TABLE I

DERIVATIVES OF OXAZOLIDINE-2,4-DIONE

3-Substituent	5,5-Substituents	M. p., °C.	B. p., °C.	Mm.	$n^{25}D$	Formula	Nitrogen, % Calcd.	Found
CH_3	H, H	128	.....	..	....	$C_4H_5NO_3$	12.2	12.2
CH_3	H, CH_3	...	140–144	50	1.4574	$C_5H_7NO_3$	10.8	10.9
CH_3	$(CH_3)_2$	46	78–80	5	....	$C_6H_9NO_3$	9.7	10.0
C_2H_5	$(CH_3)_2$	61	.....	..	....	$C_7H_{11}NO_3$	8.9	8.8
CH_3	CH_3, C_2H_5	...	101–102	11	1.4507	$C_7H_{11}NO_3$	8.9	8.8
CH_3	$(C_2H_5)_2$	...	105–108	11	1.4500	$C_8H_{13}NO_3$	8.2	8.1
CH_3	$(n\text{-}C_3H_7)_2$	46	100–105	4	....	$C_{10}H_{17}NO_3$	7.0	7.1
CH_3	$—(CH_2)_5—$	95	.....	..	....	$C_9H_{13}NO_3$	7.7	7.8

ble in water at room temperature and is very soluble in the usual organic solvents except petroleum ether. The water solubility is markedly increased by the addition of urethan.

Hydrolysis is the basis of an assay method. To 20 ml. of 0.05 *N* solution was added 28.5 ml. of 0.1 *N* sodium hydroxide; immediate back titration (phenolphthalein) required 18.5 ml. 0.1 *N* hydrochloric acid; theory, 18.5 ml. That hydrolysis leads to N-methyl-α-hydroxyisobutyramide was established by exhaustive ether extraction of the hydrolysis mixture. The product is very soluble in water and sparingly soluble in ether from which it was recrystallized; m. p. 78–79° *Anal.* Calcd. for $C_5H_{11}NO_2$: N, 12.0. Found: N, 12.0.

3-Ethyl-5,5-dimethyloxazolidine-2,4-dione.—Twenty grams of 5,5-dimethyloxazolidine-2,4-dione was dissolved in 50 cc. of water, neutralized with 6.7 g. of sodium hydroxide and treated with 26 g. of silver nitrate in a minimum of water. The precipitated silver salt was washed and vacuum dried at 50°; yield, 32 g. It was suspended in 200 cc. of dry ether, and 20 g. of ethyl iodide was added. The mixture was left for three days in a stoppered flask which was shaken occasionally. The product which was isolated in nearly quantitative yield boiled at 95–102° at 3 mm. It was crystallized from dilute alcohol; m. p. 61–62°. The same reaction failed with alcohol as solvent as did several attempts at ethylation with diethyl sulfate.

5,5-Pentamethyleneoxazolidine-2,4-dione.—The Traube and Ascher[7] procedure was used with little modification. Ethyl 1-hydroxycyclohexanecarboxylate[9] and guanidine condensed spontaneously in concentrated alcoholic solution. A 0.1 mole run was diluted with several volumes of ether and extracted with 150 cc. of 15% hydrochloric acid. The aqueous phase was boiled under a reflux for one hour and on cooling the product separated in 80% yield; m. p. 110–112°. *Anal.* Calcd. for $C_8H_{11}NO_3$: N, 8.3. Found: N, 8.1.

3,5,5-Trimethylhydantoin.—To 50 g. of dimethylhydantoin and 22 g. of sodium hydroxide in 300 cc. of water was added with vigorous stirring 63 g. of dimethyl sulfate. On cooling in ice-salt, 17 g. of needles separated and 10 g. more was isolated by extraction with ether; m. p. 149°. Bailey and Randolph[10] give the same melting point for a product obtained in two steps from α-aminoisobutyric acid and methyl isothiocyanate. *Anal.* Calcd. for $C_6H_{10}N_2O_2$: N, 19.7. Found: N, 19.9.

3,5,5-Trimethylthiazolidine-2,4-dione.—Sixteen grams of 5,5-dimethylthiazolidine-2,4-dione[11] was methylated with 15.6 g. of dimethyl sulfate and 6.5 g. of sodium hydroxide in 100 cc. of water. The yield was 40%; m. p. 49–51°. *Anal.* Calcd. for $C_6H_9NO_2S$: N, 8.8. Found: N, 8.6.

Summary

A series of tri-substituted derivatives of oxazolidine-2,4-dione has been synthesized for pharmacological study. 3,5,5-Trimethyloxazolidine-2,4-dione is an effective analgesic.

3,5,5-Trimethylhydantoin and 3,5,5-trimethylthiazolidine-2,4-dione are without analgesic properties.

