tion mixture was then sublimed *in vacuo* and product (200 mg., m.p. 160–172°) collected at 200°/2 mm. After one crystallization from benzene, the material had m.p. and mixed m.p. 174–176° with an authentic specimen of 3-cyanoindole.

Attempted alkylation of ethyl acetamidocyanoacetate with IV. *Procedure A:* To a solution of sodium (0.29 g., 0.013 g. at.) in absolute ethanol (60 ml.) was added successively ethyl acetamidocyanoacetate (2.1 g., 0.012 mole) and IV (4.2 g., 0.012 mole) and the mixture was refluxed for 40 hr. The mixture was freed of solvent *in vacuo* and the residue triturated with water and filtered. The dark residue (2.2 g., m.p. 174–176°) was crystallized from ethanol; yield 1.17 g., m.p. 180–182°. Ether extraction of the aqueous filtrate as such and also after acidification did not furnish any material. The crystalline product was identified as the starting methiodide after a further crystallization from alcohol.

Procedure B: To powdered sodium (120 mg., 0.005 g. at.) in *n*-butylether (9 ml.) was added ethyl acetamidocyanoacetate (1.1 g., 0.006 mole). The mixture was heated with stirring at 130° in an atmosphere of nitrogen for 8 hr. To the resulting semi-solid was added IV (1.5 g.) and the mixture heated for an additional 6 hr. The solution was filtered hot and the filtrate, when cooled, furnished material (1.1 g.) having m.p. and mixed m.p. 198–200° with an authentic sample of IV. No other product could be obtained by concentrating the filtrate.

Treatment of III *with sodium hydroxide.* A mixture of III (0.5 g.) and 10% ethanolic sodium hydroxide solution (3 ml.) was refluxed for 5 hr. and the alcohol was removed. The residue was diluted with water and cooled overnight. The product (m.p. 171–172°, 454 mg.) was collected and recrystallized from benzene; melting point and mixed melting point with authentic 3-cyanoindole 174–176°.

3-Carboxy-1-dimethylaminomethylindole methiodide. The methiodide IV (2.3 g., 0.007 mole) was refluxed for 1 hr. with 10% sodium hydroxide solution (15 ml.). The mixture was cooled, filtered, and made acidic with hydriodic acid. The crude product was collected and crystallized from alcohol; m.p. 185–190°; yield 1 g. Repeated crystallizations from alcohol raised the m.p. to 202–204°.

Anal. Calcd. for $C_{13}H_{17}O_2N_2I$: C, 43.4; H, 4.8. Found: C, 43.6; H, 5.4. Neut. equiv.: Calcd. 360. Found: 353.2.

Ethyl-α-piperidinomethyl-α-acetamido malonate. Piperidine (3.3 g., 0.039 mole) was added to ethyl acetamidomalonate (8.7 g., 0.04 mole). Formalin (4 ml., 36%, 0.048 moles) was then added and the mixture was warmed on a waterbath for 5 min. and refrigerated overnight. The crude base (12 g.) was collected and crystallized from petroleum ether (60–80°); m.p. 67–68°; yield 8 g. (64%).

Anal. Calcd. for $C_{15}H_{26}O_5N_2$: C, 57.3; H, 8.3. Found: C, 57.3; H, 8.5.

Attempted alkylation of 3-cyanoindole with ethyl α-piperidinomethyl-α-acetamidomalonate. Under dry conditions a mixture of ethyl α-piperidinomethyl-α-acetamidomalonate (3.14 g., 0.01 mole), 3-cyanoindole (1.5 g., 0.011 mole), powdered sodium hydroxide (catalytic amount), and xylene (10 ml.) was refluxed with stirring in an atmosphere of nitrogen for 6 hr. The mixture was filtered hot, diluted with benzene, and extracted with dilute hydrochloric acid. The benzene extract furnished unreacted 3-cyanoindole (587 mg.) which after recrystallization from benzene had melting point and mixed melting point with authentic specimen 174–176°. The acid extract was made alkaline and extracted with ether. The ether extract furnished a solid which was crystallized from petroleum ether (60–80°); yield 1.3 g., melting point and mixed melting point with an authentic sample of 1-piperidinomethyl-3-cyanoindole 88–90°.

