Summary

It was found that the crystalline derivatives were readily obtainable when various hydrazine compounds were reacted with retinal. Many hydrazone-type derivatives of retinal were prepared and their physical properties, stability, toxicity and biopotency were examined.

All such derivatives are more stable than vitamin A palmitate, their toxicity being low, and some of them showed considerably higher vitamin A activity.

Retinal azine is obtained as crystals of m.p. 189° in a good yield when retinal is reacted with hydrazine-hydrate in the presence of an organic acid as a promotor. This compound is expected to have higher biological activity. *p*-Aminobenzoylhydrazone of retinal showed the biopotency equivalent to that of vitamin A.

(Received June 29, 1961)

UDC 547.538.2.07

147. Issei Iwai and Junya Ide : Studies on Acetylenic Compounds. XXIII.*² A New Ring Closure of 2-Propynyl Ethers.

(Takamine Laboratory, Sankyo Co., Ltd.*¹)

In the previous paper of this series, Okajima¹⁾ reported the Claisen rearrangement of 3-phenoxy-1-propyne (I) and 3-(2'-naphthyloxy)-1-propyne (II). The Claisen rearrangement²⁾ of (I) had been investigated by Powell and Adams,³⁾ but no definite substance could be isolated either by refluxing diisopentyl ether (b.p. 170°) solution of (I) or by boiling (I) without solvent. Okajima reinvestigated the rearrangement of (I) in various conditions, but any definite substance was not obtained. On the other hand, by heating (II) at 208° for 20 minutes, he obtained only a small amount of pale yellow needles, m.p. 180° . Considering the naphthoic activity, he suggested one of the following structures for this compound from the results of elemental analysis and infrared spectrum :

But a quantity of the sample was so small that he could not determine its structure.

In this paper, authors intend to clarify the chemical behavior of 3-(1' or 2'-naphthyloxy)-1-propyne which are expected to give phenolic compounds by the Claisen rearrangement.

*¹ Nishi-shinagawa, Shinagawa-ku, Tokyo (岩井一成, 井手純也).

*² Part XXII. Y. Yura : This Bulletin, **10**, 376 (1962).

1) Y. Okajima : Yakugaku Zasshi, **80**, 315 (1960).

2) D.S. Tarbell : Org. Reactions **2**, Chap. 1 (1944).

3) S.G. Powell, R. Adams : J. Am. Chem. Soc., **42**, 652 (1920).

Sometimes, the solvents such as paraffin oil, tetralin, kerosene, N,N-dimethylaniline and N,N-diethylaniline were employed for the Claisen rearrangement.³⁾ These solvents often reduce a polymerized product, and especially basic solvents such as N,N-dimethyl- and N,N-diethyl-aniline give better yield comparing with hydrocarbons.

For the first time the rearrangement of (II) was carried out in N,N-dimethylaniline (b.p. 193°) under refluxing, and since almost of all starting material was recovered even by prolonged heating (3 hours), N,N-diethylaniline (b.p. 215~216°) was employed as a solvent in place of N,N-dimethylaniline. The solution was refluxed for 40 minutes and then benzene was added to the reaction mixture. After removal of N,N-diethylaniline with 5% hydrochloric acid, the benzene solution was extracted with 5% sodium hydroxide solution. Any phenolic substance, however, was not given from the alkaline extracts. By chromatographic purification of the residue obtained from benzene solution furnished white plates of m.p. 41~41.5°(A). The result of the elemental analysis of the crystals was in agreement with a calculated values for C₁₃H₁₀O, and its infrared spectrum showed no absorptions of triple bond, ethynyl group and hydroxyl group. The ultraviolet absorption maximum shifted to more bathochromic comparing with that of a starting material as shown in Fig. 1. In the presence of platinum dioxide, (A) was catalytically hydrogenated to give colorless oil of b.p._{0.0001} 100~110°(bath temp.) after the absorption of 1 mole equivalent of hydrogen, which solidified on standing, m.p. 38.5~39.5°(B). The absorption maximum of the ultraviolet spectrum of (B) shifted to hypsochromic⁴⁾ in comparison with that of (A) as shown in Fig. 1.

