was concealed in elution fractions highly contaminated with diphenylurea.

Cycloheptene.—Cycloheptanol (67.13 g., 0.588 mole) and 14.7 ml. of 85% phosphoric acid were swirled together and heated under a 6-cm. column packed with wire gauze, above which was a cold finger condenser. Water and cycloheptene distilled together. When almost all the cycloheptene had distilled, the apparatus was cooled and 50 ml. of *o*-dichlorobenzene was added as a chaser solvent. The flask was reheated until dichlorobenzene began to distil. The wet solution was washed into a 500-ml. separatory funnel with dichlorobenzene and washed with an equal volume of a saturated salt solution. The upper layer was dried over sodium sulfate and distilled. Yield of cycloheptene, n^{26}D 1.4552, b.p. 112–117° (lit.[17] 115–116°), was 88%.

3-Bromocycloheptene.—The procedure of Braude and Evans[13] was used to prepare 3-bromocycloheptene. Yield of 3-bromocycloheptene, n^{27}D 1.5285, b.p. 64–71° (8 mm.) [lit.[13] 67° (8 mm.)], was 48.5%.

Cyclohept-2-enol.—Five grams (0.0286 mole) of 3-bromocycloheptene was gently refluxed with a solution of 4.1 g. of (0.033 mole) of sodium carbonate (monohydrate) in 100 ml. water. The heavy bromocycloheptene, which formed a pool at the bottom of the flask, gradually disappeared and in 30 min. was completely gone; whereupon the solution was cooled, 35 ml. of ether was added, and the aqueous layer was saturated with potassium carbonate. After the initial separation, the aqueous layer was extracted with five 20-ml. portions of ether. The combined ether solutions were dried over potassium carbonate, the solution was concentrated, and distilled under vacuum with dimethyl phthalate as a chaser solvent. Yield of cyclohept-2-enol, n^{26}D 1.4892, b.p. 83–84 (13 mm.), was 27%. The *p*-nitrobenzoate derivative had m.p. 53.1–53.3°.

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.4; H, 5.75; N, 5.35. Found: C, 64.31; H, 5.79; N, 5.37.

A phenylurethane derivative was made in the usual way. Results of a mixture melting point taken with the phenylurethane of the aqueous deamination product of 7-aminobicyclo[4.1.0]heptane hydrochloride (method B) are as follows: phenylurethane of cyclohept-2-enol, m.p. 102.5–103.5°; phenylurethane of product of nitrous deamination of 7-aminobicyclo[4.1.0]heptane, m.p. 105.5–105.7° (very pure); mixture of the two phenylurethanes, m.p. 103–105. The phenylurethane derivative was analyzed.

Anal. Calcd. for $C_{14}H_{17}O_2N$: C, 72.69; H, 7.36%. Found: C, 72.79; H, 7.31. Infrared spectra of cyclohept-2-enol and the alcohol (purified by elution chromatography) resulting from the nitrous deamination of 7-aminobicyclo[3.1.0]heptane hydrochloride (method B) were the same. Retention times of the same alcohols in a gas chromatography comparison were within 3 sec. and a mixture of the two showed no peak separation.

Oppenauer Oxidation of Cyclohept-2-enol.—In a 1-l. 4-neck flask equipped with a mechanical stirrer, a thermometer, a dropping funnel, and a condenser fitted with a calcium chloride tube was introduced 4.00 g. (0.0357 mole) of cyclohept-2-enol, 7.72 g. (0.0714 mole) of *p*-benzoquinone, 500 ml. of dry benzene, and 7.28 g. (0.0357 mole) of aluminum isopropoxide.[18] The dark violet mixture was stirred for 1 hr. at room temperature, then for 3 hr. at 70°, then overnight at room temperature. All but 150 ml. of the benzene solution was then distilled away, water was added, and the mixture was steam distilled. The distillate was saturated with sodium chloride and the upper layer was separated. The salt solution was extracted with 50 ml. of ether which was combined with the initial nonaqueous layer. The extracts were dried overnight over sodium sulfate. Benzene and ether were removed under vacuum and the residue was vacuum distilled, b.p. 73–74° (11 mm.), n^{26}D 1.4925 (34% yield). A 2,4-DNP was made and purified by elution from alumina, m.p. 143–144°. The DNP of cycloheptanone is dark yellow, of cyclohept-2-enone, prepared as for the preceding, is orange. Braude and Evans[13] reported the DNP of cyclohept-2-enone as red plates, m.p. 122°. A second preparation of the DNP derivative employing Brady's reagent at room temperature yielded an orange compound melting at 164° (λ_{max} 352 mμ, log ϵ 4.96; shoulder at 422 mμ, log ϵ 3.65, ethylacetate) which analyzed correctly for the *double adduct*.

