[CONTRIBUTION FROM THE JOHN HARRISON LABORATORY OF THE UNIVERSITY OF PENNSYLVANIA]

Morphine Studies. The Synthesis of a Tetralin–Piperidine Fused-Ring System[1]

BY E. C. HORNING AND R. U. SCHOCK, JR.[2]

One of the chief problems connected with the synthesis of morphine derivatives and morphine analogs lies in the synthesis of bridged-ring piperidine systems similar to that in morphine. This problem has been studied in a number of laboratories, and several methods have been found suitable for the preparation of certain types of analogs. A bicyclic system, containing a piperidine ring bridged at appropriate points, has been described recently by Cronyn.[3] Another bicyclic system involving a bridged-piperidine structure, in which the nitrogen was present in a quaternary salt group, was obtained by Barltrop,[4] and the method of synthesis was extended to the preparation of a tetralin analog. The synthesis of a compound (morphan) containing the carbon skeleton of morphine was recently announced by Grewe,[5] although experimental details of this work are lacking.

We have been interested in the preparation of certain tetralin analogs of morphine,[6] and in the course of the work it was necessary to investigate the problem of obtaining a tetralin–piperidine fused-ring system. At the same time, it was hoped that the investigation might result in a method sufficiently general to allow further application to the preparation of a synthetic tetrahydrodesoxycodeine. The work described here includes a study of two methods aimed at a ring system of the required sort.

The starting compound, 2,3-dimethoxyphenylacetonitrile, was alkylated with β-ethoxyethyl methanesulfonate to provide α-(2,3-dimethoxyphenyl)-γ-ethoxybutyronitrile (I). Addition of acrylonitrile led to the dinitrile II; this was converted into methyl γ-(2,3-dimethoxyphenyl)-γ-cyano-ε-ethoxycaproate (III) by means of hydrogen chloride in methanol. Formylation of the ester III with ethyl formate and sodium methoxide, followed by cyclization of the formyl derivative (IV) with sulfuric–phosphoric acids, gave the dihydronaphthalene derivative (V). Hydrolysis of the ester group, followed by hydrogenation with palladium–carbon catalyst in acetic acid, resulted in the tetralin derivative VI. The acid group was then transformed into the urethan group of compound VII through a method somewhat similar to that employed earlier,[6] except that ethanol was used during the Curtius rearrangement. Through the action of 48% hydrobromic acid under reflux, the crude urethan was converted into an amine hydrobromide (VIII). The structure of this intermediate was evident from the results of cyclization experiments; preliminary trials aimed at isolating a pure sample of this salt were not successful, and in later experiments solutions of the salt were used directly for cyclization after clarification with decolorizing carbon. There are six functional group reactions, including cleavage of three ether groups, hydrolysis of the cyano group, and hydrolysis-decarboxylation of the ester group, which occur at this point.

Cyclization of the intermediate was best carried out in aqueous solution in the presence of sodium acetate at *p*H 5. The resulting product was isolated as a crystalline acetyl derivative by acetylation in a solution maintained at *p*H 7–8 with sodium bicarbonate. The crystalline product was obtained in pure form without difficulty, and analytical data indicated that the empirical formula corresponded to a diacetyl derivative (IXb). The acetylation of only one phenol group in the parent compound, IXa, under acetylation conditions, is not without analogy in the morphine series. At the same time, the possibility that cyclization might have occurred to yield a chroman, with subsequent acetylation to provide the diacetyl derivative X, was also present. Freshly prepared solutions of the product gave an azo dye when treated with diazotized aniline or diazotized sulfanilic acid; this indicates the presence of a free phenolic group. The alternate assumption, that the compound is a chroman in which the acetyl group is hydrolyzed on contact with aqueous alkali, followed by *o*-coupling, appears far less probable.

A second method of synthesis was carried to the point indicated in the accompanying figure. It was hoped that the nitrosoketone could be reduced by the methods of Rosenmund[7] and Kindler.[7] Unfortunately, the nitrosation gave as a product an unstable oil from which very little crystalline material could be isolated.

The application of reaction methods leading to the formation of a tetralin–piperidine system are of particular interest in connection with a synthesis of tetrahydrodesoxycodeine. A useful precursor, 2-(2′,3′,-dimethoxyphenyl)-2-(β-ethoxyethyl)-cyclohexanone, has been prepared,[8] and work in this direction is under way.

