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74. **Saburo Akagi**[*1] **and Yutaka Okada**[*2] **:** Bromo Derivative of Cholestadienone.[*3]

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Karrer, *et al.*(1) first reported that bromination of cholesta-3,5-dien-7-one (I) with N-bromosuccinimide afforded a monobromide, m.p. 132~133°, which was heated with collidine to yield two substances, cholesta-1,3,5-trien-7-one, m.p. 121°, and 1-methyl-19-norcholesta-1,3,5-trien-7-one, m.p. 203°, but they corrected(2) these substances to cholesta-3,5,8(14)-trien-7-one and cholesta-3,5,8(9)-trien-7-one, respectively, and bromination was assumed to have occurred at 8-position. Walls, *et al.*(3) supported the structure of cholesta-1,3,5-trien-7-one and assumed the by-product of m.p. 203° to be cholesta-5,8(9),14(15)-trien-7-one or cholesta-5,8(14),9(11)-trien-7-one. Henbest, *et al.*(4) thought the formula (III) to be reasonable and assumed the by-product to be a dimeric isomer of the compound (III).

The present paper described the results obtained from further investigations on the bromination of cholesta-3,5-dien-7-one (I) as a part of this series. It was confirmed that the bromination occurred at 2-position, the allylic position adjacent to a double bond, and that the dehydrobromination of the monobromide afforded cholesta-1,3,5-trien-7-one (III) as the main product. The monobromide(1) was heated with collidine and gave yellow leaflets (III) of m.p. 121° and a white crystalline substance (IV) of m.p. 203° in 70% and 6% yield, respectively. The elemental analyses of (III) and (IV) agreed with cholestatrienone. (III) showed ultraviolet absorption maximum at 348 mμ, which was a large bathochromic displacement from that of many dienones, and its C=O stretching absorption band was found at a considerably lower frequency (1653 cm^{-1}).(5) These data seemed to support the presence of a conjugated trienone system in (III). When (III) was hydrogenated with Raney nickel W-4 in dioxane, it absorbed about 2 moles of hydrogen rapidly and absorbed about 1 mole slowly to yield white leaflets (VI) of m.p. 112~114°, in a good yield. (VI) was identical with 5α-cholestan-7-one in ultraviolet and infrared spectra, and the mixed melting point. When the hydrogenation was stopped after about 2.5 moles of hydrogen had been consumed, a mixture of about equal parts of 5α-cholestan-7-one (VI), m.p. 112~114°, and white leaflets (V), m.p. 127~128°, were obtained. Ultraviolet and infrared spectra of (V) agreed with those of cholest-5-en-7-one and the mixed melting point was not depressed.

Above fact agreed with the experimental results(6) that the double bond in the ring-A was more reactive to catalytic hydrogenation than Δ^5- double bond, and that a double bond existing between two rings such as $\Delta^{8(9)}$ is generally resistant to hydrogenation, which was not hydrogenated even with such a catalyst as Raney nickel.(7) From these informations it was evident that a conjugated double bond system was present in ring-A.

In order to prove more completely the presence of a conjugated double bond of cisoid

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1) P. Karrer, A.R. Naik : Helv. Chim. Acta, **32**, 2392 (1949).
2) *Idem* : *Ibid.*, **36**, 1527 (1953).
3) F. Walls, H.J. Flores, A. Sandoval : Bol. inst. quim. univ. nal. auton. Mé., **4**, 47 (1952) (C.A., **47**, 9337 (1953)).
4) H.B. Henbest, R.A.L. Wilson : Chem. & Ind. (London), **1956**, 56.
5) R.N. Jones, F. Herling : J. Org. Chem., **19**, 1252 (1954).
6) S. Akagi, K. Tsuda : This Bulletin, **9**, 464 (1961).
7) *a*) H.J.E. Loewenthal : Tetrahedron, **6**, 269 (1959). *b*) H. Wieland, W. Benend : Ann., **554**, 1 (1943).

form in ring-A, attempt was made to react (III) with maleic anhydride to obtain an adduct by the Diels-Alder reaction. (III) was heated with maleic anhydride in xylene to give white needles of m.p. 174~176° in a good yield. Ultraviolet and infrared spectra of this product indicated the presence of Δ^5-double bond and an anhydride which showed a couple of bands at 1750~1850 cm^{-1}, characteristic to the latter, and it was also found that Δ^2-double bond did not undergo rearrangement to conjugate with Δ^5. Its analytical values agreed with those for cholesta-1,3,5-trien-7-one-maleic anhydride adduct, so that the structure of (VII) was assigned to this product.

