### Experimental Section[7]

**2-[(2-Chloroethyl)ethylamino]-2′,6′-acetoxylidide Hydrochloride.**—2-[Ethyl(2-hydroxyethyl)amino]-2′,6′-acetoxylidide (13.8 g, 0.055 mol) in 50 ml of $CHCl_3$ was cooled in an ice bath. A solution of $SOCl_2$ (13.1 g, 0.110 mol) in 50 ml of $CHCl_3$ was added slowly with stirring. The mixture was warmed on a water bath for 2 hr at 50–60°. The excess $SOCl_2$ and $CHCl_3$ were removed *in vacuo*, and the residual oil was triturated with dry $C_6H_6$ until crystallization occurred. The solid material was removed by filtration and recrystallized repeatedly from $C_6H_6$–$CHCl_3$. The yield was 6.2 g of product melting at 152–154°. *Anal.* ($C_{14}H_{22}Cl_2N_2O$): C, H, N.

**2-[(2-Chloroethyl)ethylamino]ethyl 4-Butoxybenzoate·HCl.**—2-[Ethyl-(2-hydroxyethyl)amino]ethyl 4-butoxybenzoate (6.2 g, 0.02 mol) was dissolved in 20 ml of $CHCl_3$. A solution of $SOCl_2$ (6.0 g, 0.05 mol) in 20 ml of $CHCl_3$ was added in small portions with stirring. The mixture was heated for 4 hr at 65–70° on a water bath. The mixture was concentrated *in vacuo* to a thick oil. The residue was cooled and triturated with petroleum ether to induce crystallization. The product was recrystallized repeatedly from a $C_6H_6$–petroleum ether mixture. The yield of pure material melting at 103–105° was 0.9 g. *Anal.* ($C_{17}H_{27}Cl_2NO_3$): C, H, N.

(7) Melting points were taken in a Thomas-Hoover Unimelt apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

## Radioopaque Contrast Media. XVIII.[1] Derivatives of 2-(3-Amino-2,4,6-triiodophenyl)alkanoic Acids

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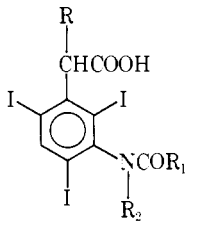
In connection with our studies concerning X-ray contrast media and particularly with the search for new oral cholecystographic agents[2] a number of derivatives of 2-(3-amino-2,4,6-triiodophenyl)alkanoic acids have been synthesized for biological evaluation.

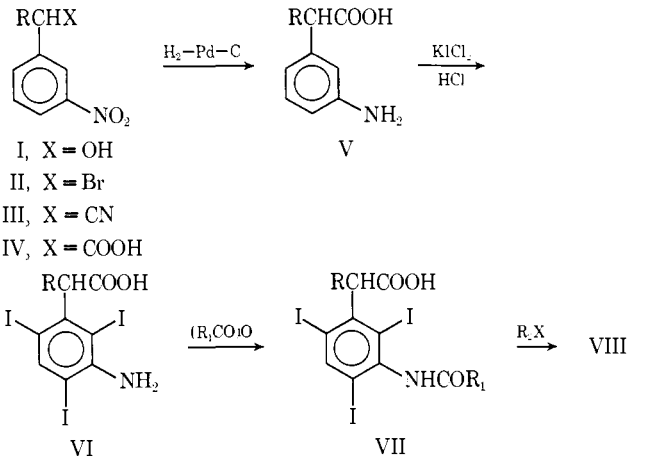


VIII

We were specially interested in the relationship between structure and biological activity such as intestinal absorption, toxicity, and biliary and urinary excretion within a homogenous group of substances.

The synthetic steps leading to the title compounds are outlined in Scheme I.

SCHEME I



I, X = OH
II, X = Br
III, X = CN
IV, X = COOH

V, VI, VII, VIII

**Pharmacology.**—The compounds were tested by Dr. G. Rosati for acute toxicity and biliary and urinary excretion.

For determination of intravenous and oral acute toxicity aqueous solutions of the Na salts were administered in mice and the $LD_{50}$ was determined after 3 days following the method of Litchfield and Wilcoxon.[3] Excretion studies were done in the rabbit, collecting bile and urine through catheters for 3 hr after intravenous injection of 100 mg/kg of the aqueous solution of the Na salts. Total $I_2$ was determined, after digestion, by the Sandell–Kolthoff reaction[4] with a Technikon autoanalyzer[5] and results calculated as per cent of administered dose.

