TABLE I

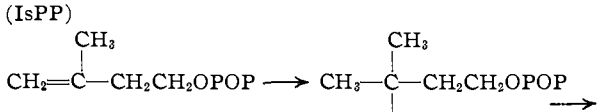
COMPOUNDS DERIVED FROM HYDROLYSATE OF PRODUCT

The fraction of yeast autolysate which was precipitated between 30% and 50% acetone concentration was dissolved and taken at *p*H 4.7 in the presence of added yeast ribonucleic acid.[6] The supernatant solution was taken to *p*H 5.5 with KOH and adsorbed on $Ca_3(PO_4)_2$ gel. The eluate obtained at *p*H 7 contained an isomerase activity of 1–3 μmole/mg. protein/hr. One mg. of enzyme was incubaetd in each of two identical tubes containing 20 μmoles of tris-(hydroxymethyl)-aminomethane buffer, *p*H 8, 6 μmoles of $MgCl_2$, 6 μmoles of MgH_2-ethylenediaminetetraacetate, and 0.4 μmole of IsPP-1-C^{14} (3660 c.p.m.) in a total volume of 0.6 ml. After incubation for one hour at 37°, 0.06 ml. of 70% $HClO_4$ was added to tube 1, followed by sufficient KOH to bring the *p*H to 7. Next, 1.0 μmole each of dimethylallyl alcohol, dimethylvinylcarbinol and isopentenol were added. The mixture was extracted with ether and subjected to gas chromatography. Prostatic phosphatase was incubated with tube 2 which was then extracted and analyzed as was tube 1. The eluted alcohols were counted in a liquid scintillation counter.

Substance	Elution time, minutes	Acid hydrolysis c.p.m.	Enzymatic hydrolysis c.p.m.
Dimethylvinylcarbinol	8–12	1160	76
Isopentenol	24–30	...	...
Dimethylallyl alcohol	38–42	1125	3320

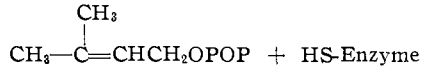
formation of an enzyme-substrate complex

(IsPP)



+ HS-Enzyme

(DmalPP)



Precedent for the sulfide catalyzed migration of an olefinic double bond is found in the Willgerodt reaction, in which a saturated intermediate state also has postulated.[7,8]

(6) O. Warburg and W. Christian, *Biochem. Z.*, **303**, 40 (1939).

(7) M. Carmack and D. L. F. DeTar, THIS JOURNAL, **68**, 2029 (1946).

(8) J. A. King and F. H. McMillan, *ibid.*, **68**, 632 (1946).

(9) National Institute of Neurological Diseases and Blindness, Bethesda, Maryland.

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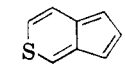
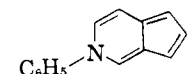
SYNTHESIS OF CYCLOPENTA[c]THIAPYRAN AND 2-PHENYL-2-PYRIDINE[1]

Sir:

The recent report of substituted cyclopenta[b]-pyrans by Boyd[2] and the claims by Mayer[3] concerning cyclopenta[b]thiapyran prompt us to report the synthesis of cyclopenta[c]thiapyran (I) and 2-phenyl-2-pyrindine (II). Both of these molecules represent new heterocyclic structures which are iso-π-electronic with the monalternant aromatic hydrocarbon azulene.

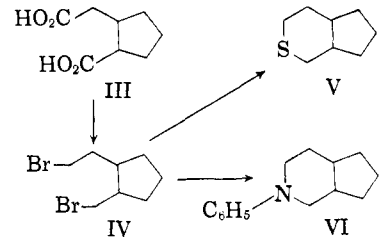


I



II

I and II were prepared as described. Esterification of cyclopropane-1-carboxy-2-acetic acid[4] (III) and reduction of the diethyl ester (or the diacid) with lithium aluminum hydride gave 80–85% of β-(2-hydroxymethylcyclopentanyl)-ethyl alcohol (b.p. 125–129° at 0.6 mm.) which was characterized as the diurethan (colorless plates, m.p. 105–107°, from carbon tetrachloride). Found for $C_{22}H_{26}N_2O_4$: C, 69.36; H, 6.67. Treatment of the diol with phosphorus and bromine afforded 63% of β-(2-bromomethylcyclopentanyl)-ethyl bromide (IV), b.p. 91–93° at 0.7 mm. Found for $C_8H_{14}Br_2$: C, 35.76; H, 5.24; Br, 58.71. Reaction of IV with sodium sulfide produced 64% of octahydrocyclopenta[c]thiapyran (V), b.p. 107–108° at 31 mm. Found for $C_8H_{14}S$: C, 67.74; H, 9.68; mol. wt., 142 (mass spectrograph). Vapor phase dehydrogenation of V over a Pd–C catalyst gave up to 32% of thrice recrystallized (from hexane) I as red plates m.p. 89–90.5°. Found for C_8H_6S: C, 71.89; H, 4.45; mol. wt., 134 (mass spectrograph). The ultraviolet and visible absorption spectra (hexane) resembled those of azulene and showed λ_{max} in mμ (log ε) at 234 (4.15), 249 (4.28), 257 (4.28), 273 (4.34), 283 (4.52), 321 (3.45), 329 (3.38), 344 (3.11), 465 (3.08), 483 (3.04), 500 (2.97), 520 (2.54), 542 (2.54) and 565 (2.26). The basic character of I was shown by its solubility in 30% sulfuric acid and the change in absorption spectra in concentrated sulfuric acid to 208 (4.08), 240 (3.95), 293 (3.48) and 332 (4.18). The compound was degraded slowly by dilute sulfuric acid and glacial acetic acid and was decomposed by alumina. It was stable to alcoholic alkali and to sublimation at 70° and 60 mm.



