

STRAITHMORE PARCHEME
100% RAB U.S.A.

SYNTHESIS OF DERIVATIVES OF
BIPHENYL, DIPHENYLMETHANE AND BIBENZYL
WITH POSSIBLE ESTROGENIC ACTIVITY

PARCHEMENT
U.S.A.

SYNTHESIS OF DERIVATIVES OF
BIPHENYL, DIPHENYLMETHANE AND BIBENZYL
WITH POSSIBLE ESTROGENIC ACTIVITY

by

CAROLYN MAE ELLIS

Bachelor of Science

East Central State College

Ada, Oklahoma

1945

Submitted to the Department of Chemistry
Oklahoma Agricultural and Mechanical College
In Partial Fulfillment of the Requirements
for the Degree of
MASTER OF SCIENCE

1948

OKLAHOMA
AGRICULTURAL & MECHANICAL COLLEGE
LIBRARY
AUG 24 1949

APPROVED BY:

Ernest M. Woodruff
Chairman, Thesis Committee

O. Dermer
Member of the Thesis Committee

Otto M. Smith
Head of the Department

D. C. McGee
Dean of the Graduate School

ACKNOWLEDGMENT

The author wishes to express her appreciation to Dr. E. M. Hoßnett under whose direction and guidance this work has been done.

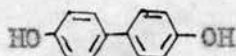
At the same time she acknowledges the financial aid rendered by the Oklahoma A. and M. College in the form of a graduate fellowship in the Chemistry Department.

TABLE OF CONTENTS

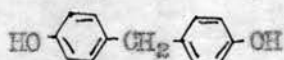
	Page
Introduction	1
Historical	3
Experimental	6
Discussion of Results	12
Summary	15
Bibliography	16
Biography	17

INTRODUCTION

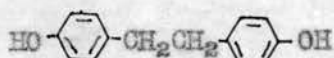
The following are some of the compounds reported to have estrogenic activity:



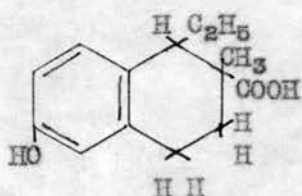
4,4'-dihydroxybiphenyl,



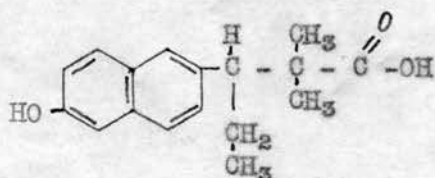
4,4'-dihydroxydiphenylmethane and



4,4'-dihydroxybibenzyl (1);



1-ethyl-2-methyl-6-hydroxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (2) and



3-(6-hydroxy-2-naphthyl)-2,2-dimethylpentanoic acid (3).

Schueler (4) states that a given substance may be estrogenic if it consists of a rather large, rigid and inert molecular structure with two active hydrogen-bond-forming groups located at an optimum distance of 8.55 Å from one another.

The estrogenic activity of the above compounds and the theory of Schueler, although it has been neither proved nor disproved, suggested that the dicarboxylic acid and the dicarboxamides of biphenyl, diphenylmethane and bibenzyl might have estrogenic activity. The distances between these hydrogen-bonding groups in this series of compounds correspond closely to the optimum distance of 8.55 Å proposed by Schueler.

It was decided to synthesize these compounds and the 4,4'-dibromo and 4,4'-dicyano derivatives of biphenyl, diphenylmethane and bibenzyl to be tested

for their estrogenic activity in chicks.

Although the acids, the bromides and the nitriles have been prepared there is little information on these compounds in the literature. Any additional knowledge concerning their preparation and properties would be useful.

HISTORICAL

4,4'-Dibromobiphenyl

Fittig (5) reported the preparation of 4,4'-dibromobiphenyl by the action of biphenyl and bromine under water. Carnelley and Thomson (6) reported the preparation by the reaction of bromine and a solution of biphenyl in carbon disulfide.

4,4'-Dicyanobiphenyl

Doebner (7) reported the preparation of 4,4'-dicyanobiphenyl by the careful heating of the calcium salt of biphenyl-4,4'-disulfonic acid with calcium cyanide in a stream of carbon dioxide. Work (8) reported the preparation from benzidine dissolved in hydrochloric acid, treated with sodium nitrite and then with cuprous cyanide.

Biphenyl-4,4'-dicarboxamide

The preparation of biphenyl-4,4'-dicarboxamide is not reported in the literature.

