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Tetrahydronaphthylamines and Related Compounds. III.[1] Synthesis of 1,2,3,4-Tetrahydro-2-naphthylamine and 6-Amino-5,6,7,8-tetrahydroquinoline Derivatives

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Amino substituted 1,2,3,4-tetrahydronaphthalene and 5,6,7,8-tetrahydroquinoline derivatives (1,2,3,4-tetrahydro-6-methoxy-N-methyl-2-phenyl-2-naphthylamine, 1,2,3,4-tetrahydro-6-methoxy-N,N-dimethyl-2-phenyl-2-naphthylamine, 5,6,7,8-tetrahydro-6-(methylamino)-6-phenylquinoline and 5,6,7,8-tetrahydro-6-(dimethylamino)-6-phenylquinoline) were synthesized. Thus, Michael adducts of methyl vinyl ketone and acrylonitrile to methyl 5-cyano-2-oxo-5-phenylcyclohexanecarboxylate (I) were used for formation of skeleton of naphthalene and quinoline, respectively. Quinoline derivative was also obtained by condensation of cyclohexanone derivative with 3-aminoacrolein. Amino function was derived from nitrile *via* Hofmann reaction of amide. Furthermore, an interesting tricyclic compound, 3,8a-ethano-3,4,4a,8a,5,6-hexahydro-3-phenyl-2,7(1H,8H)-quinolinedione, was obtained on cyclization reaction of a Michael adduct (IIa).

In connection with our studies on structure-activity relationship of analgetics, we have been interested in analgetic effect of 1,2,3,4-tetrahydronaphthylamine derivatives which constitute one of the most simple moiety of morphine. This paper describes synthesis of 1,2,3,4-tetrahydro-6-methoxy-2-phenyl-2-naphthylamines and an interesting observation on cyclization reaction of 4-cyano-2-(3-oxobutyl)-4-phenylcyclohexanone derivative which was an intermediate compound in this synthesis. Furthermore, synthesis of 6-amino-5,6,7,8-tetrahydro-6-phenylquinolines is also described.

Methyl 5-cyano-2-oxo-5-phenylcyclohexanecarboxylate (I) was prepared by condensation of phenylacetonitrile with methyl acrylate and the subsequent Dieckmann condensation of the resulting diester according to the procedure of Uyeo, *et al.*[3] Treatment of I with methyl vinyl ketone in the presence of sodium methoxide gave two Michael adducts; IIa, mp 125—127° and IIb, mp 86—88° in 30% and 25% yield respectively. On nuclear magnetic resonance (NMR) spectra of IIa and IIb, methoxyl protons exhibited at 3.9 and 3.6 ppm, respectively. Furthermore, signals of methylene region were observed at 1.7—3.5 ppm (IIa) and 2.25—3.3 ppm (IIb). Assuming deshielding effect of cyano function, it was deduced from the above result that methoxycarbonyl and cyano groups of IIa are *cis* and those of IIb are *trans*. The examination of molecular models suggested that, on intramolecular aldol condensation of the above Michael adducts, IIa would be more favorable than IIb. Actually, treatment of IIa with a mixture of acetic acid and sulfuric acid gave the enone (III) in 60% yield, whereas IIb gave an unidentified mixture in the same condition. On the other hand, on a base-catalyzed cyclization with 5% potassium hydroxide IIa gave an unexpected tricyclic compound (XIII) as described later. *cis* relationship between methoxycarbonyl and cyano groups of IIa and III was confirmed by the following result. Catalytic hydrogenation of III afforded

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1) Part II: K. Nomura, J. Adachi, M. Hanai, and K. Mitsuhashi, *Chem. Pharm. Bull.* (Tokyo), **21**, 439 (1973).
2) Location: *Gofuku, Toyama*; *a*) Present address: *Faculty of Pharmaceutical Sciences, Josai University, Sakado-cho, Saitama.*
3) N. Hazama, H. Irie, T. Mizutani, T. Shingu, M. Takada, S. Uyeo, and A. Yoshitake, *J. Chem. Soc.*, (*C*), **1968**, 2947.

the ketone (IV), which was followed by acid-catalyzed hydrolysis and the subsequent dehydration of the resulting dicarboxylic acid with acetic anhydride to yield the corresponding acid anhydride (V). The enone (III) was then dehydrogenated with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to afford the cross-conjugated dienone (VI). Saponification of VI gave the phenolic compound (VII), which was methylated with diazomethane to yield the methoxyl derivative (VIII). Treatment of VIII with sodium hydroxide and 30% hydrogen peroxide gave the amide (IX) in 78% yield. Although usual Hofmann reaction[4] of IX gave unidentified resinous material, a modified method according to Jeffreys[5] was successful. Thus, treatment of IX with bromine in methanol containing sodium methoxide afforded the urethane (X) in 80% yield. Lithium aluminum hydride reduction of X gave the desired methylamino derivative (XI), and of which Clarke–Eschweiler methylation gave the dimethylamino compound (XII).

