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THE PREPARATION AND PROPERTIES OF THE CONDENSATION PRODUCTS OF BARBITURIC ACID WITH SEVERAL ALDEHYDES AND KETONES

by

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B.Sc., University of Bombay

Bombay, India, 1950

Presented in partial fulfillment
of the requirements for the degree of
Master of Science

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1952

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INTRODUCTION

The purpose of this research was to prepare a number of new compounds by condensing various aldehydic or ketonic substances with barbituric acid, and to study the hypnotic activity of these condensation products on rats. Theoretically, the hypnotic property of the chloral and acetone derivatives should be somewhat increased in comparison to barbituric acid itself, while in the case of the other substances, due to the presence of cyclic or aromatic nucleus, there should be a reduced effect. The Knoevenagel reaction was employed in preparation of these compounds.

CHAPTER I

HISTORICAL

In 1868, W. H. Perkin described a synthesis of coumarin by heating the sodium phenolate of salicylic aldehyde with acetic anhydride. This reaction may be expressed by the following equation: (1)

HC C C C C H
$$_{3}$$
C C $_{6}$ C $_{7}$ C $_{7}$ C $_{7}$ C $_{7}$ C $_{7}$ C $_{8}$

A further study of this reaction led to the discovery of a new method for the preparation of cinnamic acid and its analogs:

$$C_6H_5CHO + (CH_3CO)_2O + CH_3 COONa$$
 $C_6H_5CH = CH - COOH$
 $C_6H_5CHO + (R-CH_2-CO)_2O + R-CH_2COONa$
 $C_6H_5CH = C - COOH$

This reaction, which is brought about by heating an aldehyde of the aromatic series with the anhydride of an aliphatic acid of the general formula R-CH₂COOH, in presence of the sodium salt of the acid, is known as the Perkin reaction. (2)

In the course of an extensive study of the unsaturated acids, Fittig and his collaborators made several important contributions to the mechanism of this reaction. They showed that the aldehyde condenses with the alpha methylene group of the acid component (salt or anhydride), and that the reaction is an additive process, resembling aldol condensations, involving intermediate beta-hydroxy compounds, which lose water to form alpha-beta unsaturated acids, in accord with the following reaction: (3)

$$C_{6}H_{5}CHO + (CH_{3}CH_{2}CO)_{2}O + CH_{3}CH_{2} - COONa$$

$$\longrightarrow \angle C_{6}H_{5}CHOH - CH - COOH_{7} \longrightarrow C_{6}H_{5} - CH = C - COOH_{6}$$

$$CH_{3}$$

$$CH_{3}$$

The relative significance of the acid-anhydride and the sodium salt in the intimate mechanism of the Perkin condensation, has been the subject of numerous investigations extending over a period of more than fifty years. Fittig studied the reaction with several anhydride-salt combinations, particularly at lower temperatures. He found that benzaldehyde, acetic anhydride and sodium acetate do not react at 100° C. even on long continued heating. When sodium n-butyrate is used in place of acetate, the reaction takes place slowly, and only alpha-ethyl cinnamic acid is formed. When the temperature of the reactants is raised to 150° C., a mixture consisting of one part alphaethyl cinnamic acid to two parts cinnamic acid is obtained. When a temperature of 180° C. is employed, the product con-

sists of only one part of alpha-ethyl cinnamic acid to ten parts of cinnamic acid. (4)

From these results, Fittig concluded that at 100° C. the reaction occurs between the aldehyde and the salt, and explained the formation of cinnamic acid at 150° C. and 180° C. by assuming that an anhydride-salt exchange occurs at higher temperatures, but not at 100° C., giving rise to sodium acetate which then reacts with the aldehyde.

Michael⁽⁵⁾ doubted the validity of Fittig's view, and brought forward strong experimental evidence in favor of Perkin's contention that the condensation occurs between the aldehyde and the anhydride. He found that acetic anhydride, on heating with sodium butyrate or caproate for a short time at 100° C., gives excellent yields of butyric and caproic anhydride, while the reverse reactions do not occur appreciably under these conditions.

$$2C_3H_7COONa + (CH_3-CO)_2O$$

$$\xrightarrow{100^{\circ} C.} 2CH_3COONa + (C_3H_7CO)_2O$$

In general, the usual Perkin reaction is limited, for practical purposes, to aldehydes of the aromatic series and closely related compounds. Modifications worked out by Knoevenagel and Doebner are used as preparative methods for derivatives of both the aliphatic and aromatic series.

