several glycoside acetates by observing rotation changes. Pentaacetyl-β-methyl-[β-*d*-galaheptoside] (2.1207 g. in 25 cc. of reagent) changed in specific rotation from +43.5 to −63.3° in forty-eight hours, and triacetyl-β-thiophenol *d*-xyloside very slowly changed in the expected positive direction.

Conversion of Tetraacetyl-α-methyl-γ-*d*-mannoside to a New Pentaacetate of *d*-Mannose.—The previously mentioned glycoside acetates and the α-aldose acetates resulting from their transformation are all of the normal stable ring type. It seemed possible that glycoside acetates of the gamma ring type might lead to the synthesis of acetates of the corresponding ring type, most of which are at present unknown, and experiments were conducted with tetraacetyl-γ-methylmannoside to test this hypothesis. Preliminary observation showed that the reagent employed for the normal glycoside acetates caused very rapid conversion and some attendant decomposition, so a solution containing only 0.02 cc. of sulfuric acid in 100 cc. of a 2:1 acetic anhydride–acetic acid mixture was employed. A solution of 5.0876 g. of tetraacetyl-γ-methylmannoside[6] (m. p. 63°, specific rotation +106.3° in chloroform) in 26 cc. of the transforming solution changed in specific rotation from +108.7 to +70.2° during the course of five days at 20°. The solution was treated in the usual manner and the sirup obtained from the carbon tetrachloride crystallized from a small amount of 50% alcohol; yield 2.2 g. (41%). Recrystallized successively from 5 parts of 50% alcohol it showed specific rotations of +89.6 and 89.3° (0.3177 g. in 25 cc. of chloroform in a 2-dm. tube rotated 2.27° to the right). The new pentaacetate of mannose crystallized in brilliant prisms and melted to a clear colorless oil at 76° (corr.).

Anal. Calcd. for $C_{16}H_{22}O_{11}$: C, 49.2; H, 5.7. Found: C, 49.3; H, 5.8. Acetyl determination: 0.1130 g. consumed 14.4 cc. of 0.1 *N* NaOH. Calcd., 14.5 cc.

At the time of its preparation (Dec., 1932) it was thought likely that the substance was an acetate of the gamma type, possessing a ring structure, but the recent conversion of an acetylated methylmannoheptoside of the gamma type to an aldehydo acetate (see the accompanying article by Montgomery and Hudson) by the transforming solution makes further investigation of the new mannose pentaacetate necessary before a structure can be assigned to it.

We are indebted to Dr. F. H. Goldman for carrying out the carbon and hydrogen determinations, and to Professor W. N. Haworth for seed crystals of γ-methylmannoside.

Summary

A convenient procedure for the preparation of α-aldose acetates from acetylated glycosides is described. This is an alternative method to the usual acetylation of sugars and in some cases (*e. g.*, the mannose series) it is a preferable one. Acetates of glycosides of the stable ring type yield acetates of this type. One acetylated glycoside of the gamma ring type (tetraacetyl-γ-methylmannoside) has been tested; it is transformed in large yield to a new crystalline pentaacetate of mannose.

WASHINGTON, D. C. RECEIVED JULY 30, 1934

(6) Haworth, Hirst and Webb, *J. Chem. Soc.*, 656 (1930); Harris, Hirst and Wood, *ibid.*, 2119 (1932).

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA, NO. 141]

Reduction Studies in the Morphine Series. IV. Allopseudocodeine[1]

BY ROBERT E. LUTZ AND LYNDON SMALL

The catalytic reduction of allopseudocodeine I in dilute acetic acid with a colloidal palladium catalyst proceeds exclusively in the "abnormal" sense, with saturation of the alicyclic double bond and reductive rupture of the ether linkage, giving tetrahydroallopseudocodeine III.[2] When the hydrogenation is carried out in ethanol in the presence of palladium on calcium carbonate, nearly equal amounts of tetrahydroallopseudocodeine and the new non-phenolic dihydroallopseudocodeine II are formed. Under similar conditions pseudocodeine, the diastereomer of allopseudocodeine, and γ-isomorphine give predominantly tetrahydro derivatives.[3] Under those special conditions which we have found to favor "normal" saturation of the double bond alone,[3] allopseudocodeine is converted in 80% yield to its dihydro derivative II; as by-products, small amounts of tetrahydroallopseudocodeine and tetrahydrodesoxycodeine IV are obtained.

