4. The constants of aminoacetic acid and the aminobenzoic acids are explained by the strong *negative* character of the NH_2 group.

BERKELEY, CAL.

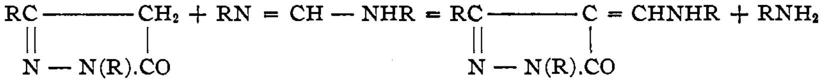
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF KANSAS.]

ON THE REACTIONS OF THE FORMAMIDINES. V. ON SOME PYRAZOLONE DERIVATIVES.

BY F. B. DAINS, H. R. O'BRIEN AND C. L. JOHNSON.

Received May 31, 1916.

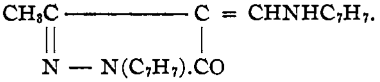
This is a continuation of a previous investigation on the pyrazolones,[1] where it was shown that the methylene group in this class of derivatives reacted with the formamidines, the hydrogen being replaced by the grouping >CHNHR. The general equation can be formulated as follows,



$$\begin{array}{l}\mathrm{RC}\text{———}\mathrm{CH_2}\\ \|\qquad\quad |\\ \mathrm{N-N(R).CO}\end{array} + \mathrm{RN=CH-NHR} = \begin{array}{l}\mathrm{RC}\text{———}\mathrm{C=CHNHR}\\ \|\qquad\quad |\\ \mathrm{N-N(R).CO}\end{array} + \mathrm{RNH_2}$$

the reaction yielding a substituted 4-amino methylene pyrazolone and the free amine. The following paper includes further experimental evidence as to the general nature of this reaction and a partial study of the action of certain reagents upon the substituted pyrazolones.

4-*m*-Toluido-methylene-1-*p*-tolyl-3-methyl-5-pyrazolone,



$$\begin{array}{l}\mathrm{CH_3C}\text{————}\mathrm{C=CHNHC_7H_7.}\\ \|\qquad\quad\ |\\ \mathrm{N-N(C_7H_7).CO}\end{array}$$

Molar quantities of the pyrazolone and di-*m*-tolyl formamidine were heated for twenty minutes in an oil bath at 150°. From the reaction product the new compound was isolated after treatment with dilute hydrochloric acid, which removed *m*-toluidine. This separated from alcohol in golden yellow crystals melting at 122°.

Calc. for $C_{19}H_{19}ON_3$: N, 13.78%. Found, 13.85%.

Under like conditions the pyrazolone and di-*o*-tolyl formamidine gave 4-*o*-toluido-methylene-1-*p*-tolyl-3-methyl-5-pyrazolone, yellow needles from alcohol which melt at 176.5°.

Calc. for $C_{19}H_{19}ON_3$: N, 13.78%. Found: 13.86%, 13.69%.

The ease of reaction of different formamidines seems to vary greatly. While many require heating at 120–150° in order to ensure condensation, others unite at much lower temperature. Thus *p*-tolyl methyl pyrazolone and di-*o*-phenetidyl formamidine at water-bath temperature gave the amine and 1-*p*-tolyl-3-methyl-4-*o*-ethoxyanilido-5-pyrazolone. It crystallizes from alcohol in canary-yellow needles with a melting point of 133°. The same reaction occurs slowly when the components are ground together in a mortar and allowed to stand.

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[1] Dains and Brown, THIS JOURNAL, 31, 1153 (1909).

Calc. for $C_{20}H_{21}O_2N_3$: N, 12.54%. Found: 12.80%.

In some cases a secondary reaction was found to occur, which resulted in the formation of varying amounts of a bispyrazolone.

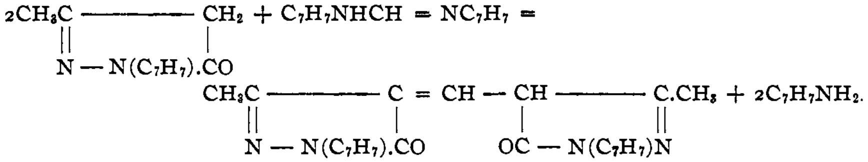
Thus the above pyrazolone and di-*p*-bromo-diphenyl formamidine gave on heating 1-*p*-tolyl-3-methyl-4-*p*-bromo-anilido-methylene-5-pyrazolone, yellow crystals from alcohol with a melting point of 196–7°.

