allowed to come to room temperature and stand for 18 hr. under anhydrous conditions. After removal of thionyl chloride *in vacuo* without heating, the residue was diluted with methylene dichloride and the solution cautiously washed with dilute ice cold sodium bicarbonate solution followed by water washes to neutrality. Drying of the solution over sodium sulfate and evaporation under reduced pressure left a light yellow oil which crystallized from methylene chloride–ether, yielding 0.17 g. of the dichloro compound III, m.p. 166–169°dec. For the analytical specimen, a 100-mg. sample of III was chromatographed on 5 g. of silica gel. Methylene dichloride-hexane (1:1) and methylene chloride eluted traces of oil while the desired product was eluted with methylene dichloride–ether (4:1). Crystallization from methylene dichloride-ether gave material of m.p.[12] 172–174° dec., λ_{max} 326 mμ, log ε 4.20. Infrared λ_{max} 5.78, 6.08, 6.55, and 8.03 (broad) μ.

Anal. Calcd. for $C_{26}H_{39}Cl_2NO_3$: C, 64.45; H, 8.11; Cl, 14.64; N, 2.89. Found[13]: C, 63.98; H, 8.15, Cl, 15.26; N, 3.09.

(b) A solution of 11.0 g. of IIb in 100 ml. of thionyl chloride which had been distilled several days previous to the reaction was allowed to stand overnight at room temperature. The mixture was worked up as described for (a) and the residue remaining after removal of methylene dichloride was treated with ether yielding 8.31 g. of tan precipitate, m.p. 163–166° dec. This precipitate was taken up in 75 ml. of methylene dichloride and absorbed onto a column of 150 g. of silica gel. Elution with the same solvent gave small amounts of brown gummy material which was discarded while elution with methylene dichloride–ether (9:1) gave 0.9 g. of 2-hydroxymethylene - 5α - androstan - 17β - ol - 3 - one 17-acetate (Ic), m.p. 182–184°, identified by ultraviolet, infrared and mixed melting point determination. The methylene chloride-ether (4:1) eluate was crystallized as in (a) yielding 4.75 g. of III, m.p. 172–174° dec. and a second crop of 0.46 g., m.p. 168–172°.

Acid hydrolysis of 2(bis-β-hydroxyethylaminomethylene)-5α-androstan-17β-ol-3-one 17-acetate. When 0.15 g. of IIb was added to 6 ml. of 2% hydrochloric acid, solution occurred immediately followed by crystallization within a few minutes. Filtration yielded 97 mg. of 2-hydroxymethylene-5α-androstan-17β-ol-3-one 17-acetate (Ic), m.p. 183–185°.

Acid hydrolysis of 2-(bis-β-chloroethylaminomethylene)-5α-androstan-17β-ol-3-one acetate. (a) *Aqueous.* Treatment of 0.1 g. of dichloro compound III with 5 ml. of 2% hydrochloric acid (overnight stirring at room temperature) gave 90 mg. of recovered dichloro compound.

(b) *Acetone.* A solution of 100 mg. of III in 2.5 ml. of acetone, 0.5 ml. of water, and 10 drops of 5% hydrochloric acid was stirred for 1 hr. at room temperature whence precipitation occurred. Cooling and filtration yielded 85 mg. of Ic, m.p. 185–187°.

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(12) The melting point varied considerably with the rate of heating. Rapid determination for this sample gave 175–177° dec.

(13) Considerable difficulty was experienced in obtaining accurate and consistent analytical figures, apparently due in part to acetone of solvation. Chlorine values were usually high while direct oxygen determination was unsatisfactory.

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

Steroidal Hormone Analogs. IX. Bisdehydrodoisynolic Acid Analogs Possessing the 1,2,3,4-Tetrahydrobenz[f]isoquinoline Nucleus[1]

NORMAN A. NELSON[2] AND RICHARD S. P. HSI

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6-Methoxy-1-naphthylacetic acid was converted to 6-methoxy-1-naphthylacetonitrile. Reduction of the nitrile yielded the amine which, on acylation with propionic anhydride, gave *N*-(6-methoxy-1-naphthyl-β-ethyl)propionamide (IIa). Cyclodehydration of the amide and hydrogenation of the product gave 4-ethyl-8-methoxy-1,2,3,4-tetrahydrobenz[f]isoquinoline (VIa) which was converted to *N*-carbethoxy-4-ethyl-8-methoxy-1,2,3,4-tetrahydrobenz[f]isoquinoline (VIb). Acylation of 2-(6-methoxy-1-naphthyl)ethylamine with diethyl malonate gave the malonamate IIb which on cyclization and reduction afforded 4-(2-hydroxyethyl)-8-methoxy-1,2,3,4-tetrahydrobenz[f]isoquinoline (VId). The latter substance was converted to *N*-carbethoxy-4-(2-hydroxyethyl)-8-methoxy-1,2,3,4-tetrahydrobenz[f]isoquinoline (VIe) and *N*-carbomethoxymethyl-4-(2-hydroxyethyl)-8-methoxy-1,2,3,4-tetrahydrobenz[f]isoquinoline (VIf).