Reaction of IV with aniline and sodium carbonate afforded 68% of 2-phenylperhydro-2-pyrindine (VI), b.p. 125–127° at 1.3 mm. Found for $C_{14}H_{19}N$: C, 83.51; H, 9.63; N, 7.27; mol. wt. of picrate, 430 (spectroscopic).[5] The structure of VI was shown by nitrosation and subsequent cleavage with base to form the known perhydro-2-pyrindine (m.p. of picrate, 142.5–143.5°).[6] Vapor phase dehydrogenation of VI over a Pd–C catalyst gave up to 25% of thrice recrystallized (fro

(1) Support for a part of this work by contracts DA-04-200-ORD 601 and DA-04-200-ORD 715 with the Office of Ordnance Research, U. S. Army, is gratefully acknowledged.

(2) G. U. Boyd, *J. Chem. Soc.*, 1978 (1958).

(3) R. Mayer, *Naturwiss.*, **13**, 312 (1958); *Angew. Chem.*, **69**, 481 (1957).

(4) R. P. Linstead and E. M. Meade, *J. Chem. Soc.*, 935 (1934).

(5) A. Gillam and E. S. Stern, "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry," Edward Arnold Ltd., London, 1954, p. 253.

(6) V. Prelog and O. Metzler, *Helv. Chim. Acta*, **29**, 1170 (1946).

hexane) II as yellow-orange prisms, m.p. 98.5–100.5°. Found for $C_{14}H_{11}N$: C, 86.92; H, 5.82; N, 7.13. The ultraviolet spectrum of II in hexane showed λ_{max} in mμ (log ε) at 251 (4.34), 274 (4.38) and 286 (4.30). The visible spectrum had a single broad peak with λ_{max} at 432 mμ and log ε 3.30. On hydrogenation over a Rh–C catalyst II took up 4.0 moles of hydrogen readily to form VI (identified by ultraviolet and infrared spectra). A solution of II in concentrated sulfuric acid showed λ_{max} in mμ (log ε) at 220 (4.15), 254 (4.0) and 295 (4.08). The last two maxima also were obtained with a solution in glacial acetic acid. II was degraded slowly by acetic acid and was decomposed by alumina or silica gel. It was stable to alcoholic alkali.

The properties of II suggest that the orange impurity in the 1,5-pyrindine obtained by Robison[7] was 1-pyrindine. Further studies on I, II and related compounds are in progress.

(7) M. M. Robison, THIS JOURNAL, **80**, 6254 (1958).
(8) Standard Oil of California Fellow, summer, 1958.

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RECEIVED JANUARY 21, 1959

16-HYDROXYLATED STEROIDS. XI.[1] THE PREPARATION AND EPIMERIZATION OF 16β-ACETOXY-17α-HYDROXY-CORTICOIDS

Sir:

The important biological and therapeutic properties of triamcinolone (9α-fluoro-11β,16α,17α,21-tetrahydroxy-1,4-pregnadiene-3,20-dione, IX) and related 16α-hydroxy-compounds[2] have created interest in the preparation of the various 16β-hydroxy analogs. This report is concerned with the synthesis and properties of the 16β-acetoxy derivatives of 17α-hydroxy-corticoids.

Treatment of 21-acetoxy-16α,17α-epoxy-4,9(11)-pregnadiene-3,20-dione (I)[3] with sulfuric acid and acetic acid[4] yielded 16β,21-diacetoxy-17α-hydroxy-4,9(11)-pregnadiene-3,20-dione (II), m.p. 173–175°; λ_{max}^{EtOH} 239 mμ (ε 15,700), found C, 67.78; H, 7.56. Addition of the elements of hypobromous acid[5] afforded the amorphous bromohydrin III which was cyclized to 16β,21-diacetoxy-9β,11β-epoxy-17α-hydroxy-4-pregnene-3,20-dione (IV), m.p. 200–202°, λ_{max}^{EtOH} 243–244 mμ (ε 15,200), found C, 65.28; H, 7.28. The latter with hydrogen fluoride gave the fluorohydrin diacetate V, m.p. 239-241.5°, λ_{max}^{EtOH} 239 mμ (ε 16,500), ν_{max}^{KBr} 3540, 3420, 1755, 1738, 1718, 1669, 1627 cm.$^{-1}$, $[\alpha]^{24}D$ + 106° (acetone), found C, 62.66; H, 7.11; F, 4.05. Dehydrogenation of V with selenium dioxide in *t*-butyl alcohol produced 16β,21-diacetoxy-9α-fluoro-11β,17α-dihydroxy-1,4-pregnadiene-3,20-dione (VI), m.p. 233.5–236°, λ_{max}^{EtOH} 238 mμ (ε 13,000), ν_{max}^{KBr} 3490, 3320, 1755, 1733, 1713, 1660, 1620, 1608 cm.$^{-1}$, $[\alpha]^{25}D$ + 76.5° (acetone), found C, 63.13; H, 6.53; F, 3.62.

