(mulled in Nujol) showed the following major bands: no bands in the OH or NH region; 6.35 (S), 6.27 (S), 6.14 (S).

Aspidofiline picrate. The picrate was prepared by treating an ethereal solution of aspidofiline with picric acid in ether; the crystalline picrate was separated and recrystallized several times from acetone, m.p. 146° (capillary, non-corrected).

Anal. Calcd. for $C_{26}H_{25}N_5O_9$: C, 56.62; H, 4.57; N, 12.70. Found: C, 56.83; H, 4.7; N, 12.49.

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Extractives from the Dipterocarpaceae

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The Dipterocarpaceae are an important family of trees which grow in southeast Asia and are characterized by an abundant secretion of resins such as dammar and gurjun which possess economic importance. References to early researches on dammar are given by Glimmann[1] and recently a comprehensive investigation of the constituents of dammar has been carried out by Mills[2,3] who determined the constitution of the neutral triterpenes present. Among those triterpenes was hydroxydammarenone-II first isolated by van Itallie[4] from the balsams of *D. hasseltii* and *D. trinervis*. King[5] *et al.* isolated this compound from three Dipterocarpus woods, "gurjun," "yang," and "keruing" and established the identity of hydroxydammarenone-II with dipterocarpol isolated by Ourisson[6,7] from the balsams of several Dipterocarpus species—*D. Dyeri, D. alatus, D. intricatus* and *D. atrocarpifolius*.

From the acidic fraction of gum dammar we have isolated asiatic acid and will report our findings in a future communication. From two woods of the *Dipterocarpus* species, *D. verrucosis* and *D. grandiflorus* we have isolated dipterocarpol in yields of 0.12% and 0.16% respectively.

(1) W. Glimmann, *Arch. pharm.* **234**, 587 (1896).
(2) J. S. Mills and A. E. A. Werner, *J. Chem. Soc.*, 3132 (1955).
(3) J. S. Mills, *J. Chem. Soc.*, 2196 (1956).
(4) L. van Itallie, *Arch. pharm.*, **250**, 204 (1912).
(5) D. H. Goodson, F. E. King, and T. J. King, *Chem. & Ind. (London)*, 190 (1956).
(6) L. Cosserat, G. Ourisson, and T. Takahashi, *Chem. & Ind., (London)*, 190 (1956).
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EXPERIMENTAL

D. Verrucosis. The wood (4 lb.) in the form of shavings was extracted continuously with light petroleum for 24 hr. The extract was concentrated to give a resin (32.7 g.) which was hydrolyzed for 6 hr. with 10% methanolic potassium hydroxide (300 ml.). The hydrolysis liquor was filtered to remove a small amount of insoluble matter, diluted with much water, and extracted with ether to give a viscous oil (17.1 g.). Chromatographic analysis of the oil on alumina (500 g.) in light petroleum solution followed by elution with petrol (b.p. 60–80°) benzene mixtures, then by benzene gave eluates (2.5 g.) which did not contain triterpenoid material. Elution with benzene-ether, ether, and finally with ether containing methanol gave gums (12.5 g.) which when dissolved in methanol slowly deposited crystalline material, m.p. 118–123°. Repeated recrystallization from light petroleum (b.p. 60–80°) gave dipterocarpol, m.p. 132–134°, $[\alpha]_D^{20}$ +67° ($CHCl_3$; *c*, 1.09); infrared bands at 3500, 1695, 1440, 1370 and 815 cm.$^{-1}$ A mixed melting point with an authentic specimen of dipterocarpol kindly supplied by Dr. T. J. King of Nottingham University showed no depression and the infrared spectra of both specimens were identical.

D. grandiflorus. Wood shavings (4 lb.) of *D. grandiflorus* were extracted as above with light petroleum (b.p. 60–80°) and the extract (33.2 g.) when hydrolyzed with methanolic potassium hydroxide gave a non saponifiable fraction (20.2 g.) which was chromatographed as above. The eluates resulting from elution with benzene-ether and ether yielded gummy material which deposited dipterocarpol from methanol solution. Repeated recrystallization from light petroleum (b.p. 60–80°) gave dipterocarpol (2.9 g.), m.p. 132–134° identical with the material obtained above from *D. verrucosis; oxime*, m.p. 176–178° (Mills[8] gives m.p. 178–179°); *semicarbazone*, m.p. 203–205°. (Ourisson[7] gives m.p. 206–207°).

