

point could not be changed by further recrystallization. The compound is soluble in boiling water, hot alcohol or boiling chloroform. but dissolves in ether with difficulty.

Found: N, 31.64. Calculated for $C_7H_7N_3$: N, 31.58.

DERIVATIVES OF CAMPHOROXALIC ACID. XIII.¹

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Received September 10, 1910.

In some of the earlier papers on this subject it has been pointed out that the condensation compounds of camphoroxalic acid and of its esters

with amines may be formulated either as C_8H_{14} $\begin{matrix} \diagup & C : CCO_2H \text{ (alkyl)} \\ & | \\ \diagdown & CO NHR \end{matrix}$, or

C_8H_{14} $\begin{matrix} \diagup & CHCCO_2H \text{ (alkyl)} \\ & | \\ \diagdown & CONR \end{matrix}$. The balance of evidence being in favor of

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the first of these formulas, it has been employed by the senior author and his colleagues in their publications.

The work described in the present communication had, for one of its objects, the accumulation of more direct positive proof of the constitution of the amino condensation compounds in question; we therefore directed our attention to the investigation of reactions which should show the presence of an imino $-NHR$, or hydroxyl $>C(OH)-$ group in the condensation compounds

Our first experiments were carried out with phenylcamphoformene-aminecarboxylic acid, C_8H_{14} $\begin{matrix} \diagup & C : CCO_2H \\ & | \\ \diagdown & CONHC_6H_5 \end{matrix}$; it is prepared very readily from

camphoroxalic acid and aniline, is easy to purify and is relatively stable. We obtained it by a slight modification of the method described by the senior author and A. Tingle.² The acid is attacked immediately by bromine, in chloroform solution; hydrobromic acid is evolved in quantity, 3,4-dibromoaniline hydrobromide is deposited in crystals and the solution contains camphoroxalic acid. The probable mechanism of this reaction appears to be the more simple on the assumption of the

¹ The previous communications of this series have appeared as follows: Bishop Tingle, *Inaug. Dissn.*, Munich, 1889, p. 34; *J. Chem. Soc.*, **57**, 652 (1890); *Am. Chem. J.*, **19**, 393 (1897); **20**, 318 (1898). Bishop Tingle and A. Tingle, *Ibid.*, **21**, 238 (1899); **23**, 214 (1900). Bishop Tingle, *THIS JOURNAL*, **23**, 363 (1901). Bishop Tingle and W. E. Hoffmann, *Amer. Chem. J.*, **34**, 217 (1905). Bishop Tingle and C. J. Robinson, *Ibid.*, **36**, 223 (1906). Bishop Tingle, *THIS JOURNAL*, **29**, 1242 (1907). Bishop Tingle and L. F. Williams, *Amer. Chem. J.*, **39**, 105, 277 (1908).

² *Loc. cit.*

first of the above formulas for phenylcamphoformeneaminecarboxylic acid, although it is by no means conclusive. The readiness with which the hydrogen atoms of the benzene nucleus undergo substitution is noteworthy.

Chromic anhydride, in acetone or in acetic anhydride solution, at the ordinary temperature, is without appreciable effect on phenylcamphoformeneaminecarboxylic acid, but potassium permanganate, dissolved in moist acetone, oxidizes it to camphorquinone. As camphoroxalic acid itself has been shown to suffer attack at the position of the double linkage, it is probable that this reaction follows a similar course, the molecule of the carboxylic acid suffering dissolution into the complexes

$C_8H_{14} \begin{array}{l} \diagup C < \\ | \\ \diagdown CO \end{array}$ and $>C(NHC_6H_5)CO_2H$, the former of which then yields the quinine.

The only product which could be obtained by the action of phosphorus trichloride on phenylcamphoformeneaminecarboxylic acid was camphoroxalic acid. Phosphorus pentachloride reacts like the trichloride, ultimately, therefore, the reaction may be expressed as one of simple hydrolysis of the CN linkage.

A considerable number of experiments were made, under varying conditions, on the interaction of methyl sulphate and phenylcamphoformeneaminecarboxylic acid. It was, of course, to be expected that a methyl group would replace the hydrogen of the carboxyl, so giving the methyl ester, but we hoped that, in addition, the hydrogen of the $-NHC_6H_5$ (formula I) might be substituted, thus giving the compound

$C_8H_{14} \begin{array}{l} \diagup C : CCO_2CH_3 \\ | \quad | \\ \diagdown CON \begin{array}{l} | \\ CH_3 \end{array} \end{array} \cdot$ This would afford direct evidence in favor of

the formula in question. Unfortunately, this double substitution could not be realized, the only product which we could obtain was *methyl phenyl-*

camphoformeneaminecarboxylate, $C_8H_{14} \begin{array}{l} \diagup C : CCO_2CH_3 \\ | \quad | \\ \diagdown CONHC_6H_5 \end{array}$. It is deposited in

yellow crystals, melting at 127° . Under the varied conditions of our experiments it does not react with methyl sulphate.

We failed to obtain any reaction between methyl sulphate and phenyl camphoformeneamine, $C_8H_{14} \begin{array}{l} \diagup C : CH \\ | \quad | \\ \diagdown CONHC_6H_5 \end{array}$. These results, apart from

other evidence, appear, therefore, to decide effectively against any formula such as $C_8H_{14} \begin{array}{l} \diagup C : C(OH)CO_2H \\ | \\ \diagdown C : NR \end{array}$, for the condensation products of camphoroxalic acid and amines.

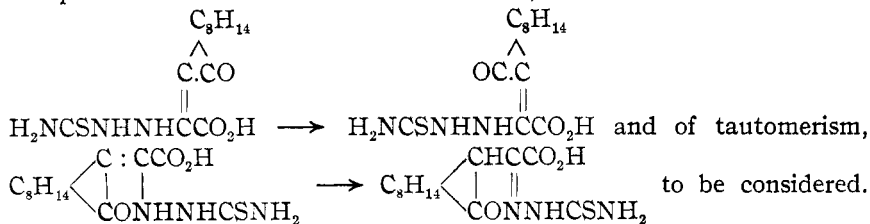
Methyl sulphate and camphoroxalic acid give the methyl ester. On one occasion, by the further action of the sulphate, this ester yielded a small quantity of what appears to be methyl methoxycamphoroxalate,

$$\text{C}_8\text{H}_{14} \begin{array}{c} \diagup \text{C} : \text{C}(\text{OCH}_3)\text{CO}_2\text{CH}_3 \\ | \\ \text{CO} \end{array} \diagdown$$
. Hitherto we have not succeeded in obtaining this substance in quantity sufficient for adequate study.

