Preliminary fractionation of the benzene-extractable alkaloids by the excellent procedure of Jacobs and Craig[4] yielded the five known crystalline alkaloids and a large amorphous fraction; only the latter was active as a hypotensive agent at low dosage. Further fractionation of this material guided by assay[3] in hypertensive patients yielded a highly active concentrate, which on 24-plate Craig distribution, using 2 *M* acetate buffer at *p*H 5.5 and benzene as the immiscible phases, exhibited two discrete peaks. The material having a peak at tube 15 ($K = 1.67$) showed activity when administered orally in doses of 0.6–0.8 mg. per patient, while the material from the second peak, at tube 6 ($K = 0.35$), was active at about 4 mg. These fractions crystallized readily from methanol–water and ethanol–water respectively, yielding germidine (m. p. 220–223° (cor.); $[\alpha]^{25}D + 13°$ (*c*, 1.67 in chloroform)) and germitrine (m. p. 197–199° (cor.); $[\alpha]^{25}D + 11°$ (*c*, 1.54 in chloroform)).

Room temperature hydrolysis of germidine with 0.1 *N* aqueous methanolic alkali afforded germine ($C_{27}H_{43}O_8N$),[5] acetic acid and α-methylbutyric acid. The former was identified by rotation, analysis and conversion into monoacetonylgermine hydrochloride.[6] The acids, after conversion into the *p*-phenylphenacyl esters followed by chromatography on alumina, yielded *p*-phenylphenacyl α-methylbutyrate[7] (m. p. 71–72° (cor.)) and *p*-phenylphenacyl acetate[8] (m. p. 109–110° (cor.)). Analysis of the free base and the crystalline thiocyanate (m. p. 242–244° dec. (cor.)) indicates germidine to be an ester of germine with one mole each of the above acids.

Hydrolysis of germitrine yielded germine, α-methylbutyric acid and methyl-ethylglycolic acid. The phenylphenacyl ester of the latter (m. p. 119–120° (cor.); $[\alpha]^{25}D + 5°$ (*c*, 0.64 in chloroform)) was identical with an authentic sample.

Analysis of the free base and the thiocyanate (m. p. 228–231° dec. (cor.)) indicates that germitrine is probably a mono-α-methylbutyrate dimethylethylglycolate of germine.

The specific rotations of the branched-chain acids (isolated from the total amorphous fraction because of an insufficient supply of the crystalline alkaloids) showed these materials to be *l*-α-methylbutyric and *d*-methylethylglycolic acids. Germidine and germitrine, injected intravenously in doses of 0.6–0.8 γ per kg., markedly lowered the blood pressure of anesthetized dogs and cats.[9]

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RECEIVED AUGUST 9, 1949

(4) W. A. Jacobs and L. C. Craig, *J. Biol. Chem*, **160**, 555 (1945).
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(8) N. L. Drake and J. Bronitsky, THIS JOURNAL, **52**, 3715 (1930).
(9) Dr. S. Krop of the Division of Pharmacology will report on these findings elsewhere.

THE BIO-OXYGENATION OF 11-DESOXYCORTICOSTERONE AT C-11[1]

Sir:

A number of chemical processes[2] have been elaborated for introducing an oxygen function at C_{11} in the partial synthesis of adrenal cortical hormones. We wish to report a biochemical process, different from any hitherto described, which leads to the production of corticosterone from 11-desoxycorticosterone.

Using methods previously reported,[3,4] it was found that after perfusing 11-desoxycorticosterone (DOC) through isolated adrenal glands the perfusate contained large amounts of glycogenic activity.[5] The method of assay employed was that of Olson, *et al.*[6] The increased glycogenic activity was observed whether plasma or blood was used as the perfusion medium, and in the absence of adrenocorticotrophic hormone (ACTH). The activity could not be accounted for in terms of DOC recovered from the perfusates. Neither perfusion of the gland in the absence of DOC and ACTH,[4] nor the circulation of DOC in the absence of the gland led to significant activity; nor was it possible to demonstrate a synergistic action of DOC upon the glycogenic steroids present in adrenal extracts (Upjohn).

