Table II. $\alpha:\gamma$ Reactivity Ratios[a]

meta Subst	k_α/k_γ at 86.5°: Piperidine	DMSO	MeOH
Me	59.8	3.35	0.855
H	35.4	2.51	1.03
COMe	22.9	1.96	...
CO_2Et	15.6	1.92	0.949
CF_3	7.13	0.866	1.08
CN	3.32	0.355	...

[a] Rate of a given *meta*-substituted 2-chloroquinoline relative to a similarly *meta*-substituted 4-chloro isomer.

if there are no important solvent–substrate specific interactions. This is the case when piperidine[3] and DMSO (Figure 3, slope, 0.73) are used as solvents. In methanol, where solvent–substrate H bonding occurs, the two series display nearly the same selectivity (Figure 4, slope, 1.04).

The $\alpha:\gamma$ reactivity ratios for a number of isomeric pairs (2-Cl-4-R and 4-Cl-2-R derivatives) are reported in Table II.

When reactions of different charge types are compared (see introductory section) obviously the effect of the negative charge of the nucleophile in the former reaction is superimposed on that of the solvent. However, also in this case change from the nonhydroxylic solvent (amine) to methanol reflects the characteristic effect of solvent–substrate H bonding because the selectivity of the methoxy dechlorination reaction (in MeOH) relative to the piperidino dechlorination (in piperidine) is smaller with the 4-chloro- (1/0.95) than with the 2-chloroquinoline (1/0.67) series,[3,7] a result which is analogous to that illustrated in Figure 2 as discussed above.

Experimental Section

Materials. Methanol,[8] piperidine,[3] and dimethyl sulfoxide[2] have been purified as described in the given references.

All the chloroquinolines examined were available from previous studies.[3,4,8]

Kinetic Procedure. The kinetic experiments were carried out using the same procedure described previously.[1,2] For the treatment of the rate data for the reactions subject to autocatalysis, see the preceding paper.[2]

(7) We must note that in ref 3 the slopes of the lines of Figure 2 thereof are in reciprocal order with respect to those herein reported where piperidine is used as the reference solvent.

(8) G. Illuminati and G. Marino, *J. Am. Chem. Soc.*, 80, 1421 (1958)

The Piperidino Dechlorination and Methoxy Dechlorination of 6- and 8-Alkyl-4-chloroquinolines. Steric Hindrance to Specific Solvation[1]

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Contribution from the Departments of Chemistry, University of Rome, Rome, Italy, and University of Trieste, Trieste, Italy. *Received January 21, 1967*

Abstract: Kinetic data for the reaction of 6- and 8-alkyl-substituted 4-chloroquinolines with piperidine in four different solvents and with sodium methoxide in methanol have been obtained and compared. The *t*-butyl group located at the position *peri* to the aza group is found to cause rate-depressing effects and significant increases in the energy and entropy of activation when the solvent is hydroxylic (methanol) whereas only minor changes are observed in aprotic or poor proton-donor solvents (toluene, DMSO, and piperidine). The results are interpreted in terms of steric inhibition of specific solvation (H bonding).

The reactivity in chloroquinoline, especially when the reactive center is at the γ position, is specifically affected by hydroxylic solvents. Hydrogen-bond interaction of these solvents with the aza group has been held responsible for a rate-enhancing effect[2] and for a change in sensitivity to substituent effects.[3]

Specific solvation can be hindered by the proximity of bulky groups.[4,5] In particular, steric hindrance to solvation may play a role in the base-weakening effect of pyridine in water[6] by two *t*-butyl groups located in the α positions. Likewise, H-bond interaction with the aza group of the quinoline ring is expected to suffer from steric hindrance when bulky groups occupy positions adjacent to it, either α or *peri*. Evidence for rate-depressing effects caused by steric hindrance of solvation has recently been found in the methoxy dechlorination of *peri*-substituted 2-chloroquinolines[7] and in the piperidino dechlorination in methanol of α-alkyl-substituted 4-chloropyrimidines.[8]

Since the 4-chloroquinoline series is particularly sensitive to H-bonding effects,[2] in order to obtain further

(1) Nucleophilic Heteroaromatic Substitution. XXVII. Work carried out under a CNR (Rome) research contract at the Universities of Rome (G. I.) and Trieste (M. C. and G. M.) on the basis of a conjoint program. Presented by G. I. at the Gordon Conference on the Chemistry of Heterocyclic Compounds (New Hampton, N. H. July 4–8, 1966).

