine gave *N,O*-dicarboethoxylated compound (V) (3) in a quantitative yield, subsequent hydrolysis of which consisted an alternative synthesis of III.

Compounds I-IV are the starting diketones for the synthesis of the corresponding enaminones (VI-XIII) as key intermediates for obtaining the desired Mannich bases (XIV-XVII) and the Mannich-type cyclisation products (XXI-XXIV). The enamination of I-IV with aniline or *o*-phenylenediamine furnished in a moderate yield by using the previously reported method (4). Thus, I trifluoroacetate was reacted with the DMS/NCS-complex followed by treatment with aniline or *o*-phenylenediamine (method A) to give 1-benzyl-3-anilino- (VI) or 1-benzyl-3-(*o*-aminoanilino)-5-oxo-3,4-dehydropiperidines (VII). In the



Scheme

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case of *N*-acylsubstituted piperidines (II-IV), both method A and the direct reaction with aniline or *o*-phenylenediamine in refluxing ethanol (method B) gave moderate yields of the corresponding 1-acyl-substituted 3-anilino-(VIII, X, and XII) and 1-acyl-substituted 3-(*o*-amino-anilino)-5-oxo-3,4-dehydropiperidines (IX, XI, and XIII) (5).

Under suitable and mild conditions the enaminone (VI) was reacted with formaldehyde and diethylamine in the presence of a catalytic amount of acetic acid to give the expected Mannich base (XIV) in 73% yield. Similarly, Mannich bases (XV-XVII) were obtained from the corresponding enaminones (VIII, X, and XII) and proved by their ir and nmr spectral data. However, these Mannich bases are unstable toward moisture and were gradually converted into the methylenebisenaminone derivatives (XVIII-XX). The result is believed to arise mainly from a condensation of the Mannich bases (XIV-XVI) and the enaminones (VI, VIII, and X) reproduced by a retro-Mannich reaction of XIV-XVI rather than a condensation of the reproduced enaminones (VI, VIII, and X) and formaldehyde, since the treatment of the enaminone (VI) with the Mannich base (XIV) in the presence of catalytic amount of acetic acid in ethanol gave a high yield of the methylenebisenaminone (XVIII), but with formaldehyde gave a low yield of XVIII(6).

On the other hand, the Mannich-type cyclisation products (XXI-XXIV) obtained by treating of the enaminones (VII, IX, XI, and XIII) with benzaldehyde in the presence of catalytic amount of acetic acid in ethanol are fairly stable. These structures are supported by their ir, nmr, and elemental analyses. Pharmacological testing is now under way.

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were measured with a Hitachi EPI G-2 spectrophotometer in chloroform unless otherwise specified, uv spectra with a Hitachi 124 spectrophotometer in ethanol, and mass spectra with a Hitachi RMU-6D mass spectrometer at 70 eV. Pmr spectra were obtained with a Hitachi R 20A spectrometer in the solvents indicated. Chemical shifts and coupling constants were measured in ppm (δ) and J (Hz) with respect to TMS.

N-Acetylpiperidine-3,5-dione (II).

Through a stirred suspension of I (6 g.) in dry ether (100 ml.), hydrogen chloride gas was bubbled for 1 hour, giving I·hydrochloride (6.7 g., m.p. 170-173°). Crude I hydrochloride (6.5 g.) was submitted to the standard catalytic hydrogenolysis over 5% palladium-carbon (1.63 g.) in methanol-water (1:1, 130 ml.) at room temperature for several hours to give piperidine-3,5-dione·hydrochloride (3.3 g.). To a solution of the hydrochloride (3.2 g.) and potassium carbonate (4.8 g.) in water (10 ml.), acetic anhydride (2.9 g.) was added dropwise. After the mixture was allowed to stand at room temperature for several hours, it was acidified with 10%-hydrochloric acid (11 ml.) and kept in refrigerator overnight. The resulting solids were collected by filtration. The solids were extracted with hot dry acetonitrile (200 ml.) to remove contaminent potassium chloride and the extract was concentrated *in vacuo* to give colourless crystals, m.p. 162-164° dec. (50% over all yield from I); pmr (DMSO-d_6): δ 2.04 (s, 3H, NCOCH_3), 4.08 (s, 4 H, NCH_2 × 2), and 5.35 (s, 1H, CH=); ir (tablet): ν 1650, 1630, and 1575 cm^{-1}.

