of these two reactions from the two rate equations

$$k_2[CH_3CH_2O—][CH_3CH_2ONO] \sim 10^9\, e^{-E_2/RT}[CH_3CH_2O—][CH_3CH_2ONO]$$

$$k_4[CH_3CH_2O—] \sim 10^{14}\, e^{-E_4/RT}[CH_3CH_2O-]$$

Equating these and solving for the concentration of ethyl nitrite we obtain

$$[CH_3CH_2ONO] = 10^5\, e^{-(E_4-E_2)/RT}$$

If we make a very rough approximation and assume that the two rates are equal at 0.01 atmospheres when the temperature is 500°K. we have

$$10^{-2} = 10^5 \times 10^{-(E_4-E_2)/4.6\times 500} \text{ or } E_4 - E_2 = 16 \text{ Cal.}$$

It is probable that reaction (2) requires a somewhat higher activation energy than does reaction (5); taking this into account as well as previous estimates[7] for analogous reactions, it seems plausible to assume that E_2 and E_4 have values in the range 12–18 Cal. and 28–34 Cal., respectively.

We wish to thank Dr. O. K. Rice for suggestions received in connection with the interpretation of these experiments.

Summary

When pure ethyl nitrite vapor at low pressures is decomposed in a flowing system, cold metallic mirrors are not affected by the gases leaving the furnace. On the other hand, if the ethyl nitrite is diluted with an inert gas, mirrors are readily removed, even when the furnace is at temperatures as low as 425° and this behavior may be explained by assuming that the interaction of a free radical with ethyl nitrite results in the production of molecules only.

The activation energy of the primary dissociation of ethyl nitrite was found to be 34.3 ± 3 Cal.

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[CONTRIBUTION FROM THE GOESSMANN CHEMISTRY LABORATORY, MASSACHUSETTS STATE COLLEGE]

The Synthesis of 5,5-Alkylphenylbarbituric Acids[1,2]

BY J. S. CHAMBERLAIN, J. J. CHAP, J. E. DOYLE AND L. B. SPAULDING

The syntheses of ethylphenylbarbituric acid, Luminal or Phenobarbital, by Rising and Stieglitz,[3] by Rising and Zee,[4,5] and by Cretcher and Nelson,[6] all start with phenylacetonitrile and by three to five steps obtain alkylphenylmalonic ester. This is then condensed with urea, by heating under pressure or at the high boiling point of the mixture, the product being the desired alkylphenylbarbituric acid. In the synthesis of Cretcher and Nelson and according to Hessler[7] and Bodreux,[8] phenylacetonitrile condenses with diethyl carbonate in ether solution, with sodamide, yielding cyanophenylacetic ester (phenylmalonic nitrile). Hörlein[9] ethylates this ester to cyanoethylphenylacetic ester and Conrad[10] and Tabern and Volwiler[11] have condensed the cyanoethylphenyl-(or cyanodialkyl)-acetic ester with urea yielding iminobarbituric acids which readily hydrolyze to the barbituric acids.

The present investigation consists of the preparation, by means of this general series of reactions, of four hitherto unprepared alkylphenylbarbituric acids. The results may be summarized as follows.

(1) The condensation of phenylacetonitrile with diethylcarbonate is best effected by using sodamide as condensing agent in absolutely anhydrous ether, with continued stirring and efficient refluxing. The product is ethyl cyanophenylacetate.

(2) A by-product results from the probable reaction of two molecules of the nitrile with one molecule of the carbonate and its formation is favored by non-anhydrous conditions and by too long refluxing. The compound proved to be α,α'-dicyano-α,α'-diphenylacetone.

(3) Alkylation of the cyanophenylacetate and the condensation of the resulting cyanoalkylphenylacetate with urea take place in ether–alcohol and in absolute alcohol in the presence of sodamide or sodium ethylate. The product of the

(1) The work reported in this paper represents part of the material contained in theses presented by Messrs. Chap, Doyle and Spaulding to the Graduate School of the Massachusetts State College in 1933 and 1934 for advanced degrees, and is published with the consent of the Director of the Graduate School.

