to give 18 g. (61%) of light yellow solid. Recrystallization from water yielded XIa as light yellow needles, m.p. 242–245°. $\lambda_{max}^{pH\ 1}$ 282 mμ (ε 18,200); $\lambda_{max}^{pH\ 11}$ 269 mμ (ε 17,500).

Anal. Calcd. for $C_7H_{11}N_3S$: C, 49.7; H, 6.5; N, 24.8. Found: C, 49.6; H, 6.4; N, 24.8.

Similarly prepared were 5-methyl-4-methylamino-2-pyrimidinethiol, m.p. 237–241°, and 4-dimethylamino-6-methyl-2-pyrimidinethiol, m.p. 292–296°.

2-(o-Chlorobenzylthio)-4-dimethylamino-5-methylpyrimidine (VIII. X = *o*-Cl; R_1, R_2, R_3 = CH_3). A mixture of 16.9 g. (0.1 mole) of XIa, 16.1 g. (0.1 mole) of *o*-chlorobenzylchloride, 75 ml. of *p*-dioxane, and 250 ml. of 0.5*N* sodium hydrochloride was heated at 70° for 3 hr. with stirring. After cooling, the aqueous layer was decanted and the oily residue was triturated several times with ice water, the water being decanted each time. Finally 250 ml. of boiling water was added to the only residue, and just enough 6*N* hydrochloric acid was added to form a clear solution. The solution was decolorized with charcoal, filtered, and the filtrate was chilled to give 15 g. (46%) of white solid. Recrystallization from a mixture of ethanol and *n*-heptane gave the product as white needles, m.p. 226–228°.

Anal. Calcd. for $C_{14}H_{16}N_3SCl \cdot HCl$: N, 12.7. Found: N, 12.7.

The ultraviolet, infrared and paper chromatographic determinations of VIII (X = *o*-Cl; R_1, R_2 R_3 = CH_3) by both methods have been found to be identical.

Acknowledgment. The authors wish to express their appreciation to Mr. Wayne H. Nyberg, Miss Phyllis G. Shaul, and Mrs. Carol R. Tuttle for their assistance in performing analytical, instrumental, and paper chromatographic measurements.

KANSAS CITY 10, MO.

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, RESEARCH DIVISION, ABBOTT LABORATORIES]

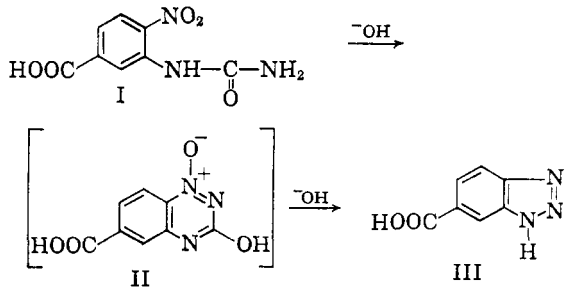
Adjacent Nitro and Guanidino Groups. II. The Base-Catalyzed Rearrangement of Benzotriazine *N*-Oxides to Benzotriazoles[1]

JOHN A. CARBON

Received July 18, 1961

The treatment of 3-amino-1,2,4-benzotriazine 1(or 2)-oxide (IV or IX) with hot alkali results in a molecular rearrangement to form benzotriazole-1-carboxamide (V) plus the hydrolysis product, benzotriazole (VI). The structure of the carboxamide (V) was proven by independent synthesis. Similarly, 3-hydroxy-1,2,4-benzotriazine 1-oxide (VII) rearranges in hot alkali to form benzotriazole (VI). In contrast, a benzotriazine lacking the *N*-oxide function, 3-amino-1,2,4-benzotriazine (VIII), fails to undergo the rearrangement. The mechanism of this interesting reaction is considered to involve an intermediate diazonium hydroxide (IVd), formed by a proton shift within an azoxy intermediate (IVc).

Although the base-catalyzed cyclization of *o*-nitrophenylguanidine (XI) to form 3-amino-1,2,4-benzotriazine 1-oxide (IV) was first reported by Arndt[2] in 1913, an apparently quite closely related transformation, discovered by Griess[3] in 1882, has escaped virtually without notice. Upon treatment of 4-nitro-3-ureidobenzoic acid (I) with hot potassium hydroxide solution, Griess[3] observed the formation of benzotriazole-5-carboxylic acid (III), an interesting reaction which to date has remained unexplained. Considering the work of Arndt[2] on the cyclization of adjacent nitro and ureido groups, the Griess reaction most likely proceeds through the intermediate, 3-hydroxy-1,2,4-benzotriazine 1-oxide-6-carboxylic acid (II), although this has never been demonstrated.



