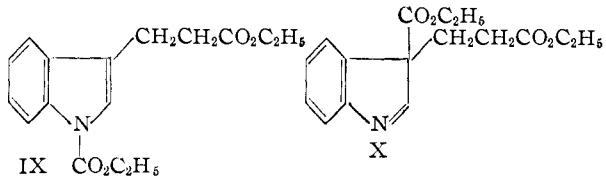
which crystallizes in "disc like" crystals is stated to melt at 188–189° while the latter which forms "fan like" crystals melts at 194°. Repetition of the work, following Maurer and Moser's directions, showed conclusively that the diacid presumed to be IV is identical with the diacid VIII. The substance made by partial hydrolysis of the triester I melted at 194° and did not depress the melting point of authentic VIII.

We now have only the Smith and Sogn synthesis to consider. The method of synthesis and the fact that 3-indolepropionic acid is obtained *directly* on base hydrolysis of the compound to which they assigned formula III leave only two possible structures for this compound: IX or X.

Repetition of Smith and Sogn's work gave their presumed malonic ester, m.p. 77–78°. This compound was not basic, a fact which rules out the



indolenine structure X, and the infrared absorption spectrum showed conclusively the absence of an N–H bond. The ultraviolet spectrum of the compound further confirmed the absence of 3,3-disubstituted indolenine structure.[4] These facts suffice to establish that the compound prepared by Smith and Sogn is ethyl 1-carbethoxy-3-indolepropionate.

(4) IX has $\lambda_{max.}$ 260 mμ (log ε = 4.03) while X would have $\lambda_{max.}$ around 245 mμ (*cf.* P. Grammaticakis, *Compt. rend.*, **210**, 569 (1940)).

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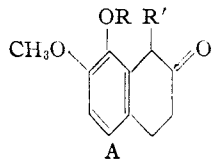
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY]

The Synthesis of Some 1-Substituted 7,8-Dimethoxy-2-tetralones

BY GILBERT STORK AND HAROLD CONROY[1]

The ketones, 5-bromo-7,8-dimethoxy-2-tetralone-1-acetic ester, 1-(β-dimethylaminoethyl)-5-bromo-7,8-dimethoxy-2-tetralone and 1-[β-(N-methylbenzylsulfonamido)-ethyl]-5-bromo-7,8-dimethoxy-2-tetralone were synthesized by a route starting from 2,3-dimethoxybenzaldehyde. These tetralones are of interest in connection with the possible extension of their ring system to that of a 13-substituted hydrophenanthrene typical of the morphine alkaloids.

Consideration of the possible approaches to the synthesis of the morphine alkaloids led to the belief that the use of a properly substituted 2-tetralone (of type A) would afford valuable intermediates



A

for this purpose. Two methods have been described for the preparation of 1-substituted 2-tetralones. Direct alkylation of a 2-tetralone is known to take place in the 1-position and has been used successfully in a number of instances,[2,3] although the tendency for dialkylation is so great that it is often difficult to obtain the monosubstituted derivative.[2,4] The second method, which involves the reaction of a 1-alkyl-3,4-dihydronaphthalene with peracids,[5,6] is not of general applicability.

A method for the synthesis of a compound of type A in which R′ is an acetic acid residue was devised, since such a grouping eventually should be transformable into the ethanamine chain of morphine. The starting material chosen was 2,3-dimethoxy-5-bromobenzaldehyde[7] (I), which was condensed with ethyl cyanoacetate to yield 2,3-dimethoxy-5-bromobenzylidene cyanoacetic ester (II). The addition of cyanide ion to the unsaturated system of II gave the dicyano ester (III).

Hydrolysis of III to 2,3-dimethoxy-5-bromophenylsuccinic acid (V) by a method which is successful in the preparation of phenylsuccinic acid[8] resulted in material that was obviously impure. However, the dicyano ester (III) was converted to V by reaction with methanolic hydrogen chloride in the presence of some water, when α-(2,3-dimethoxy-5-bromophenyl)-β-carbomethoxysuccinimide (IV) was obtained. Vigorous basic hydrolysis of IV gave V in excellent yield.

The lactone (VI) was obtained in good yield by treatment of the diacid (V) with a mixture of formalin and dilute sulfuric acid. A similar reaction has been used previously in the synthesis of some phthalide derivatives.[9] The lactone (VI) was opened to 2,3-dimethoxy-5-bromo-6-bromomethylphenylsuccinic acid dimethyl ester (VII) with methanolic hydrogen bromide.[10,11]

The diester (VII) was treated with a suspension

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

(2) J. W. Cornforth, R. H. Cornforth and R. Robinson, *J. Chem. Soc.*, 689 (1942).

(3) H. Andersag and W. Salzer, U. S. Patent 2,271,674 (1942) [*C. A.*, **36**, 3514 (1942)].

(4) J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, 676 (1946).

(5) R. Ghosh and R. Robinson, *ibid.*, 506 (1944).

(6) J. English and G. Cavaglieri, THIS JOURNAL, **65**, 1085 (1943).