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(2) Bristol Laboratories Fellow, 1946–1947. National Institute of Health Predoctorate Fellow, U. S. Public Health Service, 1947–1948. Present address: The Abbott Research Laboratories, North Chicago, Illinois.

(3) Cronyn, Paper 87 of the Division of Organic Chemistry, American Chemical Society Meeting, April, 1948.

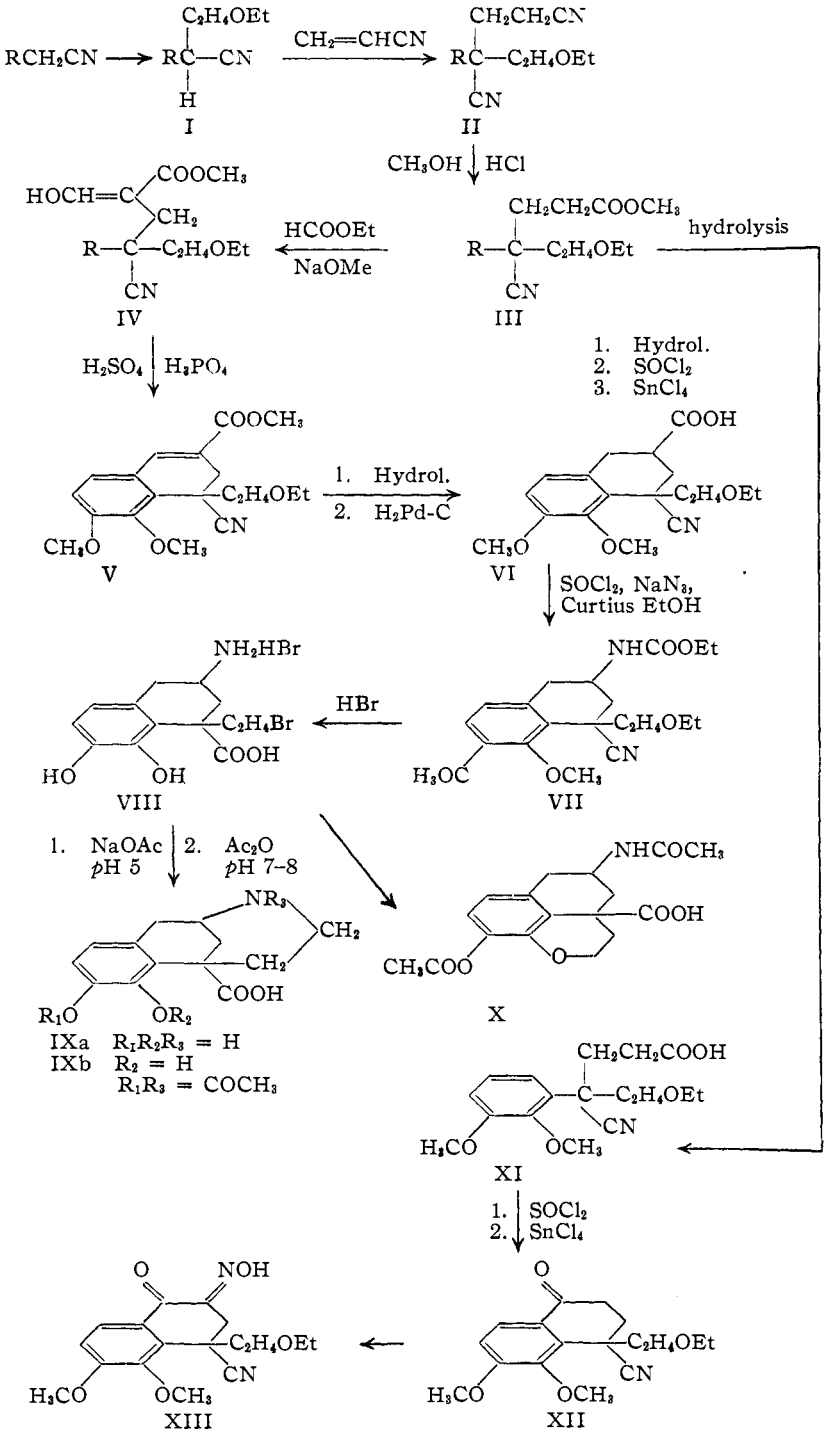
(4) Barltrop, *J. Chem. Soc.*, 399 (1947).