(2) G. Illuminati, G. Marino, and G. Sleiter, *J. Am. Chem. Soc.*, 89, 3510 (1967).

(3) F. Genel, G. Illuminati, and G. Marino, *ibid.*, 89, 3516 (1967).

(4) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963, p 234.

(5) G. S. Hammond in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, pp 427–428, 437.

(6) H. C. Brown and B. Kanner, *J. Am. Chem. Soc.*, 75, 3865 (1953). See also ref 5, p 439.

(7) G. Illuminati, P. Linda, and G. Marino, *Atti Accad. Naz. Lincei, Rend., Classe Sci. Fis., Mat. Nat.*, [8] 38, 389 (1965).

(8) M. Calligaris, P. Linda, and G. Marino, *Tetrahedron*, 23, 813 (1967).

quantitative information on steric inhibition of solvation and, consequently, on the importance of H-bond interaction it seemed of interest to study these phenomena with the 8-alkyl-substituted members of this series. To this end we now report the rate constants and the activation parameters for the methoxy dechlorination and the piperidino dechlorination of 6- and 8-alkyl-4-chloroquinolines.

Results and Discussion

The kinetics of the piperidino dechlorination of 6- and 8-alkyl-4-chloroquinolines (alkyl = Me, *t*-Bu) have been investigated in toluene, piperidine, DMSO, and methanol. The kinetic course of the reaction in this chloroquinoline series has been described in a previous paper.[2] The reactions are subject to autocatalysis in all investigated solvents except piperidine, and the "uncatalytic," second-order rate constants at a given temperature and the activation parameters are reported in Tables I and II. The kinetic data for the methoxy dechlorination reaction are collected in Table III. Additional rate constants at other temperatures for all the reactions have been included in the Experimental Section (Table IV).

Table I. Solvation Effects on the Piperidino Dechlorination of 6- and 8-R-4-Chloroquinolines, Rate Constants[a]

Solvent, temp, °C	Alkyl group position	$k_{Me} \times 10^6$	$k_{t\text{-Bu}} \times 10^6$	$k_{Me}/k_{t\text{-Bu}}$
Toluene, 150	6	1.35	0.95	1.42
	8	1.65	0.68	2.42
Piperidine, 86.5	6	0.278	0.193	1.44
	8	0.431	0.183	2.35
DMSO, 86.5	6	37.5	33.3	1.13
	8	48.1	15.5	3.10
Methanol, 86.5	6	10.0	7.6	1.31
	8	5.4	0.22	24.5

[a] k in l. mole^{-1} sec^{-1}.

Table II. Solvation Effects on the Piperidino Dechlorination of 6- and 8-R-4-Chloroquinolines, Activation Parameters

Solvent	R	E_a, kcal/mole	$-\Delta S^{\ddagger}$, eu
Piperidine	6-Me	16.1	46.3
	6-*t*-Bu	16.2	46.5
	8-Me	14.6	49.5
	8-*t*-Bu	15.1	49.8
DMSO	6-Me	14.6	40.4
	6-*t*-Bu	13.5	43.8
	8-Me	14.0	41.9
	8-*t*-Bu	15.8	39.3
Methanol	6-Me	15.0	42.0
	6-*t*-Bu	15.1	42.2
	8-Me	15.4	42.3
	8-*t*-Bu	20.7	34.0

Table III. Effects of Steric Hindrance of Solvation in the Methoxy Dechlorination of 6- and 8-R-4-Chloroquinolines[a]

R	$10^5 \times k$, 86.5°	$k_{Me}/k_{t\text{-Bu}}$	E_a	$-\Delta S^{\ddagger}$
6-Me	25.7		22.7	14.2
6-*t*-Bu	25.4	1.01	22.8	13.9
8-Me	19.4		22.0	16.7
8-*t*-Bu	0.55	35.0	27.3	9.0

[a] k in l. mole^{-1} sec^{-1}; E_a in kcal/mole; $\Delta S^{\ddagger}$ in eu.

