

Studies on the Syntheses of Analgesics. Part XXXIX (1). Synthesis of 1,2,3,4,5,6-Hexahydro-8-hydroxy-2,6-methano-3,6,11-trimethyl-2,3-benzo[*g*]diazocine and 1,2,3,4,5,10,11,12-Octahydro-7-hydroxy-1,5-dimethylpyridazino[2,3-*b*]isoquinoline [Studies on the Syntheses of Heterocyclic Compounds. Part LXI (2)].

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1,2,3,4,5,6-Hexahydro-8-hydroxy-2,6-methano-3,6,11-trimethyl-2,3-benzo[*g*]diazocine (IV) and 1,2,3,4,5,10,11,12-octahydro-7-hydroxy-1,5-dimethylpyridazino[2,3-*b*]isoquinoline (VI) were synthesized from a common intermediate, 3-(3-methoxyphenyl)-2-butanone (VII), through several steps. Reaction of VII with ethyl bromoacetate gave the mixture of ethyl 4-keto-3-(3-methoxyphenyl)-3-methylpentanoate (XIV) and ethyl 4-keto-5-(3-methoxyphenyl)hexanoate (XV) which were hydrolyzed and condensed with methylhydrazine to give the 4,5-dihydro-5-(3-methoxyphenyl)-2,5,6-trimethyl- (XVIII) and 4,5-dihydro-6-(3-methoxy- α -methylbenzyl)-2-methylpyridazine-3(2*H*)one (XIX). Reduction of XVIII and XIX followed by cyclization afforded the 2,3-benzo[*g*]diazocine (XXII) and the pyridazino[2,3-*b*]isoquinoline (XXIII) which on treatment with 47% hydrobromic acid afforded the phenolic bases (IV and VI), respectively. The mass spectrum of IV, VI, XXII and XXIII was also discussed.

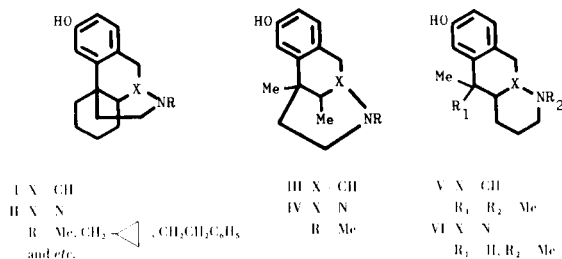
Replacement of the carbon atom of the morphinan (I) and 3-benzazocine ring (III) by the nitrogen atom would be an interesting problem from the synthetic and pharmaceutical point of view. For example, Kametani (4) and Mitsuhashi (5), independently, reported the syntheses of several kinds of the azamorphinan and benzodiazocine derivatives, among which *N*-alkyl derivatives of 9-azamorphinan were proven to possess potent analgesic activity. In the present paper, we wish to report the synthesis of the 2,3-benzo[*g*]diazocine derivative (IV) (6) and the pyridazino[2,3-*b*]isoquinoline derivative (VI), in which an additional nitrogen atom was introduced at the C₂-position of the 3-benzazocine molecule (III) in the former compound and in the latter a bridgehead

nitrogen atom replaced the carbon atom of the benzo[*g*]quinoline ring (V). Compound (V) has already been reported to show narcotic antagonistic activity (7).

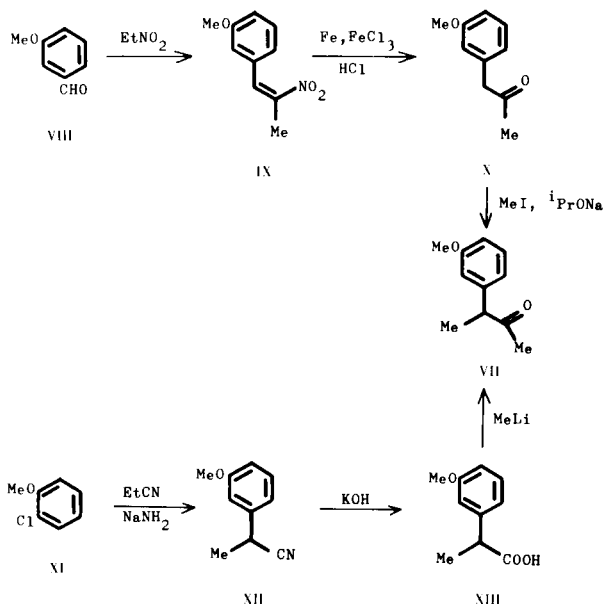
3-(3-Methoxyphenyl)-2-butanone (VII), a common intermediate for IV and VI, was obtained as follows. Condensation of 3-methoxybenzaldehyde (VIII) with nitroethane, followed by reductive hydrolysis of the nitrostyrene (IX), gave the phenylacetone (X) (8). Methylation of X by methyl iodide in the presence of sodium isopropoxide gave the ketone (VII) (9) in 52% overall yield. Moreover, 2-(3-methoxyphenyl)propionitrile (XII), prepared by the benzyne reaction of XI and propionitrile (10), was hydrolyzed and then treated with methyl lithium (11) to afford the same ketone (VII) in 48% overall yield.