(5) Grewe, *Naturwiss.*, **11**, 333 (1946).

(6) Horning and Schock, THIS JOURNAL, **70**, 2941, 2945 (1948).

(7) Rosenmund and Karg, *Ber.*, **75**, 1850 (1943); Kindler and Dschi-yin Kwok, *Ann.*, **554**, 9 (1943).

(8) Horning, Horning and Platt, THIS JOURNAL, **70**, 2072 (1948).



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Experimental

All melting points are corrected.

α-(2,3-Dimethoxyphenyl)-γ-ethoxybutyronitrile (I).—Sodamide was prepared from the reaction of 12.7 g. of sodium (0.55 mole) and 400 ml. of liquid ammonia in the presence of a trace of ferric nitrate.[9] A solution of 88.5 g. (0.50 mole) of 2,3-dimethoxyphenylacetonitrile in 100 ml. of dry benzene and 100 ml. of dry ether was added to the suspension of sodamide in liquid ammonia. The suspension was stirred for one hour or until the ammonia evaporated. Then, with vigorous stirring, a mixture of 92.4 g. (0.55 mole) of β-ethoxyethyl methanesulfonate[10] and 100 ml. of dry ether was added at such a rate that the heat of reaction maintained the mixture at gentle reflux. After heating under reflux for one hour, the mixture was cooled and diluted with 500 ml. of water. The layers were separated and the aqueous phase extracted once with 100 ml. of ether. The combined organic solutions were washed successively with 5% sodium hydroxide solution, 5% hydrochloric acid and with water. The extract was dried over magnesium sulfate, the solvents removed by distillation and the residue fractionated through a short Vigreux column. The fraction boiling at 131–140° (0.4 mm.) was collected. The yield of nearly colorless product was 105.2 g. (84%).

Anal. Calcd. for $C_{14}H_{19}O_3N$: C, 67.45; H, 7.68. Found: C, 67.48; H, 7.63.

α-(β-Ethoxyethyl)-α-(2,3-dimethoxyphenyl)-glutaronitrile (II).—The procedure followed was essentially that described by Bruson[11] for the cyanoethylation of phenylacetonitrile. A solution of 105.2 g. of the nitrile I in 90 ml. of *t*-butyl alcohol was heated to 40° and then, with stirring, the dropwise addition of a solution of 24 g. of acrylonitrile in 30 ml. of *t*-butyl alcohol was started. After the addition of a few drops, 2 ml. of a 30% aqueous solution of benzyltrimethylammonium hydroxide was added, and the temperature maintained at 40–45° by occasional external cooling. Another 2-ml. portion of catalyst was introduced after half the acrylonitrile was added. When the temperature no longer rose spontaneously, the solution was heated for one hour at 40–45° and allowed to stand overnight. The dark solution was acidified with dilute hydrochloric acid and diluted with 250 ml. of cold water. The layers were separated with the aid of ether and the aqueous layer extracted once with 50 ml. of ether. The combined extracts were washed with water and dried over magnesium sulfate. Distillation of the residue remaining after evaporation of

(9) "Organic Syntheses," **25**, 25 (1945).

(10) Newman and Magerlein, THIS JOURNAL, **68**, 942 (1947).

(11) Bruson and Riener, *ibid.*, **65**, 25 (1943).

the solvent yielded 108.5 g. (85%) of a colorless viscous oil boiling at 171–178° (0.3 mm.).

Anal. Calcd. for $C_{17}H_{22}O_3N_2$: C, 67.53; H, 7.33. Found: C, 67.68; H, 7.24.

Methyl γ-(2,3-Dimethoxyphenyl)-γ-cyano-ε-ethoxycaproate (III).—A solution of 108.5 g. of the dinitrile II in 400 ml. of absolute methanol was treated with a stream of dry hydrogen chloride for thirty minutes. The mixture was heated gently under reflux for one hour, and then approximately one-half the alcohol was removed in a current of air. Dilution of the cooled residue with water produced an oil which was separated by three 100-ml. portions of ether. The extract was washed with water, once with 50 ml. of saturated sodium bicarbonate solution and dried over magnesium sulfate. Evaporation of the solvent left a colorless residue which was distilled at reduced pressure. The fraction boiling at 176–180° (0.5 mm.) was collected; the yield was 104.7 g. (87%).