Reduction of allopseudocodeine with sodium and alcohol gives as the principal products the previously-described[4] mixture of dihydrodesoxycodeines-B and -C VI and a phenolic dihydroallopseudocodeine V. The latter is converted to

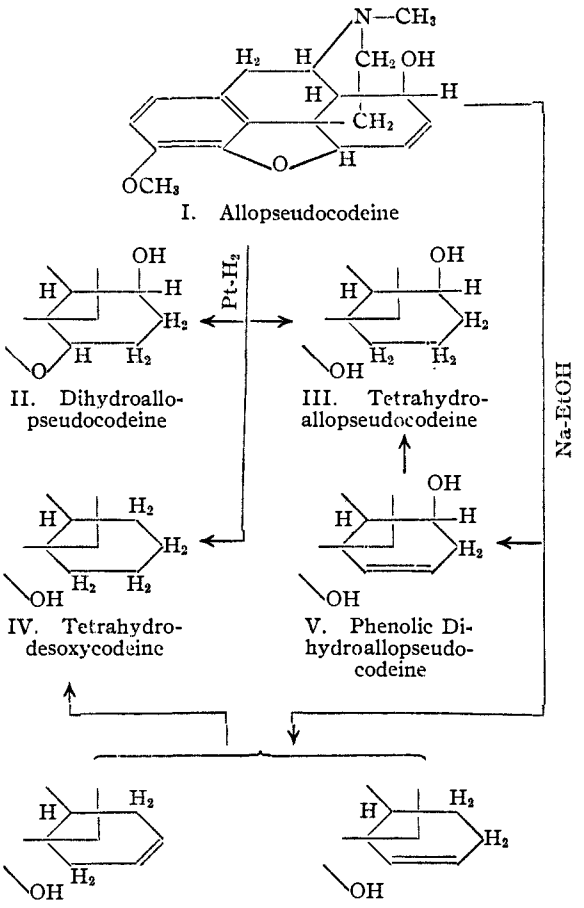
(1) The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, the University of Virginia and the University of Michigan.

(2) Speyer and Krauss, *Ann.*, **433**, 233 (1932).

(3) Lutz and Small, THIS JOURNAL, **54**, 4415 (1932); Small and Lutz, *ibid.*, **56**, 1928 (1934).

(4) Small and Lutz, *ibid.*, **56**, 1738 (1934).

tetrahydroallopseudocodeine by catalytic addition of one mole of hydrogen, and is assigned the structure V in analogy with dihydropseudocodeine-B.[5] The two dihydrodesoxycodeines are obtained in approximately the same ratio as in the parallel reductions of pseudocodeine, α-chlorocodide, or desoxycodeine-A, and are probably formed by the 1,6-addition mechanism involving desoxycodeine-A as an intermediate, as suggested in our previous communication.[5]



I. Allopseudocodeine

II. Dihydroallopseudocodeine

III. Tetrahydroallopseudocodeine

IV. Tetrahydrodesoxycodeine

V. Phenolic Dihydroallopseudocodeine

VI. Dihydrodesoxycodeines-B and -C

The bases II, III and V show no tendency whatsoever to lose the alcoholic hydroxyl with catalytic hydrogen, hence are not involved in the formation of tetrahydrodesoxycodeine. The unexpected appearance of this latter substance in the catalytic hydrogenation of allopseudocodeine affords evidence that in this type of reduction hydrogen may also react to some extent by 1,6-addition,[6] *i. e.*, at the two oxygen atoms, the resulting desoxycodeine-A then being hydrogenated quantitatively to tetrahydrodesoxycodeine. It is noteworthy that for allopseudocodeine the tendency toward reductive loss of the hydroxyl group is much greater than for pseudocodeine.[7]

Degradation of dihydroallopseudocodeine II yields a non-phenolic dihydro-ζ-methylmorphimethine which adds but one mole of hydrogen to give the non-phenolic tetrahydro-ζ-methylmorphimethine. A phenolic isomer of the latter is obtained when tetrahydroallopseudocodeine III is degraded, and can be hydrogenated to the known hexahydro-ζ-methylmorphimethine.

Saturation of the double bond in allopseudocodeine results in a diminution in convulsant action and an increase in analgesic effect; detailed pharmacological experiments are published elsewhere.[8]

Experimental

Reduction of Allopseudocodeine.—Crude allopseudocodeine hydriodide obtained by the Speyer procedure[2] was crystallized once from water (130 g. in 1 liter) to remove small amounts of pseudocodeine and isocodeine, then most advantageously converted to the free base and further purified in the form of hydrochloride or salicylate.

1. Catalytic Hydrogenation.—Twenty grams of allopseudocodeine hydrochloride in 200 cc. of glacial acetic acid with 0.2 g. of platinum oxide absorbed 1748 cc. of hydrogen (corr.) or 1.34 moles. The solvent was removed under diminished pressure, water added, and the solution treated with excess of dilute sodium hydroxide under ether. After several extractions, the ether yielded 14.3 g. (80%) of oily dihydroallopseudocodeine II, which was purified as the acid tartrate. From the alkaline mother liquors 3.2 g. (18%) of tetrahydroallopseudocodeine III was obtained. The crude dihydroallopseudocodeine contains traces of tetrahydrodesoxycodeine IV (highest yield 7%), which separates in crystalline form when the oily base is taken up in 60% alcohol. Identification of IV consisted of isolation of the two known anhydrous forms, m. p. 120° and 157–158°, mixed melting point, and conversion to des-N-methyltetrahydrodesoxycodeine, m. p. 147–148° (mixed melting point 147°). Hydrogenation of allopseudocodeine in alcohol with palladium-calcium carbonate gave approximately equal yields of II and III.