Anal. Calcd. for $C_{19}H_{18}N_8O_8$: C, 46.91; H, 3.73; N, 23.00; mol. wt., 450.9. Found: C, 46.87; H, 4.30; N, 22.56; mol. wt. (Rast), 421.

This same DNP was formed directly from cyclohept-2-enol by heating with Brady's reagent.

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[17] H. Pines, *J. Am. Chem. Soc.*, **67**, 2193 (1945).

[18] A. L. Wilds, "Organic Reactions," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 178.

Iodolactonization of 3-(3-Cyclohexenyl)propionic Acid[1a]

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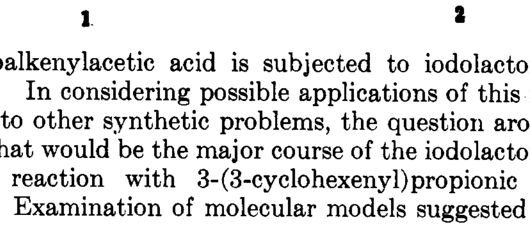
The reaction of the sodium salt of 3-(3-cyclohexenyl)propionic acid (**3**) with iodine in aqueous solution afforded the iodo-*cis*-δ-lactone **5**.

Previous studies[2] of the iodolactonization reaction have indicated that, when possible, a γ-lactone is formed in preference to a δ-lactone unless γ-lactone formation would be accompanied by the introduction of considerable strain.[2e] Furthermore, as illustrated by the conversion **1** → **2**, the formation of a *cis*-fused γ-lactone is the expected result when an appropriate cycloalkenylacetic acid is subjected to iodolactonization. In considering possible applications of this reaction to other synthetic problems, the question arose as to what would be the major course of the iodolactonization reaction with 3-(3-cyclohexenyl)propionic acid (**3**). Examination of molecular models suggested that three possible reaction paths (to form **4**, **5**, and **6**) might be possible (Chart I) with this system, whereas for the lower homologous acid **1** only the reaction path leading



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[1] (a) This research has been supported by National Institutes of Health Grant No. RG-8761; (b) National Institutes of Health Predoctoral Fellow, 1960-1963.

[2] For examples, see (a) E. E. van Tamelen and M. Shamma, *J. Am. Chem. Soc.*, **76**, 2315 (1954); (b) J. Klein, *J. Org. Chem.*, **23**, 1209 (1958); (c) J. Klein, *J. Am. Chem. Soc.*, **81**, 3611 (1959); (d) S. Beckmann, H. Geiger, and M. Schaber-Kiechle, *Ber.*, **92**, 2419 (1959); (e) J. Meinwald, S. S. Labana, and M. S. Chadha, *J. Am. Chem. Soc.*, **85**, 582 (1963); (f) A. W. Burgstahler and I. C. Nordin, *ibid.* **83**, 200 (1961); (g) H. O. House, R. G. Carlson, H. Muller, A. W. Noltes, and C. D. Slater, *ibid.*, **84**, 2614 (1962).