Attempts to obtain compounds from nitrous acid and phenyl camphoformeneaminecarboxylic acid, camphoroxalic acid, or its ethyl ester were unsuccessful. We employed sodium nitrite and also amyl nitrite, under varied conditions.

Camphoroxalic and thiosemicarbazine react readily in hot alcohol, more slowly at the ordinary temperature, to form *thiosemicarbazylcamphoformeneaminecarboxylic acid*, $\text{C}_8\text{H}_{14} \begin{array}{c} \diagup \text{C} : \text{CCO}_2\text{H} \\ | \\ \text{CONHNHCSNH}_2 \end{array} \diagdown$; in benzene,

the combination occurs much more slowly at the boiling point of the solution and is inappreciable at the ordinary temperature. The acid exists in two modifications which melt at $120-5^\circ$ and $148-9^\circ$, respectively. The lower melting form (A) is the more readily soluble in benzene, it is somewhat viscid and is produced by adding hydrochloric acid to an aqueous solution of the sodium salt of the carboxylic acid. It is also formed by recrystallizing the higher melting modification (B) from water. It changes slowly at the ordinary temperature, more rapidly when heated alone or with benzene, to the (B) form. A mixture of (A) and (B) melts at $140-5^\circ$. The modes of formation of (A) and (B) suggest that the former is an unstable hydrate of the latter. From the nature of the case it is impossible to determine this fact with certainty. There are also the possibilities of *cis*- and *trans*-isomerism,



Our chief object in preparing thiosemicarbazylcamphoformeneaminecarboxylic acid was to compare its behavior with the similar derivative of semicarbazine,¹ *i. e.*, to determine the effect of exchanging an oxygen for a sulphur atom. The contrast between the two compounds is most marked in the relative readiness with which they form closed chain derivatives. Whereas semicarbazylcamphoformeneaminecarboxylic acid,

¹ Bishop Tingle and Robinson, *Loc. cit.*

$\text{C}_8\text{H}_{14} \begin{array}{c} \diagup \text{C} : \text{CCO}_2\text{H} \\ | \quad | \\ \text{CONHNHCONH}_2 \end{array}$, undergoes further condensation without diffi-

culty, the thio derivative exhibits comparatively little tendency to change in this direction. When fused, a portion of the acid is recovered and the remainder is converted into resinous products. Absolute alcohol and dry hydrogen chloride give only *ethyl thiosemicarbazylcamphoformeneaminecarboxylate*, $\text{C}_8\text{H}_{14} \begin{array}{c} \diagup \text{C} : \text{CCO}_2\text{C}_2\text{H}_5 \\ | \quad | \\ \text{CONHNHCSNH}_2 \end{array}$, which is deposited from benzene

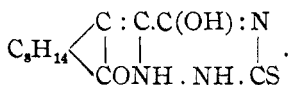
in white crystals, melting at $150-1^\circ$.

Thiosemicarbazylcamphoformeneaminecarboxylic acid is dehydrated by the action of acetic anhydride, quickly at about 100° , more slowly at the ordinary temperature. The yield is almost quantitative and the compound is deposited in bright red crystals, melting at $181-2^\circ$. When treated with a warm aqueous solution of potassium hydroxide or a boiling aqueous solution of sodium carbonate the parent acid is regenerated. These reactions make us inclined to regard the compound as being *thio-*

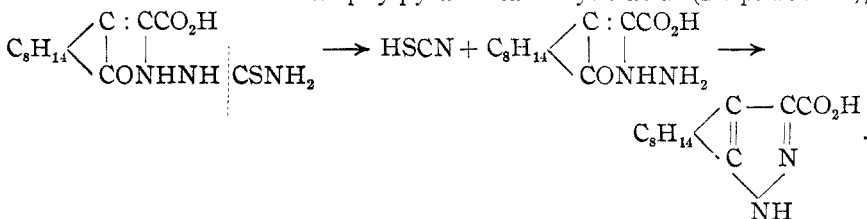
semicarbazylcamphoformeneaminecarboxylactimide, $\text{C}_8\text{H}_{14} \begin{array}{c} \diagup \text{C} : \text{C}-\text{CO}-\text{NH} \\ | \quad | \quad | \\ \text{CONH.NH.CS} \end{array}$,

its deep color, which appears to be characteristic of the compound itself and not due to traces of ferric thiocyanate, suggests that it probably

exists in a tautomeric form, such as $\text{C}_8\text{H}_{14} \begin{array}{c} \diagup \text{C} : \text{C}-\text{CO}-\text{N} \\ | \quad | \quad || \\ \text{CONH.NH.CSH} \end{array}$ or



Acetic anhydride, to which a few drops of conc. sulphuric acid have been added, hydrolyzes thiosemicarbazylcamphoformeneaminecarboxylic acid to thiocyanic acid, the presence of which was shown by means of a ferric salt, and aminocamphoformeneaminecarboxylic acid, which latter then condenses to camphylpyrazolecarboxylic acid (m. p. $261-2^\circ$),



The identity of this pyrazole derivative with that prepared from camphoroxalic acid and hydrazine, or semicarbazine by Bishop Tingle and Robinson,¹ was shown by direct comparison. Our acid melted at $261-2^\circ$,

¹ *Am. Chem. J.*, 36, 259.

whereas the melting point observed previously was 255–8°. The difference is undoubtedly due to variation in the rapidity of heating, because the carboxylic acid evolved carbon dioxide at a temperature below its melting point.¹

A slight modification of Bishop Tingle and Robinson's process for the preparation of camphylpyrazolecarboxylic acid is described in the experimental portion of this paper (vide p. 1511).

Only resinous products could be obtained by the action of concentrated sulphuric acid alone, at the ordinary temperature, on thiosemicarbazylcamphoformeneaminecarboxylic acid. We propose to make a further examination, under other experimental conditions, of the ability of this carboxylic acid to form cycloids containing sulphur.

In the hope of obtaining material suited for further investigation, we have examined the interaction of camphoroxalic acid with a number of amines. With 1,3,4-xylylidine it gives 1,3,4-xylylidyl-

camphoformeneaminecarboxylate, $C_8H_{14} \begin{array}{c} \diagup C : CCO_2NH_3C_6H_3(CH_3)_2 \\ | \\ CO \quad | \\ | \\ NHC_6H_3(CH_3)_2 \end{array}$, which

is deposited in brown crystals, melting at 93–4°. By the action of sodium carbonate, followed by hydrochloric acid, on this salt, 1,3,4-xylylidyl-

camphoformeneaminecarboxylic acid, $C_8H_{14} \begin{array}{c} \diagup C : CCO_2H \\ | \\ CO \quad | \\ | \\ NHC_6H_3(CH_3)_2 \end{array}$, is pro-

duced. The acid is deposited in yellow crystals, melting at 117–8°.

