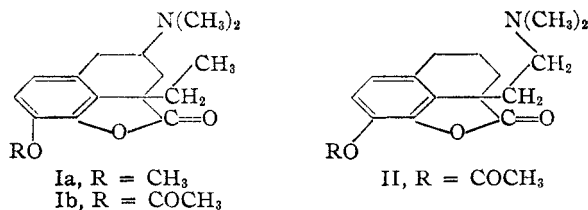


[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

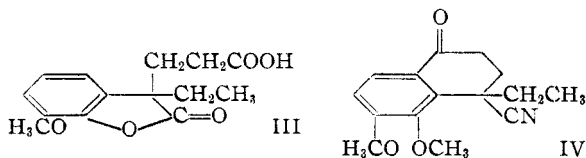
Morphine Studies. Tetralin Analogs¹

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

In a previous paper³ several unsuccessful routes directed to the preparation of 1-ethyl-1-carboxy-3-dimethylamino-7-methoxy-8-hydroxy-1,2,3,4-tetrahydronaphthalene lactone (Ia) were described. The synthesis of the corresponding 7-acetoxy lactone Ib has now been accomplished by the method described in this report. In addition, experiments directed toward the synthesis of an isomeric lactone, 1-carboxy-1-(β -dimethylaminoethyl)-7-acetoxy-8-hydroxy-1,2,3,4-tetrahydronaphthalene lactone (II) have been carried out. It was our original intention to compare analgesic properties in a series of lactones, but the unexpected instability of the lactone Ib



has made this impossible. The failure of cyclization experiments with 2-keto-3-ethyl-3-(β -carboxyethyl)-7-methoxy-1,2-dihydrobenzofuran (III), together with the successful cyclization of γ -(2,3-dimethoxyphenyl)- γ -cyanocaproyl chloride to 4-cyano-4-ethyl-5,6-dimethoxytetralone-1 (IV),³ indicated that the desired lactone structures (Ia or Ib and II) very likely constituted strained systems. The steric effect of a lactone system such as that of III in preventing cyclization to a tetralone has apparently not been encountered previously, but as a result of this effect it is evident that compounds I and II can probably be obtained only from appropriate tetralin precursors.



For the synthesis of Ib, the starting material was methyl γ -(2,3-dimethoxyphenyl)- γ -cyanocaproate.³ By condensation with ethyl formate and sodium methoxide, the expected hydroxymethylene compound (VI) was obtained. This was cyclized to the dihydronaphthalene VII with a

mixture of sulfuric and phosphoric acids; the resulting ester was saponified to the corresponding acid, and the unsaturated bond reduced by catalytic means (palladium-carbon) to give 1-cyano-1-ethyl-7,8-dimethoxy-1,2,3,4-tetrahydro-3-naphthoic acid (VIII). The over-all yield for these four steps was about 70%. The carboxylic acid group of compound VIII was converted into a dimethylamino group by a combination of the Curtius procedure and a formaldehyde-formic acid methylation; the yield for this conversion was 64%. The resulting amine IX was treated with hydrobromic acid under reflux, and the crude acid obtained in this way was heated with acetic anhydride and sodium acetate to form the lactone Ib.

This lactone was stable only in the absence of water, and only one stable derivative (a methiodide) could be obtained. On standing in the open for one week, or for a few hours in the presence of water, the liquid lactone was transformed to the crystalline amino acid X. The instability of this lactone is not unusual in the light of the behavior of intermediates in this series, and it is apparently due to strain in the fused tricyclic system. The fused-ring system of morphine includes a tetralin-furan system, and it is possible that a similar strain exists in the morphine molecule.

