The 2,4-dinitrophenylhydrazone was prepared in the conventional manner. After three recrystallizations from chloroform–methanol there were obtained bright yellow needles, m.p. 150.8–151.4°. A fourth recrystallization produced crystals which differed strikingly in form, which were now decidedly orange in color, and which had the m.p. 174.4–174.8°. When a supersaturated solution of the yellow form was seeded with the orange, the orange, higher melting crystals were obtained. The analysis was performed on the orange substance.

Anal. Calcd. for $C_{28}H_{30}O_8N_8SBr$: C, 49.71; H, 4.47; N, 10.35. Found: C, 49.47; H, 4.46; N, 10.36.

CAMBRIDGE 38, MASS. RECEIVED FEBRUARY 9, 1951

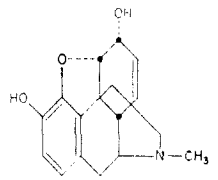
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY]

Elaboration of the 1-Substituted 7,8-Dimethoxy-2-tetralones Toward the 13-Alkyl Hydrophenanthrene System of Morphine

BY GILBERT STORK AND HAROLD CONROY[1]

The possible elaboration of the 13-alkyl hydrophenanthrene system present in morphine was investigated. Attention was given to two methods which were designed to produce a *cis*-decalin system and although they did not afford the desired results some of the transformations observed may be of general interest.

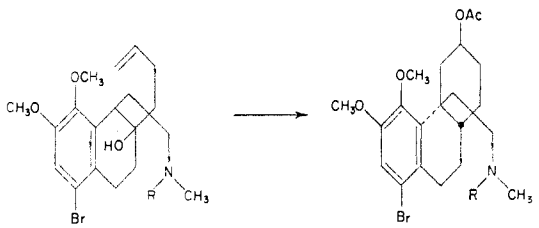
The further extension of the system present in the 1-substituted 2-tetralones described in the previous communication[2] to that of morphine (I) requires a method for the construction of the third



I

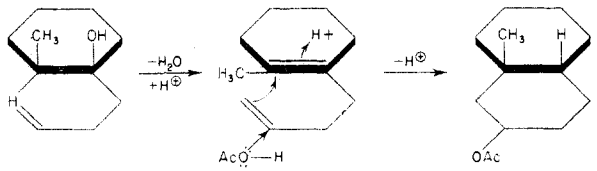
carbocyclic ring which would lead to a *cis*-decalin structure such as that present in the natural alkaloid. Two methods were considered.

A system such as II would be expected to undergo acid-catalyzed cyclization in the presence of acetic acid with the formation of III. A model for this expected ring closure is found in the formation of

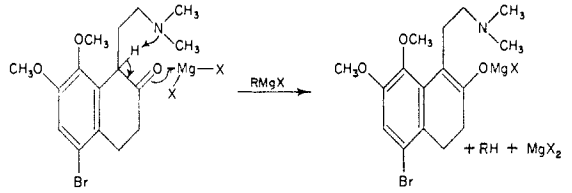


II III

the acetate of *cis*-9-methyl-2-decalol from 1-butenyl-2-methylcyclohexanol with an acetic acid–acetic anhydride–sulfuric acid mixture.[3] The exclusive formation of a *cis* product would be expected of a reaction involving a concerted addition of a proton and the electron pair of the terminal double bond to the endocyclic unsaturated center.



The preparation of II (R = CH_3) was attempted *via* reaction of 1-(β-dimethylaminoethyl)-5-bromo-7,8-dimethoxy-2-tetralone[2] (IV) with the Grignard reagent from 4-bromo-1-butene. Upon addition of the ketone to the Grignard solution there was immediate separation of a white precipitate and evolution of butene. The starting material could be recovered quantitatively as its perchlorate after hydrolysis of the reaction mixture. The same result was obtained after prolonged heating.