In this reaction, the isomer was not obtained and it seemed that only the $1\alpha,4\alpha$-addition took place, because maleic anhydride would attack only from the rear side of (III) by the steric hindrance of the methyl group in 10-position. In cyclic dienes, it is known[8] that the transoid-form diene did not form the adduct and only the cisoid-form diene did.

Therefore, attempt was made to prepare the adduct of maleic anhydride under the same condition, but neither cholesta-3,5-dien-7-one nor cholesta-4,6-dien-3-one reacted and both were recovered unchanged in 60~70% yield. These results supported the structure assigned to (VII).

When the maleic anhydride adduct (VII) was hydrolyzed with methanolic alkali solution, a colorless gummy substance, which showed characteristic absorption bands for carboxylic acid instead of anhydride, was obtained and since it did not crystallize it was converted to its 2,4-dinitrophenylhydrazone as orange needles of m.p. 152~154°, and to the dimethyl ester (VIII) of white leaflets, m.p. 147~149°.

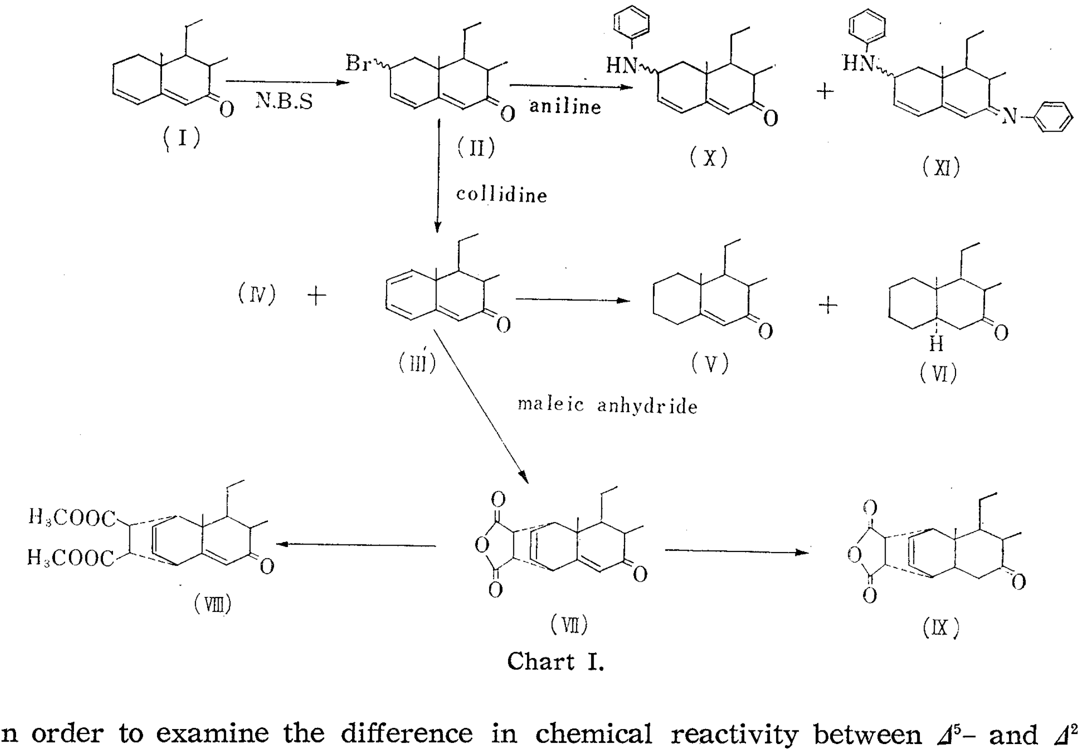

Chart I.

