Reactions of Carbodiimides. II. The Reactions of Dicyclohexylcarbodiimide with Carboxylic Acids in the Presence of Amines and Phenols[1,2]

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Abstract: Quantitative product studies have been made of the reactions of DCC with acetic acid in the presence of triethylamine, pyridine, benzylamine, and *p*-nitrophenol in acetonitrile and in carbon tetrachloride. The results can be explained qualitatively by considering the several ion pair and other complex species present in mixtures of acids and bases in aprotic media. Both the fast reaction with acetic acid dimer reported in part I and the strong decelerating effect observed with triethylammonium acetate can be correlated with the strong tendency to form complexes of the composition A_2B when an acid A reacts with a base B. Evidence is presented that the acylisourea is one of the acylating agents in the formation of both *p*-nitrophenyl acetate and of N-benzylacetamide. Acetic anhydride is formed along with *p*-nitrophenyl acetate and is responsible for part of the acetylation of *p*-nitrophenol. In contrast to triethylamine, pyridine causes increased yields of acetic anhydride. It also leads to increased yields of *p*-nitrophenyl acetate but not of N-benzylacetamide.

The reactions between carbodiimides and carboxylic acids were considered in part I.[4] However, the synthesis of amides and phenolic esters involves reactions in the presence of amines. To work out detailed mechanisms for such acylations is an extensive project which can only be approached in stages. It is necessary to know, for example, whether the anhydride, the acylisourea, or both are intermediates. It is also necessary to know how bases, including tertiary bases, affect the course of the reactions between carboxylic acids and carbodiimides. Fundamental to all of these questions is a detailed understanding of the complex acid–base equilibria in aprotic solvents. The objective of this work has been to obtain quantitative data for the reactions with added triethylamine, pyridine, benzylamine, and *p*-nitrophenol which would permit an evaluation of important general features of the acylation reactions and which would provide a basis for further studies.[5]

Since carbodiimides are highly reactive, it is necessary to give some consideration to reactions that might occur with components of the reaction mixture other than the carboxylic acids. The basic properties of carbodiimides are shown by salt formation with dry hydrogen chloride[6] and by reversible reaction with hydrogen bromide.[7] Qualitatively they are quite weak bases, for it was noted that pyridine and *p*-nitrophenol gave a more deeply colored solution than did carbodiimides and *p*-nitrophenol.[7] Hydrolysis or hydration with water occurs in the presence of mineral acids,[8] but solutions in "slightly wet" solvents with or without added triethylamine remain unchanged for many hours in the absence of acids.[7] Carbodiimides add amines,[9,10] alcohols,[11,12] and phenols,[13] but these reactions require catalysts or relatively high temperatures. It may be concluded, therefore, that under the reaction conditions employed in the present work there is no interference due to direct reaction of carbodiimides with water, amines, phenols, and alcohols singly or in combination.

Previous workers have established that the reactions of carboxylic acids and carbodiimides in the presence of a tertiary base lead to increased yields of acylurea.[14–16] It is also well known that acylation occurs in the presence of primary or secondary amines or phenols.[14,17–20]

As for the complex behavior of acids and bases, quite a lot of information is available although a number of essential values are not yet known. Several species have been identified. With acid alone, the principal equilibrium involves monomer **1** and dimer **2**,

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(3) Public Health Fellow 1963–1964.

(4) Part I: D. F. DeTar and R. Silverstein, *J. Am. Chem. Soc.*, **88**, 1013 (1966).

(5) The following abbreviations are used: DCC, dicyclohexylcarbodiimide; DCU, dicyclohexylurea; AcDCU, N-acetyldicyclohexylurea. DPC is diisopropylcarbodiimide, DPU is diisopropylurea. Bl stands for benzyl.

(6) F. Lengfeld and J. Stieglitz, *Am. Chem. J.*, **17**, 98 (1895).

(7) These reactions were studied by Dr. F. F. Rogers, Jr., Ph.D. Thesis, Florida State University, 1964.

(8) H. Lecher and K. Köberle, *Ann.*, **445**, 55 (1925). We have hydrolyzed several carbodiimides with dilute hydrochloric acid.