TABLE I
1-(3-NITROPHENYL)ALKANOLS (I)

| No. | R | Mp or bp (mm), °C | Yield, % | Formula | Analyses |
|---|---|---|---|---|---|
| 1 | $CH_3$ | 62.5[a] | 80[a] | $C_8H_9NO_3$ | |
| 2 | $C_2H_5$ | 163 (2)[b] | 95[b] | $C_9H_{11}NO_3$ | |
| 3 | $C_3H_7$ | 173 (4) | 92 | $C_{10}H_{13}NO_3$ | C, H, N |

[a] Lit.[8] mp 62.5°; yield 76%. [b] Lit.[9] bp 170–172° (12 mm).

TABLE II
1-(3-NITROPHENYL)ALKYL BROMIDES (II)

| No. | R | Mp or bp (mm), °C | Yield, % | Formula | Analyses |
|---|---|---|---|---|---|
| 4 | $CH_3$ | 42 | 55 | $C_8H_8BrNO_2$ | C, H, Br, N |
| 5 | $C_2H_5$ | 153 (3) | 58 | $C_9H_{10}BrNO_2$ | C, H, Br, N |
| 6 | $C_3H_7$ | 150 (2) | 55 | $C_{10}H_{12}BrNO_2$ | Br[a] |

[a] Br: calcd, 30.96; found, 30.18.

The 2-(3-amino-2,4,6-triiodophenyl)alkanoic acids (Table VI) and their acyl derivatives (Table VII) showed predominantly urinary excretion; N-alkylation (Table VIII) enhanced biliary excretion.

For comparison iopanoic acid was tested under the same conditions giving $LD_{50}$ p.o. = 1540 mg/kg and $LD_{50}$ i.v. = 285 mg/kg (mouse), biliary excretion 28%, urinary excretion 13% (rabbit). For further investigation 200 mg/kg of compounds **37**, **38**, and **40** in suspension in 5% arabic gum solution were administered orally to dogs. Opacification of the gallbladder and of bile

(1) (a) XVI, E. Felder, D. Pitrè, L. Fumagalli, H. Suter, and H. Zutter, *Helv. Chim. Acta*, **52**, 1339 (1969); (b) XVII, D. Pitrè and L. Fumagalli, *Chim. Ther.*, in press.

(2) (a) D. Pitrè and L. Fumagalli, *Farmaco, Ed. Sci.*, **18**, 33 (1963); (b) D. Pitrè and L. Fumagalli, *ibid.*, **17**, 340 (1962); (c) L. Fumagalli and D. Pitrè, *ibid.*, **24**, 568 (1969).

(3) J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).

(4) E. B. Sandell and J. M. Kolthoff, *J. Amer. Chem. Soc.*, **56**, 1426 (1939).

(5) Technikon Instruments Corporation "N" Method File N-56.

TABLE III
2-(3-NITROPHENYL)ALKANENITRILES (III)

| No. | R | Mp, °C | Bp(mm), °C | Crystn solvent[a] | Yield, % | Formula[b] |
|---|---|---|---|---|---|---|
| 7 | $CH_3$ | 66 | 160–170 (5) | A | 76 | $C_9H_8N_2O_2$ |
| 8 | $C_2H_5$ | 44 | 147–150 (2) | B | 48 | $C_{10}H_{10}N_2O_2$ |
| 9 | $C_3H_7$ | 42 | 135–137 (0.02) | C | 60 | $C_{11}H_{12}N_2O_2$ |

[a] Final recrystallization: A, EtOH; B, hexane; C, petroleum ether. [b] All compounds were analyzed for C, H, N.

