110. The Three Isomers of (+)-Codeine and Some Codeimethines from Them[1]

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The authors reported in the previous communication[2] that the yield of (+)-codeinone from sinomenine was raised to some 10% by the use of 7-bromo-dimethyl ketal of (+)-dihydrocodeinone. As the (+)-codeinone could be reduced to (+)-codeine with $NaBH_4$ in an almost quantitative yield, this elevation of yield allowed us to prepare the three isomers of (+)-codeine, namely (+)-isocodeine, (+)-pseudocodeine, and (+)-allopseudocodeine, and some of the corresponding codeimethines. These derivatives are listed, for brevity's sake, in Tables I and II.

Table I. Isomers of (+)-codeine*

	From sinomenine	From (−)-codeine	Racemate	Cited after Bentley's book
Isocodeine	m.p. 171° $[\alpha]_D^{13}=+151.5°$ (c 1.023, chlf.)	m.p. 171° $[\alpha]_D^{22}=-149.2°$ (c 0.985, chlf.)	m.p. 185° $\alpha=0°$ (c 1.0, chlf.)	m.p. 171–172° $[\alpha]_D=-150.6°$ (chlf.)
Methiodide	m.p. 268° dec. $[\alpha]_D^{22}=+104.0°$ (c 0.28, H_2O)	m.p. 268° dec. $[\alpha]_D^{22}=-103.5°$ (c 0.54, H_2O)	m.p. 242° dec. $\alpha=0°$ (c 0.30, H_2O)	m.p. 270° dec. $[\alpha]_D^{15}=-102°$ (H_2O)
Bioxalate	m.p. 228° $[\alpha]_D^{25}=+126.8°$ (c 0.323, H_2O)	m.p. 228° $[\alpha]_D^{25}=-128.6°$ (c 0.255, H_2O)	m.p. 242° with foaming $\alpha=0°$ (c 0.3, MeOH)	m.p. 235° dec.
Pseudocodeine	m.p. 180° $[\alpha]_D^{13}=+98.4°$ (c 1.250, EtOH)	m.p. 180° $[\alpha]_D^{22}=-96.9°$ (c 0.456, EtOH)	m.p. 224° $\alpha=0°$ (c 0.4, EtOH)	m.p. 181–182° $[\alpha]_D^{20}=-96.8°$ (EtOH)
Allo-φ-codeine	not yet crystallised	,,	—	m.p. 116–117° $[\alpha]_D^{21}=-235.4°$ (EtOH)
Methiodide	m.p. 215° dec. $[\alpha]_D^{25}=+146.5°$ (c 0.50, H_2O)	m.p. 215° dec. $[\alpha]_D^{25}=-144.7°$ (c 0.32, H_2O)	m.p. 235° dec. (foaming at 120°) $\alpha=0°$ (c 0.3, H_2O)	m.p. 215–216° $[\alpha]_D^{15}=-142°$ (H_2O)
Hydriodide	m.p. 280–282°dec. $[\alpha]_D^{22}=+154.1°$ (c 0.131, H_2O)	m.p. 280–282°dec. $[\alpha]_D^{22}=-155.2°$ (c 0.152, H_2O)	m.p. 278° dec. $\alpha=0°$ (c 0.3, H_2O)	m.p. 280–285°dec. $[\alpha]_D^{15}=-153°$ H_2O

*All melting points in Tables I, II, and III are not corrected.
All derivatives from (−)-codeine were newly prepared in our laboratory for the purpose of comparison and racemisation.

(+)-Isocodeine[3)4)] and (+)-φ-codeine[5)] were prepared by the hydrolysis of (−)-bromocodide, resp. of (+)-α-chlorocodide. (+)-Allo-φ-codeine was gathered as its hydriodide from the mother liquors of the above two hydrolysis.[6)] The hydrolysis of (−)-bromocodide was carried out after Rapoport[9)] and the separation of (+)-isocodeine and (+)-allo-φ-codeine was accomplished after the method of Knorr.[6)-8)]

Anal. For isocodeine and φ-codeine [$C_{18}H_{21}O_3N$ (299.36)]

		C	H	N	B·CH_3I I
Calc.		72.21	7.07	4.68	28.76
Found	isocodeine	71.91	7.01	4.28	28.40
	φ-codeine	72.15	7.33	4.65	28.30