As mentioned earlier, one of the Michael adduct (IIa) cyclyzed to form a new product (XIII) on treatment with 5% potassium hydroxide. The structure of XIII was deduced by the following results. Infrared (IR) and NMR spectra of it showed the absence of nitrile, olefin and ester groups, and the presence of amide and ketone. Analytical data of XIII agreed with an empirical formula $C_{17}H_{19}O_2N$. Furthermore, XIII could be introduced into the lactone (XIV) by treatment with hydrochloric acid. A probable course of the formation of XIII is illustrated in Chart 1. After intramolecular aldol condensation to the enone (XV), the nitrile function of XV would be attacked nucleophilically by hydroxide anion. An intramolecular Michael-like condensation between the resulting imino anion and α,β-unsaturated ketone group could give the lactam derivative (XIII). This consideration was supported

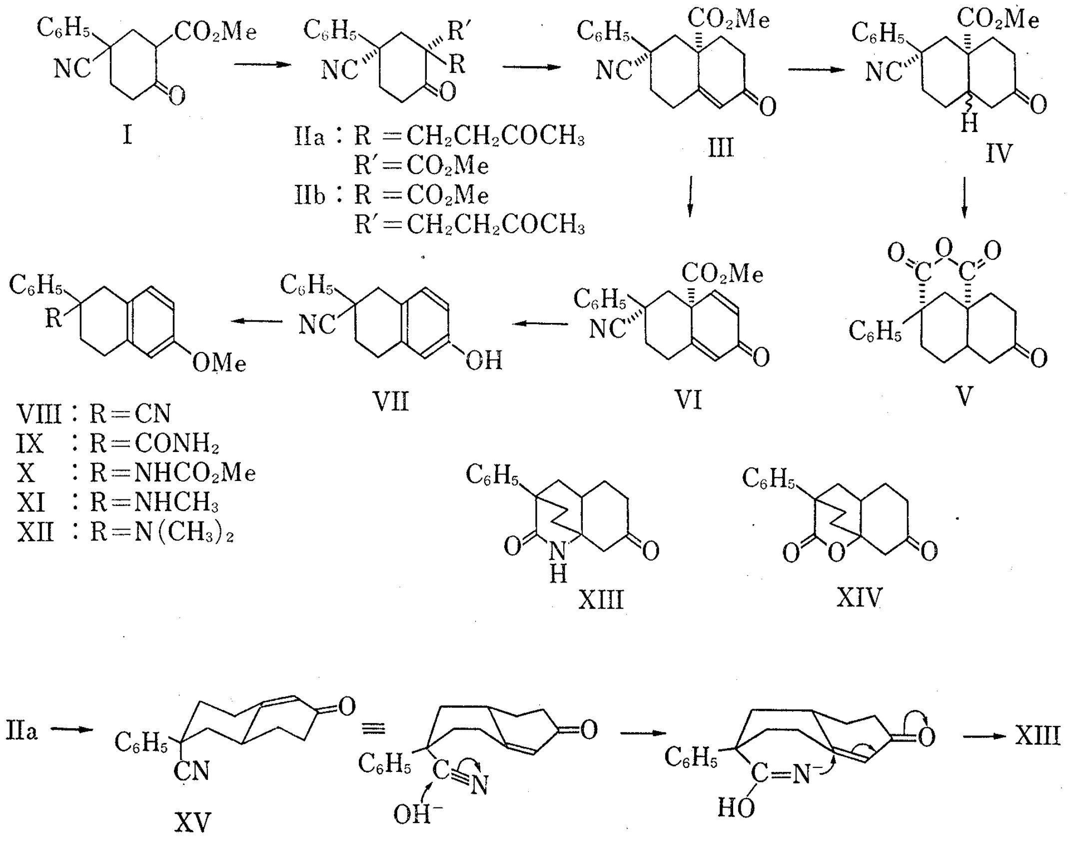

Chart 1

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4) E.S. Wallis and J.F. Lane, "Organic Reactions," Vol. 3, John Wiley & Sons, Inc., New York, N.Y., 1946, p. 267.

5) E. Jeffreys, *Ber.*, **30**, 898 (1897).

from the result that XIII was also obtained from III by heating with dilute alkali. The other Michael adduct (IIb), as was expected, gave trace of XIII under a similar condition. It was considered that in the case of IIb β-keto ester would probably be cleaved in such a drastic condition. However, under a mild condition, *i.e.*, refluxing in 1% methanolic potassium hydroxide, IIb cyclized to give the enone (XV) in 71% yield. The first stage of this reaction would be saponification of ester. This product (XV) could be also introduced to XIII in the same manner as above.

