Anal. Calcd. for $C_{23}H_{29}NO_4S$: C, 66.48; H, 7.04; N, 3.37. Found: C, 66.69; H, 7.00; N, 3.53.

2-(*trans*-3-Hydroxycyclohexyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (Xd).—A solution of 3.5 g. of 2-(*cis*-3-tosyloxycyclohexyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline and 5.0 g. of tetraethylammonium acetate monohydrate[22] in 50 ml. of acetone (purified by refluxing reagent grade acetone in the presence of calcium oxide and potassium permanganate for 2 hours before distilling it) was refluxed for 60 hours. Distillation of the solvent gave a residue which was treated with water and extracted with benzene. The dried extract was concentrated under reduced pressure giving 1.0 g. (42%) of crude 2-(*trans*-3-acetoxycyclohexyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline (Xc) which was dissolved in anhydrous ether.

The ether solution of Xc was added with stirring to 0.5 g. of lithium aluminum hydride in 200 ml. of ether. The mixture was stirred at room temperature for 1 hour and the product isolated as described above.[18] Crystallization of the product from hexane gave 760 mg. of the *trans*-amino alcohol, m.p. 111.5–113°. The analytical sample was crystallized from hexane, m.p. 112–113°; $\nu_{max}^{CCl_4}$ (10% solution) 3680 (w, unassociated hydroxyl), 3400 (m-broad, associated hydroxyl) and an absorption band characteristic of the *trans*-amino alcohol at 980 cm.$^{-1}$ (m), $\nu_{max}^{CCl_4}$ (0.01 *M* solution, 1-cm. cell) 3670 cm.$^{-1}$ (unassociated hydroxyl) and no absorption band attributable to hydrogen bonding from 3600–3100 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.52; H, 8.83; N, 5.36. Found: C, 73.64; H, 9.01; N, 5.50.

Acknowledgment.—We wish to thank Dr. V. A. Drill and his associates of the Division of Biological Research of G. D. Searle and Company for bioassays of some of the compounds. The perchlorate of III and the amino ketone IX showed little if any lipodiatic, estrogenic or androgenic activity. However, both of these compounds exhibited anti-inflammatory activity[23,24] at a level close to that of Butazolidine. The perchlorate of IV gave a similar positive response in the foot edema test[23] but a negative response in the cotton wad test.[24] The amino alcohol Xa showed no anti-inflammatory activity.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Steroidal Hormone Analogs. VIII. Amino Acid Analogs of Some Artificial Estrogens[1]

BY NORMAN A. NELSON[1a] AND HENRY B. SINCLAIR[2]

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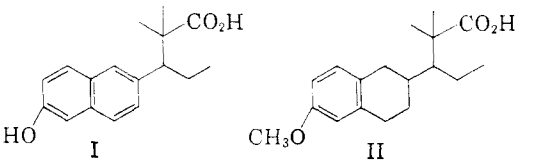
The condensation of 1,2,3,4-tetrahydro-2-naphthylamine with acetone cyanohydrin gave N-2-(1,2,3,4-tetrahydronaphthyl)-α-aminoisobutyronitrile which was hydrolyzed to N-2-(1,2,3,4-tetrahydronaphthyl)-α-aminoisobutyric acid (Vb). Pyrolysis of the tetramethylammonium salt of Vb gave methyl N-2-(1,2,3,4-tetrahydronaphthyl)-α-aminoisobutyrate (Vc). 1,2,3,4-Tetrahydro-6-methoxy-2-naphthylamine, prepared from 6-methoxy-2-tetralone *via* the oxime, was carried through a similar series of reactions yielding N-2-(1,2,3,4-tetrahydro-6-methoxynaphthyl)-α-aminoisobutyric acid and the corresponding methyl ester. Attempts to introduce substituents on the nitrogen of Vb or Vc were unsuccessful.

