Summary

The aryl thiazolidones studied correspond to the 2-arylamino or stable forms of Wheeler and Johnson.

Their sodium salts with methyl or ethyl iodide yield a mixture of 2-alkyl-2-aryl and of 3-alkyl-2-aryl thiazolidones. With benzyl chloride only the 2-benzyl derivative has been found.

These results have failed to confirm the formulation of Beckurts and Frerich, who assumed that the products they obtained were 2-alkylimino-3-aryl thiazolidones. Further unpublished investigations in this Laboratory support our experimental results.

LAWRENCE, KANSAS RECEIVED JUNE 12, 1933
PUBLISHED SEPTEMBER 5, 1933

[CONTRIBUTION NO. 115 FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

The Catalytic Hydrogenation of the Halogenomorphides: Dihydrodesoxymorphine-D[1]

BY LYNDON F. SMALL, KECHEE C. YUEN AND LOUIS K. EILERS

In a previous paper from this Laboratory[2] it was shown that catalytic hydrogenation of the halogenocodides yielded, according to the conditions, varying amounts of three hydrogenated desoxycodeine derivatives. By empirical selection of the proper catalyst and solvent, it was possible to direct the hydrogenation in such a way that the non-phenolic dihydrodesoxycodeine-D (IV) was the principal product obtained from any of the four known halogenocodides. Dihydrodesoxycodeine-D,[3] and its unsaturated analog, desoxycodeine-C (II),[4] in both of which the 4,5-ether bridge is still intact, are of particular interest pharmacologically, since they differ structurally from certain codeine derivatives (dihydrocodeine and pseudocodeine, respectively) only in having a hydrogen atom in place of the alcoholic hydroxyl of the codeine series. The demethylated analog of desoxycodeine-C, namely, desoxymorphine-C (I), which may be regarded as a derivative of γ-isomorphine, has already been described,[5] and has been found extraordinarily active in the animal body. With the view of preparing a dihydrodesoxymorphine of the dihydrodesoxycodeine-D type, corresponding in fundamental structure to dihydromorphine (Paramorfan), the catalytic hydrogenation of the halogenomorphides has been investigated.

(1) This investigation was supported by a grant from the Committee on Drug Addiction of the National Research Council from funds provided by the Bureau of Social Hygiene, Inc., and the Rockefeller Foundation.

(2) Mosettig, Cohen and Small, THIS JOURNAL, **54**, 793 (1932).

(3) Small and Cohen, *ibid.*, **53**, 2227 (1931).

(4) Small and Cohen, *ibid.*, **53**, 2214 (1931).

(5) Small and Morris, *ibid.*, **55**, 2874 (1933).

The three known halogenomorphides, on catalytic hydrogenation under identical conditions, yield varying amounts of three different products. α-Chloromorphide, in methyl alcoholic or weakly acid solution, gives largely the desired dihydrodesoxymorphine-D (III), together with some tetrahydrodesoxymorphine and a little non-crystalline material. In the case of β-chloromorphide, the product is almost exclusively dihydrodesoxymorphine-D. Bromomorphide which is believed (without good evidence) to correspond in structure to β-chloromorphide, yields, on the other hand, only small amounts of dihydrodesoxymorphine-D and a large quantity (up to 70%) of an uncrystallizable oil. This oil could not be distilled in high vacuum at any reasonable temperature, which led us to believe that it might correspond in structure to bis-dihydrodesoxycodeine. Decisive chemical evidence on this point could not be obtained, for the product resulting from methylation of the oil gave only one methiodide (amorphous), containing one atom of iodine to one molecule of desoxycodeine base; this does not necessarily exclude a dimolecular structure. An attempt to prepare a bis-dihydrodesoxymorphine for comparison, by demethylation of bis-dihydrodesoxycodeine with hydriodic acid, resulted in a phenolic base containing iodine.