On the other hand, the β-keto ester (I) was treated with acrylonitrile in the presence of a base to give the cyanoethyl compound (XVI) in 78% yield. Although it was considered that diastereomers would be obtained in this reaction as in the case of IIa and IIb, thin layer chromatography of XVI gave only one spot and NMR spectrum showed that XVI was a sole compound. In the next step, cyclization reaction of XVI with hydrogen chloride6) proceeded smoothly to give the lactam (XVII) in quantitative yield. NMR spectrum of XVII showed a signal due to olefinic proton at 5.15 ppm as triplet ($J=4$ Hz). Saponification of XVII with methanolic potassium hydroxide yielded XVIII accompanying migration of the double bond. This compound (XVIII) was then introduced to 5,6,7,8-tetrahydroquinoline derivative (XXI) by dehydrogenation with DDQ, chlorination of the resulting quinolone (XIX), and the subsequent catalytic hydrogenation. The over-all yield of XXI from I was about 14%. This tetrahydroquinoline (XXI) could be also obtained in another short step; condensation of 4-cyano-4-phenylcyclohexanone prepared by ketonic hydrolysis of I with 3-aminoacrolein in triethylamine7) (about 25% yield from I). Convert of the nitrile function of XXI to amino function was performed in the same manner as in the case of the above tetrahydronaphthonitrile (VIII). The nitrile (XXI) was submitted to hydrolysis with sodium hydroxide and hydrogenperoxide to give the amide (XXII) in 77% yield. The compound (XXII) was then treated with bromine and sodium methoxide in methanol to give the urethane (XXIII). Reduction of XXIII with lithium aluminum hydride afforded the methylamino derivative (XXIV) in 79% yield. Furthermore, the dimethylamino derivative (XXV) was prepared by Clarke–Eschweiler methylation of XXIV.

The pharmacological testing of the above amines is now under progress, and will be presented elsewhere.

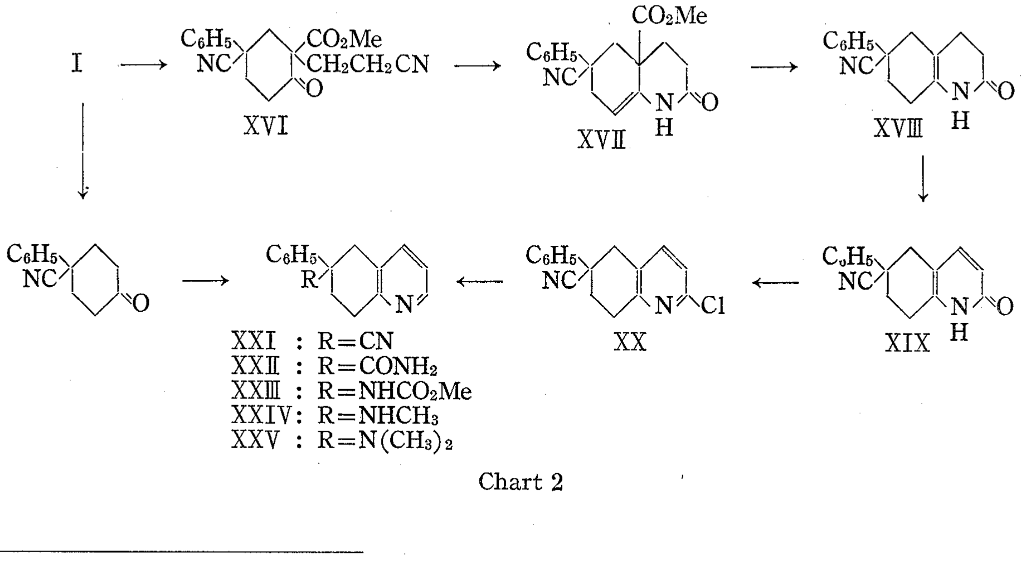

Chart 2

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6) W.E. Hahn and J. Epsztajn, [*Roczniki Chem.*,] **37**, 109 (1963) [*C.A.*, **59**, 6364 (1963)]; K. Wiesner, V. Musil, and K.J. Wiesner, *Tetrahedron Letters*, **1968**, 5643.

7) E. Breitmaier and E. Bayer, *Tetrahedron Letters*, **1970**, 3291; J. Adachi, K. Nomura, K. Shiraki, and K. Mitsuhashi, *Chem. Pharm. Bull.* (Tokyo), **22**, 658 (1974).

Experimental[8]

Methyl 5-Cyano-2-oxo-5-phenylcyclohexanecarboxylate (I)——Dimethyl 4-cyano-4-phenyl-1,7-heptanedioate was prepared from phenylacetonitrile (40 g) and methyl acrylate (72 g) in *t*-BuOH (200 ml) in the presence of 35% methanolic Triton B (20 g) according to the method of Uyeo, *et al.*[3] Colorless oil, bp 195° (1.5 mmHg). Yield, 77 g (78%). This product (45 g) was then treated with NaH (7.5 g) in toluene (300 ml) under refluxing for 6 hr. The mixture was worked up in the usual manner to give 34 g (85%) of I, colorless needles, mp 94—95° (CCl_4) (lit.[9] mp 95—96°).