Biphenyl-4,4'-dicarboxylic acid

Doebner (9) reported the preparation of biphenyl-4,4'-dicarboxylic acid by the oxidation of p,p'-ditolyl with chromic and glacial acetic acid. Liebermann (10) reported the preparation by the reaction of oxalyl chloride and aluminum chloride with biphenyl. Basford (11) reported the preparation by the oxidation of 4-cyclohexylbiphenyl-4'-carboxylic acid. Harley-Mason and Mann (12) reported the preparation by the oxidation of 4,4'-dimethoxyquaterphenyl with chromium trioxide and glacial acetic acid. They reported a yield of 85%. Gilman, Langham and Moore (13) reported the preparation by the reaction of 4,4'-dibromobiphenyl and butyllithium and subsequent carbonation. They reported a 30% yield when a 2:1 ratio of butyllithium to halide was used and 91% when the ratio was 4:1.

4,4'-Dibromodiphenylmethane

Goldthwaite (14) prepared 4,4'-dibromodiphenylmethane by the reaction of bromine with diphenylmethane in the presence of iodine.

4,4'-Dicyanodiphenylmethane

Schöpf (15) prepared 4,4'-dicyanodiphenylmethane from the corresponding acid.

Diphenylmethane-4,4'-dicarboxamide

The preparation of diphenylmethane-4,4'-dicarboxamide is not reported in the literature.

Diphenylmethane-4,4'-dicarboxylic acid

Schöpf (15) prepared diphenylmethane-4,4'-dicarboxylic acid from the dinitrile formed by the diazotization of 4,4'-diaminodiphenylmethane. Liebermann (10) reported the preparation by the reaction of oxalyl chloride and aluminum chloride with diphenylmethane.

4,4'-Dibromobibenzyl

Stelling and Fittig (16) prepared 4,4'-dibromobibenzyl by the reaction of one gram-molecular weight of bromine and bibenzyl in water. Errera (17) prepared this compound by boiling p-bromobenzyl bromide with zinc dust.

4,4'-Dicyanobibenzyl

Kattwinkel and Wolffenstein (18) prepared 4,4'-dicyanobibenzyl in addition to 4-cyanobenzoic acid by warming p-tolunitrile with a hot saturated solution of calcium persulfate for five or six days.

Bibenzyl-4,4'-dicarboxamide

The preparation of bibenzyl-4,4'-dicarboxamide is not recorded in the literature.

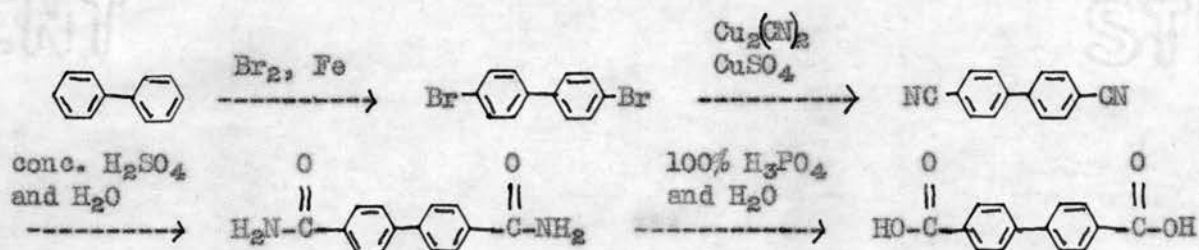
Bibenzyl-4,4'-dicarboxylic acid

Fischer and Wolffenstein (19) prepared bibenzyl-4,4'-dicarboxylic acid

by the action of calcium persulfate on p-toluic acid in the presence of sodium carbonate. Liebermann (10) prepared this acid by the reaction of oxalyl chloride and aluminum chloride with bibenzyl.

EXPERIMENTAL

The preparation of the derivatives of biphenyl, diphenylmethane and bi-benzyl was first attempted according to the following type reactions:

Preparation of the dibromo compounds

One-half mole of the hydrocarbon was dissolved in 200 ml. of carbon tetrachloride and placed in a 500-ml. three-necked round-bottom flask fitted with a stirrer, a dropping funnel and a reflux condenser. A hydrogen bromide trap was connected to the reflux condenser. Four grams of iron filings was added to the flask as the catalyst. The mixture was heated with stirring to reflux and one mole (160 g.) of liquid bromine was added dropwise through the dropping funnel at such a rate to maintain reflux. The addition of bromine required one hour. The mixture was then refluxed for an additional hour.