The discrepancy between the hydrogenation of β-chloromorphide and that of bromomorphide has its parallel in a similar observation in the halogenocodide series, but does not permit of any valid conclusion concerning the structure of the two halogenomorphides, since the mechanism of the hydrogenation of these halogeno derivatives is uncertain.[6] The change in reduction conditions, from base in organic solvent to the salt in dilute acid solution, does not produce as great an effect on the course of hydrogenation as was observed in the halogenocodide series. For the halogenomorphides, faintly acid solution increases somewhat the yield of tetrahydrodesoxymorphine, and decreases the amount of oily product formed. In the case of the halogenocodides, good yields of dihydrodesoxycodeine-D could be obtained only by hydrogenation in acid solution, and in alcohol tetrahydro-

TABLE I

CATALYTIC HYDROGENATION OF THE HALOGENOMORPHIDES

(Palladium on Barium Sulfate as Catalyst)

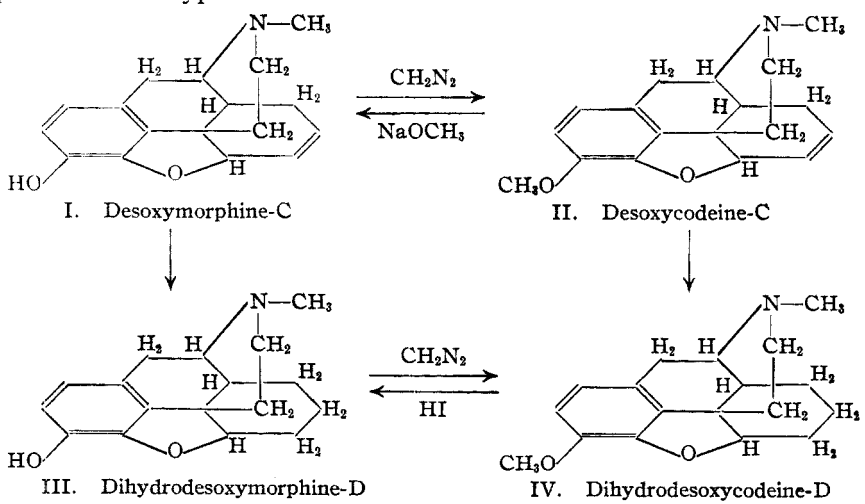
Substance	Solvent	Moles H_2	Dihydrodesoxymorphine-D, %	Tetrahydrodesoxymorphine, %	Oil, %
α-Chloromorphide	Methanol	1.86	70	11[a]	19
α-Chloromorphide	Dil. HCl	2.27	56	33	11
β-Chloromorphide	Methanol	2.0	100	..	..
β-Chloromorphide	Dil. HCl	2.28	83	17	..
Bromomorphide	Methanol	1.86	30	*a*	70
Bromomorphide	Dil. HCl	1 87	63	5	32

[a] Trace of unidentified base of m. p. 275–277°.

(6) Ref. 2, p. 795.

desoxycodeine or bis-dihydrodesoxycodeine resulted almost exclusively. In a repetition of some of the experiments of Mosettig, Cohen and Small, however, we have found that the results of hydrogenation often depend upon unrecognizable slight differences in catalyst or conditions, so that the discrepancy between the morphide and codide series may be largely illusory.

Dihydrodesoxymorphine-D, the principal product from the hydrogenation of α- and β-chloromorphides, is a colorless, well-crystallized base of m. p. 188–189°. It occurs also in a hemihydrated form of lower melting point, which can be converted to the anhydrous form by sublimation in high vacuum. It is not the same as the "dihydrodesoxymorphine" (m. p. 183°) of Knoll and Co.,[7] for the latter is beyond doubt identical with desoxymorphine-C (m. p. 189–190°).[8] The structure of dihydrodesoxymorphine-D is evident from its methylation, which leads to the nonphenolic dihydrodesoxycodeine-D (IV). Furthermore, dihydrodesoxymorphine-D can be obtained as the hydriodide in 93% yield from demethylation of dihydrodesoxycodeine-D. In view of the difficulty of preparation of the halogenomorphides, this constitutes the most practicable preparative method, for dihydrodesoxycodeine-D can be made quantitatively from the easily accessible α-chlorocodide. Dihydrodesoxymorphine-D can also be prepared by "normal" reduction of desoxymorphine-C under the special conditions developed by Lutz and Small[9] for partial hydrogenation of pseudocodeine types.



