TABLE V

PRODUCTS OF THE THERMAL DECOMPOSITION OF *cis*-2-STILBENEDIAZONIUM FLUOBORATE IN 0.1 *N* SULFURIC ACID

Diazonium salt Mmoles	Concn. m*M*	Copper	Temp., °C.	Isolation[a] procedure	Phenanthrene,[b] %	Indazole,[c] %	N_2[b] %
0.921	36.8	None	Room	B	13	59	..
.682	6.8	None	45		..	..	36
.813	8.1	None	45		..	..	38
.714[e]	7.1	None	45	A	41	..	38
1.023[e]	10.2	None	35	A	24	..	28
1.290[d,e]	12.9	None	25	A	10	..	21
1.594[e]	15.9	None	25	A	12	..	20
1.592	15	None	Reflux	B	>30	..	71
1.386	14	None	Reflux	B	40	..	75
3.404	68	2 g. Cu	45–50	B	64	..	..
1.553	77	1 g. Cu	25	C	60	11	..
1.242	12.4	None	45	C	31	44	36
0.674	6.7	1 g. Cu	45	C	83	..	..
0.682	6.8	2 g. $CuSO_4$	45	C	30	62	34
1.205	40	None	25	C	15	61	..
0.929	31	1 g. $CuSO_4$	25	C	16	65	..
1.280[f]	43	None	Reflux	C	43	23	..
1.729[f]	17	1 g. $CuSO_4$	Reflux	C	40	20	70

[a] See text. [b] Standard deviation is about 10% relative for N_2 and about 5% relative for phenanthrene by procedure C; procedures A and B are less accurate. [c] Standard deviation 15% relative. [d] *N* sulfuric acid. [e] Kinetic run, Table III. [f] *trans*-2-Hydroxystilbene formed in yields of 20% and 21%, respectively.

variety of procedures. The phenanthrene was identified in each case by its melting point, 97–98°, and in one or two examples by comparison of the ultraviolet and infrared spectra with the spectra of a highly purified sample furnished by Dr. D. D. Phillips. The indazole was identified on the basis of its melting point, 145–146°, its elementary analysis, and the fact that such a product is a reasonable cleavage fragment. The *trans*-2-hydroxystilbene was identified by its melting point, 146–147° (depressed by admixture with the indazole). Infrared spectra were run on purified samples of the indazole and of the hydroxystilbene, and as a check on the chromatographic separation, the infrared curves of the presumed fractions were compared with the above reference curves.

Procedure B.—The reaction mixture was extracted with several portions of ether, the ether evaporated, and the residue chromatographed. The fractions were identified as above.

Procedure C.—A systematic isolation procedure was developed involving continuous ether extraction followed by a chromatographic separation using Grade 4 alumina[10] (100 g. of F-20 alumina[11] with 12 g. of water added) and a benzene–heptane solvent followed by a benzene–methanol elution. The weights of the products were obtained after evaporation of the solvent, and the products were identified as above.

Nitrogen was determined with the apparatus used for the rate experiments[12] at 25°, 35° and 45°, and with a nitrometer apparatus at 100°.

Rate Experiments.—Reaction rates were determined by manometric measurement of the rate of nitrogen evolution.[12]

(10) H. Brockman and H. Schodder, *Ber.*, **74**, 73 (1941).

(11) Chromatographic grade alumina from the Aluminum Ore Company.

(12) D. F. DeTar and M. Turetzky, in preparation.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY, INDIANA UNIVERSITY]

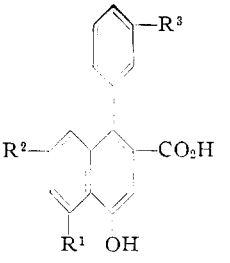
Cyclization Studies in the Syntheses of Monomethoxy-1-phenyl-4-hydroxy-2-naphthoic Acids[1]

BY L. H. KLEMM[2] AND THEODORE LARGMAN

RECEIVED SEPTEMBER 1, 1953

m-Methoxybenzophenone, synthesized by a new procedure, underwent Stobbe condensation to give a mixture of half esters which was cyclized (*via* sodium acetate and acetic anhydride) to two (of the possible three) isolable monomethoxy-1-phenyl-4-hydroxy-2-naphthoic acids, for which tentative structures have been assigned on the basis of chemical and physical properties. The Stobbe product has been hydrolyzed and subsequently reduced to yield two new acids.

