(95%) of methyl 4-nitrophthalimidoacetate, m.p. 123°, from 2.0 g. (0.008 mole) of 4-nitrophthalimidoacetic acid. Samples of these esters for microanalysis were recrystallized from methanol, which did not alter the melting points.

Anal. Calcd. for $C_{11}H_8N_2O_6$: C, 50.01; H, 3.05; N, 10.60. Found for methyl 3-nitrophthalimidoacetate: C, 50.20; H, 3.26; N, 11.10. Found for methyl 4-nitrophthalimidoacetate: C, 50.36, 50.20; H, 3.27, 3.19; N, 10.80.

Hydrogenation of the Nitrophthalimidoacetic Acids and Their Esters.—The nitro compound was mixed with 5 ml. of methanol for each gram of compound and 0.1–0.5 g. of 10% palladium-charcoal was added. The hydrogenations were done at room temperature and initial pressures of 55–65 p.s.i.g. The products were recrystallized from 50–100 ml. of methanol. 3-Aminophthalimidoacetic acid, 8.4 g. (76%), m.p. 214°, was obtained from 12.5 g. (0.05 mole) of 3-nitrophthalimidoacetic acid and 0.5 g. of Pd–C; 4.2 g. (95%) of 4-aminophthalimidoacetic acid, m.p. 242–244°, was obtained from 5.0 g. (0.02 mole) of 4-nitrophthalimidoacetic acid and 0.1 g. of Pd–C; 20.9 g. (89%) of methyl 3-aminophthalimidoacetate, m.p. 145–146°, was obtained from 26.4 g. (0.10 mole) of methyl 3-nitrophthalimidoacetate and 0.5 g. of Pd–C; and 2.64 g. (0.01 mole) of methyl 4-nitrophthalimidoacetate and 0.1 g. of Pd–C gave 1.9 g. (81%) of methyl 4-aminophthalimidoacetate, m.p. 205.5–207.5°. All of these products were yellow, crystalline powders.

Anal. Calcd. for $C_{10}H_8N_2O_4$: C, 54.55; H, 3.66; N, 12.72. Found for 3-aminophthalimidoacetic acid: C, 53.91, 53.80; H, 4.03, 3.92; N, 12.92. Found for 4-aminophthalimidoacetic acid: C, 54.16; H, 3.88; N, 13.55.

Anal. Calcd. for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found for methyl 3-aminophthalimidoacetate: C, 55.92; H, 4.49; N, 12.00. Found for methyl 4-aminophthalimidoacetate: C, 56.31; H, 4.52; N, 11.49.

3-Nitrophthalimide.[14]—An intimate mixture of 19.0 g. (0.1 mole) of 3-nitrophthalic anhydride and 6.0 g. (0.1 mole) of urea was added to 100 ml. of nitrobenzene and the mixture was refluxed with stirring for 1 hr. The reaction mixture was cooled to room temperature and filtered. The yellowish precipitate was washed with five 5-ml. portions of benzene and dried. The crude product weighed 17.7 g. (92%) and melted at 205–208°. The reported[15] melting point of 3-nitrophthalimide was 216°.

3-Aminophthalimide.[14]—A mixture of 9.6 g. (0.05 mole) of crude 3-nitrophthalimide and 250 ml. of methanol was hydrogenated in the presence of 0.50 g. of 10% Pd–C. The resulting precipitate was extracted with boiling water, from which 4.6 g. (57%) of 3-aminophthalimide separated on cooling as fine yellow crystals, m.p. 270–271° (lit.[8c] m.p. 266–267°). A transition in crystal form to glittering yellow needles was observed at 223–224°.

4-Aminophthalimide.—A sample of 4-aminophthalimide was kindly provided by Professor Robert W. Higgins.

N-(Carboxymethyl)phthalamic Acid.[16]—The method of Minard and Fox[11] for saponifying the imide ring was used. Phthalimidoacetic acid[17] (10.5 g., 0.05 mole) was titrated with 2 *N* sodium hydroxide to a phenolphthalein end point, and an equal amount of 2 *N* sodium hydroxide, plus a 1.0-ml. excess, was added. The solution was warmed on a water bath to 70°, then quickly cooled in an ice bath, and acidified with concentrated hydrochloric acid. The precipitate of N-(carboxymethyl)phthalamic acid weighed 5.0 g. (45%) and melted at 103–105° (Thiele apparatus). The reported[18] melting point was 105–106°.

Absorption Spectra.[19]—All absorption spectra were determined with a Cary Model 15 recording spectrophotometer, using 1-cm. cells and concentrations in the range 10^{-5} to 10^{-2} *M*. Neutral solutions were prepared in 95% alcohol. Spectra of acidic and basic solutions were determined using solutions which had been prepared by dilution of a stock solution in alcohol with 0.1 *N* hydrochloric acid or 0.1 *N* sodium hydroxide.

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[14] Prepared by Miss Nancy Rodman.

[15] H. Seidel and J. C. Bittner, *Monatsh.*, **23**, 415 (1902).

