Anal. Calcd. for $C_{10}H_{14}N_4O\cdot HCl$: C, 49.48; H, 6.23; Cl, 14.60. Found: C, 49.03; H 6.36; Cl, 14.45.

B.—A mixture of 5 g. (0.022 mole) of IIIa and 0.75 g. (0.44 mole) of ammonia in 30 ml. of absolute ethanol was shaken in a stoppered flask for 20 hr. The solution was filtered and evaporated. The residue was dissolved in water, and the solution was filtered and partially evaporated to give 1.5 g. (28%), m.p. 176–178° of VIIIa·HCl. Further concentration of the filtrate gave 2 g. (37%) of impure VIIIa·HCl.

1-(2-Hydroxyethyl)-1-(5-nitrofurfurylideneamino)guanidine (VIIIb) Hydrochloride.—A mixture of 3.25 g. (0.0134 mole) of VIIIa·HCl and 2.2 g. (0.0156 mole) of 5-nitro-2-furaldehyde in 15 ml. of 10% hydrochloric acid was heated at the boiling point for 5 min. On cooling the solution a yellow-orange solid precipitated. After filtering and washing with ethanol there was obtained 2.75 g. (74%), m.p. 250° dec., of VIIIb·HCl which was identical with an authentic sample.[4]

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4-Dimethylaminodi(2-thienyl)cyclohexylcarbinol and Related Compounds

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The addition of 2-thienyllithium and 2-thienylmagnesium bromide to *cis*- and *trans*-ethyl 4-dimethylaminocyclohexylcarboxylate (IIa and IIb) was studied. The reaction of the lithio derivative on either the *cis* or *trans* ester gave the corresponding dithienylcarbinol (Va or Vb). 2-Thienylmagnesium bromide reacted with IIb to give the tertiary carbinol (Vb). However, the same reaction on the *cis* ester (IIa) gave *cis*-4-dimethylaminocyclohexyl 2-thienyl ketone (IIIa). Alcoholic sodium ethoxide or polyphosphoric acid inverted IIIa to the *trans* ketone (IIIb). 2-Thienyllithium reacted with IIIa and IIIb to give the respective tertiary carbinols (Va and Vb) in excellent yields.

The reaction of 2-thienylmagnesium bromide and 2-thienyllithium with *cis*- and *trans*-ethyl 4-dimethylaminocyclohexylcarboxylate was studied as part of a program directed towards the synthesis of thihexinol,[1,2] a potent antidiarrheal agent.[3] The esters required for this work were prepared by the method shown in the Chart I. Catalytic hydrogenation of an aqueous suspension of *p*-aminobenzoic acid using a platinum oxide catalyst gave a mixture of *cis*- and *trans*-4-aminocyclohexylcarboxylic acid. Separation of the latter[4] gave the *cis*-Ia and *trans*-Ib[5] acids in yields of 40–45% and 25–30%, respectively. Esterification and subsequent methylation of the amino group gave the desired *cis*- and *trans*-ethyl 4-dimethylaminocyclohexylcarboxylates (IIa and IIb). Inversion of the *cis* to the *trans* ester was effected by prolonged heating with alcoholic sodium ethoxide.

Hydrogenation of *p*-aminobenzoic acid using a 5% rhodium-on-alumina catalyst gave a mixture of acids with the *cis* form predominating and only 10–15% of the *trans* form. Likewise, the hydrogenation of ethyl *p*-aminobenzoate using 5% rhodium-on-alumina catalyst gave a mixture of esters containing over 75% of the *cis* form. The mixture of esters was easily converted to the predominately *trans* form by the sodium ethoxide procedure mentioned previously.

