and refluxed for 4 hr. The mixture was then chilled to give 34 g. (43%) of N-[1-(dimethylamino)-2-methylpropyl]acetamide. A sample recrystallized from hexane melted at 63–65°. The n.m.r. spectrum showed a doublet centered at 0.90 p.p.m. for the two methyls of the isopropyl group, a broad absorption from 1.5 to *ca.* 2.0 p.p.m. for the tertiary proton of the isopropyl group, a single peak at 2.00 p.p.m. for the acetyl group, a single peak at 2.20 p.p.m. for the dimethylamino group, a doublet at 7.95 p.p.m. for the NH proton, and a triplet at 4.18 p.p.m. for the remaining tertiary proton.

Anal. Calcd. for $C_8H_{15}N_2O$: C, 60.7; H, 11.5. Found: C, 60.3; H, 11.4.

2-(Dimethylamino)-2,3-dihydro-3,3-dimethyl-5-benzofuranol.—N,N-Dimethylisobutenylamine (5 g., 0.5 mole) was added to a slurry of *p*-benzoquinone (5.4 g., 0.05 mole) in benzene (50 ml.) over a 0.5-hr. period at such a rate as to maintain the temperature at 40–50°. The mixture stood overnight and the solid was removed by filtration and recrystallized three times from benzene to give 5 g. (48%) of 2-(dimethylamino)-2,3-dihydro-3,3-dimethyl-5-benzofuranol, m.p. 155–157°. The n.m.r. spectrum (in acetone) showed peaks at 1.17 and 1.23 p.p.m. for the *gem*-dimethyl group, a single peak at 2.23 p.p.m. for the dimethylamino group, a single peak at 4.83 p.p.m. for the –OCHN< proton, and peaks centered at 6.55 p.p.m. corresponding to three aromatic protons. In addition, the single phenolic proton appeared as a broad peak at 5.25 p.p.m. at room temperature and was shifted to a sharper peak at 4.9 p.p.m. at 50°.

Anal. Calcd. for $C_{12}H_{17}NO_2$: C, 69.5; H, 8.3; N, 6.8. Found: C, 69.7; H, 8.0; N, 6.7.

2,3-Dihydro-3,3-dimethyl-2-piperidino-5-benzofuranol.—To a slurry of benzoquinone (108 g., 1 mole) in xylene (500 ml.), 1-isobutenylpiperidine (142 g., 1 mole) was added in portions over a 0.5-hr. period with cooling to maintain the temperature at 50–60°. After the addition was complete, the mixture was allowed to stand 0.5 hr. and 200 ml. of xylene was added along with some Super Cel. The mixture was heated to 115° and filtered while hot. On cooling, the filtrate gave 2,3-dihydro-3,3-dimethyl-2-piperidino-5-benzofuranol, which was removed by filtration and washed with xylene and hexane. The product weighed 122 g. (49%), m.p. 158°. A sample for analysis was recrystallized from benzene to a constant melting point of 164–165°. The n.m.r. spectrum of this compound, and of the benzofuranols described subsequently, showed only three aromatic protons and one phenolic proton.

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.8; H, 5.7; N, 8.6. Found: C, 72.6; H, 5.6; N, 8.6.

(1-Formyl-1-methylethyl)hydroquinone Dibenzoate.—Benzoyl chloride (3 g., 0.021 mole) was added to 2,3-dihydro-3,3-dimethyl-2-piperidino-5-benzofuranol (2.5 g., 0.01 mole) in pyridine (10 ml.) and the mixture was heated on the steam bath for 20 min. Saturated sodium bicarbonate solution (50 ml.) was added to the mixture which was then filtered. The solid was recrystallized from aqueous ethyl alcohol to give 1.5 g. of (1-formyl-1-methylethyl)hydroquinone dibenzoate, m.p. 146–147°.

Anal. Calcd. for $C_{24}H_{20}O_5$: C, 74.2; H, 5.2. Found: C, 74.2; H, 5.5.

The **2,4-dinitrophenylhydrazone** melted at 261–262°.

