Identification and determination of by-products of the codeine synthesis

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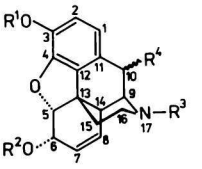
N,N,N',N'-Tetramethyl-4,4'-diaminodiphenylmethane, 6-methylcodeine, 17-norcodeine, α-codeimethine, and (3*E*)-*O*-dichlorovinylmorphine were found in the crude codeine obtained from morphine by methylation with trimethylphenylammonium hydroxide. A liquid-chromatographic method, employing column packed with reverse C—18-type phase, or alternatively gas-chromatographic one on XE-60/Chromaton N AW-DMCS were worked out for determination of these products.

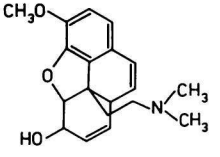
В сыром кодеине, синтезированном из морфина метилированием гидроокисью триметилфениламмония, показано присутствие *N,N,N',N'*-тетраметил-4,4'-диаминодифенилметана, 6-метилкодеина, 17-норкодеина, α-кодеиметина и (3*E*)-*O*-дихлорвинилморфина. Для определения перечисленных соединений разработан метод, использующий жидкостную хроматографию на колоннах, наполненных сорбентом с обращенной фазой типа С—18 или газовую хроматографию на носителе XE-60/Chromaton N AW-DMCS.

Methylation of morphine (*I*) with trimethylphenylammonium hydroxide [1, 2] occurs at the phenolic hydroxyl group under formation of codeine (*II*); nevertheless, the methylation reagent also attacked further active centres to give 6-methylcodeine (*III*) [3, 4] and α-codeimethine (*IV*) [5, 6]. Compounds *III* and *IV* present in technical-grade codeine were estimated by time-consuming spectral methods with preceding separation using thin-layer [5], or paper chromatography [7].

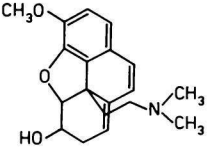
Liquid chromatography of some samples of technical-grade codeine showed the occurrence of further products in addition to codeine. Thus, *N,N,N',N'*-tetramethyl-4,4'-diaminodiphenylmethane (*V*) was obtained by extraction of the aqueous solution of technical-grade codeine of pH 4.5 with chloroform, concentration and separation by column chromatography, n-hexane being the eluent. The column was then eluted with benzene—ethanol—0.1 M-NH_4OH and the effluents were combined according to thin-layer chromatography; 6-methylcodeine (*III*), 17-norcodeine (*VII*), and compound *VI* were those separated.



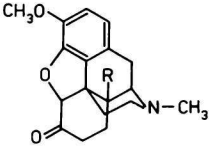
Compound	R^1	R^2	R^3	R^4
I	H	H	CH_3	H
II	CH_3	H	CH_3	H
III	CH_3	CH_3	CH_3	H
VI	CHCl=CCl	H	CH_3	H
VII	CH_3	H	H	H
VIII	CH_3	H	CH_3	OH
IX	CH_3	H	NO	H
X	CH_3CO	CH_3CO	NO	H
XI	CH_3	HCO	CH_3	H
XII	CH_3CO	CH_3CO	CH_3	H
XVI	CH_3	CH_3CO	CH_3	H



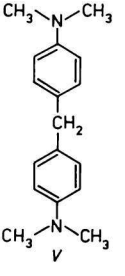
IV



XIV



XIII R = OH
XV R = H



V

Compound *VI* ($C_{19}H_{19}NO_3Cl_2$) crystallizing from acetone—hexane (volume ratio 1:1) had m.p. = 143—144.5 °C; its u.v. spectrum was in line with those of morphinane alkaloids. The i.r. spectrum displayed bands at $\tilde{\nu}/cm^{-1}$ 3580 ($\tilde{\nu}$(O—H)), 1660 ($\tilde{\nu}$(C=C)), 1620, 1490, and 1450 ($\tilde{\nu}(H_{arom})$). The electron

impact mass spectrum showed, in addition to the isotopic cluster of molecular peak ion (*m/z* 383, 381, 379), the peak at *M*—17 evidencing the presence of an alicyclically bound hydroxyl group, and a series at *m/z* 162, 124, and 70 characteristic of *N*-methylpiperidine grouping in morphinane alkaloids [8]. Further series of peaks at *m/z* 313, 311, 309; 298, 286, 294, and 272, 270, 268 are indicative of morphinane skeleton bearing a C_2HCl_2 substitution at the phenolic oxygen. The ^{1}H-n.m.r. spectrum displayed, when compared with that of codeine, an additional signal at $\delta_r = 5.73$ ppm attributable to the (*E*)-1,2-dichlorovinyloxyl group proton δ_r (calculated) = 5.61 ppm [9]. Compound *VI* is optically active, the course of its c.d. spectrum is close to that of codeine; consequently, both compounds have the same steric arrangement in the proximity of chromophores. Considering the presented arguments, compound *VI* was ascribed the structure of (5*R*, 6*S*, 9*R*, 13*S*, 14*R*)-(3*E*)-1,2-dichlorovinyloxy-4,5-epoxy-7,8-dehydro--17-methylmorphinan-6-ol.