In the alkylation of the active methylene of the phenylbutanone (VII), two different products were expected (*via a* and *b*), although more likely *a* because of its benzylic position. In fact, the reaction of VII and ethyl bromoacetate in the presence of sodium amide (12) afforded the mixed products of the γ -ketoesters (XIV and XV) which could not be separated by distillation and column chromatography using silica gel. Hydrolysis of these esters, followed by condensation with methylhydrazine, gave a mixture of the isomeric pyridazinone

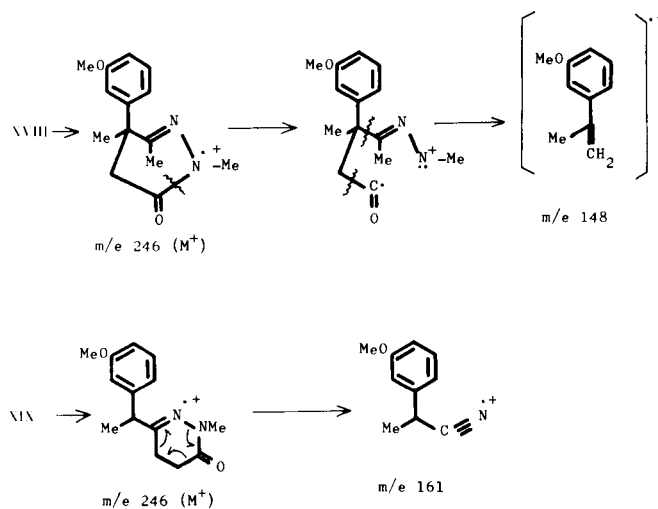
SCHEME 1



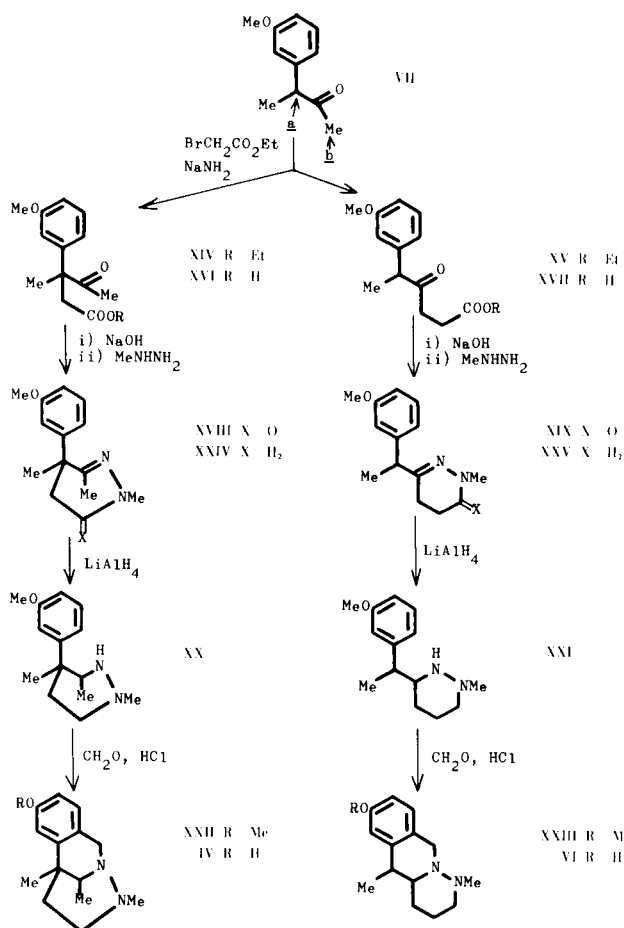
SCHEME 2



SCHEME 3



SCHEME 4



derivatives (XVIII and XIX). The former pyridazinone (XVIII) was crystallized from ether-*n*-hexane and the latter one (XIX) was obtained, after distillation of the mother liquor of the crystallization, as a colorless oil. The microanalysis of each compound supported the molecular formula of $C_{14}H_{18}N_2O_2$ and carbonyl absorption in the ir spectrum of XVIII and XIX appeared at 1670 and 1665 cm^{-1} (13), respectively. The structural differentiation between XVIII and XIX was confirmed on the basis of the nmr spectrum. In the case of XVIII, four singlets at 1.51, 1.97, 3.37 and 3.85 ppm were assigned to two *C*-methyls, one *N*-methyl and one *O*-methyl, and a pair of doublets ($J = 15.8\text{ Hz}$) due to *C*₄-methylene protons appeared at 2.47 and 2.97 ppm. In the case of XIX, a unique *C*-methyl resonance appeared as a doublet ($J = 7.5\text{ Hz}$) at 1.47 ppm, and *O*-methyl and *N*-methyl resonances showed two singlets at 3.82 and 3.44 ppm. In the mass spectra, the correct molecular ion peaks were shown at *m/e* 246 for each compound and two main peaks at *m/e* 148 for XVIII and *m/e* 161 for XIX were reasonably interpreted as α -cleavage of C=N and C=O groups shown in Scheme 3.