Anal. Calcd. for $C_{30}H_{24}N_4O_8$: C, 63.4; H, 4.3. Found: C, 63.3; H, 4.6.

3-Ethyl-2,3-dihydro-2-piperidino-5-benzofuranol.—To a slurry of *p*-benzoquinone (21.6 g., 0.2 mole) in benzene, 1-(1-butenyl)-piperidine[13] was added in portions over a 10-min. period with cooling to maintain the temperature at 25–30°. The mixture was filtered, and the filter cake was washed with cold pentane to give, after drying, 42.8 g. (87%) of 3-ethyl-2,3-dihydro-2-piperidino-5-benzofuranol. A sample for analysis, recrystallized from benzene, melted at 173–175°.

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.8; H, 8.5. Found: C, 72.8; H, 8.4.

2-(Dimethylamino)-3-ethyl-2,3-dihydro-5-benzofuranol.—In a manner similar to that described previously, N,N-diethyl-1-butenylamine[14] (63.5 g., 0.5 mole) and *p*-benzoquinone (54 g., 0.5 mole) gave 141 g. (60%) of 2-(dimethylamino)-3-ethyl-2,3-dihydro-5-benzofuranol, b.p. 143–146° (*ca.* 1.5 mm.), $n^{20}D$ 1.5380.

Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71.5; H, 9.0. Found: C, 70.8; H, 9.2.

2,3-Dihydro-2-morpholino-3-pentyl-5-benzofuranol.—In a similar manner, 4-(1-heptenyl)-morpholine[15] (46 g., 0.25 mole) and *p*-benzoquinone (27 g., 0.25 mole) gave 70 g. (96%) of 2,3-dihydro-2-morpholino-3-pentyl-5-benzofuranol, m.p. 83–84.5°.

Anal. Calcd. for $C_{17}H_{25}NO_3$: C, 70.2; H, 8.7. Found: C, 70.1; H, 8.8.

Acknowledgment.—The authors wish to acknowledge the assistance of V. W. Goodlett of these laboratories for the n.m.r. spectra and for aid in their interpretation.

(13) C. Mannich and H. Davidsen, *Ber.*, **69**, 2106 (1963).

(14) Prepared in 61% yield by the method described by Mannich and Davidsen[13]; b.p. 39–41° (12 mm.), $n^{20}D$ 1.4470. *Anal.* Calcd. for $C_8H_{17}N$: N, 11.0. Found: N, 10.9.

(15) P. L. de Benneville and J. H. Macartney, *J. Am. Chem. Soc.*, **72**, 3073 (1950).

The Transformation of 3-Amino-2-iminooxazolidines to Semicarbazone Derivatives[1]

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Heating 2-imino-3-(5-nitrofurfurylideneamino)oxazolidine hydrochloride or 3-(benzylideneamino)-2-iminooxazolidine hydrochloride in xylene affords the corresponding 2-(2-chloroethyl)semicarbazones, which have been aminated with various secondary amines. The reaction of benzaldehyde 2-(2-chloroethyl)semicarbazone with ammonia results in the formation of 1-benzylideneamino-1-(2-hydroxyethyl)guanidine. Proposed mechanisms are discussed.

As reported previously,[2] the action of thionyl chloride on 5-nitro-2-furaldehyde 2-(2-hydroxyethyl)semicarbazone (Ib) produced a quantitative yield of 2-imino-3-(5-nitrofurfurylideneamino)oxazolidine hydrochloride (IIb) rather than the chloroethylsemicarbazone IIIb. When IIb was recrystallized repeatedly from 95% ethanol or from ethanolic hydrogen chloride, a partial transformation to IIIb was effected.