(7) Knoll and Co., German Patent 414,598 (1922); *Friedländer*, **15**, 1518; *Jahresber. Chem. Tech.*, **71**, 123 (1925).

(8) Small and Morris, THIS JOURNAL, **55**, 2876 (1933). Although desoxymorphine-C and dihydrodesoxymorphine-D show the same melting point, an identity of these two substances does not come into question, for they differ in other physical properties, and give a mixed melting point depression of 15°. Moreover, desoxymorphine-C can be hydrogenated with extreme ease, while dihydrodesoxymorphine-D is indifferent to catalytic hydrogenation.

(9) Lutz and Small, *ibid.*, **54**, 4715 (1932).

In contrast to its dihydrodesoxycodeine analog, dihydrodesoxymorphine-D is unaffected by prolonged electrolytic reduction. The same unexpected difference in reactivity toward electrolytic reduction has already been noted in the cases of desoxycodeine-C and desoxymorphine-C. It may depend upon imperceptible differences in conditions, and will be the subject of further study.

Because of the differences shown by β-chloromorphide and bromomorphide in catalytic hydrogenation, the electrolytic reduction of bromomorphide was investigated. It proceeds in the same way as that of α-chloromorphide, and yields desoxymorphine-A in 79% of the calculated amount. The reduction of α-chloromorphide with amalgamated zinc and 6-normal hydrochloric acid gives a good yield of a mixture of β-isomorphine (evidently formed by hydrolysis of the α-chloromorphide) and desoxymorphine-A. Bromomorphide yields the same products.

As a result of further attempts to verify the existence of a desoxymorphine which Schryver and Lees[10] prepared by treatment of α-chloromorphide with tin and hot concentrated hydrochloric acid, we have obtained minute quantities of an alkaloid hydrochloride of m. p. 262° and $[\alpha]_D$ −78°. The same product results from heating α-chloromorphide with stannous chloride and concentrated hydrochloric acid under pressure at 100°. The new hydrochloride is not the same as that of Schryver and Lees, for which the specific rotation +140.3° was given, nor does it correspond to any of the known desoxymorphine derivatives. It seems to us questionable whether the morphine carbon–nitrogen skeleton would withstand such drastic acid treatment without undergoing fundamental structural changes, since even in the preparation of β-chloromorphide from morphine and hydrochloric acid, a considerable part of the material is converted into apomorphine.

The physiological action of dihydrodesoxymorphine-D has been studied by Dr. N. B. Eddy at the Pharmacological Laboratory of the University of Michigan and will be described in detail in a publication from that Institution. In agreement with the change in physiological action which we have observed to result from replacement of the alcoholic hydroxyl group of the morphine and codeine series by hydrogen, dihydrodesoxymorphine-D is more active than dihydromorphine. Its toxicity is about the same as that of dihydromorphine, but respiratory and analgesic effects are greater. Dihydrodesoxymorphine-D likewise shows more analgesic action than its other hydroxy analog, dihydro-γ-isomorphine.[11]

Experimental

Hydrogenation of α-Chloromorphide.—The α-chloromorphide used in these experi-

(10) Schryver and Lees, *J. Chem. Soc.*, **77**, 1024 (1900).

(11) This new derivative of the morphine isomers has been prepared by hydrogenation of γ-isomorphine under special conditions, as well as by demethylation of the non-phenolic dihydropseudocodeine, and will be described in a later paper from this Laboratory.

ments was prepared by treatment of morphine with thionyl chloride,[12] and was purified by dissolving in dilute hydrochloric acid, precipitating with sodium carbonate and extracting the amorphous precipitate rapidly into ether. After several repetitions of this process, the crystalline material from the ether was washed with cold alcohol, which removed a considerable amount of another halogeno compound. The purified material showed $[\alpha]_D$ −363.6° (methanol, c = 0.528). Insufficiently pure chloromorphide leads to very complex hydrogenation mixtures.

