# Notes

## Synthesis of Some New Hydrazone Derivatives

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**The synthesis of D-glucuronolactone and D-mannuronolactone *p*-cyanobenzoyl hydrazones is reported. Also reported is a new melting point for *p*-cyanobenzoyl hydrazide. Infrared studies supporting evidence that the hydrazones exist in the uronolactone and not in the uronic acid form is reported.**

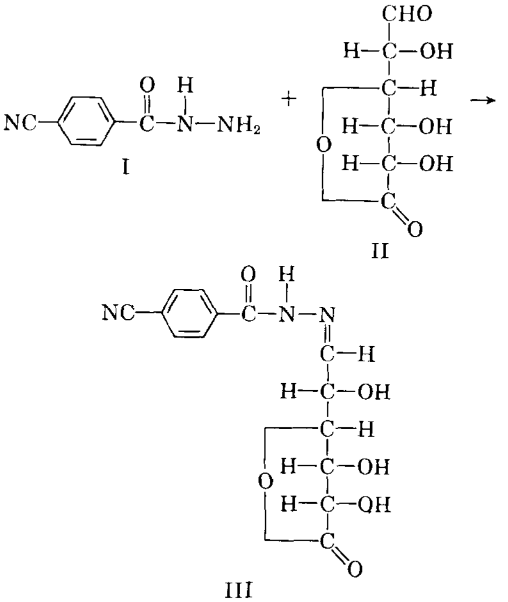
NUMEROUS