Saponification of the 9β,11β-oxide diacetate IV with potassium hydroxide in methanol in an inert atmosphere, yielded, most unexpectedly, 9β,11β-epoxy-16α,17α,21-trihydroxy-4-pregnene-3,20-dione (VII)[2a,c] identical in all respects with an authentic sample. Similarly 16β,21-diacetoxy-9α-fluoro-11β,17α-dihydroxy-4-pregnene-3,20-dione (V) was converted into 9α-fluoro-11β,16α,17α,21-tetrahydroxy-4-pregnene-3,20-dione (VIII),[2a,c] and 16β,21-diacetoxy-9α-fluoro-11β,17α-dihydroxy-1,4-pregnadiene-3,20-dione (VI) into triamcinolone (IX).[2a,c]

A further study of this epimerization revealed that treatment of 16β,21-diacetoxy-17α-hydroxy-4-pregnene-3,20-dione (X)[4] with potassium hydroxide, sodium methoxide, sodium carbonate or sodium bicarbonate gave in all cases 16α,17α,21-trihydroxy-4-pregnene-3,20-dione (XI).[6,7] Careful partition chromatography of the product in some of these experiments has revealed the presence of at least two additional products, designated as A and B, isomeric with XI.

Work is in progress to determine the structure of compounds A and B, and to establish a possible mechanism for the epimerization.

Both 9α-fluoro-16β,21-diacetates, V and VI, were inactive in the rat liver glycogen assay at a 500 μg. dose level.[8]

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(2) (a) S. Bernstein, R. H. Lenhard, W. S. Allen, M. Heller, R. Littell, S. M. Stolar, L. I. Feldman and R. H. Blank, *ibid.*, **78**, 5693 (1956); (b) S. Bernstein, M. Heller, R. Littell, S. M. Stolar, R. H. Lenhard and W. S. Allen, *ibid.*, **79**, 4555 (1957); (c) S. Bernstein, *Recent Progress in Hormone Research*, **14**, 1 (1958); (d) R. H. Freyberg, C. A. Berntsen, Jr., and L. Hellman, *Arthritis and Rheumatism*, 1, 215 (1958).
(3) L. B. Barkley, M. W. Farrar, W. S. Knowles and H. Raffelson, THIS JOURNAL, **76**, 5017 (1954); W. S. Allen, S. Bernstein, L. I. Feldman and M. J. Weiss, in preparation for publication.
(4) K. Heusler and A. Wettstein, *Chem. Ber.*, **87**, 1301 (1954).
(5) J. Fried and E. F. Sabo, THIS JOURNAL, **75**, 2273 (1953); **76**, 1455 (1954); **79**, 1130 (1957).
(6) W. S. Allen and S. Bernstein, *ibid.*, **78**, 1909 (1956).
(7) Heusler and Wettstein[4] first reported this reaction and assumed the product to be a D-homo rearrangement compound. We wish to thank Dr. Wettstein for sending us a sample of his compound, the infrared spectrum of which revealed it to be identical to authentic XI. J. Romo and A. R. De Vivar, *J. Org. Chem.*, **21**, 902 (1956), also have assumed the product obtained by treatment of 21-acetoxy-4,16-pregnadiene-3,20-dione with osmium tetroxide and then decomposition of the osmate complex with sodium sulfite in an alcohol medium to be a D-homo product since it was identical to the Heusler–Wettstein compound. Dr. Romo kindly sent us a sample of his product, which proved to be identical to authentic XI.
(8) We are indebted to L. Bortle, E. Heyder, J. Perrine, E. Ross and I. Ringler of the Experimental Therapeutics Research Section for these results.

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RECEIVED JANUARY 24, 1959

ALKALINE REARRANGEMENT OF PHENYL GROUPS LINKED TO SILICON

Sir:

It long has been recognized that strong bases may cause cleavage of phenyl groups attached to silicon,[1] as well as rearrangement of siloxane bonds.[2] Bailey and Pines[3] have reported that sodium ethoxide brings about disproportionation of crotyl-

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(2) M. J. Hunter, J. F. Hyde, E. L. Warrick and H. J. Fletcher, THIS JOURNAL, **68**, 667 (1946).
(3) D. L. Bailey and A. N. Pines, *Ind. Eng. Chem.*, **46**, 2363 (1954).