The third member of the series, the amine, $C_8H_{14} \begin{array}{c} \diagup C : CH \\ | \\ CO \quad | \\ | \\ NHC_6H_3(CH_3)_2 \end{array}$, is probably formed at a temperature above the melting point of the acid, but it could not be isolated in a crystalline condition.

Comparing these compounds with the corresponding derivatives of aniline, it is evident that they crystallize with greater difficulty and are, therefore, less suited for our projected investigations.

p-Chloroaniline and camphoroxalic acid combine readily to form *p*-chlorophenylcamphoformeneaminecarboxylic acid, $C_8H_{14} \begin{array}{c} \diagup C : CCO_2H \\ | \\ CO \quad | \\ | \\ NHC_6H_4Cl \end{array}$, which was obtained in yellow needles, melting at 182–3°. Its crystallizing power is considerable. With a larger proportion of *p*-chloroaniline it failed to form a *p*-chloroaniline salt, although possibly one could be obtained at a low temperature.

When camphoroxalic acid and *p*-chloroaniline are heated gradually up to 155–60°, without a solvent, carbon dioxide is evolved and *p*-chloro-

¹ *Loc cit.*

phenylcamphoformeneamine, $C_8H_{14} \begin{array}{c} \diagup C : CH \\ | \quad | \\ CO \quad NHC_6H_4Cl \end{array}$, is produced. It is

also formed by heating *p*-chlorophenylcamphoformeneaminecarboxylic acid above its melting point. The amine is deposited in white crystals, melting at $194-5^\circ$.

Dibenzylamine and camphoroxalic acid react quickly, in equimolecular proportion, to form an additive compound. It gives an intense reddish purple color with an alcoholic solution of ferric chloride and is resolved somewhat slowly into its constituents by the action of an aqueous solution of sodium carbonate, or by hydrochloric acid. In spite of the slowness of this decomposition, we regard the substance as being dibenzyl-

amine camphoroxalate, $C_8H_{14} \begin{array}{c} \diagup C : C(OH)CO_2NH_2(CH_2C_6H_5)_2 \\ | \\ CO \end{array}$, rather than

an acid condensation product such as $C_8H_{14} \begin{array}{c} \diagup C - C(OH)CO_2H \\ || \quad | \\ COHN(CH_2C_6H_5)_2 \end{array}$. See

Bishop Tingle and Williams.¹ The compound is deposited in white crystals, melting at $135-6^\circ$. It is also formed by the action of 2 molecular proportions of dibenzylamine on camphoroxalic acid.

When dibenzylamine camphoroxalate is heated with aniline (2 mols.) and benzene, under pressure, at 100° , it is converted into *dibenzylamine*

phenylcamphoformeneaminecarboxylate, $C_8H_{14} \begin{array}{c} \diagup C : CCO_2NH_2(CH_2C_6H_5)_2 \\ | \quad | \\ CO \quad NHC_6H_5 \end{array}$,

which was obtained in white crystals, melting at 185° . Its composition and nature is established both by its mode of formation and by the fact that it is decomposed into dibenzylamine and phenylcamphoformeneaminecarboxylic acid, when treated with dilute hydrochloric acid.

The dibenzylamine camphoroxalate described above, when fused for some time, gives the dibenzylcamphoformeneamine described by Bishop Tingle and Williams.² It is also produced when a mixture of camphoroxalic acid and dibenzylamine is heated at $135-40^\circ$. The use of 2 molecular proportions of dibenzylamine is without effect on the nature of the product.

m-Aminobenzoic acid and camphoroxalic acid form *m*-carboxyphenyl-*camphoformeneaminecarboxylic acid*, $C_8H_{14} \begin{array}{c} \diagup C : CCO_2H \\ | \quad | \\ CONHC_6H_4CO_2H \end{array}$; it is de-

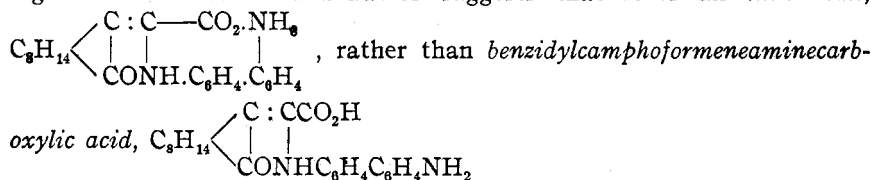
posited in white crystals, melting at $136-7^\circ$. This acid is hydrolyzed rather easily to its constituents; when heated at its melting point carbon

¹ *Am. Chem. J.*, 39, 113.

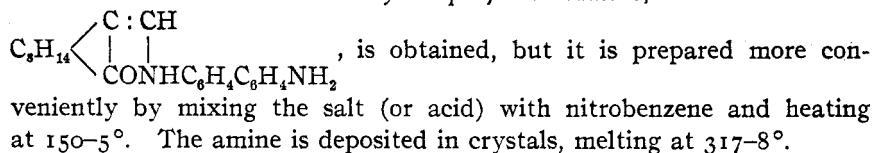
² *Ibid.*, 39, 117.

dioxide is evolved; the other product of the reaction consists of *m*-carboxy-phenylcamphoformeneamine, $C_8H_{14} \begin{array}{c} \diagup C:CH \\ | \\ CONHC_6H_4CO_2H \end{array}$. It is deposited in long yellow needles, melts at 116–7° and dissolves completely in a cold aqueous solution of sodium carbonate.

Bishop Tingle and Hoffman¹ described a condensation compound of benzidine and camphoroxalic acid which they found to melt at 190°. We have repeated this work, but have observed that better results are obtained, as regards the purity of the product, by the use of benzene as the solvent. Our condensation compound was obtained in yellow crystals, which melted at 208°. The melting point of the substance varies considerably with the rate of heating, but the identity of the two specimens was shown by their melting point when mixed. The compound is only slowly dissolved by boiling with aqueous solutions of potassium hydroxide, or of sodium carbonate and it is reprecipitated on acidifying the solutions. This behavior suggests that it is an *inner salt*,



When this salt (or acid) is heated at its melting point, water and carbon dioxide are evolved and *benzidylcamphoformeneamine*,



Camphylamine and camphoroxalic acid react readily, but the product is mostly resinous under the conditions which we employed. We succeeded, however, in isolating a white crystalline *compound*, which melted at 105°. It appears to be formed by the condensation of the constituents, because it dissolves readily in an aqueous solution of sodium carbonate, at the ordinary temperature, and gives no coloration with an alcoholic solution of ferric chloride. Its quantity was too small for further investigation.

