various compounds, it is evident that there is a general correlation with molecular weight[7] so long as rather large variations are considered. Within a small range of molecular weight, however, interactions of polar substituents with the aqueous solvent play a dominant role. This is apparent not only from the striking results which have been cited for the ortho–para isomers but also in comparisons between compounds such as acetyltryptophan and naphthalenesulfonic acid. Though the former has a higher molecular weight it shows a smaller affinity for albumin, probably because of its polar amine and carbonyl substituents.

In comparing the "denaturing" agents, heat, alkali, urea and urethan, it is apparent that the action of the latter two is to be distinguished from that of the former. Whereas heat and alkali produce a gradual alteration in combining ability of the protein, urea and urethan act very rapidly in displacing the methyl orange anion from its albumin complex. The rate of formation of the urea–protein complex can thus be isolated from the subsequent denaturation processes, as measured by other criteria[12,13,14,15] and is obviously quite rapid. The slow modifications in the properties of the protein are presumably due to a subsequent slow reaction or reactions with some component of the solvent.

Acknowledgments.—These investigations have been carried out with the aid of grants from the Lederle Laboratories and the Office of Naval Research. We are indebted also to Professor George Scatchard of the Massachusetts Institute of Technology and to Professor John T. Edsall of Harvard University for pointing out certain misconceptions in our initial treatment of the quantitative data. The continued interest and suggestions of Professor Edwin J. Cohn are also gratefully acknowledged.

(13) F. G. Hopkins, *Nature*, **126**, 328, 383 (1930).
(14) M. A. Lauffer, THIS JOURNAL, **65**, 1793 (1943).
(15) G. G. Wright and V. Schomaker, *ibid.*, **70**, 356 (1948).

Summary

A mass law analysis has been made for competitive binding of ions by a single protein. In the absence of electrostatic interactions the equations may be reduced to a convenient form for the evaluation of binding constants.

Comparison of the affinities of bovine serum albumin for a series of ortho–para isomers shows that aromatic anions with hydrogen-donating, ortho substituents are bound more strongly than corresponding para compounds. The difference is attributed to stronger interactions with the aqueous solvent in the latter substances. The importance of such interactions with polar substituents is emphasized also in comparisons of dissimilar molecules of approximately equal molecular weights.

The binding ability of bovine albumin is destroyed slowly by heat or by exposure to dilute sodium hydroxide. Urea and urethan are capable of displacing anions from their protein complexes at relatively high concentrations. Both of these substances act within a period of minutes, insofar as displacement effects are involved.

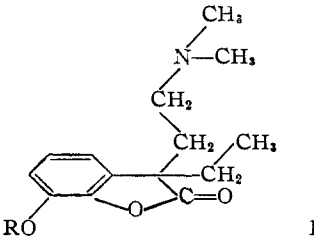
EVANSTON, ILLINOIS RECEIVED MARCH 19, 1948

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

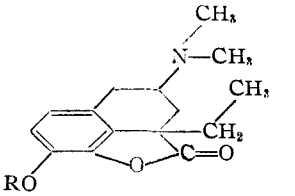
Morphine Studies. 2-Keto-7-methoxy-2,3-dihydrobenzofuran Derivatives[1]

BY E. C. HORNING AND R. U. SCHOCK, JR.[2,3]

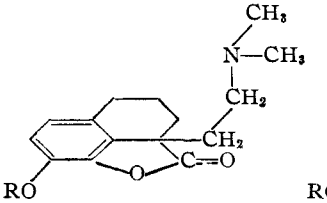
From an examination of the structure of synthetic compounds (Demerol and Amidone series) which possess physiological activity similar to that of morphine (I), it is apparent that some of the functional groups and rings of morphine do not play an important role in providing the type of activity which morphine displays. All have in common a quaternary carbon adjacent to an aromatic nucleus and a tertiary nitrogen in a β-relationship to this carbon, but a phenanthrene system is evidently not necessary. In investigating further the problem of the relation between structure and physiological activity in the morphine series, the synthesis of four model compounds has been planned (II, III, IV, V). Each of these deriva-