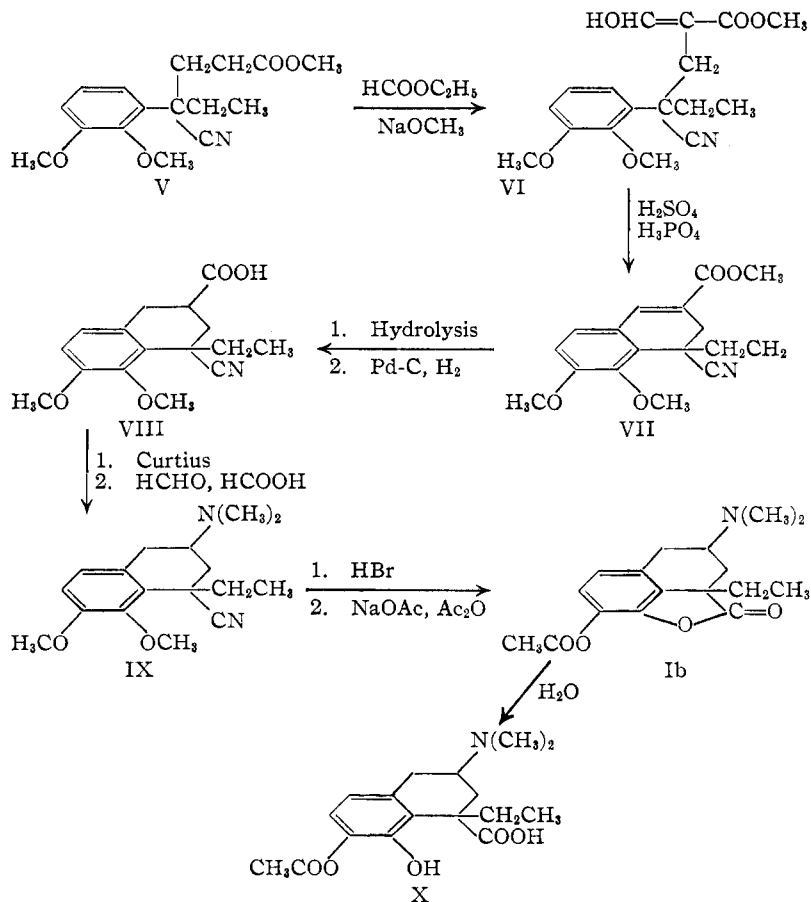
The experimental work for the proposed synthesis of the isomeric lactone II entailed first the addition of two moles of acrylonitrile to 2,3-dimethoxyphenylacetonitrile. The resulting product, γ -cyano- γ -(2,3-dimethoxyphenyl)-pimelonitrile (XI), was converted into the lactone XIX by treatment with hydrobromic acid. In general, it has been found in this series that a short reflux period with hydrobromic acid results in the selective cleavage of the 2-methoxyl group, with hydrolysis of the nitrile group occurring at the same time. If, however, related tetralin derivatives are subjected to approximately the same conditions, the hydrolysis of the tertiary nitrile group is accompanied by cleavage of both methoxyl groups. Attempts were made to cyclize the di-acid chloride from the lactone XIX to a tetralone, but without success. This behavior is the same as that exhibited by the lactone-acid III.

The tetralone XIII was obtained without difficulty in 81% yield by cyclization with stannic chloride of the di-acid chloride obtained from the acid XII. No evidence of intermolecular acylation was found. The required acid was obtained by a two-step hydrolysis procedure from the trinitrile XI. The trinitrile was converted to a dimethyl ester with methanol and hydrogen chloride, and saponification with aqueous alkali

(1) Abstracted from the dissertation of R. U. Schock, Jr., presented to the faculty of the Graduate School of the University of Pennsylvania in partial fulfillment of the requirements for the degree of Doctor of Philosophy, April, 1948.

(2) Bristol Laboratories Fellow, 1946-1947; National Institute of Health Fellow, 1947-1948.

(3) For a discussion of the objectives of these studies, see Horning and Schock, THIS JOURNAL, **70**, 2941 (1948).



yielded the dicarboxylic acid. This procedure was developed after direct alkaline hydrolysis failed to give the desired product.

