Thioacylation of Enamines. A Synthesis of Isothiazoles

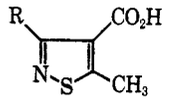
R. R. CRENSHAW, J. M. ESSERY, AND A. T. JEFFRIES

Research Division, Bristol Laboratories, Division of Bristol-Myers Company, Syracuse, New York 13201

Received April 11, 1967

A short synthesis of 3,5-disubstituted 4-cyano- (or 4-carbethoxy-) isothiazoles involving the thioacylation of β-cyano- (or β-carbethoxy-) enamines is reported. Thioacylating agents investigated were ethyldithioacetate, S-carboxymethyldithioacetate, and S-carbomethoxymethyldithioacetate. Isothiazoles prepared by this route were 3-phenyl-5-methyl-4-isothiazolecarbonitrile and the *o*-chloro and *o,o'*-dichloro derivatives, 3-phenyl-5-methyl-4-carbethoxyisothiazole, and 3,5-dimethyl-4-isothiazolecarbonitrile. The preparations of the corresponding 3-aryl-4-isothiazolecarboxylic acids from the nitriles or esters are also described.

In connection with another program, we required a short synthesis of the isothiazole-4-carboxylic acids Ia–c.

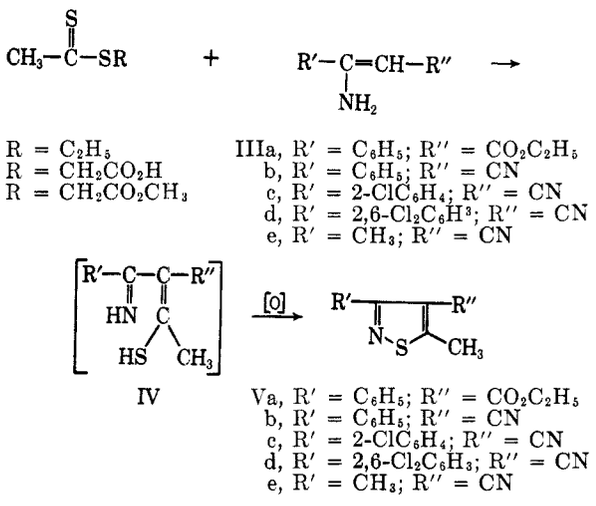


Ia, R = C_6H_5
b, R = 2-ClC_6H_4
c, R = 2, 6-$Cl_2C_6H_3$

Mononuclear isothiazoles were unknown until 1956 when Adams and Slack[1] obtained isothiazole-4,5-dicarboxylic acid by the oxidation of 5-aminobenz[*d*]-isothiazole. Since then, several syntheses of isothiazoles have appeared and the subject has recently been reviewed.[2] None of these methods, however, would provide directly isothiazoles with the substitution pattern which we desired.

The work of Adams and Slack[3] and of Goerdeler and Pohland[4] suggested to us that thioacylation of suitably substituted enamines as of type III would afford intermediates (probably of the enethiol structure IV) which could be oxidized to isothiazoles as outlined in Scheme I. These workers had oxidized β-iminothio-

SCHEME I



IIa, R = C_2H_5
b, R = CH_2CO_2H
c, R = $CH_2CO_2CH_3$

IIIa, R′ = C_6H_5; R″ = $CO_2C_2H_5$
b, R′ = C_6H_5; R″ = CN
c, R′ = 2-ClC_6H_4; R″ = CN
d, R′ = 2,6-$Cl_2C_6H^3$; R″ = CN
e, R′ = CH_3; R″ = CN

IV

Va, R′ = C_6H_5; R″ = $CO_2C_2H_5$
b, R′ = C_6H_5; R″ = CN
c, R′ = 2-ClC_6H_4; R″ = CN
d, R′ = 2,6-$Cl_2C_6H_3$; R″ = CN
e, R′ = CH_3; R″ = CN

