Syntheses in the Morphine Series. Part VI. The Synthesis of Morphine.†*

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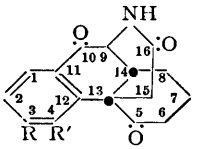
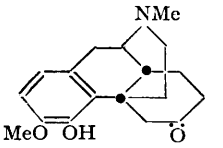
In continuation of previous experiments (Part V *) synthetic intermediates have been converted into (−)-dihydrothebainone. This constitutes a synthesis of morphine.

In Part IV of this series (Ginsburg and Pappo, *J.*, 1953, 1524) the synthesis of the tetracyclic lactam (I*a*) was described. In Part V * methods were investigated for the oxygenation at $C_{(6)}$, so that it would be possible to convert the methoxylated analogue (I*b*) into a compound such as dihydrothebainone (II). In this communication, the synthesis of the methoxylated analogue (I*b*) is described and its conversion into dihydrothebainone is reported.

(I*a*): R = R′ = H
(I*b*): R = OMe, R′ = OH

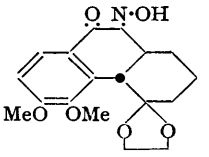


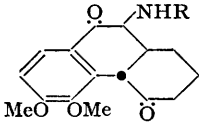


(II)

The 4-ethylene glycol ketal (III) of 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-10-hydroxyimino-5 : 6-dimethoxy-4 : 9-dioxophenanthrene was reduced catalytically with palladised carbon in the presence of hydrochloric acid, to give the hydrochloride of the corresponding 10-amino-compound (IV*a*) (cf. Ginsburg and Pappo, *loc. cit.*), the ketal grouping being lost during the reduction. The amine hydrochloride was suspended in chloroform containing pyridine, and the mixture was treated with acetylglycollyl chloride the 10-acetoxyacetamido-derivative (IV*b*) was obtained in high yield.

(III)





(IV*a*): R = H
(IV*b*): R = CO·CH$_2$·OAc

In analogy with the unique cyclisation observed with the unmethoxylated analogue of (IV*b*), which yielded the lactam (I*a*) (Ginsburg and Pappo, *J.*, 1953, 1524), treatment of (IV*b*) with toluene-*p*-sulphonic acid in the presence of ethylene glycol yielded two substances, m. p. 244—246° and 196° respectively. The higher melting product proved to be the 10-ethylene glycol ketal of the lactam (I*b*).‡ It was noted that demethylation of the 4-methoxyl group occurred during cyclisation. Thus, in the tetracyclic lactam series, demethylation of this group occurs as readily as the analogous demethylation in the tetracyclic amine series (cf. Grewe, Mondon, and Nolte, *Annalen*, 1949, **564**, 161).

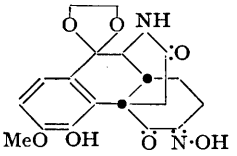
The structural assignment for the major cyclisation product, m. p. 244—246°, was made on the basis of the analytical results and the infra-red absorption spectrum which clearly showed at 5·84 μ the presence of the alicyclic carbonyl group. Although it was difficult to determine unequivocally from the infra-red spectrum whether absorption by the carbonyl group conjugated to the aromatic nucleus was absent, since the lactam function absorbs very nearly in the same region, the typical bands for the ketal grouping were present.

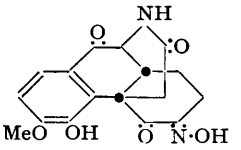
* Part V, *J.*, 1953, 2664.

† A preliminary communication on this subject has been published (Elad and Ginsburg, *J. Amer. Chem. Soc.*, 1954, **76**, 312).

‡ The numbering used for the tetracyclic products which have the skeletal structure of morphine is that used for morphine itself.

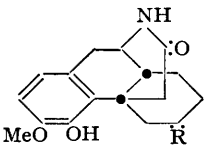
The subsequent step in the reaction sequence permitted a test of this structural assignment. The hydroxyimino-compound (V) was obtained in about 80% yield and its properties were in accord with its formulated structure. The next step afforded further convincing evidence, as careful acid treatment of (V) selectively removed the blocking group at $C_{(10)}$ without effecting hydrolysis of the oxime group at $C_{(6)}$, and the 6-hydroxyimino-5 : 10-dioxo-lactam (VI) was obtained.