In continuing our work on the preparation of azasteroids we have undertaken the synthesis of some derivatives of 1,2,3,4-tetrahydrobenz[f]isoquinoline which bear a resemblance to the potent estrogen, bisdehydrodoisynolic acid.[3]

The starting material in our work, 6-methoxy-1-naphthylacetic acid (Ia), was prepared from 2-methoxynaphthalene by methods described in the literature.[4] Treatment of 6-methoxy-1-naphthylacetic acid with phosphorus pentachloride gave a crude acid chloride which was treated with ammonium hydroxide to afford 6-methoxy-1-naphthylacetamide(Ib) in 79% yield. Attempts to reduce the amide to the corresponding amine Ic by means of lithium aluminum hydride in ether or tetrahydrofuran solution were unsuccessful, presumably because of the insolubility of the amide (or salt of the amide) in the solvents used. To circumvent this obstacle, we chose to dehydrate the amide and reduce the resulting nitrile to the desired amine. 6-

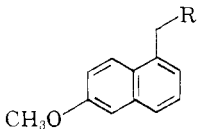
(1) This investigation was supported in part by a research grant, CY-2999 (C3), from the National Cancer Institute, Public Health Service.

(2) Department of Chemistry, The Upjohn Company, Kalamazoo, Mich.

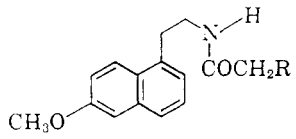
(3) For a review of the doisynolic acids, see L. F. Fieser and M. Fieser, *Steroids*, Reinhold Publishing Corp., New York, N. Y., 1959, and references contained therein.

(4) G. Stork, *J. Am. Chem. Soc.*, 69, 576 (1947); G. Haberland, *Ber.*, 69, 1380 (1936); E. Buchta, M. Klisch, S. Maier, and H. Bayer, *Ann.*, 576, 7 (1952).

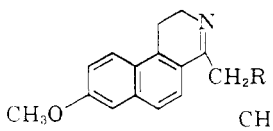
Methoxy-1-naphthylacetamide was dehydrated[5] with phosphorus trichloride to give 6-methoxy-1-naphthylacetonitrile (Ic) in 81% yield. Reduction of the nitrile using a mixture of lithium aluminum hydride and aluminum chloride,[6] and work-up of the reaction mixture using sulfuric acid gave an 80% yield of 2-(6-methoxy-1-naphthyl)ethylamine sulfate (Id).



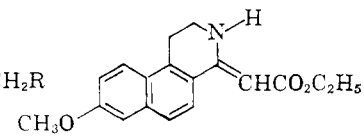
Ia. R = CO_2H
b. R = $CONH_2$
c. R = CN
d. R = $CH_2NH_3^+ \cdot 1/2SO_4^=$
e. R = CH_2NH_2



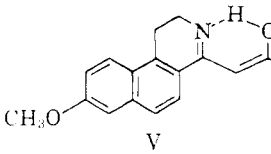
IIa. R = CH_3
b. R = $CO_2C_2H_5$



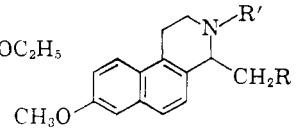
IIIa. R = CH_3
b. R = $CO_2C_2H_5$



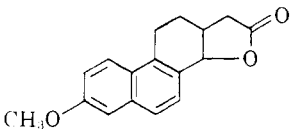
IV



V



VIa. R = CH_3; R′ = H
b. R = CH_3; R′ = $CO_2C_2H_5$
c. R = $CO_2C_2H_5$; R′ = H
d. R = CH_2OH; R′ = H
e. R = CH_2OH; R′ = $CO_2C_2H_5$
f. R = CH_2OH; R′ = $CH_2CO_2CH_3$