amides to obtain 5-aminoisothiazoles. Further examination of the literature revealed that acylation of enamines similar to III with carboxylic acid chlorides usually gave C-acylated products, but that on occasion N-acylation occurred.[5,6] Examples of electrophilic attack at enamine carbon with sulfur-containing reactants were found in the work of Goerdeler and Pohland[4] (using isothiocyanates) and Mayer, *et al.*[7] (using carbon disulfide to obtain, after oxidation of the intermediates, isothiazoline-5-thiones). As further evidence that thioacylation would occur at the enamine carbon of III, we condensed trichloromethanesulfenyl chloride with ethyl 3-aminocinnamate (IIIa) in the presence of aqueous base and obtained, as the only isolable product, 2-hydroxy-4-phenyl-5-carbethoxythiazole (formed by hydrolysis of the initially formed 2-chlorothiazole). An authentic sample of this compound was prepared by the method of Knott[8] and was shown to be identical with our product. If attack had occurred at nitrogen, as in the preparation of 1,2,4-thiadiazoles from trichloromethanesulfenyl chloride and amidines,[9] an isothiazole would have been formed.

We were thus encouraged to treat suitable dithio esters (II) with enamines (III), and did in fact obtain the corresponding isothiazoles (V) after oxidation of the intermediates (IV), which were not isolated, with iodine.[10] Hydrolysis of the 4-cyanoisothiazoles by standard procedures gave the desired acids Ia–c.

Ethyl dithioacetate (IIa) was chosen in our initial attempts since the by-product, ethanethiol, could readily be distilled from the reaction mixture. No reaction could be effected between ethyl dithioacetate and ethyl 3-aminocinnamate (IIIa) under neutral conditions, but a vigorous reaction occurred when the sodium salt of the enamine IIIa was condensed with this reagent; after oxidation with iodine a tar resulted which contained some (less than 3%)[11] of the isothiazole ester Va.

Reaction of the more active thioacylating agent S-carboxymethyl dithioacetate (IIb) with ethyl 3-aminocinnamate under a variety of conditions gave, after oxidation, tars containing up to 15%[11] of the isothiazole ester Va, together with considerable quantities

(1) A. Adams and R. Slack, *Chem. Ind.* (London), 1232 (1956).
(2) R. Slack and K. R. H. Wooldridge in "Advances in Heterocyclic Chemistry," Vol. 4, A. R. Katritzky, Ed., Academic Press Inc., New York, N. Y., 1965, pp 107–120.
(3) A. Adams and R. Slack, *J. Chem. Soc.*, 3061 (1959).
(4) J. Goerdeler and H. W. Pohland, *Ber.*, **94**, 2950 (1961); J. Goerdeler and H. W. Pohland, *ibid.*, **96**, 526 (1963)
(5) E. Benary, *Ber.*, **42**, 3912 (1909).
(6) E. Benary, F. Reiter, and H. Soenderop, *ibid.*, **50**, 65 (1917).
(7) R. Mayer, H. J. Hartmann, and J. Jentzsch, *J. Prakt. Chem.*, [4] **31**, 312 (1966).
(8) E. Knott, *J. Chem. Soc.*, 1656 (1947).
(9) J. Goerdeler, H. Groschopp, and U. Sommerlad, *Ber.*, **90**, 182 (1957).
(10) After this manuscript was completed, a publication appeared [K. Hartke and L. Peshkar, *Angew. Chem. Intern. Ed. Engl.*, **6**, 84 (1967)] which reported the reaction of dithioesters with malononitrile to give enethiolates which yielded 3-amino-4-isothiazolecarbonitriles after reaction with chloramine had introduced the ring nitrogen function.
(11) Estimated by vapor phase chromatographic analysis. In all experiments the products were collected from a preparative column and were shown to be identical (infrared) with authentic samples. For column specifications, see footnote 13.

of acetophenone and unchanged ethyl 3-aminocinnamate. Reaction of the sodium salt of the carboxydithio ester IIb with the sodium salt of the enamine ester IIIa (in dimethylformamide solution) gave unchanged IIIa as the only identifiable product, probably owing to instability of the sodium salt of the dithio ester IIb.

Use of 3-aminocinnamonitrile (IIIb) with the dithio ester IIb precluded formation of acetophenone and, after oxidation with iodine, resulted in a 34% yield of the isothiazolenitrile Vb. This yield was realized when the reactants were fused, without a solvent, under reduced pressure which permitted removal of mercaptoacetic acid; the intermediate (probably IV) then was oxidized with a solution of iodine in benzene in the presence of potassium carbonate. Condensation of the reactants IIb and IIIb in solvents (toluene, xylene, dimethyl sulfoxide, or dimethylformamide), with subsequent oxidation, gave lower yields (up to 19%) of the isothiazole Vb. Lower yields were obtained when hydrogen peroxide (in ethylene glycol–dimethyl ether) was used rather than iodine.