Several isomers of doisynolic acid represent highly active artificial estrogens which are closely related to the naturally occurring estrogens.[3] Further structural simplifications of this type of hormone are represented in the biologically active allenolic acids I[4] and II,[5] the former of which (Horeau's acid) has been used clinically. In continuing our work on azasteroids,[6,7] we were interested in incorporating a nitrogen atom into the skeleton of these compounds to determine what effect this would have on their biological properties. In addition, some of the nitrogen-containing analogs, being complex α-amino acids, could conceivably possess biological properties not associated with hormone activity. This paper describes the preparation of the α-amino acids Vb and Vd related to II.



I II

At the outset of our work we wished to establish as a model experiment that cyclohexylamine could be converted to N-cyclohexyl-α-aminoisobutyric acid since the latter compound possesses the amino acid function of the hormone analogs Vb and Vd. The reaction of cyclohexylamine with acetone cyanohydrin, using the general procedure of Jacobson,[8] gave N-cyclohexyl-α-aminoisobutyronitrile (IIIa) in quantitative yield. Hydrolysis of the nitrile with concentrated hydrochloric acid following the directions of Steiger[9] gave N-cyclohexyl-α-aminoisobutyric acid (IIIb) after its isolation from the hydrochloride through the use of lead carbonate as described by Cocker and Lapworth.[10]

We next investigated the synthesis of N-2-(1,2,3,4-tetrahydronaphthyl)-α-aminoisobutyric acid (Vb) from 2-tetralone since this amino acid is of interest for biological testing *per se*, and the

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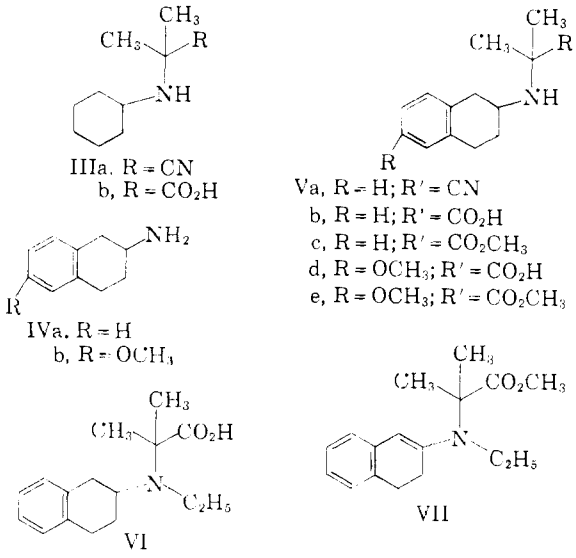

steps utilized in its synthesis could be adapted to the preparation of the more important 6-methoxy-substituted analog Vd. 2-Tetralone was converted *via* 2-tetralone oxime to 1,2,3,4-tetrahydro-2-naphthylamine (IVa) by either catalytic hydrogenation of the oxime with Raney nickel[11,12] in variable yields (1–69%) or chemical reduction with sodium in alcohol[12,13] in more consistent yields (*ca.* 55%). Treatment of the amine IVa with acetone cyanohydrin gave N-2-(1,2,3,4-tetrahydronaphthyl) - α - aminoisobutyro - nitrile (Va) which could be isolated easily as its hydrochloride or hydrolyzed directly with concentrated hydrochloric acid to N-2-(1,2,3,4-tetrahydronaphthyl)-α- aminoisobutyric acid hydrochloride. The amino acid Vb was obtained in 74% yield from the hydrochloride by adjusting the *p*H of an aqueous solution of the latter to 5.5–7.

A number of attempts were made to acetylate N-2- (1,2,3,4-tetrahydronaphthyl)- α - aminoisobutyric acid. The use of acetic anhydride and acetyl chloride in the presence of various bases as well as the use of ketene[14] and Brewster and Ciotti's method[15] of acylation resulted in either the recovery of unchanged amino acid or extensive decomposition of the starting material.

Work was then directed toward the preparation of N-ethyl-N-2-(1,2,3,4 - tetrahydronaphthyl) - α - aminoisobutyric acid (VI). Condensation of N-ethyl-1,2,3,4-tetrahydro-2-naphthylamine with acetone cyanohydrin did not occur under the conditions of the reaction as indicated by the lack of formation of water (insoluble in the reaction mixture) and recovery of the amine as the hydrochloride on addition of hydrogen chloride to the reaction mixture. As a second approach (*cf.* ref. 7) mixtures of methyl N-ethyl-α-aminoisobutyrate and 2-tetralone in xylene or in tetralin were refluxed in an apparatus having a Dean–Stark trap. In no instance did the separation of water take place, and ultraviolet spectra of the reaction mixtures revealed no maxima above 290 mμ which would be characteristic[7] of the desired enamine VII.

