Anal. Calcd. for $C_{12}H_8O_4Cl_2SN_2$: C, 41.54; H, 2.32; S, 9.23; N, 8.06; Cl, 20.42. Found: C, 41.50; H, 2.65; S, 8.95; N. 7.73; Cl, 20.25.

Reduction of I *to the cyclic hydrazo compound.* A solution of 23 g. of I in acetic acid was hydrogenated in the presence of Raney nickel at the initial pressure of 40 p.s.i. The mixture was filtered and diluted with water. The aqueous solution deposited yellow crystals which were chromatographed on alumina using a mixture of benzene–10% methanol for elution. There was isolated a 13% yield of yellowish crystals, m.p. 130°.

Anal. Calcd. for $C_{12}H_8O_2Cl_2SN_2$: C, 45.72; H, 2.24; N, 8.88; S, 10.17; Cl, 22.49. Found: C, 45.41; H, 2.30; N, 8.61; S, 10.09; Cl, 22.18.

Attempted oxidative cyclizations of II *with hydrogen peroxide.* The attempted oxidative cyclizations of II were carried out by dissolving the diamine in the organic acid, addition of an excess of 6% hydrogen peroxide and warming the reaction mixture for 24 hr. The products were isolated by pouring the mixture on ice and water, and crystallization of the solids from suitable solvents. The same procedure was employed with the parent compound di(*o*-aminophenyl)sulfone. The experimental results are summarized in Table I.

Mononitro derivative of III. A mixture of 10 ml. of nitric acid (sp. gr. 1.416) and 5 ml. of concd. sulfuric acid was added dropwise to an ice cold solution of 1 g. of III in 35 ml. of concd. sulfuric acid. The nitration mixture was kept in a refrigerator for 72 hr. and then poured on ice. The white solid was obtained in 60% yield and upon crystallization from benzene gave m.p. 264°.

Anal. Calcd. for $C_{12}H_5O_5Cl_2SN_3$: C, 38.50; H, 1.34; N, 11.23. Found: C, 38.25; H, 1.49; N, 11.67.

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Tetrahydroisoquinolinediones. I. The Structure of 4-Hydroxyisocarbostyril

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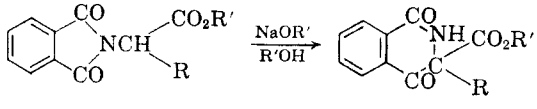
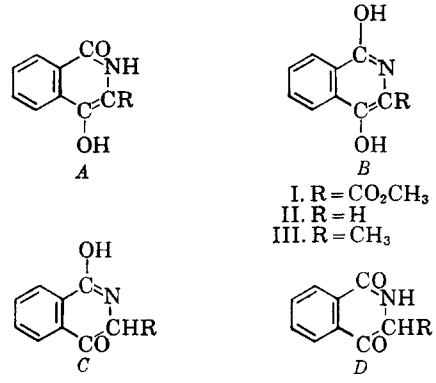
Over sixty years ago Gabriel and Colman[1] reported a base-catalyzed rearrangement of α-phthalimido esters to form derivatives of isoquinoline, hydrolysis and decarboxylation of which gave compounds that were reported as 4-hydroxy-3-



alkylisocarbostyrils (structure *A*), as the result of evidence obtained by degradation. A similar rearrangement was observed with α-phthalimido ketones.[2] These reactions will hereafter be called the Gabriel-Colman rearrangement.

There are two points in structure *A* at which tautomerism is possible, permitting the possibility of three other structures, *B*, *C*, and *D*, in equilibrium with *A*. These possibilities cannot be ruled out on the basis of previously reported structural work.

The bisenol structure *B* would appear to be the most likely structure because of its aromatic character. However, isoquinolone, in which the aromatic structure would seem even more likely, is a neutral compound whose ultraviolet absorption spectra are identical in acidic, basic, and neutral media.[3,4] This result would be possible only with an amide structure exhibiting very little tautomerism. Actually, the amide structures of isoquinolone and structure *A* are probably as aromatic as



structure *B*, as the result of completion of the electronic requirements for aromaticity by the unshared pair of electrons on the nitrogen atom. Structures *B* and *C* thus appear to be less likely than *A* and *D*.