For allo-φ-codeine hydriodide [$C_{18}H_{21}O_3$ N·HI (427.29)]

	C	H	N	I
Calc.	50.59	5.19	3.28	29.70
Found	50.99	5.32	3.44	29.80

Table II. Codeimethines from (+)-codeine

	From sinomenine	From (−)-codeine	Racemate	Cited after Bentley's book
α-Codeimethine	m.p. 118° $[\alpha]_D^{16}=+213.5°$ (c 1.173, EtOH)	m.p. 118° $[\alpha]_D^{22}=-213.0°$ (c 0.535, EtOH)	m.p. 107° $\alpha=0°$ (c 0.5, EtOH)	m.p. 118.5° $[\alpha]_D^{17}=-212°$ (EtOH)
β-Codeimethine	not yet crystallised	,,	—	m.p. 134–135° $[\alpha]_D^{17}=+438°$ (EtOH)
Benzoate	m.p. 155° $[\alpha]_D^{15}=-253.5°$ (c 0.998, H_2O)	m.p. 155° $[\alpha]_D^{22}=+252.0°$ (c 0.510, H_2O)	m.p. 145° $\alpha=0°$ (c 0.50, MeOH)	m.p. 157° $[\alpha]_D^{17}=+254°$ (H_2O)
Methiodide	m.p. 303° dec. $[\alpha]_D^{25}=-261.7°$ (c 0.26, 90% EtOH)	m.p. 303° dec. $[\alpha]_D^{25}=+260.7°$ (c 0.28, 90% EtOH)	m.p. 285° dec. $\alpha=0°$ (c 0.6, H_2O)	m.p. 300–303° $[\alpha]_D^{19}=+247°$ (90% EtOH) $[\alpha]_D^{21}=+262°$ (90% EtOH)
γ-Codeimethine	m.p. 167° $[\alpha]_D^{15}=-63.9°$ (c 1.642, chlf.)	m.p. 167° $[\alpha]_D^{20}=+65.1°$ (c 0.30, chlf.)	m.p. 147° $\alpha=0°$ (c 0.7, chlf.)	m.p. 167–169° $[\alpha]_D^{20}=+64.3°$ (chlf.)
Methiodide	m.p. 265° dec. $[\alpha]_D^{20}=-36.9°$ (c 0.26, H_2O)	m.p. 265° dec. $[\alpha]_D^{19}=+37.2°$ (c 0.32, H_2O)	m.p. 248° $\alpha=0°$ (c 0.3, H_2O)	m.p. 265° $[\alpha]_D^{17}=+34.7°$ (H_2O)
δ-Codeimethine	m.p. 123° $[\alpha]_D^{12}=-255.5°$ (c 1.186, MeOH)	m.p. 124° $[\alpha]_D^{22}=+253.0°$ (c 0.372, MeOH)	not yet crystallised	m.p. 111–113° $[\alpha]_D^{15}=+256.6°$ (MeOH)
Methiodide	m.p. 283° dec. $[\alpha]_D^{23}=-145.4°$ (c 1.023, H_2O)	m.p. 283° dec. $[\alpha]_D^{23}=+145.3°$ (c 1.00, H_2O)	m.p. 257° dec. $\alpha=0°$ (c 0.4, H_2O)	m.p. 282–284° $[\alpha]_D^{15}=+150.7°$ (EtOH)

(+)-α-Codeimethine was prepared by Knorr's method.[13)] In its isomerisation into (−)-β-codeimethine after Knorr,[14)] we could not obtain

the free crystalline methine as yet. We identified it accordingly as benzoate and methiodide.

(−)-γ-Codeimethine was prepared by Schryver and Lees' method.[3] The yield was quantitative when the pure (+)-isocodeine methiodide was used. But the impure methiodide, prepared directly from the hydrolysate of (−)-bromocodide gave this (−)-γ-methine in a pure state (yield 35–70%).

(−)-δ-Codeimethine was prepared by the isomerisation of (−)-γ-methine after Knorr.[15] We observed a little higher m.p. (124°) than was given by Knorr (113°).