Piperidino Dechlorination. On the basis of the electronic theory of substituent effects in aromatic systems the influence of a given alkyl group is expected to be similar at positions 6 and 8 of the substrate. This is indeed what is observed in most cases in diverse solvents, as shown in Table I. Thus, on changing substituent location from the 6 to the 8 position, the reactivity of the substrate varies within a small factor whether the alkyl is methyl or *t*-butyl.

There is, however, one remarkable exception to this picture and this is the reactivity behavior of the 8-alkyl derivatives in methanol. At the 6 position, the reactivity ratio, $k_{Me}/k_{t\text{-Bu}}$, is practically independent of the solvent; its average value is 1.3. At the 8 position it is still nearly constant for three out of the four investigated solvents, its value being in the range of 2.3 to 3.1. However, in methanol, the $k_{Me}/k_{t\text{-Bu}}$ value rises to 24.5. It is of interest to note that this increase is controlled by the very large reactivity drop observed on going from the 6-*t*-butyl to the 8-*t*-butyl, which is consistent with the hypothesis of a serious steric disturbance by the very bulky *t*-butyl group. The reactivity of the 8-methyl derivative is also less than that of the 6-methyl derivative; this is the reverse order to the one observed in the other solvents and indicates that a small steric effect may already be present with a *peri*-methyl group.

If piperidine is taken as a reference solvent, the effect of steric inhibition of solvation on the reaction rate is also evident by considering the free-energy relationships shown in Figure 1 (plots A and B), where the 8-alkyl groups have been included in previously established[3] linear plots. When the reaction selectivity in DMSO is compared to that in piperidine, the 8-alkyl groups fall on the line; however, if the plot for methanol *vs.* piperidine is considered, such groups fall below the line. The free-energy changes, $\Delta\Delta F^{\ddagger}$, as obtained from these deviations are 2.7 and 0.8 kcal/mole, whereby the major change is related to the *t*-Bu group.

The quantitative significance of these effects can be further worked out by considering the activation parameters (Table II). Here again the most important changes concern the 8-*t*-butyl group in methanol. In this case an increase in activation energy by 5.3 kcal/mole and in $\Delta S^{\ddagger}$ by 8 eu *with respect to the 8-methyl group* is observed. The direction and the amount of these changes are both consistent with an extensive rupture of the H bonds involved in the solvent–substrate interaction. For example, H-bond formation between phenol and triethylamine in cyclohexane involves $-\Delta H$ and $-\Delta S$ values of 5.7 kcal/mole and 10.4 eu, respectively.[9] From ΔH data concerning the interaction of several N-heteroaromatic compounds with hydroxylic species,[10] the H-bond strength of a chloroquinoline–methanol interaction in the ground state may be estimated to be in the vicinity of 3 kcal/mole. When H bonding is involved in the reactions under investigation, we deal with energy differences between transition and ground states. A strong interaction ensues in the transition state because electronic charge is displaced into the ring toward the aza group. In the presence of a *peri*-*t*-butyl group the

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(10) D. Neerinck and L. Lamberts, *Bull. Soc. Chim. Belges*, **75**, 473, 484 (1966).