VII

2-(6-Methoxy-1-naphthyl)ethylamine(Ie) was regenerated from its sulfate salt and converted to *N*-(6-methoxy-1-naphthyl-β-ethyl)propionamide (IIa) in 94% yield using propionic anhydride. A Bischler-Napieralski cyclization of IIa with phosphorus oxychloride and catalytic reduction of the intermediate dihydrobenz[f]isoquinoline IIIa afforded 4-ethyl-8-methoxy-1,2,3,4-tetrahydrobenz[f]isoquinoline (VIa), which was isolated as its perchlorate salt in 61% yield (from IIa). Attempts to effect the one step conversion of 2-(6-methoxy-1-naphthyl)ethylamine(Ie) to the tricyclic amine VIa *via* the Pictet-Spengler method[7] were unsuccessful. Acylation of 4-ethyl-8-methoxy-1,2,3,4-tetrahydrobenz[f]isoquinoline with ethyl chloroformate gave *N*-carbethoxy-4-ethyl-8-methoxy-1,2,3,4-tetrahydrobenz[f]isoquinoline (VIb) in 90% yield.

We next turned our attention to the preparation of 4-(2-hydroxyethyl)-8-methoxy-1,2,3,4-tetrahydrobenz[f]isoquinoline (VId), since this substance could serve as a precursor to other analogs of bisdehydrodoisynolic acid as well as 13-aza tetracyclic steroids.

Acylation of 2-(6-methoxy-1-naphthyl)ethylamine (Ie) with an excess of diethyl malonate gave ethyl *N*-(6-methoxy-1-naphthyl-β-ethyl)malonamate (IIb) which was cyclized with phosphorus pentoxide to afford a material in 43% yield which has been assigned structure IV. This structure is chosen in preference to the conventional tautomeric structure IIIb on the basis of its infrared spectrum. The cyclization product exhibits no significant absorption in the normal ester carbonyl region, but shows broad and intense absorption at 1640–1600 cm.$^{-1}$ which can be attributed to the vinylogous urethan and aromatic systems of IV. Furthermore, the spectrum has an absorption band at 3350 cm.$^{-1}$ which is evidently due to the stretching of a nitrogen-hydrogen bond, a bond which exists in structure IV, but not in structure IIIb.[8-10] A third possibility for the cyclization product which is perhaps less probable, is the enolized-chelated structure V; the infrared spectrum of the product is not inconsistent with such a formulation.

Catalytic hydrogenation of the cyclization product using Adams catalyst resulted in the smooth uptake of one molecular equivalent of hydrogen and gave 4-carbethoxymethyl-8-methoxy-1,2,3,4-

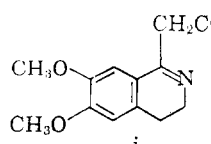
(5) F. Salmon-Legagneur, *Bull. soc. chim. France*, 580 (1952).

(6) R. F. Nystrom, *J. Am. Chem. Soc.*, **77**, 2544 (1955).

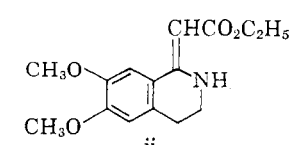
(7) See W. M. Whaley and T. R. Govindachari, *Org. Reactions*, **6**, 151 (1951).

(8) The enamine formulation for the cyclization product is not without precedent. The simpler ethyl β-aminocrotonates and analogous compounds have been shown to exist in the enamine rather than the tautomeric imino forms; see, for example, S. A. Glickman and A. C. Cope, *J. Am. Chem. Soc.*, **67**, 1017 (1945).

(9) The cyclodehydrations of several substituted *N*-(phenethyl)malonamates have been described in the literature [A. R. Battersby, H. T. Openshaw, and H. C. S. Wood, *J. Chem. Soc.*, 2463 (1953); A. Brossi, H. Lindlar, M. Walter, and O. Schnider, *Helv. Chim. Acta*, **41**, 119 (1958); see also J. M. Osbond, *J. Chem. Soc.*, 3464 (1951)]. The products, for example i, have been assigned structures analogous to IIIb in which the newly created double bond is endocyclic. Since infrared data were not given to support the structural assignments, it is possible that these compounds should be formulated as enamines, such as ii, analogous to IV.