The reduction of the carbonyl group of the tetralone XIII to a methylene group presented a problem which could not be solved in satisfactory fashion. With the Clemmensen method, the initial step was hydrolysis to the cyclic imide XVII. In separate experiments, it was found that hydrolysis and cyclization to the imide occurred with surprising ease in an acetic acid-hydrochloric acid mixture. It was possible in turn to hydrolyze the imide to an amide-acid with warm dilute alkali (the structure XVIII has been assigned to this compound), but Clemmensen reductions starting with XII or XVII were unsuccessful. The improved Wolff-Kishner technique⁴ gave a small amount of the tetralin XIV. It is interesting to note that the 4-cyano group in this compound is easily attacked under acid conditions, but a small amount of material survived the vigorous alkaline conditions of the Wolff-Kishner method with this group unchanged. An attempt was made to improve the yield by using the imide XVII in this method, but without success. The best means found for the reduction was catalytic hydrogenation with a palladium-carbon catalyst

(4) Huang-Minlon, *THIS JOURNAL*, **68**, 2487 (1946).

at 50–60° in acetic acid in the presence of a little sulfuric acid. Unfortunately, the course of the reaction was difficult to control and the yields were not reproducible. The products were always impure, and it is believed that reduction also took place at other points in the molecule. Through repetition of the reaction, it was possible to obtain a small amount of material, and the remaining steps were attempted. It was found that the carboxyl group could be converted into a dimethyl-amino group according to the same procedure used in the synthesis of Ib, in about 40% yield. The next reaction, hydrolysis with hydrobromic acid, was less successful, and it was not possible to isolate the expected lactone after treatment with acetic anhydride-sodium acetate. In view of the difficulty in preparing XIV, and the fact that the lactone II, if obtained, might be expected to be unstable, no further attempt has been made to investigate the last steps in this sequence.

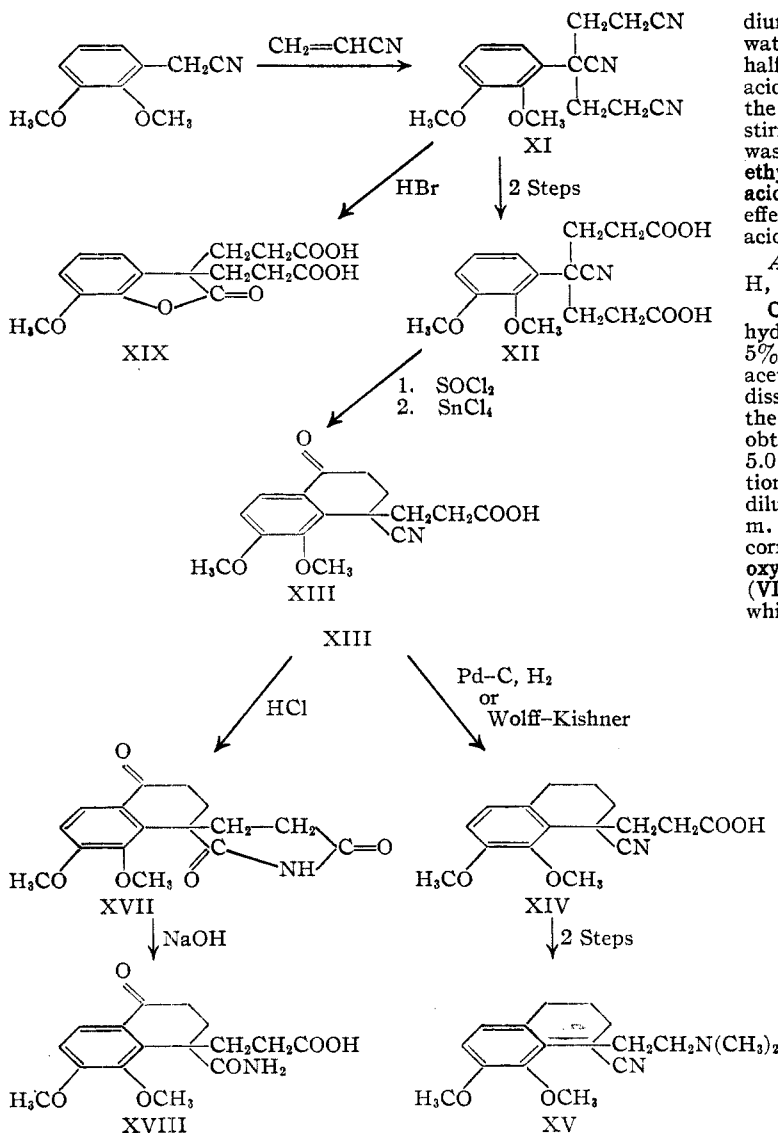
Acknowledgment.—The authors are indebted to Miss Sarah H. Miles for the analyses.