CHART I

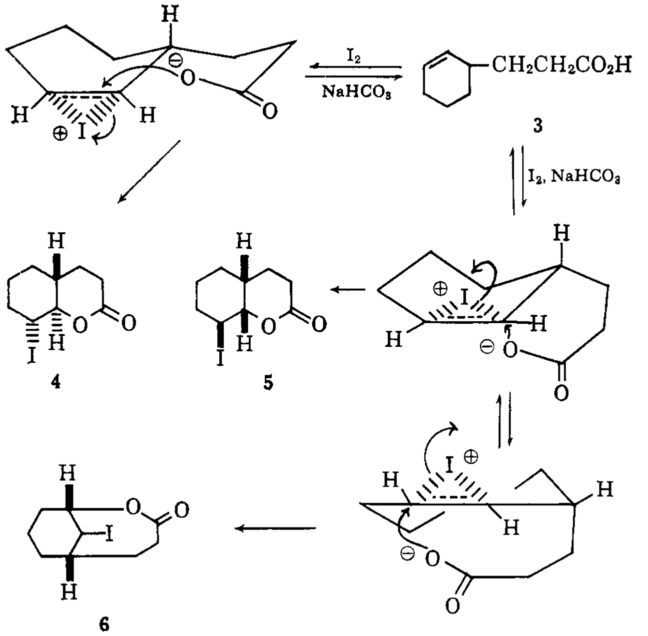
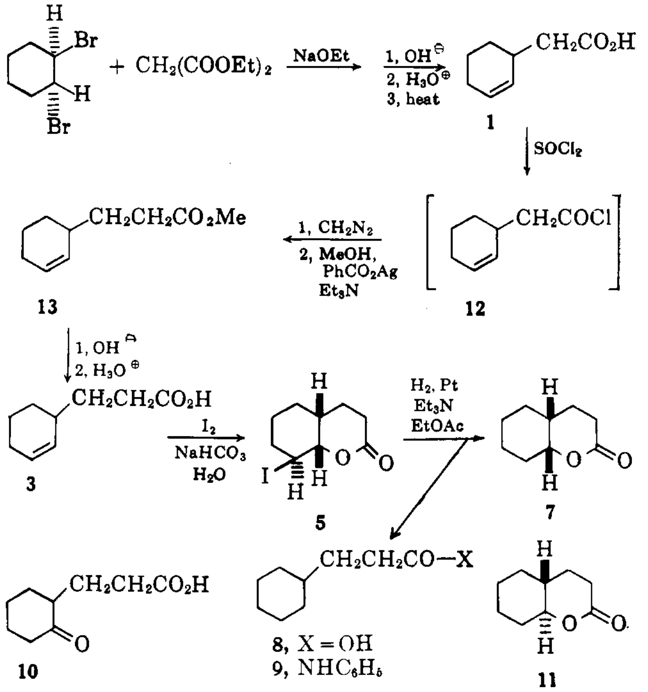


CHART II



to the *cis*-γ-lactone **2** (analogous to **5**) appeared sterically favorable.

In order to answer this question, the propionic acid **3** was synthesized as illustrated in Chart II and subjected to reaction with iodine in aqueous sodium bicarbonate. The single iodolactone **5** obtained from this reaction was shown to have the indicated structure and stereochemistry[3] by hydrogenolysis to form the *cis*-δ-lactone **7** as well as the acid **8**.[4] A mixture of the same lactone **7** as well as the *trans*-δ-lactone **11** previously had been obtained[5] by reduction of the keto acid **10** with sodium borohydride. The n.m.r. spectra of both the *cis*-lactone **7** and the iodolactone **5** exhibit narrow (half-band width, 5–7 c.p.s.) peaks (5.57 τ for **7**, 5.37 τ for **5**) attributable to an equatorial proton on a carbon bonded to oxygen (superimposed on the peak for the equatorial proton on carbon bonded to iodine in the case of the iodolactone **5**), whereas the corresponding peak in the spectrum of the *trans*-lactone **11** is at higher field (6.18 τ) and is broad (half-band width, 18 c.p.s.) indicative of an axial proton[6] as is required for the *trans*-fused lactone **11**. Consequently, the preference for forming *cis*-fused lactones in the iodolactonization reactions leading to γ-lactones also is found in reactions leading to δ-lactones even though other modes of reaction do not appear to be prohibited on steric grounds.

