Table I. Electron-Impact Fragmentation of the Thymine Moiety of Thymidine at 70 E.v. Ion Compositions Were Ascertained by High-Resolution Mass Measurement[a]

Parent ion			Daughter ion			Neutral fragment lost	Observed metastable peak (*m/e*)
Composition	*m/e*	Intensity	Composition	*m/e*	Intensity		
$C_5H_6N_2O_2$	126	32	C_4H_5NO	83	8	HNCO	54.7
C_4H_5NO	83	8	C_4H_4NO	82	5	H	81.0
C_4H_5NO	83	8	C_3H_5N	55	31	CO	36.5
C_3H_5N	55	31	C_3H_4N	54	15	H	53.1

[a] Compare Figures 5 and 9. Intensity is the height of a given peak relative to that of the most intense peak in the spectrum (100).

first. This indicates that the primary ionization process is different. Ionization of organic molecules by removal of a loosely bound, lone-pair electron from a nitrogen or oxygen atom is a highly probable result of electron bombardment,[18] and in amino- and dioxypyrimidines the primary ionization process is best interpreted as removal of a nonbonding electron from the extranuclear heteroatom, rather than the nitrogen atoms or the conjugated π-electron system of the ring. In this case the oxygen atom of the hydroxymethyl group, which is not conjugated with the ring, seems to ionize preferentially.

A similar situation occurs in the electron impact ionization of nucleosides. Biemann and McCloskey[3] showed that in these compounds the positive charge resides on the ribose moiety; transfer of the charge to the pyrimidine or purine moiety is accompanied by transfer of one or two hydrogen atoms as well, and by fission of the bond linking the ribose C-1′ to the pyrimidine N-1 or purine N-9. This explains the occurrence in the spectrum of peaks at *m/e* values corresponding to the mass of the pyrimidine or purine molecular ion, M, and at (M + 1). We have confirmed this result, and have found by high resolution mass measurement that the peaks at *m/e* 126 and 127 in the spectrum of thymidine consists of $C_6H_5N_2O_2^+$ (the composition of the thymine molecular ion) and $C_5H_7N_2O_2^+$, respectively. Primary ionization of the pyrimidine moiety apparently does not occur; the molecular ion (*m/e* 242) does not undergo the fragmentation processes characteristic of thymine. The thymine fragment ion at *m/e* 126, however, decomposes by the same paths as a 2,4-dioxypyrimidine molecular ion (Figure 5); the presence of more than 50 metastable peaks in the thymidine spectrum permits the identification of decomposition processes originating with the pyrimidine fragment. Many of these processes generate daughter ions containing a nitrogen atom; these can be positively identified as pyrimidine fragments by high-resolution mass measurement even when they are not abundant (Table I). This is a result of biochemical importance, for nucleosides can readily be obtained by enzymatic degradation of nucleic acids, while the pyrimidine–ribose bond is very resistant to hydrolysis.

We wish to point out in conclusion that this paper is not meant to be a comprehensive catalog of all the electron-impact fragmentation patterns possible for pyrimidines of biological interest. A substantial number of mass peaks and metastable ions have not been interpreted here, and alternant mechanisms may exist for some of the processes we have discussed. We have restricted our study to major fragmentation paths of potential interest to structure determination on derivatives of these compounds, especially those of biological origin. We are presently extending our studies to the purines and nucleosides.

Acknowledgment. M. B. wishes to thank the directors of Associated Electrical Industries Ltd. for providing him with the opportunity to work at Harvard. The authors are happy to acknowledge Professor Paul Doty's encouragement and support of this work.

(18) J. H. Beynon, ref. 6, p. 267.

The Synthesis and Spectra of α,β-Unsaturated Aliphatic Azo Compounds[1,2]

Bernard T. Gillis and Jack D. Hagarty

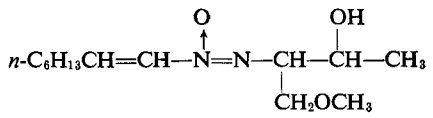
Chemistry Department, Duquesne University, Pittsburgh 19, Pennsylvania.
Received June 8, 1965

The reaction of α-chloroaldehydes and α-chloro ketones with 2 equiv. of methylhydrazine has resulted in the formation of the previously unknown α,β-unsaturated aliphatic azo compounds. The ultraviolet absorption of this new chromophore has been established. The infrared and n.m.r. spectra of these new compounds were obtained. A mechanism for the formation of the unsaturated azo compounds is proposed and the synthetic limitations of the reaction are discussed briefly.

