Syntheses of β-Substituted Thiophenes

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(Reveived February 10, 1958)

Abstract

Four β-substituted thiophene derivatives are synthesized by the new dehalogenation method using copper and quinoline. Six isomers of bromonitrothiophenes and *dl*-iso-leucine are synthesized from thiophene.

In this paper is introduced a new method of dehalogenation of halogenothiophenes with copper and quinoline, by which β-substituted thiophenes are prepared easily from thiophene derivatives. Four β-substituted thiophenes are synthesized by this method, as shown in Table I. Using this method, six isomers of nitrobromothiophene are synthesized by the procedures shown in Table II. Among six isomers, 2-bromo-5-nitrothiophene (I) and 3-bromo 2-nitrothiophene (VI) have been known,[1,2] but other four isomers have been unknown.

The nitro group in methyl nitrobromothiophenecarboxylate (VIII), which is prepared by the nitration of methyl 2-bromo-5-thiophenecarboxylate (VII) with mixed acid, must be located in the ortho-position to bromine atom, because the orientating effect of bromine to ortho or para position is larger than that of carboxylate group.

Therefore the decarboxylated product of nitro-2-bromo-5-thiophenecarboxylic acid (IX) must be 2-bromo-3-nitrothiophene (II). The nitration of 4, 5-dibromo-2-thiophenecarboxylic acid (X) gives 4, 5-dibromo-2-nitrothiophene (XI), which is prepared also by the nitration of 2, 3-dibromothiophene[1]. The product obtained from 4, 5-dibromo-2-nitrothiophene (XI) by the copper-quinoline method, must be 4-bromo-2-nitrothiophene (III), because the mixed melting point of this product with 5-bromo-2-nitrothiophene (I) is depressed. The structure of 2-bromo-4-nitrothiophene (IV) is sure, because this compound is prepared by the Hunsdiecker reaction of 4-nitro-2-thiophenecarboxylic acid (XII) of which structure is known. The product of formylation of β-bromothiophene is assured to be 3-bromo-2-thiophenealdehyde (XIII) by the following method. The bromoformylthiophene obtained from 3-bromothiophene is oxydized to give bromothiophenecarboxylic acid (XIV) of m. p. 188-189°C., which is same to the 3-bromo-2-thiophenecarboxylic acid obtained from the 3-bromo-2-thienyl magnesium bromide and carbon dioxide[1]. 4-Bromo-2-thiophenecarboxylic acid (XV) and 3-bromo-4-thiophenecarboxylic acid (XVI) have m. p. 113-114°C. and 150-152°C.,[1] respectively. Therefore the product (XIII) must be 3-bromo-2-thiophenealdehyde. 3-Bromo-2-thiophenealdehyde is nitrated and the product of nitration is oxidized to give the bromonitrothiophenecarboxylic acid (XVII). The position of nitro group in this compound should be β-position, because this compound

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gives 2, 3-dibromo-4-nitrothiophene (XIX), m. p. 99°C., by the Hunsdiecker reaction. If the nitro group is introduced into the α-position of 3-bromo-2-thiophenealdehyde (XIII), the product of the Hunsdiecker reaction must be 2, 3-dibromo-5-nitrothiophene which is known to have m. p. 74–75°C. 3-Bromo-4-nitrothiophene (V) is prepared by the decarboxylation of 4-nitro-3-bromo-2-thiophenecarboxylic acid (XVIII).

Table I. Dehalogenation with Copper and Quinoline.

