A Novel Rearrangement of Methyl 2-Mercaptobenzoate. Oxygen → Sulfur Migration of the Methyl Group

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Methyl 2-mercaptobenzoate (**1**) formed solid adduct **2a** with benzylamine and **2b** with dodecylamine. Heating **2a** or **1** in excess of benzylamine at 130° for 5 hr afforded *N*-benzyl-2-mercaptobenzamide (**6a**) in good yield. On the other hand, heating **2a** or **1** in excess of benzylamine at 170–200° for 1–2 hr gave *N*-benzyl-2-methylthiobenzamide (**3a**) in 52% yield. Under similar conditions **2b** gave *N*-dodecyl-2-methylthiobenzamide (**3b**). Evidence was presented to explain the reaction of **1** with primary aliphatic amines in terms of a two-step process involving migration of the methyl group from the oxygen to the sulfur atom, followed by dehydration of the intermediate amine salt of 2-methylthiobenzoic acid (**9**) formed. Aniline failed completely to react with **1**. Heating of **1** in tributylamine or the sodium salt of **1** in methanol at 200–210° for 16 hr yielded 2-methylthiobenzoic acid (**5**). It is proposed that the rearrangment takes place *via* an intramolecular SNi type mechanism.

In connection with broader studies aimed at the synthesis of biologically active amides of 2,2′-dithiodibenzoic acid (**7**), the reaction of methyl 2-mercaptobenzoate (**1**) with primary amines at elevated temperatures was investigated. The expected amides **6** are conventionally prepared by reduction[1] of their corresponding disulfides which, in turn, can be obtained from the diacid **8** (**8** → **7** → **6**). Although primary and secondary amines normally react by displacement of an alkoxide group, one sterically hindered methyl ester has been reported to react[2] by an SN2 displacement at the methyl group. On the other hand, certain aliphatic tertiary amines are known[3] to cause solely a reversible alkyl–oxygen cleavage. A similar behavior

$$\mathrm{RCOOR' + NR_3'' \rightleftharpoons RCOO^- R'\overset{+}{N}R_3''}$$

of amines toward methyl salicylate has been reported[4] recently. The irreversible alkyl–oxygen cleavage by sulfide and mercaptide ions has also been demonstrated.[5,6] We wish now to report that heating of

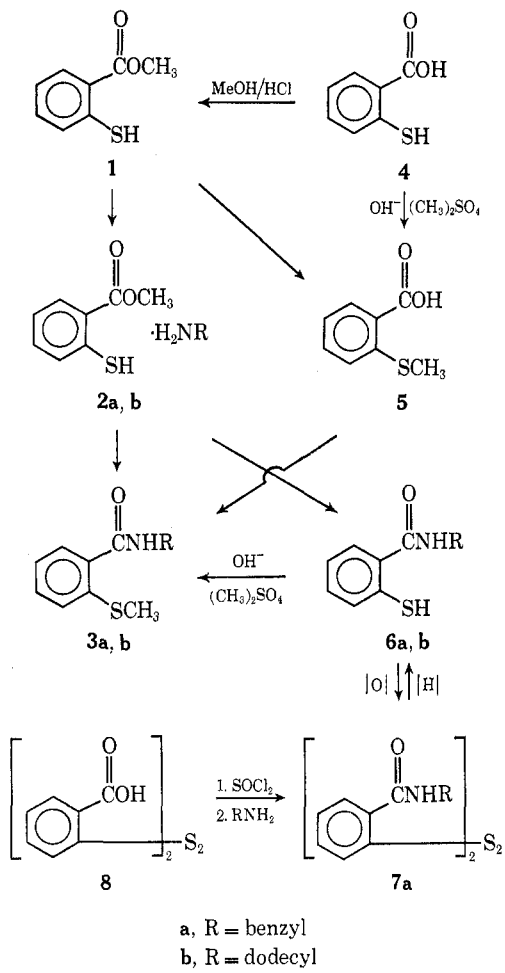
$$\mathrm{RCOOR' + R''S^- \longrightarrow RCOO^- + R'SR''}$$

methyl 2-mercaptobenzoate in basic media at 170–210° results in the migration of the methyl group from the oxygen to the sulfur atom.