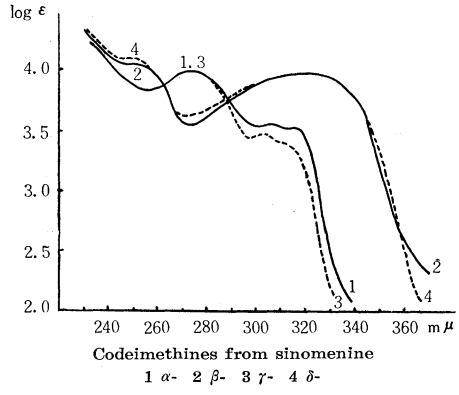
The colour reaction of the above four codeimethines against conc. sulfuric acid was principally the same with that of their antipodes.

Analysis of α-, γ-, and δ-codeimethines [$C_{19}H_{23}O_3N$ (313.38)]

		C	H	N	B·CH_3I I
Calc.		72.82	7.40	4.47	27.87
Found	α-	72.86	7.45	4.44	27.30
	γ-	72.26	7.21	4.33	27.55
	δ-	72.81	7.48	4.06	27.35

Analysis of β-codeimethine methiodide [$C_{19}H_{23}O_3N\cdot CH_3I$ (455.33)]

	C	H	N	I
Calc.	52.75	5.76	3.08	27.87
Found	52.84	5.75	3.16	27.71



Codeimethines from sinomenine
1 α- 2 β- 3 γ- 4 δ-

As regards the ultraviolet absorption, those of α- and γ-methines on one side and those of β- and δ-methines on the other are almost superimposing. This indicates that δ-methine stands to γ-methine in the same relation as β-methine to α-methine. The curves are reproduced in the left.

Table III. Some intermediates

	From sinomenine	From (−)-codeine	Racemate	Cited after Bentley's book
Codeine tosylate	m.p. 128°	m.p. 128°	—	m.p. 121–121.5° 126–128° 129–130°
Bromocodide	m.p. 162° $[\alpha]_D^{14}=-57.2°$ (c 0.981, EtOH)	m.p. 161° $[\alpha]_D^{16}=+57.3°$ (c 0.790, EtOH)	m.p. 160° $\alpha=0°$ (c 0.7, MeOH)	m.p. 162° $[\alpha]_D^{20}=+56.5°$ (EtOH)
α-Chlorocodide	m.p. 151° $[\alpha]_D^{15}=+380°$ (c 0.78, chlf.)	m.p. 151° $[\alpha]_D^{16}=-381.1°$ (c 0.591, chlf.)	m.p. 116° $\alpha=0°$ (c 0.7, MeOH)	m.p. 151–153° $[\alpha]_D^{26}=-383°$ (chlf.)

(1) (+)-Codeine tosylate was prepared from (+)-codeine and p-toluenesulfonic acid in pyridine solution. Precipitated by water and ammonia. Taken up in benzene and again precipitated by ether. Purified through Al_2O_3 column.[10)11)] (Anal. (+)-Codeine tosylate. Calc. for $C_{25}H_{27}O_5NS$ (453.54): C, 66.20; H, 6.00; N, 3.09; S, 7.07. Found: C, 65.99; H, 6.08; N, 2.68; S, 6.95.)

(2) (−)-Bromocodide. A mixture of (+)-codeine tosylate (6 gr) and fused lithium bromide (7.5 gr) in acetone (20 cc) was refluxed for three hours. The acetone was evaporated to 2/3 of the original volume and poured into water (600 cc). The base was then extracted with benzene. The residue of the benzene evaporation was recrystallised twice from ethanol. M.p. 162°.[10)] (Anal. Calc. for $C_{18}H_{20}O_2NBr$ (362.26): C, 59.68; H, 5.57; N, 3.87; Br, 22.06. Found: C, 59.39; H, 5.40; N, 3.82; Br, 22.33.)

(3) (+)-α-Chlorocodide. Prepared from (+)-codeine and PCl_5 in ice-cooled chloroform. Isolation quite analogous as with (−)-substance.[12)] (Anal. Calc. for $C_{18}H_{20}O_2NCl$ (317.82): C, 68.03; H, 6.30; N, 4.41; Cl, 11.18. Found: C, 68.23; H, 6.43; N, 4.41; Cl, 11.35.)

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