(2) Presented before the Division of Organic Chemistry at the Cleveland Meeting of the American Chemical Society, Sept. 10–14, 1934.

(3) Rising and Stieglitz, THIS JOURNAL, **40**, 723 (1918).

(4) Rising and Zee, *ibid.*, **49**, 541 (1927).

(5) Rising and Zee, *ibid.*, **50**, 1208 (1928).

(6) Cretcher and Nelson, *ibid.*, **50**, 2758 (1928).

(7) Hessler, *Am. Chem. J.*, **32**, 119 (1904).

(8) Bodreux, *Compt. rend.*, **151**, 1358 (1910).

(9) Hörlein, *C. A.*, **6**, 3312 (1912).

(10) Conrad, *Ann.*, **340**, 310 (1905).

(11) Tabern and Volwiler, THIS JOURNAL, **56**, 1130 (1934).

condensation is 5,5-alkylphenyl-4-iminobarbituric acid which, in turn, is easily hydrolyzed, in 3.3 *N* hydrochloric acid, with practically the theoretical yield of the alkylphenylbarbituric acid.

(4) The maximum yield of the barbituric acid, Luminal, was 19.2% compared with 17.2% by previous syntheses.[5]

(5) The following 5,5-alkylphenylbarbituric acids, with the intermediate cyanophenylacetates and alkylphenyliminobarbituric acids, have been synthesized, with analyses and determinations of physical constants: (A) isopropyl-, (B) isoamyl-, (C) *n*-hexyl-, (D) *n*-heptyl-.

Experimental

I. **Ethyl Cyanophenylacetate,** $C_6H_5CH(CN)COOC_2H_5$. —According to the methods previously referred to[6,7,8] and with precautions mentioned in the preceding summary, phenylacetonitrile was condensed with diethylcarbonate. The yield of the cyanophenylacetate was 70.3%, b. p., 145° (7 mm.), 165° (19 mm.), *d* 20/4 1.091.

α,α′-Dicyano-α,α′-diphenylacetone, $(C_6H_5)(CN)CH-COCH(CN)(C_6H_5)$.—After the distillation of the preceding crude product, the residue solidified. On extraction of this residue with hot ether or ligroin, to remove traces of the ester and resinous products, the remaining product was a pure white, crystalline substance. On recrystallization from hot alcohol or hot benzene the pure compound gave m. p. 260–262°. The maximum yield was about 30%, and the yield was increased by non-anhydrous conditions or by too long continued refluxing. The compound is insoluble in water, ether, ligroin or dilute acids or alkalies, slightly soluble in cold alcohol, benzene or chloroform; soluble in hot alcohol, benzene or chloroform and in hot concentrated sulfuric acid.

Anal. Calcd. for $C_{17}H_{12}ON_2$: C, 78.43; H, 4.65; N, 10.77; mol. wt., 260. Found: C, 78.05; H, 4.91; N, 10.62; mol. wt. (boiling point method, Cottrell apparatus), 247.

II. **Ethyl · Cyanoalkylphenylacetates,** $(R)(C_6H_5)(CN)-CCOOC_2H_5$.—The alkylation of the cyanophenylacetate was as follows: to 200 g. of anhydrous ether and 11.5 g. of clean sodium wire there was added, drop by drop, 95 g. of freshly distilled ethyl cyanophenylacetate, with stirring and refluxing which was continued overnight or until evidence showed the completion of the reaction. Excess sodium was destroyed by adding a little methyl alcohol and fresh ether to replace loss. One hundred grams of freshly distilled ethyl iodide (or the necessary amount of other desired alkyl halide) was then added, drop by drop, and the stirring and refluxing continued for four days. Fresh ether and more halide were added if necessary. The completion of the reaction was indicated by the fact that the mixture in the flask was no longer alkaline to litmus. A few drops of 20% sulfuric acid were now added to