The pyridazinone (XVIII), thus obtained, was reduced with lithium aluminum hydride to yield the pyridazine (XX) which was characterized as its hydrochloride, since the free base was sensitive to air and is readily oxidized to the dehydro base (XXIV) as reported for the pyridazine (5c) and cinnoline series (4h and 14). Reduction of XXIV with lithium aluminum hydride under the same condition gave XX. In case of these hydride reductions,

an attack of the metal hydride to C=N double bond would occur from the less-hindered side (a) (4h) rather than the hindered side (b) by influence of the bulky phenyl group, producing the single product (XX') in which phenyl and

C_6 -methyl groups are *cis*. The Pictet-Spengler reaction of the hydrochloride of XX with formaldehyde afforded 1,2,3,4,5,6-hexahydro-2,6-methano-8-methoxy-3,6,11-trimethyl-2,3-benzo[*g*]diazocine (XXII) in 88% yield. The direction of the cyclization in this reaction was considered to be *para* to the methoxy group as in the analogous cases of the 2,3-benzo[*g*]diazocines [4k and 5d] and the 9-azamorphinans (I and 4h₂). In this reaction only conformation XX' (phenyl group is *axial*) can cyclize readily to give XXII, since neither epimerization nor change of relative configuration was observed in the Pictet-Spengler cyclization of *cis*- or *trans*-2-phenylcyclohexylamine derivatives to form the octahydrophenanthrene derivatives (17). The alternative conformation (phenyl group is *equatorial*) of XX has a prohibitive distance for cyclization between aromatic ring and nitrogen atom. These stereoselectivities are closely related to the fact that the reduction of the ketocinnoline (XXVI) with lithium aluminum hydride gave the *trans*-decahydrocinnoline (XXVII) which was cyclized to the B/C *cis*-9-azamorphinan (XXVIII) under the Pictet-Spengler condition (4h).

The nmr spectrum of XXII showed a pair of doublets ($J = 19$ Hz) attributable to C_1 -methylene at 3.94 and 4.31 ppm, a doublet ($J = 7.5$ Hz) due to C_{11} -methyl protons at 1.02 ppm and a singlet due to C_6 -methyl at 1.23 ppm. The chemical shifts of these C -methyl protons correspond to those of *cis*-isomer of the benzazocine (III) rather than *trans*-isomer (18). *Equatorial* C_{11} -methyl of XXII would be shielded by the aromatic ring but somewhat

deshielded by inductive effect of nitrogen atom. On the contrary, *axial* C_{11} -methyl, which has a 1,3-diaxial relationship to the lone pair electrons of nitrogen, would be deshielded.

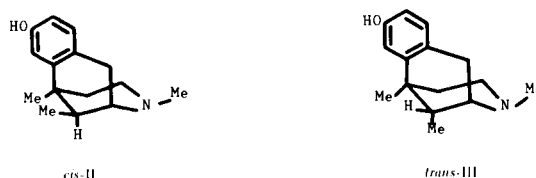
On the basis of the above discussion, the structure of XX and XXII was represented by XX' and XXII', respectively.

TABLE I

Chemical Shifts of C-Methyl Protons (in CDCl₃)

	C_6 -Me	C_{11} -Me
XXII	1.23 (s)	1.02 (d)
<i>cis</i> -III (19)	1.30 (s)	0.84 (d)
<i>trans</i> -III (19)	1.27 (s)	1.25 (d)

SCHEME 6



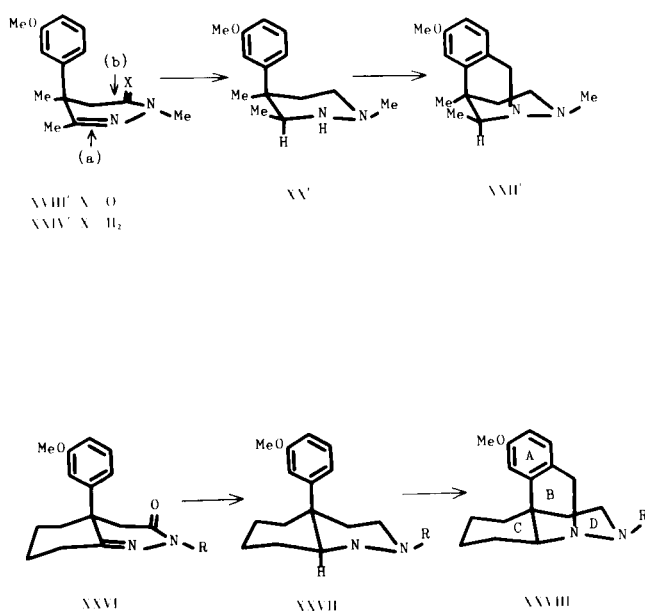
In the final step of the synthesis, treatment of XXII with 47% hydrobromic acid in acetic acid gave the desired phenolic base (IV) as colorless crystals, m.p. 233-240° dec. The nmr spectrum of IV lacked to signal of the methoxy group, but showed the signals of C_6 -methyl, N -methyl and C_1 -methylene protons as singlets, and C_{11} -methyl as doublet ($J = 7$ Hz).

