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# A further study of the reactions involved in the preparation of Luminal and new related compounds

James John Chap

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THE PREPARATION OF  
SOLUBLE POLYMER COMPOUNDS

1934

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A FURTHER STUDY OF THE REACTIONS  
INVOLVED IN THE PREPARATION OF LUMINAL  
AND NEW RELATED COMPOUNDS

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JAMES JOHN CHAP

Thesis submitted for  
the degree of  
Doctor of Philosophy

MASSACHUSETTS STATE COLLEGE

June 1934

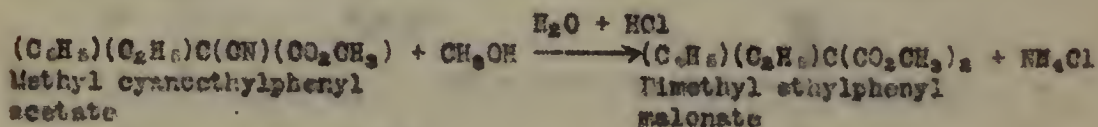
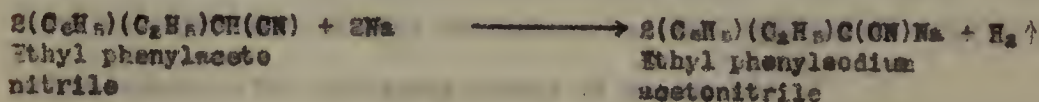
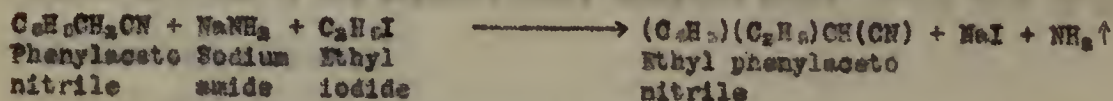
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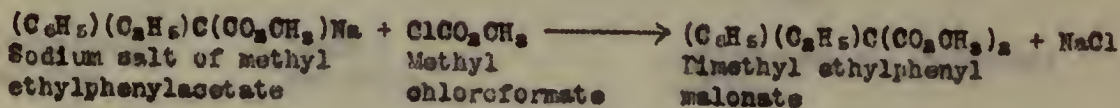
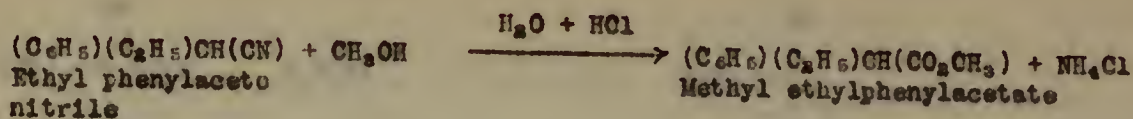
Other methods of production of dimethyl ethylphenylmalonate have been sought in recent years in the hope of improving the yield of ester obtained in the earlier synthesis of Mary Rising and Julius Stieglitz.<sup>4</sup> The yield of crude dimethyl ethylphenylmalonate was 75% of the theoretical. As the plan of preparation developed during the war constitutes the basis for the commercial preparation of pheno-barbital (Luminal), the importance of obtaining good yields is apparent. In 1927 M. Rising and Tsch-Wu Zee<sup>5</sup> published a method of preparation of dimethyl ethylphenylmalonate by a procedure summarized as follows:



Another later method of synthesis of dimethyl ethylphenylmalonate has been described by M. Rising and Tsch-Wu Zee<sup>6</sup> in which the yield of ester was the best so far obtained by any process. The yield was 43.1% based upon the phenylacetonitrile used, compared with 27.1% by the first method of Zee<sup>5</sup> and 41.0% in the war-time synthesis.<sup>4</sup> Their later plan made use of the following reactions:



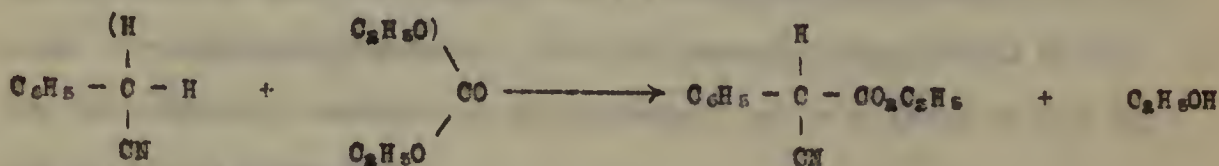




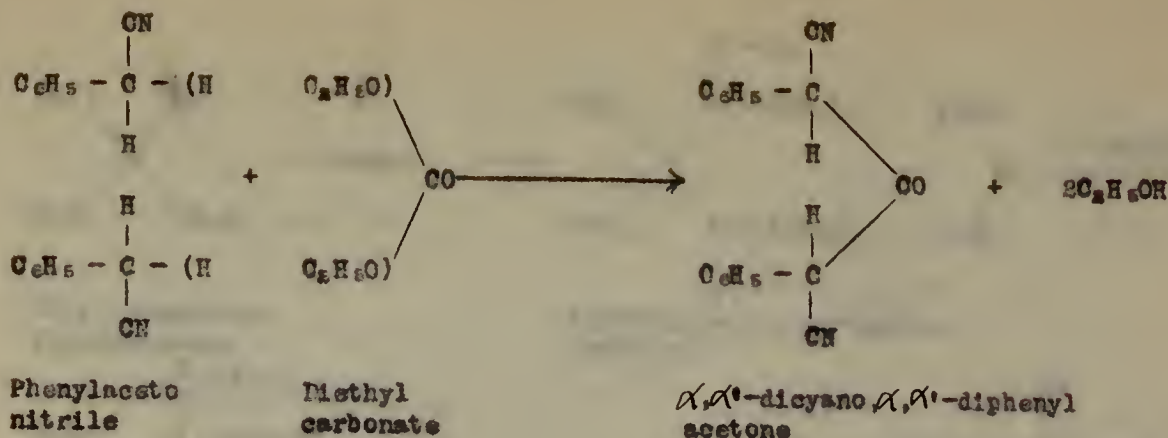
Neither of these later syntheses of Rising and Zee were studied in this laboratory, but are included here to show later that the yield of Luminal obtained by the author's newly developed method is the best of any that have been published.