1-Phenyl-4-hydroxy-2-naphthoic acid (I) and its derivatives are of interest as possible intermediates in synthetic and structural work on podophyllotoxin and other lignanes,[3] a group of phenolic constituents of some natural resins. Borsche[4] first synthesized I from benzophenone by the successive steps of Stobbe condensation, cyclization by means of sodium acetate and acetic anhydride, and hydrolysis. Only one substituted naphthol was possible as a product in this simplest case. Inasmuch as sodium acetate is a base in either acetic acid or acetic anhydride its function in the



I, $R^1 = R^2 = R^3 = H$
II, $R^1 = OCH_3$, $R^2 = R^3 = H$
III, $R^2 = OCH_3$, $R^1 = R^3 = H$
IV, $R^3 = OCH_3$, $R^1 = R^2 = H$

cyclization, a process readily visualized as occurring *via* acylation of the aromatic ring (normally an acid-catalyzed reaction) and subsequent enolization of the carbonyl group, seemed highly questionable. But typically acidic conditions give cyclization of Stobbe half-esters preponderantly to indones instead of naphthols.[5–7] It may have been for this

(1) Abstracted in part from a dissertation submitted by Theodore Largman to the Faculty of the Graduate School, Indiana University, in partial fulfillment of requirements for the Ph.D. degree, Sept., 1951. Presented at the Buffalo Meeting of the American Chemical Society, March, 1952.

(2) Dept. of Chemistry, University of Oregon, Eugene, Oregon, where inquiries should be directed.

(3) R. D. Haworth, *Ann. Reports*, **33**, 270 (1936); R. D. Haworth, *J. Chem. Soc.*, 448 (1942); J. L. Hartwell, *et al.*, THIS JOURNAL, **72**, 246 (1950); **73**, 2909 (1951); **75**, 1308, 2138 (1953).

(4) W. Borsche, *Ann.*, **526**, 1 (1936).

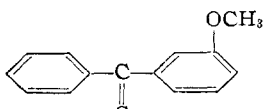
(5) W. S. Johnson and G. H. Daub, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, Chap. 1.

(6) W. S. Johnson and A. Goldman, THIS JOURNAL, **66**, 1030 (1944).

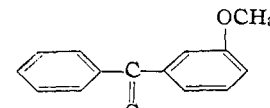
(7) W. S. Johnson and A. Goldman, *ibid.*, **67**, 430 (1945).

reason that Johnson and Goldman[6] referred to the Borsche cyclization as "sodium acetate-catalyzed." Part of the purpose of this investigation was to study further the role played by the sodium acetate in this process.

Our preliminary results using the Stobbe half ester from benzophenone showed that sodium acetate was an unnecessary additive in this case, for essentially the same yield (91%) of I was obtained without sodium acetate as with it (80%) under otherwise nearly identical conditions. In an attempt to ascertain if the presence of sodium acetate would alter the normal rules of orientation into the benzenoid ring we turned to *m*-methoxybenzophenone as the starting material instead of benzophenone, since three isomeric naphthols (II and III from V, IV from VI)[6] should be possible from the Borsche synthesis thereon. Unfortunately repeated attempts to resolve the crude Stobbe product into geometric isomers were unsuccessful. Hence, cyclization studies were made directly on the crude mixture.



V



VI

m-Methoxybenzophenone was prepared in 56% yield by reaction between diphenylcadmium and *m*-methoxybenzoyl chloride. Condensation of this ketone with diethyl succinate followed by cyclization with sodium acetate–acetic anhydride and alkaline hydrolysis of the cyclized product gave a black oily mass from which were isolated two crystalline substances, A ($C_{18}H_{14}O_4$, needles, m.p. 279.5–280°, 15% yield) and B ($C_{18}H_{14}O_4$, needles, m.p. 211–212°, yield 44%), by procedures of fractional neutralization, trituration and crystallization. No other crystalline products were isolable from the residues by our methods.