In order to make a more exact evaluation of the structures of the 4-hydroxyisocarbostyrils, the ultraviolet absorption spectra of three of these compounds have been compared with the spectra of 1,4-naphthoquinone and 1,4-dihydroxynaphthalene in neutral, basic, and acidic solutions. In structures *B* and *C* the nitrogen atom should show basic properties. However, no significant differences were observed in comparing the spectra of these compounds in acid solution with their spectra in neutral solution, indicating the absence of protonation. Structures *B* and *C* can therefore be eliminated.

In comparing the spectra of the neutral solutions (Fig. 1) with those of the basic solutions (Fig. 2), two assumptions can be made. First, compounds showing spectra closely resembling those of 1,4-naphthoquinone or 1,4-dihydroxynaphthalene will have electronic configurations similar to the configurations of these models, and should have about the same amounts of keto, enol, or enolate at both the 1,2- and the 3,4-locations. Second, for R = CO_2CH_3 (I), the extent of 3,4-enolization should be much greater than of 1,2-enolization as the result of hydrogen-bond stabilization of the 3,4-

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(2) S. Gabriel and J. Colman, *Ber.*, **33**, 2630 (1900).
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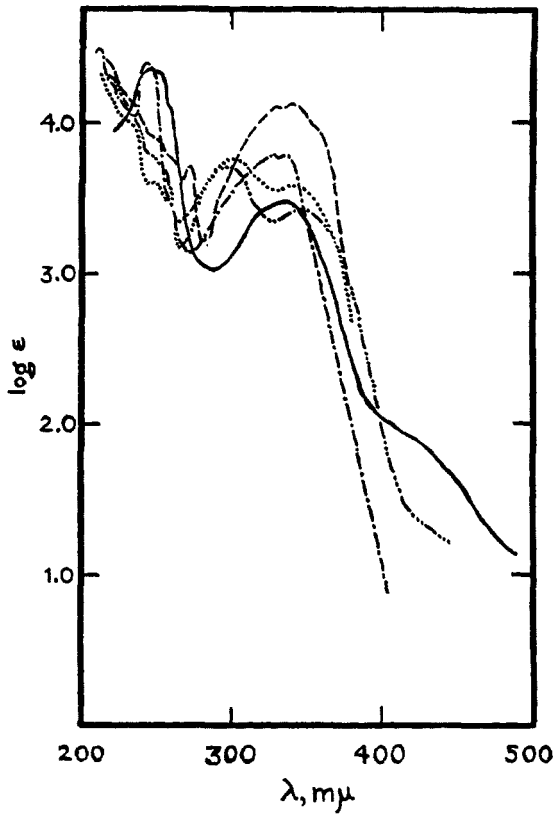

Fig. 1. Spectra of solutions in 95% ethanol of: 1,4-naphthoquinone, —; 1,4-dihydroxynaphthalene, — —; 3-carbomethoxy-1,2,3,4-tetrahydroisoquinoline-1,4-dione (I), —·—; 1,2,3,4-tetrahydroisoquinoline-1,4-dione (II), ...; 3-methyl-1,2,3,4-tetrahydroisoquinoline-1,4-dione (III), —···—