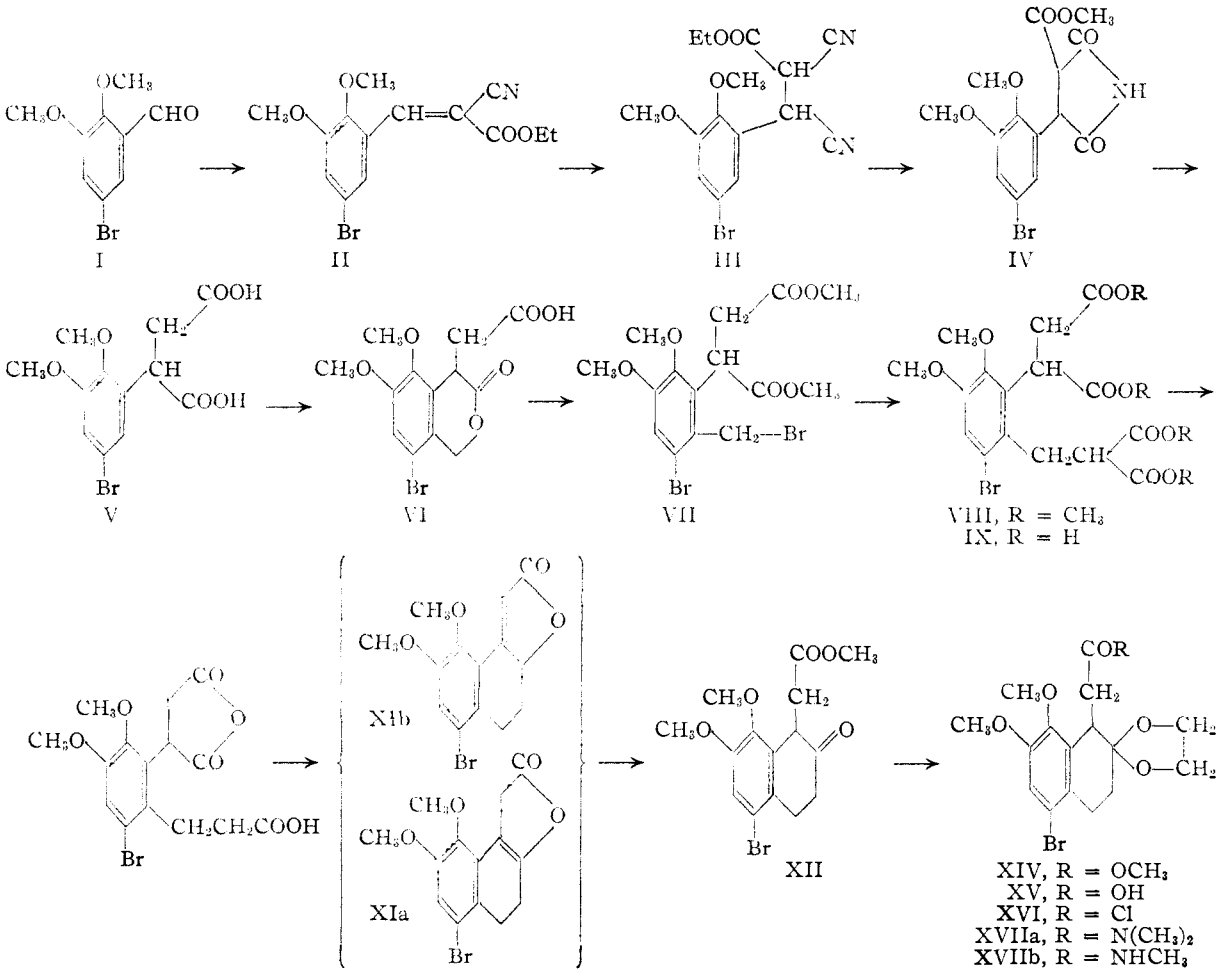
(7) W. Davies, *J. Chem. Soc.*, **123**, 1575 (1923).

(8) A. Lapworth and W. Baker, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., p. 451.

(9) R. H. F. Manske and A. E. Ledingham, *Can. J. Res.*, **22B**, 115 (1944).

