positive bromine were used, each isomer gave predominantly one product. *trans*-4-Methylcyclohexylmercuric bromide was cleaved with bromine in pyridine in air to yield pure *trans*-4-methylcyclohexyl bromide, b.p. 57.0° (9.5 mm.), m.p. 25.5–26.0°, $n^{29.9}D$ 1.4800, which had a strong characteristic equatorial C–Br infrared band at 704 cm.$^{-1}$. Similarly, *cis*-4-methylcyclohexylmercuric bromide yielded pure *cis*-4-methylcyclohexyl bromide, b.p. 57.0–57.8° (9.5 mm.), $n^{29.9}D$ 1.4843, which had a strong characteristic axial C–Br infrared band at 685 cm.$^{-1}$. The assignment of structure was made on the basis of the known stretching frequencies for equatorial and axial C-Br linkages,[4] and the physical properties of the isomeric bromides. Within the sensitivity of our methods for detecting each isomer (less than 2%), the reactions in pyridine are quantitatively stereospecific.

(4) D. H. R. Barton, J. E. Page, and C. W. Shopee, *J. Chem. Soc.*, 331 (1956).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF CALIFORNIA
BERKELEY 4, CALIFORNIA
FREDERICK R. JENSEN
LAIRD H. GALE

RECEIVED DECEMBER 22, 1958

FLUORINATED STEROIDS. I. THE SYNTHESIS OF 2α-FLUOROHYDROCORTISONE

Sir:

The introduction of fluorine into the 6α-,[1] 9α-[2] and 12α-[3] positions of the hydrocortisone structure has resulted in dramatic increases in the glucocorticoid activity of this hormone.[4] It was, therefore, of considerable interest to prepare and test 2α-fluorohydrocortisone (I). Reaction of the sodium salt of 20-ethylenedioxy-2-methoxalyl-11β,17α,21-trihydroxy-4-pregnen-3,20-dione[5] with perchloryl fluoride[6,7] in methanol, followed by base catalyzed cleavage of the methoxalyl group afforded 20-ethylenedioxy-2α-fluoro-11β,17α,21-trihydroxy-4-pregnen-3,20-dione (II), m.p. 224–226°, $[\alpha]^{25}D$ + 132° (*c*, 0.63 in $CHCl_3$); λ_{max}^{MeOH} 242 mμ (ε, 14,000); λ_{max}^{KBr} 5.87 μ (3-keto-Δ⁴). *Anal.* Found: C, 64.87; H, 8.45; F, 4.43. Hydrolysis with 8% aqueous sulfuric acid in methanol gave I with m.p. 216–220°, $[\alpha]^{25}D$ + 190° (*c*, 0.76 in MeOH); λ_{max}^{MeOH} 241 mμ (ε, 14,800); $\lambda_{max}^{CHCl_3}$ 5.90 μ (3-keto-Δ⁴,20-keto). *Anal.* Found: C, 66.02; H, 7.82; F, 5.00. The α-configuration of the fluorine in I and II is assumed from spectral evidence, on the basis that a fluorine atom at C-2 would have effects on the infrared and ultraviolet absorption spectra similar to those exhibited by chlorine and bromine atoms at this position.[8] The apparent formation of the α-epimer is interesting since, in comparison with bromo, chloro and methyl substituents, the probability of steric interaction of a 2β-fluorine with the angular methyl group at C_{10} is at a minimum and the probability of electrostatic repulsion between a 2α-fluorine and the 3-keto group is at a maximum.[9]

In contrast to the activity of the above-mentioned fluorohydrocortisone derivatives, the activity of I is undistinguished, being approximately one-third that of hydrocortisone as measured by the liver glycogen, thymus involution and asbestos pellet granuloma inhibition tests in adrenalectomized rats.[10] This relatively low activity of I stands in contrast to the high activity of 6α-fluorohydrocortisone[1] and is interesting when one considers the high activity of both the 2α-methyl[11] and 6α-methylhydrocortisone derivatives.[12]

We have prepared other 2-fluoro steroids by this procedure and have studied the utility of perchloryl fluoride for the introduction of fluorine at other sites in the steroid molecule. These results will be published in the near future.