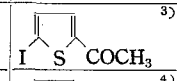
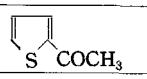
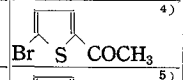
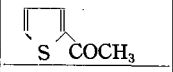
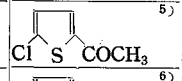
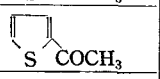
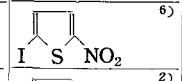
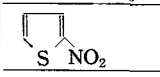
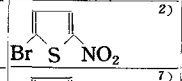
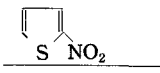
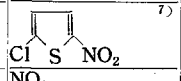
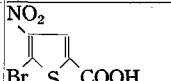
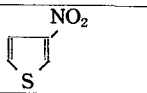
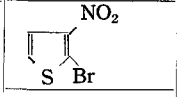
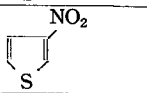
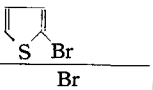
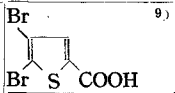
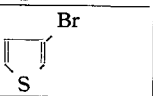
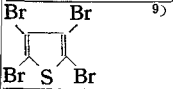
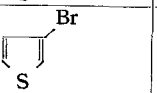
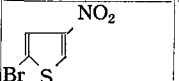
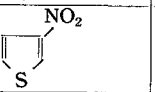
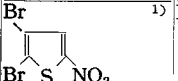
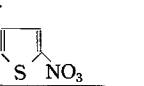
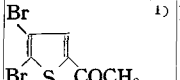
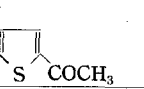
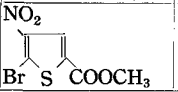
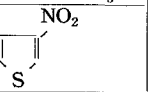
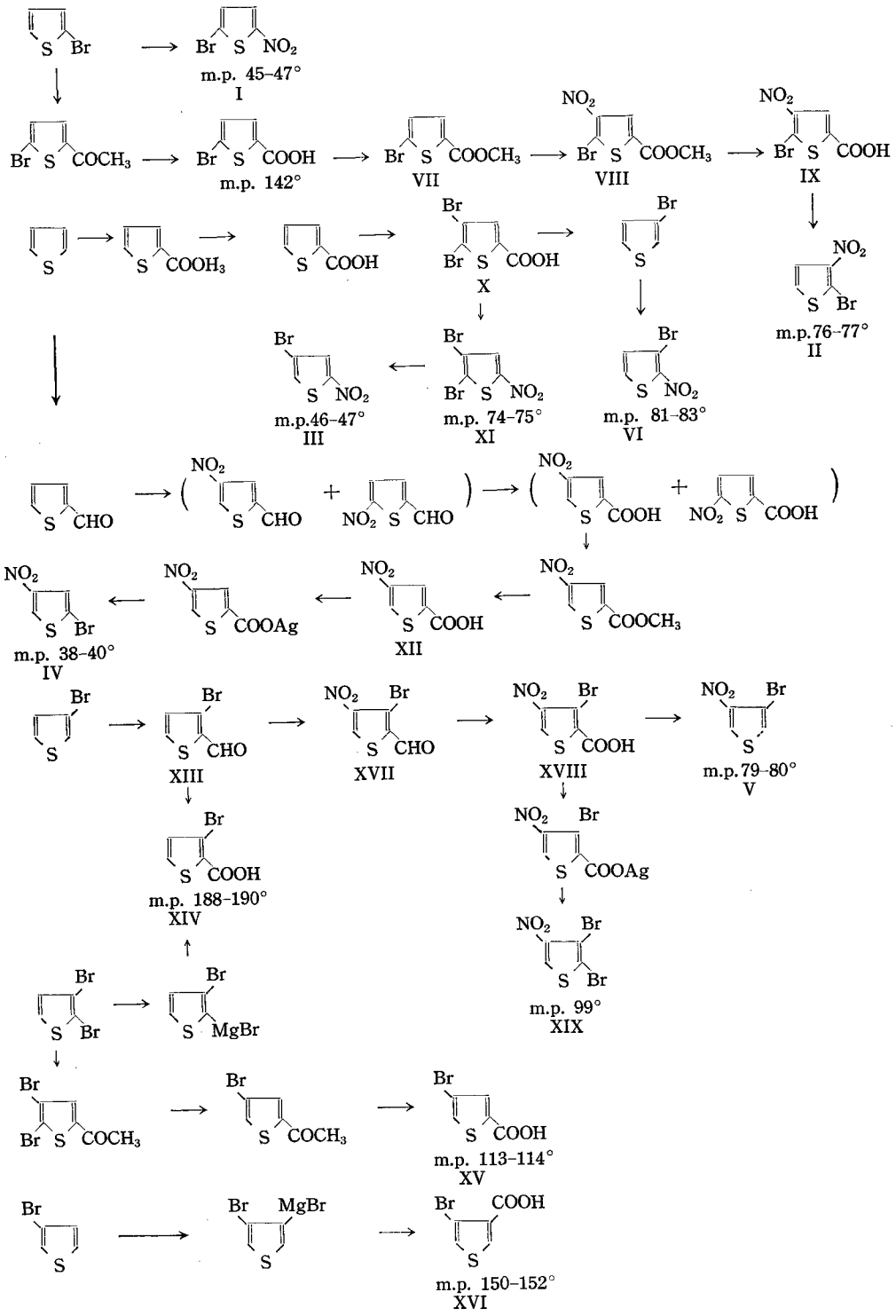