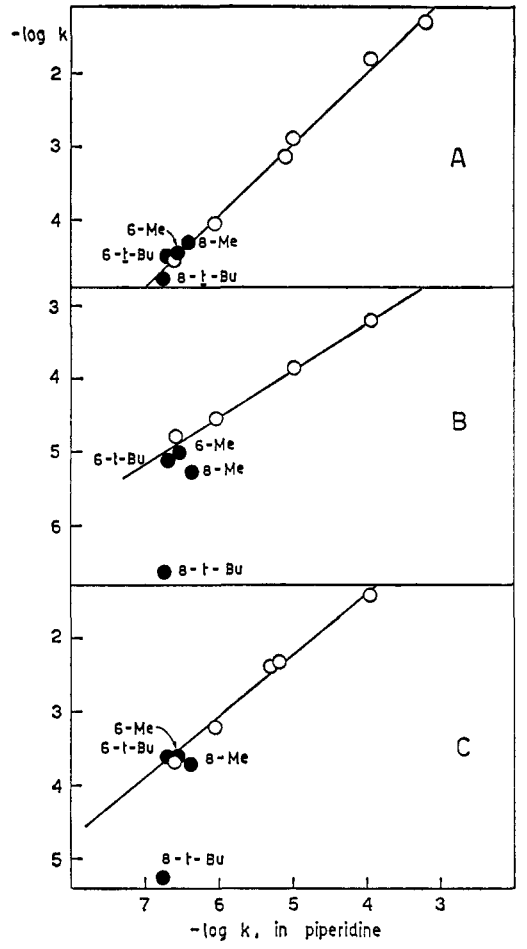

Figure 1. Free-energy correlations in some nucleophilic substitutions of 4-chloroquinolines (effects of 6- and 8-alkyl groups). Comparison with the piperidino dechlorination in piperidine of the following reactions: piperidino dechlorination in DMSO (A) and in methanol (B); methoxy dechlorination in methanol (C). The three lines are based on the substituents specified in ref 3 and indicated by the open circles.

H-bonding effect may be assumed to become negligible. Then the change in energy of activation (5.3 kcal/mole) that we observe as a result of the effect of this group provides an approximate measure of the difference in the H-bond strength between transition and ground states in the reaction of the unhindered substrates.

In view of the fact that the noncatalytic rate constants are given with an average error of 10% for the autocatalytic reactions,[2] the reality of the above changes can be checked by noting that the E_a values for the methyl and *t*-butyl groups differ from each other by an average amount of 0.4 kcal/mole in the 6 position (all tested solvents) and 1.2 kcal/mole in the 8 position (all tested solvents except methanol), whereas the corresponding $-\Delta S^{\ddagger}$ differences are 1.4 and 1.3 eu, respectively.

In summary, the behavior of the 8-alkyl derivatives in methanol yields further support to the view that strong H-bond interactions with this solvent are responsible for the rate-enhancing effects observed in the reaction of the unhindered aza-activated substrates.[2] The steric effects herein observed emphasize the point that solvation in methanol is specific in two ways, *i.e.*, it involves the aza group and must have certain steric requirements. In contrast, solvation by the other solvents probably occurs mainly by electrostatic interaction with a greater charge dispersion area in the substrate and lower stereospecificity.

Methoxy Dechlorination. In this reaction (Table III) there is observed a remarkable correspondence of the phenomena above described for the piperidino dechlorination reaction. Thus, the $k_{Me}/k_{t\text{-}Bu}$ reactivity ratio rises from 1 to 35 on going from the 6 to the 8 position, and the 8-alkyl groups fall below the line in the relative selectivity plot (Figure 1C). Furthermore, the activation energy and entropy show an increase for the 8-*t*-butyl group by 5.3 kcal/mole and 7.7 eu with respect to the 8-methyl; the change in the activation parameters is thus practically identical with that of the piperidino dechlorination in the same solvent. This finding is hardly fortuitous. It illustrates that the ΔE_a and $\Delta\Delta S^{\ddagger}$ values appear to be independent of the nucleophile in the two investigated reactions and to be characteristic of the solvent used. The solvent is held responsible for the change just as it had been noted for another property, the reaction selectivity.[3]

As to the general reaction mechanism, since the H-bonding interaction in the transition state is expected to depend on the electron-donor ability of the aza nitrogen, the quantitative analogy of the effects of steric inhibition of solvation between reactions involving nucleophiles of different charge type can be taken as evidence that similar electronic charges are displaced toward nitrogen in their respective transition states. Since the rate-enhancing effects occurring with the sterically unhindered substrates involve changes in H-bond strength in the order of 5 kcal/mole, it is likely that the electronic charge is largely displaced toward the nitrogen atom, *i.e.*, the transition states probably approach the structure of σ adducts in both cases. This tentative conclusion is of interest since, unlike nitro-activated substrates, straightforward evidence for the intervention of σ-adduct intermediates is quite scanty with heteroaromatic substrates.