Only resinous substances could be obtained from *p*-aminobenzaldehyde and camphoroxalic acid.

Experimental.

Preparation and Reactions of Phenylcamphoformeneaminecarboxylic

¹ *Am. Chem. J.*, 34, 231–50.

Acid, C_8H_{14} $\begin{cases} C : CCO_2H \\ | \quad | \\ CONHC_6H_5 \end{cases}$.—This compound was prepared according to

the directions of Bishop Tingle and A. Tingle,¹ from camphoroxalic acid and aniline, but instead of decomposing the resulting aniline phenylcamphoformeneaminecarboxylate with dilute hydrochloric acid, it was found to be more convenient to dissolve the salt in an aqueous solution of sodium carbonate and precipitate the acid by means of dilute hydrochloric acid. The yield is quantitative.

Action of Bromine on the Acid.—The bromine (4 atoms) was added gradually to phenylcamphoformeneaminecarboxylic acid, both substances being dissolved in dry chloroform. The solution was heated gently, hydrobromic acid was evolved immediately and white crystals soon deposited. These dissolve readily in alcohol or ethyl acetate, more sparingly in ether, acetone, or chloroform and they are insoluble in benzene. The purified material melts at 227–228°; it was identified as 3,4-dibromoaniline hydrobromide, $Br_2C_6H_3NH_2 \cdot HBr$.

Found: N, 4.30. Calculated: N, 4.22.

When mixed with water, the hydrobromide is dissociated into hydrobromic acid and 3,4-dibromoaniline, which crystallizes from the hot solvent in long needles, melting at 80–81°.

Found: C, 28.83; H, 2.07. Calculated: C, 28.46; H, 1.97.

The compound was identified further by the preparation of the acetyl derivative, melting at 127°. This latter was obtained by heating the 3,4-dibromoaniline at 150°, during 30 minutes, with anhydrous sodium acetate and acetic anhydride. The substance (m. p. 216°) described by Bishop Tingle and A. Tingle² as being formed from bromine and

phenylcamphoformeneamine, C_8H_{14} $\begin{cases} C : CH \\ | \quad | \\ CONHC_6H_5 \end{cases}$, is, doubtless, 3,4-di-

bromoaniline hydrobromide.

The chloroform filtrate obtained after the separation of the 3,4-dibromoaniline hydrobromide, as described above, contains camphoroxalic acid, amounting, in some experiments, to 50 per cent. of the theoretical quantity. It was separated by evaporating the chloroform and extracting the tarry residue with an aqueous solution of potassium hydroxide. No unchanged phenylcamphoformeneaminecarboxylic acid could be detected.

Oxidation Experiments.—Phenylcamphoformeneaminecarboxylic acid does not appear to be attacked by chromic anhydride, at the ordinary temperature, during several days. Experiments were made in which acetone and also acetic anhydride were employed as solvents. With

¹ *Am. Chem. J.*, **21**, 250.

² *Ibid.*, **21**, 248.

potassium permanganate, in moist acetone, a slow action takes place at the ordinary temperature. The permanganate solution was added gradually to the acid and the mixture allowed to remain during 24 hours, throughout which time the permanganate was in excess. During the evaporation of the acetone an odor of isocyanide was noticed; steam distillation of the tarry residue yielded camphorquinone, which was fully identified.

Action of Chlorides of Phosphorus on Phenylcamphoformeneaminecarboxylic Acid.—Phosphorus trichloride (2 mols.) and the acid were allowed to react at the ordinary temperature, during two days, in benzene which had been dried over sodium wire. After removal of the solvent a tarry material was obtained. It was extracted with an aqueous solution of sodium carbonate and then with one of potassium hydroxide. The undissolved residue was viscous and no crystals could be isolated from it. The alkaline solutions yielded camphoroxalic acid.

The action of phosphorus pentachloride appears to be exactly similar to that of the trichloride.

Action of Methyl Sulphate on Phenylcamphoformeneaminecarboxylic Acid.—The acid was dissolved in the calculated quantity of an aqueous solution of potassium hydroxide, and methyl sulphate (2.5 mols.) was added, while shaking, potassium hydroxide solution being run in at intervals so as to keep the mixture alkaline. An oil soon separates and after a time solidifies; it proved to be methyl phenylcamphoformeneamine-

carboxylate, $C_8H_{14} \begin{matrix} \diagup C : CCO_2CH_3 \\ | \\ CONHC_6H_5 \end{matrix}$. This ester dissolves without difficulty in acetone, ethyl alcohol, ethyl acetate, or benzene and is deposited from hot methyl alcohol, or ligroin in somewhat yellow crystals, melting at 127° .

Found: C, 72.14; H, 7.23. Calculated: C, 72.84; H, 7.35.

The ester is hydrolyzed rather slowly to the parent acid by boiling it with an aqueous solution of potassium hydroxide.

Methyl sulphate (1.1 mols.) reacts immediately, at the room temperature, with dry sodium phenylcamphoformeneaminecarboxylate (1 mol.) and sodium hydrogen carbonate (1 mol.). The product consists of the methyl ester described above; it was extracted by means of benzene.

A number of other experiments were carried out in which the conditions of temperature, etc., and of the relative proportions of acid and methyl sulphate were varied within somewhat wide limits, the object being to attack the NHC_6H_5 or the $:COH$ group of the parent acid (see pp. 1500). In each case the only product which could be isolated was the ester described above.

A further effort in the same direction was made by heating at 140° ,

methyl phenylcamphoformeneaminecarboxylate (1 mol.) and dry potassium carbonate (1.5 mols.) and adding methyl sulphate (1.5 mols.). The mixture darkened immediately; ligroin extracted from it a quantity of unchanged methyl ester and left a black powder which melted above 270° .

No reaction appears to take place between phenylcamphoformeneamine, $\text{C}_8\text{H}_{14} \begin{array}{c} \diagup \text{C:CH} \\ | \\ \text{CONHC}_6\text{H}_5 \end{array}$, and methyl sulphate, at 100° , in presence of dry sodium carbonate.

EXPERIMENTS WITH CAMPHOROXALIC ACID.—*Action of Methyl Sulphate.*—The acid was dissolved in a warm, aqueous solution of potassium hydroxide (1 mol.), and methyl sulphate and an aqueous solution of potassium hydroxide were added gradually and alternately, while shaking. An oil soon separates and finally solidifies. It consists of methyl camphoroxalate, $\text{C}_8\text{H}_{14} \begin{array}{c} \diagup \text{C:C(OH)CO}_2\text{CH}_3 \\ | \\ \text{CO} \end{array}$.¹ The same product was also

formed by heating dry sodium camphoroxalate, methyl sulphate and sodium hydrogen carbonate, in benzene, during one hour.

