The increase in the length of the carbon chain of the alcohol, *e. g.*, γ-diethylaminopropylcinnamate and β-diethylaminoethylcinnamate, results in quite an enhancement of the narcotic effect on goldfish. The hydrocinnamate is inactive in marked contrast to the cinnamate. In this case the saturation of the carbon chain of cinnamic acid causes a decrease in the anesthetic power of the ester. However, phenylpropiolate with the acetylenic linkage appears to be without narcotic effect on goldfish and to be quite toxic. Thus unsaturation alone is not the determinant of anesthetic power even when other groupings are favorable. The dibromohydrocinnamate is still more toxic so that goldfish were killed in a solution of as low as 0.001 molar concentration.

Summary

The properties and narcotic effects on goldfish of the esters, γ-diethylaminopropylcinnamate and α,β-dibromohydrocinnamate, and of the esters, β-diethylaminoethylcinnamate, hydrocinnamate and phenylpropiolate were studied.

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Some Nitrocyclohexylphenols and their Derivatives[1]

BY J. F. BARTLETT[2] AND C. E. GARLAND

Cyclohexylphenols have been prepared by a number of investigators who have used condensing agents such as fused zinc chloride, concentrated sulfuric acid and phosphorus pentoxide. Due to the ease of dehydration of cyclohexanol and the tendency for cyclohexene to polymerize, it has been found necessary to start the reaction at low temperatures. If the formation of an intermediate ether is not an essential part of the reaction mechanism, according to the views of Meyer and Bernhauer[3] we should expect the formation of cyclohexylanisole and cyclohexylphenetole as a result of the condensation of anisole or phenetole with cyclohexanol. An attempted condensation carried out under the same conditions as used for the preparation of the cyclohexylphenols failed to yield the expected products.

Since the cyclohexylphenols were observed to be rather susceptible to the oxidizing action of nitric acid this work was carried out in order to develop methods for control of their nitration. Following the method of Kartashev[4] for the nitration of phenol, in which he used ethyl acetate as a

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(1) Abstracted from a dissertation submitted by John Frank Bartlett in partial fulfilment of the requirements for the degree of Doctor of Philosophy. Contribution No. 86 of the Division of Industrial Sciences of West Virginia University.

(2) D. A. Burt Fellow in Chemistry, 1930–1931, 1931–1932.

(3) Meyer and Bernhauer, *Monatsh.*, **53** and **54**, 721–752 (1929).

(4) Kartashev, *J. Russ. Phys.-Chem. Soc.*, **59**, 819, 833 (1927); **69**, 385, 2129 (1930).

medium, it was found that the addition of phosphorus pentoxide improved the product. By regulation of the temperature either mono- or dinitro derivatives of cyclohexylphenols may be obtained.

Attempts to oxidize the cyclohexyl group in the nitro compounds to a carboxyl with alkaline permanganate, in order to determine structures, were not successful. Heating with fuming nitric acid converted some of the dinitro-*p*-cyclohexylphenol into picric acid, which indicated a 2,6-position for the nitro groups.

Ethers of dinitro-*p*-cyclohexylphenol were not obtained when the alkali salt was treated with alkyl halides. However, when the carefully dried silver salt was used a small yield was obtained. A considerable quantity of the free phenol was recovered in each reaction. The explanation offered by Hantzsch[5] for the formation of aci-nitro ethers and their subsequent rearrangement would seem applicable here.

The aminocyclohexylphenols are very susceptible to oxidation. For this reason they were acetylated with acetic anhydride as formed in the catalytic reduction. Complete reduction of the mononitro derivatives by this process was apparently more difficult to accomplish than that of the dinitrocyclohexylphenols. Mononitro-*o*-cyclohexylphenol was not reduced by hydrogen in the presence of platinum. This observation corresponds with the view of Adams and Heckel[6] in which they consider that *o*-aminophenol acted as a poison to the catalyst.

