

alkali fluorescence and the reduction of blue tetrazoleum. When substance I was treated with sulfuric acid at 22° for 2 hr. it exhibited the same spectra as U.S.P. I with λ_{\max} . at 237, 282, 395 and 478 $m\mu$ and O.D. ratios of 0.98:1:0.47:0.55 and II gave the same spectra as cortisone with λ_{\max} . at 284, 343 and 420 and O.D. ratios of 1:0.38:0.31. The concentration of I and II was determined by the quantitative Porter-Silber⁸ test for the dihydroxyacetone side-chain and each gave typical spectra with λ_{\max} . at 410 $m\mu$. Substance I gave $\epsilon_{242} 15.8 \times 10^3$ (MeOH) and II gave $\epsilon_{237} 15.8 \times 10^3$.

The dihydroxyacetone side chain of I and II was oxidatively removed with NaBiO_3 .¹ The ring oxidation products of I and II were inseparable from authentic 11 β -hydroxy- Δ^4 -androstene-3,17-dione and Δ^4 -androstene-3,11,17-trione respectively in both benzene-hexane:methanol:water¹ and heptane:benzene 1:1-formamide, each of which gives excellent resolution from closely related 17-ketosteroids. The yield of both oxidation products was comparable to that obtained from U.S.P. steroids and both gave positive tests for the Δ^4 -3 ketone and 17-keto groups.

Homogeneous II was obtained after a single chromatogram in solvent III, whereas I was resolved further in solvent IV. The recovery of cortisol (I) was 17 $\mu\text{g.}$ and cortisone (II) 37 $\mu\text{g.}/100$ ml. of plasma, with an over-all recovery of ca. 60-70%.

At full sexual maturity Pacific salmon show extensive degeneration of the pituitary and a marked hyperphasia of the adrenal gland, and this has been postulated to play a dominant role in the degenerative changes and death of the fish after spawning.⁹ The high levels of I and II lend support to the suggested high secretory activity of the gland. The plasma levels of I and II at various stages of sexual maturity will be reported elsewhere.

Compounds I and II exhibited infrared spectra identical with cortisol and cortisone, respectively.

Acknowledgment.—We are grateful to Beckman Instruments, Inc., for recording the infrared spectra of the micro size samples.

(8) R. H. Silber and C. C. Porter, *J. Biol. Chem.*, **210**, 923 (1954).

(9) O. H. Robertson, *Science*, **125**, 1295 (1957).

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RECEIVED DECEMBER 27, 1958

**ELECTROPHILIC ALIPHATIC SUBSTITUTION. I.
ELECTROPHILIC SUBSTITUTION STUDIES WITH
cis- AND *trans*-4-METHYLCYCLOHEXYLMERCURIC
BROMIDES¹**

Sir:

We wish to report the synthesis of a pair of simple isomeric organo-mercury compounds, *cis*- and *trans*-4-methylcyclohexylmercuric bromides, which are suitable for studying the stereochemistry of electrophilic substitution at a saturated carbon atom. Furthermore the bromine cleavage of the *cis*- and *trans*-4-methylcyclohexylmercuric bromides

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

has been investigated and the results clearly indicate that this electrophilic reaction proceeds stereospecifically with retention of configuration. This example indicates that the steric course of electrophilic cleavage of organometallic compounds is retention even in the absence of structural features which might alter the course of, or participate in, the reactions.²

A mixture of the isomeric 4-methylcyclohexylmercuric bromides was prepared by treating 4-methylcyclohexylmagnesium bromide with mercuric bromide. The less soluble *trans*-isomer was purified by recrystallization, m.p. 159.1-159.6°. *Anal.* Calcd. for $\text{C}_7\text{H}_{13}\text{HgBr}$: C, 22.26; H, 3.47; Br, 21.16. Found: C, 22.10; H, 3.65; Br, 20.99. The *cis*-isomer was purified by chromatography, m.p. 130.8-131.2°. *Anal.* Found: C, 22.14; H, 3.34.