IV

These facts would seem to be best explained by the assumption that the nitrogen atom functions as an internal base with the result that there is complete, concerted enolization of the ketone. In the absence of a basic center, close in space to the C-1 hydrogen atom, Grignard additions have successfully been accomplished on 2-tetralones.[4,5]

As a test of this hypothesis of the role of the nitrogen atom the non-basic sulfonamide[2] (V) was employed. It did indeed react with the butenyl Grignard solution, but in a more complex fashion than that originally anticipated. The infrared absorption spectrum of the product obtained indicated the presence of approximately 20% of unchanged ketone, which was removed quantitatively as the sparingly soluble semicarbazone. The remaining alcohol fraction contained a considerable proportion of the tetralol (VI) formed by reduction of the original ketone, as was demonstrated by isolation of its crystalline acetate after acetylation of the mixture. Appreciable reduction with this butenyl Grignard reagent is not surprising, and can be accounted for by the low energy of the transition state leading to the formation of a conjugated diene and reduction of the ketone.

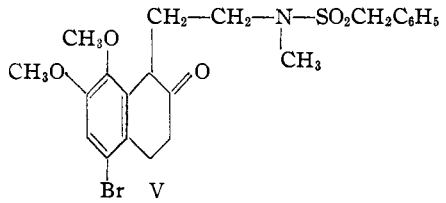
(1) Atomic Energy Commission Predoctoral Research Fellow, 1949–1950.

(2) G. Stork and H. Conroy, THIS JOURNAL, **73**, 4743 (1951).

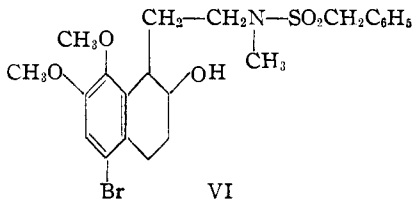
(3) R. P. Linstead, A. F. Millidge and A. L. Walpole, *J. Chem. Soc.* 1140 (1937).

(4) R. Royer and Ng. Ph. Buu-Hoi, *Compt. rend.*, **222**, 746 (1946).

(5) R. Royer, *Ann. Chim.*, [12] **1**, 395 (1946).



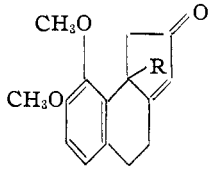
V



VI

Evidence that some of the desired tertiary alcohol (II, R = $C_6H_5CH_2SO_2$–) was obtained is given in the experimental section. The latter compound could be separated from the secondary alcohol (VI), but could not be obtained in crystalline condition, and attempted cyclization under the Linstead conditions did not lead to any definite products.

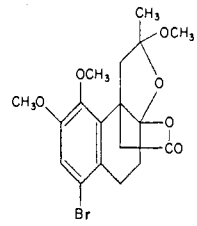
The unpromising results obtained in the application of the Linstead cyclization led us to direct our attention to an alternative scheme involving the formation and eventual ring enlargement of the cyclopentenone ring structure shown in A.



A

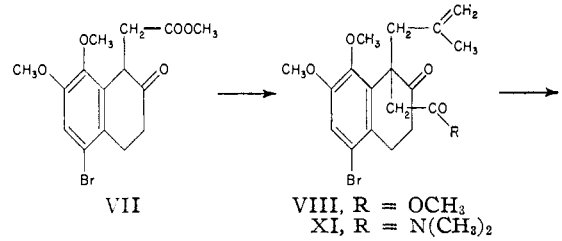
The keto-ester[2] (VII) was alkylated with methallyl chloride and sodium hydride to give the 1-methallyl derivative (VIII). When this methallyl derivative was oxidized with performic acid in formic acid, there was obtained after hydrolysis of the formate a crystalline lactone which had the properties to be expected of a compound expressed as IX, although the alternative formulation (IXa) cannot be rejected. The infrared absorption spectrum (Fig. 1) showed the presence of a five-membered lactone (5.65 μ), and a hydroxyl group (2.85 μ). There was no absorption band which could be attributed to a ketone carbonyl. The infrared spectrum of the formate obtained directly from the oxidation mixture before treatment with base indicated that lactonization had taken place in the hydroxylation reaction proper and *not* during the hydrolysis step.