The further confirmation of the structure of IV and XXII was made by the mass spectrometry. The ion peaks at m/e 232 and m/e 246 showed the correct molecular ions for IV and XXII, respectively. The other main peaks of high relative abundance would be rationalized by the following fragmentation pathway shown in Scheme 7.

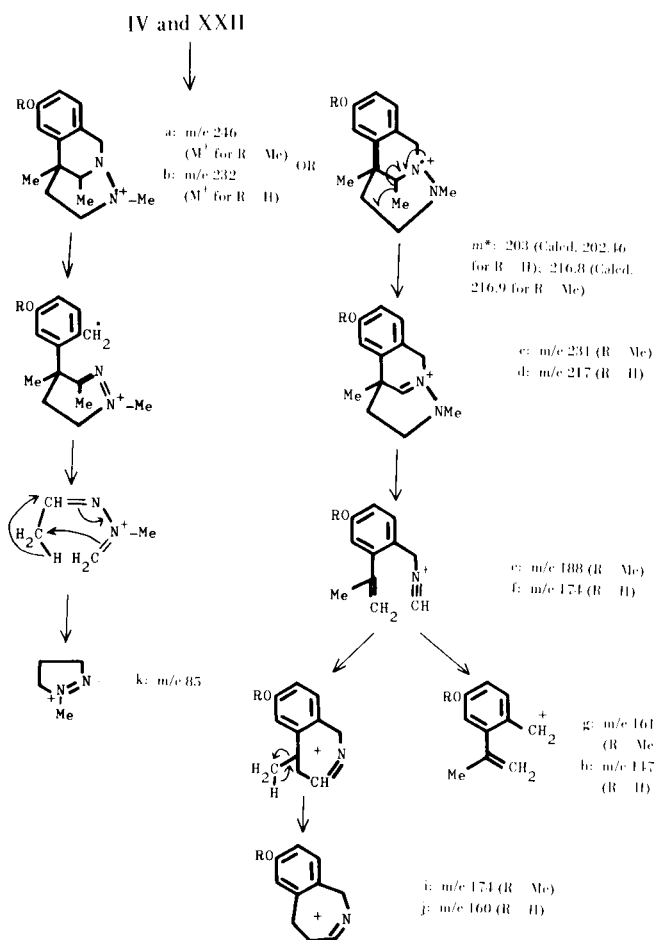
The loss of C_{11} -methyl radical (β to the nitrogen atom) from the molecular ion (M^+) was predominant, as documented by the metastable ion (m^*) peaks, leading to the ion *c* and *d* (base peaks) which might undergo a *retro* Diels-Alder reaction to give the ions *e* and *f*, followed by the loss of HCN or recyclization. The common peak of high intensity for both compounds was assigned to the ion *k* at m/e 85 which might be stabilized by the formation of a dihydropyrazole ring.

On the other hand, the other pyridazinone (XIX) was reduced with lithium aluminum hydride to give the

SCHEME 5



SCHEME 7

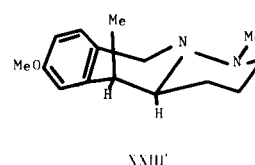


pyridazine (XXI) as its hydrochloride. This compound (XXI) would be a mixture of diastereoisomers, since stereoselective reduction could not proceed in this type of reaction. The free base of XXI was also found to be oxidized by air to the presumed dehydro base (XXV), the reduction of which with lithium aluminum hydride under the same condition recovered XXI. Cyclization of the hydrochloride of XXI with formaldehyde and hydrochloric acid afforded the pyridazino[2,3-*b*]isoquinoline (XXIII). The ir spectrum of XXIII showed a group of weak absorptions around 2800 cm^{-1} which would be a Bohlmann band characteristic for *trans*-quinolizidine type compounds (20).

In the nmr spectrum of XXIII, the signal of *C*-methyl protons was observed as a doublet ($J = 7\text{ Hz}$) at 1.30 ppm, and the newly created C_{10} -methylene as a pair of doublets ($J = 13.5\text{ Hz}$) at 3.56 and 4.13 ppm. Albertson (7) reported, in the nmr spectra of the *N*-substituted derivatives of the *trans*-benzoquinoline (V), that the

signals of the geminal *C*-methyl protons appeared at 0.98-1.17 for one and 1.30-1.38 for another (19). Furthermore, Katritzky (21) and Kotake (22) reported that the chemical shift of *axial* C_1 -, C_2 - or C_4 -methyl protons of quinolizidine derivatives appeared at lower field than that of the corresponding *equatorial* methyl protons. The comparatively low chemical shift (1.30 ppm) of *C*-methyl protons in XXIII would be caused by a long-range effect of lone pair of nitrogen. Thus, the configuration of *C*-methyl of XXIII would be determined to *axial* while the *trans*-pyridazino[2,3-*b*]isoquinoline structure (XXIII') is allowable as the conformation of XXIII.

