[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENTS OF THE UNIVERSITY OF SOUTH CAROLINA, THE UNIVERSITY OF KENTUCKY AND THE UNIVERSITY OF GEORGIA]

Some Pyridylhydantoins[1]

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The following hydantoins have been prepared for testing for anticonvulsant activity: 5-methyl-5-(2-pyridyl), 5-ethyl-5-(2-pyridyl), 5-hexyl-5-(2-pyridyl), 5-methyl-5-(3-pyridyl), 5-ethyl-(3-pyridyl), 5-hexyl-(3-pyridyl) and 5-phenyl-5-(2-picolyl). New ketones prepared as intermediates are hexyl 2-pyridyl ketone and hexyl 3-pyridyl ketone.

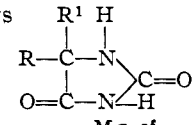
Several hydantoins carrying a pyridyl group at the 5-position have been prepared and are to be tested for anticonvulsant activity.

As intermediates in the hydantoin preparations, the corresponding alkyl pyridyl ketones were synthesized. The alkyl 2-pyridyl and the alkyl 3-pyridyl ketones were prepared by the reaction of the alkyl Grignard reagents with the appropriate pyridyl cyanide. Phenyl 2-picolyl ketone was prepared by the reaction of 2-picolyllithium with benzoic anhydride. No previous report on hexyl 2-pyridyl ketone or hexyl 3-pyridyl ketone could be found.

The ketones were converted to the corresponding hydantoins by reaction with potassium cyanide and ammonium carbonate by the method of Bucherer[4] as modified by Henze and Speer.[5] Of the seven hydantoins reported here, one, 5-ethyl-5-(3-pyridyl)-hydantoin had been reported previously in the patent literature.[6] However, as the hydantoin was prepared by a slightly different method and no yield was given and since it was wanted to complete this series for pharmacological testing, it is included here.

TABLE I

5,5-DISUBSTITUTED HYDANTOINS



R	R¹	M.p., °C.	N, % Calcd.	N, % Found	M.p. of hydrochloride, °C.	Cl, % Calcd.	Cl, % Found	Yield, %
Methyl	2-Pyridyl	164–165	21.99	22.04	213.5–218	15.58	15.50	80
Ethyl	2-Pyridyl	179–180.7	20.48	20.57	220–222	14.68	14.57	68
n-Hexyl	2-Pyridyl	137.5–140	16.10	16.23	196–201	11.92	12.01	81
Methyl	3-Pyridyl	165–170	21.99	21.87	255–260	15.58	15.55	80
Ethyl	3-Pyridyl	160–161	...	[a]	249–250	14.68	14.70	36
n-Hexyl	3-Pyridyl	156–163	16.10	16.60	208–212	11.92	12.01	73
Phenyl	2-Picolyl	195.5–196	15.73	15.90	.....	...	...	73

[a] Calcd. for $C_{10}H_{11}O_2N_3$: C, 58.54; H, 5.40. Found: C, 58.46; H, 5.48.

Experimental[7]

2-Pyridyl Cyanide.—2-Bromopyridine was heated with cuprous cyanide by the method of Craig,[8] b.p. 118–122° at 25 mm.

3-Pyridyl Cyanide.—This compound was prepared by a modification of the method of LaForge[9] from 100 g. of nicotinamide and 100 g. of phosphorus pentoxide; yield 73 g. (85%), b.p. 204–208°, m.p. 50–51°.

All ketones except the phenyl 2-picolyl ketone were obtained by treating the appropriate pyridyl cyanide with a small excess of the corresponding alkyl magnesium halide. The methyl and ethyl ketones were separated from the reaction mixtures by steam distillation and the hexyl ketones by extraction with chloroform. The ketones were identified by the physical properties of their derivatives as given in the references cited below.

Methyl 2-Pyridyl Ketone.—Yield 49%, b.p. 78° at 12 mm.; picrate,[10] m.p. 130–131°; phenylhydrazone,[10] m.p. 155.5–156°.

Ethyl 2-Pyridyl Ketone.—Yield 75%, b.p. 71.8–72.8° at 5 mm., $n^{25}D$ 1.5119; picrate, m.p. 126.5–127.5°; phenylhydrazone,[11] m.p. 139–141°.

Anal. Ketone, Calcd. for C_8H_9ON: N, 10.37. Found: 10.58. Picrate, Calcd. for $C_{14}H_{12}O_8N_4$: N, 15.38. Found: N, 15.40.