When this hydroxy-lactone (IX or IXa), in the form of its sodium salt in aqueous methanolic solution, was treated with potassium periodate and then with acidified methanol another crystalline lactone, formulated as X, was obtained. The same compound was obtained in two other ways: Ozonization of the methallyl keto-ester (VIII) followed by decomposition of the ozonide with warm water and treatment with acid methanol gave crystals possessing an infrared spectrum identical with that of the substance obtained from the periodate reaction. Furthermore, VIII was converted by the oxalyl chloride method to the acid chloride, and it was possible to obtain the N,N-dimethylamide (XI) in good yield. The ozonide prepared from this amide was treated with warm water, whereupon there was an immediate and copious evolution of dimethylamine and again the same methoxy-lactone (X) could be isolated.



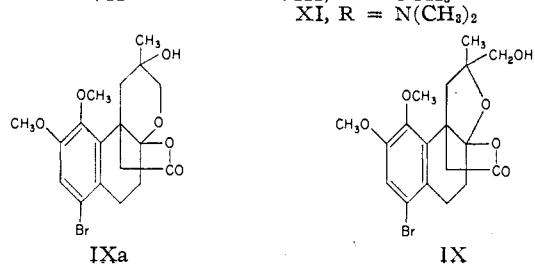
X

The formation of lactone IX in the performic acid hydroxylation is an interesting example of the interaction of properly situated functional groups. It can be rationalized readily on the basis of the following mechanism which requires no special comment

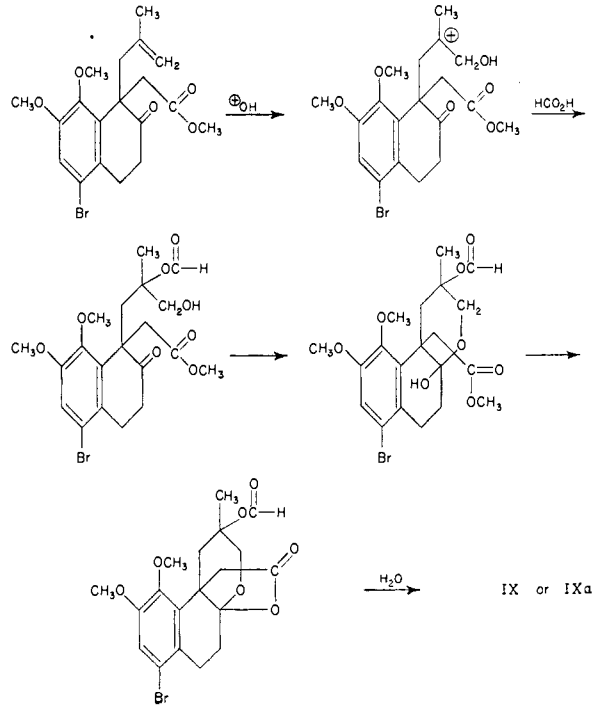


VII

VIII, R = OCH_3
XI, R = $N(CH_3)_2$



IXa IX



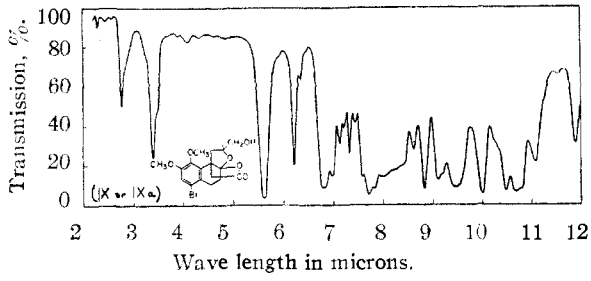


Fig. 1.