Anal. Calcd. for $C_{18}H_{25}O_5N$: C, 64.46; H, 7.51. Found: C, 64.51; H, 7.37.

γ-(2,3-Dimethoxyphenyl)-γ-cyano-ε-ethoxycaproic Acid (XI).—The ester-nitrile was hydrolyzed with aqueous alkali. It was found that greater yields were obtained if the intermediate ester was not distilled, but was saponified immediately after distillation of the solvent ether. Thus, the methyl ester obtained from 70.0 g. of the dinitrile II was boiled under reflux for two and one-half hours with a solution of 18 g. of sodium hydroxide in a mixture of 400 ml. of water and 10 ml. of ethanol. Upon acidification of the cooled alkaline solution with dilute hydrochloric acid, a colorless oil precipitated which was separated with two 75-ml. portions of ether. The extract was dried over magnesium sulfate and the ether distilled, leaving 72.7 g. (97%) of an oily residue. The product, γ-(2,3-dimethoxyphenyl)-γ-cyano-ε-ethoxycaproic acid XI, did not crystallize on standing and was not purified further. Derivatives prepared for characterization could not be crystallized.

1-Cyano-1-(β-ethoxyethyl)-7,8-dimethoxy-1,2,3,4-tetrahydro-3-naphthoic Acid (VI). A. Formylation.—Sodium methoxide was prepared from 4.6 g. of sodium (0.2 mole) and absolute methanol. Then, at room temperature, a solution of 33.5 g. of the nitrile-ester III (0.1 mole) and 14.8 g. of ethyl formate (0.2 mole) in 100 ml. of dry ether was added to a vigorously stirred suspension of the sodium methoxide in 100 ml. of dry ether. After one and one-half hours, an additional 0.2 mole of ethyl formate was added and the stirring continued for another hour, at which time all suspended material was in solution. The solution was allowed to stand for fifteen hours; then 200 ml. of cold water was added and the layers separated. The aqueous layer was washed once with 50 ml. of ether and this extract combined with the original organic layer. From this ether solution there was obtained 5.6 g. of unchanged III which was pure enough for further use. The aqueous layer was acidified with dilute acetic acid and extracted with two 75-ml. portions of ether. The extract was washed once with 50 ml. of saturated sodium bicarbonate solution, dried, and the solvent evaporated. There was obtained 29.2 g. of the formyl derivative, as a pale yellow oil. The yield was 80% or 97% based on unrecovered nitrile-ester.

B. Cyclization.—A solution of 64.7 g. of the formyl derivative in 60 ml. of glacial acetic acid was added to a mixture of 175 ml. of 85% phosphoric acid and 45 ml. of concentrated sulfuric acid, keeping the temperature below 0°. The solution was allowed to stand at −5° for thirty minutes and 1.5 hours at room temperature. Pouring upon ice produced a viscous gum which was separated with three 100-ml. portions of ether. The extract was washed once with 75 ml. of 5% sodium hydroxide solution and then concentrated. The residue was heated under reflux for one and one-half hours with a solution of 16 g. of sodium hydroxide in 600 ml. of water and 20 ml. of ethanol. Acidification of the hot solution produced a gum which crystallized after standing twenty-four hours in an ice-chest. The dried crystalline **1-cyano-1-(β-ethoxyethyl)-7,8-dimethoxy-3,4-dihydro-3-naphthoic acid** melted at 165–166° and weighed 55.2 g. (93%). Recrystallization from dilute acetic acid raised the melting point to 167–168°.

Anal. Calcd. for $C_{18}H_{21}O_5N$: C, 65.24; H, 6.39. Found: C, 65.31; H, 6.35.