The carbon tetrachloride was steam-distilled and the remaining oil was crystallized by cooling in an ice bath. The 4,4'-dibromo compound thus obtained was recrystallized from alcohol.

In the case of 4,4'-dibromodiphenylmethane, crystallization did not occur readily. The water was decanted from the oil remaining after steam distillation. The oil was vacuum-distilled and the portion which boiled at 220-225° C. at 25 mm. was seeded with a few crystals of 4,4'-dibromobiphenyl and allowed to stand in the ice box for a few days until crystallization occurred.

Melting Point

<u>Compound</u>	<u>Literature</u> (°C.)	<u>Observed</u> (°C.)	<u>Yield</u> (%)
4,4'-Dibromobiphenyl	164 (5), 162 (6)	162-164	69.5
4,4'-Dibromodiphenylmethane	64 (14)	62	16.5
4,4'-Dibromobibenzyl	114-115 (16)	114-115	65.0

Preparation of the 4,4'-dicyano compounds

The preparation of the 4,4'-dicyanobibenzyl was attempted following the Rosenmund-von Braun nitrile synthesis described by Koelsch and Whitney (20). According to this method the bromo compound, twice the calculated amount of cuprous cyanide, and a few crystals of cupric sulfate, as the catalyst, are heated in a sealed soft glass test tube at 250° C. for one hour. The organic matter is extracted by heating with acetone. This method is satisfactory for small quantities, using an oil bath to maintain the constant temperature. Using 1.9 g. of 4,4'-dibromobibenzyl a 12% yield was obtained, while a second run using 1.35 g. gave a 33% yield.

For larger quantities using a Pyrex ignition tube and a tube furnace to maintain the temperature, the yield was very low due to the formation of carbonaceous material. The reaction mixture formed upon cooling a very hard solid which was impossible to pulverize. The solid material was allowed to stand in concentrated ammonium hydroxide, but this did not help the purification. Fifty-three grams of 4,4'-dibromobibenzyl gave no yield at all. A second run using 54 g. gave a 6.2% yield.

A modification of the above procedure using quinoline as a solvent was tried. The dry mixture was dissolved in a minimum amount of quinoline and refluxed for two hours. A solution of 6 N hydrochloric acid was added to the mixture with stirring. The mixture was allowed to cool, the aqueous portion

was decanted and the residue was filtered and recrystallized from alcohol. This residue contained large quantities of tar which caused much difficulty in purification. Successive recrystallization from alcohol was a slow but fairly satisfactory method of removing the tar. Using 6.16 g. of 4,4'-dibromobiphenyl and 50 ml. of quinoline, a 12.2% yield was obtained, while 5 g. of 4,4'-dibromobiphenyl and 50 ml. of quinoline gave a 39% yield.

Another modification of this same procedure involved heating the dry mixture in an open test tube. The tube was heated over an open flame until the contents had just melted. The temperature of the mixture was not allowed to exceed 250° C. The reaction mixture was then heated with a solution of sodium cyanide. This treatment removed all the copper salts and recrystallization from alcohol was much simplified.

This latter modification of the Rosenmund-von Braun nitrile synthesis proved to be the most satisfactory and was therefore used for the preparation of the 4,4'-dicyano compounds. The per cent yields shown below are for small quantities, 1-5 g., of the dibromo compound.

<u>Compound</u>	<u>Melting Point</u>		<u>Yield</u> (%)
	<u>Literature</u> (°C.)	<u>Observed</u> (°C.)	
4,4'-Dicyanobiphenyl	234 (7)	210-220	40
4,4'-Dicyanodiphenylmethane	165 (15)	160-161	45
4,4'-Dicyanobiphenyl	198 (18)	194-198	40

Hydrolysis of the 4,4'-dicyano compounds with concentrated sulfuric acid

Two and one-half grams of the 4,4'-dicyano compound was heated with 70 ml. of concentrated sulfuric acid at 75-80° C. for five hours. The resulting solution was poured over cracked ice and allowed to stand overnight. The white solid was separated by filtration and washed repeatedly with water.

