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Studies on the Syntheses of Spiro-dienone Compounds. V.[1] An Improved Synthetic Method of Spiro-dienone Compounds. Syntheses of *dl*-Mecambrine, *dl*-Amurine and *dl*-Domesticine

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Photolysis of sodium salt of 2-bromo-N-ethyl-4′-hydroxybenzanilide in N,N-dimethylformamide gave 2′-ethylspiro[cyclohexa-2,5-diene-1,1′-isoindoline]-3′,4-dione in good yield. This reaction was utilized in the syntheses of *dl*-mecambrine, *dl*-amurine, and *dl*-domesticine.

Previously, we reported that the photolysis of 2-bromo-N-ethyl-4′-hydroxybenzanilide (I) in aqueous sodium hydroxide gave 2′-ethylspiro[cyclohexa-2,5-diene-1,1′-isoindoline]-3′,4-dione (II).[1a,3] This new reaction was utilized in the syntheses of several proaporphine and morphinadienone alkaloids.[4] In order to improve this new synthetic method of spiro-dienone system *via* photochemical reaction, we investigated the photolysis of phenolate ion of I in N,N-dimethylformamide (DMF)[1b] and hexamethylphosphoramide (HMPA).

We now wish to report the improved synthetic method of spiro-dienone system and also the syntheses of *dl*-mecambrine (III),[5] *dl*-amurine (IV)[6] and *dl*-domesticine (X)[6] by employing this method.

A mixture of the phenol (I), sodium amide and DMF was stirred for 20 min and then irradiated with a 100 W high pressure mercury lamp for 1.5 hr. Chromatography of the crude product gave the dienone (II) and the starting material (I) in 51% and 37% yield, respectively. The product (II) was identified by comparison with authentic sample.[3] When the photolysis was run in the presence of sodium hydride, II was obtained in 70% yield. However, when the photolysis was run in the presence of lithium hydride, II was obtained in 8% yield[7] and the starting material (I) was recovered in 40% yield. The photolysis of I in HMPA in the presence of sodium amide and sodium hydride gave II in 9% and 7% yield, respectively.

In order to extend the above reaction to the syntheses of proaporphine and morphinadienone alkaloids, this reaction was applied to the syntheses of *dl*-mecambrine (III) and *dl*-amurine (IV).

For the syntheses of III, 8-bromo-1,2,3,4-tetrahydro-1-(4-hydroxybenzyl)-2-methyl-6,7-methylenedioxyisoquinoline (V) was prepared as follows. Fusion of 3-bromo-4,5-methyl-

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[1] *a*) Part III: Z. Horii, Y. Nakashita, K. Kunisawa, and C. Iwata, *Chem. Pharm. Bull.* (Tokyo), **21**, 2679 (1973); *b*) Part IV: C, Iwata, Y. Nakashita, and R. Hirai, *Chem. Pharm. Bull.* (Tokyo), **22**, 239 (1974).

[2] Location: *6-1-1, Toneyama, Toyonaka, Osaka.*

[3] Z. Horii, C. Iwata, S. Wakawa, and Y. Nakashita, *Chem. Commun.*, **1970**, 1039.

[4] *a*) Z. Horii, Y. Nakashita, and C. Iwata, *Tetrahedron Letters*, **1971**, 1167; *b*) T. Kametani and K. Fukumoto, *Accounts Chem. Research*, **5**, 212 (1972) and references cited therein.

[5] While preparing this manuscript, Kametani and his co-workers reported that the photolysis of V in aqueous sodium hydroxide–methanol gave III in 1% yield. T. Kametani, H. Suga, S. Shibuya, and K. Fukumoto, *Tetrahedron*, **27**, 5375 (1971).

[6] T. Kametani, S. Shibuya, H. Sugi, O. Kusama, and K. Fukumoto, *J. Chem. Soc.* (*C*), **1971**, 2446 : The photolysis of VI in aqueous sodium hydroxide–methanol gave IV and X in 5% and 7% yield, respectively.

[7] This result may be attributed to the poor solubility of lithium hydride.

enedioxyphenethylamine[8] with methyl *p*-hydroxyphenylacetate[9] gave the amide (VI) which was converted into the ester (VII) by condensation with ethyl chloroformate. Bischler–Napieralski reaction of VII with phosphorus oxychloride and phosphorus pentoxide, followed by reduction with sodium borohydride, gave the tetrahydroisoquinoline (VIII). Treatment of VIII with 37% formaldehyde solution, followed by reduction with sodium borohydride, gave the starting material (V).