Methyl 5-Cyano-2-oxo-1-(3-oxobutyl)-5-phenylcyclohexanecarboxylate (IIa and IIb)——To a mixture of NaOMe in MeOH (prepared from 35 mg of Na and 60 ml of MeOH) and I (16 g) in benzene (90 ml) was added a solution of methyl vinyl ketone (5.4 g) in MeOH (15 ml) and benzene (45 ml) at room temperature under a stream of N_2. The mixture was stirred at the same temperature for 24 hr. After dilution with water, the aqueous layer was extracted with benzene. The combined benzene solution was washed with brine, dried over Na_2SO_4, and concentrated. The residue was recrystallized from ether to give 5.2 g (30%) of colorless needles of IIa, mp 125—127°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 2260 (CN), 1735, 1720 (C=O). NMR ($CDCl_3$) δ: 2.15 (3H, s, $-COCH_3$), 1.7—3.5 (10H, m), 3.9 (3H, s, $-OCH_3$), 7.5 (5H, m, arH). *Anal.* Calcd. for $C_{19}H_{21}O_4N$: C, 69.70; H, 6.47; N, 4.28. Found: C, 69.84; H, 6.48; N, 4.39.

The mother liquor was concentrated to give 4 g (25%) of colorless cubes of IIb, mp 86—88°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 2260 (CN), 1735, 1715 (C=O). NMR ($CDCl_3$) δ: 2.15 (3H, s, $-COCH_3$), 2.25—3.3 (10H, m), 3.6 (3H, s, $-OCH_3$), 7.5 (5H, m, arH). *Anal.* Calcd. for $C_{19}H_{21}O_4N$: C, 69.70; H, 6.47; N, 4.28. Found: C, 69.88; H, 6.29; N, 4.33.

Methyl 6-Cyano-3,4,5,6,7,8-hexahydro-2-oxo-6-phenyl-4a(2H)-naphthalenecarboxylate (III)——To a mixture of concd. H_2SO_4 (12 ml) and AcOH (72 ml) was added IIa (3 g), and the mixture was then warmed at 90° on a water bath for 15 min. The mixture was poured on ice-water, and extracted with $CHCl_3$. The extract was washed with 10% Na_2CO_3 and water, dried over Na_2SO_4, and concentrated. Recrystallization of the residue from EtOH gave 1.66 g (58.6%) of colorless plates of III, mp 128—129°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 2250 (CN), 1735, 1670 (C=O), 1620 (C=C). NMR ($CDCl_3$) δ: 1.6—3.3 (10H, m), 3.9 (3H, s, $-OCH_3$), 6.05 (1H, s, $>C=CH-$), 7.45 (5H, s, arH). *Anal.* Calcd. for $C_{19}H_{19}O_3N$: C, 73.76; H, 6.19; N, 4.53. Found: C, 73.70; H, 6.22; N, 4.49.

Methyl 6-Cyanodecahydro-2-oxo-6-phenyl-4a-naphthalenecarboxylate (IV)——A mixture of III (500 mg) and 10% Pd-C (150 mg) in MeOH (30 ml) was hydrogenated at room temperature in the usual manner to afford 400 mg (80%) of colorless sticks of IV, mp 124—126° (EtOH). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 2250 (CN), 1730, 1710 (C=O). *Anal.* Calcd. for $C_{19}H_{21}O_3N$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.39; H, 6.74; N, 4.45.

Decahydro-2-oxo-6-phenyl-4a,6-naphthalenedicarboxylic Anhydride (V)——A mixture of IV (200 mg) and 70% H_2SO_4 (9 g) was warmed on a water bath for 1.5 hr. The mixture was extracted with $CHCl_3$. The extract was worked up as usual to give 61 mg (30%) of the corresponding dicarboxylic acid, mp 227—230° (AcOEt). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3300—2500, 1700 (COOH). *Anal.* Calcd. for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.23; H, 6.39.

This product (30 mg) and Ac_2O (60 mg) were refluxed for 2 hr. After cooling, the mixture was concentrated *in vacuo*. The crystalline residue was recrystallized from benzene to afford 27 mg (95%) of V, mp 90—92°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1795, 1760, 1720 (C=O). *Anal.* Calcd. for $C_{18}H_{18}O_4$: C, 72.46; H, 6.08. Found: C, 72.74; H, 6.34.

Methyl 6-Cyano-5,6,7,8-tetrahydro-2-oxo-6-phenyl-4a(2H)-naphthalenecarboxylate (VI)——A mixture of III (4 g) and DDQ (4.4 g) in dioxane (80 ml) was refluxed for 24 hr. After cooling and filtration, the filtrate was concentrated *in vacuo*. To the residue was added water, and extracted with $CHCl_3$. Evaporation of $CHCl_3$ and recrystallization from MeOH afforded 3.6 g (90%) of colorless prisms of VI, mp 160—161°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 2240 (CN), 1665 (C=O). NMR ($CDCl_3$) δ: 6.38 (1H, d, $J=10$ Hz), 6.40 (1H, s), 6.85 (1H, d, $J=10$ Hz). *Anal.* Calcd. for $C_{19}H_{17}O_3N$: C, 74.25; H, 5.85; N, 4.56. Found: C, 74.46; H, 5.76; N, 4.73.