1-Piperidinomethyl-3-cyanoindole. To piperidine (0.86 g., 0.01 mole) cooled in ice was added successively acetic acid (2 ml.) and 36% formalin (1 ml., 0.012 mole), maintaining the temperature below 5°. 3-Cyanoindole (1.3 g., 0.009 mole) was added and the mixture heated for 8 hr. on a water bath and then poured into sodium hydroxide solution. The liquid which separated solidified when left overnight in the refrigerator and was crystallized from petroleum ether; m.p. 88–90°; yield 1.3 g. (54%).

Anal. Calcd. for $C_{15}H_{17}N_3$: C, 75.3; H, 7.2. Found: C, 75.6; H, 7.1.

Acknowledgment. We are grateful to Mr. Selvavinayakam for the analyses and Dr. Gurbaksh Singh for the infrared data reported herein. Two of the authors (S.R. and S.Su.) are indebted to the government of India and the University of Madras, respectively, for awards of fellowships.

MADRAS 25, INDIA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE FLORIDA STATE UNIVERSITY]

Pyrroles. XII. The Reaction of Pyrrolealdehydes with Arylacetonitriles[1,2]

WERNER HERZ AND JAY BRASCH[3]

Received September 27, 1957

Triton B is an excellent catalyst for the preparation of pyrrole-substituted acrylonitriles from 2-pyrrolealdehyde. Secondary cyclic amines like piperidine, morpholine, and pyrrolidine, although capable of functioning as catalysts, enter into reaction with 2-pyrrolealdehyde and form bimolecular pyrrole Mannich bases. The acrylonitriles could not be hydrolyzed satisfactorily. Other attempts to prepare pyrrole analogs of stilbene are described.

In continuation of earlier work on the synthesis of 2-vinylpyrroles,[4] we were interested in preparing pyrrole analogs of stilbene. The decarboxylation of substituted cinnamic acids is a convenient method for the preparation of certain styrenes and stilbenes.[5] However, condensation between 2-pyrrolealdehyde and 2-*N*-methylpyrrolealdehyde, on the one hand, and phenylacetic acid on the other, could not be effected under the usual conditions.[6]

(1) Paper XI, W. Herz, *J. Org. Chem.*, **22**, 1260 (1957).

(2) Supported in part by the Office of Ordnance Research, U. S. Army, under Contract No. DA-01-009-ORD-436.

(3) Abstracted from the M.S. Thesis of Jay Brasch, August 1957.

(4) W. Herz and C. F. Courtney, *J. Am. Chem. Soc.*, **76**, 576 (1954).

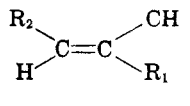
(5) R. B. Wagner and H. D. Zook, *Synthetic Organic Chemistry*, John Wiley & Sons, Inc., New York, N. Y., 1953, p. 44.

(6) See ref. 5, pp. 55–56, for leading references.

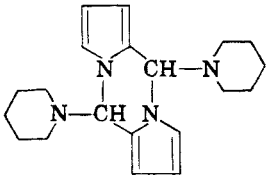
We therefore studied the reaction of these aldehydes with arylacetonitriles in the hope that hydrolysis of the condensation products (I) would lead to the desired substituted cinnamic acid analogs.

On condensing 2-pyrrolealdehyde with 2-pyrroleacetonitrile in the presence of piperidine, there was obtained a colorless basic substance of m.p. 160° which did not exhibit the properties expected of 1,2-dipyrroleacrylonitrile (I, R_1,R_2 = 2-pyrrole). When the condensation was carried out between 2-pyrrolealdehyde and phenylacetonitrile, the substance of m.p. 160° was also isolated, but dilution of the mother liquors with water yielded yellow crystals of m.p. 98–99° which proved to be 1-phenyl-2-pyrroleacrylonitrile.

These experiments suggested that there was some reaction between 2-pyrrolealdehyde and piperidine, and indeed, when these reagents were mixed in anhydrous ethanol, the base of m.p. 160° precipitated in 47% yield. Elemental analysis and molecular weight determinations indicated the formula $C_{20}H_{28}N_4$, the infrared spectrum showed the absence of NH and C=O groups, and the ultraviolet spectrum exhibited no absorption bands characteristic of a particular chromophore. Attempts to determine the neutral equivalent of the base failed due to color formation and reactions near the equivalence point. Analogous bases were formed on treatment of 2-pyrrolealdehyde with morpholine and pyrrolidine, but no reaction ensued when the aldehyde was mixed with aliphatic secondary amines or any tertiary amines.[7] Similarly *N*-methyl-2-pyrrolealdehyde proved inert when mixed with alicyclic secondary amines, which suggests that a free NH group on the pyrrole nucleus is necessary for such condensation.