Malonic acid, owing to the powerful activating effect of its two carboxyl groups, directed on the same carbon atom, undergoes condensation with aliphatic and aromatic aldehydes under very mild conditions. This condensation was first effected in a medium composed of glacial acetic acid and a little acetic anhydride. (6)

$$CH_3 \cdot CH_2 - CHO \cdot CH_2 - (COOH)_2$$
 CH_3COOH
 CH_3COOH
 $CH_3 - CH_2CH = CH \cdot COOH + CO_2 + H_2O$

Following the condensation of the diethyl ester of malonic acid with aldehydes, under the influence of primary and secondary amines. Knoevenagel successfully tried a similar reaction with malonic acid and benzaldehyde in the presence of ammonia. The mechanism of this reaction seems to follow in two steps, in the first of which the aldehyde condenses with ammonia (or alkyl amine) to form an alkylidine amine (intermediate product), which then reacts with the malonic acid to form the unsaturated acid, accompanied by the evolution of carbon dioxide. In the case of benzaldehyde, the reaction may be expressed in accord with the following equations: (7)

Knoevenagel and others were able to carry out this reaction either by adding amine to an alcoholic solution of the aldehyde and malonic acid or by first interacting the acid with amine and then adding molecular proportions of the aldehyde. For example, the condensation of benzaldehyde with malonic acid and the subsequent formation of cinnamic acid could be accomplished equally readily by reacting the hydrobenzamide of benzaldehyde with malonic acid, or by treating a mixture of aldehyde and malonic acid with alcoholic ammonia, or by simply treating benzaldehyde with neutral or acid ammonium malonate. All these reactions proceed smoothly and readily at water bath temperatures.

The most satisfactory method used in condensing members of the aliphatic series is Doebner's modification, in which pyridine is used as the solvent. (8) In such cases pyridine exerts the function of amine catalyst.

$$CH_3 \cdot CHO + CH_2(COOH)_2 \xrightarrow{Pyridine} CH_3 - CH = CH \cdot COOH + H_2O + CO_2$$

Doebner's modification, using pyridine as a solvent, has been improved and higher yields are obtained by the addition of small amounts of piperidine to the reaction mixtures. Further modifications have made it possible to carry out the reaction quite successfully by using only a small amount of pyridine as a catalyst, instead of using it as a solvent. (9) Substituted pyridine bases, however, differ quantitatively in their effectiveness in catalyzing the reaction.

CHAPTER II

DISCUSSION

In this research, to prevent hydrolysis or decomposition of barbituric acid into ammonia, urea and related products, absolute alcohol was used as a reaction medium. In the procedure one component (aldehyde or ketone) of the reactants is soluble in alcohol, while the other (barbituric acid) remains insoluble throughout the entire course of the reaction. Doebner's modification using pyridine as a solvent with or without piperidine as the catalyst was tried and found to proceed satisfactorily. Due, however, to the difficulty of recovering the resultant compounds because of their solubility in pyridine, a modified procedure of Doebner's modification (10) was tried. In this, absolute alcohol was used as the solvent and a small amount of pyridine was added to catalyze the reaction.

Unsaturation in the products formed was determined by the usual reactions with cold concentrated sulfuric acid, two percent potassium permanganate solution and with bromine in carbon tetrachloride. The response to these tests was positive in all cases with the exception of the chloral derivative, which did not yield satisfactory results when the bromine test was employed. All of these compounds, except

the acetophenone derivative, gave immediate precipitation on treatment with two percent potassium permanganate solution. The reaction with all compounds in conducting this test was exothermic, which is indicative of strong unsaturation.