Results and Discussion

Addition of benzylamine to an equimolar amount of **1** in the absence of solvent or in ether gave crystalline adduct **2a** in 90% yield. As expected, heating of **1** in excess of benzylamine at 130° for 5 hr gave amide **6a**, which could be best isolated after its oxidation to the known[1] disulfide **7a** by methanolic iodine. The overall yield was 70% (**1** → **2a** → **6a** → **7a**) (Scheme I). On the other hand, when adduct **2a** was heated in the absence of solvent at 175° for 1 hr, it was converted completely (tlc) into products other than the expected

SCHEME I



a, R = benzyl
b, R = dodecyl

6a. Chromatography of the reaction mixture yielded *N*-benzyl-2-methylthiobenzamide (**3a**) in 52% yield. Unequivocal proof was provided with the independent synthesis of **3a** by methylation of **6a** with dimethyl sulfate–sodium hydroxide. Compound **6a**, in turn, was prepared[1] from **8** (**8** → **7a** → **6a**).

The reaction **1** → **2** → **3** also occurred in ethylene glycol, glycerine, or excess of benzylamine at 175–195° (1–2 hr) and appeared to be generally for primary aliphatic amines. For example, heating equimolar amounts of **1** and dodecylamine in a nitrogen atmosphere gave *N*-dodecyl-2-methylthiobenzamide (**3b**) in 25% yield. Under the same conditions, aniline

(1) (a) F. Gialdi, R. Ponci, and A. Baruffini, *Farmaco, Ed. Sci.*, **15**, 856 (1960); (b) R. G. Bartlett and E. W. McClelland, *J. Chem. Soc.*, 818 (1934).

(2) H. E. Zaugg, P. F. Helgren, and A. D. Schaefer, *J. Org. Chem.*, **28**, 2617 (1963).

(3) (a) M. S. Newman and H. A. Lloyd, *J. Amer. Chem. Soc.*, **74**, 2672 (1952); (b) E. L. Eliel and R. P. Anderson, *ibid.*, **74**, 547 (1952); (c) A. C. Pierce and M. M. Joullié, *J. Org. Chem.*, **27**, 3968 (1962).

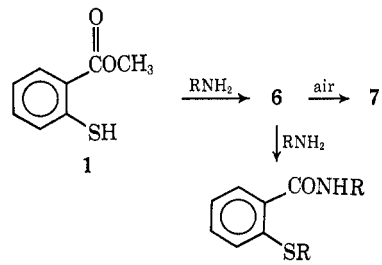
(4) (a) T. Kametani, K. Kigasawa, and T. Hayasaka, *Yakugaku Zasshi*, **87**, 265 (1967); *ibid.*, **88**, 445 (1968); (b) T. Kametani, K. Kigasawa, H. Sugahara, M. Hiiragi, T. Hayasaka, T. Iwata, and H. Ishimary, *Chem. Pharm. Bull.*, **15**, 613 (1967).

(5) (a) J. H. Brewster and E. L. Eliel, *Org. React.*, **7**, 99 (1953); (b) W. R. Vaughan and J. B. Baumann, *J. Org. Chem.*, **27**, 739 (1962).

(6) J. C. Sheehan and G. D. Daves, Jr., *ibid.*, **29**, 2006 (1964).

failed to react with **1**, since the recovery of both starting materials was better than 90%.

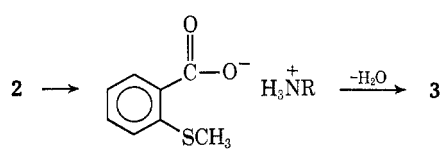
The moderate yield of **3** is not surprising because of two side reactions occurring concurrently, *i.e.*, the amidation of the ester group to **6**, and the relatively less known[5a,7] alkylation of the mercapto group by aliphatic amines. Although small amounts of **6** and



11

7 always accompany the rearrangement products, by-product **11** could not be isolated. The alkylation of pure **6** to **11** (R = benzyl) by benzylamine, however, has been reported[8] and corroborated in our laboratory.