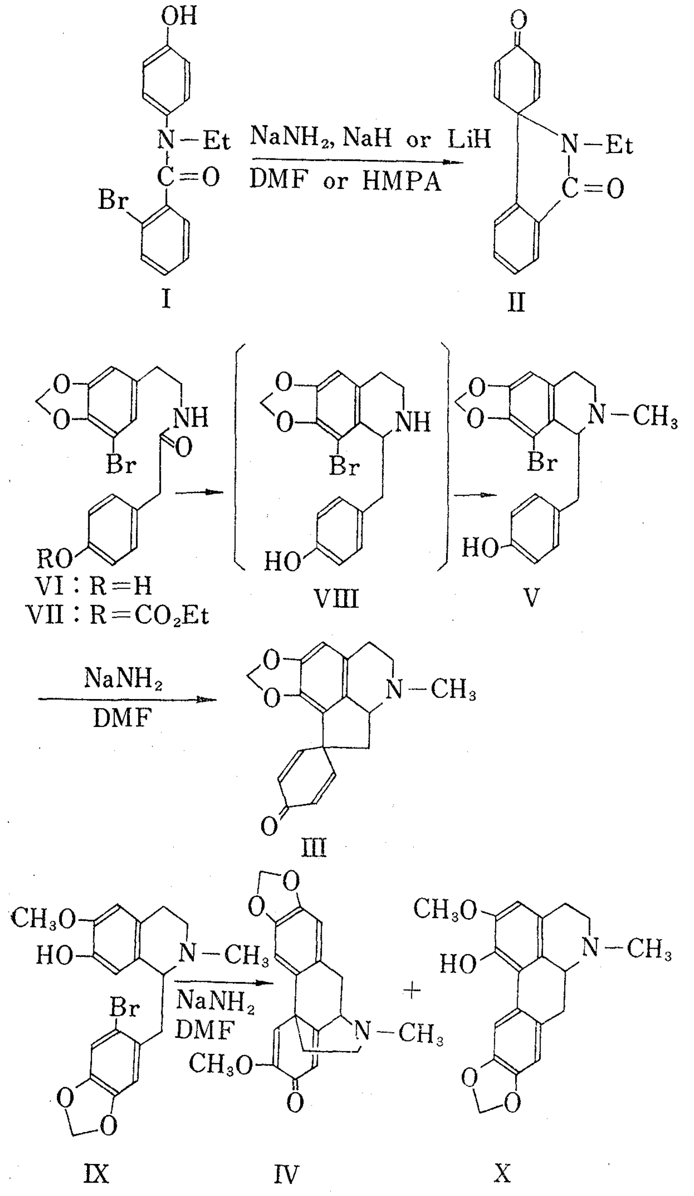

Chart 1

A mixture of V, sodium amide and DMF was irradiated for 2hr under similar conditions to those described above to give III in 10% yield, which showed a typical dienone system in the infrared (IR) spectrum ($\nu_{max}^{CHCl_3}$ cm^{-1}: 1668, 1650, and 1622). This product (III) was identified by comparison with natural mecambrine.

Similarly, irradiation of a mixture of 1-(2-bromo-4,5-methylenedioxybenzyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (IX),[6] sodium amide and DMF under similar conditions to those described above gave IV and *dl*-domesticine (X) in 5% and 31% yield, respectively. The product (IV) showed a typical dienone system in the IR spectrum ($\nu_{max}^{CHCl_3}$ cm^{-1}: 1675, 1645, and 1620). These products, IV and X were identified by comparison with natural amurine and domesticine, respectively. Since the *ortho* position of phenol ring of IX is easier to be attacked by phenyl radical than the *para* position, it is reasonable that the cyclization reaction gives X as major product.[10]

This improved synthetic method of spiro-dienone system could be very useful for the syntheses of the other proaporphine and morphinadienone alkaloids and also for the syntheses of aporphine alkaloids.

Experimental[11]

Photolysis of 2-Bromo-N-ethyl-4′-hydroxybenzanilide (I) in DMF——A) In the Presence of NaNH$_2$: A mixture of 300 mg of I, 150 mg of NaNH$_2$ and 100 ml of DMF was stirred for 20 min at room tempera-

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[8] M. Tomita and Y. Aoyagi, *Chem. Pharm. Bull.* (Tokyo), **16**, 523 (1968).

[9] H. Salkowski, *Ber.*, **22**, 2137 (1889).

[10] *cf.* R.J. Spangler and D.C. Boop, *Tetrahedron Letters*, **1971**, 4851.