The esters IIa and IIb on treatment with 2-thienyllithium were converted, in excellent yields, to the corresponding *cis* and *trans* tertiary carbinols Va and Vb, respectively. The *trans* tertiary carbinol Vb was also obtained by the reaction of 2-thienylmagnesium bromide and the *trans* ester IIb. This reaction also produced small amounts (10–15%) of the *cis* ketone IIIa.[5] However, when IIa was reacted with 2-thienylmagnesium bromide, only the *cis* ketone IIIa was obtained. Addition of 2-thienyllithium to the *cis* ketone IIIa gave the *cis* tertiary carbinol Va and small amounts of the *trans* tertiary carbinol Vb. The isolation of Vb from this reaction mixture is probably due to isomerization of IIIa by the strongly basic lithium reagent. The *cis* ketone IIIa, was isomerized to the *trans* ketone IIIb by treatment with alcoholic sodium ethoxide or polyphosphoric acid. Addition of thienyllithium to the *trans* ketone IIIb gave the *trans* carbinol in 88% yield. Compound IIIb was also prepared by methylation of the amino ketone IV obtained in poor yield from either the *cis* acid Ia or the *trans* acid Ib, by the Friedel–Crafts acylation of thiophene in the presence of polyphosphoric acid.

Experimental[6]

***cis*- and *trans*-4-Aminocyclohexylcarboxylic Acid.**—A suspension of 139 g. (1 mole) of *p*-aminobenzoic acid in 2.5 l. of water was hydrogenated in a 4-l. rocking autoclave in the presence of 10 g. of platinum oxide catalyst at room temperature, and an initial hydrogen pressure of 200–300 p.s.i. The reduction was allowed to proceed overnight. The catalyst was filtered off and the clear solution was concentrated *in vacuo* on a steam bath to a volume of 650–700 ml. To the cool residue, 3 l. of ethanol was added and the precipitated *cis* acid was filtered. The filtrate was then diluted with 5 l. of ether and allowed to crystallize overnight. The precipitated *trans* acid was filtered and dissolved in 350 ml. of water, and after Darco treatment was precipitated with 4.3 l. of ethanol, m.p. above 400°. Average yield of *trans* acid on six such runs was 44 g. (30%).

The crude *cis* acid was dissolved in 700 ml. of water and after Darco treatment was precipitated with 2.5 l. of ethanol. Average yield of *cis* acid from six runs was 63 g. (43%), m.p. 324–325° dec., lit.[4a] m.p. 304–305°.

***cis*-Ethyl 4-Aminocyclohexylcarboxylate.**—The *cis* acid (52 g.) suspended in 500 ml. of absolute ethanol was saturated with

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(1) Registered trade-mark of the White Laboratories Division of Schering Corp.

(2) *trans*-4-Trimethylammonium-di(2-thienyl)cyclohexylcarbinol bromide.

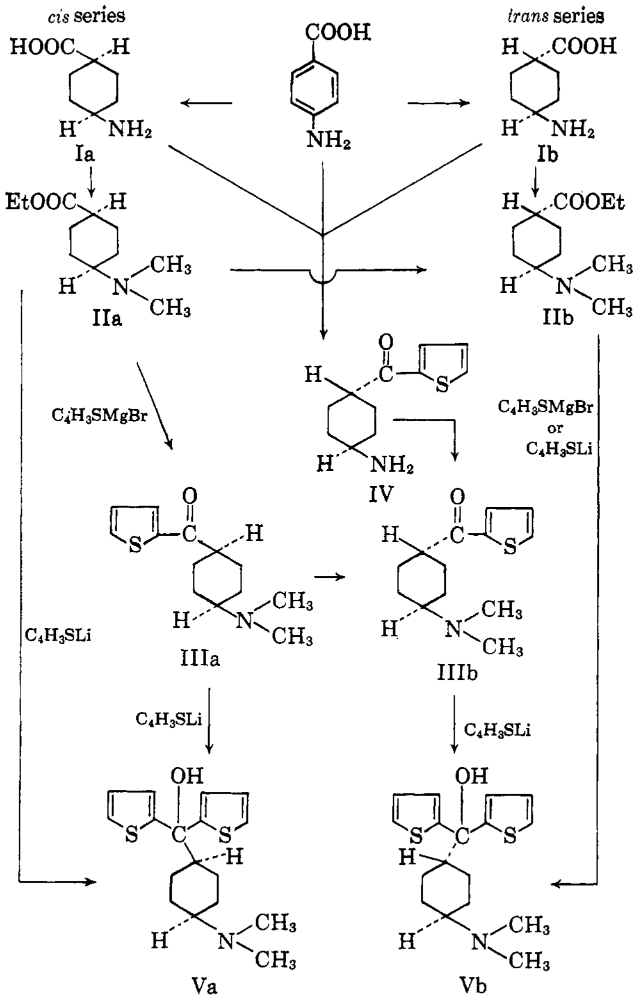
(3) E. Henderson, *Am. J. Digest. Diseases*, **5**, 961 (1960).