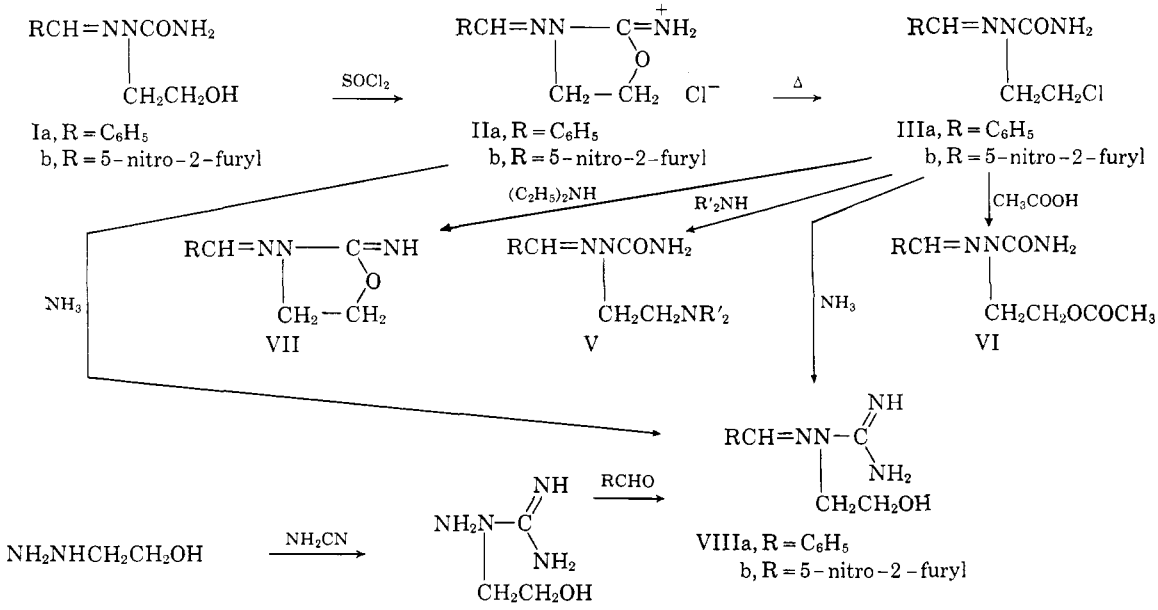
(1) Presented at the 19th International Congress of Pure and Applied Chemistry, London, July 10–17, 1963.

(2) K. Hayes, F. Ebetino, and G. Gever, *J. Am. Chem. Soc.*, **77**, 2282 (1955).

To investigate this transformation further, heated suspensions of IIb in toluene and xylene were examined. After 30 min. in boiling xylene, a 96% yield of IIIb was obtained, while 2 hr. in boiling toluene resulted in a 73% yield of IIIb. The benzaldehyde analog Ia underwent the same reaction with thionyl chloride and subsequent ring opening of the iminooxazolidine hydrochloride in boiling xylene.

The mechanism of ring cleavage of the iminooxazolidines probably involves chloride ion attack at the C-5 position. This is supported by the observation

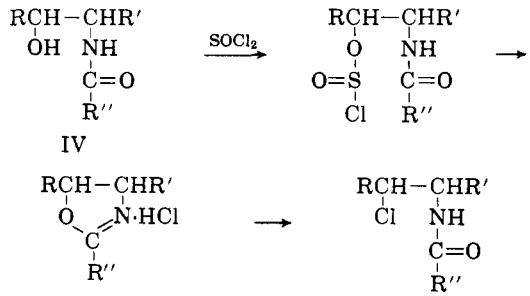
CHART I



that high concentrations of chloride ions in ethanol increased the rate of semicarbazone formation.

Since the chloroethylsemicarbazone (III) is recovered unchanged from thionyl chloride, III is not an intermediate in the formation of II from I. The chlorination most likely proceeds through a chlorosulfinate intermediate. These reactions are summarized in Chart I.

A somewhat analogous reaction of β-hydroxyethylamides IV with thionyl chloride, reported by Fry,[3] gave β-chloroethylamides at reflux temperature and



oxazolinium chlorides in the cold. The oxazolinium chloride then rearranged to the amide on heating. β-Chloroalkylamides were reported to be inert to thionyl chloride, and were therefore eliminated as intermediates in the formation of oxazolines.