Experimental

All melting points are corrected.

1-Cyano-1-ethyl-7,8-dimethoxy-1,2,3,4-tetrahydro-3-naphthoic Acid (VIII). **A. Formylation.**—The following procedure was adopted after decreased yields were encountered using either methyl formate or sodium ethoxide in the condensation. A solution of 49.5 g. (0.17 mole) of methyl γ -(2,3-dimethoxyphenyl)- γ -cyanocaproate⁸ (V) and 25.0 g. (0.34 mole) of ethyl formate in 50 ml. of dry ether was added at room temperature to a suspension of sodium methoxide in 100 ml. of dry ether. The sodium methoxide was obtained from the reaction of 7.8 g. (0.34 mole) of sodium and absolute methanol, with evaporation of the excess alcohol on the steam-bath at the water pump. After stirring for one and one-half hours, a second portion of 25.0 g. of ethyl formate was added and the stirring continued for an additional hour. At this time all suspended material had dissolved. After standing for fifteen hours, 300 ml. of ice water was added and the layers separated. The aqueous phase was washed once with 100 ml. of ether, acidified with dilute acetic acid, and extracted with two 100-ml. portions of ether. The latter extract was washed once with saturated sodium bicarbonate solution, dried and the ether evaporated. There was obtained 47.9 g. (ca. 88%) of the hydroxymethylene derivative. The first extract yielded 3–4 g. of unreacted ester, pure enough for use in further condensations.

B. Cyclization.—The hydroxymethylene compound (16.7 g.) was dissolved in 20 ml. of glacial acetic acid, and this solution was then added to a mixture of 55 ml. of 85% phosphoric acid and 12 ml. of concentrated sulfuric acid,



keeping the temperature below 0° . After standing with occasional stirring for thirty minutes at -5° , the flask was removed from the freezing bath and allowed to stand at room temperature for one and one-half hours. A colorless viscous gum separated on pouring upon ice; this was extracted with three 75-ml. portions of ether. Usually the addition of ether caused the separation of a small amount of a crystalline solid, m. p. $131-135^\circ$, which proved to be methyl 1-cyano-1-ethyl-7,8-dimethoxy-1,2-dihydro-3-naphthoate (VII). Purification by recrystallization from ethyl acetate-petroleum ether (b. p. $35-60^\circ$) raised the melting point to $135-136^\circ$.

Anal. Calcd. for $\text{C}_{17}\text{H}_{19}\text{O}_4\text{N}$: C, 67.75; H, 6.36. Found: C, 67.60; H, 6.18.

It is believed that the amorphous material obtained here is a mixture of ethyl and methyl esters formed by ester interchange between ethyl formate and V. The viscous material solidified on standing but it was not possible to isolate a single, pure compound by recrystallization.

The combined ether extracts were washed once with 50 ml. of 5% sodium hydroxide solution and once with water. The residue remaining after evaporation of the ether was combined with the solid ester which separated, and the mixture boiled under reflux with a solution of 6.0 g. of so-

dium hydroxide in a mixture of 150 ml. of water and 30 ml. of ethanol for one and one-half hours. The hot alkaline solution was acidified with dilute hydrochloric acid and the mixture allowed to stand with occasional stirring until crystallization ensued. There was obtained 11.9 g. (79%) of 1-cyano-1-ethyl-7,8-dimethoxy-1,2-dihydro-3-naphthoic acid as a colorless solid. Purification was effected by recrystallization from dilute acetic acid; m. p. $186-187^\circ$.

Anal. Calcd. for $\text{C}_{16}\text{H}_{17}\text{O}_4\text{N}$: C, 66.88; H, 5.96. Found: C, 66.84; H, 5.76.