Calc. for $C_{18}H_{16}O_3MgBr$: Br, 21.60%. Found: 21.29%.

In addition there is formed a bromine-free compound, difficultly soluble in alcohol, which crystallizes from chloroform in orange needles, melting at 249°. It gave on analysis the figures demanded for methenyl-bis-methyl-*p*-tolyl-pyrazolone.

Calc. for $C_{23}H_{22}O_2N_4$: N, 14.51%. Found: 14.77%, 14.78%.

This constitution was confirmed by the fact that the same methenyl bispyrazolone was obtained, together with *m*-toluidine, when di-*m*-tolyl formamidine (one mol) was heated with the methyl *p*-tolyl pyrazolone (two mols).



$$\begin{array}{lll} 2CH_3C & \text{————} & CH_2 + C_7H_7NHCH = NC_7H_7 = \\ \| & & | \\ N \text{—} & N(C_7H_7).CO & \end{array}$$

$$\begin{array}{lllllll} CH_3C & \text{————} & C & = CH \text{—} & CH & \text{————} & C.CH_3 + 2C_7H_7NH_2. \\ \| & & | & & | & & \| \\ N \text{—} & N(C_7H_7).CO & & & OC \text{—} & N(C_7H_7)N & \end{array}$$

Analogous results were obtained in one experiment when a mixture of *o*-tolyl-3-methyl-5-pyrazolone and di-*p*-chloro-diphenyl formamidine was heated. Besides *p*-chloro-aniline, the only product isolated was methenyl-bis-1-*o*-tolyl-3-methyl-5-pyrazolone, which crystallizes from alcohol in orange-colored needles, melting at 190°.

Calc. for $C_{23}H_{22}O_2N_4$: N, 14.51%. Found: 14.75%.

The same product is obtained when the methyl-tolyl-pyrazolone is heated with orthoformic ester at 120°, thus showing the analogy in behavior of this class of compounds with both orthoformic ester and the formamidines.[1]

Another method of obtaining these derivatives is to heat an anilido-methylene-pyrazolone with an unsubstituted pyrazolone. Thus anilido-methylene-methyl-phenyl-pyrazolone and the methyl-phenyl-pyrazolone yield aniline and the bispyrazolone.

1-*o*-Tolyl-3-methyl-5-pyrazolone and the Formamidines.—Instead of simply fusing the components alone in an oil bath, in the following cases, it was found that better and cleaner yields of the amino-methylene derivatives were obtained when the substances were heated in a high boiling solvent such as xylene or kerosene. In this way the following were synthesized:

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[1] THIS JOURNAL, 31, 1153 (1909).

1-*o*-Tolyl-3-methyl-4-anilido-methylene-5-pyrazolone, reddish brown crystals from alcohol, which melt at 140°.

Calc. for $C_{18}H_{17}ON_3$: N, 14.43%. Found: 14.14%, 14.43%.

1-*o*-Tolyl-3-methyl-4-*m*-xylido-5-pyrazolone, yellow needles, melting point, 232°.

Calc. for $C_{20}H_{21}ON_3$: N, 13.09%. Found: 13.29%, 13.19%.

1-*o*-Tolyl-3-methyl-4-*o*-ethoxyanilido-methylene-5-pyrazolone, yellow crystals from alcohol which melt at 160°.

Calc. for $C_{20}H_{21}O_2N_3$: N, 12.53%. Found: 12.64%.

1-*o*-Tolyl-3-phenyl-5-pyrazolone, which was made from *o*-tolyl hydrazine and benzoyl-acetic ethyl ester, was found to react with the same ease with the substituted formamidines, a fact illustrated by the following preparations.

1-*o*-Tolyl-3-phenyl-4-anilido-methylene-5-pyrazolone, from the pyrazolone and di-phenyl formamidine in boiling xylene solution, crystallizes from alcohol in light yellow needles, which melt at 169°.

Calc. for $C_{23}H_{19}ON_3$: N, 11.90%. Found: 11.92%, 11.87%.

The same pyrazolone and di-*m*-xylyl formamidine gave 1-*o*-tolyl-3-phenyl-4-*m*-xylido-methylene-5-pyrazolone, yellow crystals also from alcohol, melting point 142°.