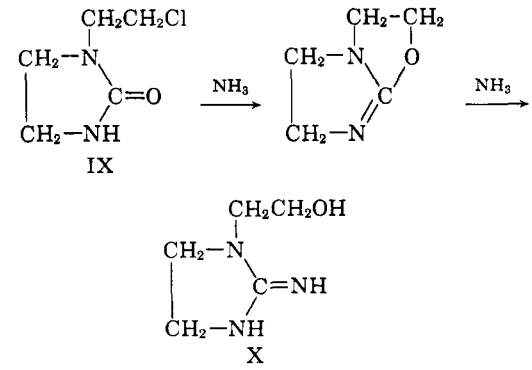
Attention was next directed to a study of the reactions of the chloroethylsemicarbazones with amines. Morpholine, 1-piperazineethanol, piperidine, and dimethylamine were combined with benzaldehyde 2-(2-chloroethyl)semicarbazone (IIIa) in benzene to give the corresponding aminoethylsemicarbazones V. These compounds were then converted into nitrofuraldehyde semicarbazones by acid hydrolysis and condensation with 5-nitro-2-furaldehyde. The morpholino derivative was also prepared, but in lower yield, by treating IIIb with morpholine in dimethylformamide. If acetic acid is used as a solvent in place of dimethylformamide, the acetoxyethylsemicarbazone VI is obtained instead of the morpholino derivative.

(3) E. M. Fry, *J. Org. Chem.*, **14**, 887 (1949).

Diethylamine failed to give the amino derivative when combined with III in dimethylformamide or benzene, but gave small amounts of the iminooxazolidine VII (Chart I).

Ammonolysis of IIIa in absolute ethanol produced a hydrochloride salt which showed the correct analysis for the aminoethylsemicarbazone and which could be converted to a 5-nitrofurfurylidene derivative. However, the infrared spectrum of the nitrofuran derivative showed an OH band at 2.85 μ in addition to NH bands, and the ultraviolet spectrum showed a maximum at 366 mμ, whereas the chloro- and amino-alkylated semicarbazones exhibit maximal absorption at 375–383 mμ. Several substituted 5-nitrofurfurylideneaminoguanidines have been reported to absorb at 360–365 mμ,[4] and a comparison of the data indicated that the product of the ammonia reaction is 1-(2-hydroxyethyl)-1-(5-nitrofurfurylideneamino)guanidine hydrochloride (VIIIb).[4] This compound was previously prepared by reacting 2-hydrazinoethanol with cyanamide, and then condensing the aminoguanidine with 5-nitro-2-furaldehyde (Chart I).

These results indicate that strong nucleophiles, dimethylamine, morpholine, piperidine, and 1-piperazineethanol, react by direct displacement of chlorine from III, whereas weaker nucleophiles, ammonia and diethylamine, cause intramolecular displacement of chlorine and cyclization to the iminooxazolidine VII.



(4) F. F. Ebetino and G. Gever, *ibid.*, **27**, 188 (1962).

TABLE I

BENZALDEHYDE- AND 5-NITRO-2-FURALDEHYDE-SUBSTITUTED AMINOETHYLSEMICARBAZONES (V)

R	R'$_2$N	Yield, %	M.p., °C.	$\lambda_{max}^{H_2O}$, mμ	Log ε	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
C_6H_5	Piperidino	33	131			65.66	8.08	20.42	65.50	7.69	20.20
C_6H_5	N'-Hydroxyethyl Piperazino	40	155			60.16	7.89	21.93	59.98	7.81	21.55
C_6H_5	$(CH_3)_2N$	43	115.5			61.51	7.74	23.91	61.75	7.75	24.03
5-Nitro-2-furyl	Piperidino[a]	63	251.5	375	4.23	45.20	5.83	10.26[b]	45.52	5.75	10.31[b]
5-Nitro-2-furyl	N'-Hydroxyethyl Piperazino[c]	83	208	383	4.22	37.75	5.88	15.92[b]	37.92	5.52	15.87[b]
5-Nitro-2-furyl[d]	$(CH_3)_2N$	36	160	375	4.21						

[a] Hydrochloride. [b] Calcd. and found for chlorine. [c] Dihydrochloride monohydrate. [d] See ref. 8.

Ammonia then attacks the C-2 position of VII to produce the hydroxyethylguanidine VIII. This mechanism is supported by the fact that VIIIa can be obtained directly from the reaction of IIa with ammonia.