In order to examine the difference in chemical reactivity between Δ^5- and Δ^2-double bonds, (VII) was hydrogenated with Raney nickel W-4 and about 1 mole of hydrogen was absorbed to form white leaflets of m.p. 178~180°. Its ultraviolet absorption maximum showed a week peak (ε 103) at 291 mμ due to the nonconjugated carbonyl group, and infrared spectrum indicated the absorption of a 7-keto group at 1717 cm^{-1}, indicating that the double bond at Δ^5 had readily been hydrogenated. These data did not afford any informa-

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[8] L.F. Fieser, M. Fieser : "Steroids," 21~24 (1959). Reinhold Publishing Corp., New York.

tion with regard to the Δ^2-double bond, but it is assumed that Δ^5-double bond was more reactive than Δ^2, and the hydrogenated product was assumed to be (IX).

The reaction of (II) with aniline was then taken up. (II) was heated with aniline at 100° for 1.5 hours. If the bromine atom is reactive, dehydrobromination should have occurred to form a double bond, but in this substance, as in the case of cholest-5-en-7-one, substitution occurred to yield 2-(phenylamino)cholesta-3,5-dien-7-one (X) and a small amount of 2-(phenylamino)-7-(phenylimino)cholesta-3,5-diene (XI). When (II) was heated at 130~135°, only 2-(phenylamino)-7-(phenylimino)cholesta-3,5-diene (XI) was obtained in a good yield.

The structures assumed for the compound (IV) by Walles, *et al.*[4] is not be acceptable. As was found, (III) reacts with maleic anhydride comparatively easily and it seems possible that (IV) is the dimeric isomer suggested by Henbest.[5] The intensity of ultraviolet absorption maximum also suggests the dimeric structure for (IV).

Experimental

Cholesta-1,3,5-trien-7-one (III)——A solution of 1 g. of (II) in 3 cc. of freshly distilled methyl-ethyl-collidine was heated at 190~200° for 3 hr. The cooled mixture was diluted with 20 cc. of petr. ether, the methyl-ethyl-collidine hydrobromide that precipitated was filtered and washed with two 10-cc. portions of petr. ether. The combined filtrate and washings were washed with dil. HCl solution, H_2O, dil. Na_2CO_3 solution, and H_2O, and dried over anhyd. Na_2SO_4. The crystalline substance obtained on evaporation of the solvent was dissolved in hot MeOH, and a small amount of insoluble substance that separated out was crystallized from AcOEt to yield 50 mg. of white crystalline substance (IV), m.p. 203°. UV : λ_{max}^{EtOH} 284 mμ. IR ν_{max}^{Nujol} cm^{-1} : 1663 (C=O), 1635 (C=C), 1600 (C=C). *Anal.* Calcd. for $C_{27}H_{40}O$: C, 85,20; H, 10.59. Found : C, 85.10; H, 10.34.

MeOH solution was evaporated, the residue was dissolved in 20 cc. of petr. ether, and adsorbed on 20 g. of Al_2O_3. The column was washed with petr. ether and this washing was discarded. The eluate from petr. ether-benzene (1:1) afforded 600 mg. of a yellow crystalline substance which was recrystallized from MeOH-petr. ether to yellow leaflets, m.p. 121°. UV λ_{max}^{EtOH} mμ (ε) : 230 (15,200), 348 (9,200). IR ν_{max}^{Nujol} cm^{-1} : 1653 (C=O), 1588 (C=C), 1548 (C=C). *Anal.* Calcd. for $C_{27}H_{40}O$: C, 85.20; H, 10.59. Found : C, 84.80; H, 10.52.

(II) was heated with pyridine at 120° for 2 hr., the reaction mixture was diluted with Et_2O, and a white amorphous substance precipitated. This substance seemed to be the pyridinium salt of (II) from its UV and IR spectra, and analytical values.

Hydrogenation of Cholesta-1,3,5-trien-7-one (III)——i) A suspension of 1 g. of Raney Ni W-4 and 30 cc. of dioxane was shaken in H_2 stream until H_2 was no longer absorbed. Then 500 mg. of (III) was added and shaken. About 2 moles of H_2 was absorbed rapidly during several minutes and then about 1 mole of H_2 was absorbed slowly during 1 hr. After filtration, dioxane was evaporated in a reduced pressure to leave a white crystalline substance. Recrystallization from EtOH afforded 350 mg. of white leaflets (VI), m.p. 112~114°, which was identical with cholestan-7-one in UV and IR spectra, and mixed melting point. UV : λ_{max}^{EtOH} 292 mμ (ε 44). IR : ν_{max}^{Nujol} 1708 cm^{-1} (C=O). *Anal.* Calcd. for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found : C, 84.14; H, 12.11.

