10-Oxomorphine, a decomposition product of morphine

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A new decomposition product, the constitution of which was proposed on the basis of spectral data and its configuration confirmed by correlation with morphine, was isolated from morphine hydrate.

Из гидрата морфина был изолирован новый продукт разложения, строение которого было подтверждено на основании спектральных данных и конфигурация была доказана по корреляции с морфином.

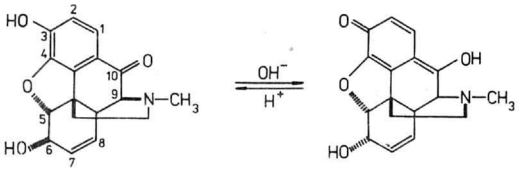
So far, the examination of decomposition products of morphine was focussed to aqueous solutions [1—8] from which morphine-*N*-oxide and pseudomorphine [2, 7] were isolated and identified. In injections of morphine hydrochloride stabilized with $NaHSO_3$ a blue-fluorescing substance was found, the constitution of which has not been established as yet [9]. Decomposition of morphine hydrochloride was also investigated in the crystalline substance. Thin-layer chromatography showed the presence of some degradation products; they have not been identified [10].

Morphinane alkaloids are known to undergo oxidation mostly in position C-10 [11]. Photochemical oxidation of 3-methoxy-*N*-methylmorphinane affords 3-methoxy-10-oxo-*N*-methylmorphinane [12]. 10-Hydroxycodeine was, however, isolated from opium; it is supposed that it was formed from codeine [13]. A cautious oxidation of codeine or 3-alkoxymorphine with chromic acid at room temperature leads to the corresponding 10-hydroxy derivatives [14, 15], 3-allyl-10-hydroxymorphine affords 10-hydroxymorphine [16, 17].

Thin-layer chromatography of morphine hydrate stored in a crystalline state revealed the presence of a compound which, when exposed to an ultraviolet light of 365 nm wavelength, fluoresced intensively green in acid and blue in alkaline medium. This substance was formed from morphine by oxidation, as evidenced by ageing of morphine on silica gel in a stream of oxygen. This substance (*I*) was isolated from a solution of morphine hydrochloride by precipitation with ammonia

followed by a preparative thin-layer chromatography. It was also found in 30 years old injections of morphine hydrochloride stabilized with chlorocresol. The high-resolution mass spectrum of *I* displayed a peak of molecular ion at 299.11590 (for $C_{17}H_{17}NO_4$ calculated 299.11575). The peak at *m/e* 282 (*M* — 17) indicated the presence of a hydroxyl group attached to an alicyclic ring; the series of ions at *m/e* 162, 124, and 70 is characteristic of an *N*-methylpiperidine grouping. Further peaks at *m/e* 270 (*M* — 29), 256 (*M* — 43), 242, 229, 188, 94, 81, 77, 69, 57, 43 characterize morphinane alkaloids [18] and 17-nor derivatives thereof. Ultraviolet spectrum of *I* showed maxima undergoing a considerable bathochromic shift in an alkaline medium, this being diagnostic of the presence of a phenolic group; a like shift reveal *p*-substituted aromatic ketones. When contrasting this u.v. spectrum with that of morphine, one observes new bands at 252 and 335 nm, whereas the band characteristic of morphinane alkaloids appeared at 296 nm. Such an absorption characteristics was reported with 10-keto derivatives of morphinane alkaloids [15]. Also comparison of the i.r. spectrum with that of morphine indicates the presence of a new band at 1670 cm^{-1} attributable to a stretching vibration of a carbonyl group. The ^{1}H-n.m.r. spectrum (in p.p.m. at the δ scale) shows signals of doublets associated with aromatic protons H-1 and H-2 at 7.42 and 6.84 (2H, $J_{1,2} = 8$ Hz) shifted downfield in relation to codeine (6.73 and 6.56) and morphine (6.93 and 6.59) [19, 20]. Two doublets at 5.85 and 5.30 (2H, $J_{7,8} = 10$ Hz) were ascribed to protons H-7 and H-8, singlet at 2.47 (3H) to an N—CH_3 group. Positions of signals of H-5 (4.98, 1H, $J_{5,6} = 6$ Hz) and H-14 (2.77, 1H, $J_{8,14} = 3$ Hz) are in accordance with those reported for codeine and morphine. Signals of H-10 (2.50 and 2.91 in morphine) are absent. Substance *I* is voltametrically oxidable on a graphite electrode; this feature is met in morphinane series only with alkaloids having a free phenolic group (morphine, pseudomorphine, morphine-*N*-oxide) [21].

