10% sodium carbonate solution and was extracted with chloroform. The chloroform layer was washed with water, dried over sodium sulfate, and the solvent was removed. The residue was mixed with 7.5 g of 5% palladium on carbon in a test tube, placed in a bath at 250°, and the temperature was raised to 285° over a 10-min interval. The reaction mixture was treated with chloroform, filtered, and the solvent was removed. There remained 4.0 g (83%) of a solid. Recrystallization from ethanol gave an analytical sample, mp 113–114°.

Anal. Calcd for $C_{14}H_{13}N$: C, 86.12; H, 6.71; N, 7.17. Found: C, 86.11; H, 8.86; N, 6.94.

The samples from A and B were shown to be identical by the methods of mixture melting point and infrared analysis.

Registry No.—**4**, 7551-08-8; **5**, 14128-30-4; **6**, 14128-31-5; **7**, 7546-56-7; **8**, 7551-09-9; **9**, 7546-57-8; **10**, 14171-84-7; **11**, 14128-34-8; **12**, 14171-85-8.

1-Acylindoles. III. A Novel Synthesis of 9-Acyltetrahydrocarbazole and 5-Acyl-γ-carboline Derivatives

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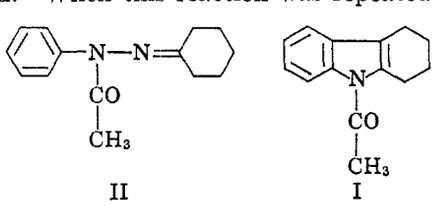
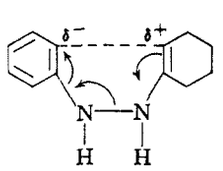
Perkin and Plant[1] claimed to have prepared 9-acetyl-1,2,3,4-tetrahydrocarbazole (I) by boiling cyclohexanone N^1-acetylphenylhydrazone (II) in dilute sulfuric acid. When this reaction was repeated by Suvorov and Sorokina,[2] the deacylated 1,2,3,4-tetrahydrocarbazole (III), mp 117–119°, but not the 9-acetyl compound I, was found to be the product. Suvorov and Sorokina stated that acylation of the N^1 atom of the hydrazone derivative should stabilize the p-electron pair of that nitrogen atom and thus retard formation of a new C–C bond. This would make Fischer carbazole formation difficult. Therefore they concluded that hydrolysis of the acetyl group precedes Fischer cyclization.



II I

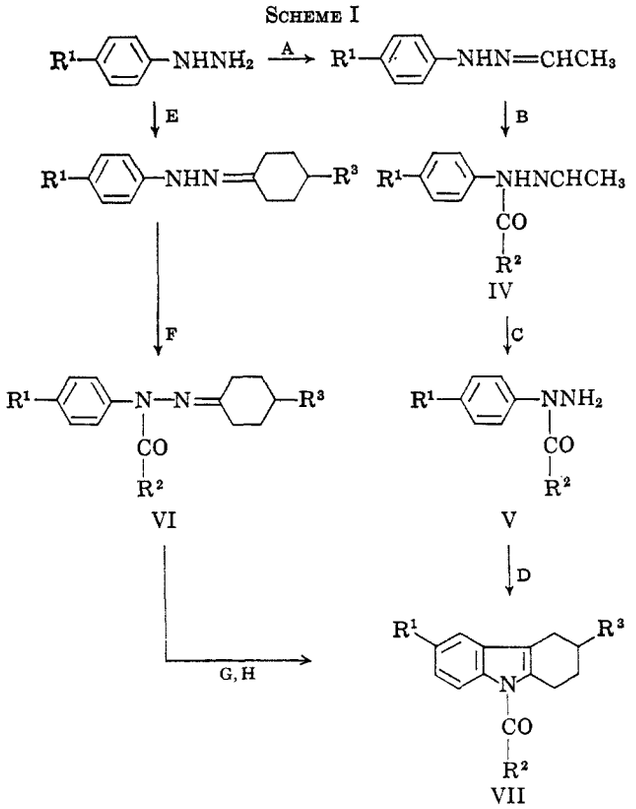


This work was then repeated by the present author, who obtained both the 9-acetyl derivative (I), mp 77–78°, and the deacylated material, mp 115–118°, as products.

In a previous publication,[3] the author has shown that deacylation of the N^1 atom of hydrazones is not necessary for Fischer indole cyclization and therefore participation by the p-electron pair of that atom in the formation of the new C–C bond is not important. This same conclusion may be applied in the case of tetrahydrocarbazole formation. Thus the deacylation observed during tetrahydrocarbazole formation from hydrazones may not be a step which necessarily precedes cyclization as postulated by Suvorov and Sorokina.