ii) In the same way as described above, 300 mg. of (III) was hydrogenated with about 0.6 g. of Raney Ni W-4 in 30 cc. of dioxane. Hydrogenation was stopped when about 2.5 moles of H_2 was absorbed. The mixture was treated as above to afford 160 mg. of white crystalline substance of m.p. 117~123°. This was dissolved in 10 cc. of petr. ether containing benzene and adsorbed on 10 g. of Al_2O_3. The column was eluted with petr. ether-benzene (2:1, 1:1, 1:2) and 70 mg. of white crystalline substance obtained from the first eluate was recrystallized from EtOH to white leaflets, m.p. 112~114°, which was identical with 5α-cholestan-7-one (VI) in mixed melting point and IR spectrum. From the second eluate, 80 mg. of white crystalline substance was obtained. Recrystallization from EtOH gave white leaflets, m.p. 127~128°, which was identical with cholest-5-en-7-one in UV and IR spectra, and mixed melting point. UV : λ_{max}^{EtOH} 238 mμ (ε 13,500). IR ν_{max}^{Nujol} cm^{-1} : 1671 (C=O), 1636 (C=C). *Anal.* Calcd. for $C_{27}H_{44}O$: C, 84.31; H, 11.56. Found : C, 83.96; H, 11.38.

Cholesta-1,3,5-trien-7-one-Maleic Anhydride Adduct (VII)——i) A mixture of 1 g. of (III) and 0.5 g. of freshly sublimated maleic anhydride was heated in 2.5 cc. anhyd. xylene at 135° for 8 hr. Xylene was removed in a reduced pressure, leaving a reddish oil, which crystallized on adding MeOH. MeOH was added to this crystalline substance which was dissolved in a minimum amount of Me_2CO and it was allowed to stand in a refrigerator to deposit 740 mg. of colorless plates, m.p. 172~175°. Further recrystallization gave analytical sample of m.p. 174~176°. UV : λ_{max}^{EtOH} 249 mμ (ε 12,200). IR ν_{max}^{Nujol} cm^{-1}:

1663 (C=O), 1630 (C=C), 1858, 1833, 1770 (acid anhydride). $[\alpha]_D^{25}$ $-118°$ (c=1.08, $CHCl_3$). *Anal.* Calcd. for $C_{31}H_{42}O_4$: C, 77.79; H, 8.85. Found: C, 77.84; H, 9.01.

ii) In the same manner as described above, 1.2 g. of (Ⅲ) was treated with 0.6 g. of freshly sublimated maleic anhydride. The residue was shaken for 15 min. with slight warming with a mixture of 30 cc. of MeOH and 120 cc. of *N* KOH, and extracted twice with Et_2O. The alkaline solution was acidified with conc. HCl under cooling and extracted with three 50-cc. portions of Et_2O. The extract was washed thoroughly with H_2O, dried over anhyd. Na_2SO_4, and Et_2O was evaporated to leave 1.2 g. of an oil. This was foamy and could not be crystallized from any organic solvents. Therefore 500 mg. of this product was treated with 2,4-dinitrophenylhydrazine and yielded a crystalline hydrazone which was recrystallized from MeOH to deep orange crystalline powder, m.p. 152~154°. *Anal.* Calcd. for $C_{37}H_{48}O_8N_4$: C, 65.61; H, 7.15; N, 8.28. Found: C, 65.99; H, 7.33; N, 8.33.

To a solution of 700 mg. of the foamy substance dissolved in 40 cc. of Et_2O, Et_2O solution of CH_2N_2 was added dropwise. N_2 evolved vigorously and yellowish color of CH_2N_2 solution faded. After evolution of N_2 was over, CH_2N_2 was added in excess and the mixture was allowed to stand overnight. Et_2O was evaporated to give a white crystalline product. Recrystallization from MeOH yielded 600 mg. of leaflets, m.p. 147~149°. UV: λ_{max}^{EtOH} 247 $m\mu$ (ε 12,400). IR ν_{max}^{Nujol} cm^{-1}: 1670 (C=O), 1642 (C=C), 1745 ($-COOCH_3$). *Anal.* Calcd. for $C_{33}H_{48}O_5$: C, 75.70; H, 9.22. Found: C, 75.59; H, 9.34.