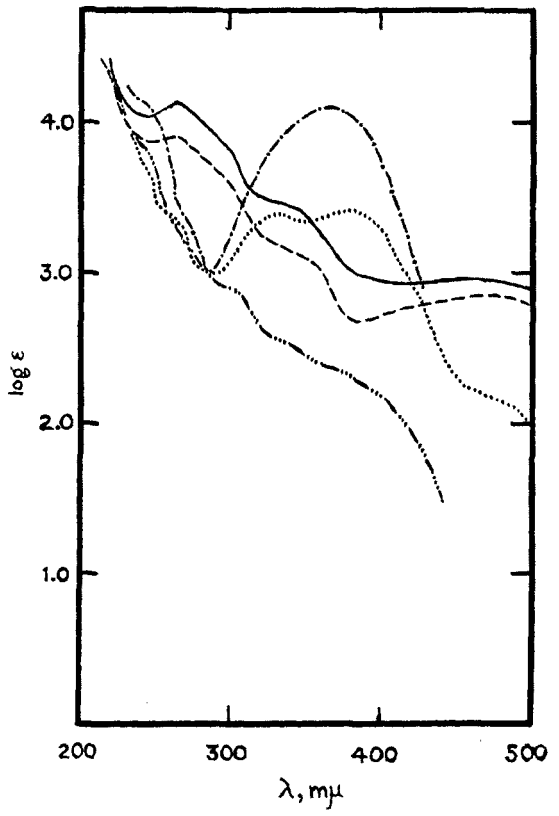

Fig. 2. Spectra of solutions in dilute sodium hydroxide of: 1,4-naphthoquinone, —; 1,4-dihydroxynaphthalene, ——; 3-carbomethoxy-1,2,3,4-tetrahydroisoquinoline-1,4-dione (I), —·—; 1,2,3,4-tetrahydroisoquinoline-1,4-dione (II), ...; 3-methyl-1,2,3,4-tetrahydroisoquinoline-1,4-dione (III), —···—

enol. Spectra similar to this case should indicate a predominance of structure *A* or of the enolate ion derived from it.

In neutral solution, the spectra for R = H (II) and for R = CH_3 (III) were similar to each other, but unlike those of the models. This result suggests that structure *D* is the most likely possibility. The failure of the spectra to resemble the spectrum of 1,4-naphthoquinone is probably due to the saturation of II and III at positions 2 and 3.

In basic solution the spectrum of II was shifted so that both of its principal peaks lay within the broad absorption band shown by I in basic solution. This result suggests that the enolate species produced was mainly that obtainable from structure *A*.

On the other hand, the spectrum of III in basic solution showed the flattening-out of peaks characteristic of 1,4-naphthoquinone and 1,4-dihydroxynaphthalene. This result suggests that the enolate species in basic solutions of III is the one derived from the bisenol structure *B*. An explanation lies in the possibility that the methyl group suppresses the 3,4-enolization to such an extent that the tendencies for enolization are about equal for the 1,2- and 3,4-locations.

It may tentatively be concluded that *D* best represents the structure of these compounds under neutral conditions, rather than *A*. Accordingly, the generic name *tetrahydroisoquinolinedione* is preferable to *hydroxyisocarbostyril*.

These investigations are being extended to include the spectra of tetrahydroisoquinolinediones with other substituents, including some *N*-alkyl derivatives. The mechanism of the Gabriel-Colman rearrangement is also under investigation.

EXPERIMENTAL

1,4-Naphthoquinone and 1,4-dihydroxynaphthalene. Eastman "White Label" 1,4-naphthoquinone was used after purification by steam distillation. 1,4-Dihydroxynaphthalene was prepared by reduction of purified 1,4-naphthoquinone with stannous chloride, following the method of Russig.[5]

Methyl phthalimidoacetate and methyl DL-*α-phthalimidopropionate.* Anhydrous hydrogen chloride was passed through a solution of 0.10 mole of the α-phthalimido acid[6] in 100 ml. of absolute methanol in a 1-l., three-neck round bottom flask. The exothermic reaction quickly subsided, and was followed, in the case of the phthalimidoacetic acid,

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(6) J. H. Billman and W. F. Harting, *J. Am. Chem. Soc.*, **70**, 1473 (1948).

by partial crystallization of the ester. At the end of 20 min., the gas flow was stopped, the reaction flask was chilled in an ice bath, and 200 ml. of saturated sodium bicarbonate solution was added with stirring, followed by addition of enough solid sodium bicarbonate to bring the *p*H to 8 to "Alkacid" paper. The precipitated esters were filtered by suction, washed on the filter with cold water until the washings were neutral, and dried. No further purification was needed to prepare the esters for rearrangement. The yields were 92–96% for methyl phthalimidoacetate, m.p. 111–112°, and 96% for methyl DL-α-phthalimidopropionate, m.p. 66–67°.

Small portions of each ester were recrystallized from methanol-ligroin (1:1). The purified methyl phthalimidoacetate melted at 114–115° (corrected).

Anal. Calcd. for $C_{11}H_9NO_4$: C, 60.27; H, 4.14; N, 6.39. Found: C, 60.58; H, 4.27; N, 6.51.

The purified methyl DL-α-phthalimidopropionate melted at 66–67° (corrected).