The method of preparation of ethylphenylbarbituric acid (Luminal), which was developed in this laboratory and also applied to related compounds, is indicated in the following series of reactions:

(1) Diethyl carbonate is condensed with phenylacetonitrile to form ethyl cyanophenylacetate.

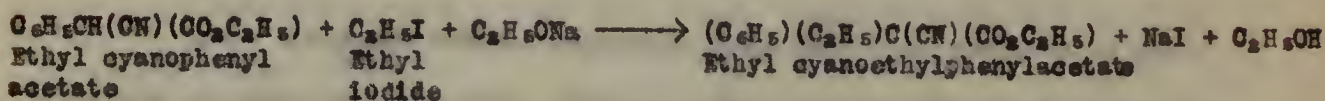


The modified Hessler<sup>7</sup> method of Cretcher and Nelson<sup>8</sup> - sodium amide as the condensing agent, in ether - was repeated with results closely checking their maximum yields. A crystalline by-product was obtained in the reaction, not indicated in the literature, which gave evidence that, to some extent, the following transformation takes place:



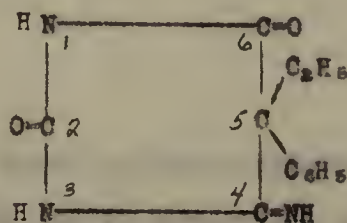
The latter product ( $\alpha, \alpha'$ -dicyano,  $\alpha, \alpha'$ -diphenyl acetone) is increased in amount by lack of anhydrous conditions and prolonged refluxing.

(2) The ethylation of ethyl cyanophenylacetate in absolute alcohol-ether solution according to

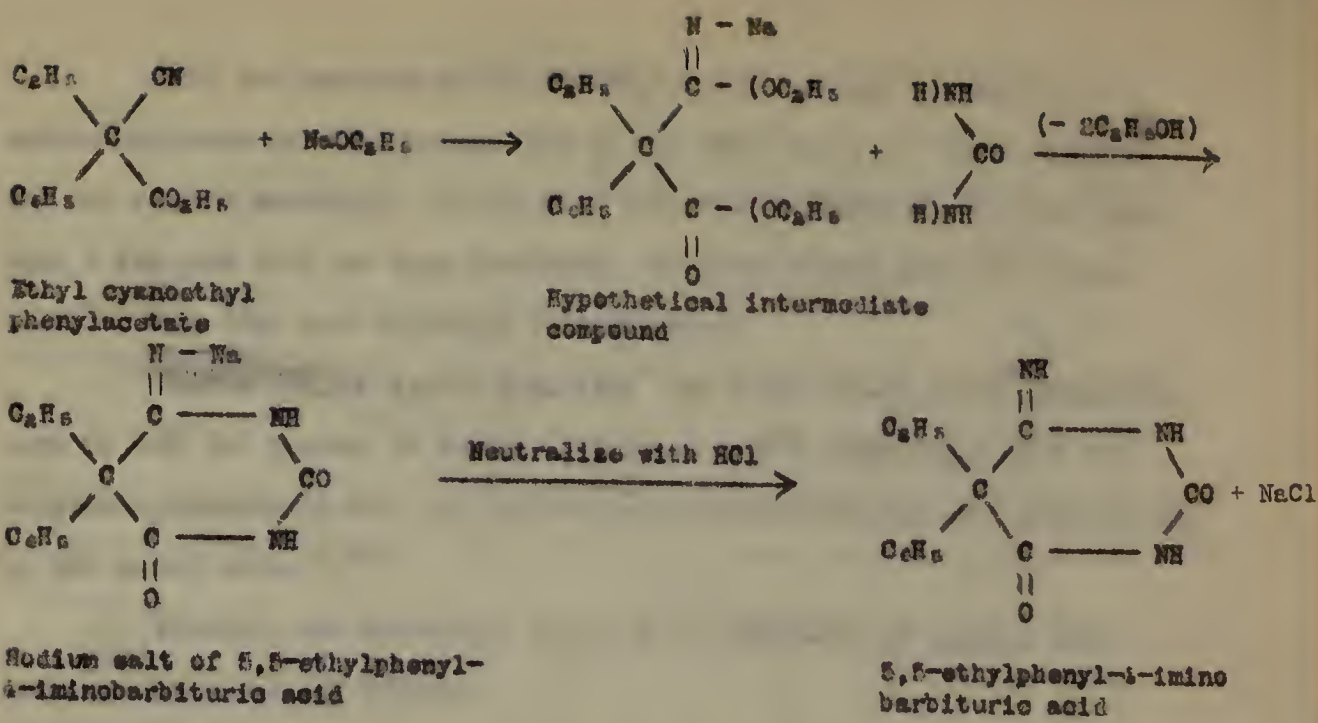


led to very satisfactory results. Other new representatives which have been prepared as successfully by substituting the ethyl cyanophenylacetate in this type of reaction were, for example, ethyl isoamylcyanophenylacetate and ethyl cyano - n. - heptylphenylacetate. The ethyl cyanoethylphenylacetate is the only one previously described in the literature<sup>6</sup> and as a matter of fact by name and patent number only.