(1) This investigation was supported by Public Health Service Research Grant AI-02923 from the National Institute of Allergy and Infectious Diseases.

(2) Presented in part at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1964, Paper No. 155, Abstract of Papers, p. 87S.

Our investigations of hydrazones and their oxidation products suggested the reaction of α-halo ketones and aldehydes with alkylhydrazines as a possible synthesis of the previously unknown α,β-unsaturated aliphatic azo compounds. This new type of compound was desired not only to establish the spectroscopic properties of the basic chromophore, but also as a precursor of the synthetically unknown α,β-unsaturated aliphatic azoxy compounds, of which the antibiotic Elaiomycin (**1**)[3] is the only known example.



1

The successful synthesis of the unsaturated azo compounds depended upon 1,4-dehydrohalogenation of α-halo hydrazones. A similar dehydrohalogenation was postulated by Wharton, Dunny, and Krebs[4a] in the Kishner reduction of α-halo ketones by hydrazine. Also, Wolfrom, *et al.*,[5] have observed a limited and only slightly related deacetoxylation in the acetylated acyclic phenylhydrazones of D-glucose, D-galactose, and D-mannose. Debenzoyloxylation failed in this same series.[6] In our work, 2 equiv. of methylhydrazine were allowed to react with 1 equiv. of an α-halocarbonyl compound. The first equivalent of methylhydrazine could be expected to form the hydrazone, while the second equivalent might induce dehydrohalogenation.

Thus, when 1-chloro-2-propanone was treated with 2 equiv. of methylhydrazine in chlorobenzene, an exothermic reaction occurred and furnished a compound free of halogen. Spectral studies indicated the absence of a carbonyl or N–H function in the product. An extended ultraviolet chromophore was present, and its n.m.r. spectrum showed two broadened peaks in the vinyl region, characteristic of a terminal methylene group whose two hydrogens are in different environments. These facts and analytical data supported the assignment of the α,β-unsaturated azo structure to the product, 2-(methylazo)propene (**2**).

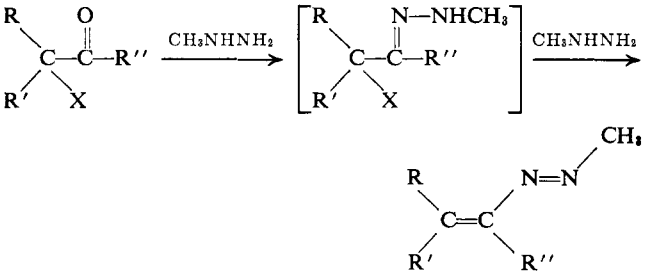
Similarly, the treatment of α-chlorocyclohexanone and α-chloroisobutyraldehyde with 2 equiv. of methylhydrazine in methylene chloride gave the compounds 1-(methylazo)cyclohexene (**3**) and 1-(methylazo)isobutylene (**4**), respectively. Again, the structural assignments were based on infrared, ultraviolet, and n.m.r. spectral studies as well as elemental analyses. These reactions were successful even though carried out in methylene chloride.[7]

When 3-chloro-3-methyl-2-butanone was treated with slightly more than 2 equiv. of methylhydrazine without solvent, the characteristic yellow color of the unsaturated azo compound developed and 2-(methylazo)-3-methyl-2-butene (**5**) was obtained in 42% yield.

The α-chlorocarbonyl compounds appear to give more satisfactory results than α-bromocarbonyl compounds. Although 3-bromo-2-butanone was converted to 2-(methylazo)-2-butene (**6**), the conversion was successful only in methylene chloride.

Aromatic α-halo ketones all failed to give any azo compounds. For example, phenacyl chloride reacted with methylhydrazine[8] to form 2,5-diphenylpyrazine, identified by independent synthesis. α-Bromoisobutyrophenone developed no color characteristic of the expected chromophore when treated with methylhydrazine and after refluxing overnight the reaction yielded only high-boiling products. When α-chlorodeoxybenzoin was allowed to react with 1 equiv. of methylhydrazine and 1 equiv. of triethylamine in methylene chloride, benzil monomethylhydrazone was formed in 77% yield. The same chloro ketone when allowed to react with 2 equiv. of methylhydrazone in ether formed benzil monomethylhydrazone in 42% yield.