Catalytic Hydrogenation of Maleic Anhydride Adduct (VII)——In the same manner as described above, 800 mg. of (Ⅶ) was hydrogenated with 1 g. of Raney Ni in 25 cc. of dioxane. About 1 mole of H_2 was absorbed. After filtration, dioxane was evaporated in a reduced pressure and crystallization of the residue from MeOH gave 290 mg. of a white crystalline substance, m.p. 176~178°. Concentration of the mother liquor gave 100 mg. of a white crystalline substance, m.p. 173~175°. Petr. ether was added to this crystalline substance, which was dissolved in a minimum amount of Me_2CO, allowed to stand in a refrigerator, and gave white needles (Ⅷ), m.p. 178~180°. UV: λ_{max}^{EtOH} 291 $m\mu$ (ε 103). IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O), 1860, 1787, 1776 (acid anhydride). $[\alpha]_D^{25}$ $+147°$ (c=1.19, $CHCl_3$). *Anal.* Calcd. for $C_{31}H_{44}O_4$: C, 77.49; H, 9.23. Found: C, 77.48; H, 9.19.

Reaction of 2-Bromocholesta-3,5-dien-7-one (II) with Aniline——i) To a solution of (Ⅱ) in 8 cc. of benzene, 12 cc. of aniline was added and the mixture was heated at 100° for 1.5 hr. When the reaction mixture was cooled to room temperature, 200 mg. of white crystals (1), m.p. 207~210°, separated. The residue left after evaporation of benzene in a reduced pressure crystallized from petr. ether to 400 mg. of white crystalline substance (2), m.p. 239~243°. Further recrystallization was repeated for analytical sample, m.p. 247~249°, which was identical with 2-(phenylamino)cholesta-3,5-dien-7-one (X) in analytical values. The IR absorption spectra showed that these substances (1) and (2) were identical. UV: $\lambda_{max}^{CHCl_3}$ 273 $m\mu$ (ε 32,000). IR ν_{max}^{Nujol} cm^{-1}: 3410 (N-H), 1660 (C=O), 1621 (C=C). $[\alpha]_D^{25}$ $+3.7$ (c=1.06, $CHCl_3$). *Anal.* Calcd. for $C_{33}H_{47}ON$: C, 83,32; H, 9.96; N, 2.94. Found: C, 83.15; H, 9.80; N, 3.16.

The mother liquor was concentrated to 10 cc. and adsorbed on 5 g. of Al_2O_3. The eluate from petr. ether gave a crystalline product which was recrystallized from petr. ether-MeOH to 25 mg. of yellow needles, m.p. 210~211°, identical with 2-(phenylamino)-7-(phenylimino)cholesta-3,5-diene (Ⅺ) in analytical values. UV: $\lambda_{max}^{CHCl_3}$ 415 $m\mu$ (ε 20,800). IR ν_{max}^{Nujol} cm^{-1}: 3346 (N-H), 1622 (C=C). *Anal.* Calcd. for $C_{39}H_{52}N_2$: C, 85.53; H, 9.55; N, 5.10. Found: C, 85.45; H, 9.27; N, 5.45.

ii) A solution of 500 mg. of (Ⅱ) in 10 cc. of freshly distilled aniline was heated at 130~135° for 1.5 hr. The solution was evaporated in a reduced pressure, the residue was dissolved in 10 cc. of petr. ether containing benzene, and adsorbed on 20 g. of Al_2O_3. The column was washed with petr. ether and this washing was discarded. From the benzene eluate, 380 mg. of yellow crystalline product, m.p. 204~210°, was obtained, which was recrystallized from petr. ether to yellow needles, m.p. 210~211°. IR spectrum of this substance was identical with that of 2-(phenylamino)-7-(phenylimino)cholesta-3,5-dien-7-one.

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Summary

Bromination of cholesta-3,5-dien-7-one (I) with N-bromosuccinimide afforded 2-bromocholesta-3,5-dien-7-one (Ⅱ) and dehydrobromination of (Ⅱ) yielded cholesta-1,3,5-trien-7-one (Ⅲ), whose structure was established by leading it to the maleic anhydride adduct (Ⅶ) and hydrogenation.

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