Experimental

Preparation of the Cyclohexylphenols.—The preparation of the ortho and para cyclohexylphenols was carried out by condensing cyclohexanol with phenol, in the proportion of one mole of each, in the presence of various condensing agents. Schrauth and Gorig[7] had used phosphorus pentoxide as a condensing agent in the preparation of this material. In addition to this reagent, concentrated sulfuric acid and fused zinc chloride were used as condensing agents in the preparation of the cyclohexylphenols. In general the condensing agent was added to a well-cooled mixture of cyclohexanol and phenol and the mixture heated, with stirring, on a water-bath for two or three days.

At the end of the condensation the reaction mixture was poured onto ice. When zinc chloride was used as the condensing agent ammonium hydroxide was added to precipitate the zinc and after the addition of ether the mixture was filtered. When concentrated sulfuric acid or phosphorus pentoxide was used as the condensing agent the mixture, after being poured onto ice, was neutralized with sodium carbonate, ether added and the mixture filtered. The ether was then removed from the extract and the residue subjected to distillation. The part which distilled above 200° was retained and redistilled. On redistillation the fraction distilling above 250° was retained. This fraction was extracted with petroleum ether to remove *o*-cyclohexylphenol. The *p*-cyclohexylphenol was filtered off and purified by recrystallization from hot alcohol. The petroleum ether extract was subjected to distillation, after removing the petroleum ether, and the fraction which distilled between 283–288° was retained. This fraction proved to be *o*-cyclohexylphenol and was a liquid due to the presence of small amounts of impuri-

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(5) Hantzsch, *Ber.*, **39**, 1073 (1906); **40**, 330 (1907).

(6) Adams and Heckel, THIS JOURNAL, **47**, 1712 (1925).

(7) Schrauth and Gorig, *Ber.*, **57**, 856 (1924).

ties. It was obtained as a solid by subjecting it to distillation under a vacuum of four millimeters. At this pressure the ortho derivative boiled between 124–126°.

The yield of the cyclohexylphenols when fused zinc chloride or concentrated sulfuric acid was used as the condensing agent was about 60%. When phosphorus pentoxide was used as the condensing agent the yield was increased to 70%.

Dinitro Derivatives of the Cyclohexylphenols.—A solution of cyclohexylphenol in anhydrous ethyl acetate was subjected to the action of fuming nitric acid (sp. gr. 1.5) in the presence of phosphorus pentoxide. At the end of the reaction the mixture was poured onto ice and the heavy oil which separated was removed and dissolved in hot alcohol, from which, on cooling, crystals of the dinitro derivative separated.

In these nitrations the amount of the fuming nitric acid used was 2.5 times the amount theoretically required to yield the dinitro derivative. while the amount of phosphorus pentoxide was one-half (by weight) that of the cyclohexylphenol used. The amount of solvent was such as to give a 10% solution of cyclohexylphenol.

The nitrations were started at a temperature of 0–5° and not allowed to rise higher until all of the fuming nitric acid had been added. They were then allowed to stand at room temperature for two days.

The dinitro derivatives of the ortho and para cyclohexylphenols are pale yellow crystalline solids. They are insoluble in water but may be readily recrystallized from hot alcohol. They form highly colored salts with alkalies which are only slightly soluble in water.

Mononitro Derivatives of Cyclohexylphenols.—The preparation of these compounds was similar to that of the dinitro derivatives. The amount of fuming nitric acid used was 1.5 times the amount theoretically required to yield the mononitro derivative. The reaction was started at a temperature of −20° and kept below −15° for ten hours. The temperature was then allowed to increase to zero and kept at this point for six additional hours. The reaction mixture after being poured onto ice was extracted with ether and the ethereal solution dried over anhydrous sodium sulfate. After removing the ether the residue was subjected to distillation under a vacuum of 1–2 millimeters. The products were red oils, insoluble in water but soluble in organic solvents such as ether and alcohol. They formed highly colored salts with alkalies which were only slightly soluble.