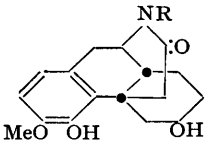
(V) 

 (VI)

Now that the carbonyl group at $C_{(5)}$ had served its purpose of introducing a potential oxygen function at $C_{(6)}$ (as is required, for example, in dihydrothebainone), it became necessary to remove the oxygen functions at $C_{(5)}$ and $C_{(10)}$. A serious difficulty appeared to prevent this, namely, the presence of the α-diketone system at $C_{(5)}$ and $C_{(6)}$. The alkaline conditions required in the Wolff–Kishner reduction would be expected to be sufficiently stringent to effect a benzilic acid rearrangement in ring C from its present form to a hydroxy-*cyclo*pentanecarboxylic acid system. For this reason the oxime grouping in (VI) was not hydrolysed before the reduction. Furthermore, since cases are known in which heating of a hydrazone, even in the absence of alkali, resulted in conversion of a carbonyl group into a methylene group (cf. Todd, " Organic Reactions," Vol. 4, p. 384, Wiley, New York, 1948), the Huang-Minlon procedure was used but alkali was omitted in this instance. When the temperature of the reaction mixture containing the dihydrazone of (VI) reached 140°, evolution of nitrogen began and the reduction was essentially complete in 3 hours. After isolation of the product (VII*a*), no carbonyl absorption appeared in its infra-red absorption spectrum. The 6-oxime grouping, however, remained intact. Acid hydrolysis of (VII*a*) afforded the ketone (VII*b*).

(VII*a*) : R = :N·OH
(VII*b*) : R = :O





(VIII*a*) : R = H
(VIII*b*) : R = Me

Attempted ketalisation in order to block the 6-oxo-group failed. The ketone (VII*b*) was therefore subjected directly to reduction with lithium aluminium hydride. The resulting epimeric mixture de-*N*-methyldihydrothebainols (VIII*a*) was methylated by means of formaldehyde–formic acid to yield dihydrothebainol (VIII*b*) which failed to crystallise, and apparently consisted of a mixture of the axial and equatorial racemates. Since oxidation of this mixture should give only one ketone and because of the small amount of material at hand, the isolation of the dihydrothebainols epimeric at $C_{(6)}$ was not attempted.

The behaviour of both known dihydrothebainols on oxidation by potassium *tert.*-butoxide–benzophenone was next investigated. " Dihydrothebainol A," m. p. 142°, has been prepared by electrolytic reduction or sodium amalgam reduction of (—)-dihydrothebainone (Speyer and Siebert, *Ber.*, 1921, **54**, 1519). " Dihydrothebainol B," m. p. 165°, was obtained by reduction of the ketone with a platinum catalyst in the presence of acid (Skita, Nord, Reichert, and Stukart, *ibid.*, p. 1560). Attempted stereospecific reduction of (—)-dihydrothebainone by means of sodium borohydride and lithium aluminium hydride severally was successful only in part. In both instances, mixtures of the axial and the equatorial isomer were formed. Since after repeated crystallisation the " A " isomer (probably equatorial) was obtained pure in the sodium borohydride reduction, whilst the " B " isomer (probably axial) was thus obtained from the lithium aluminium hydride reduction, it appears that each predominates in one of these reductions. However, chromatography of the mother-

liquors clearly showed that both isomers were present in each case. Although it has been shown for other alcohols in the morphine series, that the axial alcohol is oxidised much faster than its equatorial isomer, by means of potassium *tert.*-butoxide–benzophenone (Rapoport, Naumann, Bissell, and Bonner *J. Org. Chem.*, 1950, **15**, 1103), no appreciable difference in rate could be detected in the rates of oxidation of the dihydrothebainols A and B.