(1) (a) A. Bowers and H. J. Ringold, THIS JOURNAL, **80**, 4423 (1958); (b) J. A. Hogg, *et al.*, *Chemistry and Industry*, 1002 (1958).

(2) J. Fried and E. F. Sabo, THIS JOURNAL, **79**, 1130 (1957).

(3) J. A. Hogg, Sixth Nat. Medicinal Chem. Symposium A. C. S., Madison, Wisconsin, June 23–25, 1958.

(4) 21-Fluoro-21-deoxyhydrocortisone is reported to be approximately one-half as active as cortisone acetate: J. E. Herz, J. Fried, P. Grabowich and E. F. Sabo, THIS JOURNAL, **78**, 4812 (1956).

(5) Australian Patent No. 23,672.

(6) We wish to thank the Pennsalt Chemicals Corporation for a generous sample of this material. Fluorination via the interaction of perchloryl fluoride with active methylene compounds has been reported: see C. E. Inman, E. A. Tyczkowski, R. E. Oesterling and F. L. Scott, *Experientia*, **14**, 355 (1958); C. E. Inman, R. E. Oesterling and E. A. Tyczkowski, THIS JOURNAL, **80**, 6533 (1958).

(7) Recently, Gabbard and Jensen [*J. Org. Chem.*, **23**, 1406 (1958)] reported the synthesis of 2α-fluorocholestanone by the reaction of perchloryl fluoride with cholestan-3-one pyrrolidyl enamine.

(8) (a) R. N. Jones, D. A. Ramsey, F. Herling and K. Dobriner, THIS JOURNAL, **74**, 2828 (1952); (b) B. Ellis and V. Petrow, *J. Chem. Soc.*, 1179 (1956).

(9) See E. J. Corey [THIS JOURNAL, **76**, 175 (1954)] for a discussion of the factors determining the relative stability of epimeric α-bromo ketones in the steroid field.

(10) We wish to thank L. Bortle, E. Heyder, A. Monteforte, E. Ross and I. Ringler of the Experimental Therapeutics Research Section of these Laboratories for these assays.

(11) J. A. Hogg, F. H. Lincoln, R. W. Jackson and W. P. Schneider, THIS JOURNAL, **77**, 6401 (1955).

(12) G. B. Spero, *et al.*, *ibid.*, **78**, 6213 (1956).

ORGANIC CHEMICAL RESEARCH SECTION
LEDERLE LABORATORIES DIVISION
AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK
HENRY M. KISSMAN
ARLENE M. SMALL
MARTIN J. WEISS

RECEIVED JANUARY 19, 1959

ELECTROPHILIC ALIPHATIC SUBSTITUTION. II. RESOLUTION AND STEREOCHEMICAL STUDIES OF *sec*-BUTYLMERCURY COMPOUNDS[1]

Sir:

We wish to report the preparation of optically pure *sec*-butylmercuric bromides, the assignment of configuration to the enantiomorphs, and preliminary results of our stereochemical studies with these isomers.[2,3]

The assignment of configuration and maximum rotation to *sec*-butylmercuric bromide permits a broad investigation of the stereochemistry and stereospecificity of the reactions of *sec*-butylmer-

(1) This research was supported in part by a grant from the Research Corporation.

(2) The resolution of *sec*-butylmercuric bromide recently has been reported in a communication by H. B. Charman, E. D. Hughes and C. K. Ingold, *Chem. and Ind.*, 1517 (1958). The reactions reported by us were mostly completed prior to the submission of the above communication.