i



ii

(10) In contradistinction to our assignment, N. H. Cromwell, F. A. Miller, A. R. Johnson, R. L. Frank, and D. J. Wallace [*J. Am. Chem. Soc.*, **71**, 3337 (1949)] have reported the absence of N—H stretching bands near 3300 cm.$^{-1}$ in several *N*-alkyl-β-amino-α,β-unsaturated ketones. For a brief discussion concerning this apparent discrepancy see N. A. Nelson *et al.*, *J. Org. Chem.*, **26**, 2599 (1961).

tetrahydrobenz[f]isoquinoline (VIc) which was characterized as its picrate derivative. The infrared spectrum of VIc shows the intense absorption (at 1740 cm.$^{-1}$) of a normal ester carbonyl function. Lithium aluminum hydride reduction of the crude ester VIc led to the formation of 4-(2-hydroxyethyl)-8-methoxy-1,2,3,4-tetrahydrobenz[f]isoquinoline (VId) in 74% yield. Acylation of the amino alcohol VId with ethyl chloroformate gave a 91% yield of *N*-carbethoxy-4-(2-hydroxyethyl)-8-methoxy-1,2,3,4-tetrahydrobenz[f]isoquinoline (VIe).

The ultraviolet absorption data for the urethan VIb and the amino alcohol VId have been compared with those of the lactone VII and the *cis*- and *trans*-3-methoxy-16-equilenones.[11] The close agreement in the positions of maxima, minima, and inflections and their comparable extinction coefficients, lends support to the conviction that the cyclizations of compounds II a and b occurred at the electronically favored 2-position of the naphthalene nucleus rather than at the alternative 8-position.

Incidental to the preparation of analogs bearing a close resemblance to bisdehydrodoisynolic acid, we have investigated the alkylation of 4-(2-hydroxyethyl)-8-methoxy-1,2,3,4-tetrahydrobenz[f]-isoquinoline(VId) with methyl bromoacetate. The reaction afforded a 45% yield of *N*-carbomethoxymethyl-4-(2-hydroxyethyl)-8-methoxy-1,2,3,4-tetrahydrobenz[f]isoquinoline (VIf) accompanied by the hydrobromide salt of VId. Treatment of the salt yielded 44% unchanged starting material. It is of interest to note that under the conditions of the reaction the hydrobromide salt of the starting material was precipitated exclusively (as indicated from lack of carbonyl absorption in the infrared spectrum of the salt).

EXPERIMENTAL[12]

6-Methoxy-1-naphthylacetamide (Ib) A mixture of 20.0 g. of 6-methoxy-1-naphthylacetic acid,[4] in 400 ml. of anhydrous benzene and 21.0 g. of phosphorus pentachloride was warmed for 2 hr. at 60–65°, at 75–80° for 1 hr. and finally at 80–90° 3 hr. The benzene and phosphorus oxychloride were removed under reduced pressure and the dark residue was dissolved in 100 ml. of anhydrous tetrahydrofuran (dioxane is also suitable). This solution was added over a period of 15 min to 800 ml. of cold coned. ammonium hydroxide with efficient stirring. The mixture was stirred in the cold for 2 hr. and allowed to stand in the refrigerator overnight. The solid material formed in the mixture was collected on a filter and washed successively with 10% hydrochloric acid, 10% sodium hydroxide solution, and water. Recrystallization of the crude product from 800 ml. of ethanol gave 15.8 g. (79%) of 6-methoxy-1-naphthylacetamide, m.p. 213.7–214.7°, ν_{max}^{KBr} 1630 cm.$^{-1}$ (s, unsubstituted amide carbonyl).

Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.69; H, 6.19; N, 6.51.

6-Methoxy-1-naphthylacetonitrile (Ic). A mixture of 68 g. of 6-methoxy-1-naphthylacetamide and 113 g. of phosphorus trichloride in 500 ml. of anhydrous benzene was refluxed with stirring for 17 hr. The resulting mixture was filtered and the filtrate was washed with ice water, sodium bicarbonate solution, water, and then dried. The solution was concentrated to about 150 ml., and 300 ml. of hexane was added to effect crystallization of the product, yield 50.2 g. (81%), m.p. 72.5–76°. An analytical sample of 6-methoxy-1-naphthylacetonitrile was obtained by sublimation, m.p. 78.6–79.6°, ν_{max}^{KBr} 2250 cm.$^{-1}$ (m, CN stretching).

Anal. Calcd. for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 78.99; H, 5.52; N, 7.11.