Sodium fusion and subsequent qualitative nitrogen analysis showed nitrogen to be present. A quantitative nitrogen analysis was made and the results were as follows:

ANALYSIS FOR NITROGEN

<u>Sulfuric Acid Hydrolysis Product of:</u>	<u>Calculated for the dicarboxamide</u>	<u>Found</u>
Biphenyl Derivative	11.67 %	8.44 %
Diphenylmethane Derivative	11.02	9.18
Bibenzyl Derivative	10.45	5.57

The sulfuric acid hydrolysis was tried under less drastic conditions as follows: Three-tenths of a gram of 4,4'-dicyanobibenzyl was heated with 25 ml. of concentrated sulfuric acid at 60° C. for three hours. The mixture was poured over cracked ice and allowed to stand overnight. The white solid was separated by filtration and refluxed for five hours with a mixture of 20 g. of potassium hydroxide, 150 ml. of alcohol and 150 ml. of water. Very little dicarboxamide was formed since practically all the solid dissolved in this mixture.

Hydrolysis of 4,4'-dicyanobibenzyl with benzoyl peroxide Catalyst

A mixture of 0.5 g. of 4,4'-dicyanobibenzyl, 5 g. of benzoyl peroxide, 50 ml. of glacial acetic acid, 1 g. of anhydrous sodium acetate and 4.7 ml. of water was heated in a water bath overnight at 60° C. The solution was then poured over cracked ice. A yellow solid precipitated on standing. The solid was separated by filtration and refluxed for two hours with a mixture of 20 g. of potassium hydroxide, 150 ml. of alcohol and 150 ml. of water. Since all the solid dissolved in this mixture there was no yield of the dicarboxamide.

Hydrolysis of 4,4'-dicyanobibenzyl with alkaline hydrogen peroxide

A mixture of 0.5 g. of 4,4'-dicyanobibenzyl, 12 ml. of 3% hydrogen peroxide and 5 drops of a 20% sodium hydroxide solution was heated in a water bath at 40° C. for two hours. There was no yield and 0.45 g. of the nitrile was recovered.

The recovered nitrile was treated with 15 ml. of a 10% hydrogen peroxide solution at 40° C. for one hour. There was no yield and 0.4 g. of the nitrile was recovered.

The recovered nitrile was treated with 15 ml. of a 5% sodium hydroxide solution in 30% hydrogen peroxide. There was a trace yield.

Treatment of substance produced by hydrolysis with concentrated sulfuric acid

Two grams of the substance produced by hydrolysis with concentrated sulfuric acid was further hydrolyzed by heating with 35 ml. of 100% phosphoric acid at 110° C. for four hours. This mixture was poured over cracked ice and allowed to stand overnight. The solid was separated by filtration and washed repeatedly with water.

Sodium fusion and subsequent qualitative nitrogen analysis showed nitrogen to be absent.

These final hydrolysis products dissolved upon heating in a solution of alcoholic potassium hydroxide. This clear solution was acidified with dilute hydrochloric acid and a white solid precipitated which was insoluble in water.

Melting Point

<u>Compound</u>	<u>Literature</u> (°C.)	<u>Observed</u> (°C.)	<u>Yield</u> (%)
	decomposes above 300 (11)		
Biphenyl-4,4'-dicarboxylic acid	does not melt (9)	did not melt	75
Diphenylmethane-4,4'-dicarboxylic acid	334-336° (16)	325-330	60
Bibenzyl-4,4'-dicarboxylic acid	above 320 (19)	did not melt	78

Preparation of bibenzyl-4,4'-dicarboxylic acid through the Grignard reagent

Two and one-half grams of magnesium turnings was placed in a three-necked round-bottom flask fitted with a water-cooled condenser, a stirrer and a dropping funnel. A mixture of 5 g. of (0.0147 mole) of 4,4'-dibromobibenzyl and 3.2 g. (0.0294 mole) of ethyl bromide dissolved in 250 ml. of anhydrous ether was added slowly through the dropping funnel. The reaction was started by the addition of a small crystal of iodine. After the reaction had ceased, the mixture was poured onto dry ice and hydrolyzed with 6 N sulfuric acid. The aqueous layer was separated and treated with excess sodium hydroxide solution and then filtered. This clear filtrate was acidified and the solid which formed was separated by filtration. The product of this reaction was a mixture of the bromo-acid and the di-acid, which was impossible to separate by recrystallization from alcohol. Bromine was present in both fractions as shown by the Beilstein flame test.