From these results, it was supposed that ring-closure reaction occurred and an unsaturated bond adjacent to a naphthalene nucleus was newly formed. On the other hand, 1-methyl-naphtho[2,1-*b*]furan (III), m.p. 59°, was already synthesized by Stoemer,⁵⁾ but the characteristics of (A) were quite different from those of (III). Moreover, if (A) was 1-methylene-1,2-dihydronaphtho[2,1-*b*]furan (IV), (A) would be changed into (III) by treating with mineral acid, but (III) was not obtained by this treatment from (A). Therefore, the most probable structure for (A) appeared to be 3*H*-naphtho[2,1-*b*]pyran (V), which was synthesized by the following route :

4) R. A. Friedel, M. Orchin : "Ultraviolet Spectra of Aromatic Compounds" John Wiley & Sons, Inc. (1951).

5) R. Stoemer : Ann., **312**, 491 (1900).

2,3-Dihydro-1H-naphtho[2,1-b]pyran-1-one (IX) was prepared according to the method of Levine, *et al.*⁶⁾ (IX) was reduced to 2,3-dihydro-1H-naphtho[2,1-b]pyran-1-ol, m.p. 108° (X) with sodium borohydride. The structure of (X) was confirmed by elemental analysis and the infrared spectrum. Dehydration of (X) with phosphorous oxychloride in pyridine produced colorless needles of m.p. 40~41° (V) which showed no absorption of hydroxyl group in the infrared spectrum and no depression in melting point on admixture with (A). Moreover, the infrared and ultraviolet spectra of (V) and (A) were coincided each other. From these results, it was concluded that (II) did not undergo the expected Claisen rearrangement but the ring-closure reaction to give (V). The compound (V), however, is different from the substance of m.p. 180° which has been obtained by Okajima from (II) by heating without solvent.

Furthermore, this type of the reaction was also examined on methyl and phenyl derivatives of (II). 1-Phenyl-3-(2'-Naphthyloxy)-1-propyne which was prepared from 2-naphthol and 1-phenyl-3-bromo-1-propyne according to the method of Okajima, gave pale orange needles (C), m.p. 118~119° in good yield (95%) by refluxing in N,N-diethylaniline. The elemental analysis of the product was in agreement with the calculated values for $\text{C}_{19}\text{H}_{14}\text{O}$. The compound (C) showed no depression on the mixed melting point with 1-phenyl-3H-naphtho[2,1-b]pyran (XIII) derived from (IX) by the Grignard reaction followed by dehydration. Catalytic hydrogenation of (C) over platinum dioxide afforded colorless needles of m.p. 134~135° (D) after the absorption of one equivalent mole of hydrogen. By the results of mixed melting point, infrared and ultraviolet spectra of both compounds, (D) was identified as 1-phenyl-2,3-dihydro-1H-naphtho[2,1-b]pyran (XIII) which obtained from (XIII) by catalytic hydrogenation over platinum dioxide.

Similarly, refluxing diethylaniline solution of 1-(2'-naphthyloxy)-2-butyne (XVI) m.p. 69~70° which was prepared from sodium acetylide of (II) by methylation with methyl iodide in liquid ammonia, gave a pale yellow oil, (E) b.p._{0.05} 104~112° (bath temp.). The infrared and ultraviolet spectra of (E), whose analytical values corresponded to $\text{C}_{14}\text{H}_{12}\text{O}$, were identical with that of 1-methyl-3H-naphtho[2,1-b]pyran (XVII), prepared from (IX) by the same procedure as (XIII) employing methylmagnesium iodide in place of phenylmagnesium bromide. The catalytic hydrogenation of (E) over palladium-barium sulfate furnished colorless plates (F) m.p. 59~60° after the absorption of one mole equivalent of hydrogen. The elemental analysis of (F) was in agreement with the calculated values for $\text{C}_{14}\text{H}_{14}\text{O}$, which showed no depression in melting point with 1-methyl-2,3-dihydro-1H-naphtho[2,1-b]pyran (XVIII) obtained by catalytic hydrogenation of (XVII).

6) A. Levine, G. Bryant: J. Am. Chem. Soc., **69**, 2341 (1947).

Furthermore, the similar reaction of 1-phenyl-3-(1'-naphthyloxy)-1-propyne (XX) was examined. Refluxing of N, N-diethylaniline solution of (XX) gave pale yellow needles of m.p. $97\sim 98^\circ(\text{G})$ in good yield (70%), whose elemental analysis was in agreement with the calculated values for $\text{C}_{19}\text{H}_{14}\text{O}$. The infrared spectrum of (G) showed no absorption of a triple bond and the absorption maxima of ultraviolet spectrum of (G) shifted bathochromically comparing with (XX). Oxidative degradation of (G) with potassium permanganate afforded phthalic acid and benzoic acid. Therefore, the ring-closure must occur to 2-position but not to α' -position of naphthalene nucleus.