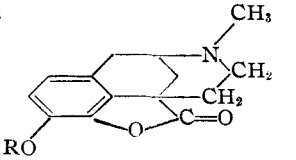
II



III



IV R = H, CH_3 or $COCH_3$



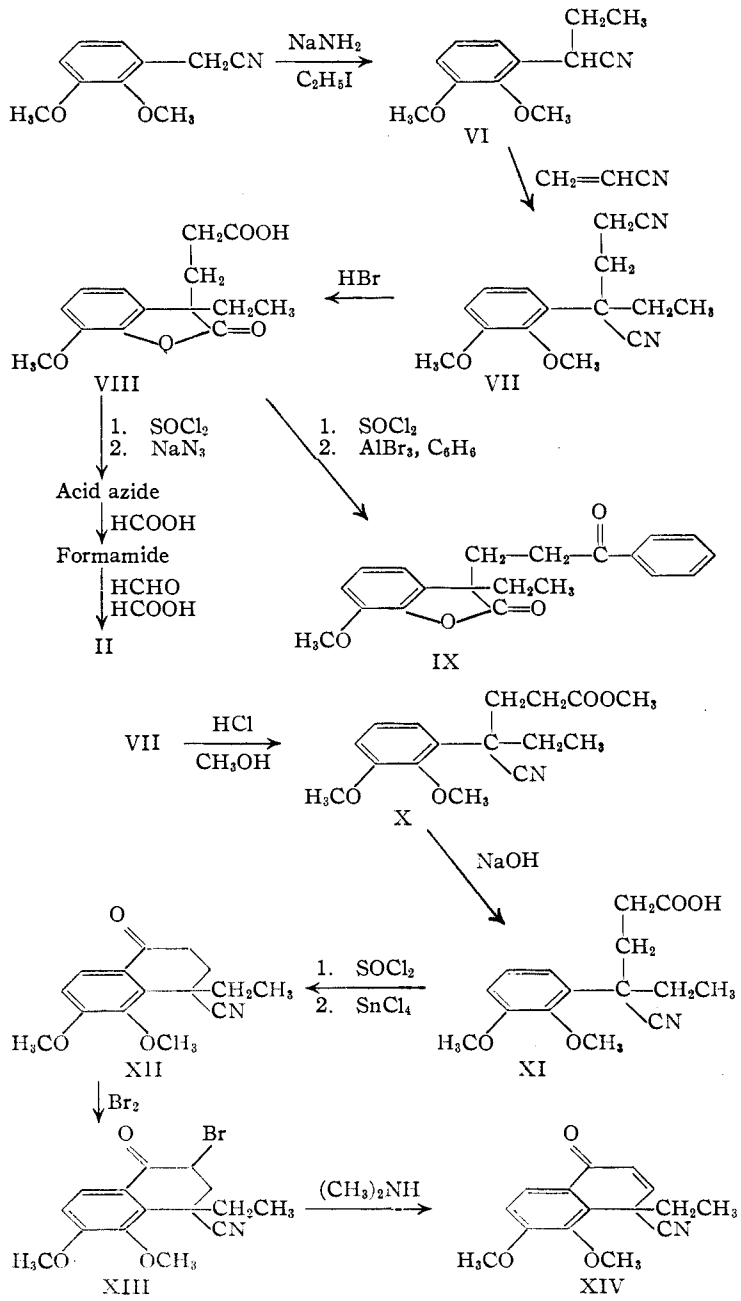
V

(1) Presented before the Division of Organic Chemistry, Second Meeting in Miniature of the Philadelphia Section of the American Chemical Society, Philadelphia, Pa., January 22, 1948.

(2) Abstracted from the thesis of R. U. Schock, Jr., presented to the Faculty of the Graduate School of the University of Pennsylvania in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

(3) Bristol Laboratories Fellow, 1946–1947; National Institute of Health Fellow, 1947–1948.

tives duplicates, in part, what is considered to be essential portions of the morphine molecule and each compound successively approaches more closely to the structure of morphine. This paper reports the synthesis of II, an open-chain analog, and some of the routes explored for the preparation of III, a tetralin analog.



The starting material for these syntheses was 2,3-dimethoxyphenylacetonitrile.[4] Sodamide alkylation of this compound with ethyl iodide served to introduce the ethyl side-chain, and the product (VI) added acrylonitrile to form the dinitrile VII. It was found that by a short reflux period with 48% hydrobromic acid it was possible to demethylate only the *ortho* methoxyl group of VII. At the same time both cyano groups were hydrolyzed and cyclization to the lactone-acid VIII occurred. The carboxyl group was then converted by the Curtius method to a formylated amino group by decomposing the acid azide in the presence of formic acid. This formamide was alkylated with a mixture of formalin and formic acid[5] to yield II as a crystalline solid.