DISCUSSION OF RESULTS

The bromination of biphenyl, diphenylmethane and bibenzyl involved nothing more than a classical procedure using a low temperature and iron catalyst. Purification of 4,4'-dibromobiphenyl, 4,4'-dibromodiphenylmethane and 4,4'-dibromobibenzyl is easily accomplished by recrystallization from alcohol.

It was very difficult to obtain satisfactory yields in the exchange of the bromo for the cyano group. Many runs were made using each of the modifications of the Rosenmund-von Braun nitrile synthesis. The original method of heating the dry mixture in a sealed tube was abandoned since using an oil bath for small quantities was too dangerous and using an ignition tube and heating larger quantities in a tube furnace gave large amounts of carbonaceous material. The use of quinoline was abandoned because of the tar formation which made purification a very long and tedious process. Quinoline, however, is a good solvent for cuprous salts and has a boiling point of 239° C. which is near enough to the reaction temperature of 250° C.

Finally, heating the dry mixture in an open test tube was tried and satisfactory yields were obtained. This method of exchange of bromo for cyano group is very easily carried out and can be done in a minimum of time. Removal of the copper salts is easily accomplished by the sodium cyanide treatment. Unfortunately, satisfactory yields are obtained only when 1-5 g. of the dibromo compound is used.

4,4'-Dicyanobiphenyl and 4,4'-dicyanobibenzyl are amorphous and are very difficult to manipulate. These compounds are difficultly soluble in hot alcohol and prolonged boiling under reflux is necessary before recrystallization is possible. 4,4'-Dicyanodiphenylmethane is crystalline in form, has a lower melting point than the other two, and is soluble in hot alcohol.

As shown by the quantitative nitrogen analysis of the sulfuric acid hydrolysis product of the dicyano compounds, the dicarboxamides were not prepared in a pure state. Since the nitrogen analysis was lower than the calculated amount, the hydrolysis went further than was expected. Therefore, the hydrolysis product probably consisted of a mixture of unreacted nitrile, the dicarboxylic acid and the nitrile-acid.

The concentrated sulfuric acid hydrolysis of 4,4'-dicyanobibenzyl was tried under less drastic conditions of lower temperature and a shortened heating period. The hydrolysis product was heated in a mixture of alcohol, potassium hydroxide and water. This mixture should dissolve all the compounds present except the dicarboxamide. All the hydrolysis product dissolved in the mixture. Therefore, partial hydrolysis with sulfuric acid is not a satisfactory method of preparing these dicarboxamides.

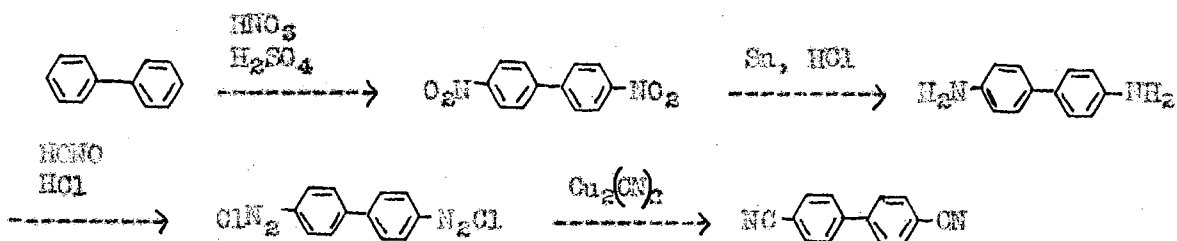
Hydrolysis of 4,4'-dicyanobibenzyl with alkaline hydrogen peroxide or with a little water in acetic acid in the presence of benzoyl peroxide was also unsatisfactory since the unreacted nitrile was recovered.

The preparation of bibenzyl-4,4'-dicarboxylic acid was attempted through the double Grignard reagent of 4,4'-dibromobibenzyl. The reaction did produce an acid which was soluble in alcoholic potassium hydroxide and precipitated upon acidification. However, the product contained bromine as shown by the Beilstein flame test. The attempt to isolate a pure acid, either the bromo-acid or the di-acid, was unsuccessful and therefore a neutralization equivalent was not run.

The preparation of the dicarboxamides of biphenyl, diphenylmethane and bibenzyl is not impossible. Their preparation should succeed by the classical method of treating the dicarboxylic acid with thionyl chloride and ammonia. It has been shown that their preparation by the hydrolysis of the dinitrile is

not practical from two standpoints. First, it is difficult to stop at the desired stage and, second, purification is difficult. By heating such a hydrolysis product with a mixture of alcohol, water, and potassium hydroxide, it would appear possible to remove the nitrile and the acid, leaving the dicarboxamide. This method of purification, however, is seldom satisfactory. It is possible that a suitable recrystallization solvent for the dicarboxamides might be found.