On the other hand, 4-phenyl-2H-naphtho[1,2-b]pyran (XXI) was synthesized by another route. There are many reports⁷⁻⁹⁾ concerning to the preparation of 2,3-dihydro-4H-naphtho[1,2-b]pyran-4-one (XXIV). In this case, (XXIV) was prepared from 1-naphthol (XIX) by cyanoalkylation followed by treating with sulfuric acid according to the method of Colonre, *et al.*¹⁰⁾ An authentic sample of (XXI) was synthesized from (XXIV) by Grignard reaction and followed by dehydration. The compound (G) showed no depression in melting point on admixture with (XXI). The infrared and ultraviolet spectra of both compounds superimposed to each other. Catalytic hydrogenation of (G) over palladium-carbon catalyst afforded dihydro compound (H) of m.p. $99\sim 100^\circ$ which was identified as 4-phenyl-3,4-dihydro-2H-naphtho[1,2-b]pyran (XXII) of m.p. $100\sim 100.5^\circ$ obtained by hydrogenation of (XXI).

7) P. Pfeiffer, J. Grimmer : Ber., **50**, 921~924 (1917).

8) St. von Kostonecki, G. Froemsdorff : Ber., **35**, 860 (1902).

9) D. Chakravato, J. Dutta : J. Indian Chem. Soc., **16**, 639 (1939).

10) J. Colonre, A. Guyot : Bull. soc. chim. France, **1958**, 325 (1958).

Propargyl ethers of 2-naphthol was expected to give 1-substituted 2-naphthol derivatives by the Claisen rearrangement caused by naphthoid activity, same as the case of allylic ether of 2-naphthol. On the contrary to our expectation, the former compounds give 3*H*-naphtho[2,1-*b*]pyran derivatives. And it is found that phenyl propargyl ether of 1-naphthol also gives 2*H*-naphtho[1,2-*b*]pyran derivatives.

From these results, it is concluded that the derivatives of naphthyl propargyl ether undergo a new ring-closure reaction to give naphthopyran derivatives. The yield of 1-phenyl-3*H*-naphtho[2,1-*b*]pyran from the corresponding ether exceeded to that of 4-phenyl-2*H*-naphtho[1,2-*b*]pyran from the corresponding 1-naphthyl ether. This fact would be resulted by δ -effect of carbon-atom due to the naphthoid activity.

Experimental*³

3*H*-Naphtho[2,1-*b*]pyran (V) from (II)—A solution of 5 g. of 2-naphthyl 2-propynyl ether (I) in 20 cc. of *N,N*-diethylaniline was refluxed for 40 min. To the dark red colored reaction mixture was added 20 cc. of benzene, and washed with 5% HCl. The benzene solution was washed with H₂O and dried over Na₂SO₄. Concentration under reduced pressure gave a brown gummy substance which was taken up in benzene and chromatographed over Walen neutral alumina (grade II). From benzene eluate were obtained 1.93 g. (40%) of pale yellow needles m.p. 40~41.5°, which recrystallized from EtOH to m.p. 41~41.5°. *Anal.* Calcd. for C₁₃H₁₀O: C, 85.69; H, 5.53; O, 8.78. Found: C, 85.96; H, 5.61; O, 8.43. UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (log ϵ): 242 (4.66), 261 (3.64) (shoulder), 290 (3.51) (shoulder), 301 (3.66), 314 (3.69), 347 (3.59).

3*H*-Naphtho[2,1-*b*]pyran (V) from (X)—To a solution of 3 g. of (X) in 40 cc. of pyridine was added dropwise 13 cc. of POCl₃ with stirring under cooling with ice-water. After the addition, the reaction mixture was boiled under refluxing for 1 hr., and poured into 100 g. of crushed ice after cooling. The precipitate was filtered and a recrystallized from 95% EtOH to give pale yellow needles, m.p. 40.5~41.5° (2 g., 66%). *Anal.* Calcd. for C₁₃H₁₀O: C, 85.69; H, 5.53; O, 8.78. Found: C, 85.69; H, 5.61; O, 8.70. UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (log ϵ): 242 (4.69), 261 (3.63) (shoulder), 291 (3.49) (shoulder), 301 (3.67), 314 (3.67), 348 (3.61).