Numerous attempts were made to obtain a tetralin-lactone structure by cyclization of the acid chloride of VIII under the usual conditions for intramolecular acylation. Under mild conditions, in the presence of aluminum chloride, aluminum bromide or stannic chloride, the acid chloride or acid was recovered unchanged. More vigorous conditions usually led to destruction of the compound. With aluminum bromide in benzene as a solvent, the ketone IX was isolated in good yield. The failure of these cyclization experiments is believed to be due to steric limitations imposed by the lactone ring.

Experiments were then directed toward formation of the tetralin system prior to lactonization. The α-bromoketone XIII was prepared without difficulty, but reaction with dimethylamine at room temperature led to the unsaturated ketone XIV in practically quantitative yield.

Further studies are underway on possible routes to tetralin-lactone structures and these results will be reported later.

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

Experimental

All melting points are corrected.

α-(2,3-Dimethoxyphenyl)-butyronitrile (VI).—Sodamide was prepared by the reaction of 12.7 g. (0.55 mole) of sodium and 400 ml. of liquid anhydrous ammonia in the presence of a trace of ferric nitrate.[6] 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 the liquid ammonia. The suspension was stirred for one hour or until the ammonia had evaporated. Then, with vigorous stirring, a mixture of 100 ml. of ethyl iodide and 100 ml. of dry ether was added at such a rate that the heat of reaction maintained

(4) Horning, Horning and Platt, THIS JOURNAL, **69**, 2929 (1947).

(5) The fact that aldehydes, in the presence of formic acid, alkylate certain acylated amines was contributed by E. C. Wagner and Ezra Staple and is, in part, the subject of a doctoral dissertation undertaken by Mr. Staple.

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

the mixture at gentle reflux. After heating under reflux for one hour the mixture was cooled and diluted with 500 ml. of cold water. The layers were then separated and the aqueous phase extracted once with 100 ml. of ether. The combined organic solutions were washed successively with water and 1% acetic acid and dried over magnesium sulfate. The ether and benzene were distilled leaving a residue which was fractionated through a short Vigreux column. There was obtained, after a small forerun consisting principally of unchanged starting material, 86.0 g. (84%) of product boiling at 171–181° (23 mm.). Redistillation gave a sample for analysis as a pale yellow oil boiling at 178–179° (23 mm.); $n^{25}D$ 1.5157.

Anal. Calcd. for $C_{12}H_{15}O_2N$: C, 70.22; H, 7.37. Found: C, 70.31; H, 7.40.

α-Ethyl-α-(2,3-dimethoxyphenyl)-glutaronitrile (VII).—The procedure followed was essentially that of Bruson[7] for the cyanoethylation of phenylacetonitrile. A solution of 30.8 g. (0.15 mole) of the nitrile VI in 40 ml. of *t*-butyl alcohol was heated to 40° and then, with stirring, the dropwise addition of a solution of 16 g. of acrylonitrile in 15 ml. of *t*-butyl alcohol was begun. After the addition of a few drops, 1.0 g. of 30% methyl alcoholic potassium hydroxide was added and the temperature maintained at 40–45° by occasional external cooling. Another gram of catalyst was introduced after half the acrylonitrile was added. When the heat of reaction was no longer evident, 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. Occasionally the mixture contained a small amount of an insoluble solid which was removed by filtration prior to separation of the layers. The combined extracts were washed with water and dried over magnesium sulfate. Distillation of the residue after evaporation of the solvent yielded three fractions: 4–5 g. of a colorless liquid boiling at 80–85° (21 mm.) which was not investigated, 7.6 g. of starting material boiling at 135–145° (4 mm.), and 26.2 g. of product boiling at 193–200° (3 mm.).

Based on unrecovered starting material, the yield was 87%. The pure compound was a pale yellow viscous oil, b. p. 190–191° (2 mm.).

Anal. Calcd. for $C_{15}H_{18}O_2N_2$: C, 69.74; H, 7.02. Found: C, 69.94; H, 6.95.