The semisolid racemic dihydrothebainol mixture obtained in this investigation was oxidised by means of potassium *tert.*-butoxide in the presence of benzophenone, and the racemic ketone obtained was identical in its infra-red spectrum (in the range 2—15 μ) with (−)-dihydrothebainone.

The racemic ketone was treated with one-half molar equivalent of (+)-tartaric acid in acetone solution. The salt thus obtained had the same rotation as (−)-dihydrothebainone (+)-tartrate. Conversion into the free base gave (−)-dihydrothebainone, $[\alpha]_D^{21}$ −75° (in EtOH). Values of $[\alpha]_D^{20}$ −80·12° (in EtOH) and $[\alpha]_D^{18}$ −72·5° (in absolute EtOH) have been reported (Skita *et al.*, *loc. cit.*; Schöpf and Winterhalder, *Annalen*, 1927, **452**, 232).

The synthesis of optically active dihydrothebainone constitutes the second total synthesis of morphine. Gates and Tschudi (*J. Amer. Chem. Soc.*, 1952, **74**, 1109) have accomplished the first total synthesis of morphine and their brilliant work involved the conversion of dihydrothebainone into morphine. Conditions for the cyclisation of dihydrothebainone into 1-bromodihydrocodeinone have been reported by Schöpf and Pfeifer (*Annalen*, 1930, **483**, 157). Demethylation of codeine to morphine has been reported by Rapoport, Lovell, and Tolbert (*J. Amer. Chem. Soc.*, 1951, **73**, 5900).

Rapoport has recently concluded his elegant series of proofs regarding the stereochemistry at the various asymmetric centres of the morphine molecule (Rapoport and Lavigne, *ibid.*, 1953, **75**, 5329 and references listed therein). He has shown that the B and the C ring of morphine are *cis*-locked. In both the Gates and Tschudi synthesis of morphine and in ours (cf. Ginsburg and Pappo, *J.*, 1953, 1524) compounds in which the respective rings are *trans*-locked were converted into derivatives of the natural *cis*-series. In our case, the cyclisation of the *trans*-compound to one of *cis*-configuration proceeds by an unknown mechanism. It is now clear, however, from the results of *X*-ray investigations of the morphine structure, carried out in two laboratories, that a *cis*-B : C junction exists in morphine. We are indebted to Mrs. Dorothy Hodgkin, F.R.S., for disclosing this information to us, before its publication.

Experimental

4-Ethylene Glycol Ketal of 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*Octahydro*-10-*hydroxyimino*-5 : 6-*dimethoxy*-4 : 9-*dioxophenanthrene*.—Sodium (1·2 g.) was dissolved in dry ethanol (25 ml.) and a solution of the 4-ethylene glycol ketal of 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-5 : 6-dimethoxy-4 : 9-dioxophenanthrene (15·1 g.) in dry dioxan (60 ml.) was added in one portion. *n*-Amyl nitrite (11 ml.) was added and the mixture was kept in the refrigerator for 48 hr. Ether and dilute acetic acid were added with cooling. The aqueous phase was extracted with three portions of ether and the combined ether extracts were extracted with three portions of Claisen's alkali. Acidification with acetic acid precipitated the 10-hydroxyimino-derivative (12·6 g., 76%). The product obtained by this modified procedure is identical with that reported by Ginsburg and Pappo (*J.*, 1953, 1524).

10-*Amino*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-5 : 6-*dimethoxy*-4 : 9-*dioxophenanthrene Hydrochloride*.—The above hydroxyimino-compound (12·6 g.; employed without further purification) was suspended in ethanol (300 ml.) and hydrogenated in the presence of palladised charcoal (10%; 2 g.) and hydrochloric acid (35%; 6 ml.) at an initial hydrogen pressure of 60 lb./sq. in. Hydrogen uptake ceased after 2 hr. The catalyst was filtered off and the solvent removed at the water pump. Ethanol (100—150 ml.) was added to dissolve the hydrochloride, and ether was then added until the solution was turbid. After standing in the refrigerator the *amine hydrochloride* (5·5—6·5 g., 50—60%) was obtained as colourless crystals, m. p. 206—208° (decomp.). Recrystallisation from ethanol–ether raised the m. p. to 210—212° (decomp.) (Found: C, 58·0; H, 6·2; N, 4·2; Cl, 10·85. $C_{16}H_{20}O_4NCl$ requires C, 58·15; H, 6·15; N, 4·3; Cl, 10·8%).