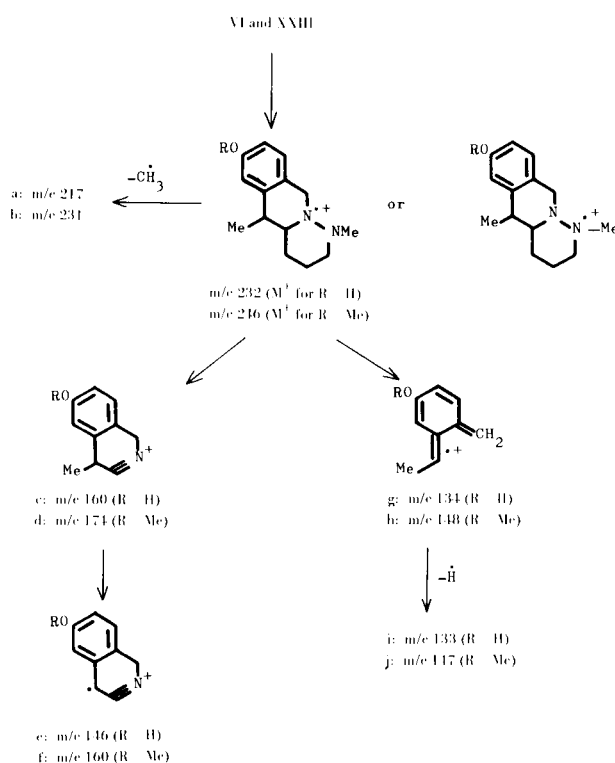
SCHEME 8



Demethylation of XXII was carried out in 48% hydrobromic acid in acetic acid to give 1,2,3,4,5,10,11,12-octa-hydro-7-hydroxy-1,5-dimethylpyridazino[2,3-*b*]isoquinoline (VI) as colorless crystals, m.p. $176-178^\circ$.

In the mass spectrum of VI and XXIII (Scheme 9), their molecular ion peaks appeared at m/e 232 and 246,

SCHEME 9



respectively. The base peaks at m/e 134 and 148 for each compound might be derived through the *retro* Diels-Alder fission of the molecule ion. The other *retro* Diels-Alder fission accompanying the loss of hydrogen radical would lead to ions c and d.

EXPERIMENTAL

All melting and boiling points are uncorrected. Nmr spectra were determined with a JNM-MH-60 spectrometer using tetramethylsilane as an internal reference and carbon tetrachloride, deuteriochloroform or deuteriochloroform-trifluoroacetic acid (1:1) as solvents. Mass spectra were determined by the direct sample introduction technique on a HITACHI RMU-71 spectrometer at 70 eV of the chamber voltage and 200° of the chamber temperature.

3-(3-Methoxyphenyl)-2-butanone (VII).

(a) The nitrostyrene (IX) was obtained by the usual method (8) in 65% yield as yellow crystals, m.p. 40-42° oil, b.p.₁ 128-133° (Lit. 8), after recrystallization from ethanol. To a stirred mixture of 40 g. of IX, 100 ml. of benzene, 120 ml. of water, 45 g. of iron powder and 1.5 g. of ferric chloride was added 80 ml. of 36% hydrochloric acid at 65-70° during 2.5 hours. The mixture was heated for a further 1.5 hours and then filtered while hot. The insoluble solid was washed thoroughly with hot benzene. Evaporation of the combined filtrate and washing followed by fractions gave X as a faintly yellow oil (31.6 g., 93%), b.p. 0.8-1.0 95-102° [b.p.₃ 107-112° (Lit. 8)], ir (liq. film, cm^{-1}): 1710 (C=O); nmr (δ in carbon tetrachloride): 2.02 (3H, s, COCH₃), 3.55 (2H, s, CH₂CO), 3.74 (3H, s, OCH₃). To a cooled mixture of sodium 2-propoxide and 2-propanol (prepared from 1.3 g. of sodium and 80 ml. of 2-propanol) was added 8.2 g. of X, and the resulting solution was treated with 7.8 g. of methyl iodide with stirring. The mixture was heated at 60-70° for 2 hours and then evaporated *in vacuo*. The residue was mixed with water and extracted with ether. Distillation of the ethereal extract gave 7.8 g. (88%) of VII as a colorless oil, [b.p. 0.8-1.0 78-84°, b.p.₁₆ 136-138° (Lit. 11b)], ir (liq. film, cm^{-1}): 1710 (C=O); nmr (δ in carbon tetrachloride): 1.32 (3H, d, J = 7 Hz, CH₃-CH<), 1.94 (3H, s, COCH₃), 3.57 (1H, q, J = 7.0 and 7.0 Hz, CH₃-CH<), 3.75 (3H, s, OCH₃).