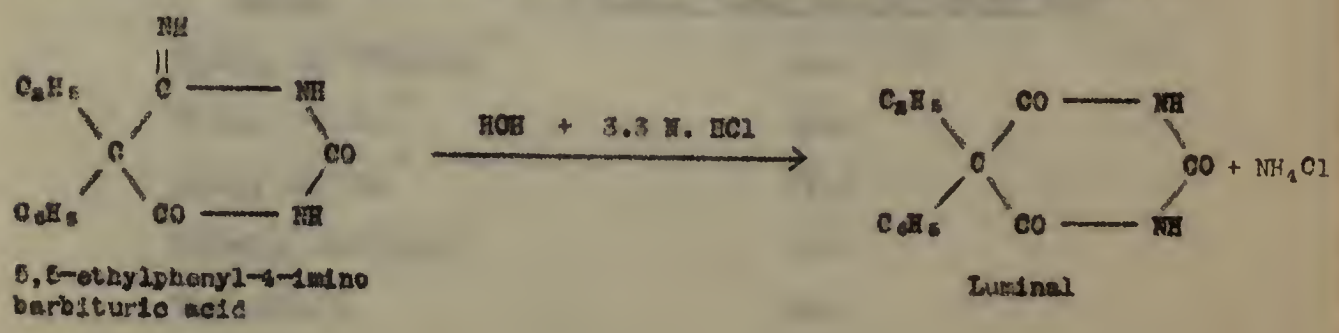
(3) Finally a new compound 5,5-ethylphenyl-2-iminobarbituric acid



is obtained by condensing ethyl cyanoethylphenylacetate with urea in the presence of sodium ethylate according to the following:



Again other new related compounds which have been prepared by substituting the corresponding ethyl alkylcyanophenylacetate for ethyl cyanoethyl phenylacetate in this type of reaction were, for example, 5,5-isoamylphenyl-4-iminobarbituric acid and 5,5-n-heptylphenyl-4-iminobarbituric acid. These substances all hydrolyze on prolonged boiling with 3.3 N. HCl to give the corresponding alkylarylbarbituric acids, as the reaction for Luminal indicates:



Conrad<sup>7</sup> was the first to prepare iminobarbituric acid and barbituric acid by the reactions shown, but he worked only with the aliphatic members.

With the compound  $C_6H_5CH(OH)(CO_2C_2H_5)$  now easily prepared,<sup>9</sup> it seemed desirable to alkylate and then by the above method to obtain Luminal and new related compounds. Of the many possible alkylphenylbarbituric acids only a few have thus far been described. Cretcher<sup>10</sup> states that barbituric acids of this type were difficult to synthesize.

Messrs. Lucian Bayard Spaulding<sup>10</sup> and James Edward Doyle<sup>11</sup> presented work in 1938 for degrees of Master of Science on the preparation of 5,5-n-hexylphenylbarbituric acid and 5,5-isopropylphenylbarbituric acid respectively by the method above.

Briefly, the advantages of the above synthesis of Luminal which merit attention are as follows:

- (1) Elimination of the preparation of the intermediate  $C_6H_5CH(CO_2R)_2$  which shortens the method.
- (2) Elimination of the use of pressure apparatus necessary to condense  $C_6H_5CH(CO_2R)_2$  with urea, since  $C_6H_5CH(OH)(CO_2C_2H_5)$  condenses with urea by simply boiling.
- (3) Yields are larger as comparison shows:

<u>Method</u>	<u>% Luminal based upon <math>C_6H_5CH_2CN</math> used</u>
Rising and Stieglitz <sup>8</sup>	16.4
Rising and Zee <sup>5</sup>	10.9
Rising and Zee <sup>5</sup>	17.2
Cretcher and Nelson <sup>6</sup>	10.8
The author's	18.4

## EXPERIMENTAL

### I. The Preparation of N,N - Ethylphenylbarbituric Acid (Luminal).

1. Ethyl cyanophenylacetate,  $C_6H_5CH_2NCCOOC_2H_5$ . — Ethyl cyanophenylacetate was prepared carefully according to the directions of Cratcher: "Three hundred grams of anhydrous ether and 42 g. of pulverized sodamide were placed in a dry two-liter three-necked, round-bottomed flask. A mercury sealed stirrer passed through the middle neck and a dropping funnel and tall reflux condenser were fitted to the side necks. During constant stirring, 117 g. of freshly distilled phenylacetonitrile was added drop by drop. A vigorous reaction ensued with evolution of ammonia. After all of the nitrile had been added, the reaction mixture was boiled in a water-bath for one-half hour. After cooling to room temperature, 150 g. of freshly distilled ethyl carbonate was added drop by drop. Replacement of the ether lost by evaporation is frequently necessary. After all of the carbonate had been added, the flask was warmed another half hour; then it was cooled in an ice-bath and treated with dilute hydrochloric acid until the aqueous layer was acid to litmus. The product was filtered and the ethereal layer separated and dried over calcium chloride.

After removal of the ether and fractionally distilling in vacuo, 133 g. of the desired ester was obtained, boiling (7mm.) at  $140 - 148^\circ$  (nearly all at  $145^\circ$ ). This is a yield of 70.3%.

A portion was further purified by redistillation. It was a colorless liquid and boiled at  $165^\circ$  at 19 mm.;  $d_4^{20} = 1.091$ .

The residue remaining after the distillation of the crude product solidified. The extraction of residue with boiling ligroin or ether seemed to remove only resins and to leave behind a pure white crystalline product.

On recrystallization from benzene or alcohol the compound  $\alpha, \alpha'$ -dicyano,  $\alpha, \alpha'$ -diphenyl acetone showed a melting point of 260 - 262° C.

