sospermine derivatives.[6] When dihydrodemethoxygeissospermine ($C_{39}H_{48}N_4O_2$, m.p. 182–184°, from reduction of I with sodium in ammonia) was heated with selenium, alstyrine was formed. On the other hand, decarbomethoxygeissospermine ($C_{38}H_{46}N_4O$, m.p. 254–255°) obtained by treatment of I with methanolic potassium hydroxide, gave, as expected, a desmethylalstyrine which was further degraded to *o*-aminopropiophenone and 4-methyl-5-ethylpicolinic acid (m.p. 156–158°). The latter was identical with a synthetic sample prepared from 2-methyl-5-ethylpyridine-4-carboxaldehyde[7] by Wolff–Kishner reduction, condensation with benzaldehyde, and oxidation to the picolinic acid.

The above evidence definitely establishes the structure of the C_3-substituent as a β-aldehydoester. Its position is fixed at C_{15} by the nature of the various alstyrines produced, and these also establish the remaining skeletal structure of geissoschizine. Confirmation of the indolic N–H and enolic O–H was provided by infrared bands at 2.90 and 3.30 μ, respectively, which were shifted to 3.88 and 4.00 after exchange in deuterium methoxide. Thus structure II is established for geissoschizine.

(6) Preliminary studies showed that similar alstyrines were obtained from I and II. However, greater availability and higher yields of alstyrines made the geissospermine derivatives more suitable. Since geissoschizoline (in common with most indoline alkaloids) fails to yield alstyrines under these conditions, the products obtained must arise from the indolic portion of the geissospermine derivatives.

(7) F. D. Popp and W. E. McEwen, THIS JOURNAL, **80**, 1181 (1958).

(8) National Science Foundation Postdoctoral Fellow, 1958–1959.

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6α-FLUORO-16α-METHYL ANALOGS OF CORTICAL HORMONES

Sir:

Since the initial demonstration in these laboratories[1] of the enhanced adrenal cortical activity of the 2α-methyl analogs of corticoids, we[2] and others[3] have been investigating the effect of methyl substitution elsewhere in the hydrocortisone molecule. We have also shown[4] that the 6α-fluoro group potentiates the biological activity of hydrocortisone.

The present report concerns the synthesis of a series of highly active hydrocortisone analogs containing both the 6α-fluoro and 16α-methyl groups.[5]

16α-Methylprogesterone[6] was converted by microbial fermentation[7] to 11α-hydroxy-16α-methylprogesterone, m.p. 161–163°, $[\alpha]_D$ +149° (chf.) which was oxidized with sodium dichromate to 16α-methyl-11-ketoprogesterone, m.p. 183–185°, $[\alpha]$ +225° (chf.), λ_{max} 238 mμ (15,850). This was subjected to a process involving diglyoxalation, bromination and Faworskii rearrangement with sodium methoxide[8] to give a mixture of methyl 3,11-diketo-16α-methyl-4,17(20)-[*cis*]-pregnadien-21-oate, m.p. 175–176°, $[\alpha]_D$ +165° (chf.), λ_{max} 232.5 mμ (23,750) and methyl 3,11-diketo-16α-methyl-4,17(20)-[*trans*]-pregnadien-21-oate, m.p. 192–195°, $[\alpha]_D$ + 131° (chf.), λ_{max} 232.5 mμ (24,100). The 3-ethylene-ketal of the *trans* ester then was epoxidized with peracetic acid to give methyl 3-ethylenedioxy-5α,6α-oxido-11-keto-16α-methyl-17(20)-[*trans*]-pregnen-21-oate, m.p. 187–191°, $[\alpha]_D$ −63° (chf.), λ_{max} 225 mμ (13,850). On reaction with hydrogen fluoride the oxide was opened and the ketal lost, giving methyl 5α-hydroxy-6β-fluoro-3,11-diketo-16α-methyl-17(20)-[*trans*]-pregnen-21-oate, m.p. 230–234°, $[\alpha]_D$ −6° (chf.), λ_{max} 224 mμ (13,850). Reketalization (at C-3) with ethylene glycol, lithium aluminum hydride reduction and acetylation of the resulting 21-alcohol produced 3-ethylenedioxy-6β-fluoro-16α-methyl-17(20)-[*trans*]-pregnene-5α,11β,21-triol, 21-acetate, m.p. 176–180°, $[\alpha]_D$ −1° (chf.). Oxidation of this material with N-methylmorpholine oxide-peroxide[9] and a catalytic amount of osmium tetroxide gave 3-ethylenedioxy-6β-fluoro-5α,11β,17α,21-tetrahydroxy-16α-methylpregnan-20-one 21-acetate, which was not purified, but was treated with anhydrous hydrogen chloride in chloroform–ethanol to give 6α-fluoro-16α-methylhydrocortisone, 21-acetate (I) m.p. 242–245° (dec.), λ_{max} 237 mμ (14,950). 6α-Fluoro-16α-methylhydrocortisone, m.p. 210–216°, was obtained from this by hydrolysis with potassium bicarbonate in methanol.

