violet spectra. Furthermore, it quantitatively gave codeine by reduction with sodium borohydride.

Experimental

14-Bromocodeinone (II)——Thebaine (62.2 g.) was treated with N-bromosuccinimide in 2 : 1 (by volume) Me_2CO-H_2O mixture under the condition of Conroy's report,[3] and then gave 14-bromocodeinone, yellow crystals. The yield, after drying at 60°, was 54.0 g. (71.8%).

Codeinone (III)——To a solution of 14-bromocodeinone (15 g., 0.04 mol.) in 40 ml. of AcOH, Zn-dust (3.12 g., 0.04×1.2 mol.), activated by dil. HCl, was added in small portions with stirring during 15 min., maintaining at 15~17° by external cooling. After addition, the mixture was stirred for 3.5 hr. at room temperature (20~22°) and then poured into 250 ml. of ice-water. This mixture was filtered to remove a trace of unreacted Zn-dust and the filtrate was made alkaline with conc. NH_4OH, extracted with three 150 ml. portions of $CHCl_3$. The organic phase was washed with H_2O, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was dissolved in 50 ml. of benzene and to this solution, 400 ml. of petr. ether was added. After the separation of solid, the filtrate was concentrated *in vacuo*. The residue was crystallized, m.p. 163~166°. After recrystallization from AcOEt, it showed m.p. 181~182°, undepression on admixture with authentic sample[4,5] and IR spectra of the two samples were identical. The total yield was 3.55 g. (30.0%). *Anal.* Calcd. for $C_{18}H_{19}NO_3$: C, 72.73; H, 6.40; N, 4.71. Found : C, 73.14; H, 6.39; N, 5.02.

Codeine (IV)——To the solution of codeinone (4.0 g.) in 20 ml. of MeOH, $NaBH_4$ (10 g.) in 240 ml. of MeOH was added, and allowed to stand at room temperature (20~25°) for 1.5 hr., then concentrated under reduced pressure to about 1/3 volume, and diluted with 200 ml. of 10% NaOH. The solution was heated on the steam-bath until boiling, diluted with 300 ml. of H_2O and extracted with four 100 ml. portions of $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4, and the solvent was removed by distillation *in vacuo*. The residue was crystallized, m.p. 149~152°. After recrystallization from benzene, it showed m.p. 154~156°, undepressed on admixture with natural codeine and IR and UV spectra of both samples were identical. The yield was 3.7 g. (91.8%).

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Summary

Treatment of 14-bromocodeinone, prepared from thebaine, with zinc-dust in glacial acetic acid gave codeinone, m.p. 181~182°. Codeinone was quantitatively reduced to codeine with sodium borohydride.

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Katsuaki Matsui, Saburo Akagi, and Fukutaro Ugai : Chemical Constituents of the Alkaloid-free Fraction from Opium.

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The alkaloid-free press-cake, which obtained from opium in the usual manner, was extracted with methanol and the extract was evaporated under a reduced pressure.

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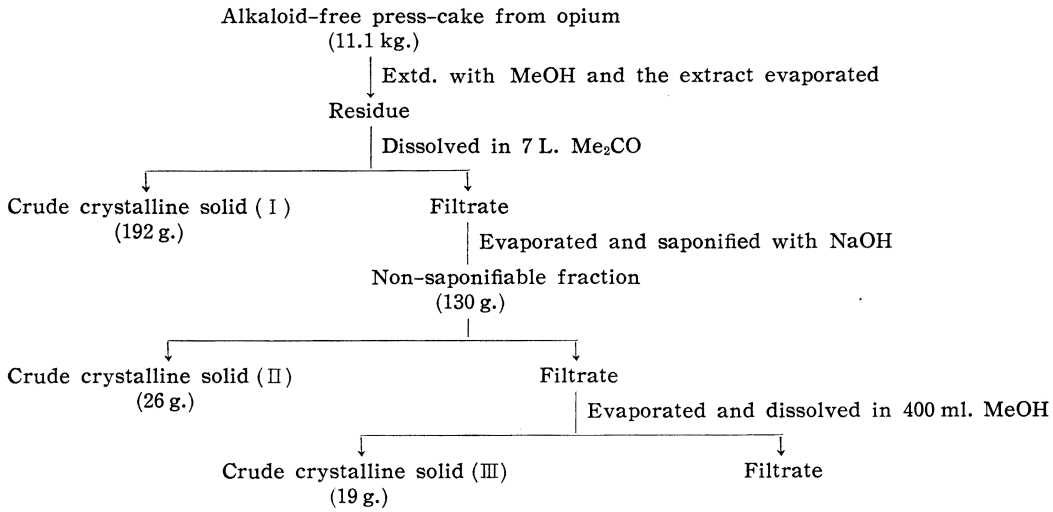
The residue gave three crude crystalline solids (I, II, III) as shown in Chart 1.

