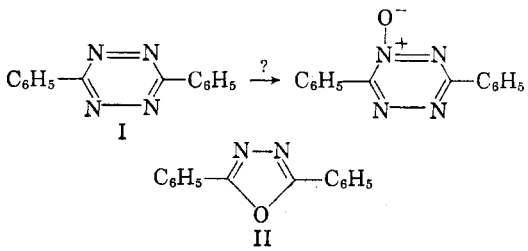
the *N*-oxide of a tetrazine was attempted—more particularly that of 3,6-diphenyl-1,2,4,5-tetrazine, which is fairly readily available. *N*-Oxides of this type have apparently not been described before, although several analogs are known in the triazine series.[2]



The starting material I, prepared by an improved method,[3] was allowed to react with an excess of peracetic acid at 50–60°: the initial red-purple color of I disappeared giving a colorless solution, from which 2,5-diphenyl-1,3,4-oxadiazole[4] (II) was isolated in good yield.

EXPERIMENTAL

1,2-Dihydro-3,6-diphenyl-1,2,4,5-tetrazine.[3] Ethyl benzimidoate hydrochloride was first prepared by passing dry hydrogen chloride through a cooled (ice bath) stirred mixture of benzonitrile (165.0 g.) and absolute ethanol (93.0 g.) until an increase in weight (91.0 g.) had occurred. The mixture was allowed to stand overnight at 3–5°, and the almost solid contents filtered under suction, washed with cold ethanol, then with ether, and dried *in vacuo* over phosphorus pentoxide. A second crop was collected from the filtrate: total yield, 182 g. (61%).

The dihydrotetrazine was prepared in the next step. To a stirred mixture of hydrazine hydrate (99–100%, 13.0 g.) in water (68.5 ml.) was gradually added the above benzimidoester hydrochloride (46.5 g.). Ethanol (37.5 ml.) was added and the mixture heated with stirring on the steam bath for 1 hr. (material began to precipitate after about 15 min.). The mixture was cooled in ice water, filtered, and the yellow residue washed successively with water, methanol, and ether. The dihydrotetrazine was oxidized (partially) to the red tetrazine on exposure to air when traces of solvent were present, but was more stable when dry. Additional material was obtained from the filtrate, and a total yield of 25.5 g. (76%) was obtained, m.p. (*in vacuo*), 183°. If the m.p. were determined in an open capillary, the substance turned red and melted at 191° (the m.p. of the parent tetrazine).

If the heating of the reaction mixture on the steam bath were prolonged (*e.g.*, to 20 hr., as in the original directions of Carboni and Lindsey[3]), then some of the dihydrotetrazine isomerized[5] to 4-amino-3,5-diphenyl-1,2,4,4*H*-triazole[8] (m.p. 264°), which could be isolated by a rather tedious fractional crystallization. The product as prepared above seemed to be free of this impurity (as determined by infrared analysis).

Oxidation of the dihydrotetrazine to the tetrazine. This followed very closely the method of Carboni and Lindsey[3,9]; the reaction seemed to be practically instantaneous. When dihydrotetrazine was used which was contaminated with the isomeric aminotriazole, the latter was oxidized to the colorless 3,5-diphenyl-1,2,4-triazole[10] m.p. 191°.

Oxidation of 3,6-diphenyl-1,2,4,5-tetrazine. To the tetrazine (1.00 g.) was added a mixture of peracetic acid (40% solution, 30 cc.) which had been buffered[11] to pH 5 with 3.0 g. of hydrated sodium acetate: the heterogeneous mixture was stirred at 50–60° for 24 hr., during which time there was feeble effervescence, and after which time all color had disappeared. Dilution of the mixture with water gave a colorless solid (0.70 g., 84%) which was shown to be 2,5-diphenyl-1,3,4-oxadiazole by infrared analysis and melting point comparisons with an authentic sample.[4]

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REED COLLEGE
PORTLAND 2, ORE.

(2) *Cf.*, for example, H. v. Euler, H. Hasselquist, and O. Heidenberger, *Chem. Ber.*, **92**, 2266 (1959).

(3) Based on that of R. A. Carboni and R. V. Lindsey, Jr., *J. Am. Chem. Soc.*, **81**, 4342 (1959); R. A. Carboni, private communication.

(4) T. Ikeda, S. Kanahara, and N. Nishikawa, *Ann. Rept. Fac. Pharm., Kanazawa Univ.*, **6**, 1 (1956); *Chem. Abstr.*, **51**, 3609^a (1957).

(5) Rearrangements of this type account for (a) confusion in the early literature[6] regarding structures of the products, and (b) the very low yields of dihydrotetrazines obtained when attempts were made to prepare them directly by heating hydrazine with various nitriles.[7]

(6) Compare the excellent account of the chemistry of 1,2,4,5-tetrazines in J. G. Erickson, P. F. Wiley, and V. P. Wystrach, "The Chemistry of Heterocyclic Compounds," Interscience, New York, 1956, Vol. 10, pp. 179–249.

(7) E. Müller and L. Herrdegen, *J. prakt. Chem.*, (2), **102**, 113–155 (1921).

(8) *Cf.* "Beilsteins Handbuch der Organischen Chemie," Vierte Auflage, Hauptwerk, **26**, 83.

(9) *Idem*, *J. Am. Chem. Soc.*, **80**, 5795 (1958).

(10) Ref. 8, p. 81.