Efforts were turned next to the preparation of methyl N-2-(1,2,3,4-tetrahydronaphthyl)-α-aminoisobutyrate (Vc) in order to determine if alkylation of the nitrogen atom of this compound could be accomplished. The methyl ester was obtained in 61% yield by reaction of the amino acid Vb with polyphosphoric acid in methanol. In reactions aimed at attaching an ethyl group to the nitrogen atom of Vc, each of the following reagents was used under a variety of conditions: ethyl *p*-toluenesulfonate, triethyl phosphate and ethyl bromide. Under conditions vigorous enough to cause a reaction, only polymeric material was obtained.

The pyrolysis of the tetramethylammonium salt of N-2-(1,2,3,4-tetrahydronaphthyl)-α-aminoisobutyric acid (Vb) was studied to determine if this might lead to N-alkylation of the amino acid or to O-alkylation yielding Vc.[16] In the related thermal decomposition of betaines,[17] the competition between N- and O-alkylation does not exist, and esters are the observed products unless some other mode of decomposition is available. The only product isolated (51%) from the pyrolysis of the tetramethylammonium salt was shown to be methyl N-2-(1,2,3,4-tetrahydronaphthyl)-α-aminoisobutyrate (Vc) by comparison of its infrared spectrum with that of the authentic sample described above and by a mixed melting point determination of the hydrochlorides of the two samples.

N-2-(1,2,3,4-Tetrahydro-6-methoxynaphthyl)-α-aminoisobutyric acid was prepared by a similar route to that employed for the amino acids above. 6-Methoxy-2-tetralone[7] was converted to 6-methoxy-2-tetralone oxime which was reduced by catalytic hydrogenation to 1,2,3,4-tetrahydro-6-methoxy-2-naphthylamine (IVb) in 57% yield. The amine was allowed to react with acetone cyanohydrin and, after hydrolysis of the intermediate amino nitrile with hydrochloric acid and neutralization, N-2-(1,2,3,4-tetrahydro-6-methoxynaphthyl)-α-aminoisobutyric acid (Vd) was isolated in 70% yield. Pyrolysis of the tetramethylammonium salt of this amino acid afforded 62% of methyl N-2-(1,2,3,4-tetrahydro-6-methoxynaphthyl)-α-aminoisobutyrate (Ve).

Experimental[18]

N-Cyclohexyl-α-aminoisobutyronitrile (IIIa).—To 40.0 g. of cyclohexylamine was added 34.5 g. of acetone cyanohydrin with cooling. After allowing the reaction mixture to stand at room temperature for 12 hours, the organic layer

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(18) Melting points and boiling points are uncorrected. The infrared spectra were determined with a Baird (model B) or Perkin–Elmer (model 21) spectrophotometer fitted with a sodium chloride prism. In reporting infrared spectra, (s) denotes strong, (m) medium and (w) weak absorption. Ultraviolet spectra were determined with a Cary recording spectrophotometer (model 11MS). The microanalyses were performed by Dr. S. M. Nagy and his associates.

was separated and crystallized to give 67 g. (100%) of N-cyclohexyl-α-aminoisobutyronitrile, m.p. 55–56°. The analytical sample was crystallized from ethanol, m.p. 55.4–56.1°; ν_{max}^{KBr} 3360(m) and 1500(m, NH), 2220(w, CN), 1383 and 1366 cm.$^{-1}$ (m, $C(CH_3)_2$).

Anal. Calcd. for $C_{10}H_{18}N_2$: C, 72.24; H, 10.91. Found: C, 72.46; H, 10.77.

N-Cyclohexyl-α-aminoisobutyronitrile hydrobromide, prepared by saturating an ether solution of the amino nitrile IIIa with hydrogen bromide, was crystallized from ethanol–ether, m.p. 243–246° dec.