2,3-Dihydro-1*H*-naphtho[2,1-*b*]pyran (VI)—A solution of 1.333 g. of 3*H*-naphtho[2,1-*b*]pyran (V) in 20 cc. of EtOH was shaken in H₂ at an ordinary pressure over 200 mg. of PtO₂ and 227 cc. of H₂ uptake was observed (90% of calcd. amount at 27°) for 30 min. After removal of the catalyst, the solvent was distilled under reduced pressure. The colorless oily residue, b.p._{0.006} 100~110° (bath temp.), was crystallized to give white needles, m.p. 38.5~39.5. *Anal.* Calcd. for C₁₃H₁₂O: C, 84.75; H, 6.57; O, 8.68. Found: C, 84.81; H, 6.78; O, 8.41. UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (log ϵ): 233 (4.85), 258 (3.45) (shoulder), 268 (3.61), 278 (3.69), 289 (3.57), 320 (3.34), 334 (3.39).

2,3-Dihydro-1*H*-naphtho[2,1-*b*]pyran-1-one (IX)—Starting from 300 g. of 2-naphthol, 120 g. of white powder, m.p. 44~45°, was obtained according to the method of Levine *et al.*⁽⁶⁾ *Anal.* Calcd.

*³ All m.p.s are uncorrected.

for $C_{13}H_{10}O_2$: C, 77.98; H, 6.04; O, 15.98. Found: C, 77.63; H, 6.01; 16.36. O, UV $\lambda_{\max}^{EtOH}$ $m\mu$ (log ϵ): 221 (4.52), 236 (4.34) (shoulder), 264 (3.94), 311 (3.89), 344 (3.68). IR $\nu_{\max}^{CCl_4}$ cm^{-1} : 1675 (=CO).

2,3-Dihydro-1H-naphtho[2,1-b]pyran-1-ol (X)—A solution of 20.0 g. of (IX) and 1.843 g. of $NaBH_4$ in 125 cc. of EtOH was allowed to stand at room temperature for 15 hr. After the excess $NaBH_4$ was decomposed with AcOH, almost EtOH was removed under reduced pressure. The residue was poured into crushed ice and white precipitate appeared was filtered and recrystallized from CCl_4 to give white needles, m.p. 109~109.5° (18 g.). Anal. Calcd. for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04; O, 15.98. Found: C, 77.76; H, 6.13; O, 16.11. IR $\nu_{\max}^{CCl_4}$: 3300~3400 cm^{-1} (OH). UV $\lambda_{\max}^{EtOH}$ $m\mu$ (log ϵ): 231 (4.80), 257 (3.45) (shoulder), 265 (3.59), 276 (3.66), 287 (3.54), 318 (3.28), 333 (3.38).

1-Phenyl-3-(2'-naphthoxy)-1-propyne (XI)—A solution of 20 g. of 1-phenyl-3-bromo-1-propyne, 15 g. of 2-naphthol and 15 g. of K_2CO_3 in 80 cc. of Me_2CO was boiled under reflux for 8 hr. After cooling an inorganic substance was filtered, Et_2O was added to the filtrate and washed successively with 5% NaOH solution, water, and dried over Na_2SO_4 . The removal of Et_2O afforded 19 g. of viscous oil which solidified on scratching. Recrystallization from petr. benzin gave colorless powder, m.p. 92~93°. Anal. Calcd. for $C_{19}H_{14}O$: C, 88.34; H, 5.46; O, 6.20. Found: C, 88.40; H, 5.75; O, 5.85. IR $\nu_{\max}^{CCl_4}$: 2230 cm^{-1} ($-C\equiv C-$). UV $\lambda_{\max}^{EtOH}$ $m\mu$ (log ϵ): 225 (5.15), 272 (4.06), 312 (3.40), 318 (3.39), 327 (3.57).