(9) Auwers and Krollpfeiffer, *Ber.*, **48**, 1389 (1915).

(10) Bailey and Randolph, *ibid.*, **41**, 2504 (1908).

(11) Wheeler and Barnes, *Am. Chem. J.*, **24**, 79 (1900).

NORTH CHICAGO, ILLINOIS RECEIVED MAY 16, 1944

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE STATE COLLEGE OF WASHINGTON]

The Nitration of 4-Phenylphenyl Acetate

BY STEWART E. HAZLET, DALE A. STAUFFER, LEE C. HENSLEY AND HARRIS O. VAN ORDEN

The behaviors of 4-phenylphenyl benzoate[1] and 4-phenylphenyl 4-toluenesulfonate[2] when nitrated are analogous to the reactions encountered when that benzoate[3] and 4-phenylphenyl benzenesulfonate[4] are brominated. In each instance the entering substituent goes to that position in the ester molecule most remote from the acyloxy group. The bromination of 4-phenylphenyl acetate,[5] on the other hand, parallels the bromination of 4-phenylphenol.[6] Further, the nitration of 4-phenylphenol yields 2-nitro-4-phenylphenol.

By procedures as similar as possible to those employed in earlier studies, the nitration of 4-phenylphenyl acetate has been investigated; several sets of conditions were employed. The acetate is more difficult to nitrate than 4-phenylphenol, for, attempting to nitrate the ester under those conditions required for the formation of 2-nitro-4-phenylphenol from 4-phenylphenol, no substitution was effected, and starting material

(1) Hazlet and Van Orden, THIS JOURNAL, **64**, 2505 (1942).

(2) Bell and Kenyon, *J. Chem. Soc.*, 3049 (1926).

(3) Hazlet, Alliger and Tiede, THIS JOURNAL, **61**, 1447 (1939).

(4) Hazlet, *ibid.*, **59**, 1087 (1937).

(5) Hazlet and Kornberg, *ibid.*, **61**, 3037 (1939).

(6) (a) Raiford and Colbert, *ibid.*, **47**, 1457 (1925); (b) Colbert and others, *ibid.*, **56**, 202, 2128 (1934).

was recovered from the reaction mixture. Under somewhat more severe conditions a portion of the starting material was recovered, but some 2,6-dinitro-4-(4-nitrophenyl)-phenol was produced. Under the conditions used for the nitration of diphenyl,[7] the only product obtained was 2,6-dinitro-4-(4-nitrophenyl)-phenol. In one procedure, however, a nitro ester was obtained; nitration of 4-phenylphenyl acetate according to the method used by Bell and Kenyon[2] for the nitration of the 4-toluenesulfonate yielded some 4-(4-nitrophenyl)-phenyl acetate together with some 2,6-dinitro-4-(4-nitrophenyl)-phenol.

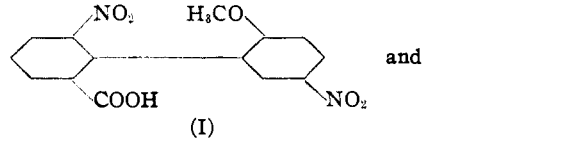
In the nitration reactions encountered in this study, yields were low. As no attempts were made to isolate products other than esters or phenols, this is not too surprising, for undoubtedly considerable oxidation occurred.

The compound of principal interest is 4-(4-nitrophenyl)-phenyl acetate, which was obtained in very small yield under one set of nitration conditions. Because no other nitro ester was obtained, it appears that the first substitution of the nitro group for a hydrogen atom occurs at the position in the molecule most distant from the acetyloxy group.

One explanation of the behavior noted which recommended itself was that which Holleman[8] pointed out: there may be "a stereochemical influence, the larger. . . atom" (or group) "being unable to substitute a H atom so easily in the ortho position in the neighborhood of the substituent already present." This would require the interpretation that the nitro group or nitrating agent is functionally larger than the bromine atom or brominating agent.

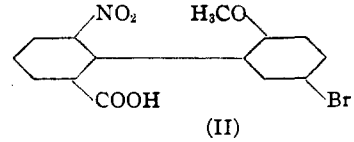
From the results of substitution studies which are on record[8] this interpretation is difficult. Also atomic radii and the "interference values" which have been calculated for various groups relative to the restricted rotational behavior of optically active substituted diphenyls[9] suggest that the opposite is true—that the bromine atom exerts a greater steric effect than the nitro group.