Selenium dioxide dehydrogenation of I formed 6α-fluoro-16α-methylprednisolone 21-acetate (II), m.p. 173–176°, resolidifying and melting again at 232–234° (dec.). Application of the well-known series of reactions[10]; dehydration at 11, bromo-

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

(2) G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek and J. A. Hogg, *ibid.*, **78**, 6213 (1956); G. B. Spero, J. L. Thompson, F. H. Lincoln, W. P. Schneider and J. A. Hogg, *ibid.*, **79**, 1515 (1957); G. S. Fonken and J. A. Hogg, *Tetrahedron*, **2**, 365 (1958); J. C. Babcock and J. A. Campbell, THIS JOURNAL, in press.

(3) G. Cooley, B. Ellis, D. N. Kirk and V. Petrow, *J. Chem. Soc.*, 4112 (1957); A. Bowers and H. J. Ringold, THIS JOURNAL, **80**, 3091 (1958); G. E. Arth, D. B. R. Johnston, J. Fried, W. W. Spooncer, D. R. Hoff and L. H. Sarett, *ibid.*, **80**, 3160 (1958); G. E. Arth, J. Fried, D. B. R. Johnston, D. R. Hoff, L. H. Sarett, R. H. Silber, H. S. Stoerk and C. A. Winter, *ibid.*, **80**, 3161 (1958); E. P. Oliveto, R. Rausser, A. L. Nussbaum, W. Gebert, E. B. Hershberg, S. Tolksdorf, M. Eisler and P. L. Perlman, *ibid.*, **80**, 4428 (1958); E. P. Oliveto, R. Rausser, L. Weber, A. L. Nussbaum, W. Gebert, C. T. Coniglio, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman and M. M. Pechet, *ibid.*, **80**, 4431 (1958); D. Taub, R. D. Hoffsommer, H. L. Slates and N. L. Wendler, *ibid.*, **80**, 4435 (1958); E. P. Oliveto, R. Rausser, H. L. Herzog, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman and M. M. Pechet, *ibid.*, **80**, 6687 (1958); J. A. Zderic, H. Carpio and H. J. Ringold, *ibid.*, **81**, 432 (1959); J. Fried, G. E. Arth and L. H. Sarett, *ibid.*, **81**, 1235 (1959); C. H. Robinson, O. Gnoj and E. P. Oliveto, *J. Org. Chem.*, **24**, 121 (1959).

(4) G. B. Spero and J. A. Hogg, U. S. Patent 2,838,497, June 10, 1958; J. A. Hogg, G. B. Spero, J. L. Thompson, B. J. Magerlein, W. P. Schneider, D. H. Peterson, O. K. Sebek, H. C. Murray, J. C. Babcock, R. L. Pederson and J. A. Campbell, *Chem. and Ind.*, 1002 (1958). See also the subsequent reports by A. Bowers and H. J. Ringold, THIS JOURNAL, **80**, 4423 (1958), and J. S. Mills, A. Bowers, C. C. Campillo, C. Djerassi and H. J. Ringold, *ibid.*, **81**, 1264 (1959).

(5) During the preparation of this communication a report appeared by J. A. Edwards, A. Zaffaroni, H. J. Ringold and C. Djerassi, *Proc. Chem. Soc.*, 87 (1959), describing one member of this series.

(6) R. E. Marker and H. M. Crooks, Jr., THIS JOURNAL, **64**, 1280 (1942).

(7) The organism used was *Rhizopus nigricans* (A.T.C.C. 6227b).

(8) J. A. Hogg, P. F. Beal, A. H. Nathan and F. H. Lincoln, U. S. Patent 2,790,814.

(9) W. P. Schneider and A. R. Hanze, U. S. Patent **2,769,821** (Nov, 6, 1956).

(10) J. Fried and E. Sabo, THIS JOURNAL, **76**, 1455 (1954).

hydrin formation, closure to the 9,11β-oxide and opening with hydrogen fluoride gave 6α,9α-difluoro-16α-methylprednisolone 21-acetate (III), m.p. 257–259° (dec.), $\lambda_{max}^{alc.}$ 238 mμ (ϵ 16,500). Satisfactory analyses were obtained for the compounds.

The biological effects of these new hydrocortisone analogs will be reported in detail elsewhere by members of the Upjohn Company Endocrinology Department. As examples of the type of potentiation of activity observed, 6α-fluoro-16α-methylhydrocortisone acetate (I), 6α-fluoro-16α-methylprednisolone acetate (II), and 6α,9α-difluoro-16α-methylprednisolone acetate (III) were, respectively, approximately 40, 160 and 700 times as active as hydrocortisone in the liver glycogen deposition assay.[11]

(11) R. O. Stafford, L. E. Barnes, B. J. Bowman and M. M. Meinzinger, *Proc. Soc. Exp. Biol. Med.*, **89**, 371 (1955). We are indebted to Mr. S. C. Lyster for these assays.