1-Phenyl-3H-naphtho[2,1-b]pyran (XII) from (XI)—A solution of 2 g. of (XI) in N,N-diethylaniline (40 cc.) was boiled under reflux for 4.5 hr. After removal of N,N-diethylaniline under reduced pressure, 100 cc. of Et_2O was added to the residue and washed successively with 5% HCl, 5% NaOH, solution, water and dried over Na_2SO_4 . The removal of Et_2O gave brown viscous oil (1.9 g.) which solidified on scratching. Recrystallization from 99% EtOH afforded pale orange needles m.p. 118~119°. Anal. Calcd. for $C_{19}H_{14}O$: C, 88.34; H, 5.46; O, 6.20. Found: C, 87.77; H, 5.40; O, 6.83. UV $\lambda_{\max}^{EtOH}$ $m\mu$ (log ϵ): 244 (4.57), 302 (3.69), 313 (3.70), 345 (3.65).

1-Phenyl-3H-naphtho[2,1-b]pyran (XII) from (XIV)—To a solution of 2.5 g. of (XIV) in 35 cc. of dehyd. pyridine was added dropwise 10 cc. of $POCl_3$ with stirring under cooling with ice-water. The reaction mixture was refluxed for 1.5 hr. After cooling, it was poured into 80 g. of crushed ice. The precipitate was filtered and recrystallized from 95% EtOH to pale orange needles, m.p. 118~119°. Anal. Calcd. for $C_{19}H_{14}O$: C, 88.34; H, 5.46; O, 6.20. Found: C, 88.14; H, 5.91; O, 5.95. UV $\lambda_{\max}^{EtOH}$ $m\mu$ (log ϵ): 224 (4.58), 301 (3.70), 313 (3.72), 345 (3.64).

1-Phenyl-2,3-dihydro-1H-naphtho[2,1-b]pyran (XIII)—A solution of 500 mg. of 1-phenyl-3H-naphtho[2,1-b]pyran (XII) in 20 cc. of EtOH was shaken in H_2 at an ordinary pressure over 66 mg. of PtO_2 and 47 cc. of H_2 uptake was observed (99.9% of calcd. amount at 25.5°) for 20 min. After removal of the catalyst, the solvent was distilled off under reduced pressure to give a viscous residue. A treatment of it with charcoal gave colorless needles, m.p. 134~135° (from EtOH). Anal. Calcd. for $C_{19}H_{16}O$: C, 87.66; H, 6.15; O, 6.19. Found: C, 87.88; H, 6.33; O, 5.97. UV $\lambda_{\max}^{EtOH}$ $m\mu$ (log ϵ): 234 (4.81), 258 (3.58) (shoulder), 267 (3.71), 277 (3.45), 289 (3.67), 320 (3.42), 334 (3.54).

1-Phenyl-2,3-dihydro-1H-naphtho[2,1-b]pyran-1-ol (XIV)—To the Grignard solution prepared from 3.9 g. of Mg and 15.7 cc. of bromobenzene in 70 cc. of dehyd. Et_2O was added dropwise 26.0 g. of (IX) in 80 cc. of dehyd. Et_2O under cooling with ice-water during 40 min. Then the reaction mixture was refluxed for 3 hr. with continuous stirring. After cooling the reaction mixture was decomposed with sat. NH_4Cl solution, the organic layer was separated and the aqueous layer was extracted with Et_2O . The combined organic layer washed successively with 5% HCl, 10% $NaHCO_3$ and water until neutral to litmus, and dried over Na_2SO_4 . The evaporation of Et_2O under reduced pressure and recrystallization from CCl_4 gave white powder, m.p. 159~160°. Anal. Calcd. for $C_{19}H_{16}O_2$: C, 82.57; H, 5.86; O, 11.57. Found: C, 82.64; H, 5.58; O, 11.78. IR $\nu_{\max}^{CCl_4}$: 3500 cm^{-1} (OH).