These facts were brought to our attention quite by accident when it was observed[4] that the poor yields encountered in the base-catalyzed cyclization of various compounds containing adjacent nitro and guanidino groups to form fused-ring triazine 1-oxides were due to the formation of acidic by-products, subsequently identified as fused-ring triazoles.

The treatment of 3-amino-1,2,4-benzotriazine 1-oxide (IV) with refluxing 10% sodium hydroxide solution resulted in the formation of two base-soluble compounds, identified as benzotriazole-1-carboxamide (V) and benzotriazole (VI). The structure of benzotriazole-1-carboxamide (V), a compound not described in the literature, was proven by (a) elemental analyses, (b) infrared spectrum, (c) thermal conversion to benzotriazole (VI), and (d) by an unambiguous synthesis from benzotriazole and cyanic acid. This amide (V) possesses a strong carbonyl absorption in the infrared at 5.7 μ and a moderate absorption at 6.2 μ (amide II). Heating of V at 160° results in a quan-

(1) For the preceding paper in this series, see J. A. Carbon, *J. Org. Chem.*, **26**, 455 (1961).

(2) (a) F. Arndt, *Ber.*, **46**, 3522 (1913); (b) F. Arndt and B. Rosenau, *Ber.*, **50**, 1248 (1917).

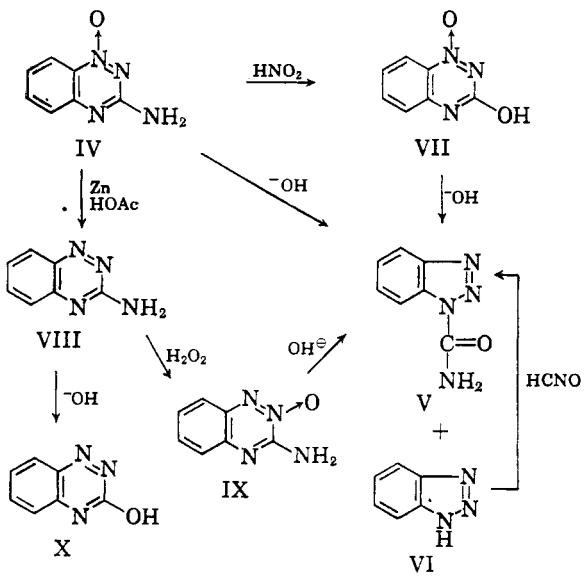
(3) P. Griess, *Ber.*, **15**, 1878 (1882).

(4) J. A. Carbon, unpublished work.

titative conversion to benzotriazole (VI) and cyanuric acid.

The closely related compound, 3-hydroxy-1,2,4-benzotriazine 1-oxide (VII), proved to be appreciably more stable in hot alkali. However, prolonged refluxing of solutions of VII in 10% sodium hydroxide resulted in the formation of benzotriazole (VI) in 45% yield. None of the intermediate benzotriazole-1-carboxylic acid could be isolated from this reaction mixture, probably due to the ready decarboxylation of this acid.

In view of the above results, it was considered desirable to investigate the behavior of the reduced compound, 3-amino-1,2,4-benzotriazine (VIII),[2] and the isomeric *N*-oxide, 3-amino-1,2,4-benzotriazine 2-oxide (IX),[2] toward hot aqueous alkali. These compounds were previously prepared by Arndt[2] by reduction of IV with tin and hydrochloric acid to produce the intermediate 1,2-dihydro compound, followed by oxidation with potassium ferricyanide to form VIII. Oxidation of VIII with hydrogen peroxide in acetic acid gave an *N*-oxide isomeric with IV, which Arndt has formulated as the 2-oxide (IX).[2b]