Anal. Calcd. for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.09; H, 5.84; N, 8.92.

N-Carboethoxypiperidine-3,5-dione (III).

a) To a solution of piperidine-3,5-dione hydrochloride obtained from I (800 mg.) and potassium carbonate (886 mg.) in water (5 ml.), ethyl chloroformate (581 mg.) was added under ice-cooling. After stirring at room temperature for 3 hours, the reaction mixture was acidified with 10% hydrochloric acid (3 ml.), and extracted with chloroform. The extract was concentrated *in vacuo* to give a syrup, which was purified by column chromatography on silica gel with chloroform-methanol (1:1) as eluting solvents to give III (50% over all yield from I); pmr (deuteriochloroform): δ 1.30 (t, 3H, J 7, $NCO_2CH_2CH_3$), 4.13 (s, 4H, NCH_2 × 2), 4.17 (quartet, 2H, J 7, $NCO_2CH_2CH_3$), 5.56 (s, 1H, CH=), and 6.60 (bs, 1H, OH); ir: ν 1685 and 1610 cm^{-1}. The analytical sample was obtained by recrystallisation of the methylated compound of III from *N*-hexane; m.p. 59-60°.

Anal. Calcd. for $C_9H_{13}NO_4$: C, 54.27; H, 6.58; N, 7.03. Found: C, 54.16; H, 6.49; N, 7.18.

b) To a solution of V (500 mg.) in acetonitrile (10 ml.), 10% hydrochloric acid (2 ml.) was added. The mixture was stirred at 80° for 2 hours and concentrated *in vacuo* to give a syrup, which was purified by column chromatography as above to give III (70% yield).

N-*p*-Toluenesulphonylpiperidine-3,5-dione (IV).

To a solution of piperidine-3,5-dione hydrochloride obtained from I (471 mg.) and potassium carbonate (430 mg.) in water (20 ml.), *p*-toluenesulphonyl chloride (477 mg.) was added under ice-cooling. After stirring at room temperature for 6 hours, 10% sodium hydroxide (10 ml.) was added to the mixture. The aqueous layer was washed with ethyl acetate and acidified with 10% hydrochloric acid (10 ml.). Extraction of the resulting solids with ethylacetate followed by concentration *in vacuo* gave crystals, which were recrystallised from chloroform to give IV, m.p. 144-145° (47% over all yield from I); pmr (DMSO-d_6): δ 2.49 (s, 3H, $C_6H_4CH_3$), 3.75 (s, 4H, NCH_2 × 2), 5.04 (s, 1H, CH=), and 7.20-7.70 (m, 4H, ArH); ir (tablet): ν 1595, 1560, 1350, and 1165 cm^{-1}.

Anal. Calcd. for $C_{12}H_{13}NO_4S$: C, 53.92; H, 4.90; N, 5.24. Found: C, 54.01; H, 4.99; N, 5.41.

1-Carboethoxy-3-carboethoxyloxy-5-oxo-3,4-dehydropiperidine (V).

a) To a solution of piperidine-3,5-dione hydrochloride obtained from I (1.9 g.) and potassium carbonate (1.1 g.) in water (3 ml.), ethyl chloroformate (1.4 g.) was added dropwise. The mixture was stirred at room temperature for 3 hours and extracted with chloroform. The extract was concentrated *in vacuo* to give a syrup. Additional syrup was obtained by the same treatment of the aqueous layer with ethyl chloroformate (1 g.). The combined syrup was purified by column chromatography on silica gel with chloroform as an eluting solvent to give V (55% over all yield from I); pmr (deuteriochloroform): δ 1.29 (t, 3H, J 7, $NCO_2CH_2CH_3$), 1.39 (t, 3H, J 7, $OCO_2CH_2CH_3$), 4.12 (s, 2H, NCH_2), 4.18 (quartet, 2H, J 7, $NCO_2CH_2CH_3$), 4.31 (quartet, 2H, J 7, $OCO_2CH_2CH_3$), 4.37 (s, 2H, NCH_2), and 6.25 (s, 1H, CH=); ir: ν 1770, 1680, and 1635 cm^{-1}; m/e 257 (M^+). Spectroscopic data were fully consistent with the proposed structure, while satisfactory analytical data could not be obtained because of instability.