2-(6-Methoxy-1-naphthyl)ethylamine sulfate (Id). Aluminum chloride (6.8 g.) in 100 ml. of anhydrous ether was added rapidly with stirring to a slurry of 1.93 g. of lithium aluminum hydride in 100 ml. of ether. The mixture was stirred for 5 min. and a solution of 10.0 g. of 6-methoxy-1-naphthylacetonitrile in 250 ml. of ether was added at such a rate as to cause gentle refluxing. After heating the mixture under reflux for 1 hr., it was cooled and the excess reducing agent was decomposed by the cautious addition of water followed by 300 ml. of 3*N* sulfuric acid. Cooling the aqueous layer afforded fine colorless needles which were recrystallized from an ethanol-water mixture (about 4:1 by volume) to give 10.2 g. of 2-(6-methoxy-1-naphthyl)ethylamine sulfate, m.p. 217–219°.

Anal. Calcd. for $C_{26}H_{32}N_2O_6S$: C, 62.38; H, 6.44; N, 5.60; S, 6.40. Found: C, 62.27; H, 6.45; N, 5.41; S, 6.14.

N-(6-Methoxy-1-naphthyl-β-ethyl)propionamide (IIa). A mixture of 13 g. of freshly distilled propionic anhydride and 3.33 g. of 2-(6-methoxy-1-naphthyl)ethylamine (Ie, prepared by treatment of the corresponding sulfate salt, Id, with base) was refluxed in a nitrogen atmosphere for 2.5 hr. The reaction mixture was added to a solution of 11.2 g. of potassium hydroxide and 200 ml. of methanol and the resulting solution was refluxed for 2 hr. The volume of the solution was reduced to about 100 ml. and the resulting solution was allowed to stand at room temperature for 2 hr. before being concentrated further under reduced pressure. The residue was treated with water and the product was collected to give 4.0 g. (94%) of colorless crystals, m.p. 106–115°. An analytical sample of *N*-(6-methoxy-1-naphthyl-β-ethyl)propionamide, recrystallized from benzene-hexane, had m.p. 116.8–117.8°, $\nu_{max}^{CHCl_3}$ 3450 (m, NH stretching) and 1660 cm.$^{-1}$ (s, monosubstituted amide carbonyl).

Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44. Found: C, 74.61; H, 7.72.

In other runs, when treatment of the acylation reaction mixture with methanolic potassium hydroxide was omitted, low yields of the expected amide IIa were obtained along with appreciable amounts of a crude crystalline material which absorbed strongly in the infrared at 1690 cm.$^{-1}$. This latter material, presumably the diacylation product, was converted quantitatively to *N*-(6-methoxy-1-naphthyl-β-ethyl)-propionamide on treatment with base.

4-Ethyl-8-methoxy-1,2,3,4-tetrahydrobenz[f]isoquinoline (VIa). A solution of 5.14 g. of *N*-(6-methoxy-1-naphthyl-β-ethyl)propionamide and 50 ml. of phosphorus oxychloride was heated under a nitrogen atmosphere at 110–115° for 2 hr. and at 115–120° for 9 hr. The brown solution was allowed to stand at room temperature overnight. The excess phosphorus oxychloride was distilled under reduced pressure and to remove traces of the reagent, toluene (two 50-ml. portions) was added and removed under reduced pressure. The dark residue was treated with 50 ml. of water and 150 ml. of 5% hydrochloric acid. The acidic solution was extracted with ether then rendered alkaline with concen-

(11) A. L. Wilds and T. L. Johnson, *J. Am. Chem. Soc.*, **70**, 1166 (1948); A. L. Wilds, J. A. Johnson, Jr., and R. E. Sutton, *J. Am. Chem. Soc.*, **72**, 5524 (1950).

(12) Melting points are uncorrected. The infrared spectra were determined with a Baird (model B) 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 11 MS). The microanalyses were performed by Dr. S. M. Nagy and his associates.

trated potassium hydroxide solution and the precipitated product was extracted with ether and dried over potassium carbonate. Distillation of the ether gave 3.60 g. (75%) of crude 1,2 - dihydro - 4 - ethyl - 8 - methoxybenz[f]isoquinoline (IIIa), m.p. 90–143°, which was used without further purification.