Mononitro Derivatives of *p*-Cyclohexylanisole and Phenetole.—Twenty-two grams of *p*-cyclohexylphenetole dissolved in 150 cc. of anhydrous ethyl acetate to which 15 g. of phosphorus pentoxide had been added was cooled to 0° and 35 g. of fuming nitric acid slowly added. The temperature was not allowed to rise above 5° during the addition of the acid. The mixture was kept at a low temperature for six hours, then allowed to rise to room temperature and finally heated to 75° for six hours. The product was isolated in the same manner as in the preparation of the mononitrocyclohexylphenols. The nitration of the *p*-cyclohexylanisole was entirely analogous to that of the *p*-cyclohexylphenetole.

Preparation of the Ethyl and Methyl Ethers of Dinitro-*p*-cyclohexylphenol.—The methyl and ethyl ethers of dinitro-*p*-cyclohexylphenol were prepared by making the silver salt of the nitro body according to the method of Drew[8] and combining this material with the corresponding alkyl halide in the presence of absolute ethyl or methyl alcohol. The ethyl ether of the dinitro-*p*-cyclohexylphenol was obtained as a white crystalline solid after several recrystallizations from alcohol. The methyl ether of dinitro-*p*-cyclohexylphenol was a red liquid and was purified by distillation under a vacuum.

Reduction of Nitrocyclohexylphenols.—Nitro derivatives of cyclohexylphenols were dissolved in acetic anhydride and subjected to the action of hydrogen under pressure in the presence of a platinum catalyst.[9] When the reduction was complete, as shown by

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(8) Drew, *J. Chem. Soc.*, **117**, 1618 (1920).

(9) Adams and Voorhees, THIS JOURNAL, **44**, 1397 (1922).

the fact that hydrogen was no longer taken up, the reduction mixture was chilled and the platinum filtered off. The filtrate was then poured onto ice and the reduction product separated as a white crystalline solid.

Using this method the following nitro derivatives were reduced: dinitro-*p*-cyclohexylphenol, dinitro-*o*-cyclohexylphenol, and mononitro-*p*-cyclohexylphenol.

The acetyl derivatives of the aminocyclohexylphenols were obtained as white crystalline solids, insoluble in water but soluble in alcohol or glacial acetic acid. They were purified by recrystallization from a mixture of alcohol and water. The reduction of the mononitro-*p*-cyclohexylphenol was slower than the others, requiring six hours for completion, whereas the reduction of the dinitrocyclohexylphenols was complete in thirty minutes. These acetyl derivatives are entirely stable in contact with air, but it is not practical to isolate the free amines.

The mononitro-*o*-cyclohexylphenol could not be reduced by this method and the ethyl and methyl ethers of mononitro-*p*-cyclohexylphenol showed only partial reduction. These materials as well as the ethyl and methyl ethers of dinitro-*p*-cyclohexylphenol may be reduced by the use of zinc and glacial acetic acid but the products have not as yet been obtained in a pure state.

Analyses and data on physical properties are given in Table I.

TABLE I

PREPARATION, DATA AND ANALYSES

	Compound	Yield, %	B. p., °C.	M. p., °C.
1	Dinitro-*p*-cyclohexylphenol	73		84–85
2	Dinitro-*o*-cyclohexylphenol	65		106.5–107.5
3	Dinitro-*p*-cyclohexylphenetole	50		83–84
4	Dinitro-*p*-cyclohexylanisole	25	204–208 (7 mm.)	
5	Mono-nitro-*o*-cyclohexylphenol	35	144–146 (3–4 mm.)	
6	Mono-nitro-*p*-cyclohexylphenol	40	140–144 (2 mm.)	
7	Mono-nitro-*p*-cyclohexylanisole	50	148–152 (4 mm.)	
8	Mono-nitro-*p*-cyclohexylphenetole	50	146–150 (4 mm.)	
9	Tri-acetyldiamino-*p*-cyclohexylphenol	90		212–213
10	Tri-acetyldiamino-*o*-cyclohexylphenol	90		200–202
11	Di-acetylmonoamino-*p*-cyclohexylphenol	90		173–174