This unexpected product was increased in amount when long standing reagents were used and also when refluxed more than suggested. The maximum yield of pure substance obtained was 40.0 g. or 30% of the theoretical.

Properties

A phenyl hydrazone is readily obtained.

<u>Insoluble</u>	<u>Slightly soluble</u>	<u>Soluble</u>
Ether	Cold alcohol	Hot alcohol
Ligroin	Cold benzene	Hot benzene
Water	Cold Chloroform	Hot chloroform
Dilute acids		Hot conc. H <sub>2</sub> SO <sub>4</sub>
Dilute alkalis		

Identification

Analyses:

Substance, 0.2015 g. ; CO<sub>2</sub>, 0.5767 g. ; H<sub>2</sub>O, 0.0885 g.

Substance, 0.4669 g. ; Vol. of 0.1 N. acid, 35.45 c.c. (Kjeldahl).

Calculated for C<sub>17</sub>H<sub>12</sub>ON<sub>2</sub>: C, 78.46%; H, 4.61%; N, 10.76%.

Found " " : C, 78.05%; H, 4.91%; N, 10.62%.

The compound was further identified by the determination of its molecular weight by the boiling point elevation using the modified Cottrell apparatus.

Substance, 0.3568 g. ; Weight of CCl<sub>4</sub>, 75.0 g. ; Elevation, 0.075° C.

Molecular weight for C<sub>17</sub>H<sub>12</sub>ON<sub>2</sub> requires 260. Found 247.4.

2. Ethyl cyanoethylphenylacetate,  $(C_6H_5)(C_2H_5)C(CN)(CO_2H_5)$ . —

This ester was produced satisfactorily by the modifications developed in this laboratory of the method of alkylation of Rising and Stieglitz.<sup>2</sup>

Two hundred grams of anhydrous ether and 11.5 g. of clean sodium were placed in a dry 1 - liter three-necked, round-bottomed flask. A mercury sealed stirrer passed through the middle neck and a separatory funnel and a tall reflux condenser were fitted to the side necks. During constant stirring, 95 g. of freshly distilled ethyl cyanophenylacetate were added drop by drop. A vigorous reaction ensued with the evolution of hydrogen. After all of the ester had been added, the reaction mixture was refluxed on a steam-bath over night. Then 60 g. of absolute methyl alcohol were added to react with any unused sodium along with 100g. more of anhydrous ether. After a period of two hours, 100g. of freshly distilled ethyl iodide (b.p.  $72^{\circ}C.$ ) were added dropwise. Then the mixture was refluxed for four days with constant stirring. The internal temperature of flask was  $45^{\circ}C.$ , that is, on the thermometer that replaced the dropping funnel. At this time most of the ether was distilled off and the internal temperature now read as  $72^{\circ}C.$  Another 20 g. portion of ethyl iodide was added and refluxed again over night. That the reaction had gone to completion was shown by the fact that the mixture in the flask was no longer alkaline to litmus. However a few drops (10) of 20% by weight of  $H_2SO_4$  sol'n were added to make the solution acid. Then enough water was added to dissolve the sodium iodide formed in the reaction and to cause the ether layer containing the ethylated ester to separate. The ether layer was separated from aqueous layer. The aqueous layer contained a small amount of ester and was extracted twice with ether. All ether layers were combined and dried over calcium chloride. The calcium chloride was filtered off after nine hours of standing. The ether was distilled off and the remaining dark red liquid distilled in vacuo.

Up to 130°C., at 11 mm., there was obtained a dark red liquid and some purple iodine fumes were formed. This change was complete below 130°C. and a pale yellow liquid remained in the distilling flask. From 130 to 140°C., a fraction of impure ethylated ester was obtained, and from 140 to 150°C., the main fraction distilled. The yield of colorless product boiling principally at 117°C. was 80 g. or 76% of the theoretical based on the ethyl cyanophenylacetate used;  $d_4^{20} = 1.055$ . The U.S. Patent 1,036,627 abstract does not state anything concerning preparation or properties.

The ethylated ester was identified by analysis.

Substance, 0.1764 g. ; CO<sub>2</sub>, 0.4643 g. ; H<sub>2</sub>O, 0.1108 g.

Substance, 0.4235 g. ; Vol. of 0.1 N. acid, 20.40 c.c. (Kjeldahl).

Calculated for C<sub>12</sub>H<sub>13</sub>O<sub>2</sub>N: C, 71.90%; H, 6.96%; N, 6.45%.

Found " " : C, 71.78%; H, 7.03%; N, 6.74%.

The compound was further identified by the determination of the molecular weight by the depression of the freezing point using Beckmann's apparatus.

Substance, 0.5230 g. ; Weight of benzene, 21.98 g. ; Depression, 0.218°C.

Molecular weight for C<sub>12</sub>H<sub>13</sub>O<sub>2</sub>N requires 217. Found 215.

#### Notes on improvement of alkylation

(1) The use of anhydrous ether to avoid loss due to the saponifying action of sodium ethylate in alcoholic solution and to allow refluxing at a lower temperature.

(2) The use of continuous stirring to insure thorough mixing of reactants while refluxing.

(3) The use of a three necked, round-bottomed flask, which permits the very slow introduction of the ester by means of a dropping funnel.

The ester seems to react with the sodium more completely to form a mono-sodium salt, thus insuring the greatest possible yield of the ethylated ester.



3. 5,5-Ethylphenyl-4-aminobarbituric Acid,  $(C_6H_5)(C_2H_5)C \cdot \overline{CONHCOONH} \cdot C-NH_2$ .