Chart 1. Isolation of crude Crystalline Solids (I, II, III)



Acetylation of the crude crystalline solid (I) followed by chromatography gave an acetate (V), m.p. 121~122°, $[\alpha]_D^{25}$ −20° (c=2, $CHCl_3$), and an acetate (VI), m.p. 164~165°, $[\alpha]_D^{25}$ −25° (c=2, $CHCl_3$).

Hydrolysis of (V) or (VI) with methanolic potassium hydroxide gave white prisms (VII), m.p. 288~290°. The Liebermann-Burchard test and the reduction of Fehling's solution indicated that (VII) was a steroidal glucoside.

Table I. Comparison of Constants obtained in the Present Work with those of Salway[1] Matlack[2] Kondo[3] Swift[4] Joshi[6] on Corresponding Compounds

	Present work		Salway[1]		Matlack[2]	
	m.p. (°C)	$[\alpha]_D^{25}$	m.p. (°C)	$[\alpha]_D$	m.p. (°C)	$[\alpha]_D$
β-Sitosteryl glucoside	288~290	—	295~300	—	280	—
β-Sitosteryl glucoside tetraacetate	164~165	−25	166~167	−22.9	164~165	—
β-Sitosteryl glucoside tetrabenzoate	196~198	+16	198	+18.3	198	—
β-Sitosterol	136~137	−35	138	−32.2	136~137	—
β-Sitosteryl acetate	127~128	−41	—	—	124~125	—
β-Sitosteryl benzoate	146~147	−13.5	—	—	—	—

	Kondo[3]		Swift[4]		Joshi[6]	
	m.p. (°C)	$[\alpha]_D^{25}$	m.p. (°C)	$[\alpha]_D$	m.p. (°C)	$[\alpha]_D$
β-Sitosteryl glucoside	252~254	—	298	−40	272~275	—
β-Sitosteryl glucoside tetraacetate	166~166.5	—	171	−33.7	167~168	−25.1
β-Sitosteryl glucoside tetrabenzoate	—	—	201	+15.9	—	—
β-Sitosterol	138	—	137~138	−38.2	—	—
β-Sitosteryl acetate	—	—	125~126	−40.3	—	—
β-Sitosteryl benzoate	—	—	147~148	−13.6	—	—

1) A. H. Salway : J. Chem. Soc., **1913**, 1022.
2) M. B. Matlack : J. Am. Pharm. Assoc., **18**, 24 (1929).
3) K. Kondo : Nippon Kagaku Zasshi, **57**, 1128 (1936).
4) L. J. Swift : J. Am. Chem. Soc., **74**, 1099 (1952).

From the infrared spectrum,[5,6] melting point and optical rotation of (Ⅶ), and those of its derivatives, (Ⅶ) was identified as the β-sitosteryl-D-glucoside (Table I).

The identification of the β-sitosterol obtained by hydrolysis of (Ⅶ) was established on the basis of close agreement of its infrared spectrum,[5] melting point and optical rotation, and those of its derivatives with the values obtained by other investigators.

From the filtrate obtained by hydrolysis of (V), palmitic acid was isolated. On the basis of the carbon and hydrogen analysis, (V) was assigned to the molecular formula $C_{57}H_{96}O_{10}$. From these findings, (V) was assumed to be the monopalmityl-triacetyl-D-glucoside of β-sitosterol.

Chromatography of the crude crystalline solid (Ⅱ) gave a white prisms (Ⅸ), m.p. 81~82°. and needles (X), m.p. 124~126°, $[\alpha]_D^{25}$ +46°(c=2, $CHCl_3$). From the infrared spectrum, melting point and optical rotation of (Ⅸ) and (X), and those of their derivatives, (Ⅸ) was identified as (+)-10-nonacosanol, and (X) was identified as *cyclo*-laudenol, which isolated by Bentley *et al.*[7] from opium.

Chromatography of the crude crystalline solid (Ⅲ) gave needles (XI), m.p. 112~115°, $[\alpha]_D^{25}$ +54°(c=2, $CHCl_3$), which gave a deep red solution with a strong green fluorescence in the Liebermann-Burchard test.

From the infrared spectrum,[8] melting point and optical rotation of (XI), and those of its derivatives, (XI) was identified as *cyclo*-artenol, which isolated by Bentley *et al.*[9] from the seed of *Strychnos nux-vomica* L.