(9) J. Macholdt-Erdniss, *Chem. Ber.*, **91**, 1992 (1958).

(10) D. F. DeTar, R. Silverstein, and F. F. Rogers, Jr., *J. Am. Chem. Soc.*, 87, 1024 (1965).

(11) J. Stieglitz and R. W. Noble, *Ber.*, 38, 2243 (1905).

(12) E. Schmidt, F. Moosmüller, and R. Schnegg, German Patent 956,499; *Chem. Abstr.*, **54**, P5471*a* (1960).

(13) E. Vowinkel, *Chem. Ber.*, **96**, 1702 (1963).

(14) For reviews, see, *e.g.*, (a) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," John Wiley and Sons, Inc., New York, N. Y., 1961, p 1016; (b) N. F. Albertson, *Org. Reactions*, **12**, 157 (1962); (c) M. Goodman and G. W. Kenner, *Advan. Protein Chem.*, **12**, 465 (1957).

(15) (a) M. Smith, J. G. Moffatt, and H. G. Khorana, *J. Am. Chem. Soc.*, **80**, 6204 (1958); (b) H. G. Khorana, "Some Recent Developments in the Chemistry of Phosphate Esters of Biological Interest," John Wiley and Sons, Inc., New York, N. Y., 1961; (c) H. G. Khorana and A. R. Todd, *J. Chem. Soc.*, 2257 (1953).

(16) (a) F. Zetzsche and A. Fredrich, *Ber.*, **72**, 1477 (1939); **73**, 1114 (1940); F. Zetzsche and G. Röttger, *ibid.*, 73, 465, (1940); (b) G. Schulz and K. Fiedler, *ibid.*, **89**, 2681 (1956); (c) H. Zahn and F. Schade, *ibid.*, **96**, 1747 (1963).

(17) J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955).

(18) For a review see H. G. Khorana, *Chem. Rev.*, **53**, 145 (1953).

(19) A. Buzas, C. Egnell, and P. Freon, *Compt. rend.*, **252**, 896 (1961).

(20) A Buzas, C. Egnell, and P. Freon, *ibid.*, **256**, 1804 (1963).

RCOOH **1**
$\mathrm{(RCOOH)_2}$ **2**
$\mathrm{(RCOOH)}_n$ **3**
$\mathrm{RCOO^{-}R_3NH^{+}}$ **4**
$\mathrm{RCOOH{:}NR_3}$ **5**
$\mathrm{RCOOH \cdot R_3NH^{+}RCOO^{-}}$ **6**
$\mathrm{2RCOO^{-}2R_3NH^{+}}$ **7**
$\mathrm{R_3N{:}RCOO^{-}R_3NH^{+}}$ **8**

and there are indications that higher polymers (**3**) are of some importance even in 0.1 *M* acetic acid in carbon tetrachloride.[21] These equilibria are solvent dependent, since some solvents form hydrogen bonds to the carbonyl group ($CHCl_3$), some to the acidic proton (acetonitrile, esters, ethers, ketones), and some to both (alcohols, water). The dimerization constant for acetic acid is reported to be 1500 in carbon tetrachloride,[22] 140 in chloroform,[22] and 0.5 in acetonitrile.[4] The units are in terms of moles and liters throughout.[23]

With a relatively strong base such as triethylamine or other aliphatic amine, acetic acid forms the ion pair salt (**4**), while with the weaker pyridine it forms the hydrogen-bonded complex (**5**) instead.[26] When the ratio of triethylamine to acetic acid is not too large, one of the principal species present is the hydrogen-bonded complex (**6**). Evidence for such a complex has been obtained for many acid–base pairs and by a variety of experimental techniques.[27–29] This tendency is still more pronounced for stronger acids than for acetic acid. With acetic acid and triethylamine in carbon tetrachloride the equilibrium constant for reaction of dimer **2** with amine to form **6** is too large to measure, and the equilibrium constant between **6** and amine to form 2 moles of **4** is about 2.[27] One to one mixtures of acetic acid and triethylamine consist primarily of **6** plus **4** plus amine.