6-Cyano-5,6,7,8-tetrahydro-6-phenyl-2-naphthol (VII)——A solution of VI (1.5 g) in MeOH (105 ml) and 10% KOH (30 ml) was stirred at room temperature for 3 hr. After removal of the solvent, the residual aqueous solution was washed with ether, made acidic with 5% HCl, and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and concentrated. Recrystallization from benzene gave 0.72 g (58%) of colorless prisms of VII, mp 167—168°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3360 (OH), 2240 (CN). NMR ($CDCl_3$) δ: 2.1—2.45 (2H, m), 2.5—3.3 (4H, m), 3.45 (1H, s, $-OH$), 6.6 and 6.65 (2H, AB-q, $J=7$ Hz, arH), 6.85 (1H, s, arH), 7.15—7.6 (5H, m, arH). *Anal.* Calcd. for $C_{17}H_{15}ON$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.70; H, 6.02; N, 5.72.

1,2,3,4-Tetrahydro-6-methoxy-2-phenyl-2-naphthonitrile (VIII)——To a previously prepared CH_2N_2 in ether (from 6 g of N-nitrosomethylurea) was added VII (130 mg), and the mixture was allowed to stand

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[8] All melting points were uncorrected. NMR spectra were taken on a JNM-C-60H spectrometer using TMS as an internal standard.

[9] E.C. Horning, M.G. Horning, M.S. Fish, and M.W. Rutenberg, *J. Am. Chem. Soc.*, 74, 773 (1952).

at room temperature for 1 week. The mixture was filtered to remove insoluble material, and the filtrate was concentrated on a water bath. The residue was dissolved in benzene, washed with 5% NaOH and water, dried over Na_2SO_4, and concentrated. Removal of the solvent and recrystallization from MeOH gave 75 mg (60%) of colorless needles of VIII, mp 142—146°. IR ν_{max}^{KBr} cm^{-1}: 2240 (CN). NMR ($CDCl_3$) δ: 3.8 (3H, s, $-OCH_3$). *Anal.* Calcd. for $C_{18}H_{17}ON$: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.89; H, 6.29; N, 5.12.

1,2,3,4-Tetrahydro-6-methoxy-2-phenyl-2-naphthamide (IX)——To a solution of VIII (300 mg) in 95% EtOH (10 ml) and 6N NaOH (0.35 ml) was added dropwise 30% H_2O_2 (4.08 ml) at room temperature over a 30 min period. The mixture was then heated at 60° for 8 hr. After cooling, the mixture was concentrated *in vacuo* to give crystalline residue. Recrystallization from EtOH afforded 280 mg (78%) of colorless needles of IX, mp 182—184°. IR ν_{max}^{KBr} cm^{-1}: 3400 (NH), 1670 (C=O). *Anal.* Calcd. for $C_{18}H_{19}O_2N$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.72; H, 6.69; N, 5.02.

Methyl 1,2,3,4-Tetrahydro-6-methoxy-2-phenyl-2-naphthalenecarbamate (X)——To a solution of IX (200 mg) in MeOH (10 ml) containing NaOMe (30 mg of Na) was added Br_2 (210 mg). The mixture was refluxed for 3.5 hr. After dilution with water, the mixture was extracted with $CHCl_3$. The extract was worked up as usual to give crystalline material. Recrystallization from EtOH gave 177 mg (80%) of colorless cubes of X, mp 146—148°. IR ν_{max}^{KBr} cm^{-1}: 3280 (NH), 1690 (C=O). NMR ($CDCl_3$) δ: 3.5 (3H, s, $-OCH_3$), 3.75 (3H, s, $-OCH_3$), 5.1 (1H, br. s, –NHCO–), 6.5—7.6 (8H, m, arH). *Anal.* Calcd. for $C_{19}H_{21}O_3N$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.26; H, 6.54; N, 4.53.

1,2,3,4-Tetrahydro-6-methoxy-N-methyl-2-phenyl-2-naphthylamine (XI)——A mixture of X (200 mg) and $LiAlH_4$ (72 mg) in ether (10 ml) was refluxed for 6 hr. After addition of saturated potassium sodium tartrate solution, the mixture was extracted with ether. The extract was washed with brine, dried over Na_2SO_4, and concentrated. Distillation of the residue gave 138 mg (80%) of a colorless oil of XI, bp 140—150° (0.1 mmHg, bath temp.). IR ν_{max}^{film} cm^{-1}: 3400 (NH), 2760 (NMe). NMR ($CDCl_3$) δ: 1.95—2.35 (2H, m), 2.14 (3H, s, $-NCH_3$), 2.5—3.4 (4H, m), 3.3 (1H, s, –NH–), 3.74 (3H, s, $-OCH_3$), 6.72 and 6.68 (2H, AB-q, $J=9$ Hz, arH), 6.96 (1H, s, arH), 7.05—7.55 (5H, m, arH).