Fifteen grams of α-chloromorphide dissolved in 150 cc. of absolute methanol was hydrogenated in the presence of 1.04 g. of palladium–barium sulfate (= 0.05 g. Pd metal). The absorption amounted to 2064 cc. of hydrogen, most of which was taken up in the first three hours, total time, eleven hours. The solution was freed of colloidal palladium by filtering through a layer of Norit, and the methanol removed at 40° in vacuum with a bubble-tube. The colorless resin which resulted was taken up in 100 cc. of water, and the alkaloid precipitated out by slow addition of ammonia, shaking into ether after each addition. Toward the end, the separation of crystalline tetrahydrodesoxymorphine caused troublesome emulsions. The ether was distilled down to 100 cc., and the crystalline tetrahydrodesoxymorphine, with a little dihydrodesoxymorphine-D, was filtered out. After washing with acetone to remove dihydrodesoxymorphine-D (0.6 g.) the tetrahydro product (together with that filtered off during the extraction) weighed 1.5 g. It had the m. p. 228–230°, and was identified by conversion to tetrahydrodesoxycodeine with diazomethane.

The ether solution from which the tetrahydrodesoxymorphine had been separated was distilled down to a yellow oil, which crystallized on rubbing with ethyl acetate. The crystals (3.6 g.) melted at 172–184°, and were purified from ethyl acetate; during this process, 60 mg. of a sparingly soluble base, m. p. 272–276°, was isolated. Analysis of this high-melting base gave the values C, 74.47; H, 7.53. It gave on methylation a colorless oil. The ethyl acetate mother liquors from the main portion gave on further evaporation 5 g. of a base of m. p. 155–170° which proved to be dihydrodesoxymorphine-D hemihydrate. The total yield of dihydrodesoxymorphine-D was 9.2 g.

As an alternative procedure, which is advantageous when much oily material is present, the residue from ether distillation may be extracted with cold acetone, the latter distilled to dryness and the residue treated with absolute alcoholic oxalic acid. Dihydrodesoxymorphine-D acid oxalate crystallizes well even in the presence of large amounts of impurities.

Dihydrodesoxymorphine-D.—Anhydrous dihydrodesoxymorphine-D melts at 188–189°, and has the specific rotation in absolute methanol $[\alpha]_D^{28}$ −76.8° (c = 1.614).

Anal. Calcd. for $C_{17}H_{21}O_2N$: C, 75.23; H, 7.81. Found: C, 74.82, 74.91; H, 7.85, 7.96.

Dihydrodesoxymorphine-D crystallizes best from acetone or ethyl acetate; in alcohol solution it turns red rapidly. It is precipitated by addition of water to its solution in acetone in the form of regular rectangular plates. It sublimes between 140 and 170° at 0.001 mm. pressure. The alkaloid behaves abnormally in camphor: The mixture shows two melting points, 133.5 and 166°, and on cooling, two solidification points, at about the same temperatures.

Two grams of dihydrodesoxymorphine-D in 200 cc. of 20% sulfuric acid was reduced electrolytically at 6 amp. on a 60 sq. cm. electrode for five hours at 10°, and for four more hours at 25°. The starting material, 1.8 g., was regained: m. p. 188–189°, $[\alpha]_D^{27}$ −75.3°.

Dihydrodesoxymorphine-D, 1.3 g., in ethereal solution with a few cc. of methanol was allowed to react with 0.2 g. of diazomethane for twenty-four hours. The yield of

(12) Wieland and Kappelmeier, *Ann.*, **382**, 306 (1911).

crude crystalline methylation product was nearly quantitative. After purification from acetone it had the m. p. 106–107° of dihydrodesoxycodeine-D, and showed $[\alpha]_D^{20}$ −81.3° in alcohol.