The method of Conrad for the preparation of diethylbarbituric acid was followed:

Sodium ethylate was prepared from 200 g. of absolute ethyl alcohol and 15.0 g. of sodium. To it were added 65 g. of ethyl cyanoethylphenyl acetate and 20 g. of urea. This mixture was heated under reflux for eight hours. The alcohol was distilled off on a steam bath. The residue was dissolved in 800 c.c. of water and the unaltered ester removed by extraction with ether. The aqueous layer was acidified with a slight excess of concentrated hydrochloric acid. A pure white amorphous substance was precipitated. After filtering and drying, the crude product weighed 25 g. or 36% of the theoretical. Upon recrystallization from water the 5,5-ethylphenyl-4-aminobarbituric acid melted at 264 to 265° C.

Properties

<u>Insoluble</u>	<u>Slightly soluble</u>	<u>Soluble</u>
Cold water	Hot water	Hot alcohol
Cold benzene	Hot benzene	Hot chloroform
Cold ligroin	Ether	Dilute sodium hydroxide
	Cold alcohol	
	Cold chloroform	
	Hot ligroin	

Identification

Analyses:

Substance, 0.1880 g. ;  $CO_2$ , 0.4276 g. ;  $H_2O$ , 0.0925 g.

Substance, 0.2791 g. ; Vol. of 0.1 N. acid, 35.74 c.c. (Kjeldahl).

Calculated for  $C_{12}H_{13}O_2N_3$ : C, 62.30%; H, 5.67%; N, 16.18%.

Found " " : C, 62.05%; H, 5.51%; N, 17.52%.

Molecular Weight (Boiling Point).

Substance, 0.2174 g. ; Weight of ethyl alcohol, 39.36 g. ; Elevation, 0.025° C.  
 Calculated for  $C_{12}H_{13}O_5N_3$ : 251.15. Found: 251.1.

4. 5,5-Ethylphenylbarbituric Acid,  $(C_6H_5)(C_2H_5)C \cdot CO \cdot NH \cdot CO \cdot NH \cdot CO$ . -

Ten grams of 5,5-ethylphenyl-4-izino-barbituric acid were added to 500 c.c. of 3.3 N. hydrochloric acid and the solution was boiled for a short time. Upon cooling a pure white crystalline substance was precipitated. After filtering and drying, the crude product melted at 171° C. and weighed 10 g. or 100% yield. Upon recrystallization from water the melting point was 173° C. A mixed melting point of 171° C. was obtained with a mixture of this pure compound and a sample prepared by the method of Pising and Stieglitz.<sup>2</sup> The compound was also identified by analysis:

Substance, 0.1695 g. ;  $CO_2$ , 0.3634 g. ;  $H_2O$ , 0.0810 g.

Substance, 0.3178 g. ; Vol. of 0.1 N. acid, 27.10 c.c. (Kjeldahl).

Calculated for  $C_{12}H_{13}O_5N_3$ : C, 62.04%; H, 5.21%; N, 12.05%.

Found " " : C, 61.63%; H, 5.35%; N, 11.97%.

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## II. The Preparation of N,N - Isononylphenylbarbituric Acid.

### 1. Ethyl isononylcyanophenylacetate, (CH<sub>3</sub>)<sub>2</sub>CHCH<sub>2</sub>CH<sub>2</sub> · C(CN) (C<sub>6</sub>H<sub>5</sub>) (CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>).

The most satisfactory results were obtained in both yield and purity of the product when sodamide was used according to our modifications of the method of alkylation of Beaudou and Taboury.<sup>13</sup>

Two hundred grams of anhydrous ether and 19.1 grams of finely powdered sodamide were placed in a dry 1 - liter three necked, round-bottomed flask. During constant stirring, 97g. of freshly distilled ethyl cyanophenylacetate were added dropwise. A vigorous reaction ensued with the evolution of ammonia. The formation of a tan precipitate was the evidence for the existence of the sodium salt of ethyl cyanophenylacetate. After all of the ester had been added, the reaction mixture was refluxed on steam-bath over night. At this time ten more grams of ethyl cyanophenylacetate along with 50 g. of absolute ethyl alcohol were added to insure the using up of all the sodamide. After a period of refluxing for two hours, 70 g. of freshly distilled isononyl iodide (b.p. 147° C.) were added dropwise through the separatory funnel. Then the mixture was refluxed for four days with constant stirring. Internal temperature of flask during this time was 39° C., that is, on thermometer that replaced the dropping funnel. After the excess ether was distilled off, the contents of the flask were refluxed again over night with the internal temperature observed as 78° C. That the reaction had not gone to completion was shown by the fact that the mixture in the flask was still alkaline to litmus. Dilute H<sub>2</sub>SO<sub>4</sub> (20% by weight) was added until mixture in the flask was slightly acidified. Then enough water was added to dissolve the sodium iodide formed in the reaction and to cause the ether layer containing the alkylated ester to separate. The ether layer was

separated from the aqueous layer. The aqueous layer contained a small amount of ester and was extracted twice with ether. All ether layers were combined and dried over calcium chloride. The calcium chloride was filtered off after about eight hours of standing. The ether was distilled off and the remaining dark red liquid distilled in vacuo.

Up to  $140^{\circ}\text{C}$ ., at 11 mm., there was obtained a dark red liquid and some purple iodine fumes were formed. This change was complete below  $140^{\circ}$  and a dark red liquid still remained in the distilling flask. From  $140$  to  $165^{\circ}$  the remaining liquid came over. The latter product was redistilled and the fractions collected at a pressure of 11 mm. were between  $140$  to  $164^{\circ}$  and  $164$  to  $174^{\circ}$ . The higher fraction boiled chiefly at  $169^{\circ}$  and weighed 73.8 g. The lower fraction was redistilled and 7 g. more of a liquid boiling between  $164$  to  $170^{\circ}$  were obtained. The total yield of a straw-colored liquid boiling principally at  $169^{\circ}$  at 11 mm. was 80.3 g. or 88.2% of the theoretical. A portion was purified, for identification, by successive distillations until colorless;  $d_4^{20} = 1.005$ .