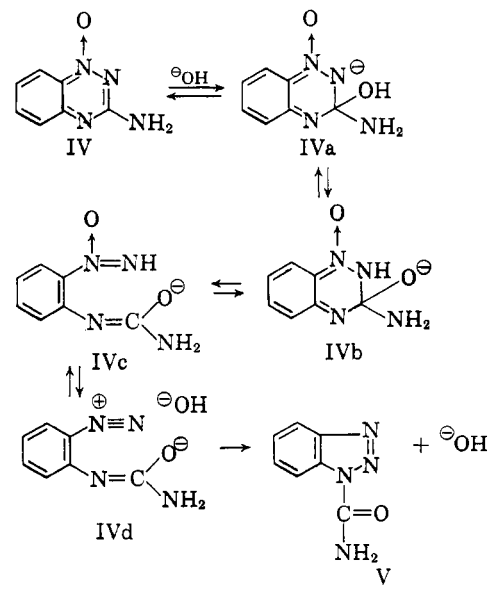
As the reduction of benzotriazine 1-oxides with zinc and aqueous ammonium chloride has been reported[5,6] to proceed directly to the desired benzotriazines without the formation of any 1,2-dihydro derivatives, we first attempted the removal of the 1-oxide function under these conditions. However, compound IV was recovered unchanged after stirring with zinc and aqueous ammonium chloride for twenty-two hours, probably due to its extreme insolubility.

An alternate procedure, treatment of IV with zinc in hot acetic acid containing a little water, gave excellent results, however. The formation of the isomeric 2-oxide (IX) proceeded as described by Arndt[2b] in 38% yield.

As might be predicted from theoretical considerations (see below), the 1-desoxy compound (VIII) did not rearrange to benzotriazole in aqueous alkali. After subjection of VIII to boiling 10% sodium hydroxide for thirty hours, the only isolable product was a 54% yield of 3-hydroxy-1,2,4-benzotriazine (X) (1,2,4-benzotriazin-3-one), produced by hydrolysis of the 3-amino group.

In contrast, 3-amino-1,2,4-benzotriazine 2-oxide (IX) proved to be remarkably sensitive to aqueous alkali, being completely destroyed by 1*N* sodium hydroxide at 100° in ten minutes (probably less).[7] Neutralization of the alkaline reaction mixture gave the identical products formed from the 1-oxide, namely, benzotriazole (VI) and its 1-carboxamide (V).

Any considerations of the reaction mechanism of this interesting ring contraction must take into account the necessity of having one of the two adjacent nitrogen atoms in the triazine ring present as an *N*-oxide. Also, the transformation of 3-amino-1,2,4-benzotriazine 1(or 2)-oxide (IV or IX) to benzotriazole-1-carboxamide (V) is, in the classical sense, a true molecular rearrangement, since the empirical formulas of the starting material and product are identical. The presence of free benzotriazole in these reaction mixtures is undoubtedly due only to hydrolysis of the 1-carboxamide (V), which is the true product of the rearrangement.



(5) F. J. Wolf and K. Pfister III, U. S. Patent 2,489,356 (1949).

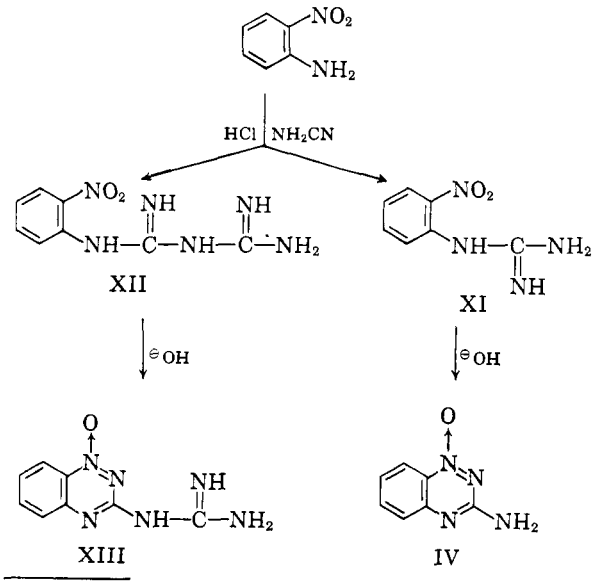
(6) J. Jiu and G. P. Mueller, *J. Org. Chem.*, 24, 813 (1959).