Spectral data and the finding that Wolff—Kizhner reduction of *I* led to a substance identical with morphine entitle to ascribe the structure of 4,5α-epoxy-7,8-dehydro-10-oxo-17-methylmorphinane-3,6α-diol to substance *I*. Basing upon the change in the u.v. spectra in relation to pH, the keto-enol tautomerism is anticipated (Scheme 1)



Ia *Ib*

Scheme 1

Since the fragmentation pattern of morphinane alkaloids has not been verified with labelled substances we prepared 17-CD_3-codeine and compared its mass spectrum with that of codeine. Both alkaloids revealed a concurrent fragmentation pattern differing by 3 mass units in ions bearing the *N*-methyl group. The i.r. spectrum of the labelled codeine displayed new absorption bands due to asymmetric stretching vibrations of the CD_3 group at 2200 cm^{-1}, symmetric stretching vibration of CD_3 group at 2180 and 2050 cm^{-1}, and a rocking vibration of the same group at 890 cm^{-1}.

Experimental

Melting points were determined on a Kofler micro hot-stage, mass spectra were taken with a JMS-100D spectrometer at an ionizing electron energy 70 eV and 200—250°C, the molecular weight was determined with an AEI-MS 902 apparatus, the u.v. spectra with a Specord UV VIS (Zeiss, Jena), the i.r. spectra in KBr discs with a Perkin—Elmer 457, the ^{1}H-n.m.r. spectra with a Tesla BS 487 B instruments in D_5-pyridine at 60°C, tetramethylsilane being the internal reference substance. Optical rotation was measured with a Perkin—Elmer 141 polarimeter at 589 nm, voltametric oxidation was examined on a graphite electrode impregnated with silicone rubber OH-VM 7111D (Radelkis, Budapest) connected with an OH-105 polarograph (Radelkis, Budapest); potentials refer to a saturated calomel electrode. Silufol UV-254 (Kavalier, Votice) was the carrier for analytical t.l.c. and Kieselgel F-254 (Merck) for preparative t.l.c. Solvent systems S_1 (benzene—methanol 4 : 1), S_2 (chloroform—methanol 4 : 1), S_3 (methanol—ammonia 99 : 1), S_4 (methanol—acetic acid—benzene 8 : 1 : 1), two-dimensional t.l.c. in S_5 (tetrachloromethane—*n*-butanol—methanol—ammonia 40 : 30 : 30 : 2), S_6 (methanol—acetone—ammonia 80 : 20 : 3.5), S_7 (chloroform—methanol 2 : 1), and S_8 (dichloromethane—methanol—ammonia 85 : 15 : 7); visualization by 254 and 365 nm light.