Experimental[7]

3-Cyclohexenylacetic Acid (1).—A solution of *trans*-1,2-dibromocyclohexane, obtained by reaction of 82.15 g. (1.0 mole) of cyclohexene with 160 g. (1.0 mole) of bromine in 350 ml. of cyclohexane, was added, dropwise and with stirring over a 4-hr. period, to an ethanolic solution of diethyl sodiomalonate and excess sodium ethoxide prepared from 160.17 g. (1.0 mole) of diethyl malonate and 70 g. (3.04 g.-atoms) of sodium.[8] After the resulting mixture had been refluxed overnight with stirring, the mixture was concentrated under reduced pressure and then partitioned between diethyl ether and dilute, aqueous hydrochloric acid. After the ethereal solution had been dried and concentrated, distillation of the residue separated 70 g. (30%) of crude diethyl 3-cyclohexenylmalonate, b.p. 110–125.5° (0.9 mm.), which was allowed to react overnight with a solution of 0.65 mole of potassium hydroxide in refluxing aqueous methanol (1:4 by volume). The crude acidic fraction, separated in the usual way, was distilled with accompanying decarboxylation to give 30 g. (21%) of the unsaturated acid 1 as a colorless liquid, b.p. 101.5–104° (1 mm.), $n^{24}\text{D}$ 1.4800 [lit.[9] b.p. 135–136° (15 mm.), $n^{25}\text{D}$ 1.4783]. The product, which showed a single spot on thin layer chromatography[10] and a single peak on gas chromatography, has infrared absorption[12] centered at 2900 cm.$^{-1}$ (broad, OH) as well as a peak at 1705 cm.$^{-1}$ (carboxyl C=O). The n.m.r. spectrum[12] has a series of partially resolved peaks in the region 4.2–4.6 τ (2H, vinyl C–H) with complex absorption in the region 7.2–8.8 τ.

3-(3-Cyclohexenyl)propionic Acid (3).—A mixture of 26.0 g. (0.185 mole) of the acid 1 and 37 g. (0.37 mole) of thionyl chloride was refluxed for 3 hr. and then distilled to separate 25.22 g. (86.8%) of the crude acid chloride 12, b.p. 58–60° (1 mm.), $n^{25}\text{D}$ 1.4860–1.4865. A solution of 25.0 g. (0.154 mole) of the acid chloride 12 in 100 ml. of ether was added to an ethereal solution containing 0.5 mole of diazomethane (from N,N′-dimethyl-N,N′-dinitrosoterephthalamide). After nitrogen evolution ceased, the

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(3) Although the hydrogenolysis experiment recorded here obviously does not define the stereochemistry of the iodine atom, there is ample reason to expect the iodine atom and carboxyl function to add in a *trans*, coplanar manner [D. H. R. Barton and R. C. Cookson, *Quart. Rev.* (London), **10**, 44 (1958)]. In addition, the further transformations of several similarly formed halolactones [*e.g.* ref. 2g and G. Berti, *Tetrahedron*, **4**, 393 (1958)] clearly require a *trans* arrangement of the halogen and carboxyl functions.

(4) This acid presumably arises from reaction of the iodolactone with the amine to reform the unsaturated acid **3** (*cf.* ref. 2b and 2c) followed by hydrogenation of the carbon–carbon double bond.

(5) H. O. House, H. Babad, R. B. Toothill, and A. W. Noltes, *J. Org. Chem.*, **27**, 4141 (1962).

(6) (a) J. I. Musher, *J. Am. Chem. Soc.*, **83**, 1146 (1961); (b) N. O. Bruce, *ibid.* **84**, 3022 (1962).

(7) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated magnesium sulfate was employed as a drying agent. The infrared spectra were determined with either a Baird Model B, or a Perkin-Elmer Model 21, infrared recording spectrophotometer fitted with a sodium chloride prism. The ultraviolet spectra were determined with a Cary recording spectrophotometer, Model 14. The n.m.r. spectra were determined at 60 Mc. with a Varian, Model A-60, n.m.r. spectrometer. The mass spectra were obtained with a CEC, Model 21-130, mass spectrometer. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory.

(8) The procedure of M. Mousseron and F. Winternitz, *Bull. soc. chim. France*, 604 (1946).

(9) A. T. Blomquist, J. Verdol, C. L. Adami, J. Wolinsky, and D. D. Phillips, *J. Am. Chem. Soc.*, **79**, 4978 (1957).