Three grams of crude IIIa was dissolved in 75 ml. of glacial acetic acid and hydrogenated at room temperature and atmospheric pressure in the presence of 300 mg. of Adams catalyst. This resulted in the uptake of one molecular equivalent of hydrogen. Removal of the catalyst by filtration and concentration of the filtrate under reduced pressure gave an oil which was treated with sodium carbonate solution. Extraction of the product with ether gave 3.1 g. of crude 4-ethyl-8-methoxy-1,2,3,4-tetrahydrobenz[f]isoquinoline (VIa) as a light yellow oil which slowly solidified. The product was characterized as its perchlorate derivative which was obtained in 82% yield, m.p. 187–190°. The analytical sample of *4-ethyl-8-methoxy-1,2,3,4-tetrahydrobenz[f]isoquinoline perchlorate* was crystallized from absolute ethanol–ether and melted at 196–197.5°, $\lambda_{max}^{C_2H_5OH}$ 235 (ε 57,500), 265 (ε 6,150), 275 (ε 5,940), 319 (ε 1,820), and 333 mμ (ε 2,230) with inflections at 229 (ε 55,000), 256 (ε, 5,050), 285 (ε 3,980), 306 (ε 1,100), and 328 mμ (ε 1,600) and minima at 252, 271, 301, and 323.5 mμ.

Anal. Calcd. for $C_{16}H_{20}ClNO_5$: C, 56.22; H, 5.90; N, 4.10. Found: C, 56.00; H, 5.68; N, 4.22.

N-Carbethoxy-4-ethyl-8-methoxy-1,2,3,4-tetrahydrobenz[f]-isoquinoline (VIb). To a solution of 1.5 g. of crude 4-ethyl-8-methoxy-1,2,3,4-tetrahydrobenz[f]isoquinoline (VIa) in 10 ml. of dry pyridine and 10 ml. of anhydrous ether was added a solution of 3.0 g. of ethyl chloroformate in 10 ml. of anhydrous ether with cooling as necessary. The mixture was allowed to stand at room temperature for 1 hr. before adding 100 ml. of ether. The ether solution was washed with water, dilute hydrochloric acid, and saturated salt solution. Distillation of the ether gave 1.75 g. (90%) of a residue as colorless plates, m.p. 134–139°. The analytical sample of *N*-carbethoxy-4-ethyl-8-methoxy-1,2,3,4-tetrahydrobenz[f]-isoquinoline was crystallized from hexane and had m.p. 143–144°, $\nu_{max}^{CHCl_3}$ 1675 cm.$^{-1}$ (s, urethan carbonyl), $\lambda_{max}^{C_2H_5OH}$ 234 (ε 63,000), 254.5 (ε 4,670), 264 (ε 5,600), 274.5 (ε 5,650), 284.5 (ε 3,680), 306 (ε 990), 319 (ε 1,750), and 333.5 mμ (ε 2,280) with an inflection at 328 mμ (ε 1,530) and minima at 252, 258, 269, 283, 299, 308.5, and 323.5 mμ.

Anal. Calcd. for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.68; H, 7.22; N, 4.55.

4-Carbethoxymethyl-8-methoxy-1,2,3,4-tetrahydrobenz[f]isoquinoline (VIc). 2-(6-Methoxy-1-naphthyl)ethylamine sulfate (13.3 g.) was stirred with 300 ml. of 10% sodium hydroxide solution and the mixture was extracted with ether. The ether extract was washed, dried, and concentrated giving a residue which was mixed with 75 g. of diethyl malonate and heated under a nitrogen atmosphere at 150° for 15 hr. The excess diethyl malonate was distilled, finally at 100° (1 mm.) on a rotary evaporator. The residue (15.0 g., 90%) was a viscous oil which solidified on standing at room temperature for 1 week, $\nu_{max}^{CCl_4}$ 3350 (m, NH stretching), 1740 (s, ester carbonyl), and 1660 cm.$^{-1}$ (s, amide carbonyl). Attempts to obtain a pure sample of ethyl *N*-(6-methoxy-1-naphthyl-β-ethyl)malonamate (IIb) by recrystallization led to a solid with a wide melting point range (70–159°). However, the crude product above proved satisfactory for the next step.

To a boiling solution of 15.0 g. of crude ethyl *N*-(6-methoxy - 1 - naphthyl - β - ethyl)malonamate in 350 ml. of anhydrous toluene was added (with caution at the start) 30.0 g. of phosphorus pentoxide with vigorous stirring. Two more portions of phosphorus pentoxide of 30.0 g. each were added 10 and 25 min. after the addition of the first portion. Refluxing with stirring was continued for 45 min. after the last addition. The mixture was chilled and 500 ml. of cold water was cautiously added with stirring. The toluene layer was extracted three times with 40 ml. of 2*N* hydrochloric acid. The extracts and aqueous layer were combined without delay and rendered alkaline with saturated potassium carbonate solution. Thorough extraction of the resulting alkaline suspension with ether and removal of the ether after drying the extract over magnesium sulfate gave 6.12 g. (43.4%) of a yellow solid which resisted attempts of purification, $\nu_{max}^{CHCl_3}$ 3350 (m, NH stretching) and 1640 – 1600 cm.$^{-1}$ (s-broad, vinylogous urethan and aromatic groupings) and no absorption bands in the region of 1760–1700 cm.$^{-1}$