(4) (a) G. Wendt, *Ber.*, **75**, 427 (1942), (b) R. K. Patel and O. Gisvold, *J. Am. Pharm. Assoc.*, **42**, 321 (1953).

(5) The *trans* form of the acid is contaminated by traces of the *cis* form. See Experimental section.

(6) All melting points are corrected. Microanalyses were performed by Mr. Edwin Connor of these laboratories.

CHART I



anhydrous hydrogen chloride under reflux with stirring for 6 hr. and allowed to stand overnight at room temperature. The excess alcohol was removed on the steam bath *in vacuo;* the residue was dissolved in water, made basic with sodium hydroxide, saturated with potassium carbonate, and extracted with chloroform. The chloroform extracts were washed with a saturated solution of potassium carbonate and distilled, b.p. 117–118° (11 mm.), $n^{27}\text{D}$ 1.4660, yielding 52 g. (83%).

The **hydrochloride** after recrystallization from ethanol–ether had m.p. 194–195°, lit.[4b] m.p. 193–194°.

trans-**Ethyl 4-Aminocyclohexylcarboxylate.**—The *trans* acid (50 g.) was treated under reflux with 200 ml. of thionyl chloride for 2 hr. The excess thionyl chloride was removed *in vacuo* and 50 ml. of anhydrous benzene was added and removed *in vacuo.* Absolute ethanol (300 ml.) was added dropwise and the mixture was refluxed for 0.5 hr. After cooling, the product hydrochloride was precipitated by absolute ether and recrystallized from a mixture of methanol–ether, m.p. 206–207°, yielding 45 g.

Anal. Calcd. for $C_9H_{17}NO_2 \cdot HCl$: C, 52.17; H, 8.69. Found: C, 52.33; H, 8.84.

The ester hydrochloride (45 g.) was dissolved in water, the solution was neutralized with sodium hydroxide and extracted with chloroform, and the product was distilled, b.p. 119–120° (9 mm.), $n^{26}\text{D}$ 1.4625, yielding 30 g. (51%).

Anal. Calcd. for $C_9H_{17}NO_2$: C, 63.13; H, 10.00. Found: C, 62.67; H, 10.01.

cis-**Ethyl 4-Dimethylaminocyclohexylcarboxylate.**—To 52 g. of the *cis* amino ester was added 80 g. of 85% formic acid and 70 ml. of formalin solution. The mixture was heated on the steam bath overnight and the excess solvents were removed *in vacuo.* The residue was dissolved in water and the solution was saturated with potassium carbonate and extracted with chloroform. The chloroform extracts were washed with a saturated salt solution and distilled, b.p. 125–127° (10 mm.), $n^{26}\text{D}$ 1.4590, yielding 36 g. (57%).

Anal. Calcd. for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.63. Found: C, 66.58; H, 10.67.

The **picrate** was recrystallized from ethanol, m.p. 117–118°.

Anal. Calcd. for $C_{11}H_{21}NO_2 \cdot C_6H_3N_3O_7$: N, 13.26. Found: N, 13.28.

trans-**Ethyl 4-Dimethylaminocyclohexylcarboxylate.**—From 26 g. of the *trans* amino ester by the same procedure as for the *cis* compound was obtained 17 g. of the dimethylamino ester, b.p. 123–125° (11 mm.), $n^{26}\text{D}$ 1.4573.

Anal. Calcd. for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.63. Found: C, 66.87; H, 10.69.

The **picrate** was recrystallized from ethanol, m.p. 158–159°.

Anal. Calcd. for $C_{11}H_{21}NO_2 \cdot C_6H_3N_3O_7$: N, 13.26. Found: N, 13.63.

Inversion of *cis*-**Ethyl 4-Dimethylaminocyclohexylcarboxylate to the** *trans* **Form.**—To a solution of 0.5 g. of sodium metal in 100 ml. of anhydrous ethanol was added 5 g. of the *cis* ester and the mixture was refluxed for 35 hr. The solvents were removed *in vacuo* and the residue was dissolved in water, saturated with potassium carbonate, and extracted with chloroform. The product was distilled, b.p. 119–120° (10 mm.), yielding 2 g.