An even more striking example is found in the formation of X, the formulation of which is based on analytical evidence, which showed the presence of three methoxyl groups, and the infrared spectrum

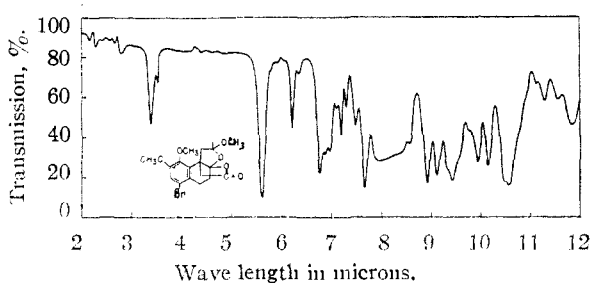
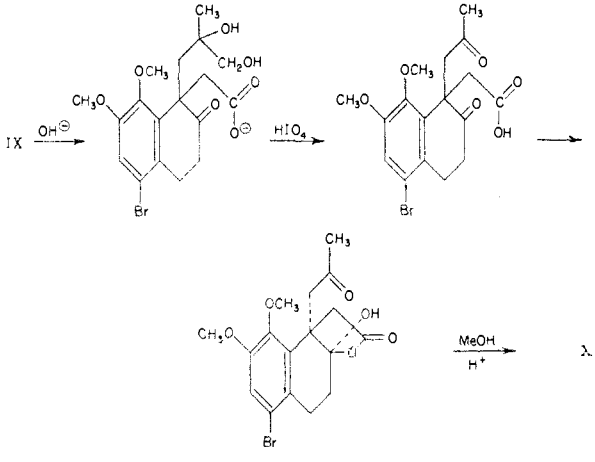
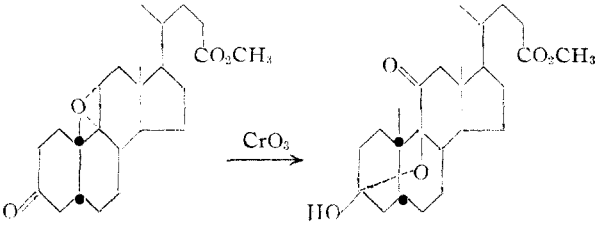


Fig. 2.

of the compound (Fig. 2) which shows the presence of no carbonyl except that present in a five-membered lactone.

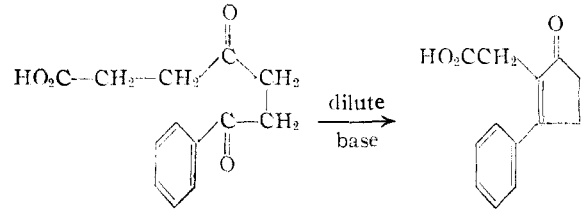


The ease of formation of X is illustrated by the previously mentioned isolation of X from the ozonolysis of VIII (or XI). This interaction of a ketone with another center in the molecule finds a parallel in the formation of the stable hemiketal ether



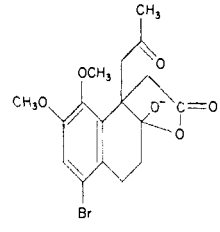
(XII) by the oxidation of methyl 3-keto-9,11-epoxycholanate.[6]

The oily hydroxy-lactone precursor of X was recovered unchanged by treatment with methanolic or aqueous methanolic base under a variety of conditions; in no case was there found any trace of the required cyclopentenone derivative (B, R = CH_2COOH). This is especially worth noting in view of the fact that other diketo acids in which an interaction of functional groups similar to that in X would be formally possible are known[7] to undergo ring closure to cyclopentenone derivatives. A typical example is



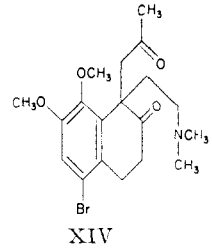
XIII

The difference between the two systems suggests that the main reason for the lack of aldol condensation with the anion derived from X may be the cancelling of any acceptor capacity of the ring carbonyl by the carboxylate anion



(This effect would be much less noticeable in molecules of type XIII in which such an interaction of the carboxylate ion and the acceptor carbonyl is sterically much less favorable.)

It would be of considerable interest in this respect to study the ring closure of the as yet unknown XIV in which the dimethylamino group would be expected to be much less effective than the carboxylate ion in preventing cyclization to a cyclopentenone of the desired type.