[16] Phyllis Ann Faegre, Senior Thesis, Upper Iowa University, 1961, p. 8.

[17] Sigma Chemical Co., St. Louis, Mo.

[18] S. Gabriel and K. Kroseberg, *Ber.*, **22**, 426 (1889).

[19] The assistance of Misses Nancy Rodman and Paddy Wright in the determination of the absorption spectra is gratefully acknowledged.

The Syntheses of *cis*- and *trans*-Δ^4-Tetrahydrohomophthalic Acids

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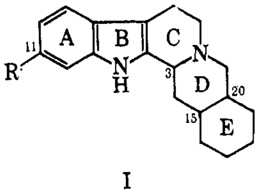
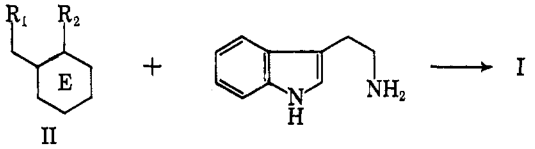
The syntheses of both *cis*- and *trans*-Δ^4-tetrahydrohomophthalic acids and the preparation of several derivatives of these new dicarboxylic acids are described.

In the field of alkaloid chemistry the basic pentacyclic skeleton of the yohimbane family is a familiar structure (I). Changes in the geometry of the hydrogen atoms attached to certain vital centers (positions 3, 15, 20) completely alter the properties of the individual members of this family. In addition to this, one can position various functional groups about this structure and by having the proper stereochemistry form many compounds of medicinal interest such as reserpine[1] and yohimbine.[2]



I

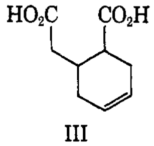
Evaluation of structure I indicates, as a synthetic route, a condensation reaction between tryptamine or some variant and an intermediate such as structure II.



II

R_1, R_2 = functional groups that will condense with amines, such as acids, acid chloride, aldehydes, etc.

An interesting untried intermediate in this direction is Δ^4-tetrahydrohomophthalic acid (III) which has the feature of a double bond which could be manipulated, when necessary, to attach desired functional groups.



III

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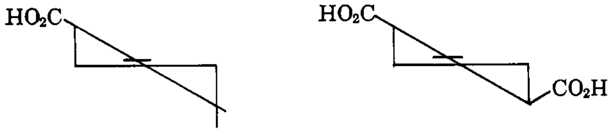
[1] For synthesis, see R. B. Woodward, F. Bader, H. Bickel, and R. Kierstead, *Tetrahedron*, **2**, 1 (1958).

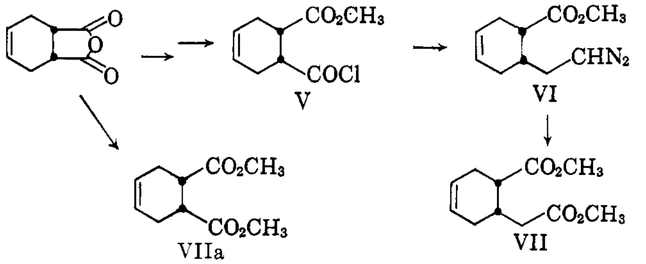
[2] For synthesis, see E. Van Tamelen, M. Shamma, A. Burgstahler, J. Wolinsky, R. Tamm, and P. Aldrich, *J. Am. Chem. Soc.*, **80**, 5006 (1958).

By synthesizing both the *cis* and *trans* isomers of III we would have intermediates common to all members of the yohimbane[3] series depending on the conformation at position 3 which would be determined by the stereochemistry[4] of the tryptamine condensation reaction.

The Δ^4-tetrahydrophthalic acids (IV) were chosen as a starting point. The *cis* isomer was commercially available, while the *trans* was obtained, after some difficulty, by a Diels–Alder reaction between fumaric acid and butadiene in a sealed tube. In order to synthesize the desired intermediate (III), one side chain had to be selectively extended (by one methylene group).


cis IV *trans*

A successful series of reactions was reached utilizing the Arndt–Eistert reaction. Starting with the acid chloride (V), the diazo ketone (VI) was prepared and used directly in the Wolff[5] rearrangement. The infrared spectra had the absorption peaks at 4.7 and 6.05 μ characteristic of diazo ketones.[6] Rearrangement in dry methanol gave the chain-extended dimethyl ester (VII) distilling at 135° (10 mm.). Its infrared spectra had peaks at 5.75 and 6.95 μ corresponding to ester and methoxy absorption. These peaks were identical with those of the nonchain-extended dimethyl ester (VIIa). Although elemental analysis distinguished between the two compounds, it was necessary to find a rapid means of identification. This was important because, if in the addition of the acid chloride (V) to diazomethane, hydrolysis had occurred, the resultant acid would react to form the nonchain-extended diester. This product would then be carried through the Wolff rearrangement without detection because the diazo ketone (VI) also had a methyl ester side chain. The boiling points of the two compounds are so close (VIIa, b.p. 120° at 5 mm.); VII, b.p. 118° at 3 mm.) that they could not be used to distinguish between them. Careful inspection of the infrared spectra of the two compounds did disclose a difference not in the frequency of the peaks but in the shape of the spectra between 7.25 and 9.0 μ. The chain-extended diester had an increasing slope (Fig. 1a) between these frequencies, while the nonchain-extended had a horizontal one (Fig. lb)