2. Reduction with Sodium and Alcohol.—A solution of 7.3 g. of allopseudocodeine in 400 cc. of boiling ethanol was treated with 40 g. of sodium during one and one-half hours. The solution was diluted with water, and alcohol distilled out under vacuum. An oil separated which was extracted into ether; 3.1 g. (44%) of mixed dihydrodesoxycodeines was obtained. The mixture showed the two melting points characteristic of the constant-propor-

(5) Lutz and Small, THIS JOURNAL, **56**, 1741 (1934).

(6) A 1,6-addition mechanism has been proposed by Schöpf [*Ann.*, **452**, 211 (1927)] to account for the formation of dihydrothebainone in the catalytic hydrogenation of thebaine.

(7) This observation, together with inferences drawn from the relative physiological activity of the codeine isomers [Eddy, *J. Pharmacol.*, **51**, 43 (1934); Foster, *ibid.*, **51**, 167, 195 (1934)], suggests interesting speculations on the configuration of the alcoholic hydroxyl group in these four bases.

(8) N. B. Eddy, *J. Pharmacol.*, **51**, 35 (1934).

tion mixture of dihydrodesoxycodeines-B and -C, the specific rotation of this mixture, and yielded the same low-melting hydrochloride. On degradation the easily isolable des-N-methyldihydrodesoxycodeine-C (m. p. and mixed m. p. 173–174°) was identified. From the alkaline mother liquor 2.6 g. (36%) of the oily phenolic dihydroallopseudocodeine V was isolated by the method usual for phenolic bases.

Dihydroallopseudocodeine (II).—This base was obtained crystalline only after purification in the form of the acid tartrate. Crystallized from ethyl acetate–ligroin mixture, II melts at 78–79° and has $[\alpha]_D^{25}$ −105° (ethanol, c = 0.85).

Anal. Calcd. for $C_{18}H_{23}O_3N$: C, 71.72; H, 7.69. Found: C, 71.68; H, 7.78.

Phenolic dihydroallopseudocodeine (V) is an alkali-soluble base which could not be obtained in crystalline form. It came to analysis in the form of perchlorate and methiodide (table). Hydrogenation of 0.38 g. of V in dilute acetic acid with platinum oxide resulted in absorption of 0.9 mole of hydrogen, with formation of 0.33 g. of tetrahydroallopseudocodeine III.

Tetrahydroallopseudocodeine (III) as obtained from hydrogenation of I or V showed physical properties differing considerably from those in the literature.[8] It crystallizes from 50% alcohol or ethyl acetate in thin diamond or six-sided scales of m. p. 113–118°, soluble with difficulty in ether. It sublimes in vacuum to give an anhydrous form of m. p. 145.5° (corr.) which is transformed to the low-melting solvated form by crystallization from dilute alcohol. The anhydrous form shows $[\alpha]_D^{25}$ −58° (ethanol, c = 0.93), solvated form $[\alpha]_D^{25}$ −52° (ethanol, c = 1.04).

Anal. Calcd. for $C_{18}H_{25}O_3N$: C, 71.24; H, 8.31. Found (sublimed base): C, 71.18; H, 8.38.

Dihydro-ζ-methylmorphimethine (VII).—This base was obtained in the usual way by treatment of II methiodide with hot alkali. It crystallized from ethyl acetate–ligroin mixture as three-sided or double four-sided pyramids of m. p. 99°; in ethanol $[\alpha]_D^{25}$ +117° (c = 0.94).

Anal. Calcd. for $C_{19}H_{25}O_3N$: C, 72.33; H, 7.99. Found: C, 72.47; H, 8.23.

Tetrahydro-ζ-methylmorphimethine (VIII) (non-phenolic) was obtained in practically quantitative yield by hydrogenation of VII. It crystallized from ligroin–ethyl acetate mixture as sheaves of blunt-pointed needles of m. p. 110°, $[\alpha]_D^{25}$ −26° (alcohol, c = 0.57).

Anal. Calcd. for $C_{19}H_{27}O_3N$: C, 71.87; H, 8.58. Found: C, 71.88; H, 8.77.