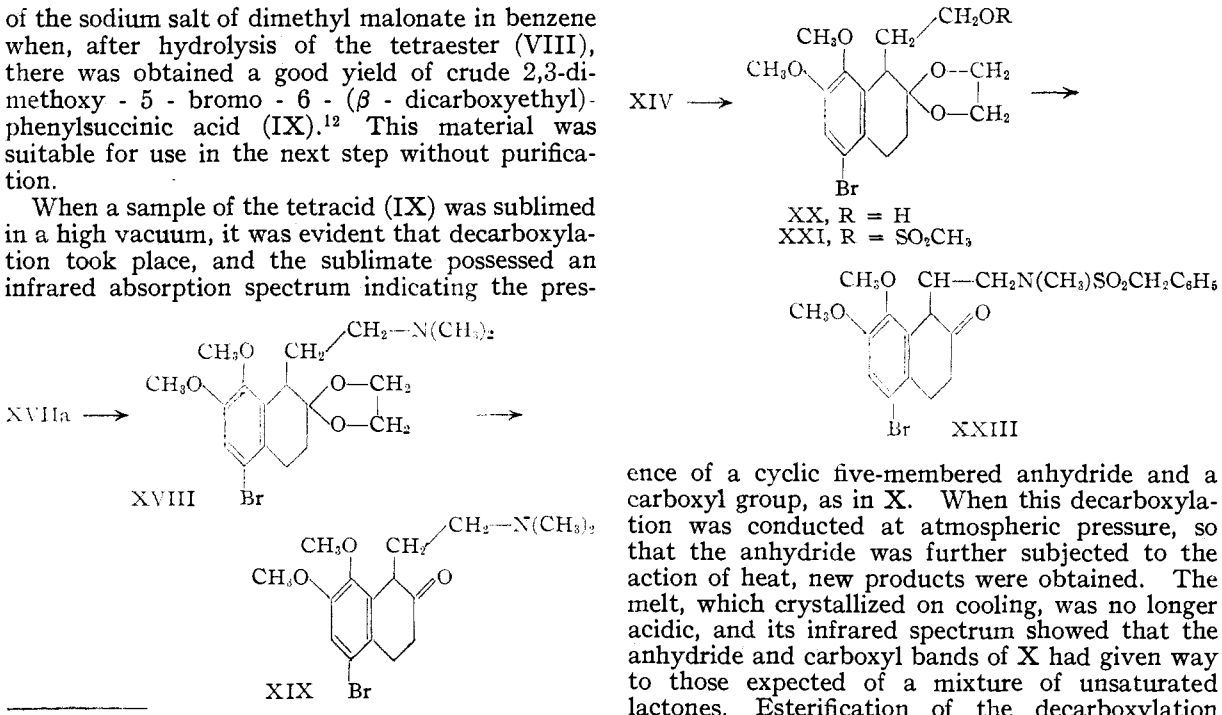
(10) This reaction is similar to the formation of o-chloromethylphenylacetic ester from homophthalide (S. Murahashi, *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **30**, 180 (1936)).

(11) From one early run which had not been so thoroughly cooled as the others a rather large proportion of a compound, m.p. 80°, was obtained in addition to some diester (VII). This substance contained no replaceable bromine; when it was dissolved in benzene and the cold solution saturated with hydrogen bromide VII was obtained. The compound is evidently 2,3-dimethoxy-5-bromo-6-methoxymethylphenylsuccinic acid dimethyl ester, formed by solvolysis of the intermediate benzylcarbonium ion. None of this compound was isolated from reaction mixtures which were saturated with hydrogen bromide, finally at 0°.



of the sodium salt of dimethyl malonate in benzene when, after hydrolysis of the tetraester (VIII), there was obtained a good yield of crude 2,3-dimethoxy - 5 - bromo - 6 - (β - dicarboxyethyl)-phenylsuccinic acid (IX).[12] This material was suitable for use in the next step without purification.

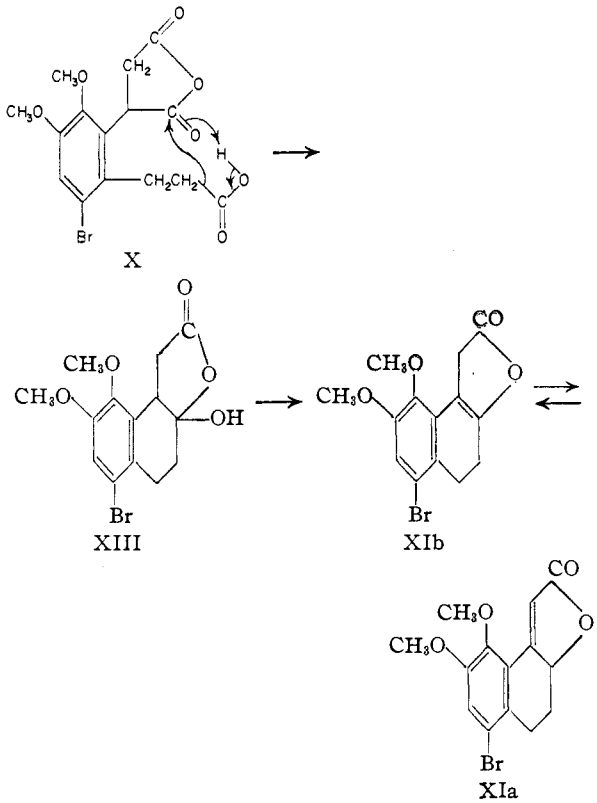
When a sample of the tetracid (IX) was sublimed in a high vacuum, it was evident that decarboxylation took place, and the sublimate possessed an infrared absorption spectrum indicating the presence of a cyclic five-membered anhydride and a carboxyl group, as in X. When this decarboxylation was conducted at atmospheric pressure, so that the anhydride was further subjected to the action of heat, new products were obtained. The melt, which crystallized on cooling, was no longer acidic, and its infrared spectrum showed that the anhydride and carboxyl bands of X had given way to those expected of a mixture of unsaturated lactones. Esterification of the decarboxylation mixture produced a nicely crystalline, sparingly soluble compound, the keto-ester (XII), which had the expected broad infrared absorption band at



(12) The chloromethyl compound corresponding to VII could be readily prepared by the use of HCl but its further reaction with malonic ester required conditions so drastic that considerable decomposition occurred.

about 5.80 μ, due to the saturated ketone and ester groups. The nature of these carbonyl functions was further confirmed by the formation of a 2,4-dinitrophenylhydrazone, which retained a sharp absorption band at 5.78 μ (ester).

