

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ARKANSAS]

DERIVATIVES OF DULCIN¹

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Since the first preparation of dulcin many derivatives of this interesting compound have been made. In some of these the character of the N side chain has been altered² while in others there is a duplication of function³ or a substitution of various groups on the benzene ring.⁴ Certain generalizations have been drawn relative to the effect of constitution upon taste⁵ but the state of existing knowledge of this subject is unsatisfactory because an insufficient number of derivatives has been examined. The preparation of new derivatives as reported in this and other papers was undertaken in this Laboratory in the hope of obtaining a more complete understanding of the basic problem.

Reaction of Dulcin with Ethyl Chloroformate.—This reaction yields both types of derivatives noted above, those with altered side chain and with duplicated function. The following compounds were prepared: ethyl *p*-phenetyl-allophanate, *p*-phenetyl-biuret, bis-(*p*-phenetyl)-urea and bis-(*p*-phenetyl)-biuret. All were found to be tasteless.

Sulfur Derivatives of Dulcin.—*p*-Anisyl- and *p*-phenetyl-thiourea have already been prepared.⁶ The taste of the former has not been reported; the latter is very bitter.⁷ A bitter taste is characteristic for the reported aromatic thioureas while numerous urea compounds are sweet tasting. In the thioanisyl- and thiophenetyl-urea reported herein (isomeric with the compounds of Dyson and George) the thio-ether group (normally giving a bitter taste) is "opposed" to the carbamido group. The result in each case is a practically tasteless compound. Thioanisyl- and thiophenetyl-thiourea in which both oxygen atoms are substituted by sulfur were also prepared. These derivatives have a strongly bitter taste which is very lasting.⁸

¹ Paper No. 215, Journal Series, University of Arkansas.

² Lumière and Perrin, *Bull. soc. chim.*, [3] 29, 966 (1903); Borsche, *Ann.*, 334, 185 (1904); Lange, Ebert and Youse, *This Journal*, 51, 1912 (1929); Gilman and Hewlett, *Iowa State College J. Sci.*, 4, No. 1, 27-33 (1929).

³ Interesting examples of such duplication are found in the diureido derivatives of phenetole (*cf.* Lorang's paper).

⁴ Spiegel, Munblit and Kaufmann, *Ber.*, 39, 3243 (1906); Lorang, *Rec. trav. chim.*, 47, 179 (1928) (contains a review of previous work).

⁵ Thate, *ibid.*, 48, 116 (1929); *cf.* also Lorang's paper.

⁶ Dyson and George, *J. Chem. Soc.*, 125, 1708 (1924).

⁷ Cohn, "Die Organischen Geschmacksstoffe," F. Siemenroth, Berlin, 1914, p. 747.

⁸ The compounds were tasted by the writer and three advanced students who passed a preliminary training and examination using solutions of dulcin and saccharin. All compounds and solutions were given code numbers and no discussion of results was per-

Experimental Part

Ethyl *p*-Phenetyl-allophanate. $p\text{-EtOC}_6\text{H}_4\text{NHCONHCO}_2\text{Et}$.—A mixture of 20 g. of dulcin and 10 g. of ethyl chloroformate was heated in the free flame until homogeneous and then in an oil-bath maintained at a temperature of 100° for two hours. Upon cooling the mix solidified. It was twice recrystallized from hot amyl alcohol or from equal parts of amyl and ethyl alcohols. The crystals were washed with petroleum ether and ethanol; yield, about 3.5 g.; white needles, m. p., 139–140°; tasteless; soluble in benzene, xylene, ethanol, amyl alcohol, hot water and acetic acid.

***p*-Phenetyl-biuret,** $p\text{-EtOC}_6\text{H}_4\text{NHCONHCONH}_2$.—Four grams of ethyl *p*-phenetyl-allophanate together with 10 cc. of concentrated ammonium hydroxide was placed in a sealed tube and heated to a temperature of 100° for four hours. At this time the tube contained a white solid and red supernatant liquid. The materials were washed from the tube with hot water and, after neutralization with dilute hydrochloric acid, subjected to filtration. The solid was dried, after which it was well washed with hot benzene (to remove unchanged allophanate), followed by petroleum ether. After recrystallization from dilute acetic acid the compound had a melting point of 185–186°; yield, 1.3 g.; white, amorphous, tasteless compound; soluble in ethanol, hot xylene, acetic acid; sparingly soluble in benzene.