(7) The extreme alkali lability of compound IX was noted by Arndt[2b]; however, the products of the decomposition were not identified. The claim by the authors (ref. 2b, p. 1252) that nitrogen is liberated upon treatment of IX with hot alkali could not be confirmed. It is noteworthy that the unknown silver salt (48.0% silver by analysis), obtained by Arndt from this alkaline decomposition, could very well have been a silver salt of benzotriazole (Calcd. for $C_6H_4N_3Ag$: Ag, 47.8%).

The rearrangement can be looked upon as an attack by the hydroxyl ion at the 3-position of the triazine ring to form an intermediate such as IVa, which should easily give IVb through proton migration. The key steps in the proposed mechanism are the formation of the azoxy intermediate (IVc) and its rearrangement to the diazonium hydroxide (IVd). The presence of a transitory diazonium intermediate in the rearrangement is considered likely since (a) a temporary deep red color appears during the early stages of the rearrangement[8] and (b) diazonium intermediates are known to be involved in the formation of benzotriazoles by the nitrous acid treatment of *o*-diamines.[9] Thus the final step, IVd → V, would be predicted on the basis of known methods for the synthesis of benzotriazoles.

It is readily apparent from a consideration of the proposed reaction pathway why compound VIII, lacking the *N*-oxide function, fails to undergo the rearrangement. Since the intermediate diazonium hydroxide (IVd) cannot form from compound VIII, this may be taken as further proof that the reaction involves a diazonium intermediate.

As an interesting sidelight to this investigation, we have discovered that the standard synthesis[2,6,10] of 3-amino-1,2,4-benzotriazine 1-oxide (IV), by condensation of *o*-nitroaniline with cyanamide to produce *o*-nitrophenylguanidine (XI), followed by ring-closure in hot alkali, actually produces two products. The second product (XIII) was apparently overlooked by previous workers in the field[2,6,10] because of a remarkable coincidence of melting points (see Experimental). This minor product has been identified as 3-guanidino-1,2,4-benzotriazine 1-oxide (XIII), apparently arising by base-catalyzed ring closure of *o*-nitrophenylbiguanide (XII). The latter material is formed either from the reaction of *o*-nitrophenylguanidine (XI) with excess cyanamide or from the reaction of *o*-nitroaniline with dicyandiamide.



The investigation of further aspects of the chemistry of adjacent nitro and guanidino groups is continuing and will be reported at a later date.

EXPERIMENTAL[11]

3-Guanidino-1,2,4-benzotriazine 1-oxide (XIII). The preparation of 3-amino-1,2,4-benzotriazine 1-oxide (IV) was carried out as previously described,[2a,6] except the crude product was recrystallized from Methyl Cellosolve instead of ethanol. The mother liquor from the recrystallization was diluted with an equal volume of water, allowed to stand for several hours, and the orange solid isolated by suction filtration. This material (m.p. 260–264° dec.) consisted of a mixture of IV (m.p. 279–280° dec.) plus XIII, which was readily separated by making use of the fact that XIII forms a water-insoluble hydrochloride salt. The mixture was suspended in an excess of hot 10% hydrochloric acid, filtered to remove the insoluble salt, and the free base regenerated by suspending in 5% sodium hydroxide solution, to obtain orange needles, m.p. 269–270° dec. (3.3%) (yield based on *o*-nitroaniline). An analytical sample was obtained as orange tiny needles of unchanged decomposition point from *N,N*-dimethylformamide–water.

Anal. Calcd. for $C_8H_9N_6O$: C, 47.05; H, 3.95; N, 41.16; O, 7.83. Found: C, 47.19; H, 3.81; N, 40.92; O, 7.51.

The *monohydrochloride* salt of XIII was obtained as pale yellow leaflets from water, m.p. > 300°.

Anal. Calcd. for $C_8H_9ClN_6O$: C, 39.92; H, 3.77; Cl, 14.73; N, 34.91; O, 6.67. Found: C, 39.98; H, 4.04; Cl, 14.89; N, 35.09; O, 6.74.

