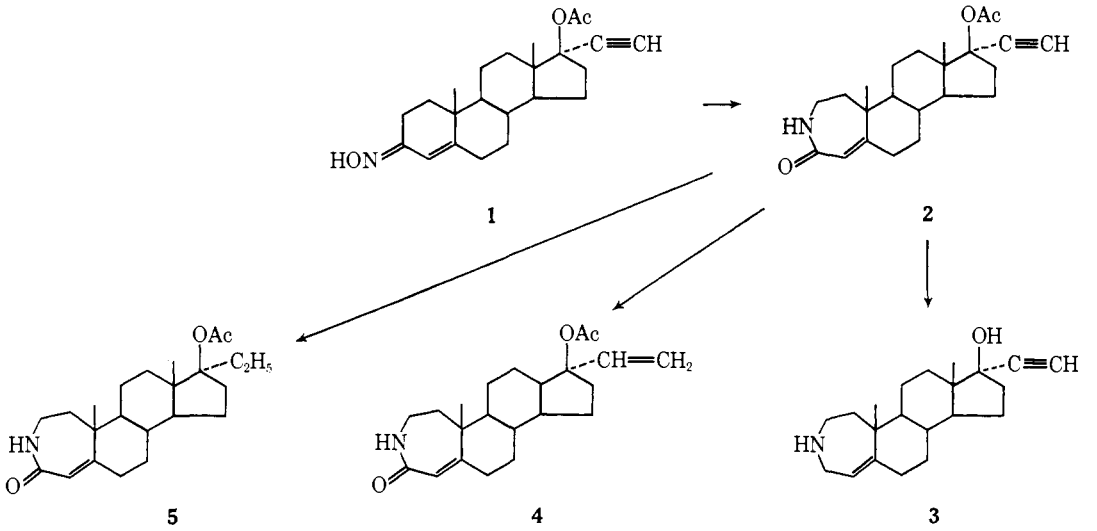
SCHEME I



syn isomer (lower streak) was found to be 30% and the *anti* isomer was 70%.

3-Aza-17α-ethynyl-17β-acetoxy-A-homoandrost-4a-en-4-one (2).—To a solution containing 17.6 g of 1 in 500 ml of purified dioxane there was added 10 ml of $SOCl_2$. The mixture was stirred at room temperature for 1.5 hr and poured into a large amount of water. The excess acid was neutralized with $NaHCO_3$ and the solution was extracted (CH_2Cl_2). The organic layer was washed (H_2O), dried (Na_2SO_4), and filtered. The filtrate was stirred for 3 hr with 150 g of IR-45 Amberlite (Rohm and Hass) and filtered. The filtrate was evaporated to give a semisolid which could be recrystallized from C_6H_6–C_6H_{14} (1:3) to give 4.4 g (83% based on *syn* isomer) of **2**: mp 245–247°; $[\alpha]D$ −41.1°; $\lambda_{max}^{CHCl_3}$ 2.9, 3.0, 5.73, and 6.05 μ; λ_{max}^{EtOH} 220 mμ; pmr ($CDCl_3$), 0.9 (C-18), 1.17 (C-19), 2.03 (C-17, OAc), 2.58 (C-17, C≡CH), and 5.72 ppm (C-4a). *Anal.* ($C_{23}H_{31}NO_3$) C, H, N.

3-Aza-17α-ethynyl-A-homoandrost-4a-en-17β-ol (3).—To a solution of 3.5 g of **2** in 150 ml of THF there was added over a period of 1 hr 7.0 g of $LiAlH_4$. The mixture was refluxed for 26 hr with continuous stirring. The excess $LiAlH_4$ was decomposed with Et_2O saturated with H_2O followed by H_2O. The mixture was filtered and the inorganic hydroxides were washed with EtOAc. The filtrates were combined, washed (H_2O), dried (Na_2SO_4), and evaporated. The solid residue was warmed with alcoholic KOH and poured into a large amount of H_2O. The solid thus separated was collected by filtration and recrystallized from EtOAc to give 1.4 g (40%) of **3**: mp 206–208°; $[\alpha]D$ −41°; $\lambda_{max}^{CHCl_3}$ 2.78 and 3.01 μ, no uv absorption between 200 and 360 mμ; pmr ($CDCl_3$), 0.87 (C-18), 1.1 (C-19), 2.55 (C-17, C≡CH), and 5.41 ppm (C-4a). *Anal.* ($C_{21}H_{31}NO$) C, H, N.