A similar mechanism has been proposed for the conversion of 1-(2-chloroethyl)-2-imidazolidinone (IX) into 1-(2-hydroxyethyl)-2-iminoimidazolidine (X) with ammonia.[5] With more nucleophilic compounds, methylamine and benzylamine, however, aminoethyl derivatives of IX are formed.

Experimental[6]

5-Nitro-2-furaldehyde 2-(2-Chloroethyl)semicarbazone (IIIb).—A suspension of 50 g. (0.2 mole) of 2-imino-3-(5-nitrofurfurylideneamino)oxazolidine hydrochloride[2] in 750 ml. of xylene was heated at reflux temperature for 30 min. The mixture was cooled; the solid was filtered and rinsed with ether, water, and then ethanol. The yield of product melting at 191–195° was 49 g. (98%). A sample was recrystallized to constant melting point, 192–194°, from nitromethane; $\lambda_{max}^{5\% C_2H_5OH}$ 378 mμ (log ε 4.21).

Anal. Calcd. for $C_8H_9ClN_4O_4$: C, 36.86; H, 3.48; Cl, 13.60; N, 21.49. Found: C, 37.00; H, 3.03; Cl, 13.25; N, 21.60.

Benzaldehyde 2-(2-Hydroxyethyl)semicarbazone (Ia).—To a warm solution of 106 g. (1 mole) of benzaldehyde in 600 ml. of 50% ethanol was added 155.5 g. (1 mole) of 2-(2-hydroxyethyl)-semicarbazide hydrochloride[7] and 160 g. (1.95 moles) of sodium acetate. The mixture was heated on a steam bath for 30 min. and filtered hot. While heating the filtrate on a steam bath, 1450 ml. of water was added. On cooling the solution 174 g. (84%) of solid was obtained. An analytical sample melted at 121.5–122.0° after several recrystallizations from water.

Anal. Calcd. for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32; N, 20.28. Found: C, 57.80; H, 6.15; N, 20.14.

3-Benzylideneamino-2-iminooxazolidine Hydrochloride (IIa).—To a suspension of 174 g. (0.84 mole) of benzaldehyde 2-(2-hydroxyethyl)semicarbazone in 560 ml. of benzene was added gradually a solution of 236 ml. of thionyl chloride in 400 ml. of benzene. After the initial exothermic reaction had subsided, the mixture was heated at 60–65° for 3.5 hr. The yield of product after filtering and washing with benzene was 183 g. (97%), m.p. 160–165°. Attempts to obtain a satisfactory analytical sample were unsuccessful because of the hygroscopic nature of the compound.

The hydrochloride salt was converted to the *free base* by treating an aqueous solution with concentrated ammonium hydroxide. The base after recrystallization from cyclohexane melted at 101.5–103.5°.

Anal. Calcd. for $C_{10}H_{11}N_3O$: C, 63.47; H, 5.86; N, 22.21. Found: C, 63.53; H, 5.94; N, 22.52.

Benzaldehyde 2-(2-Chloroethyl)semicarbazone (IIIa).—A suspension of 3-benzylideneamino-2-iminooxazolidine hydrochloride in 1 l. of xylene was heated at reflux temperature for 20 min. The solution was filtered at 70° and then cooled to precipitate the product, 140 g. (80%), m.p. 125–127°. After two recrystallizations from 2-propanol, the melting point was raised to 127–129°.

Anal. Calcd. for $C_{10}H_{12}ClN_3O$: C, 53.25; H, 5.36; Cl, 15.71. Found: C, 52.95; H, 5.31; Cl, 15.40.

Benzaldehyde 2-(2-Morpholinoethyl)semicarbazone.—A suspension of 50 g. (0.221 mole) of the chloroethylsemicarbazone (IIIa) in 150 ml. of benzene was treated with 38.6 g. (0.442 mole) of morpholine. The mixture was heated at reflux temperature for 35 min., filtered hot, and then cooled. The product separated as white crystals, 40.5 g. (66.4%), m.p. 135–140°. Recrystallization from 2-propanol raised the melting point to 143–144°.