The tentative assignment of the configurations of the *cis*- and *trans*-4-methylcyclohexylmercuric bromides based on melting points, relative stability, and product distribution from the Grignard reaction, was confirmed by preparing the corresponding *cis*- and *trans*-1-deutero-compounds. The C-D stretching frequencies for equatorial and axial deuterium atoms in cyclohexane systems have been determined previously.³ *trans*-1-Deutero-4-methylcyclohexylmercuric benzoate was prepared from the corresponding 1-deutero-alkylmercuric bromide, m.p. 99.4-99.8°; *Anal.* Calcd. for $\text{C}_{14}\text{H}_{17}\text{DO}_2\text{Hg}$: C, 40.04; H, 4.56; Hg, 47.78. Found: C, 40.12; H, 4.38; Hg, 47.65. The infrared spectrum showed characteristic C-D stretching absorptions at 2127 cm.^{-1} (weak), 2148 cm.^{-1} (strong) and 2168 cm.^{-1} (medium); therefore the deuterium is predominantly axial. *cis*-1-Deutero-4-methylcyclohexylmercuric benzoate was prepared similarly, m.p. 44.2-44.9°; *Anal.* Found: C, 40.48; H, 4.38; Hg, 47.60. The infrared spectrum showed characteristic C-D stretching absorptions at 2141 cm.^{-1} (medium), 2166 cm.^{-1} (strong), and 2191 cm.^{-1} (shoulder); therefore the deuterium is predominantly equatorial. Our results indicate that the benzoymercuri group, as compared to the methyl group, has a relatively small preference for an equatorial over an axial conformation.

The isomeric 4-methylcyclohexylmercuric bromides were cleaved with a variety of brominating agents in several solvents. The competing free radical and polar processes, which were earlier noted in the iodine cleavage of 4-camphylmercuric iodide,^{2c} were encountered here. By varying the reaction conditions, either process could be made to predominate. When either isomeric organo-mercury compound was cleaved by bromine in carbon tetrachloride solution under nitrogen, the free radical cleavage predominated and the product distribution was 47.5% *cis*- and 52.5% *trans*-4-methylcyclohexyl bromides. When more polar solvents, or hypobromous acid and other sources of

(2) For examples using stereochemically complex compounds see (a) A. N. Nesmeyanov, O. A. Rustov, and S. S. Poddubnaya, *Izvest. Akad. Nauk, S.S.S.R. Otdel. Khim. Nauk*, 649 (1953); and (b) S. Winstein, T. G. Traylor and C. S. Garner, *THIS JOURNAL*, **77**, 3741 (1955); (c) S. Winstein and T. G. Traylor, *ibid.*, **78**, 2597 (1956).

(3) E. J. Corey, M. G. Howell and A. Boston, *ibid.*, **78**, 5036 (1956).

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_D^{29} 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_D^{29} 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. Shoppe, *J. Chem. Soc.*, 331 (1956).

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RECEIVED DECEMBER 22, 1958

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

Sir:

The introduction of fluorine into the 6 α -,¹ 9 α -,² and 12 α -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 2 α -fluorohydrocortisone (I). Reaction of the sodium salt of 20-ethylenedioxy-2-methoxalyl-11 β ,17 α ,21-trihydroxy-4-pregnen-3,20-dione⁵ with perchloryl fluoride^{6,7} in methanol, followed by base catalyzed cleavage of the methoxalyl group afforded 20-ethylenedioxy-2 α -fluoro-11 β ,17 α ,21-trihydroxy-4-pregnen-3,20-dione (II), m.p. 224–226°, $[\alpha]_D^{25} + 132^\circ$ (*c*, 0.63 in CHCl_3); $\lambda_{\text{max}}^{\text{MeOH}}$ 242 μ (ϵ , 14,000); $\lambda_{\text{max}}^{\text{KBr}}$ 5.87 μ (3-keto- Δ^4). *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°, $[\alpha]_D^{25} + 190^\circ$ (*c*, 0.76 in MeOH); $\lambda_{\text{max}}^{\text{MeOH}}$ 241 μ (ϵ , 14,800); $\lambda_{\text{max}}^{\text{CHCl}_3}$ 5.90 μ (3-keto- Δ^4 ,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

(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 2 α -fluorocholestanone by the reaction of perchloryl fluoride with cholestan-3-one pyrrolidyl enamine.

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 2 β -fluorine with the angular methyl group at C₁₀ is at a minimum and the probability of electrostatic repulsion between a 2 α -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 6 α -fluorohydrocortisone¹ and is interesting when one considers the high activity of both the 2 α -methyl¹¹ and 6 α -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.

(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).

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RECEIVED JANUARY 19, 1959

ELECTROPHILIC ALIPHATIC SUBSTITUTION. II. RESOLUTION AND STEREOCHEMICAL STUDIES OF *sec*-BUTYLMERCURY COMPOUNDS¹

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).