Compounds *V*, *VI*, and *VII* are further, hitherto not reported by-products of codeine synthesis. According to h.p.l.c. recordings, some samples of codeine contained another compound that was not succeeded to be isolated; comparison of retention times let us presume this compound to be identical with α-codeimethine (*IV*). Table 1 lists retention times t_r, capacity factors k', relative retentions α, and

Table 1

HPLC data of retention time t_r, capacity factor k', relative retention α, and change of Gibbs energy $\Delta(\Delta G)$ relative to codeine of morphinane derivatives

Compound	$\frac{t_r}{\text{min}}$	k'	α	$\frac{\Delta(\Delta G)}{\text{J mol}^{-1}}$
I	2.78	0.78	0.31	2921
VIII	2.93	0.93	0.37	2573
IX	3.11	1.11	0.44	2112
X	3.46	1.46	0.58	1399
II	4.50	2.50	0.00	0000
VII	4.50	2.50	0.00	0000
XI	4.62	2.62	1.05	−122
XII	4.89	2.89	1.16	−377
XIII	4.97	2.97	1.19	−448
XIV	5.11	3.11	1.24	−568
XV	5.95	3.95	1.58	−1190
III	6.40	4.40	1.76	−1471
IV	6.56	4.56	1.82	−1521
XVI	6.76	4.76	2.30	−2115
VI	10.12	8.12	3.25	−3066

changes in Gibbs energy $\Delta(\Delta G)$ relative to codeine of various synthetic derivatives of morphinane. These data might be of use for orientation in chromatographic data of codeine and its derivatives.

Substances *III*, *V*, and *VI*, which are most frequented in technical-grade codeine were determined by liquid or gas chromatography employing the external standard method. For liquid chromatography columns packed with silica gel containing a chemically bound phase C—18 were used. These substances are well resoluted at the given conditions: $R_{s\,II,III} = 3.0$, $R_{s\,III,VI} = 3.9$. The detector response was linear within $c = 6.7 \times 10^{-3}$—3.5×10^{-6} mol dm^{-3}. The determination accuracy was checked on a sample of technical-grade codeine as follows: $w(III) = (0.32 \pm 0.07)$ %, $s = 0.01$ %, $s_r = 3.2$ %; $w(V, t_r = 18.2 \text{ min}) = (0.730 \pm 0.008)$ %, $s = 0.011$ %, $s_r = 1.08$ %; $w(VI) = (0.7081 \pm 0.014)$ %, $s = 0.019$ %, $s_r = 2.7$ % (for $n = 10$; $\alpha = 0.05$). G.c.-column for determination of *III* and *VI* in technical-grade codeine was packed with the XE-60/Chromaton N AW-DMCS polymer; $t_r(III) = 4.8$ min, $t_r(II) = 6.0$ min, $t_r(VI) = 10.6$ min, resolution $R_{s\,III,II} = 2.0$, $R_{s\,II,VI} = 4.6$. The FID detector response was linear within $c = 0.2$—3×10^{-4} mol dm^{-3}. The determination accuracy was checked as described with h.p.l.c., following values being found: $w(III) = (0.317 \pm 0.012)$ %, $s = 0.017$ %, $s_r = 5.4$ %; $w(VI) = (0.722 \pm 0.035)$ %, $s = 0.049$ %, $s_r = 6.9$ %. The coincidence of results of determination for *III* and *VI* by gas and liquid chromatographies with the same sample was evaluated by the *F*-test and no statistically significant difference was found; the liquid chromatography, however, offers more precise results.