Spectrophotometry

Light absorption in ultraviolet and in the visible spectra is due to the electrons. Organic compounds having saturation show absorption bands with a maximum below 2000 A. whereas longer ultraviolet or visible spectra are always (11)associated with multiple linkages or such unsaturated atoms. Selective absorption of light wavelength 2000 to 7700 A. is always associated with the presence of a molecule of certain specific grouping or chromophores, such as N. Cl. etc. (12) Chromophores are certain groups of atoms in an organic compound which cause characteristic absorption of visible light irrespective of the nature of the rest of the compound. The addition of a -C C- link to a congugated chain increases wavelength maximum by roughly 300 % and log E by about 0.3. (13) A comparison of the optical properties of aromatic and ethylenic compounds by Kuhn and Grundamn (Ber. 1937.70.1318) led to the conclusion that the benzene nucleus as a chromophoric unit is approximately equivalent to one and one-half congugated double bonds. The absorption spectra of barbituric acid and barbital showed maxima at 258 and 256, respectively, with molecular extinction coefficients at 24,000 and

245,000. (14) These are in accord with the absorption spectra of barbituric acid which were obtained in this work. On studying the effect of the PH of the solution on the absorption spectrum of barbituric acid, curves obtained showed varying molecular extinction coefficients ranging between 6,000 to 30,000 with a wavelength maxima between 2550 Å to 2600 Å. (15) Bathochromic effects of substituents such as --NH₂, --OR and halogens, attributed to the interaction between unsaturated electrons of multiple bonds and the unshared electron pair of the substituent, resulted in increased resonance and decreased transition energy. The effects depend primarily on the nature of the element vicinal to the ethylenic group in order of (16)

C (N 70 >Cl >CH3

N > S

OH > Cl < Br

0 > 5

To compare the effects of some of these bathochromes on wavelength maxima, the following data were found: (17)

Benzene - 2543 Å

Toluene - 2620 A

Chloro benzene - 2640 Å

Dichloro benzene - 2690 Å

Dimethyl benzene - 2633 A

STUDY OF THE ULTRAVIOLET ABSORPTION SPECTRUM
OF BARBITURIC ACID

Percentage solution of the compound in O:lN sodium hydroxide was 0.000937.

Wavelength in m _{A4} .	Density	Log.E.	Wavelength in m _A .	Density	Log.E.
218	0.593	2.7914	256	1.25	3.1255
220	0.6	2.7965	258	1,29	3.1369
222	0.532	2.7542	260	1,23	3,1183
224	0.512	2.7375	262	1,19	3,1038
226	0.449	2.6805	264	1.1	3,0418
230	0.473	2.7042	266	0,93	2,9921
232	0.482	2.7117	268	0.75	2.9033
234	0.472	2.7022	270	0.572	2.7856
236	0.477	2.7068	275	0.282	2.4784
238	0.469	2.6994	280	0.187	2,3000
240	0,513	2.7384	290	0.144	2,1867
242	0.56	2.7761	300	0.127	2.1319
244	0.623	2,8228	310	0.113	2.0813
246	0.7	2,8734	320	0.103	2,0411
248	0.81	2.9364	330	0.094	2.0037
250	0.9	2.9823	350	0.082	1.9421
252	1.03	3.0411	380	0.064	1.8345
254	1.12	3.0774	400	0.054	1.7604

m₄. = millimicron

E. = Extinction Coefficient

TABLE II

STUDY OF THE ULTRAVIOLET ABSORPTION SPECTRUM
OF THE CHLORAL DERIVATIVE OF BARBITURIC ACID

Percentage solution of the product in O·lN sodium hydroxide was 0.00185.

Wavelength in mu.	Density	Log.E.	Wavelength in m _u .	Density	Log.E.
230	0,668	2.5576	275	0.85	2.6628
232	0.68	2.5652	280	0.586	2.5007
238	0.75	2.6079	285	0.402	2.337.7
240	0.79	2.6304	290	0.304	2.2156
245	0.949	2.7101	295	0.248	2.1274
248	1.07	2.7622	300	0.204	2.0425
250	1.15	2.7932	305	0.166	1.9525
252	1.28	2.840	310	0.139	1.8753
254	1.33	2.8727	320	0.086	1.6672
256	1.47	2.9	325	0.067	1.5588
258	1.52	2,9093	330	0.053	1.4572
260	1.67	2.9544	335	0.045	1.3870
262	2.36	3.1059	340	0.043	1.3664
264	1.5	2.9089	345	0.039	1.3238
266	1.42	2.8851	350	0.037	1.2956
268	1.28	2.840	360	0.035	1.277
270	1.15	2.7932	370	0.033	1.2749

TABLE III

STUDY OF THE ULTRAVIOLET ABSORPTION SPECTRUM OF THE ACETONE DERIVATIVE OF BARBITURIC ACID

Percentage solution of the product in O·lN sodium hydroxide was 0.00375.