3-Aza-17α-vinyl-17β-acetoxy-A-homoandrost-4a-en-4-one (4).—One gram of **2** was dissolved in 10 ml of pyridine and treated with 200 mg of 5% Pd–C. The mixture was hydrogenated at room temperature and atmospheric pressure until 1 mole of H_2 was consumed. It was filtered and the filtrate was poured over a large amount of ice and H_2O. The solid thus separated was collected by filtration and recrystallized from EtOAc to give 1.0 g (99%) of **4**: mp 238–240°; $[\alpha]D$ +8.7; $\lambda_{max}^{CHCl_3}$ 2.90, 5.75, and 6.05 μ; λ_{max}^{EtOH} 220 mμ; pmr ($CDCl_3$), 0.98 (C-18), 1.16 (C-19), 2.0 (C-17, OAc), 5.14 (C-17, vinyl multiplets), and 5.72 ppm (C-4a). *Anal.* ($C_{23}H_{33}NO_3$) C, H, N.

3-Aza-17α-ethyl-17β-acetoxy-A-homoandrost-4a-en-4-one (5).—Two grams of **2** was dissolved in 20 ml of AcOH and treated with 1 g of 5% Pd–C. The mixture was hydrogenated at room temperature and atmospheric pressure until 2 moles of H_2 was consumed. It was filtered and the filtrate was poured over ice and H_2O. The solid thus separated was collected by filtration and recrystallized from EtOAc to give 1.7 g (87%) of **5**: mp 248–250°; λ_{max}^{KBr} 3.1, 5.75, and 6.0 μ; λ_{max}^{EtOH} 220 mμ; pmr ($CDCl_3$), 0.88 (C-18), 1.17 (C-19), 2.0 (C-17, OAc), and 5.72 ppm (C-4a). *Anal.* ($C_{23}H_{35}NO_3$) C, H, N.

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Compounds Related to Insect Juvenile Hormone

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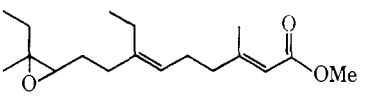
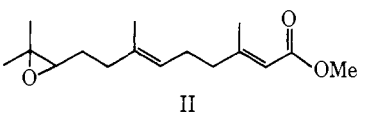
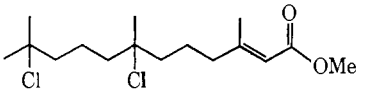
The structure of the insect juvenile hormone (JH) obtained from the cecropia moth, *Hyalophora cecropia* L., has recently been reported as I,[1] and I has been synthesized and found to be highly active.[2,3] Previously, methyl farnesate 10,11-epoxide (II)[4] and methyl 7,11-dichloro-3,7,11-trimethyl-2-dodecenoate (III)[5,6] were also found to be highly active.



I



II



III

(1) H. Röller, K. H. Dahm, C. C. Sweely, and B. M. Trost, *Angew. Chem.*, **79**, 190 (1967); *Angew. Chem. Intern. Ed. Engl.*, **6**, 179 (1967).

(2) K. H. Dahm, B. M. Trost, and H. Röller, *J. Am. Chem. Soc.*, **89**, 5292 (1967).

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(5) J. H. Law, C. Yuan, and C. M. Williams, *Proc. Natl. Acad. Sci. U. S.*, **55**, 576 (1966).

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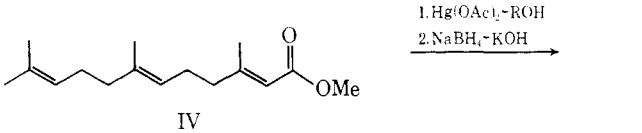
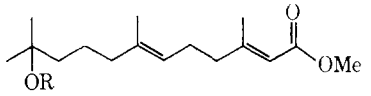
The bulk around C-11 might be the cause of the enhancement of JH activity of I–III over that of methyl farnesate (IV). This hypothesis was tested by preparing methyl 11-methoxy-3,7,11-trimethyl-2,6-dodecadienoate (V) and methyl 11-ethoxy-3,7,11-trimethyl-2,6-dodecadienoate (VI) by the alkoxymercuration of methyl farnesate and then by demercuration with $NaBH_4$.[7]



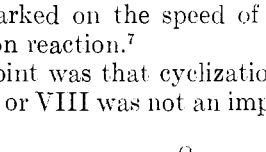
IV



V, R = Me
VI, R = Et

Two points were noteworthy in the reaction. The first was the rapidity of the alkoxymercuration. Earlier reports gave reaction times of 36 hr for methyl cinnamate,[8] several hours for ethylene,[9] and 14 hr for one double bond in methyl linoleate.[10] We have observed that the reaction was over in 30 min and probably much sooner. In fact, $Hg(OAc)_2$ must be added to methyl farnesate; reverse addition invariably led to a mixture of the starting material, monoadduct, and diadduct. Brown has remarked on the speed of the related hydroxymercuration reaction.[7]

The second point was that cyclization to form products such as VII or VIII was not an important reaction.



VII, R = Me
VIII, R = Et

The nuclear magnetic resonance spectra of V and VI retained the signal at τ 8.42 for Me at C-7; the highest field signal was at τ 8.95, which would seem too low for the *gem*-Me_2 in VII and VIII; also, there were signals for two vinylic protons, at τ 4.43 (H on C-2) and 4.95 (H on C-6), which conclusively ruled out structures VII and VIII.