The alkylated ester was identified by analysis:

Substance, 0.1892 g. ;  $\text{CO}_2$ , 0.513 g. ;  $\text{H}_2\text{O}$ , 0.1376 g.

Substance, 0.3153g. ; Vol. of 0.1 N. acid, 12.30 c.c. (Kjeldahl).

Calculated for  $\text{C}_{11}\text{H}_{21}\text{O}_2\text{N}$ : C, 74.08%; H, 8.17%; N, 4.87%.

Found " " : C, 73.94%; H, 8.23%; N, 5.08%.

The compound was further identified by the determination of the molecular weight by the depression of the freezing in benzene using Beckmann's apparatus.

Substance, 0.3015 g. ; Weight of benzene, 21.98 g. ; Depression,  $0.267^{\circ}\text{C}$ .

Calculated molecular weight for  $\text{C}_{11}\text{H}_{21}\text{O}_2\text{N} = 255$ ; found 267.

2. 5,5-Isocumylphenyl-4-iminobarbituric Acid,  $(C_6H_5)(C_6H_{11})C \cdot CONHCONH \cdot C'NH$ .

The procedure on page 12 was followed.

The materials taken were:

Ethyl isocumylcyanophenylacetate (b.p. 164 to 174° C. at 11mm.).....	70 g.
Sodium.....	12.5 g.
Absolute ethyl alcohol.....	200 g.
Urea.....	20 g.

The yield of 5,5-isocumylphenyl-4-iminobarbituric acid was 7.5 g. or approximately 10% of the theoretical. A melting point of 251° C. was obtained for the compound after recrystallizing from alcohol.

Properties

<u>Insoluble</u>	<u>Slightly soluble</u>	<u>Soluble</u>
Cold alcohol	Hot water	Hot alcohol
Cold water	Hot ligroin	Hot chloroform
Cold ligroin	Hot benzene	Dilute sodium hydroxide
Cold benzene	Cold chloroform	
Dilute HCl	Cold alcohol	
	Ether	

Identification

Analyses:

Substance, 0.2126 g. ; CO<sub>2</sub>, 0.6118 g. ; H<sub>2</sub>O, 0.13296 g.

Substance, 0.1409 g. ; Vol. of 0.1 N. acid, 15.44 c.c. (Kjeldahl).

Calculated for C<sub>12</sub>H<sub>16</sub>O<sub>2</sub>N<sub>2</sub>: C, 65.69%; H, 7.01%; N, 15.36%.

Found " " : C, 65.59%; H, 6.96%; N, 15.34%.

Molecular Weight (Boiling Point):

Substance, 0.2036 g. ; Weight of ethyl alcohol, 39.35 g. ; Elevation, 0.023° C.  
 Calculated molecular weight for  $C_{15}H_{19}O_3N_2$  = 273.18; found 255.

3. 5,5-Isocamylphenylbarbituric Acid,  $(C_6H_{11})(C_6H_5)C \cdot CONHCONH \cdot CO$ . - The procedure on page 13 was followed.

The materials taken were:

5,5-Isocamylphenyl-4-aminobarbituric acid.....6 g.  
 3.3 N. HCl.....250 c.c.

The yield of 5,5-isocamylphenylbarbituric acid was 6 g. or approximately the theoretical. Recrystallized from water the compound showed a melting point of 181° C.

Properties

<u>Insoluble</u>	<u>Slightly soluble</u>	<u>Soluble</u>
Cold ligroin	Ether	Hot alcohol
Cold benzene	Hot water	Hot chloroform
Cold water	Hot ligroin	Dilute NaOH
Dilute HCl	Hot benzene	
	Cold alcohol	
	Cold chloroform	

IdentificationAnalyses:

Substance, 0.1948 g. ;  $CO_2$ , 0.4689 g. ;  $H_2O$ , 0.1155 g.  
 Substance, 0.3269 g. ; Vol. of 0.1 N. acid, 23.47 c.c. (Kjeldahl).  
 Calculated for  $C_{15}H_{19}O_3N_2$ : C, 65.65%; H, 6.51%; N, 10.22%.  
 Found " " : C, 65.64%; H, 6.89%; N, 10.05%.

Molecular Weight (Boiling Point):

Substance, 0.1556 g. ; Weight of ethyl alcohol, 39.35 g. ; Elevation, 0.017° C.  
 Calculated molecular weight for  $C_{15}H_{19}O_3N_2$  = 274.16; found 269.2.

III. The Preparation of 5,5 - n. - Heptylphenylbarbituric Acid.

1. Ethyl cyano-n.-heptylphenylacetate,  $(C_7H_{15})(C_6H_5)C(CN)(CO_2C_2H_5)$ . - The ester was prepared by the procedure on page 14.

The materials taken were:

Ethyl cyanophenylacetate (b.p. 148 to 158° C. at 11 m.m.).....105 g.  
Sodamide (finely powdered).....23.2 g.  
n.-Heptyl bromide (b.p. 178.8° C. at 760 m.m.).....100 g.  
Anhydrous ether.....300 g.  
Absolute ethyl alcohol.....60 g.

The ethyl cyano-n.-heptylphenylacetate (b.p. 187 to 193° C. at 9 m.m., principally at 190°) amounted to 120 g. or 75% of the theoretical;  $d_4^{20} = .957$ .

The alkylated ester was identified by analysis:

Substance, 0.1879 g. ;  $CO_2$ , 0.5169 g. ;  $H_2O$ , 0.1480 g.