Oxalate of XI: colorless prisms, mp 210—212° (MeOH). *Anal.* Calcd. for $C_{18}H_{21}ON \cdot C_2H_2O_4$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.28; H, 6.20; N, 3.85.

1,2,3,4-Tetrahydro-6-methoxy-N,N-dimethyl-2-phenyl-2-naphthylamine (XII)——A mixture of XI (70 mg), HCO_2H (0.5 ml), and 37% formalin (0.5 ml) was heated on a steam bath for 4 hr. After dilution with water, the mixture was made alkaline with K_2CO_3 and extracted with ether. The extract was worked up as usual to give 58 mg (78.7%) of a colorless oil of XII. IR ν_{max}^{film} cm^{-1}: 2760 (NMe_2). NMR ($CDCl_3$) δ: 2.22 (6H, s, $-N(CH_3)_2$), 3.72 (3H, s, $-OCH_3$).

Picrate of XII: yellow needles, mp 200—201° (EtOH). *Anal.* Calcd. for $C_{19}H_{23}ON \cdot C_6H_3O_7N_3$: C, 58.82; H, 5.13; N, 10.98. Found: C, 58.57; H, 5.10; N, 10.73.

1,2,3,4,5,6,7,8-Octahydro-6-oxo-2-phenyl-2-naphthonitrile (XV)——A solution of IIb (2 g) in MeOH (64 ml) and 5% KOH (16 ml) was refluxed for 3 hr. After removal of the solvent *in vacuo*, the residue was extracted with $CHCl_3$. Usual working up of the extract gave 1.1 g (71.6%) of colorless cubes of XV, mp 138—140° (acetone). IR ν_{max}^{KBr} cm^{-1}: 2230 (CN), 1660 (C=O). NMR ($CDCl_3$) δ: 1.2—3.3 (11H, m), 6.0 (1H, s, $>C=CH-$), 7.5 (5H, m, arH). *Anal.* Calcd. for $C_{17}H_{17}ON$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.49; H, 6.61; N, 5.43.

3,8a-Ethano-3,4,4a,8a,5,6-hexahydro-3-phenyl-2,7(1H,8H)-quinolinedione (XIII)——1) A mixture of IIa (3.4 g) and 5% KOH (300 ml) was refluxed for 3 hr under N_2 stream. After cooling, the mixture was extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and concentrated. The crystalline residue was recrystallized from EtOH to give 1.14 g (40%) of colorless needles of XIII, mp 250—255°. IR ν_{max}^{KBr} cm^{-1}: 3300 (NH), 1720, 1675 (C=O). NMR ($CDCl_3$) δ: 1.5—2.6 (13H, m), 5.8 (1H, br. peak, disappeared with addition of D_2O, –CONH–), 7.25 (5H, s, arH). Mass Spectrum *m/e*: M^+, 269.139 (Calcd. M^+, 269.142). *Anal.* Calcd. for $C_{17}H_{19}O_2N$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.88; H, 7.16; N, 5.39.

2) A mixture of III (40 mg) and 5% KOH (2.5 ml) was refluxed for 2.5 hr. The mixture was worked up in the same manner as above to give 19 mg (54.6%) of XIII. This product was identified with the product in the procedure 1) by comparison of IR spectra and mixed melting point measurement.

3) Treatment of XV (50 mg) with 5% KOH (2.5 ml) under refluxing for 2 hr gave 22 mg (41%) of XIII, which was identical with the product obtained in the procedure 1) by the same means as above.

Decahydro-8a-hydroxy-2,7-dioxo-3-phenyl-3-naphthoic Acid Lactone (XIV)——A mixture of XIII (50 mg) and concd. HCl (3 ml) was heated on a steam bath for 3 hr. After cooling, the mixture was extracted with benzene. The extract was worked up as usual to give a viscous oil, which was then chromatographed on alumina (neutral, 3 g). Elution with benzene gave 30 mg (60%) of XIV. For analysis recrystallization from ether–benzene afforded colorless needles, mp 155—157°. IR ν_{max}^{KBr} cm^{-1}: 1770, 1710 (C=O). *Anal.* Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.64; H, 6.75.

Methyl 5-Cyano-1-(2-cyanoethyl)-2-oxo-5-phenylcyclohexanecarboxylate (XVI)——A mixture of I (10 g), acrylonitrile (2.5 g) and 40% methanolic Triton B (1.25 g) in N,N-dimethylformamide (60 ml) was heated at 60° for 4 hr. After removal of the solvent *in vacuo*, the residue was dissolved in $CHCl_3$, washed with 5% HCl and water, and dried over Na_2SO_4. Evaporation of the solvent gave an oily residue, which was chromatographed on alumina (neutral). Elution with benzene afforded 9.16 g (78%) of XVI. Recrystallization from EtOH gave colorless needles, mp 95—98°. IR ν_{max}^{KBr} cm^{-1}: 2240 (CN), 1725 (C=O). NMR ($CDCl_3$) δ: 1.7—3.5 (10H, m), 3.9 (3H, s, $-OCH_3$), 7.25—7.7 (5H, m, arH). *Anal.* Calcd. for $C_{18}H_{18}O_3N_2$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.56; H, 5.67; N, 9.06.