10-*Acetoxyacetamido*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-5 : 6-*dimethoxy*-4 : 9-*dioxophenanthrene*.—The amine hydrochloride (4·5 g.) was suspended in chloroform (60 ml.), and dry pyridine (5 ml.) was added. The mixture was boiled for 2 min., then cooled in ice, and a solution of

acetylglycollyl chloride (4·4 g.) in chloroform (20 ml.) was added dropwise during 1 hr. Finally, the mixture was refluxed for 30 min. The clear light orange solution was washed twice with dilute hydrochloric acid and with water. The chloroform was removed at the water-pump, and the residual heavy oil crystallised upon trituration with ethanol. The *acetoxyacetamide* formed colourless crystals, m. p. 169—171° (from ethanol) (4 g., 76%) (Found : C, 61·7; H, 5·8; N, 3·6. $C_{20}H_{23}O_7N$ requires C, 61·7; H, 6·0; N, 3·6%). A second crop (0·5 g.) of slightly lower-melting material was obtained from the mother-liquor.

Cyclisation.—A mixture of the acetoxyacetamide (5·4 g.), ethylene glycol (30 ml.), toluene (50 ml.), benzene (30 ml.) and toluene-*p*-sulphonic acid (0·1 g.) was refluxed for 8—9 hr., with an "azeotropic" receiver to collect the volatile products. After cooling, solid sodium carbonate was added to give a slightly alkaline reaction and the two layers were separated. The ethylene glycol layer was diluted with water, the organic layer was separated, and the solvents were removed under reduced pressure. The solid residue was extracted with boiling heptane–benzene. Upon cooling, the extract deposited crystals, m. p. 193—195°. Recrystallisation raised the m. p. to 196° (from heptane–benzene). This substance was obtained in very low yield and was not further characterised.

The fraction insoluble in heptane–benzene was dissolved in boiling ethanol. After standing, the *ketal-lactam* (10-dioxalan of I*b*) crystallised, and had m. p. 244—246° (from ethanol or toluene) (Found : C, 63·2; H, 5·7; N, 4·0%; active H, 1·7. $C_{19}H_{21}O_6N$ requires C, 63·5; H, 5·9; N, 3·9%; active H, 2·0). The *mono*-2 : 4-*dinitrophenylhydrazone*, prepared in the usual way, had m. p. 241—242° (from ethanol–chloroform) (Found : N, 13·8. $C_{23}H_{21}O_8N_5$ requires N, 14·1%); the ketal group had been hydrolysed.

The Dioxo-lactam (I*b*).—The ketal-lactam (1 g.) was added to a mixture of ethanol (25 ml.) and water (10 ml.), and concentrated hydrochloric acid (5 drops) was added. The mixture was heated at 60° for 2 hr. On cooling, colourless crystals of the *dioxo-lactam* (0·5 g.), m. p. 216—218° (from heptane–benzene), were obtained (Found : C, 65·0; H, 5·5. $C_{17}H_{17}O_5N$ requires C, 64·8; H, 5·4%). The product becomes yellow in air. The 2 : 4-dinitrophenylhydrazone, prepared in the usual way, had m. p. 241—242° (from ethanol–chloroform). Admixture with the 2 : 4-dinitrophenylhydrazone reported above caused no m. p. depression.