Calc. for $C_{25}H_{23}ON_3$: N, 11.02%. Found: 11.16%, 11.40%.

1-*o*-Tolyl-3-phenyl-4-*p*-chloroanilido-methylene-5-pyrazolone, yellow crystals which melt at 181°.

Calc. for $C_{23}H_{17}ON_3Cl$: N, 11.34%. Found: 11.05%, 11.12%.

Derivatives of 1-phenyl-3-methyl-5-pyrazolone. This reacts at water-bath temperature with di-*o*-ethoxyphenyl formamidine, yielding 1-phenyl-3-methyl-4-*o*-ethoxyanilido-methylene-5-pyrazolone, yellow needles which melt at 170°.

Calc. for $C_{19}H_{19}O_2N_3$: N, 13.09%. Found: 13.23%.

1-Phenyl-3-methyl-4-*m*-xylidomethylene-5-pyrazolone, golden yellow needles difficultly soluble in alcohol, melting at 173°.

Calc. for $C_{19}H_{19}ON_3$: N, 13.65%. Found: 13.63%, 13.77%.

It has been shown that not only do compounds with a methylene grouping react with the formamidines, but also that their aldehyde condensation products in some cases behave in a similar manner. Thus 4-benzal-3-methyl-isoxazolone unites with the formamidines yielding benzal aniline and the amino-methylene derivatives much more readily and smoothly than does the free methyl isoxazolone.[1]

This same fact holds true in the case of the aldehyde condensation products of the pyrazolones. When 4-benzal or anisal-1-phenyl-3-methyl-5-pyrazolone is heated with diphenyl formamidine,[2] there is ob-

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[1] Dains and Griffin, THIS JOURNAL, **35**, 962 (1913).

[2] *Ibid.*, **31**, 1153 (1909).

tained benzal aniline and 4-anilido-methylene-methyl-phenyl-pyrazolone, m. p. 154°.

$$C_{10}H_8ON_2 : CHC_6H_5 + C_6H_5N = CHNHC_6H_5 = C_{10}H_8ON_2CHNHC_6H_5 + C_6H_5CH : NC_6H_5.$$

Tambor[1] obtained from piperonal and methyl-phenyl-pyrazolone (equal mols), the red piperonal-methyl-phenyl-pyrazolone (m. p. 166–7°), while piperonal (one mol) and the pyrazolone (two mols) gave piperonal-di-(methyl-phenyl-pyrazolone), a white compound melting at 143°. Repeating this work it was found that the white piperonal-dipyrazolone has the higher melting point of 163°. This was heated with diphenyl formamidine with the hope of replacing the $C_6H_5N <$ rest with two pyrazolone groups. This aim was not realized, the reaction product yielding aniline, anilido-methylene-methyl-phenyl-pyrazolone (m. p. 154°) and the red piperonal pyrazolone. The white piperonal-dipyrazolone evidently dissociates into the simple pyrazolone and the red aldehyde condensation product.

The Action of the Amino-methylene-pyrazolones with Various Reagents. Hydrochloric Acid. — The amino-methylene derivatives are capable of forming hydrogen chloride addition products, stable in benzene, though decomposed by water. Thus dry HCl gas precipitates from a benzene solution of 1-phenyl-3-methyl-4-*m*-xylidomethylene-5-pyrazolone a white hydrochloride melting at 189–90°.

Calc. for $C_{19}H_{19}ON_3HCl$: HCl, 10.67%. Found: 10.73%.

In like manner, dry hydrogen chloride gas, when passed into a benzene solution of anilido-methylene-methyl-phenyl-pyrazolone, gave a white HCl addition product, melting and decomposing at 186°.

However, if the anilido compound is boiled in an alcoholic solution of hydrochloric acid, decomposition ensues with the formation of aniline and varying but small amounts of methenyl-bismethyl-phenyl-pyrazolone (m. p. 180°).