(3) Several organomercury compounds containing more than one optical center have been resolved: L. T. Sandborn and C. S. Marvel, THIS JOURNAL, **48**, 1409 (1926); E. Griffith and C. S. Marvel, *ibid.*, **53**, 789 (1931); J. Romeyn and G. F. Wright, *ibid.*, **69**, 697 (1947); A. N. Nesmeyanov, O. A. Reutov and S. S. Poddubnaya, *Izvest. Akad. Nauk S.S.S.R., Otdel Khim. Nauk*, 649 (1953); and O. A. Reutov and Tsin-Chzhu Lu, *Doklady Akad. Nauk S.S.S.R.*, **110**, 575 (1956).

cury compounds. Such investigations are in progress in this laboratory.

Additionally, we have found that the cleavage by mercuric bromide of dialkylmercury compounds, which are free of possible complicating stereochemical features, occurs with retention of configuration. In contrast, the reduction of *sec*-butylmercuric bromide by sodium stannite to yield di-*sec*-butylmercury occurs with racemization of *both* R-groups.

The resolution was accomplished through the *sec*-butylmercuric mandelates. The (−)-*sec*-butylmercuric mandelate was recrystallized to constant optical rotation using dioxane as solvent, and then converted to (−)-*sec*-butylmercuric bromide by reaction with sodium bromide. The rotation of (−)-*sec*-butylmercuric bromide thus obtained is $[\alpha]^{22}D$ −25.8° (*C* 5, ethanol), $[\alpha]^{22}D$ −25.9° (*C* 3, acetone) (lit.[2] $[\alpha]^{20}D$ −24.0° (*C* ~5, acetone)).

The cleavage of active *sec*-butylmercuric bromide by bromine to form 2-bromobutane has been studied under various conditions, and the results are similar to those obtained with the *cis*- and *trans*-4-methylcyclohexylmercuric bromides.[4] Depending upon reaction conditions, active or inactive *sec*-butyl bromide is obtained. In pyridine as the solvent, (+)-*sec*-butylmercuric bromide, $[\alpha]^{22}D$ + 3.76°, was treated with bromine to yield D-(+)-2-bromobutane, $[\alpha]^{22}D$ + 4.15°. Since this reaction has been shown to proceed with retention of configuration,[4] the configurational assignment is D-(+)-*sec*-butylmercuric bromide. The rotation of optically pure D-(+)-2-bromobutane is $[\alpha]^{25}D$ + 28.6°.[5] Assuming the bromine cleavage in pyridine is completely stereospecific, the empirically calculated rotation for optically pure D-(+)-*sec*-butylmercuric bromide is $[\alpha]^{22}D$ − 25.9°, which value is identical with the experimental value reported here. This appears to be the most reliable stereospecific method for making active secondary bromides.[5,6]

Using compounds which have more than one asymmetric center[7] and neighboring methoxy group,[8] the cleavage of dialkylmercury compounds by mercuric halides has been reported to occur, respectively, with racemization and with retention of configuration. With simple aliphatic compounds we have found the reaction occurs with retention of configuration. *sec*-Butylmagnesium bromide was added to (−)-*sec*-butylmercuric bromide, $[\alpha]^{22}D$ − 6.49°, to give (−)-*sec*-butyl-(±)-*sec*-butylmercury, $[\alpha]^{22}D$ − 5.52°. The dialkyl compound with mercuric bromide gave (−)-*sec*-butylmercuric bromide (91%), $[\alpha]^{22}D$ − 3.36°. (The rotation of the final product was approximately one-half that of the starting material.)

The stereochemistry of the reduction of 2-methoxycyclohexylmercuric iodide by sodium stannite to yield di-2-methoxycyclohexylmercury has been studied by Traylor and Winstein.[9] Their suggested mechanism implied that only *one* alkyl group loses its configuration in the course of the reaction. We have found that with *sec*-butylmercuric bromide, *both* of the alkyl groups are predominantly racemized. The product (di-*sec*-butylmercury) is optically stable to the reaction conditions. (+)-*sec*-Butylmercuric bromide, $[\alpha]^{22}D$ + 5.4°, was treated with sodium stannite solution to give (+)-di-*sec*-butylmercury, $[\alpha]^{22}D$ + 0.22°, in 87% yield. Cleavage of this compound with mercuric bromide gave (+)-*sec*-butylmercuric bromide, $[\alpha]^{22}D$ + 0.23°.