Table Ⅱ. Comparison of Constants obtained in the Present Work with those of Bentley[9] on Corresponding Compounds

	Present work		Betley[9]	
	m.p. (°C)	$[\alpha]_D^{25}$	m.p. (°C)	$[\alpha]_D^{25}$
cyclo-Artenol	112~115	+52.5	115	+54
cyclo-Artenyl acetate	122~123	+59	122~124	+59.5
cyclo-Artenyl benzoate	130~131	+72	130	+76
cyclo-Artanyl acetate	130~131	+58	130~132	+59

Experimental

Extraction of the Crude Crystalline Solid——11.1 kg. of powdered alkaloid-free press-cake from opium was extracted twice with boiling MeOH with stirring, and the combined extracts were evaporated under a reduced pressure. The residue was dissolved in 7 L. of Me_2CO, and the solution was kept for 24 hr. in a refrigerator. The crude crystalline solid (I, 192 g.) that precipitated on cooling the solution was collected by filtration, and the filtrate was evaporated under a reduced pressure. The residue was dissolved in 2.24 L. of MeOH, and refluxed with a saturated NaOH (560 g.) solution for 3 hr. The non-saponifiable fraction (130 g.) was isolated by means of iso-propyl ether in the usual manner.

A solution of the non-saponifiable fraction in Me_2CO (600 ml.) was kept for 24 hr. in a refrigerator, and the separated crude crystalline solid (Ⅱ, 26 g.) was collected by filtration. The filtrate was evaporated under a reduced pressure, and the residue in MeOH (400 ml.) was kept for 24 hr. at room temperature. The crude crystallized solid (Ⅲ, 19 g.) was collected.

Acetylation and Chromatography of Crude Crystalline Solid (I)——A mixture of 192 g. of (I) in Ac_2O (200 g.) and dry pyridine (400 ml.) was kept for 24 hr. at room temperature, the solvents were removed by heating under a reduced pressure, and the residue was dissolved in 1.7 L. of MeOH. A precipitate that formed on cooling the MeOH solution for 24 hr. was collected, and thrice recrystallized from EtOH. The yield was 40.3 g. (Ⅳ), m.p. 132~142°.

A solution of (Ⅳ, 40.3 g.) in benzene was percolated through a column (4×40 cm.) of neutral

5) R.M. Ma, P.S. Schaffer: Arch. Biochem. Biophys., **47**, 419 (1953).
6) D.V. Joshi, S.F. Boyce: J. Org. Chem., **22**, 95 (1957).
7) H.R. Bentley, J.A. Henry, D.S. Irvin, D. Mukerji, F.S. Spring: J. Chem. Soc., **1955**, 596.
8) A.R.H. Cole: J. Chem. Soc., **1954**, 3810.
9) H.R. Bentley, J.A. Henry, D.S. Irvin, D. Mukerji, F.S. Spring: *Ibid.*, **1953**, 3673.

alumina (400 g.), and the chromatogram eluted with a) benzene (3.6 L.), b) benzene-Et_2O (1 : 1, 3.6 L.), c) benzene-MeOH (1 : 1, 2 L.). Evaporation of fraction a) gave a solid 14.3 g. (IVa), m.p. 110~113°, and fraction b) gave a solid 12.3 g. (IVb.), m.p. 160~163°.

Monoparmityl-triacetyl-D-glucoside of β-Sitosterol (V)——A solution of (IVa, 14.3 g.) in benzene was percolated through a column (3×30 cm.) of neutral alumina (175 g.), and the chromatogram eluted with benzene (1.2 L.). Evaporation of benzene gave a solid, which was twice recrystallized from EtOH to white crystalline mass, m.p. 121~122°, $[\alpha]_D^{25}$ −20° (c=2, $CHCl_3$), yield, 4.5 g. *Anal.* Calcd. for $C_{57}H_{96}O_{10}$: C, 72.72; H, 10.28. Found C, 72.67; H, 10.28.

The filtrate, which obtained by the hydrolysis of (V) (3.0 g.) with MeOH-KOH (1.5 g.) was evaporated under a reduced pressure, and the residue was diluted with water, and acidified with HCl. A white crystallized solid was collected, and washed with water, and recrystallized from MeOH to white crystalline scales, m.p. 57~60°, yield 0.2 g, which showed no depression in m.p. on admixture with palmitic acid.

β-Sitosteryl-D-glucoside tetraacetate (VI)——12.3 g. of (IVb) was thrice recrystallized from EtOH to plates, m.p. 164~165°, $[\alpha]_D^{25}$ −25° (c=2, $CHCl_3$), yield, 9.8 g. *Anal.* Calcd. for $C_{43}H_{68}O_{10}$: C, 69.30; H, 9.20. Found : C, 69.21; H, 8.96.