(b) The phenylpropionitrile (XII), obtained in 67% yield by the benzyne reaction (10), was hydrolyzed with 40% potassium hydroxide to give XIII in 84% yield. Treatment of XIII with an excess of methyl lithium (11) in dry ether afforded VII in 88% yield. The ir and nmr spectra were superimposable on those of the ketone (VII) prepared by the above method (a).

Ethyl 4-Keto-3-(3-methoxyphenyl)-3-methylpentanoate (XIV) and Ethyl 4-Keto-5-(3-methoxyphenyl)hexanoate (XV).

To a stirred suspension of 1.87 g. of sodium amide in 20 ml. of dry benzene was added drop by drop under reflux a solution of 7.12 g. of the ketone (VII) in 30 ml. of dry ether within 1.5 hours, and the mixture was refluxed for 17 hours. To this mixture was added dropwise a solution of 7.35 g. of ethyl bromoacetate in 30 ml. of dry ether, and the refluxing was continued for 5 hours. After cooling, the excess of sodium amide was decomposed with water. The organic layer was separated, washed with water, dried over sodium sulfate, and distilled to give 3.7 g. (54%) of the recovered VII, b.p. 0.8-1.0 75-82°, and 2 g. (19%) of a mixture of XIV and XV as a pale yellow viscous oil, b.p. 0.8-1.0

136-142°, ir (liq. film, cm^{-1}): 1735 (ester C=O), 1710 (ketone C=O).

Anal. Calcd. for C₁₅H₂₀O₄: C, 68.16; H, 7.63. Found: C, 68.21; H, 7.64.

4,5-Dihydro-5-(3-methoxyphenyl)-2,5,6-trimethylpyridazin-3-(2H)-one (XVIII) and 4,5-Dihydro-6-(3-methoxy- α -methylbenzyl)-2-methylpyridazin-3(2H)one (XIX).

A mixture of 3.4 g. of the preceding ketoester (XIV and XV), 15 ml. of methanol, 8 ml. of water and 3 g. of sodium hydroxide was heated on a water bath for 3 hours, and then methanol was distilled off. The residue was washed with ether, and the aqueous layer was acidified with 36% hydrochloric acid to separate an oil which was extracted with ether. Evaporation of the ethereal layer, after drying over sodium sulfate, gave 2.5 g. of a pale yellow syrup which was dissolved in 20 ml. of benzene, to a solution of which was added 1 ml. of methylhydrazine. This mixture was refluxed for 4 hours in water-bath. After cooling, the mixture was successively washed with water, 5% sodium hydroxide, water, 3% hydrochloric acid and then water, dried over magnesium sulfate, and evaporated to leave 2.7 g. of a pale yellow syrup, which was crystallized from ether-*n*-hexane to give 850 mg. (33%) of XVIII as colorless crystals, m.p. 88-89°. Further recrystallization from 2-propanol gave colorless plates, m.p. 90-91°, ir (potassium bromide, cm^{-1}): 1670 (C=O); nmr (δ in deuteriochloroform): 1.51 (3H, s, >C-CH₃), 1.97 (3H, s,

Ar-N=C-CH₃), 2.47 and 2.97 (each 1H, d, J = 15.8 Hz, -CH₂-), 3.37 (3H, s, N-CH₃), 3.85 (3H, s, O-CH₃), 6.75-7.6 (4H, m, Ar-H); mass (m/e): 246 (M⁺), 231 (M⁺-CH₃), 148 [M⁺-(CH₃C=NNCH₃-C=O)].

Anal. Calcd. for C₁₄H₁₈N₂O₂: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.20; H, 7.48; N, 11.07.

The above mother liquor of crystallization was evaporated and the remaining oil was distilled under reduced pressure to give 760 mg. (28%) of XIX as a colorless viscous oil, b.p._{0.9} 150-152°, ir (liq. film, cm^{-1}): 1665 (C=O); nmr (δ in deuteriochloroform): 1.47 (3H, d, J = 7.5 Hz, >CH-CH₃), 2.28 (4H, s, -CH₂-CH₂-), 3.41 (3H, s, N-CH₃), 3.82 (3H, s, O-CH₃), 3.65 (1H, q, J = 7.5 Hz, CH-CH₃), 6.65-7.35 (4H, m, Ar-H); mass (m/e): 246 (M⁺), 161 [M⁺-(CH₂CH₂CONCH₃)].

Anal. Calcd. for C₁₄H₁₈N₂O₂: C, 68.27; H, 7.37; N, 11.37. Found: C, 67.93; H, 7.35; N, 11.45.

1,2,3,4,5,6-Hexahydro-4-(3-methoxyphenyl)-1,3,4-trimethylpyridazine (XX) Hydrochloride (14).

A solution of 0.6 g. of XVIII in 20 ml. of dry dioxane was added dropwise to a suspension of 0.5 g. of lithium aluminum hydride in 30 ml. of dry dioxane at 80-90° within 1.5 hours, and the mixture was gently refluxed for 5.5 hours. The excess of lithium aluminum hydride was decomposed with water under ice-water cooling in a current of nitrogen. The organic layer separated by filtration was dried over potassium carbonate for 3 minutes, and the ethereal solution of dry hydrochloric acid was added to the above filtrate. Removal of the solvent gave a reddish brown solid which was recrystallized from 2-propanol-ether to afford 330 mg. (50%) of hydrochloride of XX as colorless crystals, m.p. 156-158°, ir (potassium bromide, cm^{-1}): 3160 (NH), 3100-2400 (NH₂Cl⁺).