Dammarendiol-II. Reduction of dipterocarpol, isolated from *D. grandiflorus*, with lithium aluminium hydride followed by chromatography of the product on alumina gave dammarendiol-II, m.p. 130–133°, $[\alpha]_D^{20}$ +33° (*c*, 1.01). Mills[3] gives m.p. 131–133°, $[\alpha]_D^{20}$ +34°.

Acknowledgment. The authors are indebted to the Director of the Chemistry Department, Forest Research Institute, Federation of Malaya, for authentic specimens of the woods which were examined.

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9,11-Dihalosteroids

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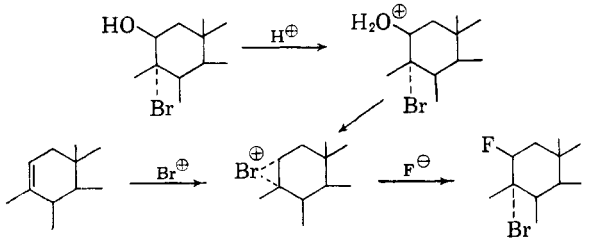
Exploratory experiments directed to the development of a program for the systematic investigation of dihalosteroids, in particular those with fluorine at C-11, were undertaken in these laboratories in 1957. The 11β-fluoro-9α-halosteroids were made either by the use of an *N*-haloamide in anhydrous hydrogen fluoride containing about 30% pyridine or by the reaction of an 11β-hydroxy-9α-bromosteroid with this same solvent pair.

The first of these methods is essentially the same as that reported by Robinson, Finckenor, Oliveto, and Gould[1] and by Bowers[2] and this method is the superior one from a preparative point of view. Both methods are presumed to proceed *via* a 9,11β-bromonium ion intermediate which is converted to the product by the nucleophilic attack of a fluoride ion on C-11.



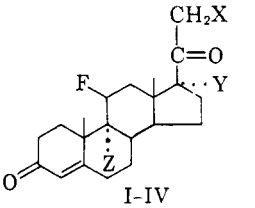
Satisfactory analyses of the dihalosteroids were difficult to obtain and in some cases chromatography followed by several crystallizations was required to obtain a pure sample. The reason for this is illuminated by the reaction of *N*-chlorosuccinimide with 17α,21-dihydroxy-4,9(11)-pregnadiene-3,20-dione 21-acetate in hydrogen fluoride–pyridine. In addition to the expected 9α-chloro-11β-fluoro-17α,21-dihydroxy-4-pregnene-3,20-dione 21-acetate (I) there was obtained a compound $C_{23}H_{29}ClO_5$. It is apparent from the formula that chlorine has been substituted for hydrogen but the location of the chlorine has not been established. In no instance was a similar bromine compound isolated but its existence is suspected.

The reaction of hydrogen fluoride–pyridine with an 11β-hydroxy-9α-halosteroid suggested itself as a possible route to the 9α,11β-difluorosteroids. An attempt to prepare 9α,11β-difluoro-4-pregnene-3,20-dione by this method failed. It would appear that fluorine is too electronegative to enter into onium ion formation.

The oral progestational potency of 9α-bromo-11β-fluoro-4-pregnene-3,20-dione (II), 9α-chloro-11β-fluoro-4-pregnene-3,20-dione (III), and 9α-bromo-11β-fluoro-17α-hydroxy-4-pregnene-3,20-dione 17-acetate (IV) are presented in Table I. In the 11β-fluoroprogesterone series activity is increased by the substitution of chlorine for bromine. This is contrary to the result obtained in the 11β-hydroxyprogesterone series.[3] The substitution of acetoxy for hydrogen at C-17 in progesterone produced the expected enhancement of activity.[4]

TABLE I

ORAL PROGESTATIONAL POTENCY



I-IV

	X	Y	Z	Oral Clauberg Assay[a] (Subcutaneous Progesterone = 1)
I	OAc	OH	Cl	
II	H	H	Br	<1
III	H	H	Cl	1
IV	H	OAc	Br	5

[a] See ref. 5a, b.

EXPERIMENTAL[6]

Hydrogen fluoride–pyridine reagent. When anhydrous hydrogen fluoride was added to pyridine cooled in an ice bath, pyridine hydrofluoride sometimes separated as a white crystalline solid and if the hydrogen fluoride addition were continued, ultimately a fuming, clear solution was obtained. A solution of about 70% hydrogen fluoride–30% pyridine was routinely used. This could be stored in polyethylene bottles at room temperature for many months although it was usually used immediately after preparation.