4-(2'-Naphthoxy)-2-butyne (XVI)—4.1 g. of Na was added in small pieces to 200 cc. of liq. NH_3 and then 28.0 g. of 3-(2'-naphthoxy)-1-propyne (II) in 100 cc. of dehyd. Et_2O was added dropwise. After stirring 1.5 hr. at -40° , 28.4 g. of MeI in 100 cc. of Et_2O was added dropwise during 40 min. The reaction mixture was stirred for 4 hr. at -45° and 9 g. of NH_4Cl was added in many portions, and allowed to stand overnight under cooling by dry ice- Me_2CO . Liq. NH_3 was allowed to evaporate at room temperature under continuous stirring. The reaction mixture was poured into 60 g. of crushed ice, the organic layer was separated and the aqueous layer was extracted with Et_2O . The combined extract was washed successively with dil. H_2SO_4 , 10% $NaHCO_3$ solution and water until neutral to litmus and dried over Na_2SO_4 . The solvent was distilled under reduced pressure. The residue solidified on cooling and scratching. Recrystallization three times from 99% EtOH gave thin yellow needles, m.p. 69~70°, yield, 6 g. Anal. Calcd. for $C_{14}H_{12}O$: C, 85.68; H, 6.16; O, 8.16. Found: C, 85.63; H, 6.21; O, 8.12. IR $\nu_{\max}^{CCl_4}$: 2240 cm^{-1} ($-C\equiv C-$). UV $\lambda_{\max}^{EtOH}$ $m\mu$ (log ϵ): 226 (4.76), 254 (3.38) (shoulder), 262 (3.50), 271 (3.54), 282 (3.37) (shoulder), 313 (3.03), 319 (2.98), 327 (3.15).

1-Methyl-3H-naphtho[2,1-b]pyran (XVII) from (XVI)—The solution of 2.0 g. of 4-(2'-naphthoxy)-2-butyne (XVI) in 40 cc. of dehyd. N,N-diethylaniline was boiled under reflux for 4 hr. and solvent was removed under reduced pressure. The residue was dissolved in 30 cc. of Et_2O and was washed

successively with 5% HCl, 10% NaHCO₃ solution, water and dried over Na₂SO₄. After removal of the solvent under reduced pressure, the vacuo distillation gave a pale yellow oil, b.p._{0.015} 104~112° (bath temp.) (49%). *Anal.* Calcd. for C₁₄H₁₂O: C, 85.68; H, 6.16; O, 8.16. Found: C, 85.92; H, 5.93; O, 8.15. UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (log ϵ): 243 (4.65), 282 (3.61) (shoulder), 301 (3.68), 312 (3.57), 346 (3.64).

1-Methyl-3H-naphtho[2,1-b]pyran (XVII) from (XV)—To a solution of 5 g. of 1-methyl-2,3-dihydro-1H-naphtho[2,1-b]pyran-1-ol (XV) in 35 cc. of dehyd. pyridine was added dropwise 13 cc. of POCl₃ under cooling with ice-water. Then the reaction mixture was refluxed for 3 hr. and poured into 80 g. of crushed ice and extracted with Et₂O. The ethereal solution was washed successively with 5% H₂SO₄, water and dried over Na₂SO₄. After removal of Et₂O, the residue was submitted to vacuo distillation to give a pale yellow oil, b.p._{0.02} 105~110° (bath temp.). *Anal.* Calcd. for C₁₄H₁₂O: C, 85.68; H, 6.16; O, 8.16. Found: C, 85.58; H, 6.04; O, 8.38. UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (log ϵ): 243 (4.71), 291 (3.63) (shoulder), 301 (3.74), 311 (3.64) (shoulder), 347 (3.71).

1-Methyl-2,3-dihydro-1H-naphtho[2,1-b]pyran (XVIII)—A solution of 503 mg. of (XVII) in 20 cc. of EtOH was shaken in H₂ at an ordinary pressure over 500 mg. of Pd-BaSO₄ and 600 cc. of H₂ was absorbed (96% of calcd. amount at 25°). After removal of the catalyst, the solvent was distilled off. After standing overnight, the residue solidified. Recrystallization of it from EtOH gave colorless needles, m.p. 59~60°. *Anal.* Calcd. for C₁₄H₁₄O: C, 84.81; H, 7.12; O, 8.17. Found: C, 84.72; H, 7.29; O, 7.99. UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (log ϵ): 233 (4.85), 258 (3.46) (shoulder), 267 (3.63), 277 (3.70), 288 (3.58), 320 (3.33), 334 (3.42).

1-Methyl-2,3-dihydro-1H-naphtho[2,1-b]pyran-1-ol (XV)—To the Grignard solution prepared from 4 g. of Mg and 25.6 g. of MeI in 90 cc. of dehyd. Et₂O was added dropwise 32.7 g. of (IX) in 120 cc. of dehyd. Et₂O during 1.5 hr. and the reaction mixture was stirred for 3 hr. and decomposed with sat. NH₄Cl solution. The usual process and recrystallization from CCl₄ furnished white needles, m.p. 117~118°. *Anal.* Calcd. for C₁₄H₁₄O: C, 78.48; H, 6.59; O, 14.93. Found: C, 78.79; H, 6.59; O, 14.62. IR $\nu_{\text{max}}^{\text{CCl}_4}$: 3540 cm⁻¹ (OH). UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (log ϵ): 232 (4.83), 256 (3.53), 266 (3.64), 277 (3.70), 288 (3.58), 306 (3.09) (shoulder), 318 (3.36), 332 (3.39).