Anal. Calcd. for $C_{10}H_{19}BrN_2$: C, 48.59; H, 7.75. Found: C, 48.42; H, 7.96.

N-Cyclohexyl-α-aminoisobutyric Acid (IIIb).—A solution of 10.0 g. of N-cyclohexyl-α-aminoisobutyronitrile in 150 ml. of concentrated hydrochloric acid was cooled in an ice-bath, saturated with hydrogen chloride at 0–5°, and allowed to stand in a stoppered flask at room temperature overnight. The mixture was then refluxed for 3 hours, placed in an evaporating dish and concentrated to dryness on the steam-bath; 500 ml. of water was added to the residue and the concentration repeated. The residue (15.8 g.) was triturated with a total of 250 ml. of boiling absolute ethanol in three portions. The addition of 100 ml. of ether to the combined ethanolic extracts caused the precipitation of a white powder which was removed by filtration after 2 hours. The filtrate was diluted with 50 ml. of water, the organic solvents were removed by distillation and the aqueous residue was cooled in an ice-bath. Lead carbonate was added until effervescence was no longer visible. The mixture was cooled for several hours, filtered, and the lead chloride washed with 300 ml. of ice-water. The filtrate and washings were combined and saturated with hydrogen sulfide. Removal of the lead sulfide by filtration and evaporation of the filtrate gave 11.1 g. of crude N-cyclohexyl-α-aminoisobutyric acid. An analytical sample was prepared by sublimation at 195–200° (1.5 mm.), m.p. 250–256° (rapid heating).

Anal. Calcd. for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.94; H, 10.65; N, 7.48.

N-2-(1,2,3,4-Tetrahydronaphthyl)-α-aminoisobutyric Acid (Vb).—A solution of 55 g. of β-tetralone[19] and 150 ml. of methanol was added dropwise with stirring to a cold solution of 29 g. of hydroxylamine hydrochloride, 21 g. of potassium carbonate and 100 ml. each of water and methanol. The mixture was stirred at 0° for 3 hours, diluted with 350 ml. of water, placed in a refrigerator overnight and then filtered to give 58 g. (96%) of β-tetralone oxime, m.p. 80–84° (lit.[20] 86.5–87.5°). The oxime was used immediately as it is photosensitive.

To a boiling solution of 10 g. of β-tetralone oxime and 100 ml. of absolute ethanol in a nitrogen atmosphere was added 17 g. of sodium in thin strips at such a rate as to maintain control of the reaction. The mixture was heated under reflux for an additional 4 hours, cooled and treated with 200 ml. of methanol (to destroy excess sodium) followed by 200 ml. of 6 *N* hydrochloric acid with cooling. The mixture was concentrated to 250 ml. by distillation and the concentrate was then washed with ether, made strongly basic with sodium hydroxide and extracted with ether. The dried ether extract was distilled and gave 5.1 g. (56%) of 1,2,3,4-tetrahydro-2-naphthylamine, b.p. 80–83° (1 mm.) [lit.[21] 118.5° (8 mm.)].

A mixture of 17.2 g. of 1,2,3,4-tetrahydro-2-naphthylamine and 10.1 g. of acetone cyanohydrin was allowed to stand at room temperature overnight. The addition of 400 ml. of concentrated hydrochloric acid to the mixture caused the precipitation of **N-2-(1,2,3,4-tetrahydronaphthyl)-α-aminoisobutyronitrile hydrochloride**, a small sample of which was removed for analysis, m.p. 125.2–126.8°; λ_{max}^{EtOH} 212 (ε 9440), 265.3 (ε 489) and 272.3 mμ (ε 535).

Anal. Calcd. for $C_{14}H_{19}ClN_2$: C, 67.05; H, 7.63; N, 11.17. Found: C, 66.97; H, 7.61; N, 10.91.