There is abundant evidence for other complexes such as **7** and **8** in more concentrated solution although the exact compositions are based on rather scanty data.

Any proposed reaction mechanism must eventually be based on a detailed evaluation of all of these ion-pair equilibria and of the contribution that each species makes.

Results

Products of the Reactions of DCC with Acetic Acid in the Presence of Triethylamine or Pyridine. To examine the effect of bases, the product studies reported in Table I were carried out quantitatively. Yields are reported in mole per cent based on the DCC taken in order to show clearly the amount of reactants accounted for: total DCC taken = DCC recovered + Ac_2O + AcDCU; and total AcOH taken = AcDCU + $2x Ac_2O$ (assuming complete reaction, as is the case). However, care is needed in evaluating the data. Complete conversion to anhydride, for example, is represented by DCC = 50, Ac_2O = 50, and AcDCU = 0.

Table I. Products of the Reaction of Acetic Acid and Dicyclohexylcarbodiimide in the Presence of Triethylamine or Pyridine[a]

Reactants, amine	Time, hr	Products DCC	Products Ac_2O	Products AcDCU
None[b]	40	32	30	38
0.01 TEA	24	26	22	48
0.02 TEA	24	22	20	59
0.04 TEA	24	21	14	67
0.04 TEA	86[c]	12[c]	9[c]	75[c]
0.08 TEA	22	21	10[f]	67
0.01 Py	30	42	40	18
0.02 Py	30	43	42	14
0.04 Py	30	44	42	12
0.08 Py	30	44	44	9
0.04[d]	24	21	12	68
None[b,e]	26	44	46	10
0.04 TEA[e]	50	29	36	42
0.04 TEA[e]	53	29	32	40
0.04 TEA[e]	26	33	35	38
0.04 Py[e]	26	44	44	17

[a] Temperature about 25°, solvent acetonitrile unless noted, TEA is triethylamine, Py pyridine, entries in product columns are mole per cent based on DCC taken (moles of product × 100/moles of DCC taken). There are in each reaction 0.04 *M* HOAc, 0.04 *M* DCC, and the specified amount of amine. In each case there is an excess of DCC, and the amount of acetic acid present at the time of the assay was always very small. [b] Reference 4. [c] The triethylamine used in this run had not had the phthalic anhydride treatment and hence some acetic anhydride was lost and some acetylamide was presumably assayed as AcDCU. [d] 0.04 TEA + 0.01 Py. [e] In carbon tetrachloride. [f] Also 3% of free acetic acid.

The expected effect of triethylamine in reducing the yield of acetic anhydride and increasing the yield of acetyldicyclohexylurea is shown for both acetonitrile and for carbon tetrachloride solutions. However, the effect of pyridine in acetonitrile is the opposite.[30]

A few kinetic data are presented in Table II. These utilized DPC rather than DCC because of the solubility of DPU.[5] The runs were satisfactorily first order, the data covered most of the extent of the reaction, and the calculated zero time concentration of DPC corre-

Table II. The Rate of Reaction of Diisopropylcarbodiimide with Acetic Acid in the Presence of Triethylamine[a]

AcOH	Diimide	TEA	10^4k, $\sec^{-1}$
0.39[b]	0.020	0	82
0.20[b]	0.010	0	35
0.40	0.020	0.20	5.8
0.40	0.040	0.20	6.8
0.40	0.02	0.40	2.5

[a] Solvent acetonitrile. Reaction temperature about 25°. Entries in columns 1, 2, and 3 are concentrations, moles per liter. [b] Data from ref 4.

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[21] J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 416.

[22] G. M. Barrow and E. A. Yerger, *J. Am. Chem. Soc.*, **76**, 5248 (1954).

[23] By a graphical procedure, using the 2400–3600-cm^{-1} region, a value of 2400 was obtained for acetic acid in carbon tetrachloride and of 180 for propionic acid in chloroform. (Propionic acid has a value of 2500 in carbon tetrachloride.) The value in benzene is 28.[24,25]

[24] J. Wenograd and R. A. Spurr, *J. Am. Chem. Soc.*, **79**, 5844 (1957).