These observations strongly suggested that the isolated adrenal introduced an 11-oxygen function into desoxycorticosterone. Further work has resulted in the isolation from these perfusates of corticosterone, m. p. 173.3–180° (178–180.5°),[7] $[\alpha]^{30}D + 227°$ (*c*, 0.240, ethanol), as the principal crystalline transformation product. The identity was established conclusively by the melting point, 173–181°, of a mixture with an authentic sample of corticosterone (Upjohn), m. p. 173–179° (176.5–181°), and by the formation of an acetate, m. p. 150.5–152.5°, whose mixture with authentic corticosterone 21-acetate, m. p. 151.5–152.5°, melted at 150.5–152°.

Similar perfusion experiments employing 11-desoxycorticosterone 21-acetate also yielded corticosterone, the ester group apparently being hydrolyzed in the course of the perfusion.

These studies have been extended to a variety of steroids including progesterone, 4-androstene-3,17-dione, 17-hydroxyprogesterone, epi-androsterone, androsterone, 17-hydroxy-11-desoxycorticosterone and 5-pregnen-3-ol-20-one, and the

(1) The work described in this paper was supported by a grant from G. D. Searle and Company.
(2) For a comprehensive review of these processes, see L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," third edition, Reinhold Publishing Corp., New York, N. Y., p. 452, 1949.
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(4) O. Hechter, *Federation Proc.*, **8**, 70 (1949).
(5) O. Hechter and G. Pincus, unpublished observations.
(6) R. E. Olson, *et al.*, *Endocrinology*, **35**, 430 (1944).
(7) All comparison melting points were taken on powdered samples in open Pyrex capillaries. The melting points in parentheses were obtained for intact crystals whether determined in a capillary or on a Fisher–Johns block.

transformation products formed by the gland are being separated and identified.

THE WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY, SHREWSBURY, MASSACHUSETTS, AND THE DEPARTMENT OF PHYSIOLOGY, TUFTS COLLEGE MEDICAL SCHOOL, BOSTON, MASSACHUSETTS
OSCAR HECHTER, ROBERT P. JACOBSEN, ROGER JEANLOZ, HAROLD LEVY, CHARLES W. MARSHALL, GREGORY PINCUS, VICTOR SCHENKER

RECEIVED JULY 29, 1949

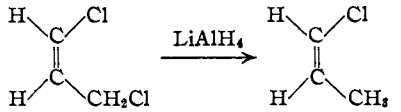
THE CONFIGURATION OF THE 1,3-DICHLOROPROPENES

Sir:

Considerable interest has been shown[1] in the structure of the two isomeric 1,3-dichloropropenes and there has not been complete agreement as to which isomer should be assigned the *cis* configuration and to which the *trans* configuration. This difference of opinion has been caused, in part, by the lack of an unequivocal proof of structure. The configuration of each of the two isomers of 1,3-dichloropropene has now been determined by chemically transforming each isomer into a compound the configuration of which has been established.

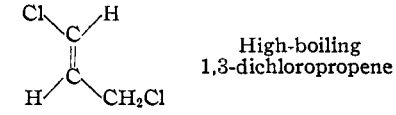
The low boiling isomer of 1,3-dichloropene (b. p. 57.5° (150 mm.), $n^{25}D$ 1.4652, d^{25}_4 1.2048) was refluxed for four hours with sufficient lithium aluminum hydride in isopropyl ether[2] to replace one chlorine atom with a hydrogen atom. By this treatment there was obtained a 50% conversion with a 46% yield of *cis*-1-chloropropene-1 having the following constants: b. p. 32.5° (749 mm.), $n^{20}D$ 1.4054 (lit.[3] b. p. 32.0–32.2° (747 mm.), $n^{20}D$ 1.4053). Similar treatment of the high boiling isomer of 1,3-dichloropropene (b. p. 112.2° (760 mm.), $n^{25}D$ 1.4712, d^{25}_4 1.2139) gave a 56% conversion with a 50% yield of *trans*-1-chloropropene-1, b. p. 37.2° (750 mm.), $n^{20}D$ 1.4048 (lit.[3] b. p. 36.7° (747 mm.), $n^{20}D$ 1.4054). In neither reaction was there any indication of the formation of a mixture of *cis*- and *trans*-1-chloropropene-1.