b) To a solution of I (2 g.) and triethylamine (3.3 g.) in chloroform (20 ml.), ethyl chloroformate (7.0 g.) was added. The reaction occurred exothermally. The mixture was allowed to stand at room temperature for 2 hours, poured into water (50 ml.), and extracted with ether (15 ml. × 4). The combined extract was washed with saturated aqueous sodium chloride (10 ml.), dried (magnesium sulphate), and evaporated *in vacuo* to give a syrup, which was subjected to a short column chromatography on silica gel with ethyl acetate as an eluting solvent to give V (95% over all yield from I).

1-Benzyl-3-anilino-5-oxo-3,4-dehydropiperidine (VI).

Method A.

A solution of I (406 mg.) and trifluoroacetic acid (228 mg.) in dry methylene chloride (4 ml.) was added to a separately prepared cloudy solution of *N*-chlorosuccinimide (294 mg.) and dimethyl sulphide (0.18 ml.) in dry methylene chloride (20 ml.) at —20° under argon (3). To the cloudy solution, aniline (280 mg.) was added at —20°. The reaction mixture was allowed to warm slowly to room temperature, stirred for 3 hours, neutralised with 10% aqueous sodium hydroxide (3 ml.), and extracted with methylene chloride (10 ml. × 4). The extract was washed with saturated aqueous sodium chloride, dried over magnesium sulphate, and concentrated *in vacuo* to give a solid which was purified by column chromatography to give VI, m.p. 160-162° (56% yield); pmr (deuteriochloroform); δ 3.04 (s, 2H, NCH_2), 3.31 (s, 2H, NCH_2), 3.58 (s, 2H, $NCH_2C_6H_5$), 5.49 (s, 1H, CH=), and 6.8-7.4 (m, 10H, ArH × 2); ir: ν 3400, 1610, 1585, and 1520 cm^{-1}; uv: λ 310 nm (log ε 4.29).

Anal. Calcd. for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.07. Found: C, 77.56; H, 6.53; N, 10.13.

Method B.

A mixture of I (100 mg.) and aniline (92 mg.) in ethanol (10 ml.) was refluxed for 10 hours and the mixutre was concentrated *in vacuo* to give a solid, which was purified by column chromatography on silica gel with chloroform-methanol (5:1) as eluting solvents to give crystals. Recrystallisation from methanol gave VI (20% yield).

1-Benzyl-3-(*o*-aminoanilino)-5-oxo-3,4-dehydropiperidine (VII).

As described for VI by method A, reaction of I (406 mg.) with *o*-phenylenediamine (228 mg.) in the presence of trifluoroacetic acid (228 mg.) gave VII (17% yield); pmr (DMSO-d_6): δ 2.93 (s, 2H, NCH_2), 3.38 (s, 2H, NCH_2), 3.38 (s, 2H, NH_2), 3.62 (s, 2H, $CH_2C_6H_5$), 4.72 (s, 1H, CH=), 4.80-4.98 (bs, 1H, NH), 6.52-6.98 (m, 4H, ArH), and 7.32 (s, 5 H, C_6H_5); ir: ν 3400, 1625, 1590, and 1500 cm^{-1}; m/e 293 (M^+). The spectroscopic data were fully consistent with the proposed structure, while satisfactory analytical data could not be obtained because of instability.

1-Acetyl-3-anilino-5-oxo-3,4-dehydropiperidine (VIII).

Method A.

Reaction of II (310 mg.) with aniline (280 mg.) in the absence of trifluoroacetic acid gave VIII, m.p. 211-212° (50% yield); pmr (DMSO-d_6): δ 2.05 (s, 3H, CH_3CO), 3.98 (s, 2H, NCH_2), 4.46 (s, 2H, NCH_2), 5.38 (s, 1H, CH=), 6.95-7.45 (m, 5H, ArH), and 9.1-9.4 (bs, 1H, NH); ir: ν 3380, 1630, 1600, 1580, and 1540 cm^{-1}; uv: λ 308 nm (log ε 4.34); m/e 230 (M^+).