Substance, 0.2592 g. ; Vol. of 0.1 N. acid, 9.42 c.c. (Kjeldahl).

Calculated for  $C_{15}H_{25}O_2N$ : C, 75.21%; H, 8.77%; N, 4.87%.

Found " " : C, 75.02%; H, 8.81%; N, 5.06%.

The ester was further identified by determination of its molecular weight by the freezing point depression in benzene.

Substance, 0.2715 g. ; Weight of benzene, 21.98 g. ; Depression, 0.218° C.

Calculated molecular weight for  $C_{15}H_{25}O_2N$  = 287; found 290.

2. 5,5-n.-Heptylphenyl-4-iminobarbituric Acid,  $(C_7H_{15})(C_6H_5)C \cdot \overline{CONHCONH} \cdot C_1NH$ .

The procedure on page 12 was followed.

The materials taken were:

Ethyl cyano-n.-heptylphenylacetate (b.p. 187 to 193° C. at 9 m.m.)....90 g.  
 Sodium.....15 g.  
 Absolute ethyl alcohol.....200 g.  
 Urea.....25 g.

The yield of 5,5-n.-heptylphenyl-4-iminobarbituric acid was 6.5 g. or about 7% of the theoretical. Recrystallized from 95% ethyl alcohol it melted at 259° C.

### Properties

<u>Insoluble</u>	<u>Slightly soluble</u>	<u>Soluble</u>
Cold alcohol	Ether	Hot alcohol
Cold water	Hot water	Hot chloroform
Cold ligroin	Hot ligroin	Dilute NaOH
Cold benzene	Hot benzene	
Dilute HCl	Cold chloroform	

### Identification

#### Analyses:

Substance, 0.1714 g. ; CO<sub>2</sub>, 0.4255 g. ; H<sub>2</sub>O, 0.1188 g.

Substance, 0.3409 g. ; Vol. of 0.1 N. acid, 33.83 c.c. (Kjeldahl).

Calculated for C<sub>17</sub>H<sub>25</sub>O<sub>2</sub>N<sub>2</sub>: C, 67.73%; H, 7.70%; N, 13.95%.

Found " " : C, 67.76%; H, 7.63%; N, 13.86%.

#### Molecular Weight (Boiling Point):

Substance, 0.1652 g. ; Weight of ethyl alcohol, 59.175 g. ; Elevation, 0.012° C.

Calculated molecular weight for C<sub>17</sub>H<sub>25</sub>O<sub>2</sub>N<sub>2</sub> = 302.19; found 299.9.



3. 5,5 - n. - Heptylphenylbarbituric Acid,  $(C_7H_{15})(C_6H_5)C \cdot CONHCONH \cdot CO$ . - The procedure on page 13 was followed.

The materials taken were:

- 5,5-n.-heptylphenyl-4-iminobarbituric acid .....5 g.
- 3.3 N. HCl.....200 c.c.

The yield of 5,5-n.-heptylphenylbarbituric acid was 5 g. or approximately the theoretical. It was recrystallized from 95% ethyl alcohol and showed a melting point of 150°C.

Properties

<u>Insoluble</u>	<u>Slightly soluble</u>	<u>Soluble</u>
Cold water	Ether	Hot alcohol
Cold ligroin	Hot water	Hot chloroform
Cold benzene	Hot ligroin	Dilute NaOH
Dilute HCl	Hot benzene	
	Cold alcohol	
	Cold chloroform	

Identification

Analyses:

Substance, 0.1838 g. ; CO<sub>2</sub>, 0.4544 g. ; H<sub>2</sub>O, 0.1321 g.

Substance, 0.5569 g. ; Vol. of 0.1 N. acid, 43.22 c.c. (Kjeldahl)

Calculated for C<sub>17</sub>H<sub>24</sub>O<sub>3</sub>N<sub>2</sub>: C, 67.51%; H, 7.34%; N, 9.27%.

Found " " : C, 67.42%; H, 7.44%; N, 9.21%.

Molecular Weight (Boiling Point):

Substance, 0.1722 g. ; Weight of ethyl alcohol, 39.35 g. ; Elevation, 0.018°C.

Calculated molecular weight for C<sub>17</sub>H<sub>24</sub>O<sub>3</sub>N<sub>2</sub> - 302.19; found 279.5.

Summary of Properties, Yields and Analyses.

Alkyl Substituted Oromphenylacetic Ethylesters.

Alkyl Radical	$T_d^{20}$	Boiling Point °C.	M. P.	Yield	Carbon Calcd.	Obs.	Hydrogen Calcd.	Obs.	Nitrogen Calcd.	Obs.	Mol. Wgt. Calcd.	Obs.
Ethyl	1.065 <sup>14</sup>	147	11	75	71.90	71.78	6.96	7.05	6.45	6.74	217	218
1so-Amyl	1.006 <sup>14</sup>	178	18	88.2	74.08	73.94	8.17	8.25	5.41	5.48	259	263
n.-Heptyl	0.967 <sup>14</sup>	190	9	75	75.21	75.02	8.77	8.81	4.87	5.08	287	290