COMPOUNDS, PROPERTIES AND ANALYSES

	Alkyl (R)	Solubility	Yield, %	B. p., °C./mm.	$d^{20}/_4$	Mol. wt. Calcd.	Mol. wt. Found	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
	II. Ethyl Cyanoalkylphenylacetates, $(R)(C_6H_5)(CN)CCOOC_2H_5$												
1	Ethyl		76.0	147 11	1.065	217.13	215 (f. p.)	71.84	71.78	6.96	7.03	6.45	6.74
2	Isopropyl		28.1	165 25									
3	Isoamyl		88.2	169 11	1.005	259.17	263 (f. p.)	74.08	73.94	8.17	8.23	5.41	5.49
4	*n*-Hexyl		60.5	182–184 10								5.12	5.23
5	*n*-Heptyl		75.0	190 9	0.957	287.21	290 (f. p.)	75.21	75.02	8.77	8.81	4.88	5.08
	III. 5,5-Alkylphenyl-4-iminobarbituric Acids, $(R)(C_6H_5)\overset{\frown}{C}CONHCONH\overset{\frown}{C}=NH$			M. p.									
6	Ethyl	Hot alc. or chl.	36.0	264		231.13	254 (b. p.)	62.30	62.05	5.67	5.51	18.18	17.92
7	Isopropyl	Eth., hot alc.	7.5	290									
8	Isoamyl	Hot alc. or chl.	10.0	251		273.17	255 (b. p.)	65.89	65.59	7.01	6.99	15.38	15.34
9	*n*-Hexyl	Alc. s. s. hot H_2O	6.0	235–238									
10	*n*-Heptyl	Hot alc. or chl.	7.0	259		301.21	299.9 (b. p.)	67.73	67.70	7.70	7.63	13.95	13.85
	IV. 5,5-Alkylphenylbarbituric Acids, $(R)(C_6H_5)\overset{\frown}{C}CONHCONH\overset{\frown}{C}O$												
11	Ethyl (Luminal)	Alc., hot H_2O	100±	172				62.04	61.68	5.21	5.35	12.07	11.97
12	Isopropyl	Hot H_2O or alc.	100±	169									
13	Isoamyl	Hot alc. or chl.	100±	181		274.16	269.2 (b. p.)	65.65	65.64	6.61	6.69	10.22	10.05
14	*n*-Hexyl	Hot alc.	100±	152–155				66.63	66.73	6.99	7.17	9.72	9.45
15	*n*-Heptyl	Hot H_2O, alc. ether, chl.	100±	150		302.19	279.5 (b. p.)	67.51	67.42	7.34	7.44	9.27	9.21

ensure acidity and then sufficient water to dissolve the sodium iodide and to cause a separation of the ether layer. The ether layer was removed and the aqueous solution extracted with fresh ether. The combined ether solutions were dried and the ether distilled. The residue was fractionally distilled under reduced pressure. The alkylphenyl derivatives given under II in the table were prepared in this way.

III. (R)(C_6H_5)$\overline{\text{C}}$CONHCONHC=NH, **5,5-Alkylphenyl-4-iminobarbituric Acids.**—The condensation of the cyanoalkylphenylacetates with urea, with the formation of 5,5-alkyl-4-iminobarbituric acids, was by the method of Conrad.[10] Sodium ethylate, prepared from 13 g. of sodium wire in 200 g. of absolute ethyl alcohol, was placed in the previously described three-necked flask and to it were added 65 g. of ethyl cyanoethylphenylacetate, or an equivalent amount of one of the other cyanoalkylphenylacetates, and 20 g. of urea. The mixture was heated, stirred and refluxed for eight hours. The alcohol was then distilled off and the residue dissolved in about 800 cc. of water. The unchanged acetate was removed by extraction of the water solution with ether. The aqueous solution was then acidified with a slight excess of concentrated hydrochloric acid. Pure white precipitates were obtained, filtered off and dried as crude products. The compounds prepared are given under III in the table.