Methyl camphoroxalate, methyl sulphate and dry sodium carbonate, at $150\text{--}80^{\circ}$, gave a small quantity of an oil which was extracted by means of ether. The oil produced no coloration with alcohol and a solution of ferric chloride. It was treated with an alcoholic solution of potassium hydroxide, at the ordinary temperature, and the residue acidified. Ligroin extracted from the product an oil which gave a deep red coloration with ferric chloride and alcohol. These results indicate that the first oily material was *methyl methoxycamphoroxalate*,

$\text{C}_8\text{H}_{14} \begin{array}{c} \diagup \text{C:C(OCH}_3\text{)CO}_2\text{CH}_3 \\ | \\ \text{CO} \end{array}$.² Further experiments not only failed to

improve the yield of this substance, but showed that its formation apparently depended on conditions which are rather difficult to duplicate, consequently the matter was not pursued further.

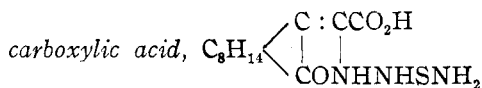
Nitrous acid, from sodium nitrite, or amyl nitrite, failed to react with phenylcamphoformeneaminecarboxylic acid, or with camphoroxalic acid and ethyl camphoroxalate. The experiments were made under varied conditions as to solvents and at temperatures ranging from -5° to that of the room.

Camphoroxalic Acid and Thiosemicarbazine.—The acid (2.25 g.) and the amine (0.91 g.) were mixed in alcoholic (95%) solution (30 cc.) and the liquid boiled in a reflux apparatus, during about 20 minutes, until a

¹ *Am. Chem. J.*, 20, 334.

² Cf. Bishop Tingle, *THIS JOURNAL*, 23, 390.

drop of it failed to give any color with ferric chloride. The reaction also proceeds slowly at the ordinary temperature, in presence of alcohol. A solution similar in concentration to that described above, gave a slight color with ferric chloride after 35 days, but no color was developed after 53 days. In benzene the reaction does not take place to any appreciable extent after 2 months at the ordinary temperature, but it proceeds slowly when heated on a boiling water bath. In all cases the product was viscous; it was purified by dissolving in a cold, aqueous solution of sodium carbonate, adding hydrochloric acid in excess and allowing the precipitate to remain over night in contact with the mother liquor. The solid material was then washed with water, dried and recrystallized from benzene. It is deposited in white flakes, melting at $148-9^{\circ}$. Analysis indicates that the substance is *thiosemicarbazylcamphoformeneamine-*



Found: N, 14.16. Calculated: N, 14.14.

The yield is quantitative.

A study of the carboxylic acid shows that it exists in two modifications. The crystals (m. p. $148-9^{\circ}$) dissolve readily in a cold, aqueous solution of sodium carbonate. On adding dilute hydrochloric acid to this solution a sticky precipitate is deposited which is soluble in excess of the mineral acid. The precipitate hardens on standing and then melts at about $120-5^{\circ}$. This lower melting material dissolves readily in warm benzene, 100 cc. of which, at the boiling point, dissolve about 20 g. of the acid. After a short time crystals appear in the boiling liquid; these melt at $148-9^{\circ}$ (the original melting point) and require more than 20 parts of boiling benzene for solution. The lower melting material (m. p. $120-5^{\circ}$) when heated on the water bath for a few hours, or if allowed to remain at the ordinary temperature during several days, shows a rise in melting point to $135-40^{\circ}$ and a diminished solubility in benzene. A mixture of approximately equal quantities of the lower (m. p. $120-5^{\circ}$) and of the higher (m. p. $148-9^{\circ}$) melting varieties melts at $140-5^{\circ}$. The higher melting form dissolves readily in warm water and is deposited in the lower melting modification. Both forms are soluble without difficulty in ethyl acetate, acetone, alcohol (95%), ether and chloroform.

The carboxylic acid gives a slight greenish tint with alcohol and ferric chloride, the color disappears on adding ether. When a small crystal of the acid is placed on moist iron a red color is produced, doubtless due to the formation of a little ferric thiocyanate. No coloration was observed, under similar conditions, with metallic lead, zinc, or copper.

Fusion of the carboxylic acid leads to the production of resinous mat-

ter; in addition, a *compound* was formed which begins to melt at about 170° . Its quantity was too small to permit of its purification.

Ethyl thiosemicarbazylcamphoformeneaminecarboxylate,

$\text{C}_8\text{H}_{14} \begin{array}{l} \diagup \text{C} : \text{CCO}_2\text{C}_2\text{H}_5 \\ | \\ \diagdown \text{CCNHNHCSNH}_2 \end{array}$, is prepared by dissolving the carboxylic acid in

a small quantity of absolute alcohol and passing dry hydrogen chloride into the solution. The ester is deposited either by exposing the liquid to air, or by allowing it to remain overnight in a closed vessel. It forms white crystals from benzene and melts at $150-1^{\circ}$. Its distinction from the parent acid (m. p. $148-9^{\circ}$) was shown by a mixed melting point and also by the insolubility of the ester in an aqueous solution of sodium carbonate. In a warm aqueous solution of potassium hydroxide it dissolves slowly.

Found: C, 55.23; H, 7.18. Calculated: C, 55.38; H, 7.07.

Under certain conditions, which were not specifically determined, a small quantity of a white material is also formed together with the ester. It dissolves readily in cold water, melts above 300° and contains ionizable chlorine. Quite possibly it is ammonium chloride.

Action of Acetic Anhydride on Thiosemicarbazylcamphoformeneaminecarboxylic Acid.—The acid (1 g.) was heated on a boiling water bath, during 5 minutes, with acetic anhydride (5 cc.). A deep red solution was obtained, from which a resinous material separated when the liquid was poured into water (100 cc.). The solid was washed several times with water, then dried and recrystallized from glacial acetic acid; it is deposited in bright red crystals, melting at $181-2^{\circ}$. The compound is obtained in quantitative yield by dissolving the carboxylic acid in a little acetic anhydride and allowing the solution to remain at the room temperature until the anhydride and acetic acid have evaporated. This red compound is *thiosemicarbazylcamphoformeneaminecarboxylactimide*,

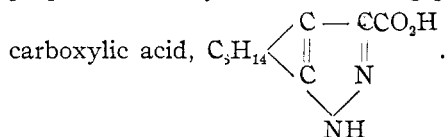
$\text{C}_8\text{H}_{14} \begin{array}{l} \diagup \text{C} : \text{C}-\text{CO}-\text{NH} \\ | \quad | \quad | \\ \diagdown \text{CONH.NH.CS} \end{array}$; it dissolves readily in benzene, ligroin, alcohol,

glacial acetic acid and also in a warm aqueous solution of potassium hydroxide; in a boiling aqueous solution of sodium carbonate dissolution takes place more slowly; when acidified each of these alkali solutions deposits the original carboxylic acid, m. p. $148-9^{\circ}$.