From these experimental data it follows that the low boiling isomer of 1,3-dichloropropene has the following configuration



Low-boiling 1,3-dichloropropene — *cis*-1-Chloropropene-1

while the high boiling isomer has the remaining configuration



High-boiling 1,3-dichloropropene

This assignment of configuration is in agreement with that proposed by Andrews and Kepner[1b] and not that proposed by Hatch and co-workers.[1a,c]

This method of ascertaining configuration is also being applied to other allylic chlorides which yield compounds of known structure upon replacement of the allylic chlorine atom by a hydrogen atom.

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RECEIVED JULY 16, 1949

PREPARATION OF ADRENAL CORTICAL HORMONES

Sir:

We have made certain observations in the partial synthesis of adrenal cortical hormones which show that it is possible to introduce the 17α-hydroxy group in 11,20-diketo steroids. In addition we have studied the preparation of the dihydroxyacetone side-chain as exemplified by Reichstein's Compounds S and P. Since the reactions appear to be generally applicable, it is possible to prepare adrenal cortical hormones of both the 11-keto series such as Kendall's Compound E and its 11-desoxy analog, Reichstein's Compound S, both of current interest in their medical application.

When the dienol acetate derived from 3α-hydroxypregnane-11,20-dione (m. p. 200–201°; $[\alpha]^{33}D$ +105° (chloroform); $C_{27}H_{38}O_6$, calcd.: C, 70.71; H, 8.35; found: C, 70.80; H, 8.21) is treated with perbenzoic acid according to the procedure of Kritchevsky and Gallagher[1] the reaction product after saponification yielded 3α,17α-dihydroxypregnane-11,20-dione, m. p. 198–201°; $[\alpha]^{32}D$ +66° (acetone). The monoacetate of this compound, m. p. 202–204°, $[\alpha]^{34}D$ +81° (acetone), upon oxidation with chromic anhydride yielded 3α-acetoxyetiocholane-11,17-dione identical in all respects with the known compound. The enol of the 11-keto group therefore either does not react or reacts to such a negligible extent that isolation of the desired product in good yield is easily possible. This establishes the formation of a 17α-hydroxy derivative from a 20-keto steroid with an 11-keto group.

The preparation of the dihydroxy acetone side-chain characteristic of the most active adrenal hormones is illustrated by the reactions leading to the formation of Reichstein's Compounds P and S. Bromination of 3α-acetoxy-17α-hydroxyallopregnan-20-one with one mole of bromine yielded the 21-bromo derivative, m. p. 184–187°; $C_{23}H_{35}O_4Br$, calcd. Br, 17.76; found: Br, 17.47. Hydrolysis

(1) (a) Hatch and Roberts, THIS JOURNAL, **68**, 1196 (1946); (b) Andrews and Kepner, *ibid.*, **69** 2230 (1947); (c) Hatch, Gordon and Russ, *ibid.*, **70**, 1093 (1948); (d) Smith and King, *ibid.*, **70**, 3528 (1948); (e) "Data Sheet" on the 1,3-dichloropropenes published by Shell Chemical Corporation, 8/4/47.

(2) Nystrom and Brown, *ibid.*, **70**, 3738 (1948).

(3) Kharasch, Englemann and Mayo, *J. Org. Chem.*, **2**, 288 (1938).

(1) Kritchevsky and Gallagher, *J. Biol. Chem.*, **179**, 507 (1949).