That A and B were actually structural isomers representing two of the three possible products II, III and IV was established by the following observations: (1) Both products were white and, hence, could hardly be indones. (2) Both gave monoacetates and, therefore, presumably contained hydroxy groups. (3) Both gave negative ferric chloride tests directly[8] but positive tests after decarboxylation by means of copper–quinoline or limited pyrolysis with zinc dust. (4) Each was soluble in 10% aqueous sodium bicarbonate or 10% aqueous sodium hydroxide directly but soluble only in the latter after decarboxylation. (5) Conductometric titration of either A or B showed two definite end-points corresponding to the presence of two weakly acidic groups of differing *pK* values[9] and falling at the expected equivalence points for structures II–IV. (6) Ultraviolet absorption curves (Fig. 1) for A and B show shapes closely similar to one another and to the known compound I.

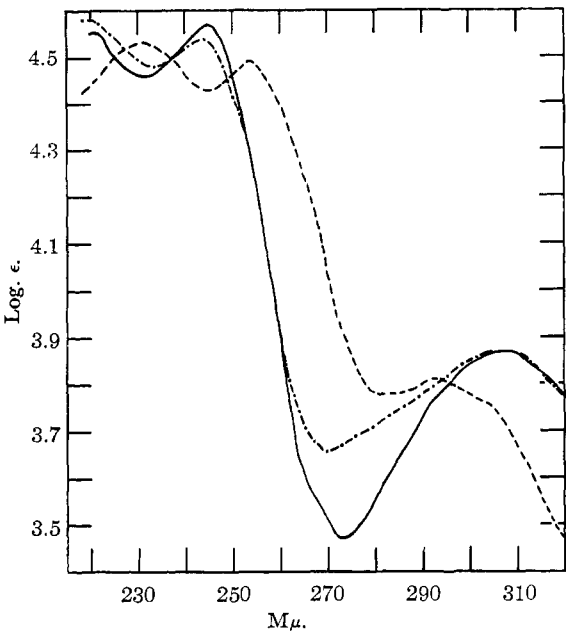


Fig. 1.—Ultraviolet absorption spectra: —, for compound I; - - - -, for conpound A; -·-·-, for compound B.

The very close fit of ultraviolet absorption curves for I and B is striking. The curve for A, however, shows a bathochromic shift ($\Delta\lambda_{max.}$ 10 mμ) in the 240–260 mμ region. In view of the fact that a corresponding shift is observed[10] on the introduction of a methoxy group into the 1-position of naphthalene ($\Delta\lambda_{max.}$ 11 mμ) or into each of the 6- and 7-positions of 1-phenylnaphthalene ($\Delta\lambda_{max.}$ 13 mμ), but not on introduction into the 2′-position (on the phenyl moiety) of 1-phenylnaphthalene ($\Delta\lambda_{max.}$ −1 mμ), it would appear that the methoxy group in B should be located in a position effectively insulated from resonance with the naphthalene nucleus. The juxtaposition (ortho or peri) of the hydroxy and methoxy groups in A (but not in B) is indicated by bathochromic shifts for both the –COH and –COC– absorbencies in the infrared spectrum of the former. Thus B, phenol and α-naphthol show a –COH band at 9.70 μ, while A and guaiacol have a common strong band at 9.77 μ. Also B exhibits –COC– absorption at 8.96 μ, while A shows a band at 9.05 μ and guaiacol at 9.02 μ (normal value 8.90 μ). The presence of an unsubstituted phenyl group in A is indicated by the common band for A and benzene at about 11.75 μ (probably a bending frequency of the phenyl group). The absence of this band in B indicates that a substituted phenyl group is present in this isomer. Consistent with these results are the assignments A ≡ II and B ≡ IV.

The failure to find any evidence for the formation of structure III is surprising though perhaps inconclusive in view of the fact that a total yield of

(8) This is consistent with observations for *m*- and *p*-hydroxybenzoic acids (see A. I. Vogel, "Practical Organic Chemistry," Longmans, Green and Company, New York, N. Y., 1948, p. 927) as well as for I. Salicylic acid, however, gives a positive test.