β-Sitosteryl-D-glucoside (VII)——Hydrolysis of (V, 3.0 g.) or (VI, 3.0 g.) with MeOH-KaOH (1.5 g.) gave a white prisms, which were insoluble in most of the organic solvents, but soluble in pyridine, m.p. 288~290°(decomp.), yield, 2.2 g. *Anal.* Calcd. for $C_{35}H_{60}O_6$: C, 72.85; H, 10.49. Found : C, 72.52; H, 10.46.

(VII) gave positive Liebermann-Burchard reaction.

β-Sitosteryl-D-glucoside tetrabenzoate——One g. of (VII) in pyridine (10 ml.) was heated with BzCl (7 ml.) for 30 min. The benzoate recrystallized from EtOH to needles, m.p. 196~198°, $[\alpha]_D^{25}$ +16° (c=2, $CHCl_3$), yield, 1.4 g. *Anal.* Calcd. for $C_{63}H_{76}O_{10}$: C, 76.21; H, 7.71. Found : C, 76.47; H, 7.96.

Hydrolysis of the β-Sitosteryl-D-glucoside (VII)——Three g. of (VII) was hydrolyzed by refluxing for 2 hr. with a mixture of 60 ml. of AmOH and 20 ml. of 16% HCl. Most of the alcohol was removed by heating under a reduced pressure, and the aqueous acid solution was diluted with water, and extracted with several portions of Et_2O. The Et_2O solution was washed with water and the washings were added to the main solution. The aqueous solution was neutralized with dil. NaOH and concentrated to 10 ml. under a reduced pressure. Fehling's solution was reduced with this concentrated solution.

β-Sitosterol (VIII)——The Et_2O extract of the hydrolysis of (VII) was dried over Na_2SO_4 and evaporated. The residue was recrystallized from EtOH to plates, m.p. 136~137°, $[\alpha]_D^{25}$ −35° (c=2, $CHCl_3$), yield, 0.9 g. *Anal.* Calcd. for $C_{29}H_{50}O$: C, 83.99; H, 12.15. Found : C, 83.65; H, 11.98.

β-Sitosteryl acetate was prepared in the usual way, m.p. 127~128°, $[\alpha]_D^{25}$ −41° (c=2, $CHCl_3$). *Anal.* Calcd. for $C_{31}H_{52}O_2$: C, 81.52; H, 11.48. Found : C, 81.45; H, 11.21.

β-Sitosteryl benzoate was prepared in the usual way, m.p. 146~147°, $[\alpha]_D^{25}$ −13.5° (c=2, $CHCl_3$). *Anal.* Calcd. for $C_{36}H_{54}O_2$: C, 83.34; H, 10.49. Found : C, 83.12; H, 10.30.

Chromatography of Crude Crystalline Solid (III)——A solution of the crude crystalline solid (III, 10.0 g.) in benzene was percolated through a column (3×26 cm.) of alumina (150 g.), and the chromatogram eluted with a) benzene (1.2 L.), b) benzene-Et_2O (19 : 1, 700 ml.), c) benzene-MeOH (19 : 1, 400 ml.), d) MeOH (200 ml.).

***cyclo*-Artenol (XI)**——Evaporation of the solution b) gave a solid, which was recrystallized from MeOH to needles, m.p. 99~102°. and raised to m.p. 112~115° after drying for 12 hr. at 65° *in vacuo*. $[\alpha]_D^{25}$ +52.5° (c=2, $CHCl_3$). Yield, 3.4 g. *Anal.* Calcd. for $C_{30}H_{50}O$: C, 84.44; H 11.81. Found : C, 84.16; H, 11.58.

cyclo-Artenyl acetate was prepared in the usual way, m.p. 122~123°, $[\alpha]_D^{25}$ +59.5° (c=2, $CHCl_3$). *Anal.* Calcd. for $C_{32}H_{52}O_2$: C, 81.99; H, 11.18. Found : C, 82.17; H, 11.20.

cyclo-Artenyl benzoate was prepared in the usual way, m.p. 130~131°, $[\alpha]_D^{25}$ +58° (c=2, $CHCl_3$). *Anal.* Calcd. for $C_{37}H_{54}O_2$: C, 83.72; H, 10.25. Found : C, 84.05; H, 10.16.

***cyclo*-Artanyl acetate**——Hydrogenation of *cyclo*-artenyl acetate in presence of Pt catalyst in AcOH gave *cyclo*-artanyl acetate, as needles from MeOH-$CHCl_3$, m.p. 130~131°, $[\alpha]_D^{25}$ +58° (c=2, $CHCl_3$). *Anal.* Calcd. for $C_{32}H_{54}O_2$: C, 81.64; H, 11.56. Found : C, 81.36; H, 11.31.

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Summary

From the alkaloid-free fraction of opium, β-sitosteryl-D-glucoside and its monopalmitate, (+)-10-nonacosanol, *cyclo*-laudenol and *cyclo*-artenol were isolated.

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