[25] Y. Nagai and O Simamura, *Bull. Chem. Soc. Japan*, **35**, 132 (1962).

[26] (a) G. M. Barrow and E. A. Yerger, *J. Am. Chem. Soc.*, **76**, 5211 (1954); (b) G. M. Barrow, *ibid.*, **78**, 5802 (1956).

[27] E. A. Yerger and G. M. Barrow, *ibid.*, **77**, 4474 (1955); infrared studies.

[28] *Cf.* also M. M. Davis and H. B. Hetzer, *J. Res. Natl. Bur. Std.*, **60**, 569 (1958).

[29] For a comprehensive study and references to earlier work see P. J. R. Bryant and A. W. H. Wardrop, *J. Chem. Soc.*, 895 (1957); conductivity studies.

[30] These results are evidently related to a similar effect of pyridine in increasing yields of *p*-nitrophenyl acetate reported previously[20] and also observed in the present study.

sponded within experimental accuracy with that taken. It is clear that the effect of triethylamine is to reduce drastically the reaction rate. Such a result was not predictable from previous speculations about the reaction mechanism. A comparison of line two with line three shows that the presence of 0.2 M AcO^-TEAH^+ also decreases the rate by a factor of 6.

Benzylamine. The acylation of benzylamine was investigated as a prototype of peptide bond formation. Results are summarized in Table III. The effect of benzylamine on the one hand is that of a base and here its behavior should parallel that of triethylamine. On the other hand it is also a nucleophile. Actually the yield of AcDCU is very nearly the same whether or not benzylamine is present. The reaction of benzylamine with acetic anhydride is very fast, and therefore acetic anhydride is not expected to be observable in this reaction whether or not it is an intermediate.

Table III. Products of the Reaction of Acetic Acid and Dicyclohexylcarbodiimide in the Presence of Benzylamine or *p*-Nitrophenol[a]

		Products			
Reactants[b]	Time, hr	DCC	Ac_2O	Ac-DCU	Other
0.01 $BlNH_2$	24	22	21	39	26 AcNHBl[e]
0.02 $BlNH_2$	24	8	6	40	50 AcNHBl[f]
0.04 $BlNH_2$	24	5	0	39	55 AcNHBl[g]
0.04 $BlNH_2$	200	5	0	45	55 AcNHBl[g]
0.04 $BlNH_2$[d]	24	4	0	40	55 AcNHBl[g]
0.08 $BlNH_2$	22	8	0	45	48 AcNHBl[g]
0.04 HONP	22	10	10	23	64 AcONP
0.04 HONP	250	0	6	24	72 AcONP
0.04 HONP[c]	22	8	0	38	61 AcONP
0.04 HONP[d]	24	5	5	8	90 AcONP

[a] Same as footnote *a* of Table I. $BlNH_2$ is benzylamine, HONP is *p*-nitrophenol. [b] Each solution contained 0.04 M DCC, 0.04 M HOAc, and either benzylamine or *p*-nitrophenol at the molar concentration specified. [c] Plus 0.01 triethylamine. [d] Plus 0.01 pyridine. [e] Maximum possible 25. [f] Maximum possible 50. [g] Maximum possible 100.

***p*-Nitrophenol.** To evaluate the reactions of *p*-nitrophenol with acetic acid and with DCC, it is necessary to consider the reaction of *p*-nitrophenol with acetic anhydride in the presence of other components of the reaction mixture. This is summarized in Table IV. It may be noted that acetic anhydride does not react with DCC,[4] and the solvent was dry enough so that there was only a partial hydrolysis even in the presence of triethylamine. It may also be noted that the reaction of acetic anhydride with *p*-nitrophenol is negligibly slow in the absence of base, and that the effectiveness of DCC as a basic catalyst is about $^1/_5$ as great as that of pyridine, while triethylamine is at least 50 times as effective as pyridine.

The results of the carbodiimide reactions are summarized in Table III. Considerable acetic anhydride is formed, and it is obvious that at least some *p*-nitrophenyl acetate is derived by acylation by acetic anhydride.