(9) H. H. Willard, L. L. Merritt and J. A. Dean, "Instrumental Methods of Analysis," second edition, D. Van Nostrand Co., Inc., New York, N. Y., 1951, p. 230.

(10) See R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951, for four of the spectra in question.

only 59% of crystalline products was obtained on cyclization. We hope, in this regard, to be able to find a system more conducive to further studies on orientation.

In other investigations the Stobbe product from *m*-methoxybenzophenone was hydrolyzed to the corresponding alkylidene-succinic acid, m.p. 166–167°, which was subsequently reduced with sodium amalgam in good yield (94%) to an alkylsuccinic acid, m.p. 79–80°.

Experimental[11]

1-Phenyl-4-hydroxy-2-naphthoic Acid (I).—Refluxing a solution of 9 g. of 3-carboethoxy-4,4-diphenyl-3-butenoic acid[12] in 40 ml. of acetic anhydride for 6 hours, removal of the volatile solvent under reduced pressure, and hydrolysis of the residue by means of 100 ml. of 10% aqueous sodium hydroxide gave 7 g. (91%) of I, m.p. 214–216°, undepressed on admixture with the product obtained by the analogous cyclization procedure (sodium acetate in acetic anhydride) of Borsche[4] on the same starting material.

***m*-Methoxybenzophenone.**—The Grignard reagent from 40.7 g. of magnesium, 267 g. of bromobenzene and 2.1 l. of anhydrous ether was cooled a few degrees below room temperature and treated with 166 g. of anhydrous cadmium chloride, added portionwise over a period of 20 minutes. The mixture was stirred and refluxed for 2 hours, whereupon a sample showed a negative Gilman test.[13] A solution of 130 g. of *m*-methoxybenzoyl chloride in 200 ml. of anhydrous ether was added dropwise over a period of 15 minutes. After 14 more hours of stirring and refluxing, the mixture was poured into ice and dilute sulfuric acid. Collection and purification of the product followed previous procedures[14]; yield 90 g. (56%) of *m*-methoxybenzophenone as a pale yellow oil, b.p. 153–155° (1.5 mm.), which partially solidified to cubic crystals, m.p. 37° (reported[15] m.p. 38°).

The 2,4-dinitrophenylhydrazone[16] crystallized from alcohol as orange prisms, m.p. 233–234° dec.

Anal. Calcd. for $C_{20}H_{16}O_5N_4$: N, 14.28. Found: N, 14.12.

Stobbe Reaction of *m*-Methoxybenzophenone and Diethyl Succinate.—Essentially following the sodium hydride method of condensation described for acetophenone,[5] a mixture of 21.2 g. of *m*-methoxybenzophenone, 35 ml. of diethyl succinate and 6 g. of sodium hydride was treated with 0.5 ml. of absolute ethanol. After 1 hour, 100 ml. of anhydrous benzene was added to facilitate stirring, which was continued for an additional 10 hours, whereupon evolution of gas had virtually ceased. Combined ethereal layers from extraction of the acidified product were extracted with 10% aqueous sodium carbonate. The alkaline solution was acidified and extracted with ether. The ethereal layer was dried (Drierite) and evaporated. The residue was placed in an oven at 90° for 30 minutes; yield 26–32 g. of red viscous ethyl half ester.

Stobbe Reaction of *m*-Methoxybenzophenone and Dimethyl Succinate.—The Stobbe reaction was repeated as before except that (a) 35 ml. of dimethyl succinate was used instead of the diethyl ester, (b) warming was required to initiate the reaction, and (c) the reaction time was 27 hours; yield 29 g. of dark red viscous methyl half ester.

The *p*-toluidine derivative was prepared by heating 2 g. of the Stobbe methyl half ester with 4 g. of *p*-toluidine at 160–170° for 2 hours. An ethereal extract of the cooled mixture was washed with excess 6 *N* hydrochloric acid and evaporated. Two crystallizations of the residual oil from ethanol gave needles, m.p. 154.5–155.5°, assigned the structure of 1-(4-tolyl)-3-[phenyl-(3-methoxyphenyl)-methylene]-2,5-pyrrolidinedione (VII).