C. Reduction.—The unsaturated acid was hydrogenated at atmospheric pressure over 5% palladium-carbon catalyst⁵ in glacial acetic acid at 65° . From 5.0 g. of the acid dissolved in 50 ml. of glacial acetic acid, in the presence of 1.5 g. of catalyst, there was obtained upon evaporation of the solvent, 5.0 g. of product melting at $158-165^\circ$. Fractional crystallization from either benzene or dilute acetic acid resulted in a compound, m. p. $183-184^\circ$, which gave analytical data corresponding to 1-cyano-1-ethyl-7,8-dimethoxy-1,2,3,4-tetrahydro-3-naphthoic acid (VIII). There are two diastereoisomers which might result from this reaction, but a second crystalline compound could not be isolated from the filtrates after crystallization of VIII.

Anal. Calcd. for $\text{C}_{16}\text{H}_{19}\text{O}_4\text{N}$: C, 66.42; H, 6.62. Found: C, 66.38; H, 6.48.

1-Cyano-1-ethyl-3-dimethylamino-7,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (IX).—The acid VIII (10.0 g.), without previous recrystallization, was allowed to stand in the presence of 10 ml. of thionyl chloride for a period of fifteen hours. The excess thionyl chloride was removed at the water pump at 50° and the residue dissolved in 50 ml. of dry reagent-grade acetone. With vigorous stirring, a solution of 2.6 g. of sodium azide in 8 ml. of water was added to the chilled solution of the acid chloride over a period of approximately one minute. After fifteen minutes the mixture was diluted with 150 ml. of cold water, and the crude azide was separated with

three 50-ml. portions of benzene. The combined extracts were washed once with saturated sodium bicarbonate solution and then dried for fifteen minutes over magnesium sulfate. The dried solution was concentrated to a volume of approximately 50 ml. and then 10 ml. of 98-100% formic acid was added cautiously to the hot solution. After the exothermic reaction and the copious frothing subsided, the solution was heated under reflux for one hour, and then the volatile constituents were removed in a current of air at steam-bath temperature. The residue was dissolved in a mixture of 20 ml. of 90% formic acid and 20 ml. of 35% formalin solution and boiled under reflux for twenty hours or until the evolution of carbon dioxide had practically ceased. To the chilled solution was added 100 ml. of 5% hydrochloric acid, and it was then extracted with 100 ml. of ethyl acetate. After neutralizing the aqueous phase with solid sodium bicarbonate, it was extracted with four 75-ml. portions of ethyl acetate. Evaporative distillation at $145-155^\circ$ (0.2 mm.) of the residue remaining after removal of the solvent gave 6.4 g. of product (64%) as a viscous, somewhat opalescent oil.

Anal. Calcd. for $\text{C}_{17}\text{H}_{24}\text{O}_2\text{N}_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 70.81; H, 8.32; N, 9.55.

(5) "Organic Syntheses," 26, 78 (1946).

The methiodide was recrystallized from absolute alcohol-ether and melted at 233–234° with shrinking at 212°.

Anal. Calcd. for $C_{18}H_{27}O_2N_2I$: C, 50.23; H, 6.32. Found: C, 50.28; H, 6.03.

1-Ethyl-1-carboxy-3-dimethylamino-7-acetoxy-8-hydroxy-1,2,3,4-tetrahydronaphthalene Lactone (Ib).—A solution of 6.4 g. of the amine IX in 40 ml. of 48% hydrobromic acid was boiled vigorously under reflux for forty minutes. The excess hydrobromic acid was distilled at reduced pressure, leaving a brown crystalline residue. To this was added 20 ml. of acetic anhydride and 8.0 g. of anhydrous sodium acetate. The mixture was heated under reflux for two and one-half hours; it was then cooled, diluted with 100 ml. of ethyl acetate, and the sodium salts removed by filtration. The ethyl acetate was distilled, and the acetic anhydride and acetic acid removed by distillation under reduced pressure. The residue was evaporatively distilled at 155–165° (0.1 mm.). There was obtained 4.3 g. (64%) of a very viscous oil. The compound was not stable and it was not possible to obtain material of the desired degree of purity.