The mixture of unsaturated lactones gave, after repeated recrystallization, a single isomer, m.p. 186.3–187.0°, formulated as XIa, which possessed infared absorption bands at 5.75 and 6.15 μ. The isomeric β,γ-unsaturated lactone (XIb) was not isolated, but its formation together with XIa is evident from the fact that the infrared spectrum of the melt possessed the very characteristic band at 5.56 μ.[13] Both lactones (XIa and XIb) would be expected to yield the keto-ester (XII) upon esterification. A possible path from the acid anhydride (X) to the lactones (XIa and XIb) is outlined below.



The formation of the lactol (XIII) is represented as a concerted process in which the loss of a molecule of carbon dioxide is concomitant with the addition of the methylene group to the anhydride carbonyl. The dehydration of the lactol to the β,γ-unsaturated lactone (XIb) calls for no special comment, while equilibration of XIb and XIa is undoubtedly facilitated by the fact that their common conjugate acid is one of low energy (substituted benzylcarbonium ion).

Conditions were developed which made possible a 35–40% over-all yield of the keto-ester (XII) from the diester (VII) without isolation of the intermediates, and the ready availability of XII allowed its utilization for the preparation of compounds possessing a substituted β-aminoethyl chain.

Two syntheses of 1-(β-dimethylaminoethyl)-5-bromo-7,8-dimethoxy-2-tetralone (XIX) are shown. The keto-ester (XII) was converted to its cyclic ketal (XIV) with ethylene glycol in the presence of *p*-toluenesulfonic acid. Hydrolysis of XIV with aqueous base afforded the crystalline ketal-acid (XV), which could be transformed into its acid chloride (XVI) by the action of oxalyl chloride upon its sodium salt. The acid chloride could in turn be converted to the N-dimethylamide (XVIIa) by the action of dimethylamine. Lithium aluminum hydride reduction of XVIIa gave the amino-ketal (XVIII) which was converted by aqueous acid to the desired amino-ketone (XIX), isolated and characterized as its perchlorate, m.p. 171°.[14]

An alternative route to the amino-ketone (XIX) through the mesylate (XXI) was developed. Lithium aluminum hydride reduction of the ketal-ester (XIV) gave the ketal-alcohol (XXI) which was converted to (XXI) with methanesulfonyl chloride and pyridine. The mesylate was heated with a dioxane solution of dimethylamine and, after hydrolysis of the ketal function, the basic fraction gave the perchlorate of XIX, which did not depress the m.p. of the previously obtained perchlorate.

Although the over-all yield of the dimethylamino ketone (XIX) prepared through the mesylate was lower than that from the first method, the mesylate provided a route to the benzylsulfonyl derivative of the secondary amine, 1-(β-methylaminoethyl)-5-bromo-7,8-dimethoxy-2-tetralone (XXIII).[14] The reaction of the mesylate with a suspension of the sodium salt of N-methylbenzylsulfonamide in boiling toluene provided the ketalsulfonamide (XXII), which gave the corresponding ketone upon hydrolysis with dilute acid.

The keto-ester (XII), the amino-ketone (XIX) and the sulfonamido-ketone (XXIII) are of interest in connection with the possible extension of the ring system to that of a 13-substituted hydrophenanthrene typical of the morphine alkaloids.

Experimental

2,3,-Dimethoxy-5-bromobenzaldehyde (I).—The method[7] of Davies was modified to permit the preparation of large quantities. Four hundred and eighty grams of sodium bicarbonate was added with mechanical stirring to a solution of 936 g. of freshly distilled 2,3-dimethoxybenzaldehyde in four liters of carbon tetrachloride. This suspension was cooled in an ice-bath during the addition of 910 g. of bromine over a period of one hour. Vigorous stirring was continued for four hours; the mixture was then allowed to stand at room temperature for 15 hours. The mixture was washed twice with dilute sodium bisulfite solution and once again with water. The solvent was evaporated under reduced pressure and the residue recrystallized from 750 cc. of a 3:1 ligroin–(b.p. 90–120°) benzene mixture. The solid was collected and washed with an equal volume of the same mixture (ice-cold). The yield of colorless needles, m.p. 81.0–81.5°, was 803–852 g. (58–62%).