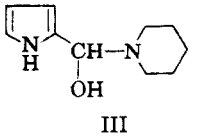


I

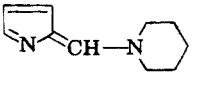


II

All of the above facts can be accommodated by assigning structure II to the base of m.p. 160°, with III or the enamine IV as possible intermediates leading to its formation. A piperidine addition compound whose structure is postulated as corresponding to III is formed when 2, 4, 5-trimethyl-3-pyrrolealdehyde and piperidine are allowed to stand for fifteen days.[8] Structures analogous to II would also represent the adducts resulting from 2-pyrrolealdehyde and morpholine or pyrrolidine.



III



IV

2-Pyrrolealdehyde has been condensed with malonic ester in the presence of piperidine;[9] the expected product was obtained in fair yield and no other products were reported. Certain substituted pyrroles also condense smoothly in a normal way.[10] In these cases the rate of the normal aldol-type condensation is presumably much faster than that of the condensation with the basic catalyst. On the other hand when the aldol condensation is sluggish, the reaction with piperidine takes precedence.[11]

Structure II is supported by the following additional facts. As a pyrrole Mannich base substituted on nitrogen it should be inert toward displacement reactions since it cannot react *via* the elimination-addition mechanism postulated for alkylations of this type.[13] This proved to be the case. On the other hand, quaternary salts derived from such bases may serve as alkylating agents. When attempts were made to prepare the hydrochloride and methiodide of II, however, the salts which were isolated proved to be piperidinium chloride and dimethylpiperidinium iodide, presumably due to spontaneous decomposition of the Mannich base salts.

Since the condensation of 2-pyrrolealdehyde with arylacetonitriles in the presence of piperidine gave low yields and was complicated by side reactions, other catalysts were investigated. Sodium ethoxide improved the yields slightly, but the major product was the sodium salt of the active methylene compound. In the search for a catalyst which would combine high basicity with non-participation in side reactions and minimum salt formation, benzyltrimethylammonium hydroxide finally proved to be the reagent of choice. Thus, in the preparation of 1-phenyl-2-pyrroleacrylonitrile, use of pyridine gave a yield of 16%, use of sodium ethoxide gave 23%, and the quaternary ammonium hydroxide raised the yield to 74%. The compounds prepared in this fashion are listed in Table I. The condensation of 2-pyrrolealdehyde with 2-pyrroleacetonitrile could not be carried out successfully.

Hydrolysis of the compounds of type I did not lead to the desired substituted cinnamic acids.

(7) These amines are probably not strong enough to catalyze the aldol reaction satisfactorily. At the same time the aliphatic secondary amines probably do not have the relatively low steric requirements of piperidine, pyrrolidine, and morpholine, which may result in the formation of compounds of type II.

(8) H. Fischer and C. Nenitzescu, *Ann.*, **439**, 175 (1924).

(9) G. R. Clemo, G. R. Fulton, and R. Raper, *J. Chem. Soc.*, 1140 (1950); W. Kutscher and O. Klamerth, *Z. physiol. Chem.*, **289**, 229 (1952).

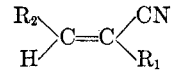
(10) H. Fischer and Z. Ceskas, *Ann.*, **508**, 187 (1934).

(11) Thus the "unidentified product" which is formed when hydantoin and 2-pyrrolealdehyde are boiled in absolute ethanol in the presence of piperidine[12] proved to be identical with the base of m.p. 160°.

(12) W. Herz and K. Dittmer, *J. Am. Chem. Soc.*, **70**, 503 (1948).

(13) J. H. Brewster and E. L. Eliel, *Org. Reactions*, **VII**, 99 (1953); H. Hellmann, *Angew. Chem.*, **65**, 473 (1953).