The remainder of the reaction mixture was saturated with hydrogen chloride at 0°. The mixture was tightly stoppered and allowed to stand at room temperature until the solid nitrile hydrochloride had dissolved (1–2 days). The solution was then heated under reflux on the steam-bath for 10 hours, poured into an evapoating dish and concentrated to dryness on the steam-bath. The residue was dissolved in 500 ml. of water, clarified with Norit, and the *p*H of the resulting solution was adjusted to 6 using potassium carbonate. The precipitate of N-2-(1,2,3,4-tetrahydronaphthyl)-α-aminoisobutyric acid was washed with a 1:1 mixture of methanol–water; yield 20.1 g. (74% based on the amount of 1,2,3,4-tetrahydro-2-naphthylamine used). This amino acid sublimes without melting; the analytical sample was prepared by sublimation at 170° (0.1 mm.), ν_{max}^{KBr} 1611(s, broad, CO_2^-); λ_{max}^{EtOH} 212 (ε 8720), 265.5 (ε 496) and 272.5 mμ (ε 578).

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.03; H, 8.30; N, 5.87.

A sample of **N-2-(1,2,3,4-tetrahydronaphthyl)-α-aminoisobutyric acid hydrochloride** was prepared by evaporating a solution of the amino acid in hydrochloric acid. The product was recrystallized from methanol–ether, m.p. 270–275° (rapid heating), ν_{max}^{KBr} 1742 (s, CO); λ_{max}^{EtOH} 212 (ε 8720), 265.3 (ε 457) and 272.5 mμ (ε 510).

Anal. Calcd. for $C_{14}H_{20}ClNO_2$: C, 62.33; H, 7.47; N, 5.19. Found: C, 62.34; H, 7.42; N, 5.12.

Methyl N-2-(1,2,3,4-Tetrahydronaphthyl)-α-aminoisobutyrate (Vc). (A) Using Polyphosphoric Acid.—Polyphosphoric acid (100 g.) was added with swirling to a suspension of 10 g. of N-2-(1,2,3,4-tetrahydronaphthyl)-α-aminoisobutyric acid in 150 ml. of methanol in a nitrogen atmosphere. The homogeneous solution was refluxed overnight, cooled, poured carefully into 350 ml. of ice and water containing 80 g. of potassium carbonate, and the resulting mixture was extracted quickly with ether. Distillation of the dried ether extract gave 5.8 g. (55%) of methyl N-2-(1,2,3,4-tetrahydronaphthyl)-α-aminoisobutyrate, b.p. 117–120° (0.5 mm.), $n^{28}D$ 1.5161, $\nu_{max}^{CCl_4}$ 1730 (s, CO), λ_{max}^{MeOH} 266 (ε 555) and 273 mμ (ε 642).

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.88; H, 8.32; N, 5.68.

(B) From the Pyrolysis of the Tetramethylammonium Salt of Vb.—A filtered solution of 3.44 g. of N-2-(1,2,3,4-tetrahydronaphthyl)-α-aminoisobutyric acid and 25 ml. of 0.589 *N* tetramethylammonium hydroxide was concentrated on the steam-bath to a gelatinous mass which was transferred to a distilling flask having a nitrogen ebullator. The flask was connected in series to a short Vigreux column, water condenser, fraction cutter, liquid nitrogen-cooled trap, Dry Ice-cooled trap and a vacuum pump. The pressure of the system was reduced to 0.2 mm. and the flask was heated in an oil-bath (130°) until the contents of the flask had solidified. The solid was then pyrolyzed by carefully heating the flask with a micro burner. After a period of vigorous boiling and evolution of gases, heating was continued to distil 1.82 g. (51%) of methyl N-2-(1,2,3,4-tetrahydronaphthyl)-α-aminoisobutyrate, b.p. 120–130° (0.2–0.3 mm.); the infrared spectrum of this material is identical with that of the analytical sample described in part (A).

Treatment of the material collected in the liquid nitrogen-cooled trap with an excess of an ethanolic solution of picric acid gave 2.67 g. (63%) of trimethylamine picrate, m.p. 213–216° dec. (lit.[22] 216°).