Wavelength in سيد.			Wavelength in m _H .	Density	Log.E.
230	0.46	2.0888	261	2.18	2.7665
235	0.482	2.1089	262	2.08	2.7429
240	0.5894	2.1962	265	2.03	2.7335
245	0.895	2.3777	268	1.65	2.6435
250	1.44	2.5844	270	1.36	2.5594
255	1.985	2.7238	275	0.718	2.2819
258	2.17	2.7625	280	0.3786	2.0374
260	2.18	2.7665	285*	0.0566	1.509

^{*}After 285 to 340, there is no appreciable change in absorption. Density remained practically the same.

TABLE IV

STUDY OF THE ULTRAVIOLET ABSORPTION SPECTRUM
OF THE CAMPHOR DERIVATIVE OF BARBITURIC ACID

Percentage solution of the product in O·lN sodium hydroxide was 0.000937

Wavelength in m _A .	Density	Log.E.	Wavelength in m4.	Density	Log.E.
218	0.848	2.9566	265	1.07	3.0577
220	0.83	2.9473	270	0.705	2.8762
224	0.8	2.9314	275	0.456	2.6872
226	0.772	2.9159	280	0.383	2.6116
228	0.758	2.908	285	0.352	2.5748
230	0.744	2.8999	290	0.328	2.5442
232	0.723	2.8874	295	0.313	2.5237
234	0.715	2.8827	300	0.288	2.4877
236	0.7	2.8734	305	0.272	2,4628
238	0.698	2.8722	310	0.256	2.4365
240	0.719	2.8850	320	0.237	2.4029
242	0.762	2.9103	330	0.217	2.3647
245	0.85	2.9577	340	0.194	2.3160
250	1.07	3.0577	350	0.176	2.2737
255	1.26	3.1287	360	0.164	2.243
260	1.32	3.1590	370	0.148	2.1987
261	1.298	3.1412	380	0.137	2.1659
262	1.26	3.1287	390	0.119	2.1038

STUDY OF THE ULTRAVIOLET ABSORPTION SPECTRUM OF THE ACETOPHENONE DERIVATIVE OF BARBITURIC ACID

TABLE V

Percentage solution of the product in O·lN sodium hydroxide was 0.00185.

Wavelength in m _u .	Density	Log.E.	Wavelength in m _{/4} .		
230	0.555	2.4771	285	0.10	1.7328
235	0.555	2.4771	290	0.09	1.687
240	0.632	2.5343	295	0.088	1.6772
245	0.863	2.6689	300	0.081	1.6413
250	1.3	2.8467	310	0.078	1.6249
255	1.65	2.9503	320	0.072	1.590
260	1.7	2.9632	330	0.065	1.5458
261	1.91	3.0136	340	0.058	1.4961
265	1.33	2.8569	350	0.052	1.4487
270	0.685	2.5684	360	0.047	1.4048
272	0.479	2.4130	380	0.044	1.3766
275	0.265	2.1559	390	0.040	1.3349
280	0.132	1.8535	400	0.038	1.3124

TABLE VI

STUDY OF THE ULTRAVIOLET ABSORPTION SPECTRUM OF THE CYCLOHEXANONE DERIVATIVE OF BARBITURIC ACID

Percentage solution of the product in O·lN sodium hydroxide was 0.000937.

Wavelength in m _A .	Density	Log.E.	Wavelength in m _µ .	Density	Log.E.
220	0.302	2.5083	262	0.588	2.7967
222	0.312	2.5225	265	0.548	2.7671
224	0.309	2.5184	270	0.343	2.5636
226	0.304	2.5112	275	0.207	2.3444
228	0.303	2.5096	280	0.137	2.165
230	0.302	2.5083	285	0.108	2.0618
232	0.293	2,4961	290	0.096	2.0103
234	0.294	2.4965	295	0.088	1.9729
236	0.287	2.4861	300	0.077	1.9049
238	0.294	2.4965	310	0.066	1.8468
240	0.313	2.5096	320	0.059	1.7995
242	0.318	2.5307	340	0.049	1.7185
244	0.342	2.5624	350	0.048	1.7096
246	0.376	2.6034	360	0.043	1.6618
248	0.413	2.6444	370	0.038	1.6081
250	0.465	2.6959	380	0.038	1.6081
255	0.592	2.8002	390	0.034	1.5597
260	0.639	2.8339	400	0.034	1,5597