The preparation of the dicyano compound from the bromo compounds was not entirely satisfactory since the yield was so small in man using large quantities. An alternate route for the preparation of the dinitrile is through nitration of the hydrocarbon, reduction, diazotization and reaction with cuprous cyanide by the Sandmeyer reaction:



This is a longer route, but better yields might be obtained. Because of lack of time this method was not tried.

SUMMARY

The bromination of biphenyl, diphenylmethane and bibenzyl was done according to the classical method for substitution of ring hydrogen for halogen. This method was found to be satisfactory for these compounds.

The best method for the exchange of the bromo for the cyano group for this series of compounds was heating the dry mixture of the 4,4'-dibromo compound, cuprous cyanide and copper sulfate just until melting occurred. Purification of the cyano compound was most easily accomplished by heating the reaction mixture with a solution of sodium cyanide to dissolve the copper salts.

Hydrolysis of the nitrile with concentrated sulfuric acid was an unsatisfactory method of preparing the dicarboxamides, since the nitrile was either recovered unreacted or hydrolyzed all the way to the acid. Alkaline hydrogen peroxide and benzoyl peroxide were also unsatisfactory for promoting hydrolysis since the unreacted nitriles were recovered.

The dicarboxylic acid was prepared by the further hydrolysis of the product from the sulfuric acid treatment by means of 100% phosphoric acid at 110° C. for four hours. An attempt to prepare the pure dicarboxylic acid through the double Grignard reagent of the dibromo compound was unsuccessful since the product consisted of a mixture of bromo-acid and di-acid.

Melting points and properties of all the compounds synthesized were recorded.

BIBLIOGRAPHY

1. Dodds and Lawson, Proc. Roy. Soc. (London), 1125, 222 (1938); via Chem. Rev., 37, 421 (1945).
2. Courrier and Moreau, Compt. rend. soc. biol., 140, 332 (1946); via C. A., 41, 3519 (1947).
3. Courrier, Jacques and Moreau, Compt. rend. soc. biol., 141, 159 (1947); via C. A., 41, 5939 (1947).
4. Schueler, Science, 103, 221 (1946); via C. A., 40, 2518 (1946).
5. Fittig, Ann., 132, 204 (1865); via Beilstein's "Handbuch", 4th ed., 5, 580.
6. Carnalley and Thomson, J. Chem. Soc., 47, 587 (1865); via Beilstein's "Handbuch", 4th ed., 5, 580.
7. Doebner, Ann., 172, 116 (1874); via Beilstein's "Handbuch", 4th ed., 9, 927.
8. Work, J. Chem. Soc., 1940, 1515-20.
9. Doebner, Ber., 9, 272 (1876).
10. Liebermann, Ber., 45, 1209 (1912).
11. Basford, J. Chem. Soc., 1936, 1593-5.
12. Harley-Mason and Mann, J. Chem. Soc., 1940, 1379-85.
13. Gilman, Langham and Moore, J. Am. Chem. Soc., 62, 2327-35 (1940).
14. Goldthwaite, Am. Chem. J., 30, 448 (1903); via Beilstein's "Handbuch", 4th ed., 5, 593.
15. Schöpf, Ber., 27, 2325 (1894).
16. Stelling and Fittig, Ann., 137, 367 (1866); via Beilstein's "Handbuch", 4th ed., 9, 934.
17. Errera, Gazz. chim. ital., 18, 237 (1888); via Beilstein's "Handbuch", 4th ed., 5, 602.
18. Kattwinkel and Wolffenstein, Ber., 34, 2483 (1901).
19. Fischer and Wolffenstein, Ber., 37, 3215 (1904).
20. Koelsch and Whitney, J. Org. Chem., 6, 795 (1941).

BIOGRAPHY

Carolyn Mae Ellis was born September 9, 1923, at Bartlesville, Oklahoma. She attended grade school and high school in various places in Oklahoma. She attended East Central State College at Ada, Oklahoma, and received the Bachelor of Science Degree in May 1945. She began graduate work at Oklahoma Agricultural and Mechanical College in the fall of 1945, being employed from that time as a graduate fellow in the Department of Chemistry.

Typed by:

Carolyn Mae Ellis