2,3-Dimethoxy-5-bromobenzylidene Cyanoacetic Ester (II).—A mixture of 800 g. of 2,3-dimethoxy-5-bromobenzaldehyde, 1200 cc. of benzene, 368 g. of ethyl cyanoacetate, 149 cc. of acetic acid and 50.7 g. of ammonium acetate was refluxed with a water separator for 12 hours or several hours after the water no longer came over (bottom layer 120 cc.). The reddish solution, while still hot, was poured into

(13) R. B. Woodward and G. Singh, unpublished observations

(14) The monomethyl amide (XVIIb) could be prepared in an analogous manner from the acid chloride, but its reduction with lithium aluminum hydride was extremely slow and led to considerable removal of the aromatically bound bromine. No definite products could be isolated, and this method is not suitable for the preparation of the methylaminoethyl derivative.

a beaker and refrigerated for ten hours. The mass of yellow needles was broken up and sucked dry on a funnel, then washed with 600 cc. of ice-cold 1:1 benzene–ligroin. The yield of light yellow material with the m.p. 119.5–121.0° and suitable for use in the next step was 857–875 g. (77–79%). For analysis a sample was recrystallized once from benzene–cyclohexane and once again from benzene, m.p. 120.3–121.0°.

Anal. Calcd. for $C_{14}H_{14}O_4NBr$: C, 49.43; H, 4.15. Found: C, 49.18; H, 3.99.

2,3-Dimethoxy-5-bromophenylsuccinic Acid (V).—To 857 g. of finely powdered 2,3-dimethoxy-5-bromobenzylidene cyanoacetic ester (II), suspended in 1200 cc. of 50% ethanol, was added 252 g. of sodium cyanide. The thick mixture was gently agitated with a stirrer, when the solid went into solution with evolution of heat. In about 20 minutes there remained a clear tan solution which was poured *immediately* into 1500 cc. of cold water. The solution was acidified by the addition of concd. hydrochloric acid, and after some time the aqueous layer decanted from the yellowish, viscous **ethyl β-(2,3-dimethoxy-5-bromo phenyl)-α,β-dicyanopropionate (III).** The latter was taken up in 1750 cc. of methanol and 50 cc. of water and the solution saturated with hydrogen chloride without cooling. The mixture containing suspended ammonium chloride was refluxed with slow stirring for five hours, then most of the solvent was blown off on the steam-bath. One and one-half liters of water and one liter of chloroform were added to the semi-solid residue, with slight warming if necessary to aid solution, and the chloroform layer was separated and washed once with water. The solvent was removed and the solid residue, consisting mostly of **α-(2,3-dimethoxy-5-bromophenyl)-β-carbomethoxysuccimimide (IV)**, was treated cautiously with a solution of 400 g. of sodium hydroxide in three liters of water. The mixture was refluxed with mechanical stirring (to avoid explosive bumping) for 70 hours or more, when practically no more ammonia was evolved. The dark solution was filtered through charcoal, cooled thoroughly in ice, and strongly acidified with concd. hydrochloric acid. Crystallization commenced shortly and after several hours in the ice-bath the solid was collected and washed with cold water. The yield of crude diacid was 894–950 g. (94–100%). For analysis a sample was recrystallized twice from hot water, m.p. 183–184°.

Anal. Calcd. for $C_{12}H_{13}O_6Br$: C, 43.25; H, 3.93. Found: C, 43.48; H, 4.19.

For analysis a sample of the succinimide derivative (IV) was recrystallized twice from methanol.

Anal. Calcd. for $C_{14}H_{14}O_6NBr$: C, 45.18; H, 3.79. Found: C, 44.88; H, 3.68.

Lactone of 2,3-Dimethoxy-5-bromo-6-hydroxymethylphenylsuccinic Acid (VI).—A suspension prepared from 900 cc. of concd. sulfuric acid, 1800 cc. of water, 600 cc. of 38% formalin and 890 g. of the crude diacid (V) was refluxed with vigorous stirring for 12 hours (caution, foaming!). In some cases the suspended material remained crystalline throughout, although the character of the precipitate changed markedly, while in other runs the solid melted to a thick brown oil which later coalesced to a mass of pea-sized hard tan pellets. In either case the yield remained about the same. After cooling the solid material was collected, washed with water, and recrystallized from three liters of 50% acetic acid. The yield of colorless to light-tan material was 546–614 g. (67–76%). For analysis a sample was recrystallized twice from aqueous acetic acid; needles, m.p. 138–139° with effervescence; resolidifies to anhydrous substance, m.p. 161°.

Anal. Calcd. for $C_{13}H_{13}O_6Br \cdot {}^1/_2H_2O$: C, 44.08; H, 3.98. Found: C, 44.07; H, 3.51.

2,3-Dimethoxy-5-bromo-6-bromomethylphenylsuccimic Acid Dimethyl Ester (VII).—Hydrogen bromide was passed in with stirring and cooling to a suspension of 546 g. of the lactonic acid (VI) in 2500 cc. of methanol. When the mixture became saturated with the gas at a temperature below 10° (several hours), 850 cc. of chloroform was added, and if a clear solution did not result, more gas was admitted. The clear tan solution was poured into cracked ice, the aqueous layer extracted several times with chloroform and the combined extracts washed twice with ice-water, then dried over sodium sulfate. The clear brown oil remaining after solvent evaporation was taken up in a mixture (850 cc.) of 4:1 cyclohexane–ethyl acetate and crystallization allowed to proceed. The solid was washed on the funnel with 170 cc. of the same solvent mixture. The yield of colorless crystals was 499–582 g. (70–81%). The m.p. was 114.5–115.5°. For analysis a sample was recrystallized once from cyclohexane–ethyl acetate, m.p. 115.0–115.5°.