[11] All melting points were uncorrected. Eikosha PIH-100 from Eikosha Co., Osaka was used as light source. Mass spectrum and ultraviolet (UV) spectra were taken on type RMU-60 and 124 Hitachi spectrometers, respectively. Organic extracts were dried over anhyd. Na$_2$SO$_4$.

ture. This mixture, through which dry N_2 gas was bubbled, was irradiated under ice–H_2O cooling for 2 hr. Excess of $NaNH_2$ was decomposed with MeOH. To the reaction mixture were added *ca.* 150 g of ice–H_2O and excess of AcOH. The acidic solution was basified with satd. $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O and dried. After the solvent was removed, the residue was chromatographed on alumina (Merck, activity II—III) with benzene–hexane–MeOH (10: 6: 0.5). The first eluate gave 114 mg (51%) of II as pale yellow needles, mp 138—139° (from petr. ether). This product was identified with authentic sample by mixed mp and the comparison of the IR spectra. The second eluate gave 110 mg (37%) of I.

B) In the Presence of NaH: A mixture of 300 mg of I, NaH (prepared from washing of 230 mg of 50% NaH in oil with petr. ether and DMF, successively) and 100 ml of DMF was stirred for 20 min and then irradiated for 2 hr under similar conditions to those described above A). The crude product was worked up as described above A) to give 156 mg (70%) of II.

C) In the Presence of LiH: A mixture of 300 mg of I, 100 mg of LiH and 100 ml of DMF was stirred for 16 hr at 80°. This mixture was irradiated for 2 hr under similar conditions to those described above A). The crude product was worked up as described above A) to give 18 mg (8%) of II and 123 mg (40%) of I.

Photolysis of I in HMPA——A) In the Presence of $NaNH_2$: A mixture of 300 mg of I, 150 mg of $NaNH_2$ and 100 ml of HMPA was stirred for 20 min at room temperature. This mixture was irradiated for 2 hr under similar conditions to those described above. To the reaction mixture were added *ca.* 150 g of ice–H_2O and excess of AcOH. The acidic solution was basified with satd. aq. $NaHCO_3$ and extracted with AcOEt. The AcOEt extract was worked up as described above to give 20 mg (9%) of II.

B) In the Presence of NaH: A mixture of 300 mg of I, NaH (prepared from washing of 230 mg of 50% NaH in oil with petr. ether and HMPA, successively) and 100 ml of HMPA was stirred for 20 min and then irradiated for 2 hr under similar conditions to those described above A). The crude product was worked up as described above A) to give 16 mg (7%) of II.

N-(5-Bromo-3,4-methylenedioxyphenethyl)-*p*-hydroxyphenylacetamide (VI)——A mixture of 4.5 g of 3-bromo-4,5-methylenedioxyphenethylamine, 3.5 g of methyl *p*-hydroxyphenylacetate and 1 ml of pyridine was heated for 3 hr at 180°. This reaction mixture was poured into ice–10% HCl (1: 1) and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried and evaporated. Chromatography of the residue on silica gel (Mallinckrodt) with $CHCl_3$–MeOH (100: 1) gave 3.5 g (50%) of the amide (VI) as colorless crystals, mp 134—136° (from acetone–ether). Mass Spectrum *m/e*: 379, 377 (M^+). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1655 (amide). *Anal.* Calcd. for $C_{17}H_{16}O_4NBr$: C, 53.98; H, 4.26; N, 3.70. Found: C, 53.88; H, 4.45; N, 3.70.

N-(5-Bromo-3,4-methylenedioxyphenethyl)-*p*-ethoxycarbonyloxyphenylacetamide (VII)——To an ice–H_2O cooling solution of 3.2 g of VI in 44 ml of pyridine was added 5 ml of ethyl chloroformate dropwise under stirring and then this mixture was heated at 60° for 2 hr. The reaction mixture was poured into ice–H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with 3% HCl and H_2O, and dried. After the solvent was evaporated under reduced pressure, the residue was recrystallized from MeOH to give 3 g of VII as colorless crystals, mp 115—116°. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1760 (ester), 1660 (amide). Mass Spectrum *m/e*: 451, 449 (M^+). *Anal.* Calcd. for $C_{20}H_{20}O_6NBr$: C, 53.51; H, 4.48; N, 3.11. Found: C, 53.53; H, 4.54; N, 3.14.