On the other hand, the results of the work of Yuan and Adams[10] on the relative stabilities of



and

(I)



(II)

indicate, since "the 5′-nitro is the stablest of all the derivatives," that if steric effects are responsible here, the influence of the nitro group is greater than that of the bromine atom. *Functionally* Watson[11] has allowed a somewhat similar interpretation in the case of the "*ortho*-effect": "for example, NO_2 is usually more effective than Br or I in spite of its smaller size." Gross observations of molecular models built using the Fisher-Hirschfelder atom models[12] confirm this view to some extent. Using data of Stanley and Adams[9] and Pauling,[13] a geometrical diagram, Fig. 1, was prepared. The interpretation may be placed upon this, that the space through which the nitro group rotates as it approaches the aromatic ring when substitution occurs is in a sense greater than that occupied by the bromine atom. (The space through which the nitro group rotates is interpreted as a portion of a cylinder with radius R (= 1.68 Å.) and line of center through the center of the hexagon of the aromatic ring and the center of the carbon atom of the ring toward which the group approaches.)

It may be, then, that the entering substituent is sterically hindered from entering the molecule

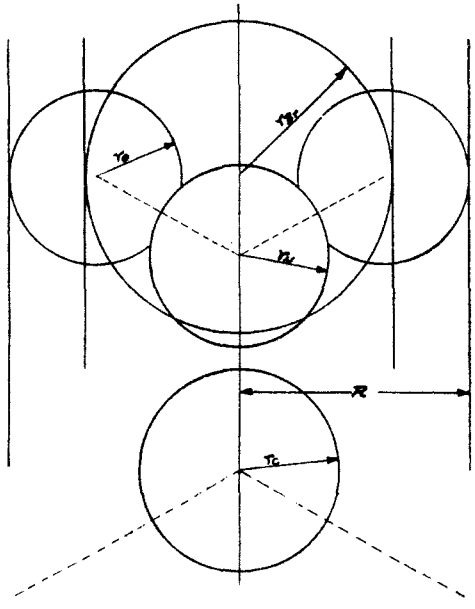


Fig. 1.—Comparison of space required for Br and NO_2 adjacent to an aromatic ring. Values used: r_C = 0.725 Å. [ref. 10]; C–Br distance = 2.11 Å. [Gilman, "Organic Chemistry," John Wiley and Sons, New York, N. Y., 1938, Chapt. 3 by Shriner, Adams and Marvel, p. 268]; r_{Br} = 1.14 Å., angle O ← N=O = 125° 16′, O–N distance = 1.20 Å., r_N = 0.65 Å., r_O = 0.615 Å. (the last two were calculated as averages between double and single bond radii of N and O [ref. 13]. Then R (calculated) would be 1.68 Å.

(7) Colbert, "Laboratory Technique of Organic Chemistry," D. Appleton-Century Co., New York, N. Y., 1933, p. 236.

(8) Holleman, *Chem. Rev.*, 1, 217 *et seq.* (1924).

(9) Stanley and Adams, THIS JOURNAL, **52**, 1200 (1930).

(10) Yuan and Adams, *ibid.*, **54**, 4434 (1932).

(11) Watson, "Modern Theories of Organic Chemistry," Oxford University Press, Oxford, 1941, second edition, p. 246.

(12) Manufactured and distributed by Fisher Scientific Co., Pittsburgh, Penn.

(13) Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1939, p. 154.

TABLE I

ACETATES OF THE NITROPHENYLPHENOLS

Phenol used	Yield (pure), %	Crystalline form	M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
2-Nitro-4-phenyl-	67	Long colorless prisms	85–86	$C_{14}H_{11}O_4N$	65.4	4.28	65.6	4.42
4-(4-Nitrophenyl)-	58	Colorless needles	138–139	$C_{14}H_{11}O_4N$	65.4	4.28	65.4	4.55
2,6-Dinitro-4-phenyl-	86	Small colorless prisms	129–130	$C_{14}H_{10}O_6N_2$	55.6	3.31	55.5	3.87
2-Nitro-4-(4-nitrophenyl)-	68	Yellow needles	137–138	$C_{14}H_{10}O_6N_2$	55.6	3.31		
2,6-Dinitro-4-(4-nitrophenyl)-	53	Light yellow chunks	148–149	$C_{14}H_9O_8N_3$	48.4	2.59	48.4	3.00

[a] *Anal.* Calcd. for $C_{14}H_{10}O_6N_2$: N, 9.27. Found: N, 9.43.

ortho with respect to acetyloxy and is in turn directed to the remote *para* position of the other ring of the diphenyl nucleus. However, some reservations are probably appropriate, and it would be well to adopt arguments similar to those of Watson[11] (with respect to the "*ortho*-effect") and to conclude that although "steric retardation may . . . be an important factor," probably the final explanation will not be made "completely in terms of a purely geometrical effect."

During the investigation, several new reference compounds were prepared, and some of their properties were determined.