The unsaturated azo compounds are probably formed stepwise, the hydrazone first, followed by a 1,4-dehydrohalogenation. While the bromide ion could be eliminated more easily in the latter step, the bromo compounds are also more prone to undergo intra- and intermolecular SN2 reactions. The mechanism is thus the same, and subject to the same side reactions, as that proposed for the Kishner reduction of α-halocarbonyl compounds with hydrazine,[4] except without the elimination of nitrogen.



2, R, R′ = H; R′ = CH_3
3, R = H; R′, R″ = $(CH_2)_4$
4, R, R′ = CH_3; R″ = H
5, R, R′ = CH_3; R″ = CH_3
6, R, R′ = H; R″ = CH_3

For the absorptions of compounds **2–6** in the ultraviolet region, the base of 217 mμ can be assigned to the chromophore plus the following increments: +5 mμ for an N-alkyl substituent, +70 mμ for an N-phenyl substituent,[5a] +10 mμ for an α-alkyl substituent, and +15 mμ for a β-alkyl substituent. The maxima are shown for the compounds in Table I below.

Experimental Section[9]

Starting Halocarbonyl Compounds. The 1-chloro-2-propanone, purchased from the Eastman Kodak Co., was distilled prior to use, b.p. 119°.[10] The α-chloro-

(3) C. L. Stevens, B. T. Gillis, and T. H. Haskell, *J. Am. Chem. Soc.*, **81**, 1435 (1959), and previous papers and references therein.

(4) (a) P. S. Wharton, S. Dunny, and L. S. Krebs, *J. Org. Chem.*, **29**, 958 (1964); (b) N. J. Leonard and S. Gelfand, *J. Am. Chem. Soc.*, **77**, 3272 (1955).

(5) (a) M. L. Wolfrom, A. Thompson, and D. R. Lineback, *J. Org. Chem.*, **27**, 2563 (1962); (b) M. L. Wolfrom, G. Fraenkel, D. R. Lineback, and F. Komitsky, Jr., *ibid.*, **29**, 457 (1964).

(6) H. el Khadem, *ibid.*, **29**, 2073 (1964).

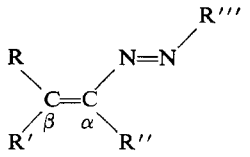
(7) H. Williams, *ibid.*, **29**, 2046 (1964), reported that methylene chloride reacts with methylhydrazine.

(8) (a) J. van Alphen, *Rec. trav. chim.*, **65**, 112 (1946); (b) J. van Alphen, *ibid.*, **65**, 117 (1946), reported the reaction of phenacyl bromide with phenylhydrazine.

(9) Boiling points and melting points are uncorrected. Microanalyses were performed by A. Bernhardt, Mulheim, Germany. Spectra of the compounds were determined on a Beckman Model DB ultraviolet spectrophotometer and a Perkin-Elmer Model 137 double-beam infrared spectrophotometer. The n.m.r. spectra were measured in carbon tetrachloride on a Varian Model A-60 at 60 Mc.p.s. with tetramethylsilane as an internal standard.

(10) E. R. Bachman and H. Sargent, *J. Am. Chem. Soc.*, **67**, 400 (1945).

Table I



Compd.	R	R′	R″	R‴	Ultraviolet λ_{max} (95% EtOH), mμ	(ε)
2	H	H	CH_3	CH_3	232; 386	(6060); (55)
3	H	$(CH_2)_4$		CH_3	249	(9570)
4	CH_3	CH_3	H	CH_3	252	(7490)
5	CH_3	CH_3	CH_3	CH_3	262	(7240)
6	CH_3	H	CH_3	CH_3	248	(8300)