When the aqueous sulfuric acid reaction medium was replaced with glacial acetic acid and gaseous hydrogen chloride in the cyclization of cyclohexanone-N^1-benzoylphenylhydrazone, a good yield of 9-benzoyl-1,2,3,4-tetrahydrocarbazole was obtained, but no deacylated product was observed (Scheme I, step G).

SCHEME I



We have also found that 9-acyl-1,2,3,4-tetrahydrocarbazoles (VII) may be produced directly from the interaction of N^1-acylarylhydrazine hydrochlorides (V) with cyclohexanone and substituted cyclohexanones (step D).

This method for the synthesis of 9-acyl-1,2 3,4-tetrahydrocarbazoles is smooth and rapid, resulting in a high and in some cases quantitative yield of product. These results support the view that participation by the p-electron pair of the acylated nitrogen atom of the hydrazone is negligible in Fischer carbazole formation.

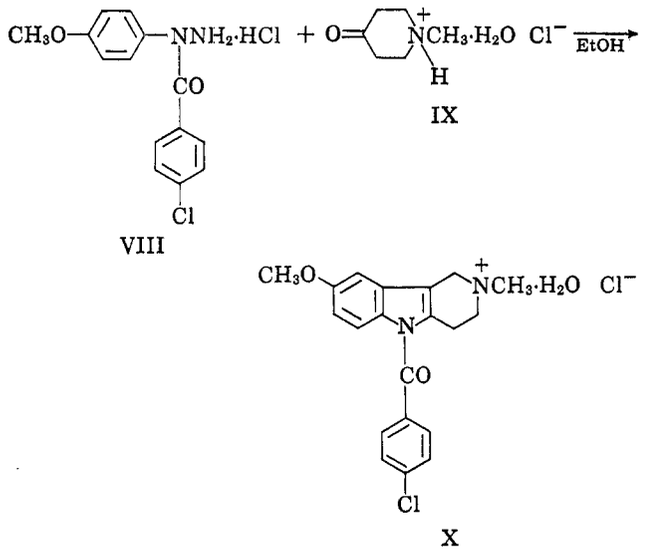
The intermediate N^1-acylarylhydrazine hydrochlorides (V) may be produced quantitatively from acetaldehyde N^1-acylarylhydrazones (IV) by cleavage with hydrogen chloride in absolute ethanol or in a mixture of ethanol and a second inert organic solvent.

In addition to the preparation of several 9-acyl-1,2,3,4-tetrahydrocarbazole derivatives by this new method, 5-*p*-chlorobenzoyl-2-methyl-8-methoxy-γ-car-

(1) W. H. Perkin and S. G. P. Plant, *J. Chem. Soc.*, 119, 1825 (1921).
(2) N. N. Suvorov and N. P. Sorokina, *Dokl. Akad. Nauk SSSR*, **136**, 840 (1961).
(3) H. Yamamoto, *Bull. Chem. Soc. Japan*, **40**, 425 (1967).

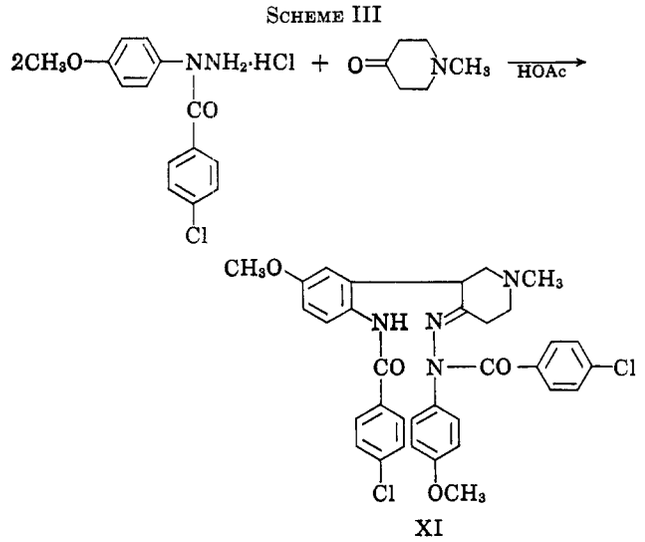
boline hydrochloride monohydrate (X) was produced in 52% yield by the interaction of N¹-(*p*-chlorobenzoyl)-*p*-methoxyphenylhydrazone hydrochloride (VIII) with N-methyl-γ-piperidone hydrochloride monohydrate (IX) (Scheme II).