2-Keto-3-ethyl-3-(β-carboxyethyl)-7-methoxy-2,3-dihydrobenzofuran (VIII).—A solution of 10.8 g. of the dinitrile (VII) in a mixture of 50 ml. of glacial acetic acid and 70 ml. of 48% hydrobromic acid was boiled under reflux for thirty minutes. The hot solution was diluted with water to the cloud point and chilled overnight, yielding 5.6 g. of colorless prisms melting at 132–134°. The filtrate was extracted with four 40-ml. portions of a mixture of benzene and ether (1:3), and the combined extracts were washed with 50 ml. of a saturated sodium bicarbonate solution. Acidification of the bicarbonate extract yielded an oil which crystallized when seeded. The combined yield of crude product was 8.5 g. (78%). Two recrystallizations from dilute ethanol yielded an analytical sample, m. p. 136–137°.

Anal. Calcd. for $C_{14}H_{16}O_5$: C, 63.62; H, 6.10. Found: C, 63.85; H, 6.37.

The rate of demethylation of the methoxyl groups in compound VII is sufficiently different to permit the isolation of the acid VIII in good yield, but the experimental conditions must be adjusted with care. Shorter reaction periods led to lowered yields and recovered dinitrile; longer reaction periods or more vigorous conditions also led to lowered yields, presumably because of further demethylation. The phenol-acid corresponding to the lactone VIII was not isolated.

The **anilide** of the acid VIII was prepared by conversion to the acid chloride with thionyl chloride, followed by reaction with aniline. Recrystallization from dilute ethanol yielded a colorless sample, m. p. 122–123°.

Anal. Calcd. for $C_{20}H_{21}O_4N$: C, 70.78; H, 6.23; N, 4.13. Found: C, 70.75; H, 6.32; N, 3.93.

2-Keto-3-ethyl-3-(β-dimethylaminoethyl)-7-methoxy-2,3-dihydrobenzofuran (II).—To a suspension of 14.2 g. (0.054 mole) of crude VIII in 20 ml. of dry ether, was added 10 ml. of thionyl chloride and one drop of pyridine. After standing for fifteen hours the volatile constituents were removed under reduced pressure at 50° and the residue dissolved in 50 ml. of dry reagent-grade acetone.[8] The acetone solution was then chilled in an ice-bath and, with vigorous stirring, a solution of 4.0 g. (0.060 mole) of sodium azide in 11 ml. of water was added over a period of one minute. After stirring for fifteen minutes, 200 ml. of cold water was added and the crude azide extracted with two 75-ml. portions of benzene. The extract was washed once with 50 ml. of a saturated solution of sodium bicarbonate and then dried for fifteen minutes over magnesium sulfate. The dried solution was concentrated to about 40 ml. The flask was then provided with a reflux condenser and 15 ml. of 98–100% formic acid added cautiously to the hot solution. The rearrangement is accompanied by considerable frothing and evolution of gas and care must be exercised in controlling the reaction. After refluxing for thirty minutes, the benzene and formic acid were removed by distillation and the residue boiled under reflux for 16 hours with 20 ml. each of 35% formalin solution and 90% formic acid. The dark solution was diluted with 100 ml. of 5% hydrochloric acid solution and extracted once with 75 ml. of ethyl acetate; it was then made alkaline by the addition of solid sodium bicarbonate. The alkaline solution was extracted with four 50-ml. portions of ethyl acetate and the residue remaining after evaporation of the solvent evaporatively distilled. There was obtained 6.9 g. of product (48% based on VIII) distilling at 110–115° (0.1 mm.). The product crystallized on standing and was purified by recrystallization from cyclohexane; the melting point was 66–67°.

Anal. Calcd. for $C_{15}H_{21}O_3N$: C, 68.41; H, 8.04. Found: C, 68.43; H, 7.93.

The **picrate**, prepared in the usual fashion, melted at 183–184° after one recrystallization from absolute ethanol.

Anal. Calcd. for $C_{15}H_{21}O_3N \cdot C_6H_3O_7N_3$: C, 51.22; H, 4.91. Found: C, 51.06; H, 4.74.

The **hydrochloride** was prepared by the addition of concentrated hydrochloric acid to a concentrated solution of the amine in ethanol and allowing the precipitated crystals to stand *in vacuo* over potassium hydroxide pellets and concentrated sulfuric acid. The pure salt melted at 216–217° after recrystallization from methyl isobutyl ketone.