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.93; H, 6.15; N, 12.24.

Method B.

Reaction of II (620 mg.) with aniline (745 mg.) in ethanol (20 ml.) as described for VI gave a solid, which was recrystallised from methanol to give VIII (50% yield).

1-Carboethoxy-3-anilino-5-oxo-3,4-dehydropiperidine (X).

a) Prepared from III by Method B.

Reaction of III (160 mg.) with aniline (121 mg.) in ethanol (4 ml.) as described for VI gave a solid, which was recrystallised from ethyl acetate to give X, m.p. 148-149° (42% yield); pmr (deuteriochloroform): δ 1.23 (t, 3H, OCH_2CH_3), 4.06 (s, 2H, NCH_2), 4.11 (quartet, 2H, OCH_2CH_3), 4.44 (s, 2H, NCH_2), 5.60 (s, 1H, CH=), 7.0-7.5 (m, 5H, ArH), and 7.75 (bs, 1H, NH); ir: ν 3380, 2970, 1680, 1600, 1580, 1540, and 1440 cm^{-1}.

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 10.76; N, 6.20. Found: C, 64.75; H, 10.66; N, 6.20.

b) Prepared from V.

A solution of V (2 g.) and aniline (1.09 g.) in ethanol (50 ml.) was refluxed for 1.5 hours. The reaction mixture was concentrated *in vacuo* to give a syrup, which was subjected to column chromatography on silica gel with ethyl acetate as an eluting solvent to give X (44% yield).

1-*p*-Toluenesulphonyl-3-anilino-5-oxo-3,4-dehydropiperidine (XII).

Reaction of IV (100 mg.) with aniline (52 mg.) in ethanol (5 ml.) as described for VI gave a solid, which was recrystallised from ethanol to give XII; m.p. 200-202° (47% yield); pmr (DMSO-d_6): δ 2.38 (s, 3H, $CH_3C_6H_4$), 3.69 (s, 2H, NCH_2), 4.19 (s, 2H, NCH_2), 4.97 (s, 1H, CH=), 6.85-7.26 (m, 9H, ArH), and 9.06-9.20 (bs, 1H, NH); ir (tablet): ν 3240, 1580, 1545, 1355, and 1165 cm^{-1}.

Anal. Calcd. for $C_{18}H_{18}N_2O_3S$: C, 63.14; H, 5.30; N, 8.18. Found: C, 62.96; H, 5.24; N, 8.07.

1-Benzyl-3-anilino-4-diethylaminomethyl-5-oxo-3,4-dehydropiperidine (XIV).

Compound VI (27.8 mg.) was added to a solution of diethylamine (25.6 mg.), aqueous formaldehyde (37%, 24.3 mg.) and one drop of acetic acid in ethanol (1 ml.). The mixture was stirred at room temperature for 1.5 hours and concentrated *in vacuo* to give a syrup, which was subjected to column chromatography on silica gel with chloroform as an eluting solvent to give XIV (73% yield); pmr (deuteriochloroform); δ 1.10 (t, 6 H, NCH_2CH_3 × 2), 2.62 (quartet, 4H, NCH_2CH_3 × 2), 3.10 (s, 2H, NCH_2), 3.43 (s, 2H, NCH_2), 3.57 (s, 2H, Et_2NCH_2), 3.61 (s, 2H, $CH_2C_6H_5$), 6.50-7.40 (m, 10H, ArH), and 7.95 (bs, 1H, NH); ir: ν 1610, 1590, and 1575 cm^{-1}. The analytical sample was obtained by recrystallisation of the dipicrate of XIV from ethanol, m.p. 154-156°.

Anal. Calcd. for $C_{35}H_{35}N_9O_{15}$: C, 51.16; H, 4.29; N, 15.34. Found: C, 51.04; H, 4.38; N, 15.20.

1-Acetyl-3-anilino-4-diethylaminomethyl-5-oxo-3,4-dehydropiperidine (XV).