SCHEME II



When N¹-(*p*-chlorobenzoyl)-*p*-methoxyphenylhydrazine was stirred with N-methyl-γ-piperidone in acetic acid at 70–75° for 5 hr, compound XI was obtained in about 8% yield. The structure of compound XI was determined by nmr spectra and elemental analysis (Scheme III).

SCHEME III



Experimental Section

Melting points are uncorrected. Infrared absorption spectra were recorded on a Simazu IR-27G spectrophotometry and nmr spectra were taken on a Varian A-60 spectrophotometer.

Acetaldehyde *p*-Methoxyphenylhydrazone. Method A_1.—A mixture of 138 g of *p*-methoxyphenylhydrazine and 290 ml of toluene was stirred and cooled in an ice bath and to it was added 48.4 g of acetaldehyde in 90 ml of toluene dropwise over 30 min under nitrogen gas. Stirring was continued for an additional 30 min at room temperature. A precipitate was removed by filtration and the filtrate was concentrated under reduced pressure (30 mm) to an oily residue, which was distilled *in vacuo* to give acetaldehyde *p*-methoxyphenylhydrazone in quantitative yield, bp 119–125° (0.2 mm).

Acetaldehyde Phenylhydrazone. Method A_2.—To a stirred mixture of 263 g of phenylhydrazine and 500 ml of toluene maintained at 5–10° was added 161 g of 80% acetaldehyde dropwise over 1 hr under nitrogen gas. The resultant crystals were removed from the reaction mixture by filtration and washed with water several times and finally with a small quantity of petroleum ether. The crystals were dried to give 120 g of needles of acetaldehyde phenylhydrazone. The total yield was 316 g (96.6%), mp 68–70°.

Acetaldehyde N¹-(*p*-Chlorobenzoyl)-*p*-methoxyphenylhydrazone (1). Method B_1.—A mixture of 89.8 g of acetaldehyde *p*-methoxyphenylhydrazone and 360 ml of pyridine was stirred and maintained at a temperature of 0–5° while 115 g of *p*-chlorobenzoyl chloride was added dropwise over 1.5 hr. The reaction mixture was stirred for an additional 4 hr in an ice bath and then it was poured into 1800 ml of cold water which resulted in the precipitate of a crystalline material. This solid was isolated by filtration, washed with 360 ml of cold water, and dried under reduced pressure at 50° to give 166 g (100%) of light yellowish brown prisms of acetaldehyde N¹-(*p*-chlorobenzoyl)-methoxyphenylhydrazone (1): mp 96–100°; ν_{max} 1663 cm^{-1} (NCO).

Acetaldehyde N¹-Benzoylphenylhydrazone (2). Method B_2.—A mixture of 40.2 g of acetaldehyde phenylhydrazone, 24 g of pyridine, and 300 ml of ether was stirred and maintained at −8–8° and to it was added dropwise 42.1 g of benzoyl chloride over 25 min. After stirring for an additional 4 hr at room temperature, a crystalline material was removed from the mixture by filtration, washed with water, and dried under reduced pressure to give 30.8 g of acetaldehyde N¹-benzoylphenylhydrazone (2), mp 88–90°. Removal of ether from the filtrate by evaporation caused the precipitation of more crystalline solid which was isolated by filtration and washed with a small quantity of ether to give an additional 8.2 g of acetaldehyde N¹-phenylhydrazone. The total yield was 47.1 g (66%): ν_{max} 1670 cm^{-1} (NCO).

Acetaldehyde N¹-Acetylphenylhydrazone (3).—By method B_2 white needles of acetaldehyde N¹-acetylphenylhydrazone (3) were obtained from 40.2 g of acetaldehyde phenylhydrazone and 24 g of acetyl chloride. The yield was 35.8 g (67.8%): mp 101–105°; ν_{max} 1670 cm^{-1} (NCO).

N¹-(*p*-Chlorobenzoyl)-*p*-methoxyphenylhydrazine Hydrochloride (4). Method C_1.—Acetaldehyde N¹-(*p*-chlorobenzoyl)-*p*-methoxyphenylhydrazone (1) (165 g) was mostly dissolved in a solvent mixture of 115 ml of methanol and 2220 ml of toluene, in which 105 g of gaseous hydrogen chloride was absorbed over 1 hr at ice–salt temperatures. Excess hydrogen chloride was then removed under reduced pressure (about 30 mm) over 1 hr. A crystalline precipitate was isolated by filtration and washed with 530 ml of toluene to give 240 g (82%) of N¹-(*p*-chlorobenzoyl)-*p*-methoxyphenylhydrazine hydrochloride in the form of white needles: mp 169–172° dec; ν_{max} 1670 cm^{-1} (NCO).