Experimental

Melting points were determined on a Kofler hot stage, electron impact mass spectra were taken with an AEI-MS 902 S, u.v. spectra with a Specord UV VIS (Zeiss, Jena), and i.r. spectra with a Perkin—Elmer, model 457, apparatus. The ^{1}H-n.m.r. spectra of $CDCl_3$ solutions were recorded with a Tesla BS 467 B spectrometer, tetramethylsilane being the reference substance. For thin-layer chromatography Silufol UV 254 sheets (Kavalier, Czechoslovakia) and solvent system chloroform—methanol—ammonium hydroxide (volume ratio 90:10:0.5) were used. Column (250 mm × 4.6 mm) packed with LiChrosorb RP 18, 10 μm was employed for liquid chromatography; mobile phase methanol—0.5 M-aqueous NH_4OH (volume ratio 65:35); mobile-phase flow rate 2.0 cm^3 min^{-1}, temperature 40 °C, detector wavelength 285 nm, feed 10^{-3} cm^3; column (200 cm × 0.2 cm) packed with 5 % XE-60/Chromaton N AW-DMCS (0.100—0.120 mm) was used for gas chromatography; column temperature 220 °C, ($t_r = 2$ min), $\theta = 220$—235 °C (temperature rate 3 °C/min), injector port temperature 260 °C, detector temperature 280 °C, nitrogen flow rate 35 cm^3/min, feed 2×10^{-3} cm^3.

Isolation of by-products of the codeine synthesis

A sample of crude codeine (100 g) was dissolved in 0.7 M-H_3PO_4 (1500 cm^3), the pH was adjusted to 4.5 by addition of 2 M-NaOH, the solution was extracted with chloroform (4×100 cm^3), the organic layer was dried and evaporated. The residue (5.1 g) was dissolved in benzene and soaked into an alumina (250 g, activity grade IV) column. The hexane effluent was concentrated, the separated crystals were filtered off and crystallized from hexane. Yield 450 mg of white crystals, m.p. = 88—90 °C.

For $C_{17}H_{22}N_2$ w_i(calculated): 80.27 % C, 8.27 % H, 11.01 % N; w_i(found): 80.17 % C, 8.56 % H, 10.82 % N. UV spectrum λ_{max}^{EtOH}/nm (log{ε}): 263 (4.36), 306 (3.45). ^{1}H-NMR spectrum (δ_r/ppm): 7.11 and 6.61 (ABq, 8 H, $J = 8$ Hz), 3.75 (s, 2 H, —CH_2—), 2.83 (s, 12 H, $N(CH_3)_2$). These data are consistent with those of *N,N,N′,N′*-tetramethyl-4,4′-diaminodiphenylmethane (*V*).

The column was then eluted (20 cm^3 instalments) with benzene containing an increasing amount of ethanol in which 0.1 mol or NH_4OH/dm^3 was dissolved. Combined fractions *10—14* (checked by thin-layer chromatography) afforded a compound identical (m.p., u.v., i.r., ^{1}H-n.m.r., mass spectra) with 6-methylcodeine (*III*) [10].

The solvent from the combined fractions *18—21* was removed and the residue was crystallized from acetone. Yield 260 mg of compound *VI*, m.p. = 143—144.5 °C, $[\alpha]_D^{20} = -142°$ (methanol).

For $C_{19}H_{19}NO_3Cl_2$ ($M_r = 380.4$) w_i(calculated): 60.01 % C, 3.68 % H, 5.04 % N, 18.65 % Cl; w_i(found): 59.83 % C, 3.73 % H, 5.01 % N, 18.14 % Cl. UV spectrum: λ_{max}^{EtOH}/nm (log{ε}): 282 sh (3.28), 287 (3.32). IR spectrum ($\tilde{\nu}$/cm^{-1}): 3580, 3040, 2940, 1660, 1620, 1490, 1450. Mass spectrum (*m/z* (%)): 383 (10), 381 (62), 379 (100), 366 (2), 364 (5), 262 (6), 309 (16), 298 (5), 296 (6), 294 (6), 272 (6), 270 (4). ^{1}H-NMR spectrum (δ_r/ppm): 6.76 (d, 1 H, H-1), 6.55 (d, 1 H, $J_{1,2} = 8$ Hz, H-2), 5.73 (s, 1 H, —OCCl = CHCl), 5.63 (d, 1 H, H-7), 5.23 (d, 1 H, $J_{7,8} = 10$ Hz, H-8), 4.92 (m, 1 H, H-5), 4.55 (m, 1 H, H-6), 3.32 (m, 1 H, H-9), 2.90 (m, 1 H, H-10b), 2.82 (m, 1 H, H-14), 2.47 (m, 1 H, H-10a), 2.40 (s, 3 H, NCH_3). CD spectrum ($c = 3.32$ mmol dm^{-3}, methanol): $[\Theta]_{310} = +59.4$, $[\Theta]_{288} = -5544$, $[\Theta]_{245} = +25\,839$, $[\Theta]_{220} = -70\,950$.

The work-up of combined fractions *38—43* afforded a compound identical with 17-norcodeine (*VII*) prepared synthetically [11].

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