Anal. Calcd. for C₁₄H₂₂N₂O·HCl: C, 62.09; H, 8.56; N, 10.35. Found: C, 62.13; H, 8.57; N, 9.88.

1,2,3,4,5,6-Hexahydro-3-(3-methoxy- α -methylbenzyl)-1-methylpyridazine (XXI) Hydrochloride (15).

To a stirred suspension of 0.5 g. of lithium aluminum hydride in 20 ml. of dry dioxane was added under gentle reflux a solution of 1.0 g. of the pyridazinone (XIX) in 20 ml. of dry dioxane during 1 hour. The mixture was refluxed for 6 hours and then worked up as described above to afford 0.7 g. of XXI-hydrochloride as a pale brown caramel, ir (liq. film, cm^{-1}): 3170 (NH), 3050-2350 ($>\text{NH}_2\cdot\text{Cl}$), which had a tendency to become a dark colored substance on heating or prolonged exposure in the air and used for the next reaction without further purification.

1,2,3,4,5,6-Hexahydro-2,6-methano-8-methoxy-3,6,11-trimethyl-2,3-benzo[*g*]diazocine (XXII) Hydrochloride.

A mixture of 0.2 g. of the hexahydropyridazine (XX) hydrochloride, 0.4 ml. of 37% formaldehyde, 10 ml. of ethanol and 0.2 ml. of 36% hydrochloric acid was heated in a water-bath for 4 hours, and then ethanol was distilled off. The residue was extracted with water and the aqueous layer was washed with ether, basified with 28% ammonium hydroxide, and extracted with ether. The ethereal extract was washed with water, dried over potassium carbonate, and evaporated to leave 160 mg. (88%) of a pale yellow oil, nmr (δ in deuteriochloroform): 1.02 (3H, d, $J = 7.5$ Hz, $>\text{CH}-\text{CH}_3$), 1.28 (3H, s, $\geq\text{C}-\text{CH}_3$), 2.56 (3H, s, $\text{N}-\text{CH}_3$), 3.24 (1H, q, $J = 7.5$ Hz, $>\text{CH}-\text{CH}_3$), 3.78 (3H, s, $\text{O}-\text{CH}_3$), 3.94 and 4.31 (each 1H, d, $J = 19.0$ Hz, $\text{Ar}-\text{CH}_2-\text{N}$), mass (m/e) (16): 247 ($\text{M}^+ + 1$, 14), 246 (M^+ , 75), 232 (18), 231 (base peak 100), 189 (26), 175 (12), 174 (18), 162 (13), 161 (28), 160 (13), 159 (11), 146 (10), 145 (15), 130 (6), 129 (8), 128 (9), 127 (5), 121 (5), 117 (10), 116 (8), 115 (18), 103 (10), 91 (14), 86 (8), 85 (72). The hydrochloride was recrystallized from 2-propanol-ether to give colorless granules, m.p. 204-207° dec.

Anal. Calcd. for $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}\cdot\text{HCl}$: C, 63.70; H, 8.20; N, 9.91. Found: C, 63.37; H, 8.33; N, 9.60.

1,2,3,4,5,10,11,12-Octahydro-7-methoxy-1,5-dimethylpyridazino[2,3-*b*]isoquinoline (XXIII).

A mixture of 0.6 g. of the hexahydropyridazine (XXI) hydrochloride, 0.7 ml. of 37% formaldehyde, 0.2 ml. of 36% hydrochloric acid and 10 ml. of ethanol was heated on a water-bath for 3 hours, and the ethanol was then distilled off. Work-up as above left 580 mg. of a reddish brown oil which was chromatographed on 20 g. of silica gel with *n*-hexane and *n*-hexane-ether. The *n*-hexane-ether (1:1) eluate gave a pale yellow solid which was recrystallized from ether to give 215 mg. (39%) of colorless prisms, m.p. 84-85°, nmr (δ in deuteriochloroform): 1.32 (3H, d, $J = 7.0$ Hz, $>\text{CH}-\text{CH}_3$), 1.45-2.95 (6H, m, $\text{Ar}-\text{CH}_2-\text{N}$), 2.55 (3H, s, $\text{N}-\text{CH}_3$), 3.56 and 4.13 (each 1H, d, $J = 13.5$ Hz, $\text{Ar}-\text{CH}_2-\text{N}$), 3.72 (3H, s, $\text{O}-\text{CH}_3$), 6.5-7.15 (3H, m, $\text{Ar}-\text{H}$), mass (m/e): 247 ($\text{M}^+ + 1$, 9), 246 (M^+ , 42), 231 (13), 174 (5), 160 (15), 149 (17), 148 (base peak, 100), 147 (27), 133 (8), 131 (5), 117 (10), 115 (8), 111 (6), 105 (6).