Methyl 6-Cyano-1,2,3,4,4a,5,6,7-octahydro-2-oxo-6-phenyl-4a-quinolinecarboxylate (XVII)——A solution of XVI (4 g) in dioxane (60 ml) saturated dry HCl was stirred at room temperature for 3 hr. Colorless crystals precipitated was filtered, and recrystallized from MeOH to give 3.96 g (99%) of colorless cubes of XVII, mp 283—285°. IR ν_{max}^{KBr} cm^{-1}: 3400 (NH), 2240 (CN), 1730, 1680 (C=O). NMR (d_6-DMSO) δ: 3.65 (3H, s, $-OCH_3$), 5.15 (1H, t, $J=4$ Hz, >C=CH–). *Anal.* Calcd. for $C_{18}H_{18}O_3N_2$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.77; H, 5.95; N, 9.05.

1,2,3,4,5,6,7,8-Octahydro-2-oxo-6-phenyl-6-quinolinecarbonitrile (XVIII)——A solution of XVII (2 g) in MeOH (320 ml) and 5% KOH (180 ml) was refluxed for 4.5 hr. After removal of the solvent, the residue was acidified with 5% HCl, and filtered. Recrystallization from MeOH gave 1.13 g (70%) of colorless prisms of XVIII, mp 183—185°. IR ν_{max}^{KBr} cm^{-1}: 2240 (CN), 1675 (C=O). NMR ($CDCl_3$) δ: 1.75—3.2 (10H, m), 6.8—7.65 (5H, m, arH), 8.65 (1H, br. s, –CONH–). *Anal.* Calcd. for $C_{16}H_{16}ON_2$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.04; H, 6.31; N, 11.11.

1,2,5,6,7,8-Hexahydro-2-oxo-6-phenyl-6-quinolinecarbonitrile (XIX)——A mixture of XVIII (330 mg) and DDQ (300 mg) in dioxane (10 ml) was refluxed for 2 hr. After cooling, the mixture was filtered. The filtrate was concentrated, diluted with water, and extracted with $CHCl_3$. The extract was worked up as usual to give 230 mg (69%) of colorless prisms of XIX, mp 280—283° (MeOH–ether). IR ν_{max}^{KBr} cm^{-1}: 2240 (CN), 1680 (C=O). NMR ($CDCl_3$) δ: 6.28 (1H, d, $J=9$ Hz, $-CH{=}C\underline{H}CO-$), 7.32 (1H, d, $J=9$ Hz, $-C\underline{H}{=}CHCO-$). *Anal.* Calcd. for $C_{16}H_{14}ON_2$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.49; H, 5.41; N, 11.34.

2-Chloro-5,6,7,8-tetrahydro-6-phenyl-6-quinolinecarbonitrile (XX)——A mixture of XIX (150 mg) and phenylphosphonic dichloride (234 mg) was heated at 130—140° for 9 hr. After cooling, the mixture was diluted with water and extracted with $CHCl_3$. Usual working up of the extract gave an oily material, which was distilled to give 80 mg (49.6%) of XX, bp 150—200° (5×10^{-3} mmHg, bath temp.), mp 130—134°. IR ν_{max}^{KBr} cm^{-1}: 2240 (CN). NMR ($CDCl_3$) δ: 2.2—2.7 (2H, m), 2.95—3.5 (4H, m), 6.8—7.7 (7H, m, arH). *Anal.* Calcd. for $C_{16}H_{13}N_2Cl$: C, 71.91; H, 4.88; N, 10.44. Found: C, 71.64; H, 4.63; N, 10.17.

5,6,7,8-Tetrahydro-6-phenyl-6-quinolinecarbonitrile (XXI)——1) A mixture of XX (55 mg), NaOAc (20 mg) in MeOH (5 ml) was hydrogenated over 10% Pd-C (20 mg) at room temperature in the usual manner. After removal of the solvent and catalyst, to the residue was added water, and extracted with $CHCl_3$. The extract was worked up as usual to give 35 mg (73%) of a colorless oil of XXI, bp 100° (4×10^{-5} mmHg, bath temp.). IR ν_{max}^{film} cm^{-1}: 2240 (CN). NMR ($CDCl_3$) δ: 6.95—7.65 (7H, m, arH), 8.45 (1H, d, $J=5$ Hz, arH). *Anal.* Calcd. for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 82.27; H, 5.82; N, 11.74.