V VI VIIa VII

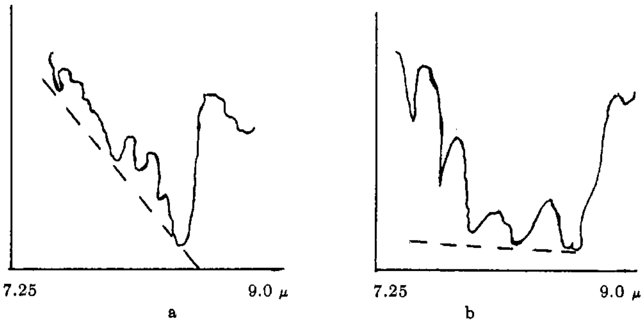
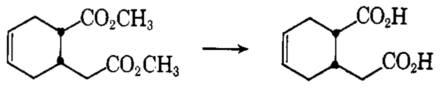
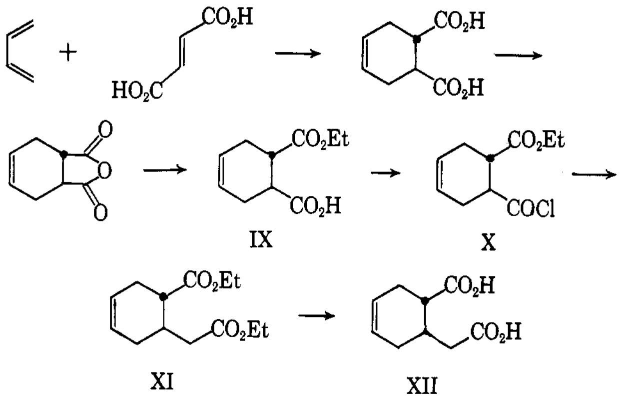


Fig. 1.—Infrared spectra ($CHCl_3$) of VII and VIIa: a, chain-extended dimethyl ester (VII); b, nonchain-extended dimethyl ester (VIIa).

The diester (VII) was hydrolyzed to the free acid with a saturated methanol solution of NaOH followed by acidification. This new dicarboxylic acid, *cis*-Δ^4-tetrahydrohomophthalic acid (VIII), melted at 155.5°–157°. The nonchain-extended acid (IV) was readily distinguished from this new acid by melting point.


VII VIII

trans-Δ^4-**Tetrahydrohomophthalic Acid.**—The synthesis of the *trans* chain-extended acid (XII) was accomplished by a route similar to the *cis*, except that the diethyl ester (XI), was prepared instead of the methyl ester. This synthesis of XII also confirmed that the *cis* acid had not isomerized during the Arndt–Eistert and Wolff rearrangements. The *trans* acid had a melting point of 154–156°. This is extremely close to that of the *cis* acid (155.5–157°), but a mixture melting point of the two was depressed to 130–144°.


IX X XI XII

Unexpectedly, both the *cis*- and *trans*-Δ^4-terahydrohomophthalic acids produced identical anhydrides (XIII), with acetyl chloride or acetic anhydride. The mixture melting points were not depressed, and their infrared spectra were identical. This indicated that either the *cis* or *trans* acid was isomerizing to its opposite configuration during anhydride formation. The problem was resolved by hydrolyzing the anhydride formed from the *cis* acid, and showing that this hydrolyzed product was not *cis* but identical with the *trans* acid. This definitely established that the *cis*-Δ^4-tetrahydrohomophthalic acid underwent isomerization during anhydride formation to give a *trans* anhydride.

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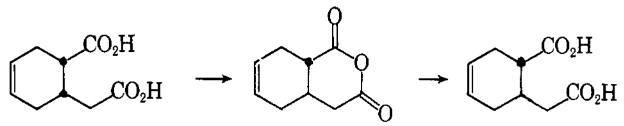
[3] E. Van Tamelen, M. Shamma, and P. Aldrich, *J. Am. Chem. Soc.*, **78**, 4628 (1956).

[4] It has been shown that the hydrogen at this position can be changed from α to β. See ref. 1.

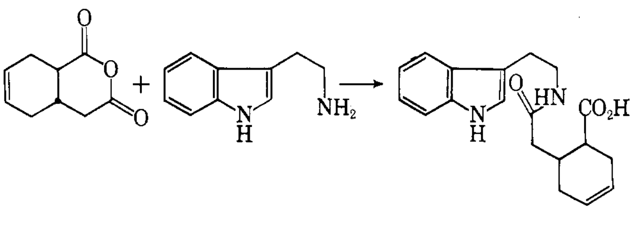
[5] L. Wolff, *Ann.*, **394**, 25 (1912).