IV. (R)(C_6H_5)$\overline{\text{CCONHCONHCO}}$, **5,5-Alkylphenylbarbituric Acids.**—The hydrolysis of the iminobarbituric acids was easily accomplished by boiling about 10 g. for a short time in about 500 cc. of 3.3 *N* hydrochloric acid On cooling the barbituric acid separates as a white crystalline product usually in the theoretical yield from the imino acid. The acids prepared are given under IV in the table

Conclusions

In the syntheses described sodamide was a most efficient condensing agent. Absolutely anhydrous reagents and conditions, continued stirring and efficient refluxing are essential. Five 5,5-alkylphenylbarbituric acids have been synthesized successfully, four of them hitherto unsynthesized by this method. In most cases the general properties and physical constants have been determined for the cyanoalkylphenylacetates, the 5,5-alkylphenyl-4-iminobarbituric acids and the 5,5-alkylphenylbarbituric acids. The pharmacological evaluation of the final barbituric acids has not yet been made.

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[CONTRIBUTION FROM THE DEPARTMENT OF AGRICULTURAL CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Chemistry of Mold Tissue. VII. The Lipids of Penicillium Aurantio-Brunneum[1]

BY E. H. KROEKER, F. M. STRONG AND W. H. PETERSON

As an extension of the previously reported study of the lipids of *Aspergillus sydowi*,[2] it seemed desirable to examine at least one representative of the *Penicillium* species of mold fungi. *Penicillium aurantio-brunneum* was selected for this purpose because it grew well on a synthetic medium and contained a fairly large amount of lipoidal material.

While the present investigation was in progress, a paper appeared by Ward and Jamieson[3] concerning the fat from *Penicillium javanicum*. The composition of this fat appears to be roughly similar to that of *A. sydowi*, and *P. aurantio-brunneum*.

Experimental Part

Extraction and Preliminary Fractionation of Crude Lipids.—The mold used was grown for ten days on a glucose–inorganic salts medium in large sterilized incubators.[4] The pads were then killed by steaming, dried at 65° and finely ground. The ground mycelium (4110 g.) was extracted with alcohol–ether (1:1), and the extracts worked up as previously described.[2] The yield of crude lipids was 475 g. or 11.6% of the mycelium.

When the crude lipids were poured slowly into three liters of ice-cold acetone, eight grams of an amorphous precipitate separated. This substance contained 3.3% phosphorus and 1.48% nitrogen, the P:N ratio, therefore, being 1:1.01. This behavior is in marked contrast to that of the *A. sydowi* lipids, which contained only a trace of acetone-insoluble phospholipids. Upon further cooling of the acetone solution in an ice–salt bath 78 g. of a dark, viscous oil separated as a distinct layer, and was drawn off (Fraction A). Still further standing of the acetone solution in the ice–salt bath resulted in the precipitation of 35 g. of a light colored solid, which was filtered off (Fraction B). The lipids remaining in the acetone still contained 0.12% phosphorus, which was not precipitable by alcoholic magnesium chloride. Of various other salts tried strontium chloride proved most efficient. The ice-cold acetone solution was, therefore, treated with 25 cc. of saturated alcoholic strontium chloride, and the precipitate (10 g.) separated after several hours of standing in the cold. It contained 2.29% phosphorus and 1.21% nitrogen; P:N ratio, 1:1.17. The remaining acetone solution on concentration yielded 375 g. of "simple lipids" containing only 0.04% phosphorus.

(1) This work was supported in part by a grant from the Wisconsin Alumni Research Foundation.

(2) Strong and Peterson, THIS JOURNAL, **56**, 952 (1934).

(3) Ward and Jamieson, *ibid*, **56**, 973 (1934).

(4) Peterson, Pruess, Gorcica and Greene, *Ind. Eng. Chem.*, **25**, 213 (1933).