1-Phenyl-3-(1'-naphthylloxy)-1-propyne (XX)—A solution of 20 g. of 1-phenyl-3-bromo-1-propyne, 15 g. of 1-naphthol and 16 g. of K₂CO₃ in 90 cc. of Me₂CO was refluxed for 10 hr. After cooling and filtering inorganic substance, the filtrate was evaporated, and the residue was dissolved in 90 cc. of Et₂O and washed successively with 5% NaOH solution and water and then dried over Na₂SO₄. The solvent was evaporated and the residue was chromatographed on alumina. From petr. ether-benzene (10:1) there was obtained 18 g. of colorless prisms, m.p. 65.6~66.5°. *Anal.* Calcd. for C₁₉H₁₄O: C, 88.34; H, 5.46; O, 6.20. Found: C, 88.46; H, 5.47; O, 6.07. IR $\nu_{\text{max}}^{\text{CCl}_4}$: 2240 cm⁻¹ (C≡C-). UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (log ϵ): 231 (4.65), 282 (3.78), 290 (3.79), 305 (3.54) (shoulder), 320 (3.25).

4-Phenyl-2H-naphtho[1,2-b]pyran (XXI) from (XX)—A solution of 2 g. of (XX) in 40 cc. of N,N-diethylaniline was refluxed for 4.5 hr. and the solvent was distilled under reduced pressure. The residue was dissolved in 100 cc. of Et₂O and washed successively with 5% HCl, 5% NaOH solution and water, and dried over Na₂SO₄. Evaporation of the solvent and treatment with charcoal gave crude solid, which was recrystallized from EtOH to afford colorless plates, m.p. 97~98 (50%). *Anal.* Calcd. for C₁₉H₁₄O: C, 88.34; H, 5.46; O, 6.20. Found: C, 88.36; H, 5.56; O, 6.08. UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (log ϵ): 226 (4.65), 248 (4.51) (shoulder), 262 (4.43), 271 (4.42), 328 (3.57) (shoulder), 338 (3.61), 352 (3.56).

4-Phenyl-3,4-dihydro-2H-naphtho[1,2-b]pyran (XXII)—A solution of 360 mg. of (XXI) in 8 cc. of EtOH was shaken in H₂ at an ordinary pressure over 100 mg. of Pd-BaSO₄ and 34.5 cc. of H₂ uptake was observed (100.8% of calcd. amount at 25.5°) for 35 min. After removal of the catalyst, the solvent was distilled under reduced pressure. The residue solidified on standing overnight, which was recrystallized from petr. ether to give colorless needles, m.p. 99~100. *Anal.* Calcd. for C₁₉H₁₆O: C, 87.66; H, 6.15; O, 6.19. Found: C, 87.86; H, 6.07; O, 6.07. UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (log ϵ): 239 (4.70), 263 (3.43) (shoulder), 270 (3.53) (shoulder), 288 (3.70) (shoulder), 296 (3.73), 311 (3.62), 325 (3.51).

2,3-Dihydro-4H-naphtho[1,2-b]pyran-4-one (XXIV)—Starting from 10 g. of 1-naphthol, 12 g. of white plates, m.p. 104~105 (from EtOH) were obtained by the method of Colonre and Guyot¹⁰. *Anal.* Calcd. for C₁₃H₁₀O₂: C, 78.77; H, 5.09; O, 16.14. Found: C, 78.83; H, 5.35; O, 15.92. IR $\nu_{\text{max}}^{\text{CCl}_4}$: 1680 cm⁻¹ (C=O). UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (log ϵ): 252 (4.57), 260 (4.14), 280 (3.91), 290 (3.92), 348 (3.70) (shoulder), 358 (3.74).

4-Phenyl-2H-naphtho[1,2-b]pyran (XXI) from (XXIV) via (XXV)—The compound (XXV) was prepared from (XXIV) by the same procedure as of (XIV). But crude substance was only given, and this substance seemed to be a mixture of (XXV) and dehydrated substance of (XXV). IR $\nu_{\text{max}}^{\text{CCl}_4}$: 3500 cm⁻¹ (OH).