TABLE IV
2-(3-NITROPHENYL)ALKANOIC ACIDS (IV)

| No. | R | Mp, °C | Crystn solvent[a] | Yield, % | Formula[b] |
|---|---|---|---|---|---|
| 10 | $CH_3$ | 96 | A | 71 | $C_9H_9NO_4$ |
| 11 | $C_2H_5$ | 117–118 | A | 74 | $C_{10}H_{11}NO_4$ |
| 12 | $C_3H_7$ | 95–97 | B | 45 | $C_{11}H_{13}NO_4$ |

[a] Final recrystallization: A, EtOH 50%; B, petroleum ether. [b] All compounds were analyzed for C, H, N.

TABLE V
2-(3-AMINOPHENYL)ALKANOIC ACIDS (V)

| No. | R | Mp, °C | Crystn solvent[a] | Yield, % | Formula[b] |
|---|---|---|---|---|---|
| 13 | $CH_3$ | 100–101 | A | 88 | $C_9H_{11}NO_2$ |
| 14[c] | $C_2H_5$ | 60–61 | B | 86 | $C_{10}H_{13}NO_2 \cdot H_2O$ |
| 15 | $C_3H_7$ | 110–111 | A | 87.5 | $C_{11}H_{15}NO_2$ |

[a] Final recrystallization: A, $CHCl_3$; B, $H_2O$. [b] Monohydrate. $H_2O$ determined by Karl Fischer method: calcd, 9.13; found, 9.21. [c] Analyses C, H, N.

## Experimental Section[7]

The general procedures are representative for the preparation of the compounds described in Tables I–VIII. Analyses, yields, and physical properties are recorded in the tables. Melting points were determined using the Tottoli melting point apparatus, and are uncorrected.

**1-(3-Nitrophenyl)alkanols (1–3, Table I).**—The 1-(3-nitrophenyl)alkanols were synthesized more efficiently by reduction of 3-nitroacetophenones with $NaBH_4$ in MeOH, than by the methods reported.[8,9]

**1-(3-Nitrophenyl)alkyl Bromides (4–6, Table II).**—To a solution of 1-(3-nitrophenyl)alkanol (0.25 mol) in 200 ml of AcOH was added HBr (1*N*) in AcOH. The mixture was heated at 90–100° for 1 hr and then evaporated to dryness under reduced pressure.

**2-(3-Nitrophenyl)alkanenitriles (7–9, Table III).**—KCN (15 g, 0.23 mol) was added to a solution of 1-(3-nitrophenyl)alkyl bromide (0.2 mol) in 160 ml of EtOH, and the mixture was heated to reflux for 3 hr. EtOH was then evaporated under reduced pressure and the residue partitioned between 200 ml of $Et_2O$ and 200 ml of $H_2O$. The $H_2O$ layer was reextracted with three 240-ml portions of $Et_2O$. The combined $Et_2O$ extracts were washed ($H_2O$) to neutrality, dried, and evaporated. The residual oil was distilled under vacuum and recrystallized from a suitable solvent.

TABLE VI
2-(3-AMINO-2,4,6-TRIIODOPHENYL)ALKANOIC ACIDS (VI)

| No. | R | Mp, °C | Crystn solvent[a] | Yield, % | Formula[c] | Mouse toxicity $LD_{50}$, mg/kg p.o. | Mouse toxicity $LD_{50}$, mg/kg i.v. | I % excretion bile | I % excretion urine |
|---|---|---|---|---|---|---|---|---|---|
| 16 | $CH_3$ | 226–228 | A | 50 | $C_9H_8I_3NO_2$[b] | 2900 | 520 | 1.4 | 34 |
| 17 | $C_2H_5$ | 146–147 | A | 53 | $C_{10}H_{10}I_3NO_2$[c] | 3750 | 550 | 4 | 26 |
| 18 | $C_3H_7$ | 182–184 | A | 50 | $C_{11}H_{12}I_3NO_2$[d] | 2100 | 170 | 5 | 16 |

[a] Final recrystallization: A, EtOH. [b] I: calcd, 70.73; found, 70.10. [c] I: calcd, 68.38; found, 68.83. [d] I: calcd, 66.69; found, 66.17. [e] Analyses: C, H, I (see *b*, *c*, *d*), equiv wt.