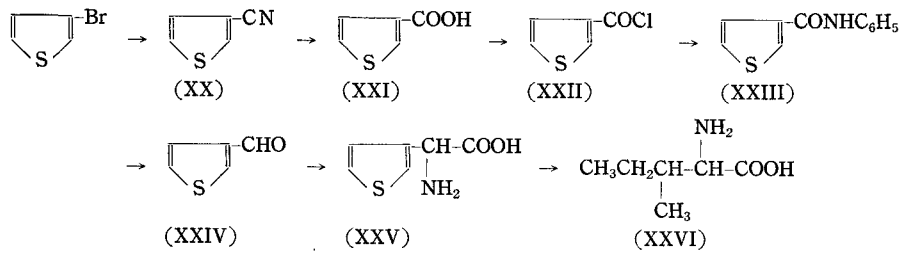
No.	Sample	Product	Physical Properties of the Product and Derivaties.	Yield, %
1	 [3]		b.p. 80–82°C./6mm. n_D^{20} 1.5666. [10,11] Oxime m.p. 111–113°C.	57
2	 [4]		b.p. 75–78°C./5mm., n_D^{20} 1.5667 Oxime m.p. 111–113°C.	44
3	 [5]		b.p. 80–85°C./6mm. Hg, n_D^{20} 1.5705 Oxime m.p. 111–113°C	24
4	 [6]		m.p. 42–44°C[1,2]	32
5	 [2]		m.p. 42–44°C.	14
6	 [7]	—	———	0
7			m.p. 75–77°C.[13]	36
8			m.p. 76–77°C.	58
9	 [8]		b.p. 75–80°C., n_D^{20} 1.5283 [11,14] 2-Thiophenemercurichloride m.p. 183°C.	10
			b.p. 145–151°C., n_D^{20} 1.5860 [8,15] 2-Bromo-5-thiophenemercuriacetate m.p. 134–135°C.	40
10	 [9]		b.p. 66–68°C./31mm., n_D^{20} 1.5863 [1,16] 3-Bromo-2-thiophenemercurichloride m.p. 121–123°C. 3-Bromo-2-nitrothiophene m.p. 81–83°C.	80
11	 [9]		b.p. 70–74°C./39mm. 3-Bromo-2-thiophenemercurichloride m.p. 121–123°C. 3-Bromo-2-nitrothiophene m.p. 81–83°C.	50
12			m.p. 76–77°C.	40
13	 [1]		m.p. 46–47°C. *Anal.* Calcd. for $C_4H_2O_2BrNS$: N,6.72. Found: N,6.20.	34
14	 [1]		b.p. 90–100°C./1mm.Hg, n_D^{20} 1.5982 Semicarbazone m.p. 210–212°C. *Anal.* Calcd. for $C_7H_8OBrN_3S$: N,16.03. Found: N,15.86.	40
15			m.p. 76–78°C.	6