Anal. Calcd. for $C_{17}H_{21}O_4N$: C, 67.35; H, 6.98. Found: C, 66.63; H, 6.83.

This compound gave no derivatives with the exception of a methiodide which did not melt sharply. It was recrystallized from acetone and melted partially at 234°, decomposing at 250°.

Anal. Calcd. for $C_{18}H_{24}O_4NI$: C, 48.55; H, 5.43. Found: C, 48.95; H, 5.63.

On standing open to the atmosphere for one week the oil solidified to a colorless crystalline solid melting at 252–253° (dec.). This was purified by recrystallization from water, although some decomposition accompanied the process. Analysis of the solid indicated that hydrolysis of the lactone ring had taken place by absorption of atmospheric moisture and, indeed, it was later prepared more expeditiously by allowing the lactone to stand in the presence of water for twenty-four hours. Scission of the lactone ring in this way produced the amino-acid 1-ethyl-1-carboxy-3-dimethylamino-7-acetoxy-8-hydroxy-1,2,3,4-tetrahydronaphthalene (X).

Anal. Calcd. for $C_{17}H_{23}O_4N$: C, 63.53; H, 7.21; N, 4.36. Found: C, 63.77; H, 6.79; N, 4.39.

γ -Cyano- γ -(2,3-dimethoxyphenyl)-pimelonitrile (XI).—The procedure followed was that developed by Bruson⁶ for the cyanoethylation of phenylacetone. To a solution of 17.7 g. (0.1 mole) of 2,3-dimethoxyphenylacetone⁷ in 25 ml. of *t*-butyl alcohol containing 1.0 g. of 30% methyl alcoholic potassium hydroxide, was added, keeping the temperature at 10–25°, 12 g. of freshly distilled acrylonitrile dissolved in 10 ml. of *t*-butyl alcohol. The suspension, after the addition was complete, was stirred for two hours. The mixture was acidified with 5% hydrochloric acid, diluted with 100 ml. of water and the layers separated with the aid of benzene. Drying the extract over magnesium sulfate, followed by concentration, left 27.2 g. (96%) of a viscous oil which slowly crystallized to a solid melting at 60–63°. If the reaction mixture was allowed to stand until crystallization was complete, the product melted at 65–66°, but the yield was only 64%. Recrystallization from methanol-*t*-butyl alcohol did not change the melting point.

Anal. Calcd. for $C_{16}H_{17}O_2N_2$: C, 67.82; H, 6.05. Found: C, 67.86; H, 6.18.

2-Keto-3,3-di-(β -carboxyethyl)-7-methoxy-2,3-dihydrobenzofuran (XIX).—A solution of 3.0 g. of XI in 15 ml. of glacial acetic acid and 20 ml. of 48% hydrobromic acid was heated on the steam cone for one and one-half hours. The hot solution was chilled, diluted with 100 ml. of water and extracted with three 40-ml. portions of ethyl acetate. The extract was dried, concentrated and hexane was added until precipitation was complete. The supernatant liquid was decanted and the semi-solid residue

taken up in hot water, treated with carbon, and the filtrate allowed to stand in the ice-box until crystallization was complete. The colorless crystalline solid weighed 1.6 g. and melted at 142–144°; the analytical sample melted at 148–149°.

Anal. Calcd. for $C_{15}H_{16}O_7$: C, 58.44; H, 5.23. Found: C, 58.38; H, 5.35.

The diacid chloride, prepared with thionyl chloride, was treated with stannic chloride in benzene solution in the usual way. No ketonic material could be isolated from the reaction mixture.