A solution of 5.29 g. of the crude cyclized product in 75 ml. of glacial acetic acid was hydrogenated in the presence of 0.20 g. of Adams catalyst at room temperature and atmospheric pressure. After one molecular equivalent of hydrogen had been absorbed and the rate of hydrogenation slowed, the catalyst was filtered and the acetic acid was removed under reduced pressure using a rotary evaporator. Water was added to the residue and the resulting mixture was washed with ether. The aqueous solution was made basic with potassium hydroxide solution and extracted with ethyl acetate. The ethyl acetate extracts were combined and washed with saturated salt solution, dried and concentrated under reduced pressure giving 5.34 g. (quantitative yield) of a yellow oil which crystallized slowly on standing, $\nu_{max}^{CCl_4}$ 3400 (*w*, NH stretching) and 1740 cm.$^{-1}$ (s, ester carbonyl). Attempts to recrystallize the crude 4-carbethoxymethyl-8-methoxy - 1,2,3,4-tetrahydrobenz[f]isoquinoline (VIc) led only to oils; however, the product was characterized as its picrate derivative.

A portion of the crude amino ester VIc (0.95 g.) in 10 ml. of absolute ethanol was added to a hot solution of 0.73 g. of picric acid in 10 ml. of absolute ethanol giving 1.25 g. (77%) of a yellow crystalline material, m.p. 182–185°. The analytical sample of *4-carbethoxymethyl-8-methoxy-1,2,3,4-tetrahydrobenz[f]isoquinoline picrate* was recrystallized from aqueous ethanol and had m.p. 187–187.5°, ν_{max}^{KBr} 1730 cm.$^{-1}$ (s, ester carbonyl).

Anal. Calcd. for $C_{24}H_{24}N_4O_{16}$: C, 54.54; H, 4.58; N, 10.60. Found: C, 54.57; H, 4.78; N, 10.69.

4-(2-Hydroxyethyl)-8-methoxy-1,2,3,4-tetrahydrobenz[f]-isoquinoline (VId). A solution of 5.34 g. of crude 4-carbethoxymethyl-8-methoxy-1,2,3,4-tetrahydrobenz[f]isoquinoline (VIc) in 100 ml. of anhydrous tetrahydrofuran was added dropwise with stirring to a slurry of 3.5 g. of lithium aluminum hydride in 150 ml. of anhydrous ether at such a rate as to cause gentle refluxing. After the addition was completed, refluxing was continued for 90 min. The yellow mixture was chilled and a solution of 30 g. of sodium potassium tartrate in 100 ml. of water was cautiously added with stirring. The organic layer was separated and the aqueous alkaline suspension was extracted with ether. The organic extracts were combined, dried, and concentrated to give 4.85 g. of yellow crystalline material which on recrystallization from benzene-hexane gave 2.25 g. (49%) of material, m.p. 131.5–134°. The analytical sample of 4-(2-hydroxyethyl)-8-methoxy-1,2,3,4-tetrahydrobenz[f]isoquinoline had m.p. 136.2–136.8°, $\lambda_{max}^{C_2H_5OH}$ 235 (ε 64,000), 254.5 (ε 5,130), 265 (ε 5,980), 275 (ε 5,690), 319.5 (ε 1,820), and 334 mμ (ε 2,290) with inflections at 285 (ε 3,660), 307 (ε 1,000), and 329 mμ (ε 1,610) and minima at 253, 258.5, 270, 301, and 324 mμ.

Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.42; H, 7.45; N, 5.58.