Anal. Calcd. for $C_{15}H_{16}O_6Br_2$: C, 39.67; H, 3.99. Found: C, 39.89; H, 4.19.

2,3-Dimethoxy-5-bromo-6-(β-dicarboxyethyl)-phenylsuccinic Acid (IX).—To a suspension of the sodium salt of dimethyl malonate prepared from 150 g. of dimethyl malonate, 26.4 g. of sodium hydride and 1500 cc. of dry benzene was added a solution of 499 g. of the diester (VII) in 1200 cc. of dry benzene. The mixture was refluxed with mechanical stirring on the steam-bath for 30 hours. After the reflux period two liters of water were added with brief stirring, the clear benzene layer separated and the solvent removed *in vacuo*. The light tan viscous oil remaining was stirred on the steam-bath with a solution of 200 g. of sodium hydroxide in 1100 cc. of water for 15 hours, when all but a small semi-solid residue (*ca.* 10 g.) had dissolved. The clear tan solution was filtered through glass wool and acidified with concd. hydrochloric acid. The tetraacid precipitated as a thick creamy suspension, and after thorough cooling in ice it was collected and dried at 60°. The dried lumps were pulverized to a fine powder. The yield of crude tetraacid, used in the next step without purification, was 520–550 g.

5-Bromo-7,8-dimethoxy-2-tetralone-1-acetic Acid, Methyl Ester (XII).—The decarboxylation reaction proper is best conducted in small batches: One hundred grams of dry, finely powdered tetraacid (IX) was placed in a 500-cc. round-bottomed flask carrying a gas exit tube. The solid was leveled in the bottom and the whole immersed in an electrically heated, thermostated oil-bath. The bath temperature was raised rapidly to 250° and maintained throughout the decarboxylation within two degrees of that figure. The solid began to melt around the edges at about 220°, and the last of it was gone about 13 minutes after the temperature of the bath reached 250°, leaving a vigorously effervescing, straw-colored liquid. Heating was continued until there was a sudden marked decrease in the rate of gas evolution, concomitant with a sharp change in color to a deep orange brown. This took 12–14 minutes more.[15] The flask was removed from the bath immediately and allowed to cool while it was slowly rotated in order to obtain a thin, even coating of orange crystals (mixture of XIa and XIb) on the inside wall. After cooling to room temperature, the solid was dissolved in 150 cc. of hot chloroform; a little sodium chloride remained undissolved at this point but was ignored.

The solutions from five such runs were combined and added to a hot mixture of 1000 cc. of concd. sulfuric acid and 2000 cc. of methanol. The solution was refluxed for 30 hours on the steam-bath, then another 1000 cc. of methanol was added and the greenish brown solution cooled thoroughly in ice. A dark oil separated and solidified after scratching or seeding; the liquid above deposited crystals of keto-ester. When crystallization was complete, the slurry was filtered and the crude keto-ester washed with methanol until no more color was removed. The light purplish crystals (*ca.* 170 g.) were dissolved in hot benzene, treated with decolorizing charcoal, filtered, and the light brown solution evaporated somewhat. After cooling the colorless needles were collected and washed with a little methanol. The combined filtrates were further evaporated when a second crop of equally good material was obtained. The total yield of colorless material, m.p. 144.3–145.0°, was 135–140 g. (35–40% based on the diester (VII)). For analysis a sample was recrystallized twice. It had m.p. 145.0–145.4°.

Anal. Calcd. for $C_{15}H_{17}O_6Br$: C, 50.42; H, 4.72. Found: C, 50.45; H, 4.91.

The 2,4-dinitrophenylhydrazone had the m.p. 179.5–180.0°; resolidified with remelting at 193–194°.

Anal. Calcd. for $C_{21}H_{21}N_4O_8Br$: C, 46.94; H, 3.94. Found: C, 46.72; H, 3.98.

A sample of the decarboxylation melt was recrystallized

(15) The gas evolution did *not* completely stop at this point, however, although the loss in weight corresponded closely to the theoretical amount. Experiments involving prolonged heating until there was *no* further gas evolution, *i.e.*, as long as three hours, invariably were complete failures.

three times from ethanol–chloroform. The α,β-unsaturated lactone (XIa) obtained had the m.p. 186.3–187.0°.

Anal. Calcd. for $C_{14}H_{13}O_4Br$: C, 51.71; H, 4.03. Found: C, 51.98; H, 4.24.

Cyclic Ketal of 5-Bromo-7,8-dimethoxy-2-tetralone-1-acetic Acid (XV).—Eighty grams of the keto-ester (XII), 350 cc. of toluene, 200 cc. of ethylene glycol and 6.0 g. of *p*-toluenesulfonic acid were refluxed with a water separator for 16 hours, when the total volume of the separated lower layer was approximately 110 cc. The solution remaining in the flask was cooled and poured into a mixture of 500 g. of cracked ice and 60 g. of potassium carbonate with vigorous shaking. The organic layer was separated, the aqueous layer extracted once with water, and the combined extracts washed twice with water. After the addition of 0.5 g. of solid potassium carbonate to the light tan solution the solvent was removed *in vacuo*. The resulting viscous ketal-ester (XIV) was hydrolyzed by boiling with a solution of 10 g. of sodium hydroxide in 100 cc. of water until the oil had dissolved. After cooling thoroughly in ice the solution was cautiously acidified by the addition of small portions of quite dilute hydrochloric acid with vigorous shaking in the ice-bath, when the ketal-acid precipitated as a white semi-solid. The acidification was continued to the point where the supernatant liquid retained a permanent milkiness (*p*H about 5). After warming to room temperature the precipitated acid coagulated to a white gum, which was removed and triturated with 50% methanol. The yield was 69 g. (80%) of colorless prisms, m.p. 170–171°. For analysis a sample was recrystallized once from ethanol–water, m.p. 170–171°.