When *Tenebrio molitor* L. was used as the test insect, V and VI were less than one-third as active as farnesyl methyl ether and about $^1/_{500}$ as active as the mixture of synthetic JH and its isomers.[3] Apparently, the causative factor(s) for the enhanced activities of I–III reside(s) in something other than the mere bulk effect of the oxygen or chlorine atoms.

Experimental Section

Analytical and preparative glpc were made with an Aerograph A-700 Autoprep on a 152 cm × 6.4 mm column of 5% SE-30 on base-washed Chromosorb P at 225° and a flow of 60 ml/min. Nmr spectra were obtained on a Varian HA-100 by E. L. Gooden of this Division. The *Tenebrio* test[11] was used for bioassays with assistance from Mrs. R. B. Henegar and Mrs. P. Hall of the Biological Investigations Unit of this Division. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

The methyl farnesate was prepared by the condensation of *trans*-geranylacetone[12] and trimethyl phosphonoacetate and was a 70:30 mixture of methyl *trans,trans*-farnesate and methyl *cis,trans*-farnesate.

Methyl 11-Methoxy-3,7,11-trimethyl-2,6-dodecadienoate (V).—A solution of $Hg(OAc)_2$ (2.6 g, 7.6 mmoles) in 50 ml of MeOH was added to a stirred, ice-cold solution of methyl farnesate (2.0 g, 7.6 mmoles) in 20 ml of MeOH during 15 min; then the mixture was allowed to stand for 30 min. A solution of KOH (1.27 g, 53 mmoles) in 20 ml of MeOH was added next. Then $NaBH_4$ (0.14 g, 3.8 mmoles) was added in small portions, and stirring was continued for 30 min. The solution was decanted from Hg, concentrated to half-volume under reduced pressure, diluted with 100 ml of H_2O, and extracted with three 50-ml portions of Et_2O. The combined Et_2O phase was extracted twice with 20-ml portions of H_2O and dried ($MgSO_4$). The removal of the ether yielded the desired product (1.66 g, 74%). The complete absence of methyl farnesate was demonstrated by gas chromatograms that had major peaks at 2.6 and 3.1 min (88% combined) and minor peaks at 3.5 (10%) and 3.8 min (2%). Analytical and nmr samples consisted of the two major peaks and were collected by preparative glpc. *Anal.* ($C_{17}H_{30}O_3$) C, H.

Methyl 11-Ethoxy-3,7,11-trimethyl-2,6-dodecadienoate (VI).—The compound was prepared in a similar manner with EtOH substituted for MeOH and with the following differences. $Hg(OAc)_2$ was added as a suspension in the EtOH, and the mixture was allowed to stand 2 hr before the addition of $NaBH_4$. The crude yield was 110%. Glpc (percentages given are exclusive of solvent peaks) demonstrated the absence of methyl farnesate, minor peaks at 2.1 and 2.3 min (12% combined), VI at 3.4 and 4.0 min (78% combined), and a minor peak at 4.5 min (10%). *Anal.* ($C_{18}H_{32}O_3$) C, H.

(7) H. C. Brown and P. Geoghegan, Jr., *J. Am. Chem. Soc.*, **89**, 1522 (1967).
(8) G. F. Wright, *ibid.*, **57**, 1993 (1935).
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(10) E. Jantzen and H. Andreas, *Chem. Ber.*, **94**, 628 (1966).
(11) W. S. Bowers and M. J. Thompson, *Science*, **142**, 1469 (1963).
(12) Commercial geranylacetone was separated by the procedure of O. Isler, R. Ruegg, L. Chopard-dit-Jean, H. Wagner, and K. Bernhard, *Helv. Chim. Acta*, **39**, 897 (1956).

An Analog of Doisynolic Acid. 3-Hydroxy-16,17-seco-16-norestra-1,3,5(10)-trien-17-oic Acid

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Many analogs of the potent estrogen *l-cis*-bisdehydrodoisynolic acid (**2c**) have been synthesized.[1,2] Although the replacement of the side-chain ethyl with a methyl group (**2c** → **2d**) caused no change in activity, a corresponding change (**2a** → **2b**) with the closely related, but much less active, *d-trans*-bisdehydrodoisynolic acid resulted in a more active compound (tested as the methyl ester).[1] Since *d-trans*-doisynolic acid (**1a**) is related in configuration to the less active bisdehydrodoisynolic acid **2a**, but is itself a potent estrogen, a similar transformation (**1a** → **1b**) would be of interest. This note describes the synthesis and estrogenic activity of **1b**.

(1) J. Heer and K. Miescher, *Helv. Chim. Acta*, **28**, 1506 (1945).
(2) For an excellent summary of the work on doisynolic acids and the nomenclature employed see L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp 487–494.