Similar results were obtained on hydrolysis with potassium hydroxide. For instance, 4-anilido-methylene-1-*o*-tolyl-3-phenyl-5-pyrazolone was heated for a few minutes with alcoholic potash. On examination the reaction mixture was found to contain aniline and a product which separated from gasoline in orange-yellow crystals, melting at 179°. This was identified as methenyl-4-4-bis-1-*o*-tolyl-3-phenyl-5-pyrazolone, which was also readily prepared by heating the pyrazolone (two mols) with ortho-formic ester (one mol) at 120°. It is difficultly soluble in alcohol.

Calc. for $C_{33}H_{26}O_2N_4$: N, 10.98%. Found: 11.00%, 11.20%.

The Action of Nitric Acid.—To a cooled solution of anilido-methylene-methyl-phenyl-pyrazolone in concentrated sulfuric acid, was added nitric

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[1] *Ber.*, 33, 869 (1900).

acid (one mol sp. gr. 1.42). The product obtained by pouring the mixture into cold water was practically insoluble in alcohol, chloroform or gasoline. It was purified by recrystallization from pyridine. From this solvent it separates in brownish yellow needles, which char between 255–265°. It is unaffected by boiling hydrochloric acid under ordinary conditions, but at 150° in a sealed tube some *p*-nitro-aniline was obtained. Analysis gave discordant figures, indicating that it was a mixture of nitro products in which both the phenyl group of the ring and the side chain were nitrated.

For comparison two derivatives were prepared with a nitro group in the side chain. Phenyl-methyl-pyrazolone condenses with di-*m*-nitro-diphenyl-formamidine in boiling kerosene solution yielding 1-phenyl-3-methyl-4-*m*-nitro-anilido-methylene-5-pyrazolone, yellow needles from alcohol melting at 175°.

Calc. for $C_{17}H_{14}O_3N_4$: N, 17.40%. Found: 17.23%.

The corresponding 1-phenyl-3-methyl-4-*p*-nitro-anilido-methylene-5-pyrazolone separates from alcohol in orange-yellow needles which melt at 170°.

Calc. for $C_{17}H_{14}O_3N_4$: N, 17.40%. Found: 17.63%.

The Action of Bromine.—The synthesis of the amino-methylene compounds by the action of aniline on ethoxy-methylene-aceto acetic ester and of the formamidines on the benzal derivatives of the isoxazolones and pyrazolones shows that they possess the constitution $>C = CHNHR$. At the same time, the mechanism of the reaction by which there is formed from them pyrazol and isoxazol compounds and their behavior with bromine prove that they also exist and react in the tautomeric form[1] $>CHCH = NR$. This latter form is capable of adding two atoms of bromine and this addition product under the influence of solvents may either lose its bromine entirely or may undergo rearrangement yielding a mono-bromo substitution product and hydrogen bromide. Thus the bromine derivatives of anilido-methylene-methyl-isoxazolone and of anilido-methylene-cyanacetic ester rearrange to the corresponding *p*-bromo-anilido compounds.[2] 4-Anilido-methylene-1-*o*-tolyl-3-phenyl-5-pyrazolone (one mol) was dissolved in glacial acetic acid and bromine (one mol) added. On standing a heavy yellow crystalline precipitate was formed. This was purified by washing with acetic acid and drying on a porous plate in a desiccator. It melted at 238°.

Calc. for $C_{23}H_{19}ON_3Br_2$: Br, 31.17%. Found: 31.05%, 31.58%.

When this dibromide is dissolved in alcohol it undergoes a change, and a new compound containing only one atom of bromine results. It melted at 143° and proved to be identical with the 4-*p*-bromoanilido-methylene-3-phenyl-1-*o*-tolyl-5-pyrazolone. This was also synthesized by heating

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[1] *Ann.*, **297**, 33 (1897); THIS JOURNAL, **31**, 1155 (1909); **35**, 962, 965 (1913).

[2] THIS JOURNAL, **35**, 963 (1913).

the pyrazolone and di-*p*-bromo-diphenyl formamidine in kerosene solution. It forms blunt yellow needles, easily soluble in alcohol, melting at 142–3°.

Calc. for $C_{23}H_{18}ON_3Br$: N, 9.73%. Found: 9.50%, 10.04%.

For the sake of comparison the corresponding 4-*m*-bromoanilido-methylene-3-phenyl-1-*o*-tolyl-5-pyrazolone was prepared from the pyrazolone and di-*m*-bromodiphenyl formamidine. This is a yellow crystalline compound, that melts at 148–50°, but is not identical with the product obtained from the dibromide.