TABLE VII
2-(3-ACYLAMINO-2,4,6-TRIIODOPHENYL)ALKANOIC ACIDS (VII)

| No. | R | R′ | Mp, °C | Crystn solvent[a] | Yield, % | Formula[e] | Mouse toxicity $LD_{50}$, mg/kg p.o. | Mouse toxicity $LD_{50}$, mg/kg i.v. | I % excretion bile | I % excretion urine |
|---|---|---|---|---|---|---|---|---|---|---|
| 19 | $CH_3$ | $CH_3$ | 170 | *b* | 71 | $C_{11}H_{10}I_3NO_3$ | 3800 | 1200 | 5 | 70 |
| 20 | $CH_3$ | $C_2H_5$ | 153 | *b* | 80 | $C_{12}H_{12}I_3NO_3$[c] | | | | |
| 21 | $CH_3$ | $C_3H_7$ | 152 | *b* | 69 | $C_{13}H_{14}I_3NO_3$[d] | 1100 | 300 | 14 | 59 |
| 22 | $C_2H_5$ | $CH_3$ | 162 | *b* | 64 | $C_{12}H_{12}I_3NO_3$ | 2800 | 950 | 7.5 | 57 |
| 23 | $C_2H_5$ | $C_3H_7$ | 135–140 | A | 93 | $C_{14}H_{16}I_3NO_3$ | 1900 | 540 | 19 | 35 |
| 24 | $C_3H_7$ | $CH_3$ | 145 | *b* | 95 | $C_{13}H_{14}I_3NO_3$ | 4000 | 700 | 13 | 30 |
| 25 | $C_3H_7$ | $C_2H_5$ | 135 | *b* | 88 | $C_{14}H_{16}I_3NO_3$ | | | | |
| 26 | $C_3H_7$ | $C_3H_7$ | 222 | B | 75 | $C_{15}H_{18}I_3NO_3$[f] | | | | |

[a] Final recrystallization: A, EtOAc; B, EtOH. [b] Purification by reprecipitation. [c] I: calcd, 63.57; found, 64.42. [d] I: calcd, 61.11; found, 61.85. [e] *Anal.* C, H, I, equiv wt. [f] I anal. only.

ducts was evaluated following Hoppe[6] and intestinal residues were observed.

Best results were obtained with **40** with regard to tolerability, gallbladder opacification, and absence of intestinal residues.

**2-(3-Nitrophenyl)alkanoic Acids (10–12, Table IV).**—A mixture of 0.1 mol of 2-(3-nitrophenyl)alkanenitriles and 200 ml of 50% $H_2SO_4$ was heated under reflux for 5 hr. The hydrolyzed product

(6) S. Margolin, I. R. Stephens, M. T. Spoerlein, A. Makovsky, and G. B. Belloff, *J. Amer. Pharm. Ass., Sci. Ed.*, **42**, 476 (1953).

(7) Where analyses are indicated by symbols of the elements, the analytical results obtained for those elements were within ±0.4% of the theoretical values.

(8) H. Lund, *Chem. Ber.*, **70**, 1520 (1937).

(9) Swiss Patent 326363 (1958); *Chem. Abstr.*, **53**, 9252*f* (1959).

TABLE VIII

2-(3-ALKYLACYLAMINO-2,4,6-TRIIODOPHENYL)ALKANOIC ACIDS (VIII)