Isolation of 10-oxomorphine

Morphine hydrate (50 g) was dissolved in 2% HCl (500 ml), pH of the solution was adjusted to 6.0 by addition of 10% NH_4OH and the precipitate removed by centrifugation. The pH of the supernatant was adjusted to 6.8 under stirring; pH of the solution reached within 10 min 6.5, whilst a gradual precipitation took place. After the precipitate was filtered off, the pH in the filtrate was adjusted again to 6.8 and the procedure was repeated. Both precipitates were combined, dissolved in 2% HCl (100 ml) and precipitated as mentioned above till substance *I* was no more present in the filtrate, this being monitored by t.l.c. in S_2. The second precipitation afforded a mixture consisting of morphine and substance *I* (2.8 g), from which 10-oxomorphine was separated by a preparative t.l.c. in S_6 and after elution with hot methanol and concentration it was purified by t.l.c. in S_7. 10-Oxomorphine was eluted with hot methanol, precipitated with carbon tetrachloride and crystallized from methanol—acetone 2 : 1. Yield 45 mg of yellow crystals, m.p. 270°C (decomp.), $[\alpha]_D^{22}$ −50° (*c* 0.355, methanol), mass spectrum: *m/e* 299 (100%), 282 (10%), 270 (4%), 256 (10%),

242 (18%), 228 (10%), 202 (14%), 188 (12%), 174 (10%), 162 (14%), 124 (27%), 70 (32%), 57 (84%), 43 (59%). λ_{max} (nm) 252, 296, 355 (log ε 3.77, 3.76, 3.62) (methanol), λ_{max} (nm) 220, 270, 370 (log ε 3.91, 3.79, 4.10) (0.2 M-KOH in methanol). IR: $\tilde{\nu}$ (cm^{-1}): 3420, 3140, 3030, 2930, 2850, 2800, 1670, 1610, 1470, 1430, 1385, 1355, 1300, 1222, 1105, 1060, 973, 943, 888, 850, 804, 770. Voltametric oxidation: pH 5.27 $E_{p/2}$ + 0.68 V; pH 6.24 $E_{p/2}$ + 0.64 V; pH 8.19 $E_{p/2}$ + 0.58 V.

Accelerated decomposition of morphine

Morphine hydrate (1 g) dissolved in methanol was soaked into silica gel (20 g; 0.200/0.063 mm), methanol evaporated under diminished pressure in a vacuum rotary evaporator through which a stream of oxygen (80 ml/min) was then passed at 70°C. After 32 h of decomposition organic substances were extracted with 1% HCl in methanol, filtered and the solvent evaporated. Compound *I* (2 mg) was isolated as mentioned before and identified on the basis of mass and u.v. spectra, by mixed melting point and R_f values in S_1—S_6.

10-Oxomorphine semicarbazone

10-Oxomorphine (20 mg), semicarbazide hydrochloride (50 mg), and sodium acetate (60 mg) were dissolved in methanol—water (1 ml each) and heated in a steam bath for 30 h. The solvent was evaporated and the residue crystallized from methanol—water 1 : 1. Yield 15 mg, m.p. 190°C (decomp.). A thermic decomposition of the semicarbazone at 200°C followed by sublimation at 220°C/1.1 kPa afforded a compound, m.p. 254°C, u.v. and mass spectra of which as well as the R_f values in S_1—S_4 were identical with morphine. Also the mixed melting point did not show any depression.

17-CD_3-Codeine

17-Norcodeine (50 mg), prepared from codeine and nitrous acid [22] was dissolved in chloroform (2 ml) and methylated with CD_3I (25 mg) in the presence of $NaHCO_3$ (50 mg). The mixture was agitated for 2 h and the methylation was monitored by t.l.c. in S_8. After the methylation was completed the solvent was evaporated and the residue dissolved in methanol was purified by preparative t.l.c. in S_8. Yield 13 mg, m.p. 155°C, mass spectrum: *m/e* 302 (100%), 285 (12%), 273 (9%), 259 (9%), 242 (11%), 232 (32%), 188 (19%), 175 (10%), 165 (36%), 127 (29%), 97 (18%), 73 (14%), 62 (25%), 43 (23%). IR: $\tilde{\nu}$ (cm^{-1}): 3560, 3350, 2900, 2820, 2220, 2180, 2050, 1620, 1596, 1490, 1445, 1430, 1370, 1340, 1270, 1260, 1150, 1140, 1110, 1045, 960, 930, 905, 890, 830, 800.

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