cyclohexanone, purchased from the Aldrich Chemical Co., $n^{30}D$ 1.4785,[11] was used directly. The α-chloroisobutyraldehyde was prepared from isobutyraldehyde and sulfuryl chloride[12] and boiled at 87–88°, $n^{25}D$ 1.4060. Similarly, 3-chloro-3-methyl-2-butanone was obtained from 3-methyl-2-butanone and sulfuryl chloride.[12] An initial distillation followed by distillation of the 3-chloro-3-methyl-2-butanone through a 45-cm. spinning-band column gave a pure product, b.p. 114–116°, $n^{20}D$ 1.4200.[13] The n.m.r. spectra of this compound showed only two sharp singlets at 1.65 and 2.33 p.p.m. from tetramethylsilane as an internal standard. No other absorptions were present. The 3-bromo-2-butanone was purchased from Eastman Kodak Co. and distilled prior to use, b.p. 129–130°, $n^{25}D$ 1.4534. The α-chlorodeoxybenzoin was obtained from the Aldrich Chemical Co., m.p. 64–66° (lit.[14] m.p. 66–68°). The α-bromoisobutyrophenone and α-chloroacetophenone were purchased from the Aldrich Chemical Co. and the Eastman Kodak Co., respectively, and were used without further purification.

2-(Methylazo)propene (**2**). To a stirred solution of 62 g. (1.348 moles) of methylhydrazine in 175 ml. of chlorobenzene was added 61 g. (0.663 mole) of 1-chloro-2-propanone with cooling. Anhydrous sodium sulfate was added as a drying agent. After addition was completed, the reaction was stirred for 1 additional hr. Upon filtration to remove the sodium sulfate, distillation furnished 16.8 g. (31%) of yellow liquid **2**, b.p. 60–64°. A redistillation gave an analytical sample, b.p. 61–64°, $n^{23}D$ 1.4300, $\lambda_{max}^{EtOH\ 95\%}$ 232 mμ (ε 6060) and 386 mμ (ε 55), respectively. The infrared spectrum of the compound was devoid of N—H and C=O stretching bands. A strong C=C stretching mode was present at 1640 characteristic of vinyl compounds, and a conjugated N=N mode at 1500 cm.$^{-1}$. The n.m.r. spectrum of **2** showed singlets at 1.75 and 3.82 and broadened singlets at 5.70 and 5.83 p.p.m. from tetramethylsilane with relative intensities of 3:3:1:1, respectively.

Anal. Calcd. for $C_4H_8N_2$: C, 57.12; H, 9.58. Found: C, 56.96; H, 9.72.

1-(Methylazo)cyclohexene (**3**). To a stirred solution of 12.5 g. (0.26 mole) of methylhydrazine in 150 ml. of methylene chloride in the presence of anhydrous sodium sulfate was slowly added 17.0 g. (0.13 mole) of α-chlorocyclohexanone. After the addition was complete, the sodium sulfate was removed by filtration and the methylene chloride was removed by distillation at atmospheric pressure. Continued distillation at a reduced pressure yielded 9.8 g. (61%) of a yellow liquid **3**, b.p. 101–105° (80 mm.), $n^{29}D$ 1.4990, $\lambda_{max}^{EtOH\ 95\%}$ 249 mμ (ε 9570). The infrared spectrum of **3** indicated the absence of N—H and C=O bands and the presence of a C=C stretching mode at 1640 and a conjugated N=N mode at 1500 cm.$^{-1}$. The n.m.r. spectrum of the compound showed singlets at 6.52 and 3.70 and multiplets in the methylene region, centered at 2.18 and 1.62 p.p.m. The integrated intensities of these absorptions were 1:3:4:4, respectively, corresponding to vinyl hydrogen, NCH_3 hydrogens, the four allyl hydrogens, and the four ordinary methylene hydrogens.

Anal. Calcd. for $C_7H_{12}N_2$: C, 67.79; H, 9.75; N, 22.56. Found: C, 67.55; H, 9.81; N, 22.44.

1-(Methylazo)isobutylene (**4**). The same procedure used for the preparation of **3** was carried out. From 23.0 g. (0.22 mole) of freshly distilled α-chloroisobutyraldehyde and 20.2 g. (0.440 mole) of methylhydrazine, a crude product was obtained after the removal of sodium sulfate and methylene chloride. A rapid distillation at reduced pressure into a Dry Ice–acetone cooled trap, followed by redistillation gave 7.5 g. (35%) of a yellow liquid **4**, b.p. 75–80° (200 mm.), $n^{26}D$ 1.4590, $\lambda^{EtOH\ 95\%}$ 252 mμ (ε 7490). The infrared spectrum of **4** contained no N—H or C=O bands, but showed a strong C=C band at 1640, and a conjugated N=N band at 1500 cm.$^{-1}$. The n.m.r. spectrum of **4** had singlets at 1.91, 2.20, 3.75, and 6.78 p.p.m. from tetramethylsilane. The relative intensities were 3:3:3:1, respectively.