C. Reduction.—A solution of 17.0 g. of the acid in 150 ml. of glacial acetic acid was hydrogenated in a low-pressure apparatus in the presence of 5% palladium–carbon catalyst at 65°. The catalyst was removed by filtration and the filtrate concentrated in a current of air on a steam cone. The crystalline residue was fractionally crystallized from dilute acetic acid in an effort to isolate each of two possible diastereoisomers. The melting points of three crops (*ca.* 129–131°) were almost the same, and the filtrates yielded a compound which was apparently identical with that obtained in the first three crops but less pure. It is believed that one isomer is formed exclusively. Recrystallization raised the melting point to 131–132°. The yield of VI was 17.0 g.

Anal. Calcd. for $C_{18}H_{23}O_5N$: C, 64.84; H, 6.95. Found: C, 64.75; H, 6.76.

Conversion of VI to 1-Carboxy-3,1-acetyliminoethano-7-acetoxy-8-hydroxy-1,2,3,4-tetrahydronaphthalene (IXb).—A mixture of 2 ml. of thionyl chloride and 1.65 g. of VI was allowed to stand overnight. The excess thionyl chloride was removed at 50° at the water pump and the residual acid chloride taken up in 25 ml. of dry reagent-grade acetone. The solution was chilled in an ice-bath, and a solution of 0.73 g. of sodium azide in 2 ml. of water was added with vigorous stirring. After fifteen minutes the mixture was diluted with 75 ml. of cold water and the crude azide separated with three 25-ml. portions of ether. The extracts were washed once with saturated sodium bicarbonate solution and dried for fifteen minutes over magnesium sulfate. To the ether extract was added 25 ml. of absolute ethanol and the solution slowly distilled on a steam cone through a short column. The residue of the ethyl urethan weighed 1.8 g. (95%). The residue was then boiled vigorously under reflux with 20 ml. of 48% hydrobromic acid for four hours, allowing the initial volatile products of reaction to escape from the reflux condenser. The dark solution was diluted with 50 ml. of hot water, treated with carbon and the colorless filtrate made slightly alkaline with solid sodium bicarbonate. Dilute hydrochloric acid was then added until the filtrate was acid. The acidified filtrate was boiled under reflux with 5.0 g. of sodium acetate trihydrate for 1.5 hours; the addition of sodium acetate brought the *p*H to approximately 5. The cooled solution was then treated with 2 ml. of acetic anhydride and solid sodium bicarbonate was added with stirring to keep the mixture alkaline (*p*H 7–8). After fifteen minutes, a further 2-ml. portion of acetic anhydride was added. After an additional fifteen minutes, the solution was acidified with dilute hydrochloric acid and extracted with four 25-ml. portions of chloroform. The combined extracts were dried over magnesium sulfate and evaporated, leaving a crystalline residue weighing 1.50 g. This material was purified by recrystallization from dilute acetic acid. The melting point of the pure compound varied from 258 to 262° (dec.) depending upon the rate of heating of the bath.

Anal. Calcd. for $C_{17}H_{19}O_6N$: C, 61.25; H, 5.74; N, 4.22. Found: C, 61.21; H, 5.68; N, 4.26.

Structure IXb, with the phenolic hydroxyl group acetylated (*viz.*, $C_{19}H_{21}O_7N$) requires: C, 60.79; H, 5.64; N, 3.73.

The presence of a phenolic group in this product was indicated by the addition of either diazotized sulfanilic acid or diazotized aniline to a freshly prepared alkaline solution of the compound; a deep orange color resulted. A small amount of the azo dye from diazotized *p*-nitroaniline was isolated in solid form, but it proved difficult to purify and was not characterized further.

4-Cyano-4-(β-ethoxyethyl)-5,6-dimethoxytetralone-1 (XII).—A solution of 63.0 g. of crude γ-(2,3-dimethoxyphenyl)-γ-cyano-ε-ethoxycaproic acid (XI) in 50 ml. of

absolute ether was treated with 30 ml. of thionyl chloride and three drops of pyridine. After standing for fifteen hours, the volatile constituents were removed at 50° at the water pump; 5 ml. of dry benzene was added and the operation repeated. The residue was dissolved in 600 ml. of dry thiophene-free benzene and chilled until the solvent began to crystallize. Then a solution of 40 ml. of stannic chloride in 40 ml. of benzene was added rapidly with shaking and the mixture allowed to stand in the ice-bath for fifteen minutes. The yellow complex was destroyed by pouring upon a mixture of 50 ml. of ether, 100 ml. of concentrated hydrochloric acid, and ice. The organic layer was then separated and washed successively with 5% hydrochloric acid, water, 5% sodium hydroxide solution, and finally with water. Drying, followed by evaporation of the solvent, left an oil which was distilled at reduced pressure. The fraction boiling at 192–198° (0.4 mm.) was collected as product; the yield was 42.2 g. (71%). The pale yellow oil solidified on standing and melted at 67–68° after recrystallization from cyclohexane-petroleum ether.