				Analyses %					
				Carbon			Hydrogen		
	d_{25}^{25}	n_D^{25}	Formula	Calcd.	Found		Calcd.	Found	
1			$C_{12}H_{14}N_2O_5$	54.18	54.21	53.98	5.26	5.46	5.39
2			$C_{12}H_{14}N_2O_5$	54.18	53.78	53.91	5.26	5.37	5.26
3			$C_{14}H_{18}N_2O_5$	N,	Calcd.	9.53	Found,	10.01,	10.00
4	1.2735	1.5710	$C_{13}H_{16}N_2O_5$	N,	Calcd.	10.00	Found,	10.08,	10.04
5	1.1640	1.5703	$C_{12}H_{15}NO_3$	N,	Calcd.	6.33	Found,	5.99,	5.84
6	1.1693	1.5726	$C_{12}H_{15}NO_3$	N,	Calcd.	6.33	Found,	6.56,	6.78
7	1.1273	1.5494	$C_{13}H_{17}NO_3$	N,	Calcd.	5.96	Found,	6.39,	6.30
8	1.1045	1.5390	$C_{14}H_{19}NO_3$	67.50	67.81	68.00	7.63	7.56	7.55
9			$C_{18}H_{24}N_2O_4$	N,	Calcd.	8.43	Found,	8.25,	8.26
10			$C_{18}H_{24}N_2O_4$	N,	Calcd.	8.43	Found,	8.82,	8.54
11			$C_{16}H_{21}NO_3$	N,	Calcd.	5.10	Found,	5.69,	5.27

Summary

1. The reaction between cyclohexanol and phenol, in the presence of certain condensing agents, has been studied.

2. A satisfactory method for control of the nitration of ortho and para cyclohexylphenol, whereby one or two nitro groups may be introduced into the phenolic nucleus, has been developed. Acetyl derivatives of the reduction products of a number of the nitrocyclohexylphenols have been obtained.

3. In the preparation of the ethyl and methyl ethers of dinitro-*p*-cyclohexylphenol it is probable that aci-ethers are formed which subsequently rearrange to give the true ethers. Undoubtedly some hydrolysis of these aci-ethers also takes place during the reaction with liberation of the free dinitro-*p*-cyclohexylphenol.

MORGANTOWN, WEST VIRGINIA

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Researches in Cyclic Acetals. II. Formation of Cyclic Acetals of 4,5-Dihydroxy-2,6-octadiene

BY C. PAULINE BURT, D. R. CORCORAN AND I. V. KOERBER

In an earlier paper the tendencies of certain aldehydes to form cyclic acetals with 4,5-dihydroxy-2,6-octadiene (dipropenyl glycol), $CH_3CH{=}CH\ CHOHCHOHCH{=}CHCH_3$ were reported.[1] It was shown that the saturated unsubstituted aliphatic aldehydes showed a marked tendency to form cyclic acetals while certain unsaturated aldehydes, halogen substituted aldehydes and benzaldehyde did not show such a tendency. These observations were in accordance with those of Hibbert and coworkers,[2] who found that unsaturation in the aldehyde residue lowered the tendency of formation of cyclic acetals of ethylene glycol.

This present investigation is an extension of the work by Burt and Howland using longer chain aldehydes, aldehydes with benzene nuclei and ketones. The saturated aliphatic aldehydes such as isobutyraldehyde, valerylaldehyde, and isovalerylaldehyde formed acetals with yields of 86, 65 and 77%, respectively. The saturated ketones did not all form ketals as readily, for while acetone had given the ketal in 71% yield and diethyl ketone gave a yield of 55%, neither[1] the methyl hexyl ketone nor pinacoline gave ketal products. Unsaturated aldehydes and ketones in both the aliphatic and aromatic series did not form acetals or ketals. No products could be isolated when methylheptenone, citral, benzylidene-acetophenone, benzylidene-acetone, acetophenone, benzophenone, *p*-tolylbenzophenone, *o*-chlorobenzaldehyde, *o*-nitrobenzaldehyde, salicylaldehyde or anisaldehyde were used. When, however, *β*-phenylpropionaldehyde (hydrocinnamaldehyde) was used, the acetal was formed with a 79% yield. In

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(1) Burt and Howland, THIS JOURNAL, **52**, 217 (1930).

(2) Hibbert, Houghton and Taylor, *ibid.*, **51**, 611 (1929).