TABLE I

COMPOUNDS OF TYPE 

	R_1	R_2	Yield, %	M.P., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
Ia	Phenyl	2-Pyrrole	74	97–98	$C_{13}H_{10}N_2$	80.38	5.19	14.4	80.80	5.03	14.2
Ib	2-Pyrrole	Phenyl	93	111–112	$C_{13}H_{10}N_2$	80.38	5.19	14.4	80.26	5.33	14.2
Ic	Phenyl	*N*-Methyl-2-pyrrole	72	99	$C_{14}H_{12}N_2$	80.72	5.89	13.4	80.28	5.98	13.2
Id	2-Pyrrole	*N*-Methyl-2-pyrrole	81	161	$C_{12}H_{11}N_3$	73.07	5.62	21.4	72.75	5.27	22.0

Use of mild base resulted in recovery of starting material. Under more drastic conditions the only identifiable products were the arylacetic acids corresponding to the original arylacetonitrile moiety. Undoubtedly a reversal of the condensation reaction takes place, but whether it precedes or follows hydrolysis of the nitrile group was not determined.

Several other attempts to prepare 1,2-dipyrrole ethylene are described briefly in the following. The thermal decomposition of benzaldazine furnishes fair yields of *trans*-stilbene[14] and a recent paper describes the application of this method to the preparation of 1,2-difurylethylene.[15] However, under similar conditions (passage through a hot tube at temperatures up to 450°, unpacked or packed with glass, with or without solvents), 2-pyrrolealdazine exhibited remarkable stability and no substance whose properties corresponded to those of the expected stilbene analog could be isolated. Recovery of 2-pyrrolealdazine was practically quantitative even after exposure to intense gamma-ray flux from a cobalt-60 source. An attempt to prepare the hydrazone of 2-pyrrolealdehyde, which it was hoped to convert to 2-pyrrolediazomethane and then to 1,2-dipyrroleethylene, also failed, the only product being 2-pyrrolealdazine.

EXPERIMENTAL[16]

1-Phenyl-2-(N-methylpyrrole)acrylonitrile (Ic). The following preparation is typical for the compounds described in Table I. A solution of 1.17 g. of phenylacetonitrile and 1.09 g. of *N*-methyl-2-pyrrolealdehyde[17] in 25 ml. of boiling anhydrous ethanol was treated with 2 ml. of 33% aqueous Triton B solution. After boiling for 10 min. and allowing to stand, a yellow precipitate formed; total yield, including material from the mother liquors, 1.5 g. (72%). Several recrystallizations from ethanol furnished yellow crystals of m.p. 99°. The infrared spectrum had characteristic bands at 1610 (phenyl, olefin, or both) and 2232 cm.$^{-1}$ (conjugated nitrile). Compound Ia exhibited a doublet at 1590 and 1600 cm.$^{-1}$, nitrile absorption near 2200 and NH absorption at 3400 cm.$^{-1}$ Substance Ib had these bands at 1590, 2215, and 3430 cm.$^{-1}$; compound Id at 1602, 2212, and 3450 cm.$^{-1}$

Attempted hydrolysis of 1-phenyl-2-pyrroleacrylonitrile. The following is illustrative of many such experiments. Hydrolysis of Ia with 10% sodium hydroxide resulted in recovery of starting material. Hydrolysis of 0.55 g. of Ia with 1 g. of potassium hydroxide in 5 ml. of ethylene glycol at 195° for 2 hr. caused evolution of ammonia. The acid fraction weighed 0.2 g., m.p. 75°, undepressed on admixture of authentic phenylacetic acid.

Attempted condensation of 2-pyrrolealdehyde with phenylacetic acid. A typical reaction is described below. A mixture consisting of 1.74 g. of dry potassium phenylacetate, 0.5 g. of potassium carbonate, 0.5 ml. of dry pyridine, 0.96 g. of 2-pyrrolealdehyde, and 1.53 g. of freshly distilled acetic anhydride was heated at 180–190° in a nitrogen atmosphere for 2 hr., cooled, and decomposed with 35 ml. of water and 4 ml. of 5*N* potassium hydroxide. The mixture was warmed until solution occurred, cooled, extracted with ether, acidified, and again extracted with ether. Distillation of the neutral fraction furnished 0.5 g. of 2-pyrrolealdehyde; evaporation of the acid fraction followed by recrystallization gave 0.86 g. of phenylacetic acid.