Demethylation of Dihydrodesoxycodeine-D.—A solution of 15 g. of dihydrodesoxycodeine-D in 45 cc. of hydriodic acid, sp. gr. 1.7, was boiled vigorously for three minutes. To the cooled solution, water (about 150 cc.) was added slowly with scratching until crystals no longer separated. The mixture was warmed nearly to boiling, whereby the crystals became pure white and more granular. The yield of dihydrodesoxymorphine-D hydriodide was 17.3 g. From the mother liquor an additional 1.5 g. of pure dihydrodesoxymorphine-D base was obtained by precipitation with ammonia.

TABLE II

DIHYDRODESOXYMORPHINE-D DERIVATIVES

Derivative	$[\alpha]_D$, solvent, c, t°C	Formula	Analyses, % Calcd.	Found	Calcd.	Found
Hydriodide[a]	−48.4°, water, 1.650,25	$C_{17}H_{21}O_2N \cdot HI$	I, 31.81	32.19	.....	....
Hydrochloride[b]	−66.8°, water, 0.898,27	$C_{17}H_{21}O_2N \cdot HCl$	Cl, 11.53	11.54	.....	....
Sulfate[c]	−57.9°, water, 1.425,29	$(C_{17}H_{21}O_2N)_2H_2SO_4 + 2H_2O$	H_2O 5.32	5.33	SO_4, 14.99[d]	15.20[d]
Acid oxalate[e]	−57.9°, water, 1.659,28	$C_{19}H_{23}O_4N$	C, 63.12	62.87	H, 6.42	6.43
Salicylate[f]	−42.8°, alc., 0.794,28	$C_{24}H_{27}O_5N$	C, 70.38	69.93	H, 6.64	6.94
Methiodide[g]	−46.6°, water, 1.009,27	$C_{18}H_{24}O_2NI$	C, 52.29	52.26	H, 5.86	5.98

[a] Best purified from water; 100 g. satd. aqueous solution at 25° contains 3.86 g. of the salt. [b] Prepd. from base with alcoholic hydrochloric acid, purified from 95% alcohol; exceedingly soluble in water. [c] Prepd. from base with sufficient cold 10% sulfuric acid to turn Congo paper; salt is sparingly soluble in cold water, very soluble in hot water, and is best suited to purification of the alkaloid. Colors slightly at 210°, unmelted at 230°. [d] Anhydrous salt, $(C_{17}H_{21}O_2N)_2H_2SO_4$. [e] Prepd. from base with absol. alcoholic oxalic acid; sparingly sol. in alcohol, very sol. in water, recryst. from 50% alcohol. [f] Prepd. in absolute alcohol with alcoholic salicylic acid, recryst. from 95% alcohol. Different preparations of the salt did not give consistent analyses; under some conditions it apparently crystallizes with a variable amount of water. [g] Prepd. by adding excess methyl iodide to suspension of the alkaloid in hot acetone; the amorphous methiodide becomes cryst. on further heating, and can be recryst. from alcohol.

Dihydrodesoxymorphine-D Hemihydrate.—This derivative was obtained as one of the products from most of the hydrogenations of the halogenomorphides, and usually separated from the ethyl acetate solution which had already yielded a crop of the anhydrous base. The conditions which determine its formation are not known; we were never able to obtain the hemihydrate from the anhydrous base. The hemihydrate does not lose its hydrate water in high vacuum below the temperature at which sublimation occurs, and a direct determination of hydrate water was not possible. The hemihydrate melts at 162–164° with gas evolution, and has $[\alpha]_D^{28}$ −78.6° (ethyl acetate, c = 1.076). It gives the anhydrous base of m. p. 188–189° quantitatively on sublimation. Its salts are identical with those of the anhydrous base, and it gives by methylation dihydrodesoxycodeine-D (70% yield).

Anal. Calcd. for $C_{17}H_{21}O_2N + 0.5H_2O$: C, 72.85; H, 7.93. Found: C, 72.85; H, 8.11.