Anal. Calcd. for $C_{14}H_{20}N_4O_2$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.91; H, 7.19; N, 20.20.

5-Nitro-2-furaldehyde 2-(2-Morpholinoethyl)semicarbazone Hydrochloride. A.—A mixture of 5.0 g. (0.0192 mole) of IIIb and 1.7 g. (0.0196 mole) of morpholine in 15 ml. of dimethylformamide was heated on a steam bath for 1 hr. The solution was diluted with water and filtered; the filtrate was made basic with sodium bicarbonate solution. The precipitate, 1.45 g., m.p. 201–206°, was added to 10 ml. of warm 10% hydrochloric acid to produce the hydrochloride salt, 1.3 g. (19.6%). Recrystallization from aqueous ethanol or from a mixture of nitromethane and aqueous ethanol produced an analytical sample, m.p. 251.5–252.5 dec., $\lambda_{max}^{H_2O}$ 378 mμ (log ε 4.22).

Anal. Calcd. for $C_{12}H_{17}N_5O_5 \cdot HCl$: C, 41.44; H, 5.21; Cl, 10.20. Found: C, 41.25; H, 5.13; Cl, 10.16.

B.—A mixture of 40 g. (0.145 mole) of benzaldehyde 2-(2-morpholinoethyl)semicarbazone in 100 ml. of water and 35 ml. of concentrated hydrochloric acid was subjected to steam distillation to remove benzaldehyde. To the hot solution was then added a solution of 20.4 g. (0.145 mole) of 5-nitro-2-furaldehyde in 50 ml. of ethanol. After cooling the solution was filtered, extracted with ether, and then made just basic with ammonium hydroxide solution. The free base was purified by recrystallization from acetonitrile to give 22 g., m.p. 205–206°. A solution of the free base in a mixture of 800 ml. of 2-propanol and 200 ml. of nitromethane when treated with 10 ml. of concentrated hydrochloric acid yielded the hydrochloride salt, 25 g. (50%), m.p. 250–251° dec.

Other aldehyde-substituted aminoethylsemicarbazones (V), obtained similarly, are given in Table I.

5-Nitro-2-furaldehyde 2-(2-Acetoxyethyl)semicarbazone.—To 5.0 g. (0.0192 mole) of IIIb in 25 ml. of acetic acid was added 1.7 g. (0.0196 mole) of morpholine. After heating the mixture at reflux temperature for 35 min., the acetic acid was evaporated under vacuum. The solid residue was slurried with 50 ml. of water and filtered to give 4.9 g. (90%), m.p. 168–177°, of yellow solid. After recrystallization from ethanol the melting point, 174–175°, and the mixture melting point were in agreement with those of an authentic sample.[9]

1-Benzylideneamino-1-(2-hydroxyethyl)guanidine (VIIIa) Hydrochloride. A.—To a suspension of 5 g. (0.022 mole) of IIa in 25 ml. of absolute ethanol was added a solution of 1.1 g. (0.065 mole) of ammonia in 15 ml. of absolute ethanol. The mixture was shaken in a stoppered flask for 4.5 hr., filtered, and evaporated to dryness. The yield of white solid was 5.2 g. (97%), m.p. 160–170°. Recrystallization from a mixture of ethanol and 2-propanol raised the melting point to 179–180°.

(5) A. F. McKay, G. Y. Paris, and M. E. Kreling, *J. Am. Chem. Soc.*, **79**, 5276 (1957).

(6) Melting points were taken on a Fisher-Johns apparatus and are uncorrected.

(7) G. Gever, C. O'Keefe, G. Drake, F. Ebetino, J. Michels, and K. Hayes, *J. Am. Chem. Soc.*, **77**, 2277 (1955).

(8) G. Gever and W. Ward, U. S. Patent 2,726,241 (1955).

(9) British Patent 888,671 (1962).

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]

Acknowledgment.—The author wishes to acknowledge Dr. J. G. Michels for preparing the analytical sample of Ia, Dr. Jerrold Meinwald for his helpful discussions of the results of this work, and the Physical and Analytical Section for the analytical and ultraviolet absorption data.

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

(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.