2) 4-Cyano-4-phenylcyclohexanone (2.5 g) was obtained from I (3.5 g) by saponification with 10% H_2SO_4 (35 ml) in AcOH (70 ml), colorless prisms, mp 120—122.5° (MeOH) (lit.[9] mp 114.5—115°). A mixture of the above ketone (1 g), 3-aminoacrolein (400 mg) and NH_4OAc (80 mg) in triethylamine (30 ml) was refluxed for 48 hr. After concentration *in vacuo*, the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was extracted with 5% HCl. From the $CHCl_3$ layer 550 mg of unchanged ketone was obtained. The aqueous layer was basified with K_2CO_3, and extracted with $CHCl_3$. Usual working up of the extract gave 315 mg (24.6% from I) of XXI, bp 150° (3×10^{-4} mmHg, bath temp.). *Anal.* Calcd. for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 82.24; H, 6.05; N, 11.95. This product was identical with XXI obtained in the procedure 1) by comparison of IR and NMR spectra.

5,6,7,8-Tetrahydro-6-phenyl-6-quinolinecarboxamide (XXII)——A mixture of XXI (120 mg), EtOH (4 ml), 6N NaOH (0.2 ml) and 30% H_2O_2 (1.02 ml) was warmed at 60° for 5 hr. After neutralization with 5% H_2SO_4, the mixture was extracted with $CHCl_3$. The extract was worked up as usual to give a crystalline material, which was recrystallized from benzene to afford 100 mg (77%) of colorless prisms of XXII, mp 210—213°. IR ν_{max}^{KBr} cm^{-1}: 1675 (C=O). NMR ($CDCl_3$) δ: 6.9—7.55 (7H, m, arH), 8.25 (1H, br. d, $J=5$ Hz, arH). *Anal.* Calcd. for $C_{16}H_{16}ON_2$: C, 76.16; H, 6.39; N, 11.10. Found: C, 75.98; H, 6.18; N, 10.92.

Methyl 5,6,7,8-Tetrahydro-6-phenyl-6-quinolinecarbamate (XXIII)——To a solution of XXII (100 mg) in MeOH (4 ml) was added Na (25 mg) and then Br_2 (80 mg) at room temperature. The mixture was refluxed for 3 hr. After removal of the solvent, to the residue was added water and extracted with $CHCl_3$. Usual working up of the extract gave 80 mg (71%) of a pale yellow oil of XXIII, bp 150—200° (1×10^{-3} mmHg, bath temp.). IR ν_{max}^{film} cm^{-1}: 1710 (C=O). NMR ($CDCl_3$) δ: 3.5 (3H, s, $-NHCO_2C\underline{H}_3$), 5.43 (1H, s, $-N\underline{H}CO_2CH_3$), 6.9—7.7 (7H, m, arH), 8.35 (1H, br. d, $J=5$ Hz, arH). *Anal.* Calcd. for $C_{17}H_{18}O_2N_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.47; H, 6.61; N, 10.04.

5,6,7,8-Tetrahydro-6-(methylamino)-6-phenylquinoline (XXIV)——A mixture of XXIII (30 mg) and $LiAlH_4$ (50 mg) in ether (10 ml) was refluxed for 6 hr. After addition of saturated potassium sodium tartrate, the mixture was extracted with ether. The extract was worked up as usual to give 20 mg (79%) of a colorless oil of XXIV, bp 150—200° (1×10^{-3} mmHg, bath temp.). IR ν_{max}^{film} cm^{-1}: 2760 (NMe). NMR ($CDCl_3$) δ: 2.2 (3H, s, $-NHC\underline{H}_3$), 6.9—7.6 (7H, m, arH), 8.4 (1H, br. d, $J=5$ Hz, arH). *Anal.* Calcd. for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.76. Found: C, 80.46; H, 7.82; N, 11.67.

5,6,7,8-Tetrahydro-6-(dimethylamino)-6-phenylquinoline (XXV)——A mixture of XXIV (51 mg), HCO_2H (0.2 ml) and 37% formalin (0.2 ml) was heated on a steam bath for 4 hr. After cooling, the mixture was made alkaline with K_2CO_3, and extracted with $CHCl_3$. The extract was worked up as usual to give 34 mg (63%) of colorless oil of XXV, bp 124° (0.06 mmHg, bath temp.). IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 2790 (NMe_2). NMR ($CDCl_3$) δ: 2.2 (6H, s, $-N(CH_3)_2$), 7.0 (1H, d.d, $J=5$, 7.5 Hz, arH), 7.2 (5H, s, arH), 7.45 (1H, d, $J=7.5$ Hz, arH), 8.3 (1H, d, $J=5$ Hz, arH).

Dipicrate of XXV: yellow rhombics, mp 219—222° (decomp., MeOH). *Anal.* Calcd. for $C_{17}H_{20}N_2 \cdot 2C_6H_3O_7N_3$: C, 49.01; H, 3.69; N, 15.77. Found: C, 48.83; H, 3.98; N, 15.83.

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