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# THE SYNTHESIS OF CODEINE AND MORPHINE GLUCURONIDES

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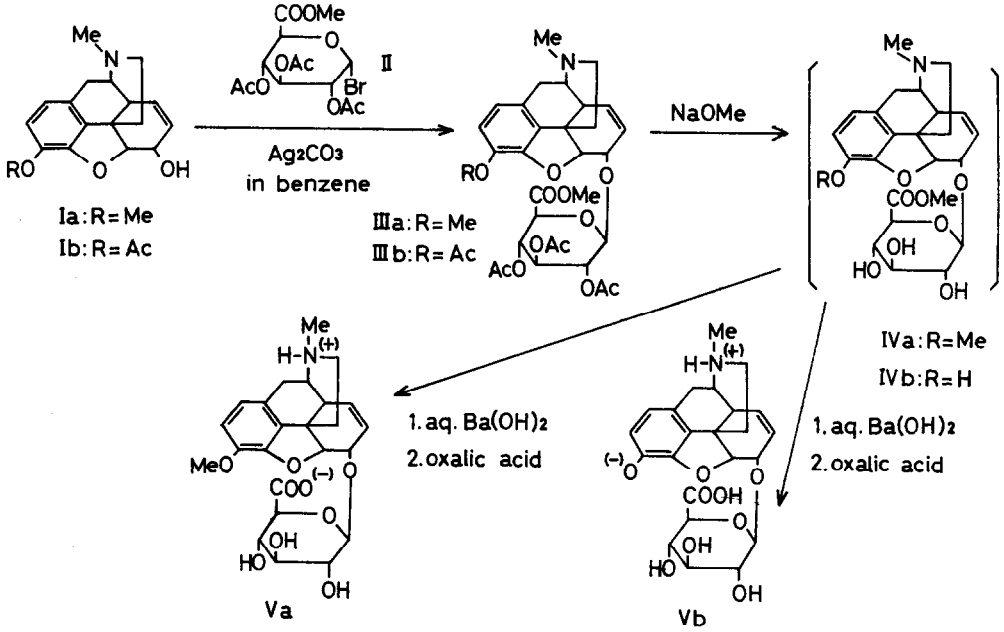
Codeine and morphine, when administered to animals and human, are excreted into their urine mostly as the glucuronides, which are not well characterized. Therefore it seems to be important to synthesize these glucuronides for the identification and characterization of the urinary metabolites and their pharmacological and toxicological studies.

We now wish to report the first synthesis of these glucuronides. Among these, codeine glucuronide was successfully synthesized by the utilization of Koenigs-Knorr reaction[1] as follows:




The condensation reaction of codeine (Ia) and acetobromo derivative of glucuronic acid (II) was performed in boiling dry benzene and the presence of freshly prepared dry silver carbonate. The reaction product was purified by silica gel column chromatography and recrystallized with

EtOH to colorless needles, m.p. 112-114°. Elemental analysis and spectral data were in good accordance with the expected structure of $C_{31}H_{37}O_{12}N \cdot 2H_2O$. UV $\lambda_{max}^{EtOH}$ mμ (log ε) : 287 (3.22), $[\alpha]_D^{26}$ - 140° (C = 0.5 in $CHCl_3$). Oxidation of codeine to codeinone which has been reported by Rapoport, et al.,[2] was not taken place under this specific condition.

β-Configuration of the glucosidic linkage was obvious from the optical rotation and also confirmed indirectly from the NMR spectrum (60 Mc, $CDCl_3$) which did not show any signals around 6.31 p.p.m. ($J_{1,2}$ = 3 cps), corresponding to that of the equatorial Cl-H[3].

Removal of the protecting groups from (IIIa) was performed stepwise; (IIIa) was converted, at first, to (IVa) by the solvolysis with a catalytic amount of NaOMe and then to (Va) by the hydrolysis with an equivalent amount of aq. $Ba(OH)_2$ and the following treatment with oxalic acid. The final product, thus obtained, was recrystallized from $H_2O$-MeOH to colorless prisms (Va), $C_{24}H_{29}O_9N \cdot {}^1/_2 H_2O$, m.p. 276-278° (decomp.). UV $\lambda_{max}^{H_2O}$ mμ (log ε) : 285 (3.23), $[\alpha]_D^{28}$ - 216° (C = 0.5 in $H_2O$). The IR spectrum of this glucuronide revealed a strong peak at 1609 $cm^{-1}$ (KBr) which suggested that it should exist as the ionized form.

The synthesis of morphine-6-glucuronide was similarly performed as that of codeine glucuronide utilizing 3-acetylmorphine as the starting material which was prepared by the selective acetylation of morphine according to the method of Welsh[4]. Elemental analysis of the methyl acetyl derivative (IIIb) afforded the formula of $C_{32}H_{37}O_{13}N \cdot {}^1/_2 H_2O$. It was recrystallized from EtOH to colorless prisms, m.p. 186-188°, $[\alpha]_D^{26}$ - 140° (C = 0.5 in $CHCl_3$). UV $\lambda_{max}^{EtOH}$ mμ (log ε) : 283 (3.35). The NMR spectrum did not show the signal owing to the equatorial Cl-H, and supported β-configurational structure of this glucuronide derivative.

The free glucuronide (Vb), $C_{23}H_{27}O_9N \cdot 2H_2O$, was recrystallized from $H_2O$-EtOH to colorless prisms, m.p. 254-256° (decomp.). UV $\lambda_{max}^{H_2O}$ mμ (log ε) : 286 (3.18), $\lambda_{max}^{0.1NaOH}$ mμ (log ε) : 298 (3.45), $[\alpha]_D^{28}$ - 172° (C = 0.5 in $H_2O$).