Table II. Syntheses of Bromonitrothiophenes.



dl-Iso-leucine is synthesized from 3-bromothiophene by the procedures shown in the following chart. It is very interesting that the desulfurization of 3-thienylglycine with Raney nickel does not give any *dl*-allo-iso-leucine, but *dl*-iso-leucine.



Experimental

3-Bromothiophene from 4, 5-dibromo-2-thiophenecarboxylic acid (General procedures of copper-quinoline method).-In a distilling flask of 500 ml. are placed a mixture of 4, 5-dibromo-2-thiophenecarboxylic acid (60 g.), copper powder (10 g.) and quinoline (140 g.), and the stream of nitrogen or air is introduced into the mixture. The mixture is heated up gradually till the vigorous reaction occurs. The temperature should be regulated to keep gentle refluxing without distillation of quinoline. After refluxing for 60 minutes, the mixture is heated to a little higher temperature to distill off quinoline along with the product. 3-Bromothiophene is separated by the acidification of the distillate (60–70 ml.) and collected with ether. The ethereal extract is washed with dil. hydrochloric acid twice and with water once, and then dried over calcium chloride. After evaporation of ether, the vacuum distillation gives 27.3 g. of the product, b. p. 66–68.5°C./31 mm.

2-Bromo-3-nitro-5-thiophenecarboxylic acid (IX).-5-Bromo-2-thiophenecarboxylic acid[4] is esterified by the usual method with methanol saturated with hydrogen chloride. The yield of methyl 2-bromo-5-carboxylate (VII) is 86%., m. p. 60–62°C. The solution of 8.3 ml. of nitric acid (d., 1.42) in sulfuric acid (25 ml.) is added at the temperature from −5 to −10°C. to the solution of methyl 2-bromo-5-thenoate (29.1 g.) in sulfuric acid (80 ml.). After adding is it stirred for additional 30 minutes at −5°C. and then poured into iced water. The product (VIII) precipitated is separated by filtration, washed and recrystallized from methanol, m. p. 98.5–102°C. Yield, 25.3 g. (72.3%). Methyl 2-bromo-3-nitro-5-thenoate (20g.) is hydrolyzed by heating with sulfuric acid (100 ml. in 200 ml. water). The yield of 2-bromo-3-nitro-5-thiophenecarboxylid acid is quantitative, 19.9g., m. p. 172–173°C., after recrystallization from water.

Anal. Calcd. for $C_5H_2O_4BrNS$: N, 5.55, Neut. Equiv., 252. Found: N, 5.03, Neut. Equiv., 254.

2-Bromo-3-nitrothiophene (II).-The mixture of 5-bromo-4-nitro-2-thiophenecarboxylic acid (90 g.) and mercuric oxide (68 g.) in glacial acetic acid (900 ml.) is heated under refluxing for 12 hrs., and then the half amount of acetic acid added is removed by distillation. The acetoxymercurated product is separated by filtration after adding 4.5 l.

of water and mixed with sodium chloride (90 g.), water (1800 ml.) and conc. hydrochloric acid (720 ml.). 2-Bromo-3-nitrothiophene is obtained by the steam distillation in the yield of 63 g. (85%) and recrystallized from ligroin, m. p. 77-78°C. The mixed melting point with 3-nitrothiophene is depressed to 45-48°C.

Anal. Calcd. for $C_4H_2O_2BrNS$: N, 6.72. Found: N, 6.36.

2, 5-Dibromo-3-nitrothiophene.-2, 5-Dibromo-3-nitrothiophene is prepared from 2-brom-3-nitro-5-thiophenecarboxylic acid (IX) by the Hunsdiecker reaction. Yield is 88%, m. p. 59-60°C, after recrystallization from ligroin.

Anal. Calcd. For $C_4HO_2Br_2NS$: N, 4.88. Found: N, 4.60.

4, 5-Dibromo-2-nitrothiophene (XI).-To a solution of 13.8 g. of 4, 5-dibromo-2-thiophenecarboxic acid (X) in 100 ml. of conc. sulfuric acid is added the mixed acid consisting of 5 ml. of fuming nitric acid and 100 ml. of conc. sulfulic acid gradually. The reaction mixture is poured onto ice and 11 g. (80%) of crystalls separated are recrystallized from petroleum ether to give yellow needles, m. p. 72-74°C.

4-Nitro-2-thiophenecarboxylic acid (XII).-2-Thiophenealdehyde is nitrated by the method reported by W. O. Foye, H. J. Hefferren, E. G. Feldmann[17] to form the mixture of 4- and 5-nitro-2-thiophenealdehyde in the yield of 79%. This mixture is oxidized to 4- and 5-nitro-2-thiophenecarboxylic acids with sodium bichromate in 35% sulfuric acid. Yield, 87%. The mixture of 4- and 5-nitro-2-thiophenecarboxylic acids is esterified by heating with methanol saturated with hydrogen chloride for 8 hrs. The methyl ester of 4-nitro-2-thiophenecarboxylic acid is separated from the mixture by repeated recrystallization from ligroin with 38% yield, m. p. 100-101°C., and hydrolyzed with the solution of sulfuric acid (55 ml.) in water (83 ml.). 4-Nitro-2-thiophenecarboxylic acid melts at 154-155°C. after the recrystallizing from benzene. Yield, 65%.

3-Bromo-4-nitrothiophene (IV).-2-Bromo-4-nitrothiophene is prepared from 4-nitro-2-thiophenecarboxylic acid by the Hunsdiecker reaction with the similar procedures used for the preparation of 2, 3-dibromo-4-nitrothiophene, m. p. 38-40°C. (from petroleum ether). Yield, 52%.