It is noteworthy that vapor phase chromatographic analysis of an aliquot of the reaction mixture from condensation of IIb and IIIb indicated that a small amount of isothiazole was present before an oxidant was added. Since efforts were made to exclude oxygen from the reaction mixture, some isothiazole Vb could have formed from disproportionation of a 2,3-dihydroisothiazole which could be present. The actual intermediate may be a complex mixture containing tautomeric dihydroisothiazoles and varying tautomeric forms of the enethiol IV. Preliminary attempts to isolate the intermediate before oxidation resulted in intractable gums, the infrared spectra of which were indicative only of the starting enamine.

The isothiazoles Vc and Vd were obtained from the carboxydithio ester IIb and the appropriate enamines but the yields were lower with increasing substitution.

The dimethylisothiazole Ve was obtained from the carboxydithio ester IIb and 3-aminocrotononitrile (IIIe), thus demonstrating that the synthesis is not limited to enamines containing aryl groups.

Since early results had suggested that reaction of the sodium salts of enamines of structure III with dithioesters might give improved yields of isothiazoles, the previously undescribed dithio ester IIc was prepared. It was thought that IIc might be as active as a thioacylating species as its corresponding acid IIb, while, unlike IIb, it could be used with sodium salts of enamines III. The dithio ester IIc was prepared by the convenient exchange reaction shown.

$$CH_3CS_2C_2H_5 + HSCH_2CO_2CH_3 \xrightarrow{\text{pyridine}} \underset{\text{IIc}}{CH_3CS_2CH_2CO_2CH_3} + C_2H_5SH\uparrow$$

Although IIc appeared to react with the sodium salt of the enamine IIIb, the only identifiable product from the tar which resulted after oxidation was unchanged enamine IIIb. Under neutral conditions IIc and IIIb gave some of the isothiazole Vb, but the yield was poor (below 5%).[11] Ethyl dithioacetate (IIa) and the sodium salt of the enamine IIIb in dimethylformamide gave (after oxidation) some isothiazole Vb, but the yield was similarly poor.

Subsequent to this work we encountered a thesis by Gougoutas[12] which reported the thiocarbonylation of methyl 3-aminocrotonate with thiophosgene to give a 54% yield of 3-methyl-4-carbomethoxyisothiazole which was used as an intermediate in the total synthesis of colchicine. Under the conditions employed by Gougoutas, however, we were unable to isolate 3-phenyl-4-carbethoxyisothiazole when ethyl 3-aminocinnamate (IIIa) was substituted for methyl 3-aminocrotonate. When 3-aminocinnamonitrile (IIIb) was condensed with thiophosgene according to Gougoutas, a small amount (2.4%) of 3-phenyl-4-isothiazolecarbonitrile was obtained.

Experimental Section[13]

2-Hydroxy-4-phenyl-5-carbethoxythiazole.—A solution of sodium hydroxide (1.20 g, 0.03 mole) in water (20 ml) was added over 20 min to a solution of trichloromethanesulfenyl chloride (3.72 g, 0.02 mole) and ethyl 3-aminocinnamate (3.82 g, 0.02 mole) in tetrahydrofuran (20 ml) that had been chilled in an ice bath. After the addition, the mixture was stirred at 22° for 19 hr. The mixture was extracted with three 60-ml portions of ether and the combined extracts were washed with water and dried over anhydrous magnesium sulfate. Concentration of the solvent to half-volume caused precipitation of white needles (1.57 g, 31%), mp 198–199°.

Anal. Calcd for $C_{12}H_{11}NO_3S$: C, 57.83; H, 4.45. Found: C, 57.78; H, 4.79.

The product was identical (infrared, mixture melting point) with a sample of 2-hydroxy-4-phenyl-5-carbethoxythiazole (mp 199–200°) prepared from ethyl thionocarbamate and ethyl α-bromobenzoylacetate according to Knott.[8]

5-Methyl-3-phenyl-4-isothiazolecarbonitrile (Vb).—A mixture of 3-aminocinnamonitrile[14] (5.00 g, 0.0347 mole) and S-carboxymethyl dithioacetate[15] (5.20 g, 0.0347 mole) was stirred at 105–109° under 0.3 mm of pressure for 28 min. Mercaptoacetic acid distilled from the reaction mixture. The residual melt was cooled under nitrogen and then was dissolved in benzene (60 ml). Potassium carbonate (7.20 g, 0.052 mole) was added, followed by a solution of iodine (13.20 g, 0.052 mole) in benzene (160 ml).