Bis-(*p*-phenetyl)-urea, $(p\text{-EtOC}_6\text{H}_4\text{NH})_2\text{CO}$.—A mixture of 5 g. of ethyl chloroformate and 18 g. of dulcin was heated in an oil-bath for two hours at a temperature of 175°. The resulting solid was washed with hot ethanol and filtered by suction. It was next washed several times with hot acetic acid, then with ether. (The acetic acid solution was reserved—see below.) The compound was recrystallized from benzyl alcohol and washed with ether: yield, 0.6 g.; white microscopic needles; tasteless; melting point, 225–226°. The identity of the compound was confirmed by analysis for nitrogen.⁹

Bis-(*p*-phenetyl)-biuret, $(p\text{-EtOC}_6\text{H}_4\text{NHCO})_2\text{NH}$.—The acetic acid washings of diphenetyl-urea (see above) when chilled in ice water gave a precipitate which was removed by filtration and washed with ether; yield, 1.4 g.; m. p., 208–209°; white microscopic oblong platelets; tasteless.

TABLE I
ANALYTICAL DATA OF DULCIN DERIVATIVES

Compound	Formula	Carbon, %		Hydrogen, %		Nitrogen, %	
		Calcd.	Found	Calcd.	Found	Calcd.	Found
Ethyl <i>p</i> -phenetyl allophanate	$\text{C}_{12}\text{H}_{16}\text{O}_4\text{N}_2$	57.15	56.71	6.35	6.98	11.11	11.01
			57.11		6.50		
<i>p</i> -Phenetyl-biuret	$\text{C}_{10}\text{H}_{12}\text{O}_3\text{N}_3$	53.81	53.48	5.83	7.40	18.83	18.51
			53.71		5.85		
Bis-(<i>p</i> -phenetyl)-biuret	$\text{C}_{18}\text{H}_{24}\text{O}_4\text{N}_3$	62.99	62.99	6.12	6.31	12.24	11.96
							11.97

***p*-Nitrothiophenol.**—This compound was prepared essentially as directed by Mayer.¹⁰ The yield from 31 g. of nitrochlorobenzene was about 10 g.

In all cases the solid compounds were tasted, also the following solutions, (1) 0.01 g. of compound in 500 cc. of water (38°), (2) 0.01 g. of compound in 50 cc. of ethanol made up to 500 cc. with water. The limited solubility of the compounds prevented the preparation of more concentrated solutions.

⁹ This compound was previously reported by Gattermann and Cantzler, *Ber.*, **25**, 1090 (1892), m. p. 225–226°; by Sonn, *ibid.*, **47**, 2441 (1914), m. p. 225° and by Migliacci and Gargiulo, *Gazz. chim. ital.*, **58**, 110 (1928), m. p. 220°.

¹⁰ Mayer, *Ber.*, **42**, 3050 (1909).

p-Nitrothiophenetole.—This was made from 20 g. of *p*-nitrothiophenol, 3 g. of sodium, 20 g. of ethyl iodide and about 100 cc. of ethanol as outlined by Monier-Williams;¹¹ yield, 15–20 g.

p-Nitrothioanisole.—The same method was used as for nitrothiophenetole. From 20 g. of *p*-nitrothiophenol, 3 g. of sodium, 24 g. of methyl iodide and about 100 cc. of methyl alcohol a yield of about 15 g. was realized.¹²

p-Thiophenetidine.—The directions of Monier-Williams were followed:¹¹ 20 g. of *p*-nitrothiophenetole, 39 g. of tin and 62 cc. of concentrated hydrochloric acid gave a yield of about 12 g.

p-Thioanisidine.—*p*-Nitrothioanisole was reduced with zinc dust and hydrochloric acid. The directions of Zincke and Jörg¹³ were modified in that the preparation was set aside for only three hours and that solid sodium sulfate was used to precipitate the amine sulfate. Twenty grams of nitrothioanisole gave 8–10 g. of the final product.

p-Thiophenetylurea, *p*-EtSC₆H₄NHCONH₂.—Five grams of *p*-thiophenetidine was put into solution in 50 cc. of water upon the addition of 5 cc. of concentrated hydrochloric acid. A solution of 5 g. of potassium cyanate in 25 cc. of water was added in small amounts while the flask was given a thorough shaking. The resulting precipitate was dried and subsequently recrystallized from acetone: yield, 2.5 g.; m. p. 149–150°; glistening white platelets; soluble in the common organic solvents and in hot water. With concentrated sulfuric acid a colorless solution is formed which becomes pale green upon application of heat and again colorless. The solid compound produces a stinging effect upon the tip of the tongue followed by a very slight bitter taste. The prepared solutions were tasteless.

p-Thioanisylurea, *p*-MeC₆H₄NHCONH₂.—Four grams of *p*-thioanisidine dissolved in a solution of 2.35 cc. of concentrated hydrochloric acid and 40 cc. of water was treated with 1.8 g. of potassium cyanate in 25 cc. of water. The compound was recrystallized when dry from dilute ethanol plus a few drops of ammonium hydroxide; yield, 1 g.; white needles, m. p. 164–165°; tasteless.