These results are explained in terms of a two-step process involving migration of the methyl group from the oxygen to the sulfur atom (**2** → **9**) followed by de-



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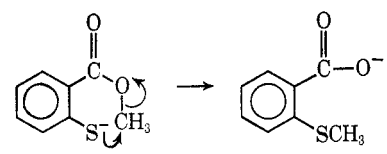
hydration. The feasibility of the dehydration step was proven by reacting 2-methylthiobenzoic acid (**5**, prepared from **4**) with excess of benzylamine at 175–180° for 4 hr. Amide **3a**, identical in all respects with the product obtained by heating **2a**, was isolated in 18% yield.

In order to avoid the amidation step and shed more light, a solution of **1** in tributylamine was heated at 210° for 5 hr. The rearrangement product, 2-methylthiobenzoic acid (**5**), was isolated in 54% yield, which was lower than expected due to possible concurrent alkylation of **1** by tributylamine. For example, tributylamine was allowed to react with **6a** to yield *N*-benzyl-2-butylthiobenzamide (**11**, mp 84–84.5°, –SR = $-SCH_2CH_2CH_2CH_3$, NHR=$NHCH_2C_6H_5$) in fair yield. The fact that the product of this reaction was not the other known isomer,[1a] *N*-butyl-2-benzylthiobenzamide (mp 91–92°), was established unequivocally by nmr studies. Thus, compounds **3a**, **6a**, *N*-benzyl-2-butylthiobenzamide, and *N*-benzyl-2-benzylthiobenzamide exhibited a doublet at 4.49–4.57 ppm, which is characteristic of the two methylene protons of the benzylbenzamido ($PhCONHCH_2Ph$) moiety. As expected, this doublet collapsed to a singlet upon deuterium exchange at the amido hydrogen. On the other hand, the SCH_2 signal for *N*-benzyl-2-butylthiobenzamide (triplet) and the SCH_2Ph signal for *N*-benzyl-2-benzylthiobenzamide (singlet) appeared at 2.78 and 4.00 ppm and were unchanged, as expected, upon deuteration.

(7) L. N. Nikolenko and V. A. Koptyug, *Zh. Obshch. Khim.*, **25**, 1757 (1955); *Chem. Abstr.*, **50**, 5557 (1956).

(8) W. Baker, A. S. El-Nawawy, and W. D. Ollis, *J. Chem. Soc.*, 3163 (1952).

Indeed, in view of the side reactions the isolation of the rearrangement products **3** or **5** in 25–55% yield was significant. Despite the possibility that amines could participate in the rearrangement of **1** by either rupturing or weakening the methyl–oxygen bond, their major role appeared to be the provision of mercaptide ions. This was supported by (a) the complete failure of neat **1** to rearrange at 200° for 16 hr, (b) the same failure of **1** in the weakly basic aniline, and (c) the rearrangement of the sodium salt of **1** in methanol (**1** → **5**) under the same conditions with the highest yield (72%). This rearrangement[9] should proceed by the way of an intramolecular SNi type mechanism, in which the migration of the methyl group is facilitated by the lower energy requirement of a six-membered transition state. However, a competitive intermolecular mechanism which is initiated by the nucleo-



philic attack of a mercaptide ion on the ester methyl group of another molecule is also possible. The fact that the intermolecular mechanism operated only to a small extent, if at all, was shown by competitive experiments, in which the sodium salt of **1** was heated in the presence of an equimolar amount of sodium thiophenoxide. Acid **5** was isolated in about 60% yield along with some (8–9%) 2,2′-dithiodibenzoic acid (**8**). The small drop in yield of **5** from 72% to 60%, partly compensated by the appearance of diacid **8**, could be attributed to the intermolecular attack of the thiophenoxide ion on **1**. The product of this attack, 2-mercaptobenzoic acid, could then easily be oxidized by air to give **8**. Since the mercaptide ion in **1** is sterically more hindered by the carbomethoxy group, as compared to the thiophenoxide ion, the reaction between two molecules of **1** becomes even less significant. We can thus conclude that the SNi mechanism is predominant at least.

Experimental Section[10]

Bis(2-benzylcarbamylphenyl) Disulfide (7a).—A solution of ester[11] **1** (5 g, 0.03 mol) in excess of benzylamine (10 ml) was stirred at 130° for 5 hr, diluted with water (250 ml), acidified with hydrochloric acid, and extracted with benzene (100 ml). The benzene extract was evaporated to dryness *in vacuo* to yield crude **6a** (7 g, 90%). A portion of crude **6a** (3.6 g) was dissolved in methanol (50 ml) and oxidized by methanolic iodine to yield very pure **7a**, mp 211–213°, 2.5 g (69%) (lit.[1b] mp 206°). This compound was identical (mixture melting point, ir, and nmr) with an authentic sample (mp 208–209.5°) prepared in a manner similar to that described[1b] in the literature (**8** → **7a**).