Anal. Calcd. for $C_{16}H_{19}O_6Br$: C, 49.62; H, 4.95. Found: C, 49.77; H, 5.07.

Cyclic Ketal of 5-Bromo-7,8-dimethoxy-2-tetralone-1-(N-dimethylacetamide) (XVIIa) and the Monomethylamide (XVIIb).—The recrystallized ketal-acid (XV) (13.2 g.) was dissolved in an exactly equivalent amount of dilute aqueous sodium hydroxide and the resulting solution was evaporated to a thick sirup *in vacuo*. Fifty cc. of benzene was added and the mixture refluxed with a water separator until no droplets of water distilled. The clear benzene solution of the sodium salt was cooled to 0°, then three drops of pyridine followed by 10 cc. of oxalyl chloride were added with shaking in an ice-bath. After 15 minutes at room temperature the solvent was removed *in vacuo* below 40°, then 50 cc. of dry benzene was added and again removed. The last traces of oxalyl chloride were pumped off in a high vacuum and the semi-solid residue taken up in dry benzene. Dry dimethylamine was passed in until the mixture was saturated, then it was washed once with aqueous potassium carbonate and twice with water. Evaporation of the solvent left the amide as a tan-colored oil which could not be induced to crystallize.

The monomethyl amide (XVIIb) was prepared in a similar manner with methylamine. In this case the oily amide was dissolved in ethyl acetate when it crystallized shortly. The yield of nearly colorless prisms, m.p. 184.5–185.0°, was 11 g. For analysis a sample was recrystallized from ethyl acetate, m.p. 185.4–186.0°.

Anal. Calcd. for $C_{17}H_{22}O_5NBr$: C, 51.01; H, 5.54. Found: C, 50.96; H, 5.69.

1-(β-Dimethylaminoethyl)-5-bromo-7,8-dimethoxy-2-tetralone (XIX) (A).—The oily ketal-amide (XVIIa) prepared from 13.2 g. of ketal-acid (*vide supra*) was dissolved in 50 cc. of dry ether and the solution added over a period of 30 minutes to 10 g. of lithium aluminum hydride in another 50 cc. of ether. The mixture was stirred at room temperature for ten hours; then poured into ice and extracted with liberal portions of ether. The emulsion was broken by the addition of a few grams of sodium sulfate. The ether solution was washed once with water and the basic material was extracted with two portions of dilute hydrochloric acid. The acid solution was washed once with ether and allowed to stand overnight at room temperature in order to hydrolyze the ketal grouping. The amino ketone was precipitated as an oil by the addition of potassium carbonate, taken up in ether, and after evaporation of the solvent, isolated as the crystalline perchlorate by treatment with a slight excess of 87% perchloric acid dissolved in 20 cc. of aqueous ethanol. After crystallization was complete the solid was collected and purified by recrystallization from aqueous ethanol. The yield was 9.8 g. of colorless needles, m.p. 171°.

(B).—The ketal-mesylate (XXI) (*vide infra*) prepared from 7.2 g. of the ketal-alcohol (XX) was dissolved in 125 cc. of dioxane and the solution saturated with dry dimethylamine. The mixture was heated at 100° for 18 hours in a bomb under 1000 lb. hydrogen pressure. The solvent was removed and the residue taken up in benzene. The benzene solution was washed with water and then extracted with dilute hydrochloric acid. The acid solution was washed once with benzene, allowed to stand overnight, and then made basic. The amine was taken up in chloroform and isolated as the perchlorate as in (A). The yield was 2.5 g.; the m.p. (171°) was undepressed in admixture with that prepared in (A). For analysis a sample was recrystallized four times from water, m.p. 171.0–171.5°.

Anal. Calcd. for $C_{16}H_{23}O_7NBrCl$: C, 42.05; H, 5.04. Found: C, 42.30; H, 5.32.

The 2,4-dinitrophenylhydrazone-perchlorate, prepared directly from the perchlorate, had the m.p. 206–207° dec. after two recrystallizations from chloroform.

Anal. Calcd. for $C_{22}H_{27}O_{10}N_5BrCl$: C, 41.49; H, 4.27. Found: C, 41.72; H, 4.53.