The **picrate** had m.p. 153–159°.

Reduction of *p*-**Aminobenzoic Acid Using a Rhodium-on-Alumina Catalyst.**—*p*-Aminobenzoic acid (27.4 g.), in 300 ml. of water, and 2 g. of rhodium (5%) on alumina was reduced in a Parr hydrogenator at 60 p.s.i. at 50°. The filtrates from two such runs were combined and processed as above to give 30 g. (53%) of *cis* acid and 9 g. (16%) of *trans* acid.

Reduction of Ethyl *p*-**Dimethylaminobenzoate Using Rhodium Catalyst.**—The ester (159 g.) dissolved in 1 l. of glacial acetic acid was hydrogenated in the presence of 10 g. of rhodium (5%) on alumina catalyst at room temperature and an initial hydrogen pressure of 1000 p.s.i. The theoretical quantity of hydrogen was absorbed in 45 min. The catalyst was filtered off and the filtrate was concentrated *in vacuo* on the steam bath. The residue was dissolved in water, made basic with ammonium hydroxide, saturated with potassium carbonate, and extracted with chloroform. The product was distilled after removal of the solvent, b.p. 120–122° (9 mm.), yielding 132 g., $n^{27}\text{D}$ 1.4572; **picrate** m.p. 114–120°.

cis-**4-Dimethylaminodi(2-thienyl)cyclohexylcarbinol (Va).**—Bromobenzene (52 g., 0.33 mole) in an equal volume of anhydrous ether was added to 4.6 g. (0.66 g.-atom) of lithium metal shot and 400 ml. of ether under nitrogen at the temperature of refluxing ether. When the lithium had completely reacted, 28 g. (0.33 mole) of thiophene was added and the mixture was stirred under reflux for 2 hr. The reaction mixture was cooled to −20° and 16.5 g. (0.083 mole) of *cis*-ethyl 4-dimethylaminocyclohexylcarboxylate (IIa) was added dropwise. A precipitate formed immediately. The mixture was allowed to warm up to room temperature and stirred for 6 hr. Ice–water was added, the layers were separated, and the water solution was extracted with ether and finally with chloroform. The combined organic layers were extracted with dilute (10%) hydrochloric acid, causing the precipitation of the hydrochloride salt which was filtered off in order to complete the acid extraction. The precipitated salt was suspended in the acid extracts and the suspension made basic with ammonium hydroxide. The oil was extracted with chloroform, and, after washing with water and removal of the solvent, the residue was distilled, b.p. 182–192° (3 mm.), yielding 23 g. (86%). The product was crystallized from hexane, m.p. 93–95°.

Anal. Calcd. for $C_{17}H_{23}NOS_2$: C, 63.51; H, 7.21; S, 19.95. Found: C, 62.94; H, 7.39; S, 20.45.

Hydrochloride.—A small sample of the precipitated salt above was recrystallized from dilute ethanol, m.p. 229–231°.

Anal. Calcd. for $C_{17}H_{23}NOS_2 \cdot HCl$: C, 57.04; H, 6.76; S, 17.91. Found: C, 57.38; H, 6.99; S, 17.61.

Methylbromide Quaternary Salt.—An ethereal solution of the carbinol (Va) was saturated with methyl bromide in an ice bath. The precipitated product was filtered and recrystallized from absolute ethanol–absolute ether, m.p. 235–237°.

Anal. Calcd. for $C_{17}H_{23}NOS_2 \cdot CH_3Br$: C, 51.91; H, 6.29. Found: C, 51.99; H, 6.43.

trans-**4-Dimethylaminodi(2-thienyl)cyclohexylcarbinol (Vb).**—The same procedure described for the corresponding *cis* compound was employed. After removal of the chloroform, the residue was triturated with petroleum ether (b.p. 30–60°) to give the product, m.p. 152–156°, which was recrystallized from benzene–petroleum ether, m.p. 156-157°, yielding 18 g. (67.5%). Concentration of the original petroleum ether fraction gave 9% of unreacted ester.