Rearrangement of 3-amino-1,2,4-benzotriazine-1-oxide (IV). Two grams (0.012 mole) of IV was mixed with 20 ml. of 10% sodium hydroxide solution and refluxed for 3.5 hr. A clear solution was obtained at the end of 3 hr. The solution was cooled to room temperature, neutralized to *p*H 4–5 with concd. hydrochloric acid, and the resulting yellow precipitate isolated by suction filtration. The dried solid (1.2 g.) was extracted with 25 ml. of hot benzene. Concentration of the extracts and chilling gave 0.55 g. (37%) of pale yellow leaflets, m.p. 92.5–93.5°, identified as *benzotriazole* (VI) by mixed melting point and infrared comparisons. The benzene-insoluble fraction was extracted into 15 ml. of hot ethanol, filtered to remove some insoluble silicates, and the filtrate concentrated and chilled to yield 0.32 g. (16%) of colorless feathery needles, gradual dec. above 130°, subsequently identified as *benzotriazole-1-carboxamide* (V). The infrared spectrum of this substance (Nujol mull) was identical in all respects with that of an authentic sample of V (see below).

Benzotriazole-1-carboxamide (V). Benzotriazole (11.9 g.; 0.10 mole) was dissolved in 120 ml. of water containing 25 ml. of concd. hydrochloric acid. The solution was decolorized with Norit, and the clear and colorless filtrate treated portionwise with 12.1 g. (0.15 mole) of potassium cyanate with stirring. After stirring at room temperature for 1 hr., the colorless precipitate was isolated by suction filtration and washed with water. After air-drying the product weighed 7.4 g. (45.7%) and possessed no definite melting point

(8) Attempts to trap an intermediate diazonium hydroxide as a coupled product by carrying out the rearrangement in the presence of β-naphthol were unsuccessful. Apparently the intramolecular ring closure (IVd → V) occurs with greater rapidity than the intermolecular coupling reaction.

(9) F. R. Benzon and W. L. Savell, *Chem. Revs.*, **46**, 1 (1950).

(10) F. J. Wolf and K. Pfister III, *J. Am. Chem. Soc.*, **76**, 3551, 4611 (1954).

(11) The melting points are uncorrected and were taken on a Fisher-Johns melting point apparatus.

(gradual decomposition above 130°). A sample was obtained as colorless feathery needles from ethanol, and dried at 55° *in vacuo* for analysis.

Anal. Calcd. for $C_7H_6N_4O$: C, 51.84; H, 3.73; N, 34.55. Found: C, 52.00; H, 3.89; N, 34.76.

The infrared spectrum (Nujol mull) of this material was identical in all respects with the substance obtained by the rearrangement of IV. The carbonyl absorption appeared at 5.7 μ in the infrared.

Thermal decomposition of V produced benzotriazole (VI) and cyanuric acid. For example, a 0.5-g. sample of V was placed in a test tube and heated at 160–170° in an oil bath for 0.5 hr. The reaction mass was cooled to room temperature, broken up into a powder, and extracted with 15 ml. of hot benzene. The filtrate gave 0.35 g. (95%) of colorless needles when concentrated and chilled, m.p. 94–96°. A mixed melting point with authentic benzotriazole was undepressed. The benzene-insoluble portion (m.p. > 300°, 80 mg.) was identified as cyanuric acid by comparison of infrared spectra.

Rearrangement of 3-hydroxy-1,2,4-benzotriazine-1-oxide (VII). 3-Hydroxy-1,2,4-benzotriazine 1-oxide (VII)[2a,6] (2.5 g., 0.015 mole) was dissolved in 25 ml. of 10% sodium hydroxide solution, and refluxed a total of 14 hr. Aliquots withdrawn at the end of 3.5 hr. and 7.5 hr. still gave VII when acidified. The reaction mixture was cooled and adjusted to *p*H 4–5 with hydrochloric acid. A work-up identical to that used for the rearrangement of IV (see above) gave 0.81 g. (45%) of benzotriazole (VI), m.p. 95.5–96.5° (mixed melting point undepressed).

3-Amino-1,2,4-benzotriazine (VIII). Attempts to prepare this compound by reduction of IV with zinc dust and aqueous ammonium chloride[5,6] resulted only in a 96% recovery of starting material. The following procedure gave satisfactory results, however.