[6] P. Yates, N. Yoda, and J. Fugger, *J. Am. Chem. Soc.*, **79**, 5756 (1957).

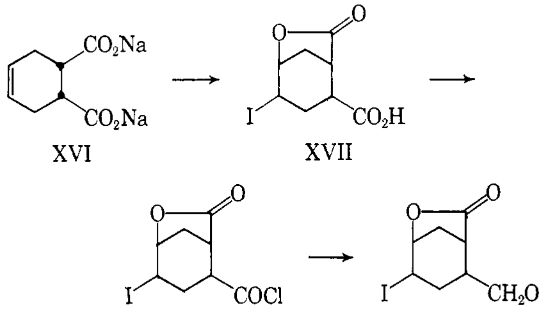


cis or *trans* XIII *trans*

Preliminary experiments have shown that the *trans* anhydride will condense with tryptamine to give a product showing infrared absorption at 5.84, 6.15, and 6.53 μ corresponding to the acid and double amide absorption expected of an N-(β-indolylethyl)tetrahydromophthalamic acid (XIV).



In connection with variations of our approach, iodolactonizations were successfully attempted. For example, in an aqueous solution of potassium iodide and iodine, the disodium salt of tetrahydrophthalic acid (XVI) formed a crystalline product melting at 161–162° in 93% yield. Theoretically γ,δ-unsaturated acids could form two possible iodolactones, the δ-iodo-γ-lactone and the γ-iodo-δ-lactone. The crystalline iodolactone prepared in this laboratory exhibited strong absorption in the 5.6-μ region[7] of the infrared, thereby indicating a five-membered lactone. This γ-lactone (XVII) was treated with an excess of oxalyl chloride to give a crystalline product melting at 108.5–110.5°. The infrared spectra showed a single peak at 5.65 μ, indicating an overlap of the acid chloride and lactone absorption bands. Refluxing the acid chloride with sodium borohydride in diglyme produced a light brown oil which crystallized after standing in a chloroform solution for several days. This new hydroxyiodolactone (XIX) melting at 124–126° showed peaks at 2.95 and 5.69 μ in the infrared (KBr), corresponding to the hydroxyl and five-membered lactone absorption. A major drawback, however, to continuing this reaction series to obtain the desired chain-extended acid was the extremely low yield (1%) of the final step.



XVI XVII XVIII XIX

Experimental

Monomethyl Ester Acid Chloride of Tetrahydrophthalic Acid (V).—To a solution of 65 g. (0.35 mole) of the monomethyl ester of *cis*-Δ^4-tetrahydrophthalic acid in 470 ml. of dry benzene was slowly added 46.8 ml. (0.55 mole) of oxalyl chloride. Reaction occurred at room temperature and continued for several hours with occasional shaking. The solution was heated to reflux in a water bath for 0.5 hr. After removing the benzene, the residue was vacuum distilled at 110° (5 mm.) to give 65.65 g. (91.3%) of pure product. The infrared spectra showed characteristic peaks at 5.56 and 5.73 μ corresponding to the acid chloride and ester absorption.

Anal. Calcd. for $C_9H_{11}O_3Cl$: C, 53.47; H, 5.45; Cl, 17.33. Found: C, 53.63; H, 5.37; Cl, 17.06.

Dimethyl Ester of Tetrahydrohomophthalic Acid (VII).—A cold solution of 29 g. (0.14 mole) of the monomethyl ester acid chloride (V) in 50 ml. of dry ether was slowly added to a cold stirred solution of 42 g. (1 mole) of diazomethane in 500 ml. of ether. The reaction mixture was stirred overnight at room temperature. After removal of the ether the dark orange liquid residue (the infrared absorption spectrum showed characteristic bands for diazo ketone[6] at 4.7 and 6.05 μ) was dissolved in 500 ml. of dry methanol and heated to reflux. Two grams of freshly prepared silver oxide was added in small portions over a 2-hr. period. Reflux was continued for 3 hr. during which time a silver mirror (often a black deposit) coated the reaction flask. The resulting mixture was filtered while hot, through a coarse sintered-glass funnel, and cooled. The yellow solution was again filtered and the excess methanol was stripped off. The residue was vacuum distilled at 135° (10 mm.) to give 21 g. (69%) of diester. The infrared spectra showed peaks at 5.75 and 6.95 μ corresponding to the ester and methoxy absorption.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.26; H, 7.55. Found: C, 62.03; H, 7.40.

1,2-Dicarbomethoxy-Δ^4-cyclohexene (VIIa).—*cis*-Δ^4-Tetrahydrophthalic anhydride (228 g., 1.5 moles) was refluxed with 364 ml. (9 moles) of anhydrous methanol and 2.5 g. of *p*-toluene sulfonic acid monohydrate for 16 hr. This was followed by 270 ml. of toluene and the mixture was distilled. The distillation was discontinued when the temperature rose to 110°. Another 364 ml. of methanol was added and the solution was refluxed for 16 hr. more. An additional 270 ml. of toluene was added and distilled as before. The last traces of toluene and methanol were removed at aspirator pressure. The residue was diluted with three 100 ml. portions of 3% sodium chloride solution. After drying over magnesium sulfate and filtering, the ether solution was concentrated and the residue was vacuum distilled at 110–113° (3 mm.) (lit.[8] b.p. 120–121° at 7 mm.) to give 270 g. (91%) of the diester.