(10) A silica gel coating was employed.

(11) A column packed with Dow Corning silicone fluid, No. 710, on ground firebrick was employed.

(12) Determined in carbon tetrachloride solution.

etheral solution was concentrated and a solution of the residual crude diazo ketone in 200 ml. of methanol was treated with 1 g. of silver benzoate in 9 ml. of triethylamine.[13] After the resulting mixture had been decolorized with Norit and concentrated, distillation separated 19.3 g. (63%) of the crude ester **13**, b.p. 72–74°, $n^{25}\mathrm{D}$ 1.4640, which was contaminated[11] with about 10% of two lower boiling impurities. A pure sample of ester **13**, $n^{25}\mathrm{D}$ 1.4645 obtained by collection[11] and subsequent short-path distillation (120° at 0.5 mm.), has infrared absorption[12] at 1737 cm.$^{-1}$ (ester C=O) with a series of partially resolved n.m.r. peaks[12] in the region 4.1–4.7 τ (2H, vinyl C–H) as well as a singlet at 6.40 τ (3H, CH_3O) and complex absorption in the region 7.5–8.8 τ.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59; mol. wt., 168. Found: C, 71.09; H, 9.63; mol. wt., 168 (mass spectrum).

A solution of 19.0 g. (0.113 mole) of the crude ester **13** and 10 g. (0.15 mole) of 85% potassium hydroxide in 100 ml. of methanol and 35 ml. of water was stirred overnight at room temperature. The crude acidic product, separated in the usual way, was distilled to give 13.3 g. (76%) of the acid **3** as a colorless liquid, b.p. 108–112° (0.3 mm.), $n^{25}\mathrm{D}$ 1.4803, which showed a single peak on gas chromatography[11] and a single spot on thin layer chromatography.[10] The sample has infrared absorption[12] centered at 2900 cm.$^{-1}$ (broad, associated O–H) and at 1710 cm.$^{-1}$ (carboxyl C=O) with a series of partially resolved n.m.r. peaks[12] in the region 4.1–4.7 τ (2H, vinyl C–H) as well as complex absorption in the region 7.4–8.9 τ.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15; mol. wt., 154. Found: C, 69.97; H, 9.06; mol. wt., 154 (mass spectrum).

Preparation of the Iodolactone 5.—To the solution obtained from 3.00 g. (0.0194 mole) of the unsaturated acid **3** in 120 ml. of 0.5 *M* aqueous sodium bicarbonate was added a solution of 10.16 g. (0.040 mole) of iodine and 20.0 g. (0.120 mole) of potassium iodide in 60 ml. of water. The resulting mixture was allowed to stand in the dark for 48 hr. with occasional swirling and then was extracted with methylene chloride. After the organic extract had been washed with aqueous sodium thiosulfate, dried, and concentrated, the residual crude lactone **5**, 5.172 g. (95%) of a pale yellow oil which exhibited a single spot on thin layer chromatography[10] was crystallized from an ethanol–hexane mixture to separate 1.757 g. of the lactone **5** as pale yellow prisms, m.p. 47.5–51°, which gave white prisms, m.p. 53–54.5°, after recrystallization. The product, which was very difficult to recrystallize and decomposed on standing, exhibited a single spot on thin layer chromatography[10] with infrared absorption[14a] at 1730 (strong) and 1780 (weak) cm.$^{-1}$ (δ-lactone C=O), and a partially resolved n.m.r.[14b] multiplet (half-band width, 5 c.p.s.) centered at 5.37 τ (2H, CH–O, and CH–I), and complex absorption in the region 7.2–8.7 τ.

Anal. Calcd. for $C_9H_{13}IO_2$: C, 38.59; H, 4.68; I, 45.31. Found: C, 38.44; H, 4.67; I, 45.35.