A yellow dibromide is readily formed when bromine is added to a glacial acetic acid solution of 4-*o*-ethoxyanilido-methylene-1-phenyl-3-methyl-5-pyrazolone. It melts at 203°.

Calc. for $C_{19}H_{19}O_2N_3Br_2$: Br, 33.11%. Found: 32.89%, 32.84%.

When this dibromide is crystallized from alcohol, a product separates in orange-yellow needles, that is bromine-free and melts at 179°.

Calc. for $C_{21}H_{18}O_2N_4$: N, 15.64%. Found: 15.45%.

The nitrogen corresponds to that required for methenyl-bis-methyl-phenyl-pyrazolone and it was readily identified as that compound.

This unexpected result may be due to the action of hydrobromic acid in the alcohol solution on the anilido compound, since it has been shown earlier in the paper that hydrochloric acid may react with this type of derivatives giving the methenyl-bis-pyrazolones.

This same type of reaction occurred in another instance. Thus in the repetition of a previous experiment when 1-*o*-tolyl-3-phenyl-4-anilido-methylene-5-pyrazolone was dissolved in chloroform and bromine (one mol) added, no precipitate was formed but on evaporating the solvent a yellow bromine addition product was obtained that melted at 238°. When this was treated with alcohol and pyridine a bromine-free compound resulted, which proved to be methenyl-bis-1-*o*-tolyl-3-phenyl-5-pyrazolone (m. p. 181°) identical with the product obtained from *o*-formic ester and the pyrazolone.

1-*p*-Bromophenyl-3-phenyl-5-pyrazolone.—When benzoyl acetic ester and the bromophenyl hydrazine are dissolved in alcohol and warmed, there is formed the above pyrazolone. This crystallizes from alcohol in white needles melting at 154–5°.

Calc. for $C_{15}H_{11}ON_2Br$: Br, 25.39%. Found: 25.13%.

This compound shows the same general reactions as do the other pyrazolones with free methylene groups. Thus, heated at 120° with benzaldehyde, it yields a brilliant scarlet 4-benzal derivative, which is practically insoluble in the ordinary solvents but dissolves slightly in pyridine but does not melt at 265°.

Calc. for $C_{22}H_{15}ON_3Br$: Br, 19.85%. Found: 19.84%, 19.73%.

Heated in kerosene solution at 125°, the bromo-diphenyl pyrazolone and diphenyl-formamidine give aniline and 1-*p*-bromophenyl-3-phenyl-4-anilidomethylene-5-pyrazolone, which crystallizes from alcohol in fine, yellow needles, melting point 188°.

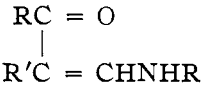
Calc. for $C_{22}H_{16}ON_3Br$: Br, 19.11%. Found: 19.44%.

The methenyl-bis-1-*p*-bromophenyl-3-phenyl-5-pyrazolone results from the interaction of orthoformic ester and the pyrazolone. It crystallizes in reddish yellow needles from pyridine in which it is difficultly soluble. In other solvents it is practically insoluble. It does not melt at 265°.

Calc. for $C_{31}H_{20}O_2N_4Br_2$: Br, 25.00%. Found: 24.87%.

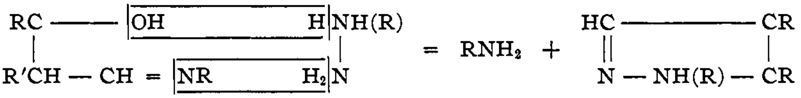
Pyrazole Synthesis.

It has been shown that anilido-methylene derivative of the type



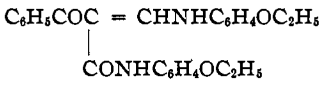
$$\begin{array}{l} RC = O \\ | \\ R'C = CHNHR \end{array}$$

react in their tautomeric forms with hydrazines yielding substituted pyrazoles as follows:[1]



Additional evidence for this reaction is afforded in the following experiments: *o*-Ethoxy-anilido-methylene-acetoacetic ester and phenyl hydrazine react at water-bath temperature yielding the ethyl ester of 1-phenyl-5-methyl-4-pyrazol-carboxylic ester.[2] The same anilido-methylene compound was heated in alcohol solution with hydrazine sulfate (with the addition of enough alkali to give the free hydrazine). The pyrazol ester first formed was saponified, since there was obtained an acid melting at 228°, evidently identical with the 4-methyl-pyrazol-3(5)-carboxylic acid described by Pechmann and Burkhard.[3] They give a melting point of 218–20°. However, this condensation with hydrazine alone is being further investigated.