(4) F. R. Jensen and L. H. Gale, THIS JOURNAL, **81**, 1261 (1959).

(5) G. K. Helmkamp, C. D. Joel and H. Sharman, *J. Org. Chem.*, **21**, 844 (1956).

(6) J. Kenyon, H. Phillips and V. P. Pittman, *J. Chem. Soc.*, 1072 (1935).

(7) A. N. Nesmeyanov, O. A. Reutov and S. S. Poddubnaya, *Doklady Akad. Nauk S.S.S.R.*, **88**, 479 (1953).

(8) S. Winstein, T. G. Traylor and C. S. Garner, THIS JOURNAL, **77**, 3741 (1955).

(9) T. G. Traylor and S. Winstein, *J. Org. Chem.*, **23**, 1796 (1958).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF CALIFORNIA
BERKELEY 4, CALIFORNIA

FREDERICK R. JENSEN
LORIS D. WHIPPLE
DONALD K. WEDEGAERTNER
JOHN A. LANDGREBE

RECEIVED DECEMBER 22, 1958

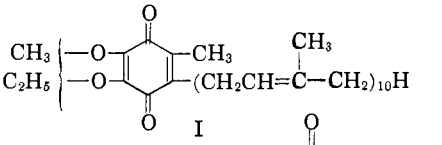
COENZYME Q. VI. ETHOXY HOMOLOGS OF COENZYME Q_{10}. ARTIFACT OF ISOLATION

Sir:

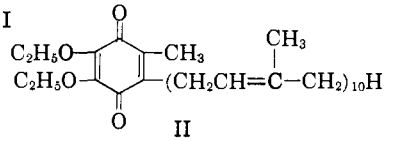
We have characterized ethoxy homologs of coeznyme Q_{10}; an artifact of isolation is evident. Ubiquinone[1,2,3] and these ethoxy homologs are very similar and differ from coenzyme Q_{10}.

Our isolation of coenzyme Q_{10} has been described,[4] and we initially observed no evidence for the presence of related quinones. Continued processing yielded lower melting material. Further purification separated coenzyme Q_{10} from another quinone, m.p. 43–43.5°. *Anal.* Found: C, 82.19; H, 10.34.

Ultraviolet, infrared and nuclear magnetic resonance spectra agree with formula I for this quinone; n.m.r. data were particularly revealing. The n.m.r. spectrum of CH_3CH_2O— was observed as



I



II

two members of the methyl triplet at −144 and −136.5 c.p.s. and three members of the $-CH_2O-$ quartet at −29, −22, and −14.5 c.p.s., the missing members being obscured by the large CH_3- and CH_3O- resonances of the rest of the molecule.

Our isolation included a step using hot ethanolic alkali. It was thought that an alcohol exchange reaction had occurred. When pure coenzyme Q_{10} was subjected to this isolation step in a simulated process, the ethoxy homolog (I) was produced. When methanol was substituted for ethanol in the isolation process, only coenzyme Q_{10} was isolated.

(1) G. N. Festenstein, F. W. Heaton, J. S. Lowe and R. A. Morton, *Biochem. J.*, **59**, 558 (1955).

(2) R. A. Morton, G. M. Wilson, J. S. Lowe and W. M. F. Leat, *Chem. & Ind.*, 1649 (1957).

(3) R. A. Morton, G. M. Wilson, J. S. Lowe and W. M. F. Leat, *Biochem. J.*, **68**, 16P (1958).

(4) B. O. Linn, A. C. Page, Jr., E. L. Wong, P. H. Gale, C. H. Shunk and K. Folkers, THIS JOURNAL, in press.