Anal. Calcd. for $C_{15}H_{22}O_3NCl$: C, 60.09; H, 7.40; N, 4.67. Found: C, 59.92; H, 7.39; N, 4.59.

Attempts to Cyclize the Acid Chloride of VIII.—Employment of stannic chloride in benzene solution following the usual procedure[9] led to recovery of unchanged acid chloride and some of the original acid. With either aluminum chloride or aluminum bromide in carbon disulfide, the products ranged from intractable resins to starting material depending upon the temperature at which the reaction was run. When the following procedure was employed, using benzene as a solvent, the ketone IX was formed.

A mixture of 3.0 g. of VIII and 6 ml. of thionyl chloride was allowed to stand overnight. The excess thionyl chloride was removed at 50° at the water pump, the last traces being removed by the addition of 2 ml. of dry benzene and again evaporating the solvent. The residue was taken up in 50 ml. of dry thiophene-free benzene and the resultant solution chilled to the freezing point; a solution of 6.6 g. of aluminum bromide in 15 ml. of benzene was then added and the mixture allowed to stand at room tem-

(7) Bruson and Riener, THIS JOURNAL, **65**, 23 (1943).

(8) The so-called "wet method" of preparing azides is that found in "Organic Reactions," Vol. III, 387 (1946).

(9) "Organic Reactions," Vol. II, 1944, p. 138.

perature for forty-five minutes. The dark solution was poured on a mixture of ice and 10 ml. of concentrated hydrochloric acid and, after standing for fifteen minutes, the mixture was steam distilled. The oily residue was separated from the aqueous phase by means of 50 ml. of ether, and the extract washed successively with 5% hydrochloric acid, water, 2% sodium hydroxide solution, 1% acetic acid and finally water; the solution was then dried over magnesium sulfate. Evaporation left 2.5 g. of a pale brown oil which crystallized on standing. Three recrystallizations from methanol yielded colorless diamond-shaped prisms of 2-keto-3-ethyl-3-(β-benzoylethyl)-7-methoxy-2,3-dihydrobenzofuran (IX), m. p. 89–90°.

Anal. Calcd. for $C_{20}H_{20}O_4$: C, 74.05; H, 6.21. Found: C, 74.19; H, 5.95.

The **2,4-dinitrophenylhydrazone** was obtained as an orange powder, m. p. 204–205° (recrystallized from ethyl acetate–ethanol).

Anal. Calcd. for $C_{26}H_{24}O_7N_4$: C, 61.90: H, 4.80. Found: C, 61.79; H, 4.68.

4-Ethyl-4-cyano-5,6-dimethoxytetralone-1 (XII).—The intermediate acid XI necessary for the cyclization was obtained by hydrolysis of the cyanoester X. The dinitrile VII (9.8 g.) was dissolved in 100 ml. of absolute methanol. Dry hydrogen chloride was passed rapidly into the solution for fifteen minutes and the mixture was heated gently under reflux for one hour. Two-thirds of the alcohol was removed by distillation or evaporation, the residue was diluted with water and the nitrile-ester separated with ether. The ether was evaporated leaving a residue of **methyl γ-(2,3-dimethoxyphenyl)-γ-cyanocaproate (X)**. A small sample of the ester was purified for analysis by evaporative distillation at 105–115° (0.06 mm.). It was a pale yellow oil.

Anal. Calcd. for $C_{16}H_{21}O_4N$: C, 65.96; H, 7.27. Found: C, 66.04; H, 7.04.

The ester was saponified by heating under reflux for one hour with a solution of 3.5 g. of sodium hydroxide in 75 ml. of water and 25 ml. of ethanol. Dilution of the cooled solution produced a cloudy appearance which disappeared upon extraction with ether. On acidification with dilute hydrochloric acid, a pale yellow oil precipitated which was separated by two 50-ml. portions of ether. The ether extract was dried and then evaporated, leaving a residue consisting of 9.7 g. (92%) of the acid-nitrile XI as an oil. The product was not purified further, but it was characterized by conversion of a small sample to the *p*-bromophenacyl ester, m. p. 104–105° (from dilute methanol).