(9) This reaction is an *aliphatic rearrangement* which differs from the *Smiles rearrangement* in two important aspects: (1) the migrating group is aliphatic not aromatic, and (2) the nucleophile attacks a contiguous aliphatic carbon atom and not a contiguous aromatic ring. For a comprehensive review of the Smiles rearrangement, see H. J. Shine in "Reaction Mechanisms in Organic Chemistry," C. Eaborn and N. B. Chapman, Ed., Elsevier, New York, N. Y., 1967, p 307.

(10) Melting points were determined with a Thomas-Hoover melting point apparatus and were not corrected. Microanalyses were performed at Galbraith Laboratories, Inc., Knoxville, Tenn. The nmr spectra were recorded on a Varian HA-100 spectrometer using tetramethylsilane as internal reference. Infrared spectra were determined with a Perkin-Elmer 221 spectrophotometer.

(11) L. Gatterman, *Chem. Ber.*, **32**, 1150 (1899); Schenley Industries, Inc., British Patent 767,027 (Jan 30, 1957); *Chem. Abstr.*, **51**, 17998 (1957).

Methyl 2-Mercaptobenzoate–Benzylamine Adduct (2a).—A solution of benzylamine (1.1 g, 0.01 mol) in ether (25 ml) was added dropwise to a stirred solution of methyl 2-mercaptobenzoate (1.7 g, 0.01 mol) in ether (25 ml) at 10°. The reaction mixture was stirred at room temperature for 1 hr, and the precipitated pure **2a** was filtered off, mp 84–85°, yield 2 g (71%). The melting point did not change after one recrystallization from ether: ir (KBr) 3400 (NH_2), 2670 ($\overset{+}{N}H$), 2575 cm^{-1} (SH); nmr ($CDCl_3$) δ 3.87 (s, 3, CH_3O), 3.82 (s, 2, CH_2), 2.54 (s, 3, SH + NH_2).

Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 65.45; H, 6.18; N, 5.09; S, 11.64. Found: C, 65.28; H, 6.3; N, 5.02; S, 11.77.

***N*-Benzyl-2-methylthiobenzamide (3a). A. From Methyl 2-Mercaptobenzoate (1 → 2a → 3a).**—Addition of benzylamine (2.15 g, 0.02 mol) to methyl 2-mercaptobenzoate (**1**, 3.4 g, 0.02 mol) resulted in an exothermic reaction yielding an oil which solidified upon standing. The adduct **2a** so obtained was heated in an oil bath at 175° for 1 hr, and the main portion of the reaction mixture (5 g) was chromatographed on alumina (150 g). Elutions with benzene and benzene–chloroform solutions (9:1 to 6:4 v/v) yielded pure **3a**, after one recrystallization from hexane: mp 129–130°; yield 2.6 g (52%); ir ($CHCl_3$) 3450 (NH), 1658 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.38 (s, 3, CH_3S), 4.60 (d, 2, $NHCH_2C_6H_5$), 6.7 (broad, 1, NH).

Anal. Calcd for $C_{15}H_{15}NOS$: C, 70.01; H, 5.87; N, 5.44; S, 12.46. Found: C, 70.05; H, 5.88; N, 5.45; S, 12.26.

This sample was identical (mixture melting point, tlc, ir, and nmr) with the samples prepared by the following routes B and C.

B. From 2-Methylthiobenzoic Acid (5 → 3a).—A mixture of 2-methylthiobenzoic acid (3.4 g, 0.02 mol) and benzylamine (8.7 ml, 0.08 mol) was stirred and heated under a nitrogen atmosphere at 175–180° for 4 hr. The reaction mixture was cooled to room temperature and diluted with water (100 ml) to precipitate solid **3a**, mp 131.5–132.5°, 0.9 g (17.5%). Recrystallization from acetone–hexane did not change the melting point. Unreacted **5** was also recovered (35%) from the mother liquor.