The ethyl ester of benzoyl-acetic acid combines at water-bath temperature with di-*o*-phenetidyl-formamidine to form the *o*-ethoxyanilide of *o*-ethoxyanilido-methylene-benzoyl acetic acid.



$$\begin{array}{l} C_6H_5COC = CHNHC_6H_4OC_2H_5 \\ \quad\quad\quad\;\; | \\ \quad\quad\quad CONHC_6H_4OC_2H_5 \end{array}$$

The white crystals from alcohol melt at 173°.

Calc. for $C_{26}H_{26}O_4N_2$: N, 6.51%. Found: 6.91%.

When this anilide is heated with phenyl hydrazine at 120°, phenetidine

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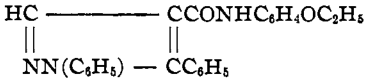
[1] THIS JOURNAL, **31**, 1153 (1909).

[2] Claisen, *Ann.*, **295**, 312 (1897).

[3] *Ber.*, **33**, 3593 (1900).

is eliminated and there is formed the *o*-ethoxyanilide of 1,5-diphenyl-4-pyrazol-carboxylic acid.



This separated from dilute alcohol in fine needles melting at 118°.

Calc. for $C_{24}H_{21}O_2N_3$: N, 10.97%. Found: 10.54%.

In the course of this investigation several compounds have been prepared, which will be briefly described, as they are not mentioned in the literature.

Di-*o*-phenetidyl formamidine and malonic ester at water-bath temperature gave a good yield of *o*-ethoxyanilido-methylene-diethyl-malonate, $C_2H_5OC_6H_4NHCH.C = (COOC_2H_5)_2$, long needles from 60% alcohol with a melting point of 66–7°.

Calc. for $C_{16}H_{21}O_5N$: N, 4.54%. Found: 4.63%.

1-*o*-Tolyl-3-methyl-4-monobromo-5-pyrazolone is formed when bromine (one mol) is added to a solution of the pyrazolone in glacial acetic acid. The yellow crystals from alcohol melt at 116°.

Calc. for $C_{11}H_{11}ON_2Br$: Br, 29.81%. Found: 30.13%, 29.99%.

1-*o*-Tolyl-3-phenyl-4-monobromo-5-pyrazolone, made in a like manner, crystallizes from alcohol in brownish yellow needles with a melting point of 110°.

Calc. for $C_{16}H_{13}ON_2Br$: Br, 24.29%. Found: 24.44%, 24.54%.

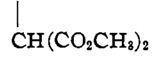
LAWRENCE, KANSAS.

THE REACTIONS OF SOME CARBOXYL DERIVATIVES OF TRIMETHYLENE.[1]

By Dorothy A. Hahn.

Received June 3, 1916.

The principal object of this investigation was the study of the products obtained by eliminating hydrobromic acid from bromine substitution products of the esters of anisoyl-phenyl-ethyl-malonic acid. These esters are easily obtained by adding the corresponding malonic esters to phenyl-anisyl-propenone:



$$C_6H_5CH = CH.COC_6H_4OCH_3 + CH_2(CO_2CH_3)_2 \longrightarrow \underset{\textstyle CH(CO_2CH_3)_2}{C_6H_5CHCH_2COC_6H_4OCH_3}$$

They contain one hydrogen atom that is very readily replaced by bromine; the resulting bromine substitution product may be either

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[1] Part of a dissertation presented to the Faculty of the Graduate School of Yale University, 1916, in candidacy for the degree of Doctor of Philosophy. The work, suggested by Prof. Elmer P. Kohler of Harvard, was done at Mount Holyoke College, and was accepted at Yale upon recommendation of Prof. Treat B. Johnson.