9α-Chloro-11β-fluoro-17α,21-dihydroxy-4-pregnene-3,20-dione 21-acetate (I). A mixture of 5.77 g. of 17α,21-dihydroxy-4,9(11)-pregnadiene-3,20-dione 21-acetate[7] and 2.00 g. (1 equiv.) of *N*-chlorosuccinimide in a polyethylene bottle was dissolved in 60 ml. of cold hydrogen fluoride–pyridine reagent. The solids dissolved rapidly, producing a very dark solution which was red by transmitted light. The reaction mixture was maintained at +2° for 1 hr. and then it was poured into a glass separatory funnel containing 0.50 l. of ethyl acetate and 0.25 l. of water. The ethyl acetate layer was washed with water and with saturated aqueous sodium bicarbonate solution. After drying with anhydrous sodium sulfate, the solvent was removed by distillation at reduced pressure. The crude product was chromatographed on silica gel. Elution with a 10% ethyl acetate solution in benzene gave a series of fractions which were crystallized from acetone or acetone–petroleum ether. Mixtures of prisms, m.p. *ca.* 210°, and rods, m.p. *ca.* 260°, were obtained from most fractions with the higher melting rod-like forms being concentrated at the end of the series. The crystals were purified by a combination of fractional crystallization and manual separation. After the final crystallization from acetone, the prismatic material weighed 495 mg., m.p. 210–213° dec.,

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(5) (a) C. W. Emmens, *Hormone Assay*, Academic Press, Inc., New York, N.Y., 1950, p. 422. (b) These values were determined by Dr. R. L. Elton, Division of Biological Research, G. D. Searle and Co.

(6) Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Rotations were determined in chloroform at 25 ±2° and at a concentration of about 1%. Ultraviolet spectra were determined in methanol. Petroleum ether was the fraction boiling at 60–71°. Microanalyses, rotations, and spectral data were supplied by the Analytical Department, G. D. Searle and Company.

(7) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **79**, 1130 (1957).

(8) E. L. Bennett, C. W. Gould, E. H. Swift, and C. Niemann, *Anal. Chem.*, **19**, 1035 (1947).

darkening above 198°, λ_{max} 240.5 mμ (16,000), $[\alpha]_D$ + 102°. A qualitative test for fluorine was negative.[8]

Anal. Calcd. for $C_{23}H_{29}ClO_5$: C, 65.65; H, 6.95; Cl, 8.43. Found: C, 65.99; H, 7.14; Cl, 8.38.

A final crystallization of the rod-like crystals from acetone gave 236 mg. of pure 9α-chloro-11β-fluoro-17α,21-dihydroxy-4-pregnene-3,20-dione 21-acetate, m.p. 276–277.5° dec., λ_{max} 238 mμ (17,800), $[\alpha]_D$ +149°. A positive Beilstein test and a positive qualitative fluorine test were obtained.

Anal. Calcd. for $C_{23}H_{30}ClFO_5$: C, 62.65; H, 6.86. Found: C, 62.47; H, 6.65.

9α-Bromo-11β-fluoro-4-pregnene-3,20-dione (II). To a solution of 1.00 g. of 4,9(11)-pregnadiene-3,20-dione[9] in 15 ml. of hydrogen fluoride–pyridine reagent was added 0.66 g. (1.5 equiv.) of *N*-bromoacetamide. After 30 min. at room temperature the reaction mixture was partitioned between 0.20 l. of ethyl acetate and 0.10 l. of water. The organic phase was washed with water and with saturated aqueous sodium bicarbonate solution. After being dried with anhydrous sodium sulfate, the solvent was removed by distillation at reduced pressure. The residue was crystallized from acetone–petroleum ether to give 205 mg. of crude product, m.p. 148–152° dec. Successive crystallizations from acetone and acetone–petroleum ether failed to give a product of constant melting point. The highest melting point was 165.5–172° dec. and the melting point of the analytical sample was 161–165° dec., λ_{max} 240 mμ (15,700). A positive Beilstein test and a positive qualitative fluorine test were obtained.

Anal. Calcd. for $C_{21}H_{28}BrFO_2$: C, 61.31; H, 6.86. Found: C, 59.59; H, 6.41.

An attempt was made to convert II to its bisethylene ketal using ethylene glycol, *p*-toluenesulfonic acid, and benzene in the usual way.[10] Chromatography of the product on silica gel failed to yield any product corresponding to the ketal, but a pure sample, m.p. 159–161° dec., of 9α-bromo-11β-fluoro-4-pregnene-3,20-dione was obtained by crystallization from acetone–petroleum ether of those fractions eluted from the column with 5% and with 10% ethyl acetate in benzene solutions.