Anal. Calcd. for $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}$: C, 73.13; H, 9.00; N, 11.37. Found: C, 72.69; H, 8.88; N, 11.14.

1,2,3,4,5,6-Hexahydro-8-hydroxy-2,6-methano-3,6,11-trimethyl-2,3-benzo[*g*]diazocine (IV).

A mixture of 60 mg. of the 8-methoxy-2,3-benzo[*g*]diazocine (XXII), 1.5 ml. of 47% hydrobromic acid and 1.5 ml. of acetic acid was heated at 135-138° in an oil-bath for 1 hour and then evaporated to dryness *in vacuo*. The aqueous extract of the residue was washed with ether, basified with 28% ammonium hydroxide

and extracted with chloroform. The chloroform extract was dried over sodium sulfate and distilled to give 43 mg. of a viscous oil which was chromatographed on 5 g. of silica gel with chloroform and chloroform-methanol (100:1 and 100:2) as eluants. Evaporation of the chloroform-methanol eluants gave 28 mg. (57%) of a colorless solid, whose recrystallization from ethanol afforded colorless crystals, m.p. 238-240° dec.; nmr [δ in deuteriochloroform-trifluoroacetic acid (1:1)]: 1.34 (3H, d, $J = 7.0$ Hz, $>\text{CH}-\text{CH}_3$), 1.50 (3H, s, $\geq\text{C}-\text{CH}_3$), 3.13 (3H, s, $\text{N}-\text{CH}_3$), 3.93 (1H, q, $J = 7.0$ Hz, $\text{CH}-\text{CH}_3$), 4.69 (2H, s, $\text{Ar}-\text{CH}_2-\text{N}$), 6.95-7.35 (3H, m, $\text{Ar}-\text{H}$), mass (m/e): 233 ($\text{M}^+ + 1$, 10), 232 (M^+ , 86), 218 (17), 217 (base peak, 100), 198 (6), 176 (5), 175 (20), 174 (28), 162 (9), 161 (10), 160 (5), 148 (9), 147 (15), 146 (8), 145 (9), 144 (5), 135 (5), 132 (3), 131 (14), 127 (5), 115 (7), 107 (5), 91 (7), 86 (5), 85 (80).

Anal. Calcd. for $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}$: C, 72.38; H, 8.68; N, 12.06. Found: C, 71.91; H, 8.68; N, 11.72.

1,2,3,4,5,10,11,12-Octahydro-7-hydroxy-1,5-dimethylpyridazino[2,3-*b*]isoquinoline (VI).

A mixture of 120 mg. of XXIII, 1.2 ml. of 47% hydrobromic acid and 1.2 ml. of acetic acid was refluxed for 1 hour in an oil-bath and worked up as above. Column chromatography of the product using silica gel and chloroform-methanol (100:1) as eluant afforded 42 mg. (43%) of a pale yellow solid which was recrystallized from ether to give colorless prisms, m.p. 176-178°, nmr [δ in deuteriochloroform-trifluoroacetic acid (1:1)]: 1.38 (3H, d, $J = 7.5$ Hz, $\text{CH}-\text{CH}_3$), 2.91 (3H, s, $\text{N}-\text{CH}_3$), 3.95 and 4.28 (each 1H, d, $J = 13.8$ Hz, $\text{Ar}-\text{CH}_2-\text{N}$), 6.5-7.05 (3H, m, $\text{Ar}-\text{H}$), mass (m/e): 233 ($\text{M}^+ + 1$, 5), 232 (M^+ , 30), 160 (8), 146 (7), 135 (13), 134 (base peak, 100), 133 (37), 132 (7), 117 (8), 115 (8), 111 (6), 107 (6), 105 (10), 103 (5).

Anal. Calcd. for $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.55; H, 8.82; N, 11.95.

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(12) Other bases, e.g. sodium alkoxide, sodium hydride, or sodium dimethylsulfynylcarbanion, resulted in little or no product.

(13) XVIII on potassium bromide; XIX as liquid film.

(14) On exposing the free base of XX in the air, the dihydrobase (XXIV) appeared to have been found; nmr (δ in deuterio-

chloroform): 1.54 (3H, s, >C-CH_3), 1.71 (3H, s, N=C-CH₃), 2.58 (3H, s, N-CH₃), 3.79 (3H, s, O-CH₃), 6.55-7.52 (4H, m, Ar-H).

(15) The free base of XXI was oxidized to presumed compound (XXV) in the air; nmr (δ in deuteriochloroform) 1.31 (3H, d, J = 8.0 Hz, >CH-CH_3), 1.75-1.95 (4H, m, N=C-CH₂CH₂-), 2.45-2.76 (2H, m, CH₃N-CH₂), 2.80 (3H, s, N-CH₃), 3.51 (1H, q, J = 8.0 Hz, >CH-CH_3), 3.82 (3H, s, O-CH₃), 6.6-7.3 (4H, m, Ar-H).

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