Reaction of VIII (50 mg.) with diethylamine (56 mg.), aqueous formaldehyde (37%, 53 mg.), and one drop of acetic acid in ethanol (1 ml.) as described for XIV gave XV (70% yield); pmr (deuteriochloroform); δ 1.08 (t, 6H, NCH_2CH_3 × 2), 2.10 (s, 3 H, CH_3CO), 2.58 (quartet, 4H, NCH_2CH_3 × 2), 3.60 (s, 2H, Et_2NCH_2), 4.04 (s, 2H, NCH_2), 4.51 (s, 2H, NCH_2), 6.90-7.50 (m, 5 H, ArH), and 9.38 (bs, 1H, NH); ir: ν 1640, 1600, 1590, 1580, 1500, 1435, and 1410. Spectroscopic data were fully consistent with the proposed structure, while satisfactory analytical data could not be obtained because of instability.

1-Carboethoxy-3-anilino-4-diethylaminomethyl-5-oxo-3,4-dehydropiperidine (XVI).

Reaction of X (130 mg.) with diethylamine (128 mg.), aqueous formaldehyde (37%, 120 mg.), and one drop of acetic acid in ethanol (2 ml.) as described for XIV gave XVI (73% yield); pmr (deuteriochloroform): δ 1.06 (t, 6 H, NCH_2CH_3 × 2), 1.20 (t, 3H, OCH_2CH_3), 2.54 (quartet, 4H, NCH_2CH_3 × 2), 3.57 (s, 2H, Et_2NCH_2), 4.04 (s, 2H, NCH_2), 4.09 (quart, 2H, $CO_2CH_2CH_3$), 4.40 (s, 2H, NCH_2), 6.85-7.50 (m, 5H, ArH), and 9.92 (s, 1H, NH); ir: ν 1680, 1580, 1500, 1445, 1415, and 1385 cm^{-1}. Spectroscopic data were fully consistent with the proposed structure, while satisfactory analytical data could not be obtained because of instability.

1-*p*-Toluenesulphonyl-3-anilino-4-diethylaminomethyl-5-oxo-3,4-dehydropiperidine (XVII).

Reaction of XII (30 mg.) with diethylamine (22.5 mg.), aqueous formaldehyde (37%, 21 mg.) in ethanol (0.8 ml.) as described for XIV gave XVII (75% yield); pmr (deuteriochloroform); δ 1.07 (t, 6H, NCH_2CH_3 × 2), 1.92 (s, 3H, $C_6H_4CH_3$), 2.54 (quart, 4H, NCH_2CH_3 × 2), 3.50 (s, 2H, Et_2NCH_2), 3.77 (s, 2H, NCH_2), 4.06 (s, 2H, NCH_2), 6.85-7.15 (m, 9H, ArH), and 9.88 (s, 1H, NH); ir: ν 1600, 1590, 1580, and 1500 cm^{-1}. Spectroscopic data were fully consistent with the proposed structure, while satisfactory analytical data could not be obtained because of instability.

4,4′-Methylenebis-(1-benzyl-3-anilino-5-oxo-3,4-dehydropiperidine) (XVIII).

a) From the Mannich Base (XIV).

The Mannich base (XIV) obtained from VI (557 mg.) was dissolved in acetone (100 ml.) and water (5 ml.). After stirring for several minutes at room temperature, white crystals resulted from the mixture. Additional stirring was continued for 10 hours and the resultant crystals were collected. Recrystallisation of the crystals from ethanol gave XVIII, m.p. 210-211° (70% over all yield from VI); pmr (deuteriochloroform): δ 3.13 (s, 4 H, NCH_2 × 2), 3.47 (s, 6H, NCH_2 × 2 and =C-CH_2), 3.57 (s, 4H, NCH_2 × 2), 6.7-7.3 (m, 20H, ArH × 4), and 10.80 (bs, 2H, NH × 2); ir: ν

1620, 1580, 1505, 1460, and 1440 cm^{-1}; m/e 568 (M^+).

Anal. Calcd. for $C_{37}H_{36}N_4O_2$: C, 78.14; H, 6.38; N, 9.85. Found: C, 78.20; H, 6.42; N, 9.79.

b) From the Reaction of the Mannich Base (XIV) and the Enaminone (VI).

A solution of the Mannich base (XIV) obtained from VI (28 mg.) and one drop of acetic aicd and VI (28 mg.) in ethanol (2 ml.) was stirred at room temperature for 3 hours to give XVIII (75% yield).

c) From the Reaction of the Enaminone (VI) and Formaldehyde.