Anal. Calcd. for $C_{21}H_{28}BrFO_2$: C, 61.31; H, 6.86. Found: C, 61.22; H, 6.49.

Preparation of 9α-bromo-11β-fluoro-4-pregnene-3,20-dione from 9α-bromo-11β-hydroxy-4-pregnene-3,20-dione. A solution of 0.50 g. of 9α-bromo-11β-hydroxy-4-pregnene-3,20-dione[11] in 10 ml. of hydrogen fluoride–pyridine reagent was kept at room temperature for 2 hr. The reaction mixture was partitioned between 0.10 l. of benzene and 0.10 l. of water. The benzene solution was washed with water and with saturated aqueous sodium bicarbonate solution. After drying with anhydrous sodium sulfate the solvent was removed by distillation at reduced pressure. Crystallization from acetone–petroleum ether and from benzene–petroleum ether gave 38 mg. of 9α-bromo-11β-fluoro-4-pregnene-3,20-dione, identical in melting point and infrared spectrum with II prepared from 4,9(11)-pregnadiene-3,20-dione. Admixture of the two samples did not depress the melting point.

9α-Chloro-11β-fluoro-4-pregnene-3,20-dione (III). Cold hydrogen fluoride–pyridine reagent (10 ml.) was added to a mixture of 1.00 g. of 4,9(11)-pregnadiene-3,20-dione and 426 mg. (1 equiv.) of *N*-chlorosuccinimide. After 1 hr. at 3° the crude product was isolated as described under the preparation of II. The crude product was triturated with ether and there was obtained 230 mg. of crystals, m.p. 135–165°. Repeated crystallization from ether–petroleum ether and from acetone–petroleum ether gave 60 mg. of pure 9α-chloro-11β-fluoro-4-pregnene-3,20-dione, m.p. 179–180°, λ_{max} 238 mμ (17,200). The analytical sample gave a positive Beilstein test and a positive qualitative fluorine test.

Anal. Calcd. for $C_{21}H_{28}ClFO_2$: C, 68.74; H, 7.69. Found: C, 68.77; H, 7.66.

9α-Bromo-11β-fluoro-17α-hydroxy-4-pregnene-3,20-dione 17-acetate (IV). A mixture of 336 mg. of 17α-hydroxy-4,9(11)-pregnadiene-3,20-dione 17-acetate[12] and 126 mg. (1 equiv.) of *N*-bromoacetamide was treated with 4 ml. of cold hydrogen fluoride–pyridine reagent. After 1 hr. at 2° the crude product was isolated as described under the preparation of II. Trituration with ether gave a first crop of crystals, 163 mg., m.p. 190–193° dec. and a second crop, 67 mg., m.p. 185–187° dec. The crops were combined and the mixture was crystallized from ether and from acetone–petroleum ether. The yield of pure 9α-bromo-11β-fluoro-17α-hydroxy-4-pregnene-3,20-dione 17-acetate was 95 mg. The melting point was variable, being 185–188° dec. and 193–196° dec., λ_{max} 240 mμ (17,100), $[\alpha]_D$ +85°. The analytical sample gave a positive Beilstein test and a positive qualitative test for fluorine.

Anal. Calcd. for $C_{23}H_{30}BrFO_4$: C, 58.85; H, 6.44. Found: C, 58.68; H, 6.31.

The attempted preparation of 9α,11β-difluoro-4-pregnene-3,20-dione. A solution of 100 mg. of 9α-fluoro-11β-hydroxy-4-pregnene-3,20-dione[11] in 10 ml. of hydrogen fluoride-pyridine reagent (77% hydrogen fluoride) was kept at room temperature overnight. The course of the reaction was followed by removing 2-ml. samples at 0.5, 1, 2, 4, and 18 hr. The samples were partitioned between ethyl acetate and water. The organic phase was washed with water, saturated aqueous sodium bicarbonate solution, and with water. After drying over anhydrous sodium sulfate the solvent was evaporated and the residue from each sample was submitted to infrared analysis. All of the samples gave a crystalline residue and all of the infrared spectra were identical with the spectrum of 9α-fluoro-11β-hydroxy-4-pregnene-3,20-dione.

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N-Acylation of 2-Amino-2-deoxy-D-glucose with Mixed Carboxylic Acid Anhydrides

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The acylation of amino compounds such as hydroxylamine,[1] substituted amino acids,[2] and amino acids[3] with mixed carboxylic acid anhydrides has been reported by several authors, and the

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