Cyclic Ketal of 1-(β-Hydroxyethyl)-5-bromo-7,8-dimethoxy-2-tetralone (XX).—The oily ketal-ester (XIV) prepared exactly as given in the preparation of the ketal-acid (XV) from 80 g. of XII, was dissolved in 900 cc. of absolute ether and the clear solution run into a stirred mixture of 14.0 g. of lithium hydride and 100 cc. of absolute ether at 0° over a perlod of 15 minutes. After the addition was complete the ice-bath was removed and stirring was continued at room temperature for two hours. The white suspension was poured into ice and thoroughly extracted with ether. The emulsion was destroyed by the addition of some sodium sulfate. The colorless oil remaining after evaporation of the solvent was taken up in ethyl acetate–cyclohexane and seeded, when crystallization began immediately. After refrigeration for about 12 hours the crystals were collected and washed on the filter with fresh solvent mixture. The yield was 72 g. (86%) of material with the m.p. 85.5–86.5°. For analysis a sample was recrystallized from ethyl acetate–cyclohexane. The m.p. was unchanged.

Anal. Calcd. for $C_{16}H_{21}O_5Br$: C, 51.48; H, 5.67. Found: C, 51.09, 51.71; H, 5.58, 6.05.

1-[β-(N-Methylbenzylsulfonamido)-ethyl]-5-bromo-7,8-dimethoxy-2-tetralone (XXIII).—A mixture of 72.0 g. of the ketal-alcohol (XX), 100 cc. of dry benzene, 16.8 g. of pyridine and 23.1 g. of methanesulfonyl chloride was kept at room temperature for four hours, then warmed gently on the steam-bath for two hours. The suspension was washed twice with ice-water and the organic layer dried over potassium carbonate. The solution was filtered and the solvent removed at room temperature *in vacuo*. The residual oily mesylate (XXI) was taken up in 250 cc. of dry toluene and added to a suspension of the sodium salt of N-methylbenzylsulfonamide prepared by the reaction of 7.8 g. of sodium hydride and 70.0 g. of N-methylbenzylsulfonamide[16] in 1000 cc. of dry toluene for one-half hour at the reflux temperature. The whole mixture was refluxed with stirring for five hours; after cooling an equal volume of water was added. The excess unalkylated sulfonamide was removed in a potassium hydroxide wash, in several portions. The organic solvent was removed by vacuum distillation, leaving a light tan oil containing the ketal-sulfonamide (XXII). The oil was taken up in a mixture of 450 cc. of water, 50 cc. of concd. hydrochloric acid and 200 cc. of methanol, and the whole was refluxed on the steam-bath for two hours.

The solvents were removed *in vacuo*, and 100 cc. of ether and some seed were added, when crystallization began. After refrigeration overnight the solid was collected and washed with ether and water. After drying, the crude material weighed 24.2 g., and after one recrystallization from ether–chloroform the yield of colorless crystals, m.p. 140–141°, was 20.1 g. For analysis a sample was recrystallized once again from ether–chloroform, m.p. 140.9–141.2°.

Anal. Calcd. for $C_{22}H_{26}O_5NSBr$: C, 53.23; H, 5.29; N, 2.83. Found: C, 53.52; H, 5.49; N, 2.85.

(16) The N-methyl benzylsulfonamide, (T. B. Johnson and J. A. Ambler, THIS JOURNAL, **36**, 382 (1914)) m.p. 110°, was prepared by the reaction of benzylsulfonyl chloride (J. M. Sprague and T. B. Johnson, *ibid.*, **59**, 1839 (1937)) with methylamine.

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 $C_{28}H_{30}O_8N_5SBr$: C, 49.71; H, 4.47; N, 10.35. Found: C, 49.47; H, 4.46; N, 10.36.

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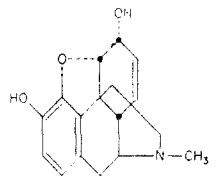
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY]

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.

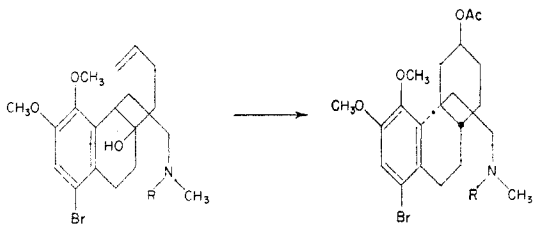
The further extension of the system present in the 1-substituted 2-tetralones described in the previous communication[2] to that of morphine (I) requires a method for the construction of the third



I

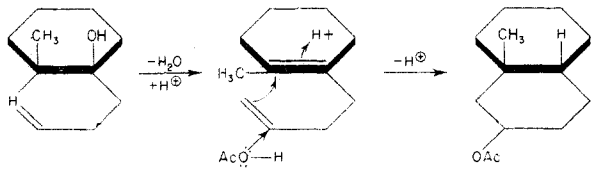
carbocyclic ring which would lead to a *cis*-decalin structure such as that present in the natural alkaloid. Two methods were considered.

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

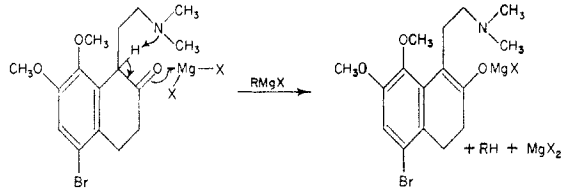


II III

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).