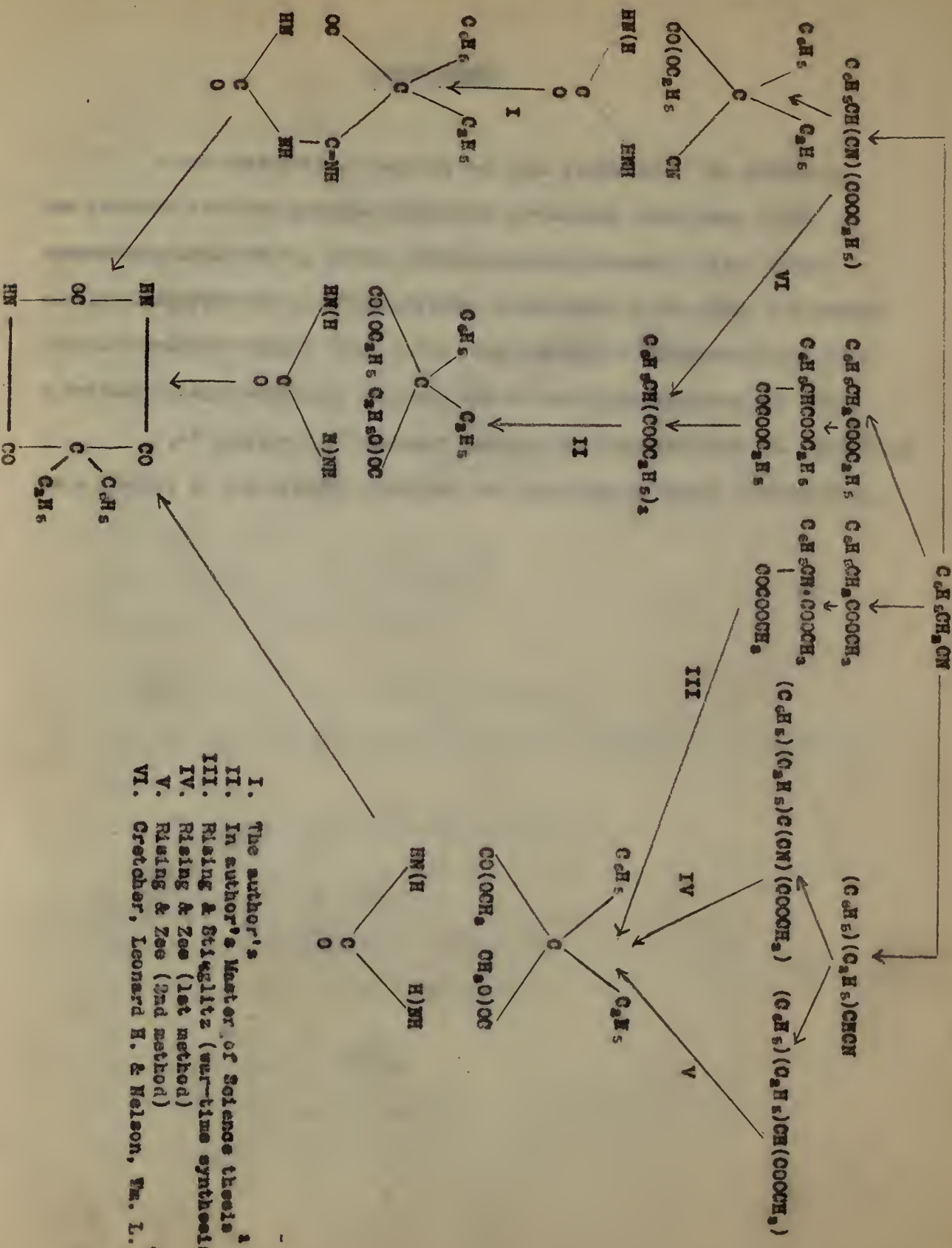
h - Alkyl Substituted - 5 - Phenyl - 4 - Indolebutiric Acids.

Alkyl Radical	Recrystallized from	M. P. °C.	Yield	Carbon Calcd.	Obs.	Hydrogen Calcd.	Obs.	Nitrogen Calcd.	Obs.	Mol. Wgt. Calcd.	Obs.
Ethyl	Water	264	38	62.30	62.06	5.67	5.51	18.18	17.92	231	264
1so-Amyl	Alcohol	261	10	65.89	65.59	7.01	6.99	15.38	15.34	273	285
n.-Heptyl	Alcohol	259	7	67.73	67.70	7.70	7.65	15.95	15.86	301	300

5 - Alkyl Substituted - 5 - Phenylbutiric Acids.

Alkyl Radical	Recrystallized from	M. P. °C.	Yield	Carbon Calcd.	Obs.	Hydrogen Calcd.	Obs.	Nitrogen Calcd.	Obs.	Mol. Wgt. Calcd.	Obs.
Ethyl	Water	178	100	62.04	61.68	5.21	5.36	12.06	11.97	232	—
1so-Amyl	Alcohol	181	100	65.65	65.64	6.61	6.69	10.22	10.06	274	269
n.-Heptyl	Alcohol	150	100	67.51	67.42	7.34	7.41	9.27	9.21	302	279.5

A Summary of the Reactions Involved in the Synthesis of Luminal.



- I. The author's
- II. In author's Master of Science thesis
- III. Rising & Steglitz (war-time synthesis)
- IV. Rising & Zee (1st method)
- V. Rising & Zee (2nd method)
- VI. Crecher, Leonard H. & Nelson, Wm. L.

### CONCLUSIONS

A new synthesis of Luminal has been performed. The following new products have been prepared and their properties described: ethyl cyanoethylphenylacetate, ethyl isoamylcyanophenylacetate, ethyl cyanon-heptylphenylacetate, 5,5-ethylphenyl-4-iminobarbituric acid, 5,5-isoamylphenyl-4-iminobarbituric acid, 5,5-n-heptylphenyl-4-iminobarbituric acid, 5,5-isoamylphenylbarbituric acid and 5,5-n-heptylphenylbarbituric acid.

$\alpha, \alpha'$ -dicyano,  $\alpha, \alpha'$ -diphenyl acetone has been isolated and identified as a product of the diethyl carbonate and phenylacetonitrile condensation.

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APPROVAL BY COMMITTEE

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