A solution of VI (27.8 mg.) and aqueous formaldehyde (37%, 12 mg.) in acetone (1 ml.) was stirred at room temperature for 1 day, but none of XVIII was obtained. However, refluxing a solution of VI (27.8 mg.) and aqueous formaldehyde (37%, 12 mg.) in ethanol (1 ml.) for 50 hours gave XVIII (25% yield).

4,4'-Methylenebis-(1-acetyl-3-anilino-5-oxo-3,4-dehydropiperidine) (XIX).

From the Mannich Base (XV).

Refluxing a stirred solution of the Mannich base (XV) obtained from VIII (100 mg.) and one drop of acetic acid in acetone (18 ml.) and water (2 ml.) for 6 hours gave VIII (33% yield) and XIX (18% yield). The analytical sample of XIX was obtained by recrystallisation from methanol, m.p. 239-241° dec.; pmr (deuteriochloroform): δ 2.09 (s, 6H, $NCOCH_3 \times 2$), 3.51 (s, 2H, CH_2-C=), 4.13 (s, 4H, $NCH_2 \times 2$), 4.56 (s, 4H, $NCH_2 \times 2$), 7.1-7.5 (m, 10H, ArH $\times$ 2), and 11.10 (s, 2H, NH $\times$ 2); ir: ν 1645, 1625 an 1575 cm^{-1}.

Anal. Calcd. for $C_{27}H_{28}N_4O_4$: C, 68.62; H, 5.97; N, 11.86. Found: C, 68.17; H, 5.91; N, 11.60.

4,4'-Methylenebis-(1-carboethoxy-3-anilino-5-oxo-3,4-dehydropiperidine) (XX).

From the Mannich Base (XVI).

Refluxing a stirred solution of the Mannich base (XVI) obtained from X (50 mg.) and one drop of acetic acid in acetone (9 ml.) and water (1 ml.) for 4 hours gave X (20% yield) and XX (40% yield). The analytical sample of XX was obtained by recrystallisation from ethyl acetate-*N*-hexane (1;1), m.p. 244-245° dec.; pmr (deuteriochloroform): δ 1.23 (t, 6H, $CO_2CH_2CH_3 \times 2$), 3.53 (s, 2H, $CH_2CH=$), 4.16 (quartet, 4H, $CO_2CH_2CH_3 \times 2$), 4.16 (s, 4H, $NCH_2 \times 2$), 4.45 (s, 4H, $NCH_2 \times 2$), 7.1-7.5 (m, 10H, ArH $\times$ 2), and 11.15 (s, 2H, NH $\times$ 2); ir: ν 1685 and 1575 cm^{-1}.

Anal. Calcd. for $C_{29}H_{32}N_4O_6$: C, 65.40; H, 6.06; N, 10.52. Found: C, 65.34; H, 6.01; N, 10.45.

2-Benzyl-1,2,3,5,6,11-hexahydro-5-phenyl-4*H*-pyrido[3,4-*b*][1,5]benzodiazepin-4-one (XXI).

Compound VII obtained from I (406 mg.) was added to a solution of benzaldehyde (212 mg.) and one drop of acetic acid in ethanol (3 ml.). The mixture was stirred at room temperature for 1 hour and concentrated *in vacuo* to give a syrup, which was subjected to column chromatography on silica gel with benzene-ethyl acetate (1:4) as eluting solvents to give a solid. Recrystallisation from ethyl acetate gave XXI, m.p. 217-219° dec. (30% over all yield from I); pmr (DMSO-d_6): δ 3.05 (s, 2H, NCH_2), 3.48 (s, 2H, NCH_2), 3.64 (s, 2H, $NCH_2C_6H_5$), 5.58 (d, 1H, J 6, NHC*H*C_6H_5), 6.18 (d, 1H, J 6, N*H*CHC$_6H_5$), 6.46-6.62 (m, 4H, ArH), 7.05 (s, 5H, ArH), 7.32 (s, 5H, $NCH_2C_6H_5$), and 8.95 (s, 1H, NH); ir: ν 3400, 1620, 1590, and 1530 cm^{-1}; m/e 381 (M^+).