***n*-Hexyl 2-Pyridyl Ketone.**—Yield 53%, b.p. 125.8–126.4° at 5 mm., $n^{25}D$ 1.4955; phenylhydrazone (decomposes on standing), m.p. 82–82.5°; picrate, m.p. 85.5–86°.

Anal. Ketone, Calcd. for $C_{12}H_{17}ON$: N, 7.33. Found: N, 7.56. Phenylhydrazone, Calcd. for $C_{18}H_{23}N_3$: N, 14.93. Found: N, 15.27. Picrate, Calcd. for $C_{18}H_{20}O_8N_4$: N, 13.33. Found: N, 13.31.

Methyl 3-Pyridyl Ketone.—Yield 43%, b.p.[9] 219–221° at 760 mm., 92–95° at 8–9 mm., $n^{20}D$ 1.5311; $HgCl_2$ addition compound,[12] m.p. 158–159.5°.

Ethyl 3-Pyridyl Ketone.—Yield 24%, b.p. 205–220°; $HgCl_2$ addition compound,[13] m.p. 129–129.5°.

***n*-Hexyl 3-Pyridyl Ketone.**—Yield 38%, b.p. 148–151° at 7 mm., $n^{25}D$ 1.5029; picrate, m.p. 97.2–97.7°; oxime, m.p. 62–63°; phenylhydrazone, m.p. 117–120°; 2,4-dinitrophenylhydrazone, m.p. 118.5–119°.

Anal. Ketone, Calcd. for $C_{12}H_{17}ON$: N, 7.33. Found: N, 7.51. Picrate, Calcd. for $C_{18}H_{20}O_8N_4$: N, 13.33. Found: N, 13.40. Phenylhydrazone, Calcd. for $C_{18}H_{23}N_3$: N, 14.93. Found: N, 14.95. 2,4-Dinitrophenylhydrazone, Calcd. for $C_{18}H_{21}O_4N_5$: N, 18.86. Found: N, 18.75. Oxime, Calcd. for $C_{12}H_{18}ON_2$: N, 13.58. Found: N, 13.64.

(1) This research was supported in part by a Frederick Gardner Cottrell grant from the Research Corporation to the University of South Carolina.

(2) From the M.S. thesis of Alva Ray Ballentine, University of South Carolina.

(3) From the M.S. thesis of George L. Rushton, University of Kentucky.

(4) H. T. Bucherer and V. A. Lieb, *J. prakt. Chem.*, **141**, 5 (1934).

(5) H. R. Henze and R. J. Speer, THIS JOURNAL, **64**, 522 (1942).

(6) German patent No. 602,218 (September 3, 1934).

(7) All melting points and boiling points are corrected.

(8) L. C. Craig, THIS JOURNAL, **56**, 231 (1934).

(9) F. B. LaForge, *ibid.*, **50**, 2477 (1928).

(10) C. Engler and P. Rosumoff, *Ber.*, **24**, 2527 (1891).

(11) C. Engler and F. W. Bauer, *ibid.*, **24**, 2530 (1891).

(12) Engler and Kiby, *ibid.*, **22**, 597 (1889).

(13) C. Engler, *ibid.*, **24**, 2539 (1891).

Phenyl 2-Picolyl Ketone.—This ketone was prepared from 2-picolyllithium and benzoic anhydride by the method of Kloppenburg and Wibaut.[14] Thirty-five g. of 2-picoline gave 10.6 g. of ketone; yield 14%. The product was a bright yellow solid melting at 60–61.5° which did not darken on standing for over a year. Kloppenburg and Wibaut reported a melting point of 54° and Scheuing and Winterhalder[15] gave a melting point of 59°; picrate,[14] m.p. 179–180°; oxime,[15] m.p. 119°; hydrochloride, m.p. 174–176°.

Anal. Hydrochloride, Calcd. for $C_{13}H_{12}ONCl$: Cl, 15.17. Found: Cl, 14.95.

(14) C. C. Kloppenburg and V. P. Wibaut, *Rec. trav. chim.*, **65**, 393 (1946).

(15) G. Scheuing and L. Winterhalder, *Ann.*, **473**, 126 (1929).

Hydantoins.—The hydantoins were prepared by the reaction of the ketones with KCN and $(NH_4)_2CO_3$. The method of Henze and Speer[5] was modified by extending the time to 48 hours. The reaction mixture was evaporated almost to dryness, made acid, and left overnight to allow HCN to escape. The mixture was made alkaline and extracted with ether, then made exactly neutral and evaporated to dryness. The hydantoin was extracted with alcohol from the large quantity of inorganic salt and recovered by evaporating the alcohol to dryness. The final purification was accomplished by recrystallization from diisobutyl ketone or a similar solvent. The results are summarized in Table I.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF CHAS. PFIZER AND CO., INC.]