Anal. Calcd. for $C_5H_{10}N_2$: C, 61.18; H, 10.27. Found: 61.08; H, 10.38.

2-(Methylazo)-3-methyl-2-butene (**5**). The addition of 35.3 g. (0.29 mole) of freshly distilled 3-chloro-3-methyl-2-butanone to 32.2 g. (0.70 mole) of methylhydrazine was carried out dropwise with cooling without solvent. After the addition was completed, the reaction mixture was stirred for an additional 2 hr. The resulting layers were separated. The organic layer was dissolved in ether and was washed twice with water. The ether solution was dried over anhydrous magnesium sulfate. Filtration to remove the drying agent and distillation gave 14.2 g. (43%) of 2-(methylazo)-3-methyl-2-butene, b.p. 64–65° (22 mm.), $n^{18}D$ 1.4574, $\lambda_{max}^{EtOH\ 95\%}$ 262 mμ (ε 7240). The infrared spectrum of **5** showed no N—H or C=O stretching modes but a strong C=C band at 1650 cm.$^{-1}$ were present, the latter which we assign to the conjugated N=N stretch. The n.m.r. spectrum showed singlets at 1.77, 2.04, 2.38, and 3.89 p.p.m. in the ratio of 1:1:1:1.

Anal. Calcd. for $C_6H_{12}N_2$: C, 64.21; H, 10.79; N, 24.99. Found: C, 64.24; H, 10.58; N, 24.93.

2-(Methylazo)-2-butene (**6**). Twenty grams (0.133 mole) of 3-bromo-2-butanone was added slowly to a mixture of 12 g. (0.26 mole) of methylhydrazine, 150 ml. of methylene chloride, and anhydrous magnesium

(11) R. L. Huang, *J. Org. Chem.*, **19**, 1366 (1954).
(12) C. L. Stevens and B. T. Gillis, *J. Am. Chem. Soc.*, **79**, 3448 (1957).
(13) D. P. Wyman and P. R. Kaufman, *J. Org. Chem.*, **29**, 1956 (1964), reported different physical constants, but the same n.m.r. spectrum.
(14) A. M. Ward, "Organic Synthesis," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 159.

sulfate. After the addition was complete, stirring was continued for 1 hr. The mixture was then further dried over additional anhydrous magnesium sulfate before filtration. The methylene chloride was then removed from the solution and the remaining liquid was distilled to yield 5.0 g. (38%) of yellow liquid **6**, b.p. 87–88° (145 mm.), $n^{25}D$ 1.4591, $\lambda_{max}^{EtOH\ 95\%}$ 248 mμ (ε 8300). The infrared spectrum of the compound was similar to the other α,β-unsaturated azo compounds. The n.m.r. spectrum of **6** exhibited numerous peaks consisting of a vinyl quartet centered at 6.5 two NCH_3 peaks at 3.78 and 3.85 (3:1), two superimposed doublets of different intensities at 1.98 and 2.10 (*cis*- and *trans*-β-CH_3), and a quartet at 1.7 p.p.m. (α-CH_3), indicative of a mixture of *cis* and *trans* isomers in a ratio of approximately 1:3.

Anal. Calcd. for $C_5H_{10}N_2$: C, 61.18; H, 10.27; N, 28.55. Found: C, 61.00; H, 10.08; N, 28.42.

Reaction of Methylhydrazine with α-Chlorodeoxybenzoin. Eleven grams (0.05 mole) of α-chlorodeoxybenzoin was dissolved in methylene chloride and this solution was added dropwise to a solution of 6.0 g. (0.11 mole) of methylhydrazine and 6.0 g. (0.06 mole) of triethylamine in methylene chloride with magnesium sulfate also present to take up the water formed. The addition was carried out so as to maintain a slow reflux. The mixture was stirred for several hours after the addition was complete. The magnesium sulfate was then removed by filtration and the solvent was removed, whereby, 12.9 g. of light yellow crystals appeared. Upon recrystallization from methanol, 8.8 g. (77%) of material, m.p. 135–137°, was obtained. This proved to be benzil monomethylhydrazone.[15] The infrared spectrum of the material was superimposable with that of authentic benzil monomethylhydrazone prepared from methylhydrazine and benzil.