p-Thiophenethylthiourea, *p*-EtSC₆H₄NHCSNH₂.—Solutions of 2 g. of *p*-thiophenetidine in 15 cc. of water and 2 cc. of concentrated hydrochloric acid, and 2 g. of ammonium thiocyanate in 10 cc. of water were mixed and slowly evaporated to dryness. The dry mass was allowed to stand for about twenty hours, then pulverized and washed with water. It was next covered with hot ethanol, which was subsequently removed by filtration. When cooled the ethanol solution deposited the compound in light yellow platelets: yield, 0.5 g.; m. p. 136–137°; lasting bitter taste.

p-Thioanisylthiourea, *p*-MeC₆H₄NHCSNH₂.—Five and four-tenths grams of *p*-thioanisidine was treated with 25 cc. of water and 3.12 cc. of concentrated hydrochloric acid. The solution was filtered and mixed with a solution of 2.65 g. of ammonium

TABLE II
SULFUR DERIVATIVES OF DULCIN

Compound	Formula	Carbon, %		Hydrogen, %		Nitrogen, %		Sulfur, %	
		Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
<i>p</i> -Thiophenetylurea	C ₈ H ₁₂ ON ₂ S	55.09	55.21	6.12	6.32	14.29	14.44	16.32	16.25
<i>p</i> -Thioanisylurea	C ₈ H ₁₀ ON ₂ S	52.75	52.99	5.49	5.43	15.38	15.47	17.58	17.46
							14.34		
<i>p</i> -Thiophenethylthiourea	C ₈ H ₁₂ N ₂ S ₂	50.95	50.75	5.66	5.76	13.21	13.18	30.19	29.87
<i>p</i> -Thioanisylthiourea	C ₈ H ₁₀ N ₂ S ₂	48.49	48.72	5.05	4.94	14.14	14.28	32.32	31.89
									31.78

¹¹ Monier-Williams, *J. Chem. Soc.*, 89, 278 (1906).

¹² Blanksma, *Rec. trav. chim.*, 20, 403 (1901).

¹³ Zincke and Jörg, *Ber.*, 44, 620 (1911).

thiocyanate in 25 cc. of water. The combined solution was slowly evaporated until a friable solid mass was obtained. This was allowed to stand overnight, then pulverized and washed with boiling water. It was then repeatedly washed with hot water, made strongly ammoniacal and alkaline by the use of sodium and ammonium hydroxide solutions. The compound was finally washed with ethanol and with ether. Some was recrystallized from benzyl alcohol but was not improved by this treatment: yield, about 4 g.; platelets of faint yellow color, m. p. 198–199°; persistent bitter taste.

Summary

Derivatives of dulcin have been prepared in which the N side chain is altered and in which the phenetyl group is duplicated; these are tasteless. Substitution of the ether oxygen of dulcin by sulfur gives tasteless derivatives, while substitution of both oxygens by sulfur yields compounds with a very bitter taste. Seven new compounds are reported.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT AT THE OHIO STATE UNIVERSITY]

NATURAL AND SYNTHETIC RUBBER. VI. THE PYROLYSIS OF NATURAL RUBBER IN THE PRESENCE OF METALLIC OXIDES

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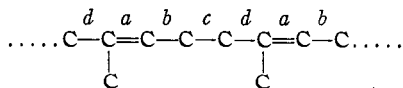
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The first paper of this series¹ describes the influence of metals on the pyrolysis of natural rubber: it shows that the presence of a metal does not change the nature of the pyrolysis products, but affects their relative proportions. In this respect magnesium and zinc are most active. The fact that both zinc oxide and magnesium oxide influence the vulcanization process makes it desirable to study the influence of these compounds on the pyrolysis of rubber.

Experiments similar to these previously reported show that zinc oxide or magnesium oxide acts similarly to zinc or magnesium; zinc oxide has by far the stronger effect. Briefly the nature and proportion of pyrolysis products obtained with zinc oxide duplicate those obtained with magnesium, within experimental error.

Let the rubber molecule be represented by a long open-chain formula, and the various bonds of the chain be designated by letters



The relative numbers of ruptures at *a*, *b*, *c* and *d* during the pyrolysis of straight rubber have been computed from the data previously reported, and are represented by *a* = 0, *b* = 0.6, *c* = 100 and *d* = 0.7. However, a similar computation indicates that, in the case of rubber pyrolyzed with

¹ Midgley and Henne. THIS JOURNAL, 51, 1215 (1929).