Anal. Calcd. for $C_{25}H_{23}N_3O$: C, 78.71; H, 11.01; N, 6.08. Found: C, 78.57; H, 10.96; N, 6.09.

2-Acetyl-1,2,3,5,6,11-hexahydro-5-phenyl-4*H*-pyrido[3,4-*b*][1,5]benzodiazepin-4-one (XXII).

Compound IX obtained from II (200 mg.) was reacted with benzaldehyde (151 mg.) and one drop of acetic acid in ethanol (3 ml.) as described for XXI to give a solid. Recrystallisation from acetic aicd-*N*-hexane gave XXII, m.p. 267-268° (16% over all yield from II); pmr (DMSO-d_6): δ 2.08 (s, 3H, CH_3CO), 4.07 (s, 2H, NCH_2), 4.63 (d, 2H, NCH_2), 5.63 (d, 1H, J 7, NHC*H*C_6H_5), 6.25 (d, 1H, J 7, N*H*CHC$_6H_5$), 6.59 (d, 4H, ArH), 7.05 (s, 5H, ArH), and 9.27 (s, 1H, NH); ir (tablet): ν 3420, 3080, 1625, 1605, 1550, and 1500 cm^{-1}; m/e 333 (M^+).

Anal. Calcd. for $C_{20}H_{19}N_3O_2$: C, 72.05; H, 5.74; N, 12.60. Found: C, 71.87; H, 5.69; N, 12.31.

2-Carboethoxy-1,2,3,5,6,11-hexahydro-5-phenyl-4*H*-pyridio[3,4-*b*][1,5]-benzodiazepin-4-one (XXIII).

Compound XI obtained from V (2.5 g.) was reacted with benzaldehyde (1.0 g.) and one drop of acetic acid in ethanol (20 ml.) as described for XXI to give a syrup, which was subjected to column chromatography on silica gel with ethyl acetate to give a solid. Recrystallisation from ethyl acetate-ethanol (9:1) gave XXIII, m.p. 220-221° (25% over all yield from V): pmr (DMSO-d_6): δ 1.24 (t, 2H, J 7, OCH_2CH_3), 4.14 (quartet, 2H, J 7, OCH_2CH_3), 4.00 (s, 2H, NCH_2), 4.58 (d, 2H, NCH_2), 5.64 (d, 1H, J 7, $NHCHC_6H_5$), 6.26 (d, 1H, J 7, $NHCHC_6H_5$), 6.4-7.2 (m, 9H, Ar), and 9.25 (s, 1H, NH); ir: ν 3390, 1680, 1620, 1605, 1590, 1550, and 1535 cm^{-1}; m/e 363 (M^+).

Anal. Calcd. for $C_{21}H_{21}N_3O_3$: C, 69.40; H, 5.82; N, 11.50. Found: C, 69.51; H, 5.79; N, 11.50.

2-*p*-Toluenesulpnonyl-1,2,3,5,6,11-hexahydro-5-phenyl-4H-pyrido-[3,4-*b*][1,5]benzodiazepin-4-one (XXIV).

Compound XIII obtained from IV (200 mg.) was reacted with benzaldehyde (80 mg.) and one drop of acetic acid in ethanol (4 ml.) as described for XXI to give a syrup, which was subjected to column chromatography on silica gel with benzene-ethyl acetate (1:1) as eluting solvents to give a solid. Recrystallisation from ethyl acetate gave XXIV, m.p. 223-225° dec. (20% over all yield from IV); pmr (DMSO-d_6): δ 2.41 (s, 3H, $CH_3C_6H_4$), 3.70 (s, 2H, NCH_2), 4.41 (d, 2H, NCH_2), 5.52 (d, 1H, J 7, NHC*H*C_6H_5), 6.20 (d, 1H, J 7, N*H*-CHC$_6H_5$), 6.4-7.8 (m, 13H, ArH), and 9.25 (s, 1H, NH); ir: ν 1620, 1595, 1540, 1400, and 1350 cm^{-1}; m/e 445 (M^+).

Anal. Calcd. for $C_{25}H_{23}N_3O_3S$, C, 67.39; H, 9.45; N, 5.20. Found: C, 67.42; H, 9.36; N, 5.11.

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