N¹-Benzoylphenylhydrazine Hydrochloride (5). Method C_2.—A mixture of 47 g of acetaldehyde N¹-benzoylphenylhydrazone (2), 50 ml of ethanol, and 50 ml of ether was cooled in an ice bath and nearly saturated with gaseous hydrogen chloride. The addition of 150 ml of ether caused the precipitation of crystalline solid which was filtered, washed with ether, and dried under reduced pressure to give 44.4 g (90%) of white crystalline N¹-benzoylphenylhydrazine hydrochloride (5): mp 186–189° dec; ν_{max} 1680 cm^{-1} (NCO).

N¹-Acetyl Phenylhydrazine Hydrochloride (6).—By method C_2 28 g of (74%) of N¹-acetylphenylhydrazine hydrochloride (6) was obtained from 35.8 g of acetaldehyde N¹-acetylphenylhydrazine (3): mp 177.5–178.5° dec; ν_{max} 1690 cm^{-1} (NCO).

Cyclohexanone Phenylhydrazone. Method E.—To 10.8 g of phenylhydrazine, 9.8 g of cyclohexanone was added with stirring. The exothermic reaction deposited white crystals within a few minutes. The reaction mixture was allowed to stand at room temperature overnight and 30 ml of 50% ethanol was added to it. The resultant precipitate was collected by filtration and dried under reduced pressure to give 17.1 g (91%) of white cyclohexanone phenylhydrazone.

Cyclohexanone N¹-Acetylphenylhydrazone (7). Method F_1.—To 17.0 g of cyclohexanone phenylhydrazone, 17 ml of acetic anhydride was added and the mixture was heated at 95° for 2 hr on a water bath. The reaction mixture was allowed to stand at room temperature overnight and was then concentrated under reduced pressure to an oily residue, which was distilled *in vacuo* to give 9.6 g (46%) of yellow oily cyclohexanone N¹-acetylphenylhydrazone (7), bp 130–134 (0.3–0.35 mm). Its nmr spectrum

showed this material to be a monoacetyl-substituted derivative, ν_{max} 1665 cm^{-1} (NCO).

Cyclohexanone N^1-Benzoylphenylhydrazone (8). Method F$_2$.—A mixture of 37.6 g of cyclohexanone phenylhydrazone, 15.8 g of pyridine, and 200 ml of ether was stirred and maintained at −9 to −5° and to it was added 28.1 g of benzoylchloride dropwise over 25 min. Stirring was continued for an additional 5 hr and the reaction mixture allowed to stand overnight. Solvent was removed by evaporation and a crude solid material was isolated by filtration, washed with a small quantity of ether, and dried under reduced pressure to give 29.7 g (51%) of white crystalline cyclohexanone N^1-benzoylphenylhydrazone (8). Recrystallization from ethyl acetate gave 17.4 g of white prisms: mp 120–121°; ν_{max} 1650 cm^{-1} (NCO).

9-(*p*-Chlorobenzoyl)-6-methoxy-1,2,3,4-tetrahydrocarbazole (9). Method D$_1$.—To 7.5 g of N^1-(*p*-chlorobenzoyl)-*p*-methoxyphenylhydrazine (4), 15 ml of cyclohexanone was slowly added. After completion of an immediate exothermic reaction, the mixture was heated at 90° with stirring for an additional filtration and washed with a small quantity of ethanol. The filtrate was added to 80 ml of 40% acetic acid and allowed to stand overnight to give copious amounts of crystals, which were filtered, washed with 20 ml of water, and dried under reduced pressure to give 8.0 g of crude light yellow crystalline 9-(*p*-chlorobenzoyl)-6-methoxy-1,2,3,4-tetrahydrocarbazole (9). Recrystallization from aqueous ethanol gave 7.0 g (89%) of light yellow prisms: mp 104–105°; ν_{max} 1674 cm^{-1} (NCO).

Anal. Calcd for $C_{20}H_{18}NO_2Cl$: C, 70.69; H, 5.34; N, 4.12; Cl, 10.43. Found: C, 70.98; H, 5.42; N, 4.01; Cl, 10.21.