Tetrahydrohomophthalic Acid (VIII).—Fifty milliliters of a saturated NaOH solution (in methanol) was added to 5.1 g. (0.024 mole) of the diester (VII) in 10 ml. of methyl alcohol. The yellow mixture was stirred for 24 hr. and then filtered. The precipitated sodium salt was dissolved in water, heated with charcoal, and filtered. The filtrate was put in an ice bath and stirred while it was acidified with concentrated HCl. The clear solution was then concentrated in half and allowed to stand at room temperature for 48 hr. The precipitate was filtered off and dried to give 1.39 g. melting at 148–152°. The filtrate was concentrated to dryness and the residue dissolved in a minimum of hot water. This yielded an additional 0.77g. Recrystallization of the combined yields from hot water gave 2.0 g. (46%) melting at 155.5–157°. Infrared spectra (KBr) showed characteristic absorption for an acid at 5.83 μ.

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.70; H, 6.52. Found: C, 58.48; H, 6.86.

***trans*-Tetrahydrophthalic Acid.**—Five grams (0.043 moles) of fumaric acid, 25 ml. of water, and 10 ml. (0.129 mole) of butadiene were reacted in a sealed tube which was heated in an oil bath to 150° for 48 hr. The reaction mixture was then dissolved in hot water and filtered. The filtrate was allowed to cool slowly and 5.9 g. (50%) of product crystallized melting at 169–171°. Recrystallization from hot water did not change the melting point (lit.[9] m.p. 172°).

Anhydride of *trans*-Tetrahydrophthalic Acid.—In a flask fitted with a water condenser (with a drying tube) 12.0 g. (0.071 mole) of the *trans* diacid and 75 ml. of acetyl chloride were refluxed for 3 hr. After concentrating and cooling the reaction, the anhydride crystallized from solution to give 7.98 g. (73.6%) melting at 187–190°. Recrystallization from ethyl acetate–petroleum ether gave m.p. 187.5–189°.

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(7) R. Rasmussen and R. Brattain, *J. Am. Chem. Soc.*, **71**, 1073 (1949).

(8) A. C. Cope and E. C. Herrick, *Org. Syn.*, **30**, 29 (1950).

(9) R. E. Buckles, *Chem. Rev.*, **57**, 641 (1957).

Monoethyl Ester of *trans*-Tetrahydrophthalic Acid (IX).—Six milliliters (0.10 moles) of ethanol and 7.98 g. (0.052 mole) of the *trans* anhydride were refluxed for 20 hr. The reaction mixture was then cooled and diluted with cold petroleum ether. Filtration yielded 3.99 g. (45%) of monoester melting at 60–63.5°.

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.60; H, 7.07. Found: C, 60.74; H, 7.16.

Monoethyl Ester Acid Chloride of *trans*-Tetrahydrophthalic Acid (X).—At room temperature 6 g. (0.03 mole) of the *trans* monoester (IX) was dissolved in 33 ml. of dry benzene and 10 ml. (0.12 mole) of oxalyl chloride was slowly added. After standing 4 hr. with occasional shaking the reaction was refluxed for half an hour on a stream cone. Concentration of the solution left a residue which was vacuum distilled at 118° (3 mm.) to give 4.57 g. (70.3%) of product. The infrared spectra ($CHCl_3$) showed characteristic peaks at 5.60, 5.75, and 7.25 μ corresponding to the acid chloride, ester, and ethoxy absorption.

Anal. Calcd. for $C_{10}H_{13}O_3Cl$: C, 55.50; H, 6.02; Cl,16.20. Found C, 55.73; H, 6.19; Cl, 16.34.

Diethyl Ester of *trans*-Tetrahydrohomophthalic Acid (XI).—A cold solution of 4.5 g. (0.021 mole) of the *trans* ester acid chloride (X) in 50 ml. of dry ether was slowly added to a cold stirred solution of 8.8 g. (0.21 moles) of diazomethane in 200 ml. of ether. The reaction was stirred for 20 hr. Removal of the ether left an orange liquid residue (the infrared absorption spectra showed characteristic bands for diazo ketone at 4.7 and 6.05 μ) which was dissolved in 250 ml. of absolute ethanol and refluxed for 5 hr. with 1 g. of freshly prepared silver oxide. After formation of a silver mirror (or black deposits) on the flask the reaction was filtered hot through a sintered-glass funnel and allowed to cool. The yellow solution was then filtered again and the excess ethanol stripped off. The residue was vacuum distilled at 127° (5 mm.) to give 2.23 g. (40%) of the diethyl ester. Infrared absorption peaks at 5.75 and 7.25 μ corresponding to the ester and ethoxy absorption were present.