Anal. Calcd. for $C_{25}H_{21}O_3N$: C, 78.30; H, 5.52; N, 3.65. Found: C, 78.46; H, 5.96; N, 3.99.

Cyclization of Stobbe Ethyl Half Ester.—A mixture of 28 g. of the foregoing Stobbe ethyl half ester (mixed V and VI), 85 ml. of acetic anhydride and 10 g. of fused sodium acetate was stirred and refluxed for 5–6 hours in an atmosphere of dry nitrogen. Volatile materials were removed by gentle warming under reduced pressure. The residue was hydrolyzed by stirring and refluxing with 250 ml. of 10% aqueous sodium hydroxide and 30 ml. of ethanol in an atmosphere of nitrogen for 3 hours. The mixture was boiled for 30 minutes with *ca.* 2 g. of Darco, filtered, cooled and acidified. A solution of the black oily precipitate in dilute sodium hydroxide was treated with Darco as before and passed through a two-inch column of activated alumina and celite (10:1). Fractionation of the product was accomplished preferably by procedure (a) or alternatively by procedure (b).

Procedure (a).—Slow partial neutralization of the filtrate by means of cold concentrated hydrochloric acid gave 2.5 g. of a cream-colored gummy solid, fraction 1, collected by filtration. Crystallization from ethanol of the precipitate obtained from addition of excess acid to the filtrate gave 13 g. of tan solid, fraction 2. Each fraction was crystallized repeatedly from dilute ethanol; combined yields 3.7 g. (15% based on the crude half ester) of compound **A**, presumably II, as needles, m.p. 279.5–280°, and 10.6 g. (44%) of B, presumably IV, as needles, m.p. 211–212°. Both isomers gave negative ferric chloride tests and were soluble in 10% aqueous sodium bicarbonate.

Anal. Calcd. for $C_{18}H_{14}O_4$: C, 73.46; H, 4.79. Found for A: C, 73.66; H, 4.94. Found for B: C, 73.43; H, 4.97.

Procedure (b).—Addition of excess concentrated hydrochloric acid caused precipitation of a brown-black mass which was washed with chloroform to remove most of the color. The residue was fractionally crystallized from dilute ethanol as before.

Structural Investigations on A and B. Acetylation.—The acetates of A and B were prepared according to the method of Vogel.[17] **A-acetate** was obtained as platelets (with a pale yellow tinge) from ethanol, m.p. 228–229°; **B-acetate**, as spherical aggregates from dilute ethanol, m.p. 187–188°.

Anal. Calcd. for $C_{20}H_{16}O_5$: C, 71.43; H, 4.80. Found A-acetate: C, 71.47; H, 4.99. Found B-acetate: C, 71.34; H, 4.99.

Decarboxylation.—A mixture of 1 g. of either A or B, 0.5 g. of copper bronze and 10 ml. of quinoline was heated at 215–230° for 2 hours, cooled, and extracted with ether. The ethereal extract was washed successively with dilute (1:5) hydrochloric acid, 5% aqueous sodium bicarbonate and water and then evaporated. After being heated in alcoholic solution with Nuchar, the residue was evaporatively distilled (1.5 mm.); yield 0.1–0.2 g. of oil which gave a positive ferric chloride test.

Pyrolysis of a mixture of 0.1 g. of either A or B and 0.5 g. of zinc dust covered with 2 more g. of zinc dust[18] produced a light green oil which gave a positive ferric chloride test.

A solution of 1 g. of B in 5 ml. of hydriodic acid (sp. gr. 1.70) and 10 ml. of glacial acetic acid was refluxed 3.5 hours in an atmosphere of nitrogen and evaporated under reduced pressure. The residue was diluted with water and extracted in ether. Removal of the ether produced an oil which gave a positive ferric chloride test and was soluble in 10% aqueous sodium hydroxide but insoluble in 10% aqueous sodium bicarbonate.

Conductometric Titrations.—Conductometric titrations of A and B were performed in a thermostated bath at 27.8° by means of a bright platinum dipping conductivity cell connected to an Industrial Instruments Company conductivity bridge, model RC-1 B, by adding measured volumes of 0.14 *N* sodium hydroxide to a solution of a weighed amount (*ca.* 115 mg.) of A or B in 85 ml. of ethanol and 140 ml. of distilled water.