Anal. Calcd. for $C_{17}H_{21}O_4N$: C, 67.30; H, 6.98. Found: C, 67.14; H, 6.89..

Nitrosation of the Tetralone XII.—Various conditions and methods were tried without good results. Nitrosation with an ester of nitrous acid in the presence of dry hydrogen chloride produced only resinous products. In the presence of sodium alkoxides with either freshly prepared butyl or isopropyl nitrite, small amounts of the desired oximinoketone XIII were obtained. The yields in all cases were too low to warrant continuance of the synthesis along this path. The following procedure is an example of a successful experiment. A solution of 1.5 g. (0.005 mole) of XII and 0.23 g. of sodium in 50 ml. of absolute ethanol was prepared. Then, 1.5 g. (0.0075 mole) of freshly prepared *n*-butyl nitrite was added, and the mixture was allowed to stand at 5° for two days. The alcohol solution was diluted with an equal volume of cold water and extracted twice with 30-ml. portions of ether. The aqueous layer was acidified with diluted hydrochloric acid and extracted three times with 30-ml. portions of ether. Drying, followed by evaporation of the solvent, left 1.5 g. of a red oil which partially solidified on standing. Trituration with ether provided 0.15 g. of pale yellow **2-nitroso-4-cyano-4-(β-ethoxyethyl)-5,6-dimethoxytetralone-1 (XIII)** which melted with darkening at 154–155° after three recrystallizations from ethyl acetate-petroleum ether.

Anal. Calcd. for $C_{17}H_{20}O_5N_2$: C, 61.43; H, 6.07. Found: C, 61.33; H, 5.81.

Summary

A method leading to a compound containing a fused-ring tetralin–piperidine system, similar to part of the morphine ring system, has been developed.

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The Preparation of the C_{10} Monocyclic Aromatic Hydrocarbons

BY S. F. BIRCH, R. A. DEAN, F. A. FIDLER AND R. A. LOWRY

Introduction

A comparatively elaborate program has been carried out over a number of years to produce a supply of hydrocarbons in a high degree of purity required in connection with spectroscopic analysis and other analytical problems. Although interest in the aromatic series at first centered primarily round the hydrocarbons in the C_6 to C_9 range, it was later found desirable to include the C_{10} compounds. At the time this work was commenced, no source of these hydrocarbons was available, and the physical data reported in the literature were extremely scanty and contradictory.

The present paper describes in general the methods and techniques employed in these laboratories for their preparation. Possibly its chief interest is on account of the steps taken at each stage to ensure that the intermediate compounds were satisfactorily purified before proceeding to the next step in the synthesis. Particular emphasis was placed on the determinations of the physical constants and purities of the intermediates at all stages of their purification and as a result the densities, refractive indices and freezing points of many compounds of known purity are recorded for the first time. At any point at which an intermediate proved relatively impure, it was possible to continue purification until a satisfactory product had been obtained. Only when a following stage permitted the easier separation of impurities was the synthesis continued without satisfactory purification being attained. Thus in some cases it was more satisfactory to purify the carboxylic acid than the nitrile from which it was obtained.

The scale of the preparation was based upon a quantity of 1500 to 2000 ml. of final hydrocarbon in a satisfactory state for purification. This quantity is appreciably smaller than that generally made available to Rossini and his co-workers for purification at the National Bureau of Standards and it would have been desirable to increase this quantity two- or three-fold. Unfortunately, the effort necessary for preparations on this scale was not available. It was felt, however, that taking considerable care in the purification of the intermediates would in great measure offset the smaller quantity of hydrocarbon available for final treatment.

The methods chosen as being most satisfactory were made as general as possible so that they would be applicable to the preparation of more than one hydrocarbon. By so doing, not only was the working out of new techniques largely avoided but the same apparatus could frequently be employed for a number of preparations. Routes were selected which enabled readily avail-