To a solution of 2 g. of crude (XXV) in 35 cc. of dehyd. pyridine was added dropwise 10 cc. of POCl₃ with stirring under ice-cooling. Then the reaction mixture was refluxed for 2 hr. the same process as 1-phenyl-3H-naphtho[2,1-b]pyran and recrystallization from EtOH gave 1.4 g. of colorless plates of m.p. 96.5~97.5. *Anal.* Calcd. for C₁₉H₁₄O: C, 88.34; H, 5.46; O, 6.20. Found: C, 88.36; H, 5.56; O, 6.08. UV $\lambda_{\text{max}}^{\text{EtOH}}$ m μ (log ϵ): 226 (4.74), 248 (4.58) (shoulder), 262 (4.49), 271 (4.37), 328 (3.65) (shoulder), 338 (3.68), 350 (4.62).

The authors express their gratitude to Mr. Matsui, the Director of this Laboratory, and Prof. K. Tsuda of the University of Tokyo for encouragement throughout this work, and especially thank for kind advices of Dr. Y. Okajima. Thanks are also due to Mr. T. Onoe, Mr. H. Nagashima, Miss C. Furukawa for microanalysis, and Miss N. Sawamoto and Mr. N. Higosaki for the measurement of infrared and ultraviolet spectra.

Summary

It has been reported that 2-naphthyl allylic ethers undergo the Claisen rearrangement to give naphthol derivatives. 2-naphthyl propargyl ether derivatives,

$\text{O}\cdot\text{CH}_2\text{C}\equiv\text{C}-\text{R}$ ($\text{R}=\text{H}, \text{CH}_3, \text{Ph}.$), replacing the double bond of allylic ethers by a triple bond, do not undergo the Claisen rearrangement but a new ring-closure to give

3*H*-naphtho[2,1-*b*]pyran derivatives. Moreover, 1-naphthyl derivatives,

also undergo the same ring-closure to give 4-phenyl-2*H*-naphtho[1,2-*b*]pyran. The structures of new pyran derivatives obtained by the new ring-closure were confirmed by the melting point, infrared and ultraviolet spectra of the authentic samples which were synthesized by another routes.

(Received July 4, 1961)

UDC 615.771.7:547.852.2

148. Takanobu Itai and Shigeru Sako : Potential Anti-cancer Agents. V. 3,6-Disubstituted 4-Nitropyridazine 1-Oxides and their Derivatives.

(National Institute of Hygienic Sciences*¹)

On the nitration of 3-methoxy- and 3,6-dimethoxy-pyridazine 1-oxides had been reported by Itai and Igeta,¹⁾ Igeta,^{2,3)} and by Nakagome.⁴⁾ In our third paper⁵⁾ of this series, syntheses of 3,6-dialkoxy-4-nitropyridazine 1-oxides and their anti-cancer actions were reported. Synthesis of 3-alkoxy-6-chloropyridazine 1-oxides were given in our fourth paper.⁶⁾ Now, nitration of 3-methoxy- and 3-hydroxy-6-chloropyridazine 1-oxides and reactions of their products will be reported in this paper.

On hydrolysis of 3-methoxy-6-chloropyridazine 1-oxide (Ia) with 5% sodium hydroxide, 6-chloro-3-pyridazinol 1-oxide (Ib) was produced. Nitration of these two compounds was carried out with sulfuric acid-nitric acid at 50°, which occurred rather easily, but was more difficult than for 3-methoxy- or 3,6-dimethoxypyridazine 1-oxides. As nitration did not occur of 3-methoxypyridazine, it was clear that contribution of

*¹ Tamagawa-Yoga, Setagaya, Tokyo (板井孝信, 佐子 茂).

1) T. Itai, H. Igeta : Yakugaku Zasshi, **75**, 966 (1955).

2) H. Igeta : This Bulletin, **7**, 938 (1959).

3) *Idem* : *Ibid.*, **8**, 550 (1960).

4) T. Nakagome : Yakugaku Zasshi, **80**, 712 (1960).

5) T. Itai, S. Sako : This Bulletin, **9**, 149 (1961).

6) *Idem* : *Ibid.*, **10**, 989 (1962).