Found: C, 55.61; H, 6.14. Calculated: C, 55.91; H, 6.09.

Action of Acetic Anhydride and Concentrated Sulphuric Acid on Thiosemicarbazylcamphoformeneaminecarboxylic Acid.—The carboxylic acid (1 g.) was mixed with acetic anhydride (1.5 cc.), well shaken and concentrated sulphuric acid (3 drops) added. Heat is generated and a light brown solution is formed. After remaining during 15-20 minutes it

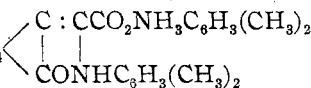
was poured into water; a viscid solid is deposited which was washed with water, then with a dilute aqueous solution of sodium carbonate and finally purified by recrystallization from ethyl acetate. The crystals obtained in this manner melted at $261-2^{\circ}$ and were shown, by analysis, by their properties and by a mixed melting point, to consist of camphylpyrazole-



The material for comparison was prepared by a slight modification of the method of Bishop Tingle and Robinson.¹ Semicarbazylcamphoformeneaminecarboxylic acid was fused; the resulting product was finely divided and mixed with a cold, dilute aqueous solution of sodium hydrogen carbonate. The resinous material fails to dissolve, but the carboxylic acid slowly passes into solution and is reprecipitated by dilute hydrochloric acid.

The aqueous filtrate, obtained after the removal of the pyrazolecarboxylic acid which was prepared from the thiosemicarbazyl derivative, was tested with a ferric salt and was shown to contain thiocyanic acid.

Action of Concentrated Sulphuric Acid on Thiosemicarbazylcamphoformeneaminecarboxylic Acid.—A little of the carboxylic acid was ground to a paste with conc. sulphuric acid, and a solution, which was formed in the course of a few minutes, was allowed to remain during 3 days in an atmosphere dried by means of sulphuric acid. At the end of this period it was diluted with water; a precipitate was produced which consisted of unchanged carboxylic acid and a resin. From this no crystals could be separated.

Action of 1,3,4-Xylidine on Camphoroxalic Acid.—The acid (1 mol.) and the amine (2 mols.) were warmed together in benzene solution, during 10 minutes; after cooling, the liquid deposits a jelly-like material which was drained and dissolved in ligroin (b. p. below 90°). When the ligroin solution is allowed to evaporate moderately quickly, at the ordinary temperature, it deposits only a tarry substance, but if the liquid is placed in a small covered beaker and allowed to remain during 3 or 4 days, brown crystals of 1,3,4-xylidine 1,3,4-xylidylcamphoformeneaminecarboxylate, C_8H_{14} , are deposited. The salt melts

at $93-4^{\circ}$ and dissolves readily in benzene, ligroin, acetone, ether, ethyl alcohol, chloroform, or ethyl acetate. An aqueous solution of potassium hydroxide decomposes the salt into an oil (1,3,4-xylidine) and the acid,

¹ *Am. Chem. J.*, 36, 259.

which, however, is prepared more conveniently in the manner described below.

Found: N, 6.49. Calculated: N, 6.25 per cent.

1,3,4-Xylidylcamphoformeneaminecarboxylic acid,

$\text{C}_8\text{H}_{14} \begin{array}{l} \diagup \text{C} : \text{CCO}_2\text{H} \\ | \quad | \\ | \quad | \\ \diagdown \text{CONHC}_6\text{H}_3(\text{CH}_3)_2 \end{array}$, is obtained from the salt mentioned above,

but is produced more readily by dissolving equimolecular proportions of camphoroxalic acid and 1,3,4-xylidine in benzene and warming the solution until a drop of it fails to produce a red color with alcohol and ferric chloride. The warming is continued while the liquid is well stirred with an aqueous solution of sodium carbonate; the two liquid layers are ultimately separated and the aqueous portion is acidified with dilute hydrochloric acid. The resulting sticky precipitate is purified by slow crystallization from low boiling ligroin. In this manner we obtained yellow crystals, melting at $117-8^\circ$. The acid dissolves readily in benzene, ligroin, ether, ethyl alcohol, acetone, chloroform, or ethyl acetate and also in an aqueous solution of sodium carbonate, from which mineral acids always precipitate it in a resinous condition. It gives no coloration with an alcoholic solution of ferric chloride.

Found: N, 4.41. Calculated: N, 4.28 per cent.

At 130° , a mixture of camphoroxalic acid and 1,3,4-xylidine evolves water and carbon dioxide; the product gave no coloration with an alcoholic solution of ferric chloride and it doubtless contained the compound

$\text{C}_8\text{H}_{14} \begin{array}{l} \diagup \text{C} : \text{CH} \\ | \quad | \\ | \quad | \\ \diagdown \text{CONHC}_6\text{H}_3(\text{CH}_3)_2 \end{array}$, but no crystals could be isolated.

p-Chloroaniline and Camphoroxalic Acid.—When equimolecular proportions of these two substances are dissolved in benzene and heated during five minutes, crystals soon appear. They were purified by recrystallization from benzene, being deposited in yellow needles, melting at $182-3^\circ$. The compound consists of *p*-chlorophenylcamphoformene-

aminecarboxylic acid, $\text{C}_8\text{H}_{14} \begin{array}{l} \diagup \text{C} : \text{CCO}_2\text{H} \\ | \quad | \\ | \quad | \\ \diagdown \text{CONHC}_6\text{H}_4\text{Cl} \end{array}$. This acid, and not the

p-chloroaniline salt, is also formed when camphoroxalic acid and *p*-chloroaniline are brought together in the ratio of 1:2 mols. The acid dissolves readily in benzene, ether, ethyl alcohol, acetone, or ethyl acetate. In ligroin the solubility is smaller. At the ordinary temperature, it dissolves easily in an aqueous solution of sodium carbonate and is reprecipitated by hydrochloric acid. The carboxylic acid gives no coloration with an alcoholic solution of ferric chloride.

Found: N, 4.29. Calculated: N, 4.20 per cent.