3-Amino-1,2,4-benzotriazine 1-oxide (IV) (3.5 g., 0.022 mole) was mixed with 50 ml. of glacial acetic acid, 5 ml. of water, and 2.6 g. (0.04 mole) of zinc dust, and heated on a steam bath with vigorous stirring until an aliquot gave no precipitate when diluted with an equal volume of water (6.75 hr. required). The solution was filtered to remove unchanged zinc, evaporated to dryness *in vacuo*, and the residue slurried in 40 ml. of water. Filtration gave 2.1 g. of a yellow solid, m.p. 211.0–211.5°. The filtrate was rendered quite strongly basic with concd. ammonium hydroxide, and after standing at room temperature for several hours, filtered to obtain an additional 0.67 g. of product (m.p. 209–210°). The total yield was 2.77 g. (87.4%). Recrystallization from ethanol did not raise the melting point (Arndt[2a] gives m.p. 207° for this compound). The infrared spectrum was identical to that of an authentic sample[2a] of VIII.

Base-catalyzed hydrolysis of 3-amino-1,2,4-benzotriazine (VIII). One gram (0.0069 mole) of VIII was suspended in 10 ml. of 10% sodium hydroxide solution and refluxed for 30 hr. The starting material slowly dissolved during this period to form a deep yellow solution. The reaction mixture was cooled to room temperature, filtered to remove a small quantity of insoluble material (infusible), and finally acidified with glacial acetic acid. The resulting yellow precipitate was filtered with suction and washed with water. This solid was extracted with 25 ml. of boiling water, filtered hot to remove silicates, and chilled to 5° to obtain 0.54 g. (54%) of yellow-brown prisms, m.p. 201–206° dec. Recrystallization from water with Norit gave yellow scales, m.p. 207–210° dec., identical in all respects with an authentic sample of 3-hydroxy-1,2,4-benzotriazine (X),[2b] obtained by the treatment of 3-amino-1,2,4-benzotriazine (VIII) with nitrous acid as directed by Arndt.[2b]

Rearrangement of 3-amino-1,2,4-benzotriazine 2-oxide (IX). One gram (0.0062 mole) of 3-amino-1,2,4-benzotriazine 2-oxide (IX)[2b] was mixed with 15 ml. of 1*N* sodium hydroxide and heated to reflux. The starting material quickly dissolved in the hot alkali to form a dark brown solution (no gas evolution observed). After 10 min. of refluxing an aliquot gave no precipitate of IX when chilled. At the end of 15 min. the solution was cooled to room temperature and acidified to *p*H 1 with hydrochloric acid to obtain 0.51 g. (51%) of tan colored needles of *benzotriazole-1-carboxamide* (V), gradual dec. above 130°, identical in all respects with an authentic sample (see above).

The filtrate from V was adjusted to *p*H 5 with ammonium hydroxide and acetic acid. The oil was extracted into methylene chloride (three portions), the extracts dried over magnesium sulfate, filtered, and evaporated to leave 0.28 g. (38%) of a brownish solid, with an infrared spectrum identical to that of an authentic sample of *benzotriazole* (VI). Recrystallization from benzene gave yellowish leaflets, m.p. 95–96°, undepressed by admixture with authentic benzotriazole (VI).

Acknowledgment. The author is indebted to Mr. E. F. Shelberg and his staff for the microanalyses and to Mr. W. Washburn and his staff for the infrared spectra.

NORTH CHICAGO, ILL.

[CONTRIBUTION FROM THE EATON LABORATORIES, DIVISION OF THE NORWICH PHARMACAL CO.]

Chemotherapeutic Nitrofurans. VII.[1] The Formation of 5-Nitrofurfurylidene Derivatives of Some Aminoguanidines, Aminotriazoles, and Related Compounds

FRANK F. EBETINO AND GABRIEL GEVER

Received July 17, 1961

A number of aminoguanidines have been prepared by the reaction of substituted hydrazines with cyanamide or *S*-methylisothiourea. These compounds in addition to some *N*-aminotriazoles and other related *N*-amino compounds have been converted to 5-nitrofurfurylidene derivatives. The reactions of 5-nitro-2-furaldehyde thiosemicarbazone with chloroacetic acid and β-propiolactone are described.

As 1-(5-nitrofurfurylideneamino)guanidine sulfate[2] (I) and 3-(5-nitrofurfurylideneamino)-2-iminooxazolidine[3] (II) have been found to exhibit chemotherapeutic activity, we have undertaken the synthesis of related nitrofuran compounds containing the $-CH{=}N-\overset{|}{N}-\overset{|}{C}{=}N-$ group.

(1) For the previous paper in this series, see J. G. Michels, *J. Org. Chem.*, **25**, 2246 (1960).