Anal. Calcd. for $C_{17}H_{23}NOS_2$: C, 63.51; H, 7.21. Found: C, 63.27; H, 7.03.

The **hydrochloride** salt was prepared by saturation of an anhydrous ether solution with anhydrous hydrogen chloride, m.p. 203-204° after recrystallization from ethanol-ether.

Anal. Calcd. for $C_{17}H_{23}NOS_2 \cdot HCl$: C, 57.04; H, 6.76. Found: C, 57.12; H, 6.56.

The methylbromide quaternary salt had m.p. 243-244°.

Anal. Calcd. for $C_{17}H_{23}NOS_2 \cdot CH_3Br$: C, 51.91; H, 6.29. Found: C, 51.76; H, 6.47.

***cis*-4-Dimethylaminocyclohexyl 2-Thienyl Ketone (IIIa).**—To an ethereal solution of 2-thienylmagnesium bromide prepared from 17.6 g. (0.72 g.-atom) of magnesium and 118 g. (0.72 mole) of 2-bromothiophene in 500 ml. of ether, a solution of 36 g. (0.18 mole) of IIa in 50 ml. of ether was added dropwise with stirring at a temperature just below reflux. The mixture was then refluxed for 2 hr. and allowed to stir for an additional 4 hr. at room temperature. Ammonium chloride (10%) solution was added and the product was extracted with ether. The combined ether solutions were extracted with dilute hydrochloric acid and the acid solution was made alkaline with ammonium hydroxide and extracted with chloroform. The solvent was removed and the product was distilled, b.p. 164–167° (2 mm.), $n^{25}\text{D}$ 1.5572, yield 31 g. (73%).

Anal. Calcd. for $C_{13}H_{19}NOS$: C, 65.82; H, 8.07. Found: C, 65.74; H, 8.04.

The **hydrochloride** was recrystallized from ethanol–ether, m.p. 174–176.

Anal. Calcd. for $C_{13}H_{19}NOS \cdot HCl$: C, 57.02; H, 7.36. Found: C, 56.99; H, 7.34.

The **oxalate** was recrystallized from ethanol-ether, m.p. 125-127.

Anal. Calcd. for $C_{13}H_{19}NOS \cdot C_2H_2O_4$: C, 55.01; H, 6.46. Found: C, 55.03; H, 6.69.

The **picrate** had m.p. 144–146°.

Anal. Calcd. for $C_{13}H_{19}NOS \cdot C_6H_3N_3O_7$: N, 12.04. Found: N, 11.99.

Reaction of IIb with 2-Thienylmagnesium Bromide.—To a solution of thienylmagnesium bromide in ether prepared from 54 g. (0.33 mole) of 2-bromothiophene and 8.1 g. of magnesium was added a solution of 16.5 g. (0.083 mole) of IIb. The reaction mixture was processed as above to give 12.5 g. (47%) of the *trans* carbinol, m.p. 154-156°. From the petroleum ether filtrates was obtained 2.5 g. (12.5%) of the *cis* ketone, b.p. 159-165° (2 mm.). The **picrate** of the ketone had a melting point 141-143° and a mixture melting point with the picrate of the ketone IIIa did not show a depression.

***trans*-4-Dimethylaminocyclohexyl 2-Thienyl Ketone (IIIb). Method A. Inversion of *cis* Ketone.**—The *cis* ketone (12 g.) was refluxed overnight with a solution of sodium ethoxide prepared from 1 g. of sodium metal in 100 ml. of absolute ethanol. The ethanol was removed and the residue was dissolved in water, acidified with acetic acid, and extracted with chloroform. The chloroform extracts were washed with dilute potassium carbonate solution and, after removal of the chloroform, the product was distilled, b.p. 160–163° (3 mm.). After crystallization from hexane it had m.p. 60-61°.

Anal. Calcd. for $C_{13}H_{19}NOS$: C, 65.82; H, 8.07. Found: C, 65.63; H, 8.06.

The **picrate** was recrystallized from ethanol, m.p. 216–217°.

Anal. Calcd. for $C_{13}H_{19}NOS \cdot C_6H_3N_3O_7$: N, 12.04. Found: N, 12.02.