Camphoroxalic acid and *p*-chloroaniline were ground together in equimolecular proportion and the mixture heated slowly by means of an oil-bath. At 65–70° the material melts; water is evolved at about 110° and the product then solidifies. It undoubtedly consists of the carboxylic acid, because it dissolves without difficulty, at the ordinary temperature, in an aqueous solution of sodium carbonate and it gives no coloration with an alcoholic solution of ferric chloride. As the heating is continued the material melts again at about 155° and evolves carbon dioxide. The temperature was maintained at 155–60° during 20 minutes, then allowed to fall to 110°, ligroin (b. p. 110–20°) was now poured onto the fused material and the mixture was shaken vigorously. Working in this manner, crystals were obtained immediately and were not seriously contaminated with resinous material. The compound consisted of

p-chlorophenylcamphoformeneamine, $C_8H_{14} \begin{array}{c} \diagup C : CH \\ | \quad | \\ CONHC_6H_4Cl \end{array}$; it is deposited

from acetone, on the addition of ligroin, in white crystals, melting at 194–5°. Yield, 61 per cent. of the calculated quantity. The compound dissolves readily in acetone, ether, ethyl acetate, alcohol, or chloroform, but it is less soluble in ligroin. It gives no coloration with an alcoholic solution of ferric chloride and is not changed by boiling with an aqueous solution of potassium hydroxide, or of hydrochloric acid. The same amine may also be obtained by heating *p*-chlorophenylcamphoformeneaminocarboxylic acid (see above), until carbon dioxide ceases to be evolved.

Found: N, 4.69. Calculated: N, 4.83 per cent.

Dibenzylamine and Camphoroxalic Acid.—Equimolecular proportions of dibenzylamine and camphoroxalic acid were dissolved in benzene and heated during 15 minutes. After remaining, at the ordinary temperature during 2 hours, the liquid deposits a white, crystalline precipitate. It was washed with more benzene and dried and then melted at 135–6°. This melting point was lowered rather than raised by recrystallizing the substance. The same compound is obtained by the use of 2 molecular proportions of dibenzylamine. The compound dissolves readily in benzene, ethyl acetate, alcohol, acetone, ether, or chloroform. When warmed with dilute hydrochloric acid the substance is resolved into camphoroxalic acid and dibenzylamine and a similar decomposition is produced by an aqueous solution of sodium carbonate, slowly at the ordinary temperature, more rapidly when heated. The dibenzylamine produced in this way was identified by means of its hydrochloride. The analytical results given below show that the substance is formed by the direct addition of dibenzylamine to camphoroxalic acid, without the elimination of water. It gives a deep reddish purple coloration with an alcoholic solution of ferric chloride. These facts and the

reactions described below lead us to regard the substance as *dibenzylamine camphoroxalate*, C_8H_{14} $\left\langle \begin{array}{l} C:C(OH)CO_2NH_2(CH_2C_6H_5)_2 \\ | \\ CO \end{array} \right.$

Found: N, 3.34. Calculated: N, 3.32 per cent.

The above dibenzylamine camphoroxalate was dissolved in benzene, aniline (2 mols.) added and the mixture heated at 100° , during 5 hours, in a sealed tube. After evaporation of the benzene, white crystals are deposited, they were washed with alcohol and, after being dried, melted at 185° .

The compound dissolves very readily in benzene, more sparingly in alcohol. When treated with an aqueous solution of sodium carbonate it is resolved into dibenzylamine and phenylcamphoformeneaminecarboxylic acid (m. p. 172°). The amine was identified by the preparation of its hydrochloride (m. p. 256°) and the acid by a mixed melting point determination. These results show that the compound in question (m. p. 185°) is *dibenzylamine phenylcamphoformeneaminecarboxylate*,

C_8H_{14} $\left\langle \begin{array}{l} C:CCO_2NH_2(CH_2C_6H_5)_2 \\ | \\ CONHC_6H_5 \end{array} \right.$. The quantity of substance at our disposal was insufficient for an analysis.

A mixture of camphoroxalic acid and dibenzylamine, in equimolecular proportion, when heated, melts about 85° ; it then becomes solid again and remelts about 125° . It was maintained at $135-40^\circ$, during 30 minutes. On cooling crystals are formed, they were washed with ligroin, and recrystallized from acetone. The compound melts at 152° ; it is not changed by boiling with aqueous solutions of potassium hydroxide or of hydrochloric acid. Analysis shows that it is the dibenzylcampho-

formeneamine, C_8H_{14} $\left\langle \begin{array}{l} C:CH \\ | \\ CON(CH_2C_6H_5)_2 \end{array} \right.$, described by Bishop Tingle

and Williams.¹ The yield is 75 per cent. of the calculated quantity. This substance is one of the most easily obtainable of its class and is well adapted for further study. The same amine is also formed by fusing either dibenzylamine camphoroxalate (see above), or a mixture of camphoroxalic acid (1 mol.) and dibenzylamine (2 mols.).

m-Aminobenzoic Acid and Camphoroxalic Acid.—Equimolecular alcoholic solutions of these substances were mixed and boiled during 5 minutes; after standing overnight a white solid separates, which is ultimately obtained in white crystals; melting at $136-7^\circ$; the melting point varies somewhat, according to the rapidity of the heating. The same compound is produced by the use of 2 molecular proportions of *m*-aminobenzoic acid. The substance consists of *m*-carboxyphenylcamphoformene-

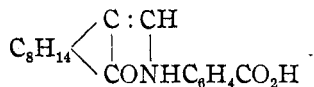
¹ *Am. Chem. J.*, 39, 117.

aminecarboxylic acid, $\text{C}_8\text{H}_{14} \begin{array}{l} \diagup \text{C} : \text{CCO}_2\text{H} \\ | \quad | \\ | \quad | \\ \diagdown \text{CONHC}_6\text{H}_4\text{CO}_2\text{H} \end{array}$; it dissolves readily in

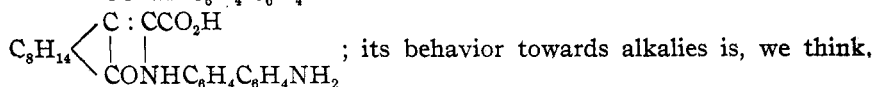
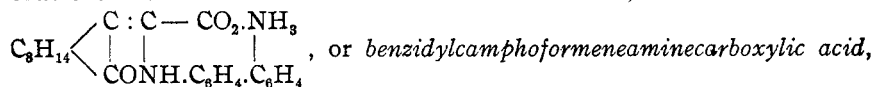
alcohol, ethyl acetate, or water, forming, in each case, a yellow solution. Rapid cooling, or quick evaporation of its solution causes the acid to be deposited in a gummy condition, but if the deposition takes place slowly crystals are produced. When dissolved in alcohol (95 per cent.) the acid gives no coloration with ferric chloride, but in water, or in 50 per cent. alcohol a portion of it is hydrolyzed to camphoroxalic acid, as is shown by its reaction with ferric chloride. A similar hydrolysis is produced by an aqueous solution of sodium carbonate, in which the dicarboxylic acid dissolves and liberates carbon dioxide; when acidified this solution reprecipitates the dicarboxylic acid in an impure condition.