Reaction of 2-pyrrolealdehyde with piperidine. A solution of 1.90 g. of 2-pyrrolealdehyde in 50 ml. of boiling anhydrous ethanol was mixed with 2 ml. of piperidine, boiled for an additional 10 min. (cherry red color) and allowed to stand. Filtration yielded 1.52 g. (47%) of dark brown crystals. After several recrystallizations from acetone-water (1:1) they were colorless and melted at 160°. The infrared spectrum showed no significant absorption in the —NH and double bond region.

Anal. Calcd. for $C_{20}H_{28}N_4$: C, 74.03; H, 8.70; N, 17.2; mol. wt. 324. Found: C, 73.90; H, 9.01; N, 16.8; mol. wt. (Rast, in camphene), 354, (ebullioscopic, in methyl ethyl ketone), 275.

The substance gave a negative ferric chloride test. The Ehrlich test was at first negative, but on standing a pink-orange color developed. It was insoluble in water and soluble in dilute sulfuric acid (the solution was initially yellow, but a reddish precipitate formed rapidly). A sealed ampoule containing 0.5 g. of the base and 15 ml. of methyl iodide on standing deposited crystals which after recrystallization from ethanol-water weighed 0.53 g. and were identified as dimethylpiperidinium iodide by analysis and mixed melting point. Dry hydrogen chloride was passed into a solution of 1 g. of the base in 25 ml. of chloroform for 5 min. The reddish brown amorphous material, wt. 1 g., was filtered and recrystallized from ethanol-water. The colorless crystals were identified as piperidine hydrochloride.

Since pyrrole Mannich bases can be hydrogenolyzed

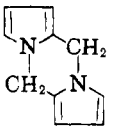
(14) L. B. Howard, G. E. Hilbert, R. Wiebe, and V. L. Gaddy, *J. Am. Chem. Soc.*, **54**, 3628 (1932); G. W. Williams and A. S. C. Lawrence, *Proc. Roy. Soc.*, **156A**, 444 (1936).

(15) N. I. Shuikin, M. V. Yushkevich, and G. S. Belikova, *Sbornik Statei Obshchei Khim.*, **2**, 1112 (1953); *Chem. Abstr.*, **49**, 4616 (1955).

(16) Melting and boiling points are uncorrected. Analyses by Drs. Weiler and Strauss, Oxford, England. Infrared spectra were determined by Miss M. N. Esquivel on a Perkin-Elmer Model 21 recording spectrometer.

(17) E. F. Ryskiewicz and R. M. Silverstein, *J. Am. Chem. Soc.*, **76**, 5802 (1954).

catalytically,[18] attempts were made to carry out such a conversion. Low pressure hydrogenation resulted in recovery of starting material. High pressure hydrogenation in ethyl acetate (ethanol was not satisfactory) gave an oil of b.p. 60° (1 mm.) which could not be identified satisfactorily but was neither the hoped-for V nor *N*-acetylpiperidine.[19] The relatively large quantity formed (2.52 g. from 2.0 g. of II) indicated that solvent was involved.



V

(18) A. Treibs and A. Zinsmeister, *Ber.*, **90**, 87 (1957).

(19) Piperidine and ethyl acetate at 200° are reported to yield *N*-acetylpiperidine.[20]

(20) F. B. Ahrens, *Ber.*, **27**, 2088 (1894).

Reaction of 2-pyrrolealdehyde with morpholine. Condensation of 2-pyrrolealdehyde with morpholine in the manner described above furnished 3.19 g. (97%) of tan crystals which were decolorized by recrystallization from ethyl acetate and then melted at 197–198°. The product resembled II in chemical behavior and solubility.

Anal. Calcd. for $C_{18}H_{24}N_4O_2$: C, 65.43; H, 7.32; N, 17.0. Found: C, 65.53; H, 7.46; N, 17.1.

Reaction of 2-pyrrolealdehyde with pyrrolidine. A mixture of 9.6 g. of the aldehyde and 14.2 g of pyrrolidine yielded 7.35 g. (50%) of brown product which was purified by recrystallization from ether, m.p. 93–94°. The substance decomposed rapidly on standing, and like its analogs, could not be titrated satisfactorily.

Anal. Calcd. for $C_{18}H_{24}N_4$: C, 18.9. Found: N, 18.8.

Acknowledgment. We are grateful to E. I. du Pont de Nemours and Co., Inc., for the gift of chemicals.