Anal. Calcd. for $C_{13}H_{20}O_4$: C, 65.00; H, 8.33. Found: C, 65.02; H, 8.58.

***trans*-Tetrahydrohomophthalic Acid (XII).**—An ethanol solution of 2.2 g. (0.009 mole) of the *trans* chain-extended diester (XI) was stirred overnight at room temperature with 25 ml. of a saturated solution of NaOH (in ethanol). The disodium salt was filtered and then hydrolyzed with concentrated HCl. The dicarboxylic acid separated in three crops (concentrate of the mother liquor): (1) 0.2 g., m.p. 146–149°; (2) 0.34 g., m.p. 129–138°; and (3) 0.37 g., m.p. 132–138°. Total weight was 0.91 g. (50%). Recrystallization from hot water yielded 0.80 g. melting at 154–156°. Mixture melting point with the *cis* dicarboxylic acid was depressed 130–144°. The infrared spectra (KBr) showed acid absorption at 5.83 μ.

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.70; H, 6.52. Found: C, 58.47; H, 6.69.

Tetrahydrohomophthalic Anhydride (XIII) from the *cis* Dicarboxylic Acid (VIII). Method A.—A 0.5-g. sample (0.003 mole) of the *cis* chain-extended dicarboxylic acid was refluxed with 9 ml. of 94% acetic anhydride for 2 hr. Removal of the excess acetic anhydride and acetic acid led to solidification of the product. Recrystallization from ethyl acetate–petroleum ether gave 0.38 g. (84%) melting at 165.5–166.5°. The infrared spectra showed the characteristic double peaks for a six-membered cyclic anhydride at 5.53 and 6.65 μ.

Anal. Calcd. for $C_9H_{10}O_3$: C, 65.06; H, 6.02. Found: C, 64.93; H, 6.07.

Method B.—One gram (0.0054 mole) of the *cis* diacid was refluxed with 18 ml. of acetyl chloride for 2 hr. The reaction was then concentrated and the light brown solid residue was recrystallized from ethyl acetate-petroleum ether to give 0.65 g. (72.5%) of the anhydride melting at 165–167°. The infrared spectra was identical with that of the previously prepared anhydride. The melting point was not depressed.

Method C.—A 0.5-g. sample (0.0021 mole) of the disodium salt of the *cis* diacid in warm chloroform was treated with 10 ml. of oxalyl chloride according to the method of Adams.[10] After heating for 5 hr. the reaction was filtered and the filtrate was concentrated. The solid residue was recrystallized from ethyl acetate–petroleum ether to give 0.20 g. (80%) of product melting at 165.5–167°. The infrared spectra was identical with that of the previously prepared sample and the mixture melting point was not depressed.

From the *trans* Dicarboxylic Acid (XII). Method A.—In 20 ml. of 97% acetic anhydride 0.3 g. (0.0016 mole) of the *trans* dicarboxylic acid was refluxed for 2.5 hr. After cooling the reaction mixture it was concentrated and the solid residue was recrystallized from ethyl acetate–petroleum ether to give 0.22 g. (81.4%) of the anhydride melting at 166–167°. The infrared spectra was identical with that of the anhydride prepared from the *cis* acid. The mixture melting point with the anhydride prepared from the *cis* acid was not depressed, m.m.p. 165–167°.

Method B.—One-half gram (0.003 mole) of the *trans* chain-extended dicarboxylic acid was refluxed for 2 hr. with 10 ml. of acetyl chloride. Concentration of the reaction yielded 0.36 g. melting at 165–167°. Recrystallization from ether acetate–petroleum ether gave a 0.2 g. (45%) of the anhydride melting 165–166°. The mixture melting point with the anhydride prepared from the *cis* acid was not depressed. The infrared spectra was also identical.

Hydrolysis of Tetrahydrohomophthalic Anhydride (XIII).—In 25 ml. of water 0.5 g. (0.003 mole) of the anhydride prepared from the *cis* dicarboxylic acid was refluxed until complete solution occurred. The reaction was concentrated and allowed to cool to room temperature. Colorless flakes crystallized after 2 days to give 0.39 g. (70.8%) which melted at 154.5–156°. The mixture melting point with the *cis* chain-extended diacid was depressed, m.m.p. 130–145°. The mixture melting point with the *trans* chain-extended diacid was not depressed.

N-(β-Indolylethyl)tetrahydrohomophthalamic Acid (XIV).—A stirred solution of 0.29 g. (0.0018 mole) of tryptamine in 50 ml. of chloroform was warmed nearly to reflux. To this was added 0.29 g. (0.0018 mole) of tetrahydrohomophthalic anhydride in 15 ml. of $CHCl_3$. The addition took 1 hr. The stirring was continued for 18 hr. after the addition was completed. The reaction mixture was then cooled and diluted with excess petroleum ether. The precipitate was filtered and dried in a vacuum desiccator to give 0.6 g. melting at 70–73° with decomposition. The infrared spectra (KBr) showed peaks at 5.84, 6.15, and 6.53 μ corresponding to the acid and amide I and II absorption.