The **hydrochloride** was recrystallized from ethanol-ether, m.p. 215-216°.

Anal. Calcd. for $C_{13}H_{19}NOS \cdot HCl$: C, 57.02; H, 7.36. Found: C, 56.98; H, 7.59.

The **oxalate** was recrystallized from ethanol–ether, m.p. 163-164°.

Anal. Calcd. for $C_{13}H_{19}NOS \cdot C_2H_2O_4$: C, 55.02; H, 6.46. Found: C, 55.40; H, 6.54.

Method B. Inversion of *cis*-Ketone by Polyphosphoric Acid.—The *cis* ketone (IIIa, 20 g.) was heated under reflux with stirring on the steam bath with 100 ml. of thiophene and 5 g. of polyphosphoric acid for 48 hr. The solvents were removed and the mixture was processed as above, b.p. 160-163° (3 mm.), yielding 13 g.

The **oxalate**, after recrystallization from ethanol-ether, had m.p. 161-162°.

Method C.—To a warm suspension of 200 g. of polyphosphoric acid and 500 ml. of thiophene was added in several small portions with stirring, 143 g. of *cis*-4-aminocyclohexylcarboxylic acid. A heavy black precipitate formed after 0.5 hr. causing the stirring to stop. Heating was continued on the steam bath for 8 hr., and the mixture was poured into water, made basic with sodium hydroxide, and extracted with chloroform. The chloroform extracts were washed with water and distilled, b.p. 159-165° (3 mm.), m.p. 81-82° after recrystallization from hexane, yield 40 g. (19%). This same compound, m.p. 78-79°, was obtained in a yield of 19% from the *trans* acid by the same procedure. The hydrochloride after several recrystallizations from ethanol-ether had m.p. 208-209°.

Anal. Calcd. for $C_{11}H_{15}NOS \cdot HCl$: C, 53.75; H, 6.56. Found: C, 53.64; H, 6.57.

The above ketone (32 g., 0.15 mole), 51 g. of formic acid, and 45 ml. of formalin were heated for 8 hr. by the aforementioned procedure. One hundred milliliters of 20% hydrochloric acid was added and the solution was concentrated *in vacuo* on the steam bath. The residue was dissolved in water, neutralized with sodium hydroxide, and extracted with chloroform. The extracts were washed with water and distilled, b.p. 165-168° (4 mm.), m.p. 60-62° recrystallized from hexane.

Anal. Calcd. for $C_{13}H_{19}NOS$: C, 65.82; H, 8.07. Found: C, 66.01; H, 8.02.

The **picrate** had m.p. 196-198°; the oxalate had m.p. 163-164°.

Reaction of IIIa with 2-Thienyllithium.—2-Thienyllithium was prepared from 30 g. (0.19 mole) of bromobenzene, 16 g. of thiophene, and 2.6 g. (0.38 g.-atom) of lithium in 300 ml. of anhydrous ether. The *cis* ketone (IIIa, 15 g., 0.06 mole) in 25 ml. of ether was added dropwise at −20°; the mixture was stirred for 6 hr. and allowed to warm to room temperature. Water was added and the organic material was extracted with ether and chloroform. The combined extracts were taken through dilute hydrochloric acid; the acid extracts were made basic with ammonium hydroxide and extracted with chloroform. The chloroform was removed and the residue was triturated with ice-cold petroleum ether and filtered, yielding 6 g. (22.5%) of the *trans* carbinol, m.p. 151-154°. Evaporation of the petroleum ether from the filtrate gave 13 g. (66%) of the *cis* carbinol, b.p. 188-195° (3 mm.), $n^{21}\text{D}$ 1.6122.

Reaction of IIIb with 2-Thienyllithium.—To a solution of 2-thienyllithium prepared from 2.7 g. (0.4 g.-atom) of lithium shot, 31.4 g. (0.2 mole) of bromobenzene, and 16.8 g. (0.2 mole) of thiophene in ether (500 ml.) was added dropwise with stirring a solution of 23 g. of the *trans* ketone IIIb in 50 ml. of anhydrous ether. The reaction mixture was processed as above to give after trituration with petroleum ether 28 g. (88%) of the *trans* carbinol, m.p. 153-155°.