Dihydrodesoxymorphine-D from Desoxymorphine-C.—A suspension of 2.27 g. of finely powdered desoxymorphine-C hydrochloride (= 2.00 g. of alkaloid) in 15 cc. of glacial acetic acid absorbed 266 cc. (= 1.4 moles) of hydrogen in the presence of 0.05 g. of platinum oxide. The product was precipitated with ammonia, extracted into

ether, and the residue from distillation of the ether rubbed up with acetone. The acetone-insoluble tetrahydrodesoxymorphine, 0.75 g., was converted to the salicylate, which melted at 232° and had $[\alpha]_D^{25}$ −31.6°. The acetone extract yielded 0.75 g. of dihydrodesoxymorphine-D, which after one crystallization from acetone melted at 185–186° and had $[\alpha]_D^{25}$ −84.6°.

Hydrogenation of α-Chloromorphide in Acid Solution.—Five grams of α-chloromorphide suspended in 100 cc. of water was brought into solution by addition of normal hydrochloric acid and hydrogenated in the presence of 1.05 g. of palladium–barium sulfate. The absorption amounted to 2.27 moles of hydrogen most of which was taken up in the first hour. By precipitation with ammonia and extraction with ether, 1.5 g. of dihydrodesoxymorphine-D hemihydrate was obtained, and 1.5 g. of the ether-insoluble tetrahydrodesoxymorphine. The aqueous layer gave a heavy Mayer's test, and yielded on further extraction 1.0 g. of anhydrous dihydrodesoxymorphine-D.

Hydrogenation of β-Chloromorphide.—The β-chloromorphide used was prepared by the action of fuming hydrochloric acid on morphine at 100°[13] and was purified most advantageously as the tartrate, $[\alpha]_D^{25}$ +7.4° (water, c = 2.708). The base liberated from the tartrate had $[\alpha]_D^{25}$ −4° (methanol, c = 2.115) and melted at about 182°. Hydrogenation of 5.34 g. of β-chloromorphide in 100 cc. of methanol in the presence of Pd–$BaSO_4$ resulted in absorption of 2 moles of hydrogen in about two hours. The product, isolated as described for α-chloromorphide, consisted of 4.5 g. of colorless crystals of dihydrodesoxymorphine-D. By crystallization from ethyl acetate, 3 g. of anhydrous base was obtained, and from the ethyl acetate mother liquors 1.5 g. of the hemihydrate.

When the hydrogenation was carried out in dilute hydrochloric acid solution, the hemihydrate form only, of dihydrodesoxymorphine-D, with about 17% of tetrahydrodesoxymorphine, was obtained.

Hydrogenation of Bromomorphide.—Bromomorphide was prepared by the method of Schryver and Lees[14] and purified from methanol. It sintered and darkened at 164°, and melted above 200°. In methanol it showed $[\alpha]_D^{28}$ +73.9° (c = 2.788). When bromomorphide was hydrogenated in methanol, with Pd–$BaSO_4$, 4.85 g. of alkaloid took up 1.86 moles of hydrogen, and yielded 1.0 g. of dihydrodesoxymorphine-D hemihydrate. The remaining material was a viscous oil, containing a trace of the high-melting base mentioned under α-chloromorphide. The oil did not give a crystalline ether on treatment with diazomethane. The methylation product in benzene with methyl iodide gave a methiodide of m. p. 235–238°, which appeared to be amorphous, and could be purified only by washing with acetone. It was not the monomethiodide of a dimolecular base, for analysis showed 29.51% iodine, and its properties were not those of bis-dihydrodesoxycodeine dimethiodide. The hydrogenation of bromomorphide in methanol with platinum oxide gave only a small amount of crystalline product, which proved to be tetrahydrodesoxymorphine.

Hydrogenation of bromomorphide in dilute hydrochloric acid gives more crystalline material than in methanol. From 4.85 g. of bromomorphide, absorption of 1.87 moles of hydrogen, 2.4 g. of dihydrodesoxymorphine-D hemihydrate, 0.2 g. of tetrahydrodesoxymorphine, and 1.2 g. of uncrystallizable oil were obtained.