Anal. Calcd. for C_4H_2BrNS: N, 6.73. Found: N, 6.58.

3-Bromo-2-thiophenealdehyde (XIII).-The mixture of 3-bromothiophene (32.6 g.), dimethylformamide (50 g.) and phosphorus oxybromide (57.4 g.) is heated under reflux for 4.5 hrs. After standing overnight, the reaction mixture is poured into iced water, neutralized with sodium acetate, and extracted with ether. The ethereal extract is washed with water, then with the aq. solution of sodium bicarbonate and dried over sodium sulfate. The vacuum distillation gives 6.5 g. of 3-bromothiophene and 20.9 g. of 3-bromo-2-thiophenealdehyde of b. p. 91-92°C/3 mm. Yield, 69%.

3-Bromo-2-thiophenecarboxylic acid (XIV).-A solution of 1 g. of sodium hydroxide in 10 ml. of water is added to silver oxide made from 0.9 g. of silver nitrate and 0.21 g. of sodium hydroxide. To this mixture, 1.0 g. of 3-bromo-2-thiophenealdehyde (XIII) is

added at 50°C. under stirring. After maintaining at this temperature under stirring, the reaction mixture is filtered and 0.9 g. of crude carboxylic acid is obtained from filtrate by acidification. After recrystallization from water, m. p. 188–190°C.

4-Bromo-2-thiophenecarboxylic acid (XV).–4-Bromo-2-thiophenecarboxylic acid is prepared by the oxydation of 4-bromo-2-acetylthiophene with chlorine and sodium hydroxide, which is synthesized from 4, 5-dibromo-2-acetylthiophene by copper-quinoline method, m. p. 113–114°C. Yield, 93%.

Anal. Calcd. for $C_5H_3O_2BrS$: Neut. equiv., 207. Found: Neut. equiv., 209.

3-Bromo-4-nitro-2-thiophenealdehyde (XVII).–To the cooled (below −10°C) solution of 3-bromo-2-thiophenealdehyde (21 g.) in conc. sulfuric acid (64 ml.) is added the mixed acid, which consists of 30 ml. of sulfuric acid and 12 ml. of fuming nitric acid during 2 hrs. After stirring for additional 20 minutes, the reaction mixture is poured into iced water. The precipitate is separated by filtration washed with water, and recrystallized from ligroin twice, m. p. 108–110°C. Yield, 11.2 g. (43%).

Anal. Calcd. for $C_5H_2O_3BrNS$: N, 5.90. Found: N, 5.97.

3-Bromo-4-nitro-2-thiophenecarboxylic acid (XVIII).–3-Bromo-4-nitro-2-thiophenealdehyde (9 g.) is oxydized with sodium bichromate in sulfuric acid. Recrystallization of the precipitate from benzene gives 4.2 g. of 3-brome-4-nitro-2-thiophenecarboxylic acid, m. p. 214–215°C. Yield, 44%.

2, 3-Dibromo-4-nitrothiophene (XIX).–Silver salt of 3-bromo-4-nitro-2-thiophenecarboxylic acid is prepared from sodium salt of the acid and silver nitrate and dried over phosphorus pentaoxide. To the mixture of the silver salt and carbon tetrachloride is added the solution of bromine in carbon tetrachloride under stirring and heated under refluxing for 2 hrs. After silver bromide is removed by filtration, the filtrate is washed with an aq. solution of sodium bisulfite, the 10% solution of sodium carbonate and water, and then dried over calcium chloride. The crystal which is obtained as the result of the evaporation of carbon tetrachloride is recrystallized from the mixture of petroleum ether and ligroin. m. p. 99°C.

Anal. Calcd. for $C_4H_2O_2BrS$: N, 4.88. Found: N, 4.69.

3-Bromo-4-nitrothiophene (V).—3-Bromo-4-nitro-2-thiophenecarboxylic acid (3 g.) is decarboxylated with mercuric oxide (15.6 g.) in acetic acid (35 ml.). The precipitate, which is obtained by adding water to the concentrated reaction mixture, is separated by filtration and heated for 2 hrs. with sodium chloride (3 g.), water (60 ml.) and conc. hydrochloric acid (24 ml.). Steam distillation gives 2.3 g. of 3-bromo-4-nitrothiophene. Recrystallization from ligroin. m. p. 79–80°C. Yield, 93%.