8-Bromo-1,2,3,4-tetrahydro-1-(4-hydroxybenzyl)-2-methyl-6,7-methylenedioxyisoquinoline (V)——A mixture of IV, 5 g of phosphorus pentoxide, 10 ml of phosphorus oxychloride and 25 ml of benzene was refluxed for 3 hr. After the solvent was decanted, the residue was washed with benzene and poured into ice–H_2O gradually. The resulting mixture was basified with dil. NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O and dried. After the solvent was evaporated under reduced pressure, the residue [760 mg, IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1760 (ester), 1670 (C=N)] was dissolved in 50 ml of MeOH. To this stirred solution was added 3 g of $NaBH_4$ in small portions under ice–H_2O cooling. The reaction mixture was stirred for 3 hr at room temperature, acidified with AcOH, and evaporated under reduced pressure. The residue was basified with conc. NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried and evaporated under reduced pressure to give 500 mg of crude VIII [IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3550, 3290 (NH, OH)], which was used without further purification. This crude VIII was dissolved in a solution of 2.7 ml of 30% formaline and 45ml of MeOH, and the mixture was refluxed for 1 hr. To this stirred mixture was added 3.4 g of $NaBH_4$ in small portions under ice–H_2O cooling and the mixture was stirred for 2 hr at room temperature. After the mixture was acidified with AcOH, the solvent was evaporated under reduced pressure. The residue was basified with conc. NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried and evaporated under reduced pressure. Chromatography of the residue on silica gel (Mallinckrodt) with $CHCl_3$–MeOH (100: 2) gave 270 mg (32%) of V as colorless crystals, mp 187—189° (from MeOH). Mass Spectrum *m/e*: 377, 375 (M^+). *Anal.* Calcd. for $C_{18}H_{18}O_3NBr$: C, 57.46; H, 4.82; N, 3.72. Found: C, 57.16; H, 4.91; N, 3.59.

***dl*-Mecambrine (III)**——A mixture of 300 mg of V, 200 mg of $NaNH_2$ and 100 ml of DMF was stirred for 20 min at room temperature. This mixture, through which dry N_2 gas was bubbled, was irradiated under ice–H_2O cooling for 2 hr. Excess of $NaNH_2$ was decomposed with MeOH. To the mixture were added *ca.* 150 g of ice–H_2O and excess of AcOH. The acidic solution was basified with $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried and evaporated. Chromatography of the residue (168 mg) on silica gel (Mallinckrodt) with $CHCl_3$–MeOH (100: 2) to give 50 mg of crude III, which was further purified by preparative thin-layer chromatography (TLC) on alumina (Merck, GF_{254}) with benzene–$CHCl_3$ (8: 3) to give 24 mg (10%) of III as colorless crystals, mp 200—201° (from ether). Mass Spectrum *m/e*: 295 (M^+). UV λ_{max}^{EtOH} mμ (log ε): 231 (4.28), 290 (3.54). The IR spectrum of this product (III) was identical with that of natural mecambrine.

***dl*-Amurine (IV) and *dl*-Domesticine (X)**——A mixture of 600 mg of IX, 400 mg of $NaNH_2$ and 200 ml of DMF was stirred for 20 min at room temperature and then irradiated for 2 hr under similar conditions to those described above. The $CHCl_3$ extract was worked up as described above to give 350 mg of the residue which was chromatographed on silica gel (Mallinckrodt) with $CHCl_3$–MeOH (100: 2). The first eluate gave 50 mg of crude IV, which was further purified by preparative TLC on alumina (Merck, GF_{254}) with AcOEt to give 24 mg (5%) of IV as a colorless oil. Mass Spectrum *m/e*: 325 (M^+). UV λ_{max}^{EtOH} mμ (log ε): 240 (4.24), 290 (3.95). The methiodide of IV was recrystallized from MeOH to give colorless crystals, mp 230—233° (decomp.). *Anal.* Calcd. for $C_{20}H_{22}O_4NI$ $1/2H_2O$: C, 50.45; H, 4.85; N, 2.95. Found: C, 50.39; H, 4.82; N, 2.81. The IR spectrum of the free base (IV) was identical with that of natural amurine.

The second eluate gave 200 mg of crude VII, which was further purified by preparative TLC on alumina (Merck, GF_{254}) with AcOEt to give 150 mg (31%) of VII as colorless crystals, mp 200—203° (from MeOH). Mass Spectrum *m/e*: 325 (M^+). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3510 (OH). UV λ_{max}^{EtOH} mμ (log ε): 220 (4.36), 281 (3.87), 308 (3.98). *Anal.* Calcd. for $C_{19}H_{19}O_4N$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.03; H, 5.88; N, 4.13. The IR spectrum of this product (VII) was identical with that of natural domesticine.

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