The wavelength maximum obtained for barbituric acid was found to be identical to that found by previous investigators. In the chloral derivative, the abrupt rise in density and higher value of the wavelength absorption is accounted for partly by the bathochromic effect of chlorine atoms and partly by the presence of one more double bond than in the parent--barbituric acid. In the case of the acetone derivative, there is only one more double bond than in the barbituric acid, and the bathochromic effect of the methyl group is less than that of chlorine; hence both wavelength and density are lower than that of the chloral compound. In the case of the camphor derivative, the side chain is saturated, and furthermore there is only one double bond. Hence the wavelength is increased only by 20 A. the hindrance in absorption--density--due to saturation being partially equalized by the presence of a methyl group (free) in the side chain. In the case of the acetophenone derivative, increase in wavelength is due to a double bond and the presence of chromophores -- benzene nucleus and methyl group. The benzene chromophore is roughly equal to one more double bond; hence wavelength maximum is only slightly lower than that of the chloral derivative. In the cyclohexanone derivative there is only one more double bond, and hence the wavelength maximum is 2600 A. The decrease in density of absorption is due to the hindrance in resonance by the presence of the saturated cyclohexane ring.

$$D = \log_{10} \frac{I}{Ix} = E \cdot 1 \cdot C$$

Where:

E = Extinction coefficient
l = Thickness of solution

Here, l = l cms

 $\begin{array}{c} \cdot \cdot \cdot D = E \cdot C \\ \cdot \cdot \cdot E = D/C, \end{array}$

layer
C = Concentration of solution

TABLE VII

RELATION BETWEEN STRUCTURAL FORMULAS AND ABSORPTION OF COMPOUNDS

Name of Compound	Probable Structural Formula	M.P.	Wavelength maximum in milli-microns		Log. of Extinction coefficient maximum
Barbituric acid	HN-C=0		25 8	1.29	3.1369
Chloral de- rivative of barbituric acid	HN-C=0 H 0=C C = C-C-C1 H HN-C=0	255° C. decomposed	262	2.36	3.1059
Acetone de- rivative of barbituric acid	HN-C=0 CH ₃ 0=C C=C CH ₃ HN-C=0	238° C. decomposed	260-261	2.18	2.7665

TABLE VII--Continued

Name of Compound	Probable Structural Formula	M.P.	Wavelength maximum in milli-microns		Log. of Extinction coefficient maximum
Camphor de- rivative of barbituric acid	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	262°C. decomposed	260	1.32	3.1590
Acetophe- none deriva- tive of bar- bituric acid	HN - C = 0 $O = C$ $C = C$	183 ⁰ C. decomposed	261	1.91	3.016
Cyclohexa- none de- rivative of barbi- turic acid	$HN - C = 0$ H_2 H_2 $C - C$ CH_2 H_2 H_3 H_4 H_5	273° C. decomposed	260	0.639	2.8339

PHARMACOLOGY:

Preliminary tests performed by use of white rats revealed a definite hypnotic activity in the case of the chloral derivative. The camphor derivative possessed some activity and the benzophenone compound was completely inactive. These results are in accord with the pharmacological findings on compounds of hypnotic activity which show that the introduction of cyclic nuclei into an active compound leads to the reduction of hypnotic activity and the introduction of aromatic nuclei makes the compound inert or entirely changes the properties.

CHAPTER III

EXPERIMENTAL

(i) CHLORAL -- derivative

21 grams of chloral hydrate was introduced into a 500 c.c. round-bottomed flask and dissolved in 250 c.c. of absolute alcohol. 10 grams of barbituric acid was then added, followed by 15 c.c. of pyridine. The mixture was refluxed for three hours between 45 to 47° C. with frequent agitation. When the reaction reached completion, the insoluble residue was filtered out and washed five times with small portions of warm alcohol and dried at room temperature. The final purification was achieved by reprecipitating from chloroform. The product was obtained as an orange-colored amorphous powder which did not melt but decomposed on heating at 255° C.