9-(*p*-Chlorobenzoyl)-3-methyl-6-methoxy-1,2,3,4-tetrahydrocarbazole (10). Method D$_2$.—*p*-Methylcyclohexanone (10 ml) was added to 7.0 g of N^1-(*p*-chlorobenzoyl)-*p*-methoxyphenylhydrazine hydrochloride (4) in 26 ml of cyclohexane and the mixture was heated at 80° for 15 min with stirring. The resultant crystals were removed by filtration and washed with a small quantity of ethanol. The filtrates were combined and added to 120 ml of 50% acetic acid which caused the precipitation of additional crystalline material. This material was isolated by filtration after cooling at 0° for 2 hr. It was then washed with cold water to produce 7.7 g of light yellow crystalline 9-(*p*-chlorobenzoyl)-3-methyl-6-methoxy-1,2,3,4-tetrahydrocarbazole (10). Recrystallization from ethanol gave 6.9 g (90%) of light yellow prisms: mp 142–143°; ν_{max} 1682 cm^{-1} (NCO).

Anal. Calcd for $C_{21}H_{20}NO_2Cl$: C, 71.28; H, 5.70; N, 10.02; Cl, 3.96. Found: C, 71.46; H, 5.34; N, 9.89; Cl, 3.92.

9-Acetyl-1,2,3,4-tetrahydrocarbazole (11). Method D$_3$.—To a solution mixture of 10 g of cyclohexanone and 30 ml of acetic acid was added 19 g of N^1-acetylphenylhydrazone hydrochloride (6) and the mixture was heated at 70–80° for 5 hr with stirring. The reaction mixture became red-violet in color and an insoluble material precipitated. After cooling, an insoluble material was removed by filtration. The filtrate was evaporated under reduced pressure to give a reddish violet oily residue, which was chromatographed on alumina (Wako, 150 g). An equimolar mixture of petroleum ether (bp 30–70°) and ether eluted 6.9 g (32%) of crystalline 9-acetyl-1,2,3,4-tetrahydrocarbazole (11). Recrystallization from ethanol gave white needles: mp 77–78°; ν_{max} 1690 cm^{-1} (NCO).

Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.59; H, 7.17; N, 7.15.

Method H.—A mixture of 4.8 g of cyclohexanone N^1-acetylphenylhydrazone and 5 ml of 20% aqueous sulfuric acid was refluxed for 8 min. Thin layer chromatography (silica gel,[4] benzene) showed that both 1,2,3,4-tetrahydrocarbazole (R_f 0.66) and 9-acetyl-1,2,3,4-tetrahydrocarbazole (R_f 0.33) were obtained in this reaction. After cooling, the mixture was extracted with chloroform. The chloroform extract was dried over sodium sulfate. After removal of sodium sulfate by filtration, the solvent was removed by distillation to give an oily substance. Recrystallization from 75% ethanol gave both 9-acetyl-1,2,3,4-tetrahydrocarbazole (11) as white needles, mp 77–78°, and light brown prisms of 1,2,3,4-tetrahydrocarbazole, mp 115–118°.

9-Benzoyl-1,2,3,4-tetrahydrocarbazole (12). Method D$_4$.—To a mixture of 3.0 g of cyclohexanone, 25 ml of cyclohexane, and 20 ml of acetic acid was added 7.5 g of N^1-Benzoylphenylhydrazine hydrochloride (5). After completion of addition, the mixture was heated at 80° for 2 hr. After cooling, an insoluble material was removed by filtration. The filtrate was concentrated under reduced pressure to give 9.9 g of a brown liquid to which was added a small quantity of ethanol. It was then allowed to stand in a refrigerator overnight to produce crystals which were isolated by filtration, washed with water, and dried under reduced pressure to give 6.9 g (83.6%) of crystalline 9-benzoyl-1,2,3,4-tetrahydrocarbazole (12) as white prisms from ethanol: ν_{max} 1680 cm^{-1} (NCO).

Anal. Calcd for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 83.03; H, 6.36; N, 5.21.

Method G.—Cyclohexanone N^1-benzoylphenylhydrazone (8) (2.9 g) was added to 11 ml of acetic acid which contained 0.365 g of gaseous hydrogen chloride and the mixture was stirred at 70–75° for 2 hr. After cooling, an insoluble material was removed by filtration. The filtrate was concentrated under reduced pressure to an oily substance, to which was added a small quantity of ethanol. It was then allowed to stand in a refrigerator overnight to give a white crystalline material which was isolated by filtration and dried to give 2.2 g (80%) of white crystalline 9-benzyl-1,2,3,4-tetrahydrocarbazole (12): mp 82–84°, undepressed when admixed with an authentic sample of 12. Identical infrared adsorption spectra were obtained from this material and from authentic 12.