| No. | R | $R_1$ | $R_2$ | Mp, °C[a] | Crystn solvent[b] | Yield, % | Formula[d] | Mouse toxicity $LD_{50}$, mg/kg p.o. | Mouse toxicity $LD_{50}$, mg/kg i.v. | I % excretion bile | I % excretion urine |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 27 | H | $CH_3$ | $CH_3$ | 197–198 | A | 84 | $C_{11}H_{10}I_3NO_3$ | 2700 | 1100 | 13 | 72 |
| 28 | H | $CH_3$ | $C_2H_5$ | 131–133 | A | 74.5 | $C_{12}H_{12}I_3NO_3$ | 2200 | 390 | 37 | 34 |
| 29 | H | $CH_3$ | $C_3H_7$ | 100–105 | c | 94 | $C_{13}H_{14}I_3NO_3$ | 1250 | 210 | 35 | 33 |
| 30 | H | $CH_3$ | $C_4H_9$ | 100–105 | c | 91 | $C_{14}H_{16}I_3NO_3$ | 1300 | 155 | 32 | 19 |
| 31 | H | $CH_3$ | $CH_2$–$C_6H_5$ | 167–168 | B | 84 | $C_{17}H_{14}I_3NO_3$[e] | 1550 | 235 | 34 | 28 |
| 32 | H | $C_3H_7$ | $CH_3$ | 164–166 | A | 76 | $C_{13}H_{14}I_3NO_3$ | 880 | 180 | 20 | 20 |
| 33 | H | $C_3H_7$ | $C_2H_5$ | 188–189 | C | 76 | $C_{14}H_{16}I_3NO_3$ | 880 | 100 | 15 | 35 |
| 34 | H | $C_3H_7$ | $C_3H_7$ | 139–140 | A | 70 | $C_{15}H_{18}I_3NO_3$ | 365 | 49 | | |
| 35 | H | $C_3H_7$ | $C_4H_9$ | 90–95 | c | 87 | $C_{16}H_{20}I_3NO_3$ | 650 | 51 | 54 | 20 |
| 36 | H | $C_3H_7$ | $CH_2$–$C_6H_5$ | 95–102 | c | 95 | $C_{19}H_{18}I_3NO_3$ | 770 | 74 | 34 | 12 |
| 37 | $CH_3$ | $CH_3$ | $CH_3$ | 155–160 | c | 87 | $C_{12}H_{12}I_3NO_3$[f] | 2800 | 620 | 27 | 22 |
| 38 | $CH_3$ | $CH_3$ | $C_2H_5$ | 125 | c | 72 | $C_{13}H_{14}I_3NO_3$ | 1300 | 380 | 38 | 16 |
| 39 | $C_2H_5$ | $CH_3$ | $CH_3$ | 115–120 | c | | $C_{13}H_{14}I_3NO_3$ | 700 | 600 | 33 | 9 |
| 40 | $C_2H_5$ | $CH_3$ | $C_2H_5$ | 184–187 | c | 85 | $C_{14}H_{16}I_3NO_3$ | 1260 | 420 | 31 | 8 |
| 41 | $C_3H_7$ | $CH_3$ | $CH_3$ | 120 | c | 70 | $C_{14}H_{16}I_3NO_3$ | 2800 | 550 | 17 | 10 |
| 42 | $C_3H_7$ | $CH_3$ | $C_2H_5$ | 116 | d | 85 | $C_{15}H_{18}I_3NO_3$ | 2800 | 170 | 28 | 15 |

[a] All these compounds sinter 20–30° before the melting point. [b] Final recrystallization: A, EtOAc; B, $C_6H_6$; C, $Me_2CO$. [c] Purification by reprecipitation. [d] *Anal.* C, H, I, equiv wt. [e] I: calcd, 57.10; found, 57.80. [f] I: calcd, 62.57; found, 63.40.

was poured into crushed ice (300 g), collected, washed ($H_2O$), and dissolved in 100 ml of 1 *N* NaOH at 70°. The solution was filtered and made acid with 1 *N* HCl. The precipitated acid was collected, dried, and recrystallized from a suitable solvent.

**2-(3-Aminophenyl)alkanoic Acids (13–15, Table V).**—A solution of 0.04 mol of 2-(3-nitrophenyl)alkanoic acid in 150 ml of EtOH was hydrogenated at room temperature and atmospheric pressure over Raney Ni catalyst. After consumption of the theoretical quantity of $H_2$ the catalyst was filtered off and the filtrate was evaporated to dryness. The crystalline residue was suspended in 80 ml of $H_2O$, collected, and recrystallized.

**2-(3-Amino-2,4,6-triiodophenyl)alkanoic Acids (16–18, Table VI).**—A solution of 0.09 mol of 1 *N* $KICl_2$[10] was added dropwise with vigorous stirring at 24° to 0.03 mol of 2-(3-aminophenyl)-alkanoic acid in 3000 ml of 0.01 *N* HCl. After a further 2-hr stirring the temperature was raised to 60° and another 0.03 mol of $KICl_2$ solution was added. The suspension was stirred at 60° for 15 hr, then cooled to room temperature, collected, and washed. The solid was dissolved in 300 ml of $H_2O$ with 10 ml of 15% NaOH and the solution was treated with a trace of $Na_2S_2O_4$ and added dropwise to a mixture of 300 ml of $H_2O$, 12 ml of 18% HCl, and 0.3 g of $NaHSO_3$. The crude product was collected by filtration, washed ($H_2O$), dried, and recrystallized from EtOH.