Yield: 13.5 grams - 66.5% theoretical.
Nitrogen found: 11.2%; Nitrogen calculated: 10.89%.

(ii) ACETONE--derivative

To a mixture of 30 c.c. of acetone and 200 c.c. of absolute alcohol, 10 grams of barbituric acid was added, followed by 15 c.c. of pyridine. The mixture was refluxed with frequent agitation for four hours at temperatures ranging between 58° C. and 64° C. The residue, removed by

filtration, was washed several times with alcohol and finally with water. The compound was then recrystallized from sulfuric acid and dried in an oven at 80° C. The final product was obtained as a fine, rose-colored powder which melted at 238° C. with decomposition.

Yield: 6.5 grams - 47.1% theoretical. Nitrogen found: 15.1%; calculated: 16.6%.

(iii) CAMPHOR -- derivative

17.2 grams of camphor was introduced into a 500 c.c. round-bottomed flask and dissolved in 250 c.c. of absolute alcohol. 10 grams of barbituric acid and 30 c.c. of pyridine was then added. The mixture then was refluxed for twenty-two hours with frequent agitation at temperatures ranging between 70° C. and 80° C. The residue, after its recovery by the usual filtration procedure, was washed with warm alcohol and dried. The final product was purified by dissolving in sodium hydroxide solution and reprecipitating the product by hydrochloric acid. The product, a rose-colored powder, decomposed at 262° C. without melting.

Yield: 9 grams - 42% theoretical. Nitrogen found: 10.34%; nitrogen calculated: 10.69%.

(iv) ACETOPHENONE -- derivative

10 grams of acetophenone was dissolved in 200 c.c. of absolute alcohol in a 500 c.c. round-bottomed flask. 20 c.c. of pyridine and 10 grams of barbituric acid was then added. The mixture was then refluxed for six hours at temperatures between 50° C. and 55° C. The residue on removing by filtration, was purified in exactly the same way as the camphor

derivative. The final product, a reddish brown powder, decomposed at 185° C. with fusion.

Yield: 5.9 grams - 50% theoretical. Nitrogen found: 12.8%; nitrogen calculated: 12.13%.

(v) BENZOPHENONE -- derivative

10 grams of benzophenone was dissolved in 150 c.c. of absolute alcohol in a 250 c.c. flask. 10 grams of barbituric acid was then added, followed by 25 c.c. of pyridine. The mixture was allowed to react at room temperatures for six days with frequent agitation. At the end of this interval, a cream-colored substance separated above the unreacted barbituric acid. This substance was separated and purified by repeated washings with alcohol followed by five percent sodium hydroxide, then by water, and finally precipitated from ethereal solution with alcohol. The product on drying melted at 126° C. without decomposing.

Yield: 9 grams - 39.4% theoretical. Nitrogen found: 9.85%; nitrogen calculated: 9.59%.

(vi) CYCLOHEXANONE -- derivative

10 grams of barbituric acid, 20 c.c. of cyclohexanone and 10 c.c. of pyridine were introduced into a round-bottomed flask, containing 250 c.c. of absolute alcohol. The flask was equipped with an air condensor and the mixture was then heated on a steam bath. After one hour's heating, the content of the flask turned a reddish black and the components all dissolved. After a few minutes a reddish-brown precipitate separated, After an additional hour's heating, the precipitate was dissolved by addition of a few cubic centimeters of O.lN hydrochloric acid and the solution was

filtered. The product was reprecipitated by neutralizing the solution with O·lN sodium hydroxide.* After thorough washing with alcohol, the product was dried in a desiccator.

Yield: 7.35 grams - 45.23% theoretical. Nitrogen found: 13.65%; nitrogen calculated: 13.46%.

^{*}The compound has amphoteric properties. It is insoluble in neutral solution.

CHAPTER IV

SUMMARY AND CONCLUSIONS

- 1. Six different aldehydes or ketones were condensed with barbituric acid by the Knoevenagel reaction.
- 2. Absorption spectra of five of these compounds were studied. The results obtained were found to be in accord with those predicated for structures of the compounds examined.

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