Methyl N-2-(1,2,3,4-tetrahydronaphthyl)-α-aminoisobutyrate hydrochloride, prepared by passing hydrogen chloride into an ethereal solution of the ester, was crystallized from methanol–ether, m.p. 171–172°, ν_{max}^{KBr} 1745 cm.$^{-1}$ (s, CO); λ_{max}^{MeOH} 212 (ε 8370), 265.5 (ε 418) and 272.5 mμ (ε 470).

Anal. Calcd. for $C_{15}H_{22}ClNO_2$: C, 63.48; H, 7.82; N, 4.94. Found: C, 63.52; H, 7.94; N, 4.96

6-Methoxy-2-tetralone Oxime.—A solution of 11.4 g. of 6-methoxy-2-tetralone[7] in 50 ml. of methanol was added dropwise with stirring to a cold solution of 5 g. of hydroxylamine hydrochloride, 5.4 g. of potassium carbonate and 50 ml. each of water and methanol. The resulting mixture was stirred for 45 minutes, then poured into 300 ml. of cold water and the product was collected on a filter after several hours, yielding 14 g. of crude product, m.p. 105–110°, which was sufficiently pure for the next step. The analytical sample of 6-methoxy-2-tetralone oxime was crystallized from

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(22) M. Delepine, *Ann. chim.* (*Paris*), (7) **8**, 439 (1896).

aqueous ethanol and dried in the dark, m.p. 113.4–119° with previous sintering, λ_{max}^{EtOH} 278 mμ (ε 2270) with shoulders at 225 (ε 8070) and 284 mμ (ε 2060).

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.33; H, 6.56; N, 7.19.

1,2,3,4-Tetrahydro-6-methoxy-2-naphthylamine (IVb).—A solution of 9.0 g. of 6-methoxy-2-tetralone oxime in 200 ml. of methanol (saturated with ammonia at 0–5°) was hydrogenated in the presence of 1.5 teaspoons of W2-Raney nickel and an initial pressure of 1470 p.s.i. for 4 hours at 55°. The oil obtained by removal of the catalyst and concentration of the filtrate was dissolved in dilute hydrochloric acid. The resulting solution was washed with ether, made strongly basic with sodium hydroxide and the regenerated amine was extracted with ether. The dried ether extract was distilled giving 4.72 g. (57%) of 1,2,3,4-tetrahydro-6-methoxy-2-naphthylamine, b.p. 108–110° (0.2 mm.) which was characterized as the hydrochloride.

1,2,3,4-Tetrahydro-6-methoxy-2-naphthylamine hydrochloride was prepared in 94% yield by saturating an ethereal solution of the amine with hydrogen chloride, m.p. 234–236° with previous softening; λ_{max}^{EtOH} 221 (ε 7960), 279 (ε 2180) and 287 mμ (ε 2020).

Anal. Calcd. for $C_{11}H_{16}ClNO$: C, 61.82; H, 7.55; N, 6.55. Found: C, 61.74; H, 7.54; N, 6.41.

N-2-(1,2,3,4-Tetrahydro-6-methoxynaphthyl)-α-aminoisobutyric Acid (Vd).—To a mixture of 4.72 g. of 1,2,3,4-tetrahydro-6-methoxy-2-naphthylamine and 2.27 g. of acetone cyanohydrin, which had been allowed to stand overnight, was added 300 ml. of concentrated hydrochloric acid (saturated with hydrogen chloride at 0–5°). The resulting mixture was allowed to stand at room temperature for 15 hours and then was heated under reflux on the steam-bath for 3 hours before being concentrated to dryness. The residue was dissolved in 50 ml. each of water and methanol, the solution was clarified with Norit and adjusted to *p*H 5.5–6 with potassium carbonate. The precipitate was collected on a filter, washed and dried, giving 4.97 g. (70%) of N-2-(1,2,3,4-tetrahydro-6-methoxynaphthyl)-α-aminoisobutyric acid; the product sublimes without melting. The analytical sample was sublimed at 225° (10^{-4} mm.), ν_{max}^{KBr} 1604 (s, CO_2^-), λ_{max}^{EtOH} 220 (ε 8180), 279 (ε 2150) and 287 mμ (ε 2010).

Anal. Calcd. for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.49; H, 8.02; N, 5.24.