Anal. Calcd. for $C_4H_2O_2BrNS$: N, 6.73. Found: N, 6.67.

3-Cyanothiophene (XX).—The mixture of 3-bromothiophene (28.8 g.), cuprous cyanide (20 g.) and quinoline (120 ml.) is heated under refluxing for 3 hrs., the vacuum distillation gives about 60 ml. of the distillate. The distillate is acidified with dil.

hydrochloric acid and extracted with ether. The ethereal extract is washed with dil. hydrochloric acid once and with water three times and then dried over sodium sulfate. After the evaporation of the ether, the vacuum distillation gives the product of b. p. 100–102°C./30 mm., 14.5 g. Yield, 75%.

3-Thiophenecarboxylic acid (XXI).—3-Cyanothiophene (10 g.) is heated under reflux with 200 ml. of conc. hydrochloric acid for 3.5 hrs. The separated crystalles are recrystallized from water, m. p. 136–137°C[18]. Yield, 9 g., 84%.

3-Thenoylchloride(XXII).—After 3-thiophenecarboxylic acid (8.8 g.) is boiled with thionylchloride (18 ml.) for 2 hrs., excess thionylchloride is distilled off under reduced pressure. To the residue of distillation is added a small amount of toluene and the mixture is distilled again to drying up. The residue is 3-thenoylchloride, m. p. 50–52°C[18]. Yield, 9.5 g., 92%.

3-Thenoanilide (XIII).—To the mixture of pyridine (100 ml.) with aniline (20 ml.) is added 5 g. of 3-thenoylchloride under cooling. After standing for several hours at room temperature, water is added to the reaction mixture and the solid product is separated by filtration and washed with water and recrystallized from methanol, m. p. 141–142°C. Yield, 6 g., 90%.

Anal. Calcd. for $C_{11}H_9ONS$: N, 6.89. Found: N, 7.02.

3-Thiophenealdehyde (XXIV).—To the hot solution of 3-thenoanilide (19.5 g,) in benzene (70 ml.) is added phosphorus pentachloride (20 g.) gradually and the reaction mixture is kept at 70°C. for 15 minutes. Benzene and phosphorus oxychloride are removed by distillation under reduced pressure. The ethereal solution of this residue is introduced into the ethereal solution of stannous chloride saturated with dry hydrogen chloride. After dry hydrogen chloride gas is bubbled into the ethereal solution for 40 minutes, the reaction mixture is stood overnight. After hydrolysing the reaction mixture with water, the ether is evaporated. The distillate which is obtained from the steam distillation of the residue is extracted with ether. The ethereal solution is dried over sodium sulfate. The vacuum distillation gives the product, β-thiophenealdehyde, b. p. 89–89.5°C/18 mm. Yield, 8.7 g., 80%. 2, 4-Dinitrophenylhydrazone, m. p. 236–237°C[18]., is prepared by the usual method.

β-Thienylglycine (XXV).—β-Thienylglycine (8.2 g.), m. p. 238–241°C., is obtained by Strecker's method from 9.7 g. of β-thiophenealdehyde.

Anal. Calcd. for $C_6H_7O_2NS$: N, 8.91. Found: N, 8.82.

N-benzoyl-β-thienylglycine is prepared by the usual method, using benzoyl chloride, m. p. 161–162.5°C.

Anal. Calcd. for $C_{13}H_{11}O_3NS$: N, 5.36. Found: N, 5.17.

***dl*-Iso-leucine (XXVI).**—Raney nickel (38 g.) is added to the hot solution of β-thienyl glycine (1.57 g.) in water (330 ml.). After standing overnight, the reaction mixture is acidified slightly with hydrochloric acid, and then is concentrated to about 200 ml. The filtrate removed from the precipitate which is formed by adding ammonia to the above

concentrated solution is concentrated again to 15 ml. When alcohol is added to this concentrated solution, the white crystals (0.3 g.) precipitate out, which are recrystallized from water, m. p. 274°C. (decomp.)[19]. The R_f value of paper chromatography of this compound and the authentic sample are identical, 0.67, when the mixture of n-butanol-acetic acid-water (4 : 1 : 1) is used as the solvent. The phenyluramidic acid of this compound is prepared by the usual method with phenylisocyanate, m. p. 123°C. The mixed melting point with the authentic sample of the phenyluramidic acid of *dl*-iso-leucine is not depressed.

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