Experimental Section

Materials. Methanol,[11] toluene,[12] piperidine,[13] and dimethyl sulfoxide[2] were purified as described in the given references. 4-Chloro-8-methylquinoline has been prepared as reported in the literature[14] and purified by steam distillation and subsequent crystallization from ethanol, mp 96–97° (lit.[14] 99°). 4-Chloro-8-methylquinoline, mp 53.5–54°, was available from previous work.[11]

The syntheses of previously unreported 6- and 8-*t*-butyl-4-chloroquinolines are described in the following.

4-Chloro-6-*t*-butylquinoline. Equimolecular amounts of *p*-*t*-butylaniline (32.3 g, 0.22 mole) and ethyl ethoxymethylene malonate were heated at 80–90° in an open vessel until the weight of the mixture was constant (about 4 hr). The condensation product was dissolved in 200 ml of boiling Dowtherm and the solution was refluxed for 2 hr. Petroleum ether was added to the cooled solution and the precipitated 3-carbethoxy-4-hydroxy-6-*t*-butylquinoline was filtered (16 g, yield 27%, mp 248–252°). It was then converted by hydrolysis into 3-carboxy-4-hydroxy-6-*t*-butylquinoline (yield 86%, mp 263° dec) and by heating at the melting temperature into 4-hydroxy-6-*t*-butylquinoline (4.5 g, yield 50%, mp 313–316°). The crude hydroxyquinoline was refluxed for about 1 hr with an excess of phosphorus oxychloride, and the reaction mixture was treated in the usual way. The 4-chloro-6-*t*-butylquinoline ob-

(11) G. Illuminati and G. Marino, *J. Am. Chem. Soc.*, 80, 1421 (1958).
(12) G. Illuminati and G. Marino, *Atti Accad. Naz. Lincei, Rend., Classe Sci. Fis., Mat. Nat.*, [8] 38, 525 (1965).
(13) G. Illuminati and G. Marino, *Ric. Sci.*, [2A] 35, 449 (1965).
(14) J. H. Burckhalter, F. H. Tendick, E. M. Jones, P. A. Jones, W. F. Holcomb, and A. L. Rawlins, *J. Am. Chem. Soc.*, 70, 1363 (1948).

tained was then purified by steam distillation and crystallization from petroleum ether (bp 30–60°) (3 g, yield 61%, mp 39.5–41.5°).

Anal. Calcd for $C_{13}H_{14}NCl$: C, 71.00; H, 6.37; N, 6.37; Cl, 16.13. Found: C, 70.61; H, 6.49; N, 6.29; Cl, 16.13.

4-Chloro-8-*t*-butylquinoline. *o*-*t*-Butylaniline hydrochloride[15] (41.6 g, 0.22 mole) and sodium oxalacetate (47.2 g) were mixed and stirred at room temperature for 20 hr. The obtained β-carbethoxy-β-anilinoacrylate (65.7 g, yield 92%) was dissolved in 500 ml of Dowtherm and heated under reflux for 1 hr. Most of the solvent was removed by distillation under reduced pressure and 4-hydroxy-3-carbethoxy-8-*t*-butylquinoline (32 g, yield 57%, mp 166–173°) was precipitated by adding petroleum ether to the residue. It was successively converted by conventional procedures into the 4-hydroxy-3-carboxy-8-*t*-butyl (21 g, mp 220° dec), the 4-hydroxy-8-*t*-butyl (12.8 g, mp 248–251°), and the 4-chloro-8-*t*-butyl derivatives. After purification by steam distillation and subsequent crystallization from petroleum ether, the chloro derivative melted at 46.5–47.5°.

Anal. Calcd for $C_{13}H_{14}NCl$: C, 71.00; H, 6.37; N, 6.37. Found: C, 70.99; H, 6.73; N, 6.28.

A previous attempt to synthesize this compound by the procedure used for the 6-*t*-butyl isomer (*i.e.*, condensation with ethyl ethoxymethylenemalonate) gave a much lower yield.

Kinetic Procedure. The procedure used for the kinetic measurements was that described in previous paper.[11,13] For the treatment of the rate data for the reactions subject to autocatalysis, see ref 2. A total of 90 independent kinetic experiments was carried out.

(15) J. B. Shalsmith and A. Mackie, *J. Chem. Soc.*, 2334 (1928).