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THE STEREOCHEMISTRY OF ALLOGIBBERIC ACID AND OF GIBBERIC ACID

Sir:

We wish to outline the evidence which permits the assignment of the stereochemistry shown in I and II, respectively, to allogibberic acid and to gibberic acid, two acid rearrangement products of the plant growth hormone gibberellic acid.[1]

(1) The carboxyl group in allogibberic acid (I) must be *cis* to the two carbon bridge of the bicyclo[1,2,3]octane system. This follows from the fact that the diacid (III) obtained from I by Cross, *et al.*,[2,3] on ozonolysis followed by sodium bismuthate cleavage is known to give an anhydride, reconvertible to I on hydrolysis, on treatment with acetic anhydride. We have now shown that the C_6 epimer of III[3] gives the *same anhydride* as III when refluxed with acetic anhydride. This behavior is compatible only with a *cis* relationship of the two acid groups in III[4] and therefore the C_6 carboxyl and the two carbon bridge are *cis* to each other.

(2) The mechanism of the rearrangement of allogibberic acid into gibberic acid (I→II) is such as to require that the two-carbon bridge in gibberic acid have the opposite configuration from that which it occupies in allogibberic acid. This mechanistic consideration is compelling but since the evidence is contradictory[5] we have established this point by demonstrating that the rotatory dispersion curve of II is the mirror image of that of the ketone from the ozonolysis of I.[6]

(1) B. E. Cross, *J. Chem. Soc.*, 4670 (1954).

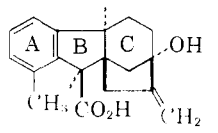
(2) B. E. Cross, J. P. Grove, J. MacMillan and T. P. C. Mulholland *Chem. and Ind.*, 954 (1956).

(3) T. P. C. Mulholland, *J. Chem. Soc.*, 2693 (1958).

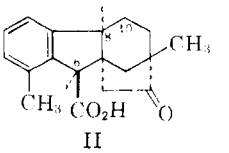
(4) H. H. Cook and R. P. Linstead, *ibid.*, 956 (1934); D. K. Banerjee, and S. K. Das Gupta, THIS JOURNAL, **74**, 1318 (1952).

(5) A. J. Birch, R. W. Rickards and J. H. Smith, *Proc. Chem. Soc.*, 192 (1958).

(6) We wish to thank Professor Djerassi for arranging t have the rotatory dispersion data taken on our compounds. We wish to thank Merck, Sharp and Dohme for a very generous gift of the gibberellic acid used in these studies.



I



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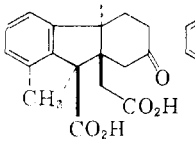
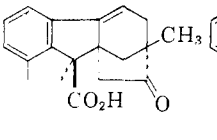
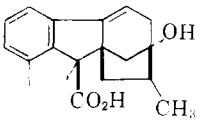


III



IV



V

This "inversion" of the two carbon bridge requires that the B/C junction be *cis* in one member of the gibberic–allogibberic acid pair while *trans* in the other. In view of this, it is illuminating that the catalytic hydrogenation of the $\Delta^{8,10}$ olefins derived from II and from the dihydro-derivative of I (IV and V, respectively)[2] results in the regeneration of the stereochemistry at C_8 present in the parent substance. The catalytic hydrogenation of these bicycloöctene systems has thus produced a *cis* B/C junction in one case and *trans* in the other. Put differently, the reduction has taken place *cis* to the two-carbon bridge in one substance and *trans* in the other. Since reduction *trans* to the two-carbon bridge takes place in only one of the two cases it must be that in which both the carboxyl and the bridge are on the same side of the plane. Since such a *trans* reduction regenerates the original stereochemistry, allogibberic acid must be I.

The structures I and II represent the relative stereochemistry of the four asymmetric centers in these molecules. It also can be shown to represent the *absolute* stereochemistry. The keto acid III, which we now know to have a *trans* B/C fusion, has a rotatory dispersion curve[6] which has the same sign of the Cotton effect as cholestanone or of the related (+)*trans*-8-methylhydrindanone.[7] The absolute stereochemistry of I and II is thus established.

(7) C. Djerassi, D. Marshall and T. Nakano, THIS JOURNAL, **80** 4853 (1958); C. Djerassi, *Record of Chemical Progress*, in press.

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C^{14}-HYBRIDS OF HUMAN HEMOGLOBINS. II. THE IDENTIFICATION OF THE ABERRANT CHAIN IN HUMAN HEMOGLOBIN S

Sir:

Both normal adult human hemoglobin and sickle cell hemoglobin (HbA and HbS) contain two each of two kinds of polypeptide chains.[1] The two α chains have the N-terminal sequence, val-leu, and the β chains the sequence val-his-leu.[2] In HbS, a valyl residue has been substituted in one kind of chain for a glutamyl residue in HbA.[3] We wish to report that substitution is in the β chain.

(1) H. S. Rhinesmith, W. A. Schroeder and L. Pauling, THIS JOURNAL, **79**, 4682 (1957), and unpublished data.

(2) H. S. Rhinesmith, W. A. Schroeder and N. Martin, *ibid.*, **80**, 3358 (1958).

(3) V. M. Ingram, *Nature*, **178**, 792 (1956); **180**, 326 (1957).