C. From *N*-Benzyl-2-mercaptobenzamide (6a → 3a).—Amide **6a** (2.4 g, 0.01 mol) was dissolved in 10% sodium hydroxide (5 ml) by warming on a steam bath and then cooled. To this solution dimethyl sulfate (1.26 g, 0.01 mol) was added, and the mixture was heated on a steam bath for 15 min, diluted with water (5 ml), made strongly alkaline with 10% sodium hydroxide (2 ml), heated for an additional 30 min, and extracted with benzene (three 100-ml portions). The combined extracts were washed with dilute sodium hydroxide and water and evaporated to dryness to yield **3a**, mp 129–130°, yield 2.2 g (84%). One recrystallization from benzene gave pure **3a**, mp 130–131°.

***N*-Dodecyl-2-methylthiobenzamide (3b).**—Dodecylamine (5.6 g, 0.03 mol) was added to ester **1** (5.1 g, 0.03 mol) with stirring. An exothermic reaction took place giving adduct **2b** as an oil, which solidified upon standing and was not characterized further. It was heated in a nitrogen atmosphere at 170–180° for 2 hr, cooled, dissolved in benzene, and chromatographed on alumina (300 g). Elutions with benzene, benzene–chloroform (9:1 to 1:9), and chloroform gave a total of 3.6 g of the product. The analytical sample was prepared by one crystallization from hexane (50 ml): mp 65–66°; 2 g (20%); ir (Nujol) 3280 (NH), 1630 cm^{-1} (C=O); nmr ($CDCl_3$) δ 0.87 (t, 3, CCH_3), 1.27 (m, 20, $(CH_2)_{10}$), 2.44 (s, 3, CH_3S), 3.44 (m, 2, CH_2NH), 6.4 (broad, 1, NH).

Anal. Calcd for $C_{20}H_{33}NOS$: C, 71.59; H, 9.91; N, 4.17; S, 9.56. Found: C, 71.75; H, 9.76; N, 4.00; S, 9.30.

2-Methylthiobenzoic Acid (5). A. By Rearrangment of 1 in Tributylamine.—Ester **1** (5.1 g, 0.03 mol) in tributylamine (28 g, 0.15 mol) was heated in an oil bath in a nitrogen atmosphere at 175–180° for 6 hr and at 205–210° for an additional 5 hr. Upon cooling the reaction mixture separated into two layers. The top layer was diluted with water, acidified with hydrochloric acid, stirred, and cooled giving crude **5** (1.1 g, mp 164–168°). The bottom layer was treated similarly to yield additional **5** which was recrystallized from ethanol (20 ml), mp 164–168°, 1.4 g. A second crop (0.8 g, mp 164–168°) was also obtained by evaporation of the mother liquor to dryness and crystallization of the residue from acetone–hexane. The three samples were combined (3.3 g, 66%) and purified by recrystallization from acetone–hexane: mp 168.5–170° (lit.[12] mp 169°), 2.1 g (47%); second crop mp 166–168°, 0.6 g (12%); nmr (acetone-d_6) δ 2.42 (s, 3, SCH_3) 5.5 (broad, 1, (COOH)). The compound was identical (mixture melting point, tlc, ir, and nmr) with an authentic sample obtained by usual methylation of **4** to **5**.

B. By Methylation of 4.—To a stirred solution of **4** (30.8 g, 0.2 mol) in aqueous sodium hydroxide (16 g, 0.4 mol in 150 ml of water), dimethyl sulfate was added dropwise in 30 min. The solution was heated on a steam bath for 2 hr, filtered, and acidified with 10% hydrochloric acid. The precipitated solid was filtered off and purified by one crystallization from aqueous ethanol and one from ethanol, mp 169–171° (lit.[12] mp 169°), 15.3 g (45%).

C. By Rearrangment of the Sodium Salt of 1 in Methanol.—A solution of **1** (5 g, 0.03 mol) in methanol (16 ml) containing an equivalent amount of sodium methoxide (1.6 g, 0.03 mol) was heated in a 45-ml stainless steel Parr bomb at 200–210° for 16 hr. The reaction mixture was cooled, evaporated to dryness under vacuum, taken up in water (100 ml), acidified with hydrochloric acid, and stirred for 1 hr. The precipitated crude produce (4 g, mp 164–170°) was purified by crystallization from acetone–hexane (mp 169–170°, 3.2 g, 64%). Mixture melting point and ir and nmr spectra showed that this sample was identical with those obtained by the aforementioned rearrangement of **1** in tributylamine (A), and methylation of **4** (B). A second crop (mp 168–169°, 0.4 g, 8%) was also obtained.