Methyl N-2-(1,2,3,4-Tetrahydro-6-methoxynaphthyl)-α-aminoisobutyrate (Ve).—In this preparation, the same procedure and apparatus was employed as in the synthesis of methyl (1,2,3,4-tetrahydronaphthyl)-α-aminoisobutyrate by procedure B above.

A mixture of 3.5 g. of N-2-(1,2,3,4-tetrahydro-6-methoxynaphthyl)-α-aminoisobutyric acid and 23.0 ml. of 0.589 *N* tetramethylammonium hydroxide was concentrated to a thick paste which was transferred to a distilling flask. Water was removed, finally at 120° (0.2 mm.) for 4 hours. The resulting solid was melted using a micro burner. Gas evolution was vigorous and on continued heating 2.29 g. (62%) of the crude product distilled, b.p. 160° (0.2–0.3 mm.). The analytical sample of Ve had b.p. 138–140° (0.06 mm.). $n^{27}D$ 1.5233, $\nu_{max}^{CCl_4}$ 1726 (s, CO), λ_{max}^{MeOH} 279.5 (ε 2180) and 288 mμ (ε 2060) with a plateau at 216–226 mμ (ε 7700).

Anal. Calcd. for $C_{16}H_{23}NO_3$: C, 69.28; H, 8.36; N, 5.05. Found: C, 69.38; H, 8.42; N, 5.00.

Acknowledgment.—We wish to thank Dr. V. A. Drill and his associates of the Division of Biological Research of G. D. Searle and Company for bioassays of some of the compounds. Compounds Vb–Ve showed essentially no lipodiatic, estrogenic, androgenic or anti-inflammatory activity. However, the hydrochloride salt of Vb exhibited a positive anti-inflammatory activity[23] at a level similar to that of Butazolidine.

(23) J. J. Selitto and L. O. Randall, *Federation Proc.*, Abstract No. 1323 (1954).

CAMBRIDGE 39, MASS.

[CONTRIBUTION FROM THE CHEMICAL PROCESS IMPROVEMENT DEPARTMENT, LEDERLE LABORATORIES, AMERICAN CYANAMID CO.]

16α-Hydroxy Steroids. V.[1] 11β-Esters of Triamcinolone

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Acetylation of the 11β- and 17α-hydroxyl groups of triamcinolone and of 16α-hydroxyhydrocortisone is readily accomplished with warm acetic anhydride and pyridine. Both a 11β,16α,21-triacetate and a 11β,16α,17α,21-tetraacetate are formed from triamcinolone. Hydrocortisone and 9α-fluorohydrocortisone were acetylated at the 11β-hydroxyl also. Some chemical proof for the assigned structures is presented.

It is commonly held that the 11β- and the 17α-hydroxyl groups of the active corticosteroids are not readily acetylated with acetic anhydride and pyridine, neither at room temperature nor at slightly elevated temperatures. Occasional exceptions in other steroid series have been noted,[2] but such treatment is generally regarded as a poor means of acetylation of these groups. We have found that acetic anhydride–pyridine smoothly acetylates the 11β- and 17α-hydroxyl groups of triamcinolone[3] (9α-fluoro-11β,16α,17α,21-tetrahydroxy-1,4-pregnadiene-3,20-dione) (IIa) yielding the 11β,16α,21-triacetate III and 11β,16α,17α,21-tetraacetate IV derivatives.

Triamcinolone triacetate (III) and tetraacetate (IV) were encountered unexpectedly in preparations of triamcinolone 16α,21-diacetate (IIb) obtained *via* microbiological dehydrogenation of 16α-hydroxy-9α-fluorohydrocortisone 16α,21-diacetate (I). *Nocardia corallina* dehydrogenates I[3] but also hydrolyzes partially the diesters involved, yielding a mixture of diacetates, monoacetates and free alcohols. Reacetylation of the fermentation extract residues without isolation of the purified steroids, using large excesses of acetic anhydride and pyridine and inadvertently warming on a steam-bath, gave the diacetate IIb which was contaminated with a major proportion of a new, more mobile component (paper chromatographic analyses) together with traces of a still more mobile component and unaltered substrate I.

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