Anal. Calcd. for $C_{17}H_{12}O(OH)_{\text{phenolic}}(CO_2H)$: neut. equiv., 294 and 147. Found for A: neut. equiv., 298 and 144. Found for B: neut. equiv., 295 and 146.

(11) All melting points were determined by means of an Eimer and Amend melting point apparatus and are uncorrected. Elemental analyses were performed by Mrs. Alma Rosen.

(12) G. H. Daub and W. S. Johnson, THIS JOURNAL, **70**, 418 (1948).

(13) H. Gilman and F. Schulze, *ibid.*, **47**, 2002 (1925).

(14) H. Gilman and J. F. Nelson, *Rec. trav. chim.*, **55**, 518 (1936).

(15) T. R. Lea and R. Robinson, *J. Chem. Soc.*, 2351 (1926).

(16) Prepared according to the procedure of G. D. Johnson, THIS JOURNAL, **73**, 5888 (1951).

(17) See ref. in footnote 8, p. 652.

(18) According to the procedure of F. Kögl, H. Erxleben and L. Jänecke, *Ann.*, **482**, 105 (1930), on thelephoric acid.

Absorption Spectra.—The ultraviolet absorption spectra of A (maxima: λ 231 mμ, log ε 4.54; λ 254, log ε 4.49; λ 294, log ε 3.81), B (maxima: λ 244, log ε 4.54; λ 307, log ε 3.87), I (maxima: λ 244, log ε 4.56; λ 307, log ε 3.85) and 6,7-dimethoxy-1-phenylnaphthalene[19] (maxima: λ 238, log ε 4.80; λ 290, log ε 3.94) were determined in ethanolic solution in the region 218–320 mμ with a Beckman spectrophotometer, model DU. Preliminary infrared absorption spectra were obtained on Nujol mulls of A and B in the range 2–13 μ by means of a Baird Associates infrared spectrophotometer using a sodium chloride prism. Similar Nujol pastes for A, B, benzene, guaiacol, phenol and α-naphthol were run in a Beckman IR-2 Spectrophotometer only in the range 8–13 μ, where significant differentiation between A and B had previously appeared.

Miscellaneous Reactions of Crude Stobbe Product (V and VI). Hydrolysis.—A mixture of 13.7 g. of the crude Stobbe ethyl half ester (mixed V and VI), 70 ml. of ethanol, 100 ml. of water, and 49 g. of barium hydroxide octahydrate was refluxed in an atmosphere of nitrogen for 3 hours. After partial distillation of the mixture, the residue was cooled, acidified with dilute hydrochloric acid and extracted with ether. The residue obtained on evaporation of the ethereal extract crystallized from ethyl acetate–petroleum ether (b.p. 97–120°) to yield 9 g. (72%, assuming the half ester was pure) of **3-carboxy-4-(3-methoxyphenyl)-4-phenyl-3-butenoic acid**, m.p. 148–153°. Repeated fractional acidification of an alkaline solution of the diacid followed by crystallization of the precipitate from the same solvent-pair produced clusters of needles, m.p. 166–167°.

Anal. Calcd. for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Found: C, 69.19; H, 5.28.

(19) W. N. Howell and A. Robertson, *J. Chem. Soc.*, 587 (1936).

The *p*-toluidine derivative, prepared from the crude diacid according to the same procedure as for the Stobbe methyl half ester, formed fine faintly pink needles from ethanol, m.p. 155–156°, undepressed on admixture with the previously obtained *p*-toluidine derivative VII.

Reduction of Stobbe Diacid.—A solution of 12 g. of crude Stobbe diacid in 300 ml. of 2.5% aqueous sodium hydroxide was treated with 320 g. of 4% sodium amalgam, added over a period of 12 hours in an atmosphere of carbon dioxide. After several hours the mixture was filtered and acidified with dilute hydrochloric acid. The precipitate crystallized from water as minute prisms; yield 11.9 g. (94%) of **3-carboxy-4-(3-methoxyphenyl)-4-phenylbutanoic acid monohydrate**, m.p. 79–80° (rapid heating).