The mixture was stirred at 28° for 15 hr, and then the supernatant solution was washed in succession with aqueous sodium thiosulfate solution, aqueous sodium hydroxide solution, and water. Drying and subsequent removal of the solvent left crystalline Vb (2.36 g, 34%). Recrystallization (Skellysolve B) gave Vb, mp 76–78°, identical (infrared, mixture melting point) with Vb prepared from an alternative synthesis.[16]

Anal. Calcd for $C_{11}H_8N_2S$: C, 65.99; H, 4.03; N, 13.99. Found: C, 66.58; H, 4.36; N, 13.80.

When the reaction was repeated using a solvent (toluene) for the initial condensation, the yield of Vb (after oxidation and isolation as described above) was 19%.

3-(2-Chlorophenyl)-5-methyl-4-isothiazolecarbonitrile (Vc).—A mixture of 3-(2-chlorophenyl)-3-aminoacrylonitrile[17] (5.00 g, 0.028 mole) and S-carboxymethyl dithioacetate[15] (4.20 g, 0.028 mole) was heated at 116–125° under 7 mm of pressure for 36 min. The mixture was cooled under nitrogen, and then was dissolved in benzene (100 ml). Potassium carbonate (5.80 g, 0.042 mole) was added, followed by a solution of iodine (10.70 g, 0.042 mole) in benzene (120 ml).

The mixture was stirred at 28° for 16 hr, and then was worked up as previously described to yield a mixture (3.10 g) of the isothiazole Vc and the starting enamine IIIc. Pure Vc (1.32 g,

(12) J. Z. Gougoutas, Ph.D. Thesis, Harvard, 1964.

(13) Melting points (capillary) are corrected. Vapor phase chromatographic analyses were obtained using an F&M Model 810 Chromatograph with 10% SE 30, Gas Chrom P in a glass column (6 mm × 5 ft); preparative samples were obtained using an F & M Model 500 Chromatograph with the same packing in a copper column (0.25 in × 6 ft), except as noted.

(14) Holzwart, *J. Prakt. Chem.*, [2] **39**, 242 (1889).

(15) K. A. Jensen and C. Pedersen, *Acta Chem. Scand.*, **15**, 1087 (1961).

(16) We are grateful to Dr. H. Kawaguchi and Dr. T. Naito of Bristol-Banyu Research Laboratories for providing samples of these isothiazoles which were first prepared in their laboratories.

(17) E. von Meyer, *J. Prakt. Chem.*, [2] **92**, 174 (1915).

20%) was obtained by chromatography on alumina (elution with 1:1 benzene–Skellysolve B). Recrystallization (ethanol) gave mp 86–87°.

Anal. Calcd for $C_{11}H_7ClN_2S$: C, 56.28; H, 3.00; Cl, 15.11. Found: C, 56.10; H, 3.11; Cl, 14.91.

3-(2,6-Dichlorophenyl)-5-methyl-4-isothiazolecarbonitrile (Vd).—A mixture of 3-(2,6-dichlorophenyl)-3-aminoacrylonitrile[18] (10.14 g, 0.048 mole) and S-carboxymethyl dithioacetate[15] (7.50 g, 0.050 mole) was heated at 150–160° under 7 mm of pressure for 20 min. The residual melt was cooled under nitrogen, and then was dissolved in benzene (180 ml). Potassium carbonate (10.32 g, 0.075 mole) was added, followed by a solution of iodine (18.90 g, 0.075 mole) in benzene (230 ml).

The mixture was stirred at 28° for 16 hr, and then was worked up as previously described to give an oil (3.48 g). Chromatography on alumina (elution with 1:1 benzene–Skellysolve B) gave Vd (0.85 g, 7%), mp 114–121°. Recrystallization (ethanol) gave mp 125–126°.