D. By Rearrangement of the Sodium Salt of 1 in Methanol in the Presence of Sodium Thiophenolate.—A solution of **1** (5 g, 0.03 mol), thiophenol (3.3 g, 0.03 mol), and sodium methoxide (3.2 g, 0.06 mol) in methanol (20 ml) was heated in a 45-ml stainless steel Parr bomb at 200–210° for 16 hr, cooled, and filtered.

The solid obtained was dissolved in water and acidified with dilute hydrochloric acid to give a precipitate, which was dissolved in hot acetone (200 ml) and clarified by gravity filtration. Upon standing at room temperature overnight, the acetone solutone solution deposited diacid **8** which was identified by the mixture melting point and ir spectrum, mp 295–298° (lit.[13] mp 288.5°), yield 0.4 g (8.7%). The filtrate was concentrated, diluted with hexane, and cooled to yield 2-methylthiobenzoic acid (1.8 g, mp 168–169°, 36%).

The methanolic filtrate was evaporated to dryness, and the residue was taken up in water (50 ml) and extracted with chloroform. The aqueous phase was then acidified with dilute hydrochloric acid yielding additional **5** (1.2 g, mp 167–169°, 24%).

***N*-Benzyl-2-benzylthiobenzamide (11, R = Benzyl).**—Amide **6a** (1.2 g, 0.005 mol) in benzylamine (4.5 ml, 0.04 mol) was stirred under nitrogen at *ca.* 190° for 10 hr. The reaction mixture was dissolved in chloroform, extracted with water (50 ml), 5% hydrochloric acid (two 50-ml portions), 5% sodium hydroxide (two 50-ml portions), and water (50 ml), and evaporated to dryness to yield an oil which solidified upon standing. The crude product was purified by crystallization from acetone–hexane: mp 98–100° (lit.[1,8] mp 97–98°, 102–103°); yield 1.2 g (72%); ir and nmr spectra are in agreement with the structure.

***N*-Benzyl-2-butylthiobenzamide.**—A solution of **6a** (1.2 g, 0.005 mol) in tributylamine (3.7 g, 0.02 mol) was heated in a nitrogen atmosphere at 185–190° for 10 hr. The reaction mixture was diluted with water (10 ml), acidified with dilute hydrochloric acid, and extracted with carbon tetrachloride (10 ml). This layer was filtered from disulfide **7a** (0.2 g, mp 206–208°), extracted with aqueous sodium hydroxide (0.4 g in 20 ml of water) and water (two 20-ml portions), dried ($MgSO_4$), and evaporated to dryness to yield an oil which partially crystallized. This crude product was taken up in hexane (10 ml), filtered off, and purified by column chromatography through silica gel and recrystallization from acetone–hexane: mp 84–84.5°; yield 0.3 g (20%); nmr ($CDCl_3$) δ 0.9 (t, 3, CH_3), 1.2–1.7 (m, 4, CH_2CH_2), 2.85 (t, 2, SCH_2), 4.67 (d, 2, $NHCH_2$).

Anal. Calcd for $C_{18}H_{21}NOS$: C, 72.20; H, 7.07; N, 4.68; S, 10.71. Found: C, 72.05; H, 7.02; N, 4.68; S, 10.81.

The aqueous extracts were combined and acidified to give crude starting material **6a**, 0.4 g (25%), mp 95–105°. The other isomer, *N*-butyl-2-benzylthiobenzamide, has been reported[13a] to have mp 91–92°.

Registry No.—**1**, 4892-02-8; **2a**, 28455-68-7; **3a**, 28455-69-8; **3b**, 28455-70-1; *N*-benzyl-2-butylthiobenzamide, 28455-71-2.

(12) O. Hinsberg, *Chem. Ber.*, **43**, 653 (1910).

(13) K. W. Rosenmund and H. Harms, *ibid.*, **53**, 2237 (1920).