γ -Cyano- γ -(2,3-dimethoxyphenyl)-pimelic Acid (XII).—Best results were obtained when the trinitrile XI was recrystallized before use. Ten grams of the trinitrile (m. p. 65–66°) was dissolved in 100 ml. of absolute methanol and a rapid stream of dry hydrogen chloride passed into the solution for fifteen minutes. The mixture was heated gently under reflux for one hour and then one-half of the alcohol was removed by distillation. Dilution of the mixture with 150 ml. of water produced an oily precipitate which was separated with two 50-ml. portions of ether. After evaporation of the ether, the residue was heated under reflux for one hour with a solution of 6.0 g. of sodium hydroxide in 150 ml. of water and 15 ml. of ethanol. The cooled solution was extracted once with 30 ml. of ether and then acidified with 5% hydrochloric acid. The crystalline precipitate weighed 10.0 g. (88%) and melted at 177–178°. Two recrystallizations from hot water raised the melting point to 178–179°.

Anal. Calcd. for $C_{16}H_{19}O_6N$: C, 59.80; H, 5.96; neut. equiv., 161. Found: C, 59.97; H, 5.81; neut. equiv., 158.

This procedure for the hydrolysis of the trinitrile was adopted after direct hydrolysis failed to give the desired product.

1-Cyano-1-(β -carboxyethyl)-4-keto-7,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (XIII).—To a suspension of 25.5 g. of the acid XII in 100 ml. of absolute ether was added 20 ml. of thionyl chloride and 5 drops of pyridine. After standing two hours with occasional shaking, the mixture was heated for ten minutes on the steam cone to complete the reaction; by this time all material was in solution. The ether was distilled and the excess thionyl chloride removed at 50° at the water pump; 5 ml. of dry benzene was added and the operation repeated. The residue was dissolved in 400 ml. of dry thiophene-free benzene and the solution chilled until the benzene started to crystallize. Then 24 ml. of stannic chloride dissolved in 20 ml. of dry benzene was added with swirling, and the mixture allowed to stand in the ice-bath for one hour.⁸ The mixture was poured upon a mixture of 50 ml. of concentrated hydrochloric acid, 50 ml. of alcohol-free ether and ice. When the yellow complex was destroyed, the organic layer was separated and washed with 5% hydrochloric acid, and twice with water. The extract was then heated under reflux with a solution of 12 g. of sodium hydroxide in 200 ml. of water. After cooling, the aqueous layer was run into 50 ml. of concentrated hydrochloric acid and ice. The precipitated acid weighed 19.5 g. (81%) and melted at 171–172°, after treatment with decolorizing carbon and recrystallization from dilute acetic acid.

Anal. Calcd. for $C_{16}H_{17}O_5N$: C, 63.36; H, 5.65. Found: C, 63.34; H, 5.46.

The colorless oxime melted at 185–186° (dec.) after recrystallization from dilute ethanol.

Anal. Calcd. for $C_{16}H_{18}O_5N_2$: C, 60.37; H, 5.70. Found: C, 60.44; H, 5.63.

1-Cyano-1-(β -carboxyethyl)-7,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (XIV).—In preliminary experiments on the catalytic reduction of one gram or smaller quantities of XIII, the products obtained were usually of better quality than larger scale runs. Occasionally the presence of a trace of hydrogen bromide appeared to give

(6) Bruson and Riener, *THIS JOURNAL*, **65**, 25 (1943).

(7) Horning, Horning and Platt, *ibid.*, **69**, 2929 (1947).

(8) This is essentially the general procedure in "Organic Reactions," Vol. II, 1945, p. 138.

products of high purity, but since this behavior was never consistent and poisoning of the catalyst always occurred, this method was abandoned. The course of the reaction is unknown, for it was impossible to isolate any intermediate that would be expected when half of the theoretical amount of hydrogen had been absorbed. Concentrated sulfuric acid was finally employed in conjunction with the palladium catalyst because somewhat purer products could be isolated than those formed in the absence of added acid.

Six drops of concentrated sulfuric acid were added to a suspension of 6.0 g. of XIII in 40 ml. of glacial acetic acid. Then 1.5 g. of 5% palladium-carbon catalyst³ was added and the mixture hydrogenated at atmospheric pressure at 50–60°. In most cases, the end of the reaction was recognized only by a change in the rate of adsorption rather than a definite cessation. The catalyst was removed by filtration and the filtrate diluted with a slush of ice and water with vigorous stirring. The dried crystalline precipitate weighed 4.1 g. (72%) and melted at 108–112°. Purification for analysis was effected by recrystallization from dilute acetic acid. The pure acid melted at 123–124°.