5-(*p*-Chlorobenzoyl)-2-methyl-8-methoxy-γ-carboline Hydrochloride Monohydrate.—A mixture of 25 ml of ethanol, 6.3 g of N^1-(*p*-chlorobenzoyl)-*p*-methoxyphenylhydrazine hydrochloride, and 3.4 g of N-methyl-γ-piperidone hydrochloride monohydrate was stirred at 70–75° for 1 hr under nitrogen gas. A crystalline precipitate was removed by filtration, washed with water several times, then with ethanol, and dried to yield 4.5 g (52.2%) of white crystalline 5-(*p*-chlorobenzoyl)-2-methyl-8-methoxy-γ-carboline hydrochloride monohydrate, mp 207–210°. Recrystallization from aqueous ethanol gave white fine needles: mp 223–225°; ν_{max} 1680 cm^{-1} (NCO).

Anal. Calcd for $C_{20}H_{22}N_2O_3Cl_2$: C, 58.68; H, 5.38; N, 6.85. Found: C, 58.31; H, 5.05; N, 6.22.

N-Methyl-3-[2′-(*p*-chlorobenzoylamido)-5′-methoxyphenyl]-γ-piperidone N^1-(*p*-Chlorobenzoyl)-*p*-methoxyphenylhydrazone.—A mixture of 20 ml of acetic acid, 7.4 g of N^1-(*p*-chlorobenzoyl)-*p*-methoxyphenylhydrazine hydrochloride, and 2.7 g of N-methyl-γ-piperidone was heated with stirring at 70–75° for 5 hr. Then deposition of ammonium chloride crystals was observed. The reaction mixture was concentrated under reduced pressure and a small quantity of water was added to it. It was then extracted with chloroform and the chloroform extract was dried over anhydrous sodium sulfate. After removal of sodium sulfate by filtration, the chloroform was removed by evaporation to give 8.4 g of a reddish brown resinous substance, which was chromatographed on alumina (Wako, 150 g) (an eluent is a mixture of ether and petroleum ether) to give 1.2 g (8.0%) of N-Methyl-3-[2′-(*p*-chlorobenzoylamido)-5′-methoxyphenyl]-γ-piperidone N^1-(*p*-chlorobenzoyl)-*p*-methoxyphenylhydrazone: mp 171–172° from ethyl acetate; ν_{max} 3290 (NH), 1669 (NCO), 1648 cm^{-1} (NCO); nmr spectrum, τ 7.63 (singlet, 3 H, methyl of N-methyl), 6.27 (singlet, 3 H, methyl of O-methyl), 6.19 (singlet, 3 H, methyl of O-methyl), 5.95–7.5 (multiplet, 7 H, methylene chain of piperidone ring), 2.10–3.22 (multiplet, 15 H, ring protones of four benzene rings), and 0.53 (singlet, 1 H, NH).

Anal. Calcd for $C_{34}H_{32}N_4O_4Cl_2$: C, 64.66; H, 5.07; N, 8.87. Found: C, 64.66; H, 5.12; N, 8.65.

Registry No.—**1,** 13815-59-3; **2,** 13815-60-6; **3,** 13815-61-7; **4,** 13815-62-8; **5,** 13815-63-9; **6,** 13815-64-0; **7,** 13815-65-1; **8,** 13815-66-2; **9,** 13815-67-3; **10,** 13815-68-4; **11,** 13815-69-5; **12,** 13815-70-8; acetaldehyde *p*-methoxyphenylhydrazone, 13815-71-9; acetaldehyde phenylhydrazone, 935-07-9; 5-(*p*-chlorobenzoyl)-2-methyl-8-methoxy-γ-carboline HCl, 13815-72-0; N-methyl-3-[2′-(*p*-chlorobenzoylamido)-5′-methoxyphenyl]-γ-piperidone N′-(*p*-chlorobenzoyl)-*p*-methoxyphenylhydrazone, 13815-73-1.

Acknowledgment.—The author wishes to thank heartily Drs. Gary Singerman and Takenari Nakagome for very helpful advice and valuable suggestions; he deeply appreciates the technical assistance given by Mr. T. Atsumi during the course of this work.

(4) Silica gel G, Merck.