(11) In original experiments this was omitted; however, it is known[7] that strong acids can cause transformation of diphenyltetrazine to the diphenyloxadiazole encountered in this work. In later experiments the buffer was added to obviate this possibility, since commercial peracetic acid can contain appreciable quantities of sulfuric acid. However, the addition of buffer seemed to have no effect on the reaction product.

3,4-Dihydroxyphenacyl Chloride Quaternary Salts of Heterocyclic Nitrogen Compounds[1]

CARL TABB BAHNER AND HAROLD KINDER

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An early indication,[2] which was not confirmed by subsequent testing, that *N*-(3,4-dihydroxy-

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TABLE I

3,4-DIHYDROXYPHENACYL CHLORIDE QUATERNARY SALTS

Bases	M.P.	Color	Yield, %	Reaction Time, min.	Reaction Temp.	Formula	Chlorine, % Calcd.	Chlorine, % Found
Benzothiazole	248	White	18	120	100	$C_{15}H_{13}O_3SNCl$	10.99	11.30
Hexamethylenetetramine	195	White	53	180	[a]	$C_{14}H_{19}O_3N_4Cl$	10.86	10.65
Isoquinoline	269	Yellow	15	45	100	$C_{17}H_{14}O_3NCl$	11.25	11.42
N-Methylmorpholine	228	White	15	30	100	$C_{13}H_{14}O_4NCl$	12.51	12.54
Pyridine	277	Brown	38	5	30–60	$C_{13}H_{12}O_3NCl$	13.40	13.43
3-Bromopyridine	255	Tan	9	10	160	$C_{13}H_{11}O_3NClBr$	10.30	10.29
Nicotinic acid	255	White	8	20	160	$C_{13}H_{12}O_5NCl$	11.48	11.61
2-Chloropyridine	302	Yellow	10	5	160	$C_{13}H_{11}O_3NCl_2$	[b,c]	
3-Chloropyridine	255	Brown	26	15	160	$C_{13}H_{11}O_3NCl_2$	11.55	11.50
3-Cyanopyridine	237	White	32	15	160	$C_{14}H_{11}O_3N_2Cl$	[c,d]	
Quinoline	265	Red-brown	18	60	100	$C_{17}H_{14}O_3NCl$	11.25	11.62

[a] In 200 ml. boiling acetone. [b] Calcd.: C, 52.01; H, 3.62. Found: C, 52.10; H, 3.68. [c] Average of two carbon and hydrogen analyses by Weiler and Strauss, 164 Banbury Road, Oxford, England. [d] Calcd.: C, 57.81; H, 3.78. Found: C, 57.73; H, 3.9 1

phenacyl)-3-bromoquinolinium chloride[3] might produce an extension of the life span of mice carrying Leukemia L1210, led us to synthesize the series of similar compounds listed in Table I. Except as indicated in the footnotes, the salts were prepared by heating 0.054 mole of 3,4-dihydroxyphenacyl chloride with 0.060 mole of the appropriate base in the absence of solvent, then recrystallizing from methanol, using activated carbon to remove colored impurities. None of them was effective against Adenocarcinoma 755 or Sarcoma S180, nor against Leukemia L1210.

CARSON-NEWMAN COLLEGE
JEFFERSON CITY, TENN.

(2) Screening data were obtained through the service of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health.

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Santonin and Related Compounds. XXIII.[1] The Aromatization of 3-Keto-9-carbethoxy-$\Delta^{1,4}$-hexahydronaphthalene

SEIITI INAYAMA AND MASAITI YANAGITA

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A survey of the literature[1,2] shows that the aromatization of a number of naphthalenic dienones proceeds in a variety of ways involving the migration of the angular methyl[2b] and/or the ring-methylene groups[2a] (and the hydroxyl or acetoxyl group).[2c] It seemed of interest to explore the course of the rearrangement of the bicyclic dienone with the electron-withdrawing group at the ring-fusion. An attractive paper has appeared describing the major shift of the carbethoxyl group at the given position in the cyclohexadienone system.[3] Plieninger and Suehiro[3] have shown that 4-carbethoxy-3,4-dimethylcyclohexa-$\Delta^{2,5}$-dien-1-one (I) rearranged with dilute sulfuric acid, predominantly to 1-carbethoxy-2,3,5-xylenol (II), which structure, though not firmly established, is beyond reasonable doubt. In addition, the parent xylenol was isolated in a small quantity. It is somewhat unexpected that the migration of the carbethoxyl group proceeded in such a way more readily than that of the angular methyl group, which has been more commonly encountered in the similar reactions.[2b]

Initially 3-keto-9-carbethoxy-$\Delta^{1,4}$-hexahydronaphthalene (III) was selected for the starting material, which was prepared in a 30% yield from the corresponding monoenone (IV)[4] by the selenium dioxide oxidation in the usual manner.[5] The dienone-ester III was characterized as the crystalline semicarbazone and 2,4-dinitrophenylhydrazone. This ketone exhibited the ultraviolet spectrum, $\lambda_{max}^{C_2H_5OH}$ 244.5 mμ, being in good agreement with the maximum (244 mμ) earlier described for the $\Delta^{1,4}$-3-dienone structure.[6] It is notable that, in contrast to the steroid chemistry,[6] the transformation of the monoenone IV into the corresponding cross-conjugated dienone III produces a remarkable batho-

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