Anal. Calcd. for $C_{18}H_{19}O_4N$: C, 66.42; H, 6.62. Found: C, 66.30; H, 6.48.

This acid was also obtained in small amount by a modification of the Wolff-Kishner reduction.⁴ A mixture of 1.0 g. of XIII, 0.9 g. of potassium hydroxide, 0.9 ml. of 85% hydrazine hydrate and 15 ml. of diethylene glycol was heated at 145–150° for one hour. The temperature was gradually raised to 195° by allowing water vapor to escape from the reflux condenser. After one and one-half hours, the black solution was cooled, acidified with dilute hydrochloric acid and diluted with 50 ml. of water. It was then extracted with 100 ml. of ether and the extract shaken with 50 ml. of 5% sodium hydroxide solution. The alkaline solution was heated with carbon and the filtrate acidified with dilute hydrochloric acid. After standing in an ice-box for two days, the colorless needles were removed by filtration; the yield was 0.15 g., m. p. 119–120°. A recrystallized sample melted unchanged on admixture with that obtained by catalytic reduction.

In an effort to decrease the amount of carbonaceous material obtained in the reaction, the cyano group was first partially hydrolyzed by treatment with a mixture of concentrated hydrochloric acid and acetic acid. A solution of 5.0 g. of XIII in 25 ml. of concentrated hydrochloric acid and 25 ml. of glacial acetic acid was heated on the steam-bath for two hours. Within ten minutes the imide XVII started to crystallize from the reaction

mixture. The mixture was cooled and the product filtered and washed, first with ethanol and finally with ether. The colorless crystalline solid weighed 4.5 g. (90%). The analytical sample was recrystallized from glacial acetic acid, m. p. 272–274° (dec.) (obtained in a melting block).

Anal. Calcd. for $C_{18}H_{17}O_5N$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.39; H, 5.46; N, 4.57.

The heterocyclic ring was cleaved by warming with dilute alkali until solution took place, followed by acidification with dilute hydrochloric acid. The amide-acid XVIII separated from ethanol or hot water in the form of colorless needles, m. p. 178–179°. Melting was accompanied by evolution of vapor and subsequent resolidification to regenerate the glutarimide XVII.

Anal. Calcd. for $C_{18}H_{19}O_6N$: C, 59.80; H, 5.96; neut. equiv., 321. Found: C, 59.67; H, 6.00; neut. equiv., 325.

Heating either the lactone-acid XIII or the imide XVII according to the Clemmensen method with a mixture of concentrated hydrochloric acid, acetic acid, zinc and toluene produced only impure materials which could not be purified. The Wolff-Kishner reaction carried out on XVII produced a small amount of amorphous material which could not be purified.

1-Cyano-1-(β -dimethylaminoethyl)-7,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (XV).—This compound was obtained in a manner analogous to that described for IX. From 3.34 g. of XIV (m. p. 108–112°) there was obtained by evaporative distillation at 120–125° (0.07 mm.); 1.4 g. (ca. 40%) of product as a pale yellow oil.

Anal. Calcd. for $C_{17}H_{24}O_2N_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 70.80; H, 8.05; N, 9.77.

The picrate separated from absolute ethanol-ethyl acetate in the form of lemon yellow leaflets, m. p. 180–181°.

Anal. Calcd. for $C_{17}H_{24}O_2N_2 \cdot C_6H_3O_7N_3$: C, 53.38; H, 5.26. Found: C, 53.52; H, 5.05.

Summary

The preparation of 1-ethyl-1-carboxy-3-dimethylamino-7-acetoxy-8-hydroxy-1,2,3,4-tetrahydronaphthalene lactone is described.

Experiments directed toward the synthesis of 1-(β -dimethylaminoethyl)-1-carboxy-7-acetoxy-8-hydroxy-1,2,3,4-tetrahydronaphthalene lactone are also described.

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