Table IV. Methoxy and Piperidino Dechlorination of 4-Chloro-6- (and-8-) alkylquinolines (Rate Constants at Diverse Temperatures)

Reagent and solvent	Subst	$k \times 10^6$ 75.2°	99.5°	115.7°
MeO^- in methanol	6-Me	95.7[a]	791[a]	2870
	6-*t*-Bu		799	2820
	8-Me	68.8	559	1910
	8-*t*-Bu		21.9	98.0
Piperidine in piperidine	6-Me		0.617	1.50
	6-*t*-Bu		0.410	1.06
	8-Me		0.894	2.01
	8-*t*-Bu		0.395	0.899
Piperidine in DMSO	6-Me	20.6	84.8	181
	6-*t*-Bu	17.8	69.8	133
	8-Me	24.2	93.6	200
	8-*t*-Bu	5.80	32.5	64.3
Piperidine in MeOH	6-Me		21	50
	6-*t*-Bu		16	38
	8-Me		11	27
	8-*t*-Bu	17[b]	4.8[c]	2.0

[a] See ref 11. [b] At 150°. [c] At 130°.

The activation parameters reported in Tables II and III were determined on the basis of the rate constants at the different temperatures reported in Tables I, III, and IV.

The Kinetics and Mechanism of the Reaction of *p*-Toluenethiol with Chloroquinolines in Methanol Solution[1]

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Contribution from the Departments of Chemistry, University of Rome, Rome, Italy and University of Trieste, Trieste, Italy. *Received January 21, 1967*

Abstract: The noncatalyzed reaction of a chloroquinoline with *p*-toluenethiol in methanol solution is faster than the reaction involving either the aryl sulfide or the chloroquinolinium ion with the nonionized form of the other reactant. All the investigated reactions follow simple second-order kinetics, but the substituent effects are anomalous. These and other facts are interpreted in terms of a complex reaction consisting of a fast acid–base preequilibrium between reactants followed by the substitution proper between aryl sulfide and chloroquinolinium ions. The nucleophilicity of the nonionized thiol with respect to solvent and substrate is also discussed in connection with the mechanism of the reaction in nonpolar aprotic solvents.

In the literature there is found a large amount of information concerning the nucleophilic reactions of organic sulfide ions in preparative as well as kinetic work. The reactions of thiols in the presence of strong bases clearly belong to this class. However, in a number of cases, the intervention of the sulfide anions is less obvious or, even, unlikely. As belonging to this group, we may mention the acid-catalyzed addition reactions to double bonds[2,3] and the substitution reactions with chloroquinolines in nonpolar, aprotic solvents (toluene).[4,5] The latter reactions exhibit complex kinetics and involve a slow, initial process followed by autocatalytic phenomena.

In the course of related work on the reactivity of aza-activated substrates we have recently discovered[6] that *p*-toluenethiol reacts quite rapidly with 4-chloroquinoline in methanol solution. In principle, protic solvents and reagents may interact with aza-activated substrates in a specific way.[7] Several aspects of the influence of specific solvation due to hydroxylic solvent–substrate interaction have been described in the preceding papers.[7–9] From such work it appears that piperidine, being only weakly protic, does not give rise

(1) Nucleophilic Heteroaromatic Substitution. XXVIII. Work carried out under a CNR (Rome) research contract at the Universities of Rome (G. I.) and Trieste (P. L. and G. M.) on the basis of a conjoint program. Presented by G. I. at the Gordon Conference on the Chemistry of Heterocyclic Compounds (New Hampton, N. H., July 4–8, 1966).

(2) E. Campaigne in "Organic Sulfur Compounds," Vol. I, N. Kharasch, Ed., Pergamon Press, Oxford, 1961, p 134 ff.

(3) W. A. Pryor, "Mechanisms of Sulfur Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 72.

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(5) G. Grassini and G. Illuminati, *ibid.*, **86**, 437 (1956).

(6) G. Illuminati and G. Marino, *Tetrahedron Letters*, 1055 (1963).

(7) G. Illuminati, G. Marino, and G. Sleiter, *J. Am. Chem. Soc.*, **89**, 3510 (1967).

(8) F. Genel, G. Illuminati, and G. Marino, *ibid.*, **89**, 3516 (1967).

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