XIV

Experimental

Reaction of 1-β-(N-Methyl benzylsulfonamido)-ethyl-5-bromo-7,8-dimethoxy-2-tetralone (V) with Butenylmagnesium Bromide.—The Grignard reagent prepared from 6.0 g. of 4-bromo-1-butene in 50 cc. of ether was added in one portion to a solution of 10.0 g. of the ketone in 30 cc. of ben-

(6) L. F. Fieser, H. Heymann and S. Rajagopalan, THIS JOURNAL, **72**, 2306 (1950).

(7) R. Robinson, *J. Chem. Soc.*, 1390 (1938).

zene at 0°. A white solid precipitated immediately. The mixture was thoroughly shaken and left in the refrigerator for 18 hours, then at room temperature for another 24 hours. The suspension was treated with dilute acid, the benzene solution washed with water and evaporated. To remove unchanged ketone the yellowish oil remaining was refluxed with a solution of 10 g. of semicarbazide hydrochloride and 7.5 g. of sodium acetate in a mixture of 20 cc. of water and 100 cc. of methanol for 10 minutes. Most of the solvent was removed on the steam-bath, and the residue taken up in ether and water, when the semicarbazone (2.2 g., m.p. 170–174°) crystallized and was removed. The combined ether extracts were washed with water, dried over potassium carbonate and the solvent was removed. The residual oil could not be induced to crystallize and it was shown to be a mixture of the tetralols (VI and II, R = $C_6H_5CH_2SO_2$–). Treatment of a sample with acetic acid–acetic anhydride–sulfuric acid mixture for several days at room temperature gave the acetate of VI, recrystallized three times from benzene, m.p. 166.5–167.0°.

Anal. Calcd. for $C_{24}H_{30}O_6NSBr$: C, 53.33; H, 5.60; Br, 14.79. Found: C, 53.71; H, 5.81; Br, 15.46.

In order to determine whether any of the desired tertiary carbinol (II, R = $C_6H_5CH_2SO_2$–) had been formed the oil was heated with 10 g. of succinic anhydride in 20 cc. of pyridine at 100° for one hour. The mixture was acidified and the gummy substance taken up in ether. The ether solution was washed with water, dried over sodium sulfate and evaporated. The residue was chromatographed on ordinary alumina. The tertiary carbinol (2.9 g.) was eluted with the 20–30% acetone in ether fraction, while the secondary tetralol (VI) remained on the alumina in the form of its acid succinate. The tertiary carbinol no longer reacted with succinic anhydride, its infrared spectrum possessed bands at 2.85 and 6.10 μ indicative of the hydroxyl and vinyl functions, but no definite products could be isolated from its reaction with acetic acid–acetic anhydride–sulfuric acid mixture according to the procedure of Linstead.

1-Methallyl-5-bromo-7,8-dimethoxy-2-tetralone-1-acetic Acid Methyl Ester (VIII).—Fifty grams of the keto-ester (VII), 50 cc. of dry benzene, 21 g. of methallyl bromide and 3.53 g. of sodium hydride were refluxed together with stirring under nitrogen. After about five minutes a vigorous reaction set in which was moderated by external cooling. The suspension was refluxed for one-half hour, then water and dilute hydrochloric acid were added and the organic layer separated and washed twice with water. The yellow solution was dried and concentrated *in vacuo*, and the oil taken up in 50 cc. of methanol. After seeding and scratching crystallization was allowed to proceed at 0° overnight. The first crop weighed 15.5 g., m.p. 91–93°. Several grams of crude material was obtained by evaporation of the mother liquors, etc. The various crops were combined and recrystallized from methanol; yield 18.5 g., m.p. 96.3–97.0°. For analysis a sample was recrystallized once more from methanol, m.p. 96.8–97.4°.

Anal. Calcd. for $C_{19}H_{23}O_5Br$: C, 55.48; H, 5.64; Br, 19.43. Found: C, 55.19; H, 5.52; Br, 19.54.