Anal. Calcd for $C_{11}H_6Cl_2N_2S$: C, 49.09; H, 2.25; Cl, 26.35; N, 10.41; S, 11.91. Found: C, 49.06; H, 2.31; Cl, 25.99; N, 10.31; S, 12.00.

3,5-Dimethyl-4-isothiazolecarbonitrile (Ve).—A solution of 3-aminocrotononitrile[19] (10.0 g, 0.122 mole) and S-carboxymethyl dithioacetate[15] (18.3 g, 0.122 mole) in benzene (200 ml) was refluxed for 65 min. The mixture was cooled to 28°, and then potassium carbonate (25.3 g, 0.182 mole) was added, followed by a solution of iodine (46.4 g, 0.183 mole) in benzene (560 ml).

After stirring the mixture 15 hr at 28°, it was washed in succession with water, aqueous sodium thiosulfate, aqueous sodium hydroxide (0.5 *N*), aqueous hydrochloric acid (0.1 *N*), and water. The benzene phase was dried and then evaporated to leave a semisolid (5.0 g). Chromatography on alumina (elution with 1:1 benzene–Skellysolve B) gave crystalline Ve (2.7 g, 16%). Recrystallization (cyclohexane) gave mp 51–54° (lit.[20] 50–54°).

Anal. Calcd for $C_6H_6N_2S$: C, 52.17; H, 4.38; N, 20.28; S, 23.17. Found: C, 52.00; H, 4.61; N, 19.99; S, 23.25.

5-Methyl-3-phenyl-4-isothiazolecarboxylic Acid (Ia).—A mixture of 5-methyl-3-phenyl-4-isothiazolecarbonitrile (1.45 g), ethylene glycol (8.9 ml), water (1.8 ml), and potassium hydroxide (0.89 g) was heated under reflux for 48.5 hr.

The mixture was poured onto ice (30 g). Acidification with hydrochloric acid (6 *N*) gave crystalline Ia which was washed with water and dried: yield, 1.45 g (91%); mp 148–151°. Recrystallization (benzene-Skellysolve B) gave mp 151–153°; the compound was identical (infrared) with Ia made from an alternative synthesis.[16]

Anal. Calcd for $C_{11}H_9NO_2S$: C, 60.27; H, 4.14; S, 14.60. Found: C, 60.46; H, 4.57; S, 14.71.

3-(2-Chlorophenyl)-5-methyl-4-isothiazolecarboxylic Acid (Ib).—The nitrile Ve (1.02 g) was hydrolyzed by the procedure previously described: yield of Ib, 1.04 g (94%); mp 185.5–186.5° (benzene–Skellysolve B); identical (infrared) with Ib made by an alternative synthesis.[16]

Anal. Calcd for $C_{11}H_8ClNO_2S$: C, 52.08; H, 3.18; S, 12.64. Found: C, 52.16; H, 3.27; S, 12.79.

3-(2,6-Dichlorophenyl)-5-methyl-4 isothiazolecarboxylic Acid (Ic).—The nitrile Vd (730 mg) was hydrolyzed by the procedure previously described: yield of Ic, 670 mg (86%); mp 213.5–215°; identical (infrared, mixture melting point) with Ic first prepared in these laboratories from an alternative synthesis.[21]

Anal. Calcd for $C_{11}H_7Cl_2NO_2S$: C, 45.85; H, 2.45; Cl, 24.61; N, 4.86; S, 11.13. Found: C, 46.10; H, 2.57; Cl, 24.56; N, 4.76; S, 11.31.

S-Carbomethoxymethyl Dithioacetate (IIc).—A solution of ethyl dithioacetate[22] (25.42 g, 0.21 mole) and methyl mercaptoacetate (22.56 g, 0.21 mole) in pyridine (64 ml) was heated under reflux for 0.5 hr. The pyridine (containing ethanethiol) then was removed by distillation (760 mm) over a 2-hr period. Distillation of the residue gave IIc, 15.36 g (45%), bp 100–109° (8 mm).

Anal. Calcd for $C_5H_8O_2S_2$: C, 36.56; H, 4.91; S, 39.04. Found: C, 36.67; H, 4.98; S, 38.46.