δ-Iodo-γ-lactone of N-(β-Indolylethyl)tetrahydrohomophthalic Acid.—A solution of 0.75 g. (0.0023 mole) of the chain-extended iodolactone acid chloride (XV) in dry pyridine was slowly added to 0.58 g. (0.0036 mole) of tryptamine in 35 ml. of pyridine. The resultant orange solution turned an opaque orange-red after stirring for 2.5 hr. at room temperature. The stirring was continued overnight. The reaction was then poured into an ice–H_2SO_4 mixture and stirred for 1 hr. This mixture was extracted with chloroform and the chloroform layers were washed with dilute sulfuric acid, sodium bicarbonate, and water. The extract was then dried over $MgSO_4$ and filtered. The filtrate was concentrated to give a light brown residue which foamed when dried in a vacuum desiccator. This residue weighing 0.51 g. (45%) gave peaks in the infrared at 5.65, 6.00, and 6.60 μ corresponding to five-membered lactone and amide I and II absorption.

γ-Lactone of 3-Hydroxy-4-iodo-1,6-dicarboxycyclohexane (XVII).—Following the method of Klein[11] with some modification, 38 g. (0.150 mole) of iodine and 75 g. (0.452 mole) of KI were dissolved in 600 ml. of water in an erlenmeyer flask. To this was added a solution of 12 g. (0.0714 mole) of Δ^4-tetrahydrophthalic acid and 19 g. (0.232 mole) of $NaHCO_3$ in 300 ml. of water. After standing 4 hr. the dark purple mixture was poured into a 2-l. beaker containing 75 ml. of concentrated HCl, 75 ml. of H_2O, and 150 g. of ice. This was stirred for 2 hr. Ten 100-ml. portions of $CHCl_3$ were used to extract the mixture. The $CHCl_3$ layers were treated with an $NaHSO_3$ solution until decolorized. This was followed by washing with a saturated NaCl solution and drying over $MgSO_4$. After filtering and concentrating, the filtrate yielded 19.5 g. (93%) of product which melted at 159–162°. Recrystallization from benzene gave a melting point of 161–162°.

Anal. Calcd. for $C_8H_9IO_4$: C, 32.45; H, 3.04; I, 42.57. Found: C, 32.65; H, 3.23; I, 42.31.

γ-Lactone of 3-Hydroxy-4-iodo-1-carboxy-6-(carbonyl chloride)-cyclohexane (XVIII).—To 3.54 g. (0.012 mole) of the iodolactone acid (XVII) in 25 ml. of benzene was added 8 ml. of oxalyl chloride. This was allowed to react at room temperature for 17 hr. The pink mixture was then heated on a steam bath with shaking until all the solid went into solution. After filtering hot and cooling the filtrate, the red solution was concentrated. The residual red oil was solidified in the vacuum desiccator. Re-

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[10] R. Adams, *J. Am. Chem. Soc.*, **42**, 599 (1920).

[11] J. Klein, *ibid.*, **81**, 3611 (1959).

crystallization from hot CCl_4 gave 3.65 g. (96%) melting at 108.5–110.5°.

Anal. Calcd. for $C_8H_8ClIO_3$: C, 30.57; H, 2.55; I, 40.45; Cl, 11.15. Found: C, 30.79; H, 2.73; I, 40.62; Cl, 10.95.

γ-Lactone of 3-Hydroxy-4-iodo-1-carboxy-6-hydroxymethylcyclohexane (XIX).—Following the method of Brown and Chaiken[12] with some modification, a three-necked flask fitted with a water condenser and stirrer and containing 25 ml. of purified diglyme was heated to 40°. To this was added 0.3 g. (0.008 mole) of sodium borohydride and the temperature was raised to 60°. The iodolactone acid chloride (4.0 g., 0.0127 mole) in 25 ml. of diglyme was slowly added over a 0.75-hr. period. The reaction mixture turned an opaque orange. Stirring and heating were continued for 3 hr., and then the mixture was cooled slowly overnight. The reaction was then poured on a 1:1 mixture of ice–HCl and stirred for 1 hr. The red solution was extracted with $CHCl_3$. The $CHCl_3$ layer was treated with 20% $NaHCO_3$, $NaHSO_3$, and water, respectively. The yellow $CHCl_3$ layer was then dried over $MgSO_4$, filtered, and concentrated. The residual liquid was vacuum distilled using a water bath at 50° to remove the diglyme. The remaining light brown oil (0.09 g.) precipitated 0.04 g. (1.1%) of product after dilution with $CHCl_3$ and standing several days. A melting point of 124–126° was obtained using a Kofler block. The infrared spectra (KBr) indicated –OH and 5-membered lactone at 2.95 and 5.69 μ, respectively.

Anal. Calcd. for $C_8H_{11}IO_3$: C, 34.04; H, 3.90; I, 45.04. Found: C, 34.20; H, 3.82; I, 45.23.