6-*Hydroxyimino-lactam* 10-*Ketal* (V).—To a solution of sodium ethoxide [prepared from 207 mg. of sodium (0·009 mole) and 10 ml. of ethanol] were added finely powdered ketal-lactam, m. p. 244—246° (1·077 g., 0·003 mole), and dry dioxan (10 ml.). *n*-Amyl nitrite (0·41 ml.) was added with ice-cooling. After 1·5 hr. the solid material had dissolved and the solution became dark brown. The mixture was refrigerated for 24 hr. Ether (50 ml.), water (25 ml.), and acetic acid (1·5 ml.) were added and the aqueous phase was extracted with 4 additional portions of ether; the 6-*hydroxyimino*-derivative precipitated from the ether solution (650—700 mg.) had m. p. 259—260° (decomp.). The analytical sample was obtained by treatment of the highly insoluble light yellow product with boiling ethanol. The m. p. was thus raised to 265—266° (decomp.) (Found : C, 58·6; H, 5·2; N, 7·1. $C_{19}H_{20}O_7N_2$ requires 58·8; H, 5·2; N, 7·2%). Evaporation of the mother-liquor under reduced pressure yielded an additional 50 mg. of the product. The product gives a green colour with alcoholic ferric chloride.

6-*Hydroxyimino*-10-*oxo-lactam* (VI).—The 6-hydroxyimino-lactam 10-ketal (V) (1·2 g.) was refluxed in ethanol (120 ml.), water (10 ml.), and concentrated hydrochloric acid (2 ml.) for 1 hr. The solvents were removed under reduced pressure and the residue heated at 100° in a high vacuum to remove ethylene glycol. The residue weighed 1 g. The analytical sample was obtained by trituration with methanol. The pure 6-*hydroxyimino*-10-*oxo-lactam* had m. p. 212—214° (decomp.) (from methanol) (Found : C, 59·3; H, 4·5; N, 7·9. $C_{17}H_{16}O_6N_2$ requires C, 59·3; H, 4·7; N, 8·1%). The crude product was sufficiently pure to be employed in the next reaction without crystallisation.

Reduction.—The crude 6-hydroxyimino-10-oxo-lactam (VI) (1 g.) and hydrazine hydrate (1 ml.) in diethylene glycol (25 ml.) were heated on a steam-bath for 8 hr. The temperature was then raised to 165° and maintained thereat for 2 hr., nitrogen being evolved continually. After dilution with water the mixture was continuously extracted with ether for 24 hr. After removal of the ether, the oxime-lactam (VII*a*) was obtained as a very viscous oil (427 mg.). A small portion was dissolved in benzene and chromatographed over Merck's acid-washed alumina; the pure compound, micro-m. p. 210—213° (from pentane), was obtained. The substance gave a large m. p. depression on admixture with the 6-hydroxyimino-10-oxo-lactam.

Mixture of Racemic Dihydrothebainols.—(*a*) The oxime-lactam (VII*a*) (400 mg.) was refluxed in ethanol (50 ml.), water (5 ml.), and hydrochloric acid (3 ml.) for 5 hr. The solvents were removed under reduced pressure, the residue was treated with chloroform, the chloroform solu-

tion was washed with water, and the solvent again removed under reduced pressure. It was not possible to prepare a ketal of the residual ketone.

(*b*) To a solution of lithium aluminium hydride (2 g.) in tetrahydrofuran (70 ml.) was added a solution of the free ketone (from *a*) (300 mg.) in tetrahydrofuran (30 ml.). The mixture was refluxed for 120 hr. under nitrogen. The solvent was removed under reduced pressure and the residue was treated with dilute hydochloric acid. Continuous extraction (24 hr.) with ether removed acid-insoluble material. The aqueous phase was evaporated to dryness under reduced pressure and the amine hydrochloride was extracted several times with boiling acetone. The acetone solution contained the hydrochloride of de-*N*-methyldihydrothebainol.

(*c*) The acetone was removed under reduced pressure, the semi-solid residue was treated with aqueous ammonia, and the free amine extracted with chloroform. After removal of the solvent, methylation was carried out by formaldehyde–formic acid as described for the unmethoxylated analogue (cf. Ginsburg and Pappo, *J.*, 1953, 1536). After the usual working-up a mixture of racemic dihydrothebainols was obtained as a sticky solid.