3-Phenyl-4-isothiazolecarbonitrile.—Thiophosgene (3.45 g, 0.03 mole) was added over 15 min to a cooled solution (0–5°) of 3-aminocinnamonitrile (4.32 g, 0.03 mole) and triethylamine (7.50 g, 0.075 mole) in dry ether (200 ml). The mixture was stirred 1 hr at 5°, and then the cooling bath was removed and the mixture was stirred for an additional 2 hr. The solution then was added to 100 ml of cold water containing 4 g of concentrated sulfuric acid. After separation of the ether layer, the aqueous layer was extracted with ethyl acetate. The combined organic phases were dried and evaporated to a red oil. This was purified by chromatography on alumina to give 338 mg of crude isothiazole; this was further purified by vapor phase chromatography to give 135 mg (2.4%) of 3-phenyl-4-isothiazolecarbonitrile, mp 49–51°, identical (infrared) with an authentic specimen, mp 54–55°.[16]

5-Methyl-3-phenyl-4-carbethoxyisothiazole (Va). A. From Thioacylation of IIIa.—A solution of ethyl 3-aminocinnamate (158 mg, 0.826 mmole) and S-carboxymethyl dithioacetate (124 mg, 0.826 mmole) in dimethyl sulfoxide (10 ml) was heated under reflux for 1 hr. After cooling the reaction mixture to 28°, a solution of iodine (320 mg, 1.26 mmole) in benzene (18 ml) was added, and then potassium carbonate (180 mg, 1.30 mmole) was added.

The solution was stirred at 28° for 16 hr, and then was diluted with more benzene and was washed in succession with aqueous sodium thiosulfate, aqueous sodium hydroxide, and water. Drying and subsequent removal of the solvent left an oil (135 mg) which was shown by vpc to contain the isothiazole Va, unchanged enamine IIIa, acetophenone, and several minor unidentified impurities; the estimated yield of Va was 15%. A sample of the isothiazole was collected from a preparative column and was shown to be identical (infrared, retention time) with authentic Va prepared as described in B.

B. From Esterification of Ia.—To a saturated solution of anhydrous hydrogen chloride in absolute ethanol (20 ml) was added 5-methyl-3-phenyl-4-isothiazolecarboxylic acid (600 mg). The solution was heated for 2 hr under reflux. After cooling, the solution was added to ice (20 g) and the mixture was extracted with two 15-ml portions of methylene chloride. The combined extracts were washed with three 15-ml portions of 3% aqueous bicarbonate and then were dried (magnesium sulfate). Removal of the solvent left an oily residue which resisted crystallization. A small sample was purified by preparative vapor phase chromatography using an F & M Model 500 chromatograph with 10% mixed SE 30, DEGS, FFAP (1:9:10) Gas Chrom P in a copper column (0.25 in × 6 ft.) The purified sample crystallized and had mp 53–54°. A seed crystal was used to crystallize the above oily residue. This material was recrystallized (Skellysolve B) to provide colorless prisms, mp 54–55°.

Anal. Calcd for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.31. Found: C, 63.02; H, 5.60.

Registry No.—Ia, 13950-59-9; Ib, 13950-60-2; Ic, 14001-95-7; IIc, 13950-61-3; Va, 13950-62-4; Vb, 13950-63-5; Ve, 13950-64-6; Vd, 13950-65-7; Ve, 13950-66-8; 2-hydroxy-4-phenyl-5-carbethoxythiazole, 13950-67-9; 3-phenyl-4-isothiozolecarbonitrile, 13950-68-0.

Acknowledgment.—We are particularly grateful to Harold D. Taylor and Marilyn A. Lloyd for the vapor phase chromatographic data and to Dr. L. C. Cheney for his interest in this work. We also thank the analytical and spectroscopic departments for their services.

(18) Prepared from 2,6-dichlorobenzonitrile and acetonitrile according to H. Kawaguchi and T. Naito, personal communication, 1965.

(19) A commercial sample (Aldrich) was recrystallized three times from benzene to give mp 48–57°; the reported melting point for the *cis* isomer is 52–53° [J. J. Conn and A. Taurins, *Can. J. Chem.*, **31**, 1211 (1953)].

(20) M. P. L. Caton, D. H. Jones, R. Slack, and K. R. H. Wooldridge, *J. Chem. Soc.*, 446 (1964).

(21) L. B. Crast, personal communication, 1965.

(22) C. S. Marvel, P. de Radzitzky, and J. J. Brader, *J. Am. Chem. Soc.*, **77**, 5997 (1955).