The 4-phenylphenol used in this work was generously supplied by the Dow Chemical Company, Midland, Michigan.

Experimental Part

The Nitrophenylphenols.—The preparations of the nitrophenylphenols used in this work have been referred to in an earlier report.[1]

4-Phenylphenyl Acetate.—The preparation of this compound was reported earlier.[5]

Acetates of the Nitrophenylphenols.—For the preparation of these compounds, 1 g. of the appropriate phenol, 0.1 g. of anhydrous sodium acetate, and 10 ml. of acetic anhydride were refluxed gently for two hours. The reaction mixture was poured into 100 ml. of cracked ice and water. The mixture was stirred frequently and allowed to stand until the excess acetic anhydride was hydrolyzed. Upon filtration, the crude ester was obtained in nearly quantitative yield. Ligroin (b. p. 90–120°) was used for recrystallizations in all cases except for the purification of 2,6-dinitro-4-(4-nitrophenyl)-phenyl acetate; a mixture of toluene and the ligroin was required for the crystallization of this compound. The properties of the esters are listed in Table I.

The Nitration of 4-Phenylphenyl Acetate.—(**A**) Ten and one-tenth grams of 4-phenylphenyl acetate was dissolved in glacial acetic and treated with nitric acid according to the method of Raiford and Colbert[6a] for the preparation of 2-nitro-4-phenylphenol. From this reaction mixture, starting material was recovered in 96% yield.

(**B**) Under slightly more severe conditions, *viz.*, 10.1 g. of 4-phenylphenyl acetate in 500 ml. of glacial acetic acid, 15 ml. of concd. nitric acid, warming for six hours on a steam-bath, and standing for two days at room temperature, 6.2 g. of crude product was obtained. This product was crystallized from methanol. In turn, ligroin (b. p. 90–120°) extraction separated the material into two portions: The ligroin insoluble fraction was recrystallized from glacial acetic acid, and, by means of a mixed melting point determination (197–199°), it was shown to be 2,6-dinitro-4-(4-nitrophenyl)-phenol, 1 g., m. p. 195–197°. The ligroin soluble portion was obtained by evaporation of the solvent, and recrystallization from methanol yielded starting material (mixed melting point determination, 87–88°), 2.5 g., m. p. 87–88°.

(**C**) By the use of conditions the same as those described by Colbert[7] for the nitration of diphenyl, 9 g. of 2,6-dinitro-4-(4-nitrophenyl)-phenol, which melted at 198.5–199.5° alone and at 199–201° when mixed with an authentic specimen, was obtained from 20 g. of 4-phenylphenyl acetate.

(**D**)[14] Eight and fifteen hundredths grams of 4-phenylphenyl acetate was added in small portions to a well stirred mixture of 12.5 ml. (18.5 g.) of fuming nitric acid (d. 1.479) and 15 ml. (15.75 g.) of glacial acetic acid, which had been warmed on a steam-bath. The reaction mixture was cooled as necessary during the addition of the ester to prevent boiling. The warming and stirring were continued for thirty minutes after all of the ester had been added to the nitrating mixture. The reaction mixture was poured onto 400 g. of cracked ice, and the solid which remained after the ice had melted was collected by filtration and placed in a vacuum desiccator over sulfuric acid. The dry product (8.2 g.) was extracted with two 25-ml. portions of propanol-1, the combined extracts were treated with Norite, and the solvent was distilled off. The semi-solid residue was extracted with 5% sodium hydroxide solution and then washed with water until it was almost colorless. The solid was crystallized from ethanol, 0.2 g., m. p. 136–137°. It was shown to be 4-(4-nitrophenyl)-phenyl acetate for, when equal amounts of it and 4-(4-nitrophenyl)-phenyl acetate—prepared as described in an earlier section of this report—were mixed, the melting point was 137–139°.

The portion of the original solid which was not soluble in hot propanol-1 was recrystallized from glacial acetic acid; 1.4 g., m. p. 198.5–200°. This was identified as 2,6-dinitro-4-(4-nitrophenyl)-phenol for, when a portion of it and a known sample were mixed, there was no depression of the melting point.

Summary

The nitration of 4-phenylphenyl acetate under several sets of conditions gave as the chief product 2,6-dinitro-4-(4-nitrophenyl)-phenol, and, in one case, a small amount of 4-(4-nitrophenyl)-phenyl acetate was obtained. Thus the nitration of the acetate does not proceed in a manner analogous to its bromination. It is suggested that steric effects may be involved and that the size of the entering group may play a role.

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(14) These nitration conditions are the same as those used by Bell and Kenyon [*cf.* ref. (2)] for the preparation of 4-(4-nitrophenyl)-phenyl 4-toluenesulfonate.