Found: N, 4.37. Calculated: N, 4.08 per cent.

The above dicarboxylic acid evolves carbon dioxide when heated at its melting point; the residue is deposited from benzene in long, yellow needles, melting at $116-7^\circ$. It dissolves completely in a cold, aqueous solution of sodium carbonate, is reprecipitated by dilute hydrochloric acid and gives no coloration with an alcoholic solution of ferric chloride. These properties indicate that the compound is *m*-carboxyphenylcamphoformeneamine,



Benzidine and Camphoroxalic Acid.—When equimolecular benzene solutions of these substances are mixed and warmed for a short time, yellow crystals are soon deposited. After recrystallization, the compound melts at about 208° , depending somewhat on the rapidity with which the temperature is raised. The substance is only slightly soluble in alcohol, or ethyl acetate, it gives no color with an alcoholic solution of ferric chloride and dissolves only slowly in a boiling aqueous solution of potassium hydroxide, or of sodium carbonate. After remaining overnight, these clear alkaline solutions deposit a slimy material. If this is removed and the liquid acidified with hydrochloric acid the original compound is reprecipitated. Boiling, concentrated hydrochloric acid slowly hydrolyzes the compound to its constituents. Analysis shows that the substance is either an inner ammonium salt,



in better accord with the salt formula.

Found: N, 6.98. Calculated: N, 7.18 per cent.

The melting point (208°) which we observed for the above compound is 18° higher than that recorded by Bishop Tingle and Hoffman¹ for a substance which they obtained from benzidine and camphoroxalic acid, in alcoholic solution. A repetition of their work shows that the two compounds are identical, except for the fact that ours is more nearly pure. A mixture of the two substances melts at the same temperature as either one alone. The difference in the melting point is due partly to this greater degree of purity and partly to the rather large variation which is produced in the melting, or more accurately, the decomposing point, by a difference in the rate at which the temperature is caused to rise. That some of the compounds of this series are extremely sensitive in this respect has been pointed out previously by Bishop Tingle and Robinson.²

Benzidylcamphoformeneamine, C_8H_{14} $\begin{array}{l} \diagup \text{C} : \text{CH} \\ | \\ \text{CONHC}_6\text{H}_4\text{C}_6\text{H}_4\text{NH}_2 \end{array}$, is formed

by direct fusion of the preceding compound, but is best prepared by grinding a quantity of it with 5 parts of nitrobenzene, the mixture being then slowly heated on an oil bath. At about 135° a clear red solution is obtained; at 150° water and carbon dioxide are evolved. The temperature was maintained at $150-5^{\circ}$ during 15 minutes and the solution then filtered and allowed to cool. The crystals which separated were collected, washed with benzene by means of a centrifuge and, finally, they were boiled with alcoholic potassium hydroxide. The purified material melts at $317-8^{\circ}$; it is not attacked by boiling with concentrated aqueous solutions of potassium hydroxide, or of hydrochloric acid. The analytical results given below and the method by which the compound is formed can leave no doubt as to its nature, but concordant data could not be obtained for its nitrogen content; the gas is evolved very slowly during the course of the combustion and some of it is evidently occluded in the filling material of the combustion tube. See K. Holdermann and R. Scholl.³

Found: C, 79.00; H, 7.79. Calculated: C, 79.77; H, 7.54.

Camphylamine and Camphoroxalic Acid.—A well-marked evolution of heat takes place when these substances are mixed, in benzene solution; the residue, obtained after evaporating the solvent, is evidently a condensation product, because it fails to give any coloration with an alcoholic solution of ferric chloride, but we were unable to obtain the substance in a crystalline condition. When camphoroxalic acid is heated at $150-5^{\circ}$, with 2 molecular proportions of camphylamine, most of the product is also tarry, but a while, crystalline *sublimate* is obtained in

¹ *Am. Chem. J.*, **34**, 231, 250.

² *Ibid.*, **36**, 229.

³ *Ber.*, **43**, 342.

small quantity. It melts at 105°, dissolves readily in alcohol and also in an aqueous solution of sodium carbonate, at the ordinary temperature. It gives no coloration with an alcoholic solution of ferric chloride.

No definite compound could be isolated from the reaction products of *p*-aminobenzaldehyde and camphoroxalic acid, at 125–30°.

Some further experiments which have been made with acetylphenylhydrazine and camphoroxalic acid have failed to improve the yield of the condensation compound described by Bishop Tingle and Williams.¹

Summary.

(1) We have studied the action of bromine, of the chlorides of phosphorus, of various oxidizing agents, of nitrous acid and of dimethyl sulphate on certain of the condensation compounds of camphoroxalic acid and amines, in order to obtain further data in respect to their constitution.

(2) The results which we have obtained are in accord with the formula, $C_8H_{14} \begin{array}{c} \diagup C : CR \\ | \quad | \\ | \quad | \\ \diagdown CONR_1R_2 \end{array}$, (R = H or CO₂H; R₁ and R₂ = H, alkyl or aryl), which has been previously assigned to these condensation compounds by the senior author and his colleagues.

(3) The interaction of thiosemicarbazine and camphoroxalic acid has been studied in order to compare the resulting compounds with those derived from semicarbazine. The replacement of CO (semicarbazine) by CS (thiosemicarbazine) greatly reduces the tendency of the primary condensation compounds to form cyclic derivatives.

(4) A considerable number of new condensation compounds have been prepared from camphoroxalic acid and the following amines: 1,3,4-xylidine, *p*-chloroaniline, dibenzylamine, *m*-aminobenzoic acid, benzidine and camphylamine. Some of these new substances are well adapted for further study. No crystalline compound could be obtained from camphoroxalic acid and *p*-aminobenzaldehyde.

The investigation will be continued in various directions.

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THE DEVIATION OF FERMENT ACTION FROM THE MONO-
MOLECULAR LAW WITH ESPECIAL REFERENCE
TO THE ESTERASES.

BY GEORGE PEIRCE.

Received July 28, 1910.

During the course of an investigation into the effect of the fluorides on the action of lipase, it became necessary to study the kinetics of the

¹ *Am. Chem. J.*, 39, 120.