1-Methallyl-5-bromo-7,8-dimethoxy-2-tetralone-1-(N,N-dimethylacetamide) (XI).—Five grams of the methallyl keto-ester (VIII) was heated with excess dilute sodium hydroxide solution until the mixture became homogeneous. One drop of phenolphthalein solution was added and the mixture neutralized with dilute hydrochloric acid, then base added until the solution acquired a permanent pink. To the thick sirup obtained by evaporation *in vacuo* was added 50 cc. of benzene, and the whole was refluxed under a water separator until dry. The benzene solution of the sodium salt thereby obtained was treated with three drops of pyridine and then 7 cc. of oxalyl chloride at 0°. After the vigorous gas evolution had subsided, the mixture was kept at room temperature for 30 minutes, then evaporated to dryness below 50°. The last traces of oxalyl chloride were removed by adding and again removing some benzene. The semi-solid residue was taken up in benzene and saturated with dry dimethylamine in the ice-bath. After washing with potassium carbonate and water, followed by evaporation of the solvent the colorless oil remaining was taken up in 10 cc. of methanol and crystallization allowed to proceed. The yield was 4.2 g. For analysis a sample was recrystallized once from ethanol, m.p. 145.0–145.6°.

Anal. Calcd. for $C_{20}H_{26}O_4NBr$: C, 56.61; H, 6.18. Found: C, 56.61; H, 6.23.

Performic Acid Oxidation of VIII: Preparation of Lactone (IX or IXa).—The methallyl keto-ester (VIII) (4.50 g.) was treated with a solution of 1.37 g. of 30% hydrogen peroxide in 17 cc. of 87% formic acid. The mixture was shaken occasionally until the solid went into solution and then was allowed to stand at room temperature for 24 hours. The formate of (IX or IXa) began to crystallize shortly after all the methallyl compound had dissolved. The solvent was removed *in vacuo* and the residue was refluxed for 30 minutes with 15% alcoholic potassium hydroxide. Water (110 cc.) was added and the clear tan solution acidified with dilute hydrochloric acid. The oil was extracted with several portions of chloroform, the combined extracts washed with water, and the solvent evaporated. The residue was crystallized from ethanol. The yield of small hard crystals, m.p. 182.5–183.0°, was 3.5 g. On recrystallization from ethanol a different crystal form was obtained: needles, m.p. 194.0–194.4°. The analysis was performed on the higher melting form.

Anal. Calcd. for $C_{18}H_{21}O_6Br$: C, 52.31; H, 5.12. Found: C, 52.23; H, 5.29.

Preparation of Lactone (X). A. Ozonization of VIII.—The methallyl keto-ester (VIII) (1.00 g.) in 25 cc. of chloroform was ozonized at 0° until the exit gas began to liberate iodine from potassium iodide solution. One equivalent of ozone was absorbed. Ten cc. of water was added and the mixture refluxed on the steam-bath for 30 min. The organic layer was separated and the solvent removed. The colorless oil was taken up in 5 cc. of methanol, and one drop of concentrated sulfuric acid was added. Scratching produced immediate crystallization. For analysis the sample was recrystallized three times from methanol–chloroform; m.p. 186.4–187.1°, rectangular plates.

Anal. Calcd. for $C_{18}H_{21}O_6Br$: C, 52.30; H, 5.12; OCH_3, 22.6. Found: C, 52.54; H, 5.17; OCH_3, 21.8.

B. **Ozonization of XI.**—The methallyl keto-amide (XI) was ozonized in exactly the same fashion. Dimethylamine was evolved upon treatment of the ozonide with water. The same compound (X) was obtained by crystallization from acidic methanol.

C. **Periodate Cleavage of the Lactone (IX or IXa).**—One gram of the lactone (IX or IXa) and 20 cc. of 10% sodium hydroxide were heated at 100° until complete solution was effected (45 minutes). The hot solution was saturated with sodium bicarbonate, then acetic acid was added dropwise until the *p*H fell to 8–9. One gram of potassium periodate was added to the clear solution and the mixture heated with occasional shaking for one hour. The odor of formaldehyde was noticeable. The mixture was acidified and extracted with chloroform. The oil left after evaporation of the solvent was taken up in methanol, a drop of sulfuric added, when crystallization commenced. The compound was identical with that obtained from the ozonization experiments.

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