N-Carbethoxy-4-(2-hydroxyethyl)-8-methoxy-1,2,3,4-tetrahydrobenz[f]isoquinoline (VIe). A solution of 0.16 g. of ethyl chloroformate in 10 ml. of ether was added to a solution of 0.34 g. of 4-(2-hydroxyethyl)-8-methoxy-1,2,3,4-tetrahydrobenz[f]isoquinoline (VId) in 20 ml. of dry pyridine under a nitrogen atmosphere. The mixture was allowed to stand at room temperature overnight and was then heated on a steam bath for 2.5 hr. The ether and pyridine were removed at reduced pressure and the residue was washed with water. Traces of moisture were removed from the residue by dissolving it in benzene and concentrating the resulting solution. The residue, 0.393 g. (91%), was distilled in a sublimation apparatus at 120–125° (bath temperature) and 0.001

mm. to give a virtually quantitative recovery of *N*-carbethoxy-4-(2-hydroxyethyl)-8-methoxy-1,2,3,4-tetrahydrobenz[f]isoquinoline as a glass-like substance, $\nu_{max}^{CHCl_3}$ 3470 (m, OH stretching) and 1665 cm.$^{-1}$ (s, urethan, carbonyl).

Anal. Calcd. for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.29; H, 7.32; N, 4.26.

N-Carbomethoxymethyl-4-(2-hydroxyethyl)-8-methoxy-1,2,3,4-tetrahydrobenz[f]isoquinoline (VIf). A solution of 2.62 g. of 4-(2-hydroxyethyl)-8-methoxy-1,2,3,4-tetrahydrobenz-[f]isoquinoline (VId) and 1.54 g. of methyl bromoacetate in 150 ml. of pure tetrahydrofuran was refluxed with stirring for 8 hr. during which time a white precipitate formed. The precipitate was removed by filtration and the filtrate was evaporated under reduced pressure to give a crystalline residue. Recrystallization of this residue from benzene-hexane gave 1.51 g. (45%) of the *N*-alkylated product, m.p. 124–127°. The analytical sample of VIf had m.p. 127.5–128°, $\nu_{max}^{CHCl_3}$ 3450 (m, OH stretching) and 1745 cm.$^{-1}$ (s, ester carbonyl).

Anal. Calcd. for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.70; H, 7.26; N, 4.38.

The white precipitate obtained from the reaction mixture proved to be *4-(2-hydroxyethyl)-8-methoxy-1,2,3,4-tetrahydrobenz[f]isoquinoline hydrobromide*. The analytical sample was crystallized from absolute ethanol–ether as a highly hygroscopic material, m.p. 197.5–198°.

Anal. Calcd. for $C_{16}H_{20}BrNO_2$: C, 56.81; H, 5.96; Br, 23.63; N, 4.14. Found: C, 56.76; H, 6.19; Br, 23.23; N, 4.14.

Treatment of the hydrobromide with base gave 1.15 g. of unchanged starting material VId, representing a 44% recovery, m.p. 135–136°.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF CONNECTICUT AND THE ORGANIC CHEMICAL INSTITUTE OF THE UNIVERSITY OF ZÜRICH]

Catalpa Glycosides. I. The Characterization of Catalposide[1]

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Catalposide has been isolated from several species of *Catalpa* and has been established as a $C_{22}H_{26}O_{12}$ compound; a D-glucoside and an ester of *p*-hydroxybenzoic acid. It contains one additional hydroxyl group and an isolated double bond.

Catalposide was isolated from the fruit of *Catalpa bignonioides* in 1888 by Claassen[3] who named it catalpin. It was reisolated from the same plant fifty-five years later by Colin, Tanret, and Chollet[4,5] who named it catalposide. Still another isolation, this time from several species of *Catalpa*, was made by Plouvier.[6] Catalposide is reported[4,5] to give a positive reducing test when boiled with Fehling's solution, a positive xanthoproteic test, a positive biuret test, to be converted to a black polymer by acid hydrolysis, and to be hydrolyzed by emulsin.[4] In a more recent publication[7] catalposide is postulated to be a complex polysaccharide.

The most striking property of catalposide is its destruction by acidic and enzymatic hydrolysis resulting in the formation of colored solutions and black, amorphous precipitates.[4,5] The sugar portion, however, is stable and remains in the hydrolyzate. From the optical rotation of this solution, it was concluded that the sugar was probably glucose.[4,5] This tendency to decompose is reminiscent of the aucubin type[8] of glucosides, that is, aucubin,[9] monotropein,[10] asperuloside,[11] plumierid,[12] and agnusid.[13] None of the papers on catalposide report any analyses or derivatives or any attempts other than a melting point and a rotation to characterize it in a quantitative manner. This paper reports the

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(2) Abstracted in part from the M.S. Thesis of T. B. Africa, the University of Connecticut, 1959. Present address: Research Laboratories, Chas. Pfizer and Co., Groton, Conn.

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