TALLAHASSEE, FLA.

[CONTRIBUTION FROM THE CHEMOTHERAPY BRANCH, U. S. ARMY CHEMICAL WARFARE LABORATORIES]

Pyridinium Aldoximes[1]

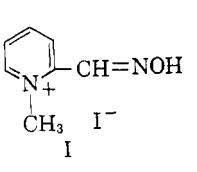
EDWARD J. POZIOMEK, BRENNIE E. HACKLEY, JR., AND GEORGE M. STEINBERG

Received September 30, 1957

A number of 1,1′-polymethylenebis(4-formylpyridinium bromide) dioximes and *N*-substituted 2- and 4-formylpyridinium halide oximes have been prepared. The bis-quaternary dioximes are active as chemotherapeutic agents in the treatment of nerve gas and other anticholinesterase poisoning in experimental animals, when administered in conjunction with atropine. The most active, 1,1′-trimethylenebis(4-formylpyridinium bromide) dioxime, appears to have advantages over previously reported treatment agents.

The "nerve gases" such as diisopropyl phosphorofluoridate (DFP), isopropyl methylphosphonofluoridate (GB) and *O*-ethyl *N*,*N*-dimethyl phosphoramidocyanidate (GA) as well as many of the organophosphorus insecticides or their metabolites function biologically by inhibition of the enzyme acetylcholinesterase[2]; inhibition being caused by phosphorylation (or phosphonylation) of the active site of the enzyme.

Nerve gas poisoning has been treated symptomatically with drugs which are pharmacologically antagonistic to acetylcholine. Such a compound is atropine and it is presently the recommended remedy.[3] As part of a program aimed at the development of prophylactics and of therapeutics which will act to repair the biological lesion, we have been involved in a search for reagents which (*a*) react rapidly with the nerve gases under physiological conditions of *p*H and temperature and (*b*) reactivate phosphorylated (or phosphonylated) enzymes. Several groups of rapid nerve gas reactants have been reported.[4]



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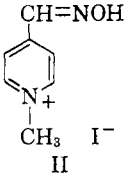

II

Recently, 2-formyl-1-methylpyridinium iodide oxime,[5] Compound I, has been reported to enhance considerably the activity of atropine in the chemotherapeusis of poisoning due to organophosphorus compounds.[6] Compound I shares the

(1) Presented at American Chemical Society, 132nd Meeting, New York, September 1957.

(2) (a) B. J. Jandorf, H. O. Michel, N. K. Schaffer, R. Egan, and W. H. Summerson, *Discussions Faraday Soc.*, **20**, 134 (1955). (b) J. E. Casida, *J. Agr. Food Chem.*, **4**, 772 (1956).

(3) W. H. Summerson, *Armed Forces Chem. J.*, **9**, 24 (1955).

(4) (a) B. E. Hackley, Jr., R. Plapinger, M. Stolberg, and T. Wagner-Jauregg, *J. Am. Chem. Soc.*, **77**, 3651 (1955). (b) G. M. Steinberg and J. Bolger, *J. Org. Chem.*, **21**, 660 (1956). (c) B. J. Jandorf, T. Wagner-Jauregg, J. O'Neill, and M. Stolberg, *J. Am. Chem. Soc.*, **74**, 1521 (1952). (d) T. Wagner-Jauregg and B. E. Hackley, Jr., *J. Am. Chem. Soc.*, **75**, 2125 (1952). (e) T. Wagner-Jauregg, B. E. Hackley, Jr., T. A. Lies, O. O. Owens, and R. Proper, *J. Am. Chem. Soc.*, **77**, 922 (1955). (f) J. Epstein, D. Rosenblatt, and M. Demek, *J. Am. Chem. Soc.*, **78**, 341 (1956).

(5) This compound has been commonly referred to in the pharmacological and biochemical literature as 2-pyridinealdoxime methiodide or 2-PAM.

(6) (a) I. B. Wilson and S. Ginsburg, *Biochim. et Biophys. Acta*, **18**, 168 (1955). (b) D. R. Davies and A. L. Green, *Discussions Faraday Soc.*, **20**, 269 (1955). (c) H. Kewitz, I. B. Wilson, and D. Nachmansohn, *Arch. Biochem. Biophys.*, **64**, 456 (1956).