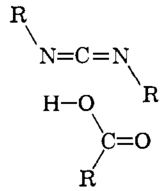
Table IV. Reactions of Acetic Anhydride in Acetonitrile[a]

Coreactants, M	Time, hr	% Ac_2O remaining
DCC 0.02	83	99[b]
DCU (satd)	18	100[c]
Et_3N[d] 0.04	36	82
Et_3N[d] 0.04, DCU (satd)	40	88[c]
Et_3N[d] 0.04, AcOH 0.04, DCU (satd)	40	93[c]
Pyridine 0.04	40	96
Pyridine 0.04, DCU (satd)	18	100[c]
HONP 0.04	18	100
HONP 0.04	7	95
HONP 0.04, DCC 0.02	1	95[e]
HONP 0.04, pyridine 0.02	1	71[f]
HONP 0.04, Et_3N 0.02	1	0[g]

[a] In most experiments the acetic anhydride was 0.04 M, in a few it was 0.02 M. [b] The DCC was also unchanged. A second experiment for 35 hr gave the same results. [c] No acylurea formed. [d] The triethylamine had been purified by refluxing with phthalic anhydride to remove traces of primary or secondary amines. [e] The rate of disappearance of anhydride is about 1.2×10^{-3} sec^{-1}. The DCC is also used up, and *p*-nitrophenyl acetate is formed. [f] The rate of disappearance of anhydride is about 6.5×10^{-3} sec^{-1}. [g] The rate is at least 50 times as fast as with pyridine.

Discussion

For the reaction of acetic acid with a carbodiimide to form the acylisourea (**11**) three paths represent the simplest possibilities: (1) a four-center reaction as shown in **9**, a six-center reaction as shown in **10**, and an ion-pair reaction similar to **12**. The four-center reaction is also possible for alcohols and phenols, and their relatively low reactivity as compared with carboxylic acids argues against this path. There is little direct evidence concerning the six-center path. However, carboxylic acids react in order of acidity: such acids as acetic and pivalic are less reactive than peptide acids, and trifluoroacetic acid reacts very rapidly. This suggests that the ion pair is the most likely intermediate. Similar considerations also led other workers to propose intermediate ionic species.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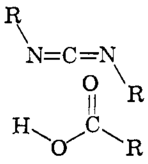
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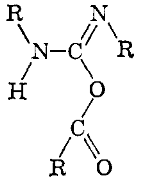
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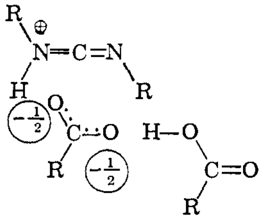
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While it should require no emphasis that free ions are not present in significant concentrations in aprotic solvents, it is perhaps not quite so obvious that there are important conceptual distinctions between the behavior expected of an ion pair $RNH^+C{=}NR^-OAc$ and that expected for the free ion $RNH^+C{=}NR$ previously postulated.[18b,31] A free ion is an independent

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(31) H. G. Khorana, *Chem. Ind.* (London), 1087 (1955); H. Schüssler and H. Zahn, *Chem. Ber.*, **95**, 1076 (1962).

species which will react with any suitable nucleophile, such as an acetate ion. This reaction will be at least roughly first order in the ion and first order in the nucleophile. However, in the first approximation, the rate of collapse of an ion pair will be independent of other species present. In any event, reaction by way of ion triplets or higher aggregates, which are the closest available analogs of the free ion reaction will not be expected to follow a simple stoichiometry.

If an equimolar amount of triethylammonium acetate is added to a solution of acetic acid (0.2 *M*) and DCC (0.02 *M*), the free ion hypothesis would predict a very large increase in rate, for the added acetate represents a manyfold (1000-fold or more) increase over the amount originally present, since carbodiimides are very weak bases. In the first approximation, the ion pair hypothesis would predict little or no change in rate. Comparison of lines 2, 3, and 4 of Table II shows that there is a sixfold decrease in rate. It is clear that the predictions of the free-ion picture are incorrect by a factor of roughly 10,000, perhaps more. The ion-pair concept is clearly better, although the first approximation prediction is only fair.