Mycomycin. IV. Stereoisomeric 3,5-Diene Fatty Acid Esters[1]

BY WALTER D. CELMER AND I. A. SOLOMONS

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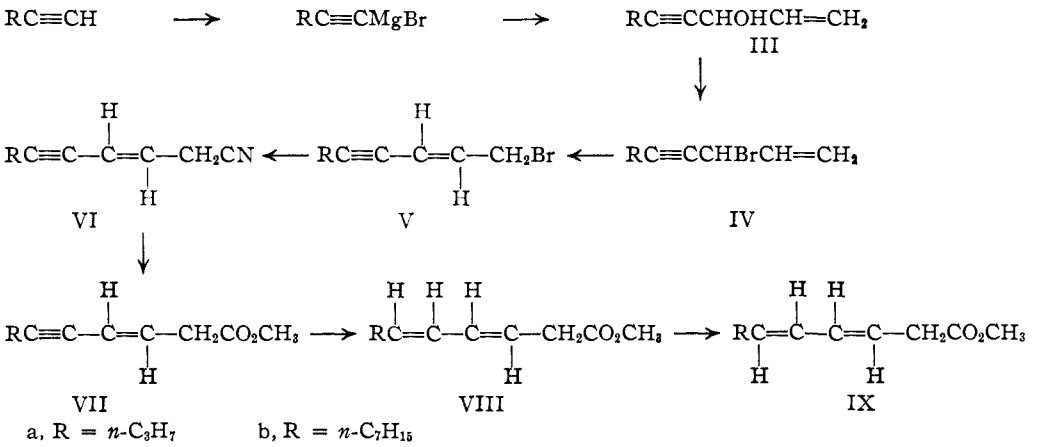
The synthesis of two stereoisomers of methyl 3,5-*n*-tridecadienoate, 3(*trans*),5(*cis*) and 3(*trans*),5(*trans*), through acetylenic intermediates is described. The synthesis is extended to the preparation of methyl 3(*trans*),5(*cis*) and 3(*trans*),5(*trans*)-*n*-nonadienoate. The 3,5-diene esters exhibit characteristic infrared absorption correlated with their stereochemical configuration. Two new examples of facile acetylene–allene isomerizations, noted in the course of this work, are discussed.

The deduced structures of both the antibiotic mycomycin, (−)3,5,7,8-*n*-tridecatetraene-10,12-diynoic acid, HC≡C—C≡C—CH=C=CH—CH=CH—CH=CH—CH_2—CO_2H (I) and its alkali-induced rearrangement product, isomycomycin, 3,5-*n*-tridecadiene-7,9,11-triynoic acid, CH_3—C≡C—C≡C—C≡C—CH=CH—CH=CH—CH_2—CO_2H (II), contain 3,5-diene groupings. With the question of their olefinic configurations remaining, stereoisomeric 3,5-diene fatty acids or their derivatives were sought as model compounds in the hope of facilitating geometric assignments. It is the purpose of this paper to describe, in detail, the synthesis and properties of 3(*trans*),5(*cis*) and 3(*trans*),5(*trans*) stereoisomers of methyl 3,5-*n*-tridecadienoate and methyl 3,5-*n*-nonadienoate. The correlations of the properties of the model diene esters with those of I and II have been discussed in a previous communication.[2] As a result of these studies, I and II were further characterized as possessing *trans,cis* and *trans,trans* stereo configurations, respectively.

The following diagram summarizes the steps used in the synthesis of the model compounds.[3]



The observed light absorption properties of the compounds involved in this synthesis were in agreement with their assigned structures and the linearity of VIIa as well as VIIb was established by reduction to the known saturated esters.

Compounds similar to the key intermediate halide V had been previously prepared by various

(1) Presented in part before the Division of Medicinal Chemistry at the 122nd Meeting of the American Chemical Society, Atlantic City, September 17, 1952, and before the Chemical Society (London) Symposium on Acetylene Chemistry at Burlington House, February 5, 1953.

(2) W. D. Celmer and I. A. Solomons, THIS JOURNAL, **75**, 1372 (1953).

(3) The methyl esters of the desired acids were suitable models because of the availability of the methyl esters of I and II for comparison purposes (especially infrared spectra). The above scheme leads to the synthetic esters in a direct manner not involving the corresponding free acids. The latter were considered less desirable in this present study because of possible uncertainties regarding their homogeneity and were not investigated, *cf.* R. Paul and S. Tchelitcheff, *Compt. rend.*, **224**, 118 (1947); *Bull. soc. chim.* (*France*), 108 (1948).