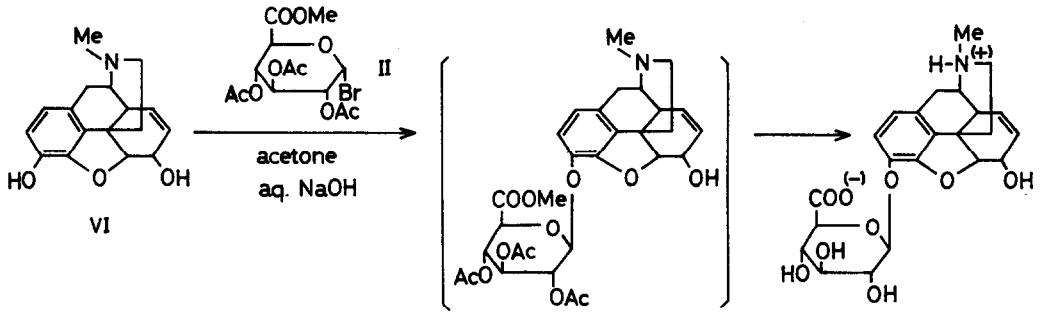
Since the UV spectrum of this glucuronide showed a marked bathochromic effect in alkaline solution, it is no doubt that it possesses the free phenolic hydroxyl group. In the IR spectrum the existence of the non-ionized carboxyl peak at 1750 $cm^{-1}$ and the strong hydrogen-bonded hydroxyl peak around 2640 $cm^{-1}$ suggested that the structure should be best described as (Vb).

Application of this method to the synthesis of morphine-3-glucuronide by the use of 6-acetylmorphine* as the starting material was not successful. Alternative method of Helferich, et al.,[5]

* It could be easily obtained from 3,6- diacetylmorphine by partial deacetylation with hydroxylamine according to the method of Wright.[6]

in which the condensation was performed in the presence of mercuric cyanide in acetonitrile, was found to form the expected glucuronide derivative in a considerable yield, however the following hydrolytic removal of the protecting groups resulted in a cleavage of the glucosidic linkage.

Finally we succeeded in this glucuronide synthesis by the condensation reaction of morphine (VI) and sugar derivative (II) in NaOH-acetone as follows:




To a solution of morphine (VI) in aq. NaOH was added a solution of (II) in acetone, and the mixture was allowed to stand over night. It formed two layers, aqueous (lower) and acetone (upper)*, and precipitated a considerable amount of unchanged morphine. With an addition of conc. aq. NaOH, this unchanged morphine was again dissolved under stirring. To this, a solution of (II) in acetone was added and the mixture was again allowed to stand over night. Such a procedure was further repeated several times more.

Thin-layer chromatographic examination of this reaction mixture seemed to support that the reaction proceeded through the sequence described in above figure. The intermediate (VII), which formed gradually over night, was distributed more into acetone layer than aqueous alkaline layer, and therefore protected from the hydrolysis of its glucosidic linkage. It was then quickly hydrolyzed during the stirring procedure to the free glucuronide (VIII) which was transferred mostly into aqueous layer, but no more unstable against alkaline.

The free glucuronide (VIII) was thus accumulated gradually in aqueous layer. The reaction mixture, after extraction of unchanged morphine with $CHCl_3$- iso PrOH (3 : 1) at pH 9.0, was passed through a column of Dowex 50W-X8 (H-form). The glucuronide (VIII) was eluted with 0.15N $NH_4OH$ and recrystallized from $H_2O$ to colorless needles, m.p. 243-246° (decomp.). UV $\lambda_{max}^{H_2O}$ mμ (log ε) : 283 (3.24), $[\alpha]_D^{28}$-132° (C = 0.5 in $H_2O$). The strong IR absorption band at 1597 $cm^{-1}$ (KBr) due

* This is probably due to salting out mechanism by NaBr which is produced in the reaction mixture.

to carboxylic ion indicated that this glucuronide had an ionized form same as codeine glucuronide.

Woods[7], and Fujimoto and Way[8] isolated "bound" morphine in a crystalline form from the dog bile and from the human urine, after dosing morphine, respectively and characterized it as morphine-3-glucuronide. We also found by thin-layer chromatography that rabbits excreted, when injected morphine, morphine-3-glucuronide in urine, but not morphine-6-glucuronide.

However there seems to be minor differences between the description on our synthetic morphine-3-glucuronide and those of above workers. Woods gave to this glucuronide the dihydrated formula[7], (Found : C, 55.15, 55.49; H, 6.82, 7.06; N, 2.96, $C_{23}H_{27}O_9N \cdot 2H_2O$ requires C, 55.6 ; H, 6.27; N, 2.82), but our synthetic sample was analyzed as $C_{23}H_{27}O_9N \cdot 2\,^1/_2\,H_2O$* (Found: C, 54.60, 54.69; H, 6.29, 6.34; N, 3.07, 2.78. It requires C, 54.53; H, 6.37; N, 2.76). The IR spectra of our sample and of Fujimoto and Way[8] were essentially identical except an extra peak at 1650 $cm^{-1}$ in ours, which was probably due to crystal $H_2O$, since it completely disappeared after drying the sample at 105° for 7 hrs in vacuo.

We also confirmed by thin-layer chromatography that the conjugated metabolite of codeine in the urine of rabbit was codeine glucuronide. In this urine, however, morphine-3-glucuronide was excreted more than codeine glucuronide as one of the codeine metabolites.

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* The sample was dried at 40° for 5 hrs. in vacuo.