Anal. Calcd. for $C_{23}H_{24}O_5NBr$: C, 58.23; H, 5.10. Found: C, 58.31; H, 4.70.

Thionyl chloride (20 ml.) was added cautiously to 9.7 g. of the acid-nitrile XI and the solution allowed to stand overnight. The excess thionyl chloride was removed at 50° at the water pump; 5 ml. of dry benzene was added and the operation repeated. The residue was taken up in 150 ml. of dry thiophene-free benzene and the solution was chilled until the benzene began to crystallize. A solution of 15 ml. of stannic chloride in 15 ml. of benzene was added with shaking and the mixture allowed to stand at room temperature for one hour. The yellow complex was decomposed by pouring upon a mixture of ice, 30 ml. of concentrated hydrochloric acid and 30 ml. of ether. The organic layer was washed successively with 5% hydrochloric acid, water, 5% sodium hydroxide solution and water and dried over magnesium sulfate. Removal of the ether left 8.6 g. of nearly colorless oil which crystallized to a solid melting at 116–118°. The yield of tetralone based on the acid-nitrile was 95%; the over-all yield based on the dinitrile VI was 88%. Recrystallization from cyclohexane yielded colorless prisms melting at 118–118.5°.

Anal. Calcd. for $C_{15}H_{17}O_3N$: C, 69.48; H, 6.61. Found: C, 69.37; H, 6.45.

The 2,4-dinitrophenylhydrazone crystallized from benzene as a dark maroon powder, m. p. 250–251°.

Anal. Calcd. for $C_{21}H_{21}O_6N_5$: C, 57.39; H, 4.82. Found: C, 57.50; H, 4.68.

The procedure for hydrolysis of the dinitrile was developed after direct hydrolysis failed to give satisfactory results.

2-Bromo-4-ethyl-4-cyano-5,6-dimethoxytetralone-1 (XIII).—One gram of the ketone XII was dissolved in 35 ml. of absolute ether. A few drops of a solution of 0.62 g. of bromine in 5 ml. of chloroform was added at room temperature; after decolorization the remainder was added dropwise at 10° slowly enough so that at no time was there an appreciable excess of free bromine. The solution was washed with 5% sodium hyroxide solution and then with water. Drying, followed by evaporation, left 1.30 g. (99%) of a colorless crystalline residue which melted at 141–143°; two recrystallizations from ethanol raised the melting point to 143–144°.

Anal. Calcd. for $C_{15}H_{16}O_3NBr$: C, 53.27; H, 4.77. Found: C, 53.25; H, 4.69.

When brominations were carried out on a larger scale a dibromo derivative was isolated in small quantity by precipitating the monobromo compound from a concentrated benzene solution with petroleum ether, the disubstituted product remaining in solution. It was recrystallized from methanol and melted at 137–138°.

Anal. Calcd. for $C_{15}H_{15}O_3NBr_2$: C, 43.29; H, 3.87. Found: C, 43.53; H, 3.69.

Reaction of XIII with Dimethylamine to Form XIV.—The bromoketone (1.0 g.) was allowed to stand at room temperature in 40 ml. of dry benzene containing 5 equivalents of dimethylamine. After twenty-four hours the solution was washed with two 40-ml. portions of water, once with 40 ml. of 5% hydrochloric acid solution and then with water. Drying over magnesium sulfate followed by evaporation of the solvent left 0.76 g. (100%) of a crystalline residue. This product melted at 132–133° after two recrystallizations from cyclohexane.

Anal. Calcd. for $C_{15}H_{15}O_3N$: C, 70.02; H, 5.88. Found: C, 70.15; H, 5.66.

The **2,4-dinitrophenylhydrazone** was crystallized from benzene and melted at 271° (dec.).

Anal. Calcd. for $C_{21}H_{19}O_6N_5$: C, 57.66; H. 4.38: Found: C, 57.67; H, 4.34.

Summary

The synthesis of 2-keto-3-ethyl-3-(β-dimethylaminoethyl)-7-methoxy-2,3-dihydrobenzofuran is described.

Preliminary experiments directed toward the synthesis of 8-hydroxy-7-methoxy-3-dimethylamino-1-ethyl-1-carboxy-1,2,3,4-tetrahydronaphthalene lactone (III) are also described.

PHILADELPHIA 4, PENNSYLVANIA

RECEIVED MARCH 18, 1948