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[12] W. G. Brown and S. W. Chaiken, *J. Am. Chem. Soc.*, **71**, 122 (1949).

The Configuration at C-20 of 11-Oxygenated 3α,20-Dihydroxy-5β-pregnan-21-oic Acids[1]

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The C-20 configuration in a pair of epimeric 3α,20-diacetoxy-11-oxo-5β-pregnan-21-oic acids (m.p. 199–200° and 261.5–262°) was determined by correlation with the configuration in 3α,20β,21-triacetoxy-5β-pregnan-11-one. 3α,20β-Diacetoxy-11-oxo-5β-pregnan-21-al was prepared by ozonization of the corresponding 21-benzylidene derivative. Reduction of the 3α,20β-diacetoxy-11-oxo-5β-pregnan-21-al at C-21 followed by acetylation gave 3α,20β,21-triacetoxy-5β-pregnan-11-one and established the 20β-configuration in the aldehyde. Oxidation of the aldehyde with potassium permanganate produced 3α,20β-diacetoxy-11-oxo-5β-pregnan-21-oic acid which was identical with the 3α,20-diacetoxy-11-oxo-5β-pregnan-21-oic acid of m.p. 199–200°. In the 20-hydroxypregnan-21-oic derivatives, C-20 configuration was established in another manner. Lithium aluminum hydride reduction of both 3α,20β,21-trihydroxy-5β-pregnan-11-one and methyl 3α,20-dihydroxy-11-oxo-5β-pregnan-21-oate (of the same configuration at C-20 as the 3α,20-diacetoxy-11-oxo-5β-pregnan-21-oic acid of m.p. 199–200°) gave the same product: 5β-pregnane-3α,11β,20β,21-tetrol.

When the 17β-steroidal glyoxal I (Fig. 1) is treated with alkali and the product is acetylated, two substances (II and III), which are isomeric at C-20, are formed.[2] We wished to determine the C-20 configuration of these compounds and their derivatives. The optical rotatory values of the hydroxyl compounds and their acetates were determined, and the data were correlated[2] according to procedures used by Fieser and Fieser[3,4] and by Sarett[5] for assigning C-20 configuration to steroids. There were reasons to suspect[2] that the C-20 configuration indicated for substances II and III by these procedures was wrong. Consequently, the transformations outlined in Fig. 2 have been performed in order to establish unequivocally the C-20 configuration in these epimeric 20-hydroxypregnan-21-oic acids.

Oliveto, *et al.*,[6] reduced the 20-keto group of the benzylidene (IV) and obtained a 20-hydroxyl derivative which was tentatively assigned the β-configuration on the basis that metal hydride reduction of 20-keto steroids usually gives predominantly 20β-hydroxyl derivatives.

We reduced several samples of this benzylidene (IV) under conditions similar to those described by the Schering group.[6] If the solution was agitated, reduction at C-20 was complete within 1 hr. Chromatography of the crystalline product on paper and examination of the chromatogram after treatment with 4% phosphomolybdic acid in absolute ethanol[7] revealed the presence of two substances (R_f 0.63 and 0.54). The starting material IV has an R_f of 0.81. There was considerable variation in the proportions of the compound with R_f 0.63 (the 20β-hydroxyl steroid V) and the one with R_f 0.54 (presumably the 20-epimer of V) obtained in several experiments in which the procedure was not altered significantly. Separation of the C-20 epimers by crystallization was difficult, both with the dihydroxyl compounds and with their diacetyl derivatives. Only the 20β-epimer was obtained in chromatographically pure form.

The diacetate VI of the 20β-epimer, obtained by acetylation of V, had physical constants in good agreement with those of the compound prepared by Oliveto, *et al.* An attempt to cleave the double bond of the acetylated benzylidene (VI) with osmium tetroxide–periodic acid[8] to obtain the aldehyde was not successful. However, the aldehyde VII was obtained in over 90% yield by ozonization of VI in chloroform–methanol at −20°. The melting points of samples of the aldehyde varied from about 90 to 125°, although the samples had identical paper chromatographic mobilities and infrared spectra.

Reduction of the aldehyde VII with hydrogen in the presence of Adams' platinum oxide and ferrous sulfate[9] proceeded readily and hydrogen uptake stopped after 1 molar equiv. had been absorbed. The corresponding

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[2] L. Lewbart, and V. R. Mattox, *J. Org. Chem.*, **28**, 1779 (1963).

[3] L. F. Fieser and M. Fieser, *Experientia*, **4**, 285 (1948).

[4] L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 612.

[5] L. H. Sarett, *J. Am. Chem. Soc.*, **71**, 1175 (1949).

[6] E. P. Oliveto, C. Gerold, and E. B. Hershberg, *ibid.*, **76**, 6111 (1954).

[7] M. L. Lewbart and J. J. Schneider, *Nature*, **176**, 1175 (1955).

[8] R. Pappo, D. S. Allen, Jr., R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1956).

[9] R. Adams and B. S. Garvey, *J. Am. Chem. Soc.*, **48**, 477 (1926).