Dihydrothebainol A.—To a solution of dihydrothebainone ($[\alpha]_D^{21}$ −75°; 2 g.) in methanol (25 ml.) was added finely powdered sodium borohydride (700 mg.) at room temperature. The temperature rose to 40°. The mixture was set aside for 2 hr. The solvent was evaporated under reduced pressure; dilute hydrochloric acid was added to the residue, and the acid solution was treated with excess of concentrated aqueous ammonia. The product was extracted with 6 portions of ether. Evaporation of the ether gave a solid residue (2 g.). Many recrystallisations from ethyl acetate or aqueous ethanol gave dihydrothebainol A (280 mg.), m. p. 140—142° (after some softening at 135°). When heated in a drying pistol the material softens. Speyer and Siebert (*loc. cit.*) report m. p. 142° (with sintering at 138°) for dihydrothebainol A.

Dihydrothebainol B.—A solution of dihydrothebainone ($[\alpha]_D^{21}$ −75°; 3 g.) in tetrahydrofuran (50 ml.) was added during 10 min. to a solution of lithium aluminium hydride (3 g.) in tetrahydrofuran (100 ml.), and the mixture was refluxed for 6 hr. The solvent was removed under reduced pressure and dilute ammonia solution was added to the residue carefully with cooling. Continuous ether-extraction (48 hr.) of the alkaline mixture followed by evaporation of the ether gave a solid (2·8 g.). Recrystallisation from ethyl acetate gave dihydrothebainol B (300 mg.), m. p. 166—169°. Skita *et al.* (*loc. cit.*) report m. p. 165° for this compound.

Optically Active Dihydrothebainone.—Dihydrothebainol A or B (200 mg.) and benzophenone (1·2 g.) were added to a mixture of dry potassium *tert.*-butoxide (prepared from 100 mg. of potassium and 15 ml. of *tert.*-butanol) in dry benzene (20 ml.), and the mixture was refluxed for 3 hr. After cooling, hydrochloric acid (3N; 15 ml.) was added and the acid layer was separated. The benzene solution was extracted with hydrochloric acid (3N; 2 × 15 ml.), and the combined acid extracts were washed with benzene and with ether. The acid solution was basified with concentrated ammonia solution and the product was extracted with chloroform. The yield of dihydrothebainone isolated from dihydrothebainol A was 96 mg. and that from dihydrothebainol B was 105 mg. The infra-red spectra of 10 mg. samples of each crude product in chloroform showed that no more alcohol was present and that the concentration of ketone in each case was practically identical.

Racemic Dihydrothebainone.—Oxidation of the crude racemic dihydrothebainols (110 mg.) as above yielded the racemic ketone (48 mg.). The infra-red spectrum of this product was identical in the range 2—15 with that of optically active dihydrothebainone.

Resolution of Synthetic Dihydrothebainone.—To racemic dihydrothebainone (42 mg.) in acetone (10 ml.) was added (+)-tartaric acid (10 mg.) in acetone (10 ml.). The acetone solution was treated with charcoal, filtered, and concentrated to about one-half of its original volume. The (+)-tartrate of (−)-dihydrothebainone was deposited and was filtered off {28 mg.; m. p. 110°, $[\alpha]_D^{20\cdot5}$ +18·2° (*c* 1·1 in H_2O)}. The analytical sample was dried in a high vacuum for 24 hr. (Found: C, 58·2; H, 6·2. Calc. for $C_{22}H_{29}O_9N$: C, 58·5; H, 6·5%). The (+)-tartrate of authentic (−)-dihydrothebainone (from natural sources) had $[\alpha]_D^{20\cdot5}$ +18·1° (*c* 1·1 in H_2O).

To this tartrate (25 mg.) in water (5 ml.) was added concentrated ammonia solution (2 ml.), and the mixture was extracted with chloroform. The extract was washed several times with water, and the solvent was evaporated. The residue of (−)-dihydrothebainone (synthetic) was allowed to crystallise. Filtration afforded (−)-dihydrothebainone (12 mg.), m. p. 122—151°, $[\alpha]_D^{21}$ −75° (*c*, 0·77 in EtOH).

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