Tetrahydro-ζ-methylmorphimethine (IX) (phenolic) was prepared as described by Speyer[2] through heating III-methiodide with strong alkali. The description of its crystalline hydriodide is completed in the table above. On hydrogenation, IX absorbed one mole of hydrogen to give hexahydro-ζ-methylmorphimethine (X) identical with that obtained by hydrogenation of ζ-methylmorphimethine.[9]

DERIVATIVES OF THE ALLOPSEUDOCODEINE SERIES

I, Allopseudocodeine; II, dihydroallopseudocodeine; III, tetrahydroallopseudocodeine; V, *phenolic* dihydroallopseudocodeine; VI, ζ-methylmorphimethine; VII, dihydro-ζ-methylmorphimethine; VIII, tetrahydro-ζ-methylmorphimethine; IX, *phenolic* tetrahydro-ζ-methylmorphimethine; X, hexahydro-ζ-methylmorphimethine.

Base	Derivative	$[\alpha]_D^t$	°C.	c, H_2O	M. p. (corr.), °C.	Formula	Calcd.	Found	Calcd.	Found	Calcd.	Found
I	Hydrochloride[a]	− 202	26	0.7	256–258[d]	$C_{18}H_{22}O_3NCl$	Cl, 10.53	10.61				
I	Salicylate	− 145	25	.91	202							
II	Acid tartrate[b]	− 50	25	.8	124–125[c] 160–163	$C_{22}H_{27}O_9N + 2H_2O$	H_2O, 7.42	7.39	C, 58.51[e]	58.50[e]	H, 6.47[e]	6.77[e]
II	Hydriodide[a]	−70	26	1.0	255[d]	$C_{18}H_{24}O_3NI$	I, 29.54	29.44				
II	Perchlorate[b]	−83	30	0.44	265–270	$C_{18}H_{24}O_7NCl + 3H_2O$	H_2O, 14.9	15.0	Cl, 8.86[e]	8.51[e]		
III	Perchlorate[b]	−35	23	.48	102–104	$C_{18}H_{26}O_7NCl + H_2O$	H_2O, 4.48	3.64	Cl, 8.86[e]	8.89[e]		
III	Methiodide[g]	−22	27	.63	241–242[d]	$C_{19}H_{28}O_3NI$	I, 28.52	28.42				
V	Perchlorate[b]	−16	25	1.07	145–147	$C_{18}H_{24}O_7NCl + H_2O$	H_2O, 4.28	4.05	Cl, 8.82[e]	8.82[e]		
V	Methiodide[a]	− 5.5	27	0.63	247–248[d]	$C_{19}H_{28}O_3NI$	I, 29.63	29.29				
VI	Acid tartrate[b]	− 126	25	.89	99–101[f]	$C_{23}H_{29}O_9N + 2H_2O$	H_2O, 7.21	7.08	C, 59.59[e]	59.63[e]	H, 6.30[e]	6.26[e]
VI	Perchlorate[b]	− 154	28	.77	117–118	$C_{19}H_{24}O_7NCl + H_2O$	H_2O, 4.37	4.27	Cl, 8.61[e]	8.91[e]		
VI	Salicylate[b]	− 141	25	1.23	118–120	$C_{26}H_{29}O_8N + H_2O$	H_2O, 3.83	3.97	C, 66.49	66.20	H, 6.65	6.73
VII	Salicylate[a]	+76	26	0.77	175	$C_{26}H_{31}O_6N$			C, 68.84	68.88	H, 6.89	6.91
VIII	Salicylate[b]				175–175.5	$C_{26}H_{33}O_6N$			C, 68.53	68.77	H, 7.30	7.67
IX	Hydriodide[h]	+47.6	28	.78	249	$C_{19}H_{28}O_3NI$[g]	I, 28.52	28.26				
X	Hydriodide[b]	−39.8	28	.45	279–281[d]	$C_{19}H_{30}O_3NI$	I, 28.26	27.91				

[a] Crystallized from alcohol. [b] Crystallized from water. [c] Solidifies and remelts. [d] Melts with decomposition. [e] Anhydrous. [f] Melts with frothing. [g] Crystallized from methanol. [h] Crystallized from acetone–water.

Summary

1. Catalytic hydrogenation of allopseudocodeine under special conditions results chiefly in a non-phenolic dihydroallopseudocodeine.

2. As minor products tetrahydroallopseudocodeine and tetrahydrodesoxycodeine are obtained. A 1,6-hydrogenation mechanism is suggested to account for the formation of the latter substance.

3. Reduction of allopseudocodeine with sodium and alcohol gives a phenolic dihydroallopseudocodeine, and dihydrodesoxycodeines-B and -C.

4. The ζ-methylmorphimethine derivatives obtained from the hydrogenated allopseudocodeines are described.

UNIVERSITY, VIRGINIA RECEIVED AUGUST 1, 1934

(9) Speyer and Koulen, *Ann.*, **438**, 57 (1924).