Reaction of α-Chloroacetophenone with Methylhydrazine. Ten grams (0.069 mole) of α-chloroacetophenone was dissolved in benzene and added to 7.0 g. (0.15 mole) of methylhydrazine also dissolved in benzene. An ammoniacal odor could be detected during the addition. The mixture was refluxed for 2 hr. since the initial reaction appeared to be slow. The benzene was removed and the residual mixture was distilled at reduced pressure. Very little volatile material was present. The undistilled material in the distillation flask (8.1 g.) was dissolved in methanol and recrystallized several times. A colorless solid, m.p. 201–202°, was obtained and was shown to be 2,5-diphenylpyrazine[16] by comparison with an authentic sample prepared by heating α-chloroacetophenone in concentrated ammonia for 2 hr. A mixture melting point of the former sample with the product of the latter reaction showed no melting point depression.

Reaction of Methylhydrazine with α-Bromoisobutyrophenone. When 34.0 g. (0.15 mole) of α-bromoisobutyrophenone was added to 14.7 g. (0.32 mole) of methylhydrazine in benzene very little heat was evolved, and no yellow color or any other color appeared. The mixture was then heated at reflux overnight. Upon distillation no material of the expected volatility resulted.

(15) M. O. Forster and D. Cardwell, *J. Chem. Soc.*, 861 (1913), reported m.p. 138°.

(16) H. O. House and E. J. Grubbs, *J. Am. Chem. Soc.*, **81**, 4733 (1959), reported m.p. 197.3–198°.

Symmetrical SN2 Reactions Using Iodide-131 Tracer. Kinetic Studies in Carbohydrates[1]

C. L. Stevens, K. Grant Taylor, and John A. Valicenti[2]

Contribution from the Department of Chemistry, Wayne State University, Detroit, Michigan 48202. *Received June 14, 1965*

Two isomeric iodo sugars were shown to have the structures of methyl-4,6-dideoxy-2,3-di-O-benzyl-4-iodo-α-D-gluco- and -galactopyranosides by conversion of each to known sugar derivatives. The rates of reaction of these sugars with iodide ion were determined using iodide-131 tracer under pseudo-first-order kinetic conditions. The galacto isomer was found to react 2.8 and 2.4 times as fast as the gluco isomer with iodide ion in acetone at 62.8 and 82.0°, respectively. Activation parameters for both reactions were obtained from the rate data, and the significance of the differences noted is discussed.

The isolation of 4-amino-4,6-dideoxyaldohexoses and their N-alkyl derivatives as components of antibiotics,[3,4] and from cell wall lipopolysaccharides of *Chromobacterium violaceum*[5] and several strains of *Escherichia coli* as sugars linked to thymidine diphosphate,[6,7] stimulated interest in the syntheses of these naturally occurring compounds.[3,8–10] Syntheses of

(1) (a) Abstracted in part from the Ph.D. Dissertation of John A. Valicenti, Wayne State University, 1965. (b) For previous work using radioactive halogen in mechanistic studies, *cf.* C. L. Stevens and John A. Valicenti, *J. Am. Chem. Soc.*, **87**, 838 (1965).

(2) Detroit News Fellow, 1964–1965.

(3) C. L. Stevens, P. Blumbergs, and F. A. Daniher, *J. Am. Chem. Soc.*, **85**, 1552 (1963); C. L. Stevens, K. Nagarajan, and T. Haskell, *J. Org. Chem.*, **27**, 2991 (1962).

(4) C. L. Stevens, Abstracts, 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965, p. 15C.

(5) R. W. Wheat, E. L. Rollins, and J. M. Leatherwood, *Biochem. Biophys. Res. Commun.*, **9**, 120 (1962).

(6) J. L. Strominger and S. S. Scott, *Biochim. Biophys. Acta*, **35**, 552 (1959).

(7) R. Okazaki, T. Okazaki, and Y. Kuriki, *ibid.*, **38**, 384 (1960).