Anal. Calcd. for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.75; H, 4.94; N, 6.05.[7]

3-Carbomethoxy-1,2,3,4-tetrahydroisoquinoline-1,4-dione (I). To a 1-l. three-neck, round-bottom flask, fitted with a mercury-seal stirrer and a Friedrichs condenser equipped with a drying tube containing calcium oxide were added 21.9 g. (0.10 mole) of methyl phthalimidoacetate, 21.6 g. of sodium methoxide, and 200 ml. of absolute methanol. Stirring and heating were initiated and the mixture became dark yellow. In about 15 min. a yellow precipitate began to form. At the end of 1 hr. the heating was stopped, the mixture was cooled to room temperature, and 100 ml. of 6*N* hydrochloric acid was added with stirring and cooling. The grayish precipitate was filtered by suction and washed on the filter with 0.1*N* hydrochloric acid until the washings were colorless, then with distilled water until the washings were neutral. The resulting mass was extracted with 500 ml. of boiling water, and the mixture was filtered through a funnel with a hot water jacket. The dried residue weighed 13.8 g. (63%) and melted at 219–220° (corrected). The reported melting point[1] is 221–222°.

1,2,3,4-Tetrahydroisoquinoline-1,4-dione (II). In a 200-ml. round-bottom flask were placed 2.2 g. (0.01 mole) of I and 20 ml. of 57% hydriodic acid. This mixture was refluxed for 1 hr., forming a clear, yellow solution which solidified on cooling to room temperature, as the result of crystallization of the hydriodide of II.[8] To this solid mass was added 100 ml. of water, and the mixture was heated to boiling, then immediately cooled, filtered, and washed on the filter with water until the washings were neutral. The resulting pale yellow powder weighed 1.5 g. (94%). It did not melt below 300°, in agreement with previous findings.[1,8]

3-Methyl-1,2,3,4-tetrahydroiosquinoline-1,4-dione (III) was prepared by a method similar to that used for I starting with 23.3 g. of methyl DL-α-phthalimidopropionate, 21.6 g. of sodium methoxide, and 200 ml. of absolute methanol. The mixture was refluxed with stirring for 3 hr., at the end of which it was deep red and contained a yellow precipitate. Addition of 100 ml. of 6*N* hydrochloric acid caused a vigorous effervescence. When the effervescence had subsided, the mixture was boiled until gas evolution ceased, and then allowed to stand overnight at room temperature. The mixture was filtered by suction and the precipitate was washed on the filter with water until the washings were neutral, leaving a residue of 7.6 g. (43%) of golden yellow crystals, m.p. 238–239.5° (corrected). The reported[1] melting point for III is 240°.

Ultraviolet absorption spectra. All absorption spectra were measured with a Cary recording spectrophotometer, using 1-cm. cells. The concentrations of the solutions were 10^{-4} to 10^{-3} molar, in 95% ethanol for neutral solutions, in 0.08–0.09*N* sodium hydroxide for basic solutions, and in 0.08–0.09*N* hydrochloric acid for acidic solutions.

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(8) G. Vanags and V. Vitols, *Zhur. Obshcheĭ Khim.*, **24**, 1953 (1955); *Chem. Abstr.*, **50**, 8644c (1956).

Potential Cytostatic Carbohydrate Derivatives. I. *N*-Mustard Urethans[1]

THOMAS F. NOGRADY

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Carbohydrates as biological carriers for nitrogen mustards were first used by Vargha *et al.*[2,3] and more recently by Reist, Spencer, and Baker.[4] These workers prepared *N*-mustard derivatives with a basic nitrogen. On the other hand, Bergel *et al.*[5] prepared *N*-mustard urethans of serine and threonine, compounds of low toxicity, of which the serine derivative was found to be very active on Walker rat sarcoma. These authors reported also the experiments of Bushby, who investigated the lower alkylurethans of *N*-mustard, and found that only the ethylurethan is active.

During our investigation of *N*-mustard derivatives of monosaccharides, we also prepared urethans of carbohydrates. By reaction of D-galactose with phosgene in dry acetone, 1,2:3,4-diisopropyliden-6-*O*-chloroformyl-D-galactopyranose (I) can be obtained.[6] When this reacted with *N*-bis(β-chloroethyl)amine in dry ether, a second molecule of the amine acting as acid acceptor, *N*-bis(β-chloroeth-

(1) This investigation was supported by the U. S. Department of Health, Education and Welfare, National Institutes of Health (Research Grant No. 2260), and by the National Cancer Institute of Canada.

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(6) W. N. Haworth, C. R. Porter, and A. C. Waine, *Rec. trav. chim.*, **57**, 541 (1938).