Reference to previous work on acid–base equilibria suggests a principle which explains both this rate decrease, and, economically, also explains the unexpectedly high reactivity of acetic acid dimer indicated in part I. This principle is the especially strong tendency to form a hydrogen-bonded complex (**6**),[27–29] and it predicts that the effect of adding 0.2 *M* triethylammonium acetate to 0.2 *M* acetic acid will be to decrease the concentration of free acetic acid. This in turn will cause a decrease in the rate of reaction. By the same token excess acetic acid can be expected to increase the stability of the simple ion-pair intermediate in the DCC reaction by forming **12** which is analogous to **6**. Furthermore, this effect should be more pronounced in carbon tetrachloride which does not hydrogen bond effectively with acetic acid than in acetonitrile which does. In fact the reaction in carbon tetrachloride is some 30 times faster than that in acetonitrile.

The effect of triethylamine on the product distribution between acetic anhydride and acetyldicyclohexylurea might be exerted solely by removal of acetic acid (eq 1 and 2), or the components of the reaction may

$$CH_3COOH + Et_3N = CH_2COO^{-}Et_3NH^{+} \qquad (1)$$

$$2CH_3COOH + Et_3N = CH_3COO^{-}Et_3NH^{+}, CH_3COOH \qquad (2)$$

react directly, *e.g.*, triethylamine might catalyze the rearrangement of acylisourea to acylurea. There is not sufficient information to reach a decision at present.

Since pyridine increases the yield of acetic anhydride, it is obvious that any effect it has as a base analogous to triethylamine must be overshadowed by some other reaction path. An obvious possibility is formation of an acylpyridinium derivative from the acylisourea and pyridine.[32]

There are other indications of interception of the acylisourea. In the reaction with *p*-nitrophenol the yield of acetyldicyclohexylurea is significantly lower than with acetic acid alone. The opposite result might have been expected if all *p*-nitrophenyl acetate were formed *via* acetic anhydride, for then an appreciably larger fraction of the acetic acid would have to recycle through the acylisourea than in the absence of *p*-nitrophenol.

The yield of acetyldicyclohexylurea is about the same with benzylamine present as with acetic acid alone. Unless benzylamine were reacting directly with acylisourea, it would be expected that the acylurea yield would be much higher as was found in comparable runs with triethylamine.

In this connection it may be noted that the peroxide synthesis reported by Greene[35] was shown to involve reaction of the peracid with an intermediate (acylisourea) since the acid anhydrides were relatively ineffective under the reaction conditions employed. The idea that amino esters may intercept the acylisourea in peptide synthesis has often been advanced to explain differences in extents of racemization,[36] but direct evidence has been lacking.

Experimental Section

The procedures followed have already been described.[4] Pure samples of all reactants and products were available for spectroscopic standards. Analyses of multicomponent mixtures were based on infrared curves measured with a Perkin-Elmer Model 137 spectrophotometer: DCC, 2115; Ac_2O, 1825; AcONP, 1760; AcOH, 1750; AcDCU, 1700; and AcNHBl, 1670 cm^{-1}. The data were processed by preliminary hand calculation and by ANALYZ, REMECH, CDIIMD, and LSTI.[4]

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[32] The isolation of acylpyridinium compounds in crystalline from the action of acid halides on pyridine has been reported: *cf.* H. Adkins and Q. E. Thompson, *J. Am. Chem. Soc.*, **71**, 2242 (1949). There is good evidence for the acetylpyridinium ion as an intermediate in the pyridine-catalyzed hydrolysis of acetic anhydride.[33,34]

[33] A. R. Butler and V. Gold, *J. Chem. Soc.*, 4362 (1961).

[34] *Cf.* S. L. Johnson, *J. Am. Chem. Soc.*, **84**, 1729 (1962); F. Covitz and F. H. Westheimer, *ibid.*, **85**, 1773 (1963).

[35] F. D. Greene and J. Kazan, *J. Org. Chem.*, **28**, 2168 (1963).

[36] *E.g.*, M. Goodman and L. Levine, *J. Am. Chem. Soc.*, **86**, 2918 (1964).