Anal. Calcd. for $C_{18}H_{18}O_5 \cdot H_2O$: C, 65.07; H, 6.07. Found: C, 64.97; H, 6.16.

The *p*-toluidine derivative, prepared according to previous directions, formed faintly pink prisms from ethanol, m.p. 175–176°, assigned the structure of 1-(4-tolyl)-3-[phenyl-(3-methoxyphenyl)-methyl]-2,5-pyrrolidinedione.

Anal. Calcd. for $C_{25}H_{23}O_3N$: C, 77.90; H, 6.01; N, 3.63. Found: C, 77.96; H, 6.36; N, 3.86.

Acknowledgments.—We gratefully acknowledge the assistance of Mr. Edward Schulz who determined the infrared spectra and helped in the interpretation thereof, and of the Graduate School of Indiana University for a grant-in-aid to enable one of us (L. H. K.) to initiate work on this project.

EUGENE, OREGON

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

Aldehydes Derived from Cortisone and Hydrocortisone[1]

BY W. J. LEANZA, J. P. CONBERE, E. F. ROGERS AND K. PFISTER 3RD

RECEIVED NOVEMBER 20, 1953

The aldehydes derived from cortisone and hydrocortisone have been synthesized and derivatives prepared therefrom. The syntheses, physical properties and biological activities of these compounds are reported.

As part of a program of systematic variation of the functional groups of cortisone and hydrocortisone, it was desirable to obtain the corresponding 21-aldehydes. These syntheses have been accomplished and details of the preparation of the aldehydes, their derivatives and related compounds form the context of this paper.

Treatment of cortisone (I) with *p*-toluenesulfonyl chloride in pyridine without cooling the reaction mixture yielded a 21-pyridinium salt which could be isolated either as the chloride IV or the tosylate V. Under similar conditions, hydrocortisone (II) yielded only the 21-pyridinium chloride VI. When the reaction with cortisone was carried out with cooling, the 21-chloro analog III could be isolated. Heating III in pyridine converted it to the pyridinium chloride IV.

The nitrones VII and VIII were prepared from the respective pyridinium salts with *p*-nitrosodimethylaniline.[2] Hydrolysis of the respective nitrones to cortisone-21-aldehyde hydrate (IX) and hydrocortisone aldehyde hydrate (X) was accomplished with dilute acid.

(1) Portions of this work were presented in a preliminary communication: E. F. Rogers, W. J. Leanza, J. P. Conbere and K. Pfister 3rd, THIS JOURNAL, **74**, 2947 (1952).

(2) F. Krönke, *Ber.*, **71B**, 2583 (1938).

The ultraviolet absorption spectra of cortisone aldehyde hydrate (IX) (λ_{max}^{MeOH} 238 mμ, E_M 15,700) and hydrocortisone aldehyde hydrate (X) (λ_{max}^{MeOH} 242 mμ, E_M 16,000) closely resemble those of cortisone and hydrocortisone. Anhydrous cortisone aldehyde (XI), obtained by heating the hydrate IX *in vacuo*, was a yellow solid which had an additional band in anhydrous chloroform at 450 mμ (E_M 36). Fleisher and Kendall[3] have shown that steroids with a glyoxal side chain, as well as methyl glyoxal, possess this band. It appears from the molecular weight data that cortisone aldehyde may have partially polymerized during the dehydration. This is in agreement with the suggestion of Reich and Reichstein[4] that Δ⁵-3-hydroxy-20-ketopregnene-21-al exists as a polymer in the anhydrous state.

Chemically the aldehyde hydrates react as typical glyoxals. Positive Schiff and silver mirror tests were observed. They form bisulfite addition products (XII, XIII), acetals (XIV, XV) and diacetates (XVI) in the usual manner. The quinoxalines (XVII, XVIII) are the best derivatives for characterization purposes. They are formed in

(3) G. A. Fleisher and E. C. Kendall, *J. Org. Chem.*, **16**, 573 (1951).

(4) H. Reich and T. Reichstein, *Helv. Chim. Acta*, **22**, 1124 (1939).