Hydrogenolysis of the Iodolactone 5.—A solution of 676 mg. (2.41 mmoles) of the iodolactone **5** and 246 mg. (2.41 mmoles) of triethylamine[15] in 9 ml. of ethyl acetate was hydrogenated at 25° and atmospheric pressure over the catalyst, 70 mg. of platinum oxide. After 1 hr. when the hydrogen uptake (101 ml. or 1.88 equiv.) ceased, the solution was filtered and concentrated, and the residue was partitioned between ether and water. The ethereal solution was washed successively with aqueous sodium bisulfite, aqueous sodium bicarbonate, and aqueous sodium chloride, and then dried and concentrated. Distillation of the yellow liquid residue (140 mg.) in a short-path still (100° at 0.1 mm.) separated 80 mg. (21%) of a colorless liquid which contained[16] the *cis*-lactone **7** (*ca.* 91%) as well as an unidentified, lower boiling impurity (*ca.* 9%). The *cis*-lactone **7**, which has the same retention time[16] as the minor lactone component from reduction of the keto acid **10**,[5] was collected. This material has infrared absorption[12] at 1735 cm.$^{-1}$ (δ-lactone C=O), a molecular ion peak at *m/e* 154, and an n.m.r. peak[12] (half-band width, *ca.* 8 c.p.s.) at 5.57 τ (1H, equatorial proton of CH–O) as well as complex absorption in the region 7.4–8.9 τ. A sample of the *cis*-lactone **7**, obtained from the previously described[5] mixture by repeated collection,[16] was shown to be identical with the sample from hydrogenolysis by comparison of gas chromatographic retention times, infrared spectra, and mass spectra. A sample of the pure *trans*-lactone **11** also was separated from the previously described mixture[5] by repeated collection.[16] This material has a molecular ion peak at *m/e* 154 with infrared absorption[12] at 1735 cm.$^{-1}$ (δ-lactone C=O). The infrared spectra of the stereoisomeric lactones differ in the presence of a peak at 1045 cm.$^{-1}$ only in the spectrum of the *trans* isomer **11** and a doublet at 993 and 1004 cm.$^{-1}$ only in the spectrum of the *cis* isomer **7**.

The aqueous bicarbonate extract from the hydrogenolysis reaction was acidified and extracted with ether. After the ethereal extract had been dried and concentrated, distillation of the residue (211 mg.) in a short-path still (140–145° at 11 mm.) separated 166 mg. (44%) of a colorless liquid which contained[17] the acid **8** (*ca.* 87%) as well as a lower boiling impurity (*ca.* 13%). A 90-mg. sample of this crude acid **8** was converted to the acid chloride with thionyl chloride and then to the anilide **9** which crystallized from aqueous ethanol as 85 mg. (63%) of white platelets, m.p. 96.5–98.5° (lit.[18] 97.5–98°). An authentic sample of the acid **8**, prepared by hydrogenation of hydrocinnamic acid over platinum in acetic acid at 60° and atmospheric pressure, was obtained as a colorless liquid, b.p. 132–134° (6 mm.), $n^{27}\mathrm{D}$ 1.4620 [lit.[19] b.p. 125–126° (4 mm.), $n^{38}\mathrm{D}$ 1.4553], which showed one peak on gas chromatography.[17] The anilide **9**, m.p. 97–99°, obtained from this authentic sample was shown to be identical with the previously described sample by a mixture melting point determination and comparison of infrared spectra (1683 cm.$^{-1}$ for amide C=O and 1520 cm.$^{-1}$ for N–H bending).

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(13) The procedure of M. S. Newman and P. F. Beal, *J. Am. Chem. Soc.*, **72**, 5163 (1950).

(14) (a) Determined in chloroform solution; (b) determined in deuteriochloroform solution.

(15) The hydrogenolysis procedure of H. W. Whitlock, Jr., *J. Am. Chem. Soc.*, **84**, 3412 (1962).

(16) A gas chromatography column packed with silicone gum XE-60 suspended on Chromosorb W was employed. This column effected partial resolution of the *cis*-lactone **7** (first eluted) and the *trans*-lactone **11** (second eluted) which we had been unable to resolve previously (ref. 5).

(17) A gas chromatography column packed with Dow Corning silicone fluid, No. 550, suspended on ground firebrick was employed.

(18) M. Metayer, *Ann. chim.* (Paris), [12] **4**, 196 (1949).

(19) G. S. Heiss and R. Adams, *J. Am. Chem. Soc.*, **48**, 2385 (1926).