Electrolytic Reduction of Bromomorphide. Desoxymorphine-A.—Six grams of bromomorphide in 250 cc. of 20% sulfuric acid was reduced at 20° with 12 amp. on a 60 sq. cm. lead cathode, time seven hours. A trace of sodium hydrosulfite was added, the base precipitated out with ammonia, and extracted several times with ether. The calculated amount of salicylic acid was added to the dried ether solution, which was then concentrated to 100 cc. A yield of 4.5 g. (79%) of desoxymorphine-A salicylate was obtained. After purification from alcohol it melted at 248–250° (gas evolution)

(13) Ach and Steinbock, *Ber.*, **40**, 4282 (1907).

(14) Schryver and Lees, *J. Chem. Soc.*, **77**, 1032 (1900).

and had $[\alpha]_D^{25}$ +93.6° (methanol, c = 0.801). The base prepared from the salicylate melted at 257–258° with decomp.

Reduction of α-Chloromorphide and Bromomorphide with Zinc.—Fifty grams of α-chloromorphide in 1 liter of 6 *N* hydrochloric acid was heated at 60° for fourteen hours with 100 g. of amalgamated zinc. After eight days further reaction at room temperature, the solution was treated with excess concd. ammonia, and the precipitated alkaloid extracted into ether. The aqueous layer contained much β-isomorphine, which was isolated by exhaustive extraction with ether, and characterized as the salicylate. The main ether extract was heated with 25 g. of salicylic acid and distilled. Twenty grams of a crystalline salicylate was obtained, m. p. 164–178°, which after repeated crystallizations from alcohol showed the constant m. p. 204–206°, $[\alpha]_D^{27}$ −53° (methanol, c = 0.849). Analysis indicated that this was a mixture of a desoxymorphine salicylate and the salicylate of one or more of the morphine isomers. By converting the mixed salicylate back to the alkaloid, desoxymorphine-A of m. p. 258° could be isolated; it did not depress the m. p. of a known sample.

Anal. Calcd. for $C_{17}H_{19}O_2N$: C, 75.80; H, 7.11. Found: C, 75.92; H, 7.15.

Reduction of bromomorphide in the same way gave the same mixture of salicylates.

Reduction of α-Chloromorphide with Tin.—When α-chloromorphide was reduced with tin and concd. hydrochloric acid as described by Schryver and Lees, 3% yield of a crystalline hydrochloride was obtained by allowing an alcoholic solution of the oily hydrochloride to stand for several weeks. It was difficultly soluble in alcohol and could be recrystallized from water. It melted sharply at 263.5° with decompn. and showed $[\alpha]_D^{27}$ −78.1° in water (c = 1.050). The hydrochloride of Lees had the rotation $[\alpha]_D$ +140.3°. The same hydrochloride (5% yield) was obtained when α-chloromorphide was reduced with stannous chloride and concd. hydrochloric acid under pressure at 100°. It was impossible to purify it to the point where it did not leave a trace of inorganic material on combustion.

Anal. Found: C, 58.73; H, 6.74.

The alkaloid liberated from this hydrochloride could not be obtained crystalline, and gave only a colorless oil on methylation.

Summary

1. Catalytic hydrogenation of the three known halogenomorphides results in varying amounts of dihydrodesoxymorphine-D, tetrahydrodesoxymorphine and an unidentified oil.

2. Dihydrodesoxymorphine-D is obtained in nearly quantitative yield by demethylation of dihydrodesoxycodeine-D. It may likewise be prepared by controlled hydrogenation of desoxymorphine-C.

3. Electrolytic reduction of bromomorphide yields chiefly desoxymorphine-A. Reduction of α-chloromorphide or bromomorphide with zinc and hydrochloric acid gives desoxymorphine-A, β-isomorphine and probably other of the morphine isomers.

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RECEIVED JUNE 14, 1933
PUBLISHED SEPTEMBER 5, 1933