**2-(3-Acylamino-2,4,6-triiodophenyl)alkanoic Acids (19–26, Table VII).**—2-(3-Amino-2,4,6-triiodophenyl)alkanoic acid (0.005 mol) was dissolved in 18 ml of $(Ac)_2O$ at 60°, 2 drops of concentrated $H_2SO_4$ were added and the temperature was raised to 90–95° for 3 hr. After evaporation to dryness, the residue was dissolved in 60 ml of $H_2O$ with 2 ml of 15% NaOH. The pH was adjusted to 9 and the solution was heated for 2 hr at 90° at constant pH, then filtered and the product was precipitated with 15% HCl. Compounds **19**, **20**, **21**, **22**, **24**, and **25** were purified by reprecipitation, **23** was crystallized from EtOAc, and **26** from EtOH.

**2-(3-Alkylacylamino-2,4,6-triiodophenyl)alkanoic Acids (27–42, Table VIII).**[11]—A solution of 0.045 mol of alkyl iodide in 2.5 ml of $Me_2CO$ was added during 0.5 hr to a solution of 0.03 mol of 2-(3-acylamino-2,4,6-triiodophenyl)alkanoic acid and 0.12 mol of KOH in 35 ml of $H_2O$. The mixture was stirred for 4 hr at 35° and then poured into 200 ml of ice–$H_2O$ and extracted twice with $Et_2O$ (30 ml). The crude product, obtained by precipitation with 18% HCl, was purified further by reprecipitation, extraction with boiling EtOAc, or recrystallization from a suitable solvent.

(10) A. A. Larsen, Ch. Moore, J. Sprague, B. Cloke, J. Moss, and J. O. Hoppe, *J. Amer. Chem. Soc.*, **78**, 3210 (1956).

(11) Intermediate 3-amino-2,4,6-triiodophenylacetic acid for compounds **27–36**, see ref 2a.

## Chlorosulfonation of 17β-Acetoxy-3-methoxyestra-1,3,5(10)-triene

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The estrogenic potencies of 2- and 4-substituted estrones, among which were included Cl, $O_2N$, and $H_2N$ derivatives, have been compared.[1b] These compounds, especially the 2-substituted and electronegatively substituted ones, all have very low estrogenic activities and this has been suggested to be one of the prerequisites for a practical lipodiatic, or antiatherogenic steroid in man.[2] The second, and effective, requirement may be a lowering of the cholesterol:lipid phosphorous (C:P) ratio.[3] This effect is shown as well by the 3-Me ethers which are considerably less estrogenic than the phenols, estrone methyl ether being 1% as estrogenic and 25% as lipodiatic, or lipid-shifting, as estrone.[2,4] A favorable change in the C:P ratio has been shown in the case of some simple estrogens to be related to an increase in serum phospholipid rather than a decrease in cholesterol[5] and this is regarded as corrective toward coronary atherogenesis[6] though without

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(2) (a) D. L. Cook, D. W. Calhoun, and R. A. Edgren, *ibid.*, **135**, 91 (1962); (b) D. L. Cook, R. A. Edgren, and F. J. Saunders, *Endocrinology*, **62**, 798 (1958); (c) R. A. Edgren and D. W. Calhoun, *Circulation*, **16**, 505 (1957); (d) R. A. Edgren and D. W. Calhoun, *Proc. Soc. Exp. Biol. Med.*, **94**, 537 (1957).

(3) R. Pick, J. Stamler, S. Rodbard, and L. N. Katz, *Circulation*, **6**, 276 (1952).

(4) D. L. Cook, *Drugs Affecting Lipid Metab. Proc. Symp. D. A. L. M. Milan, 1960*, 204 (1961).

(5) A. Corbellini, G. Lugaro, M. V. Farina, and G. Gerali, *Ital. J. Biochem.*, **12**, 393, 413 (1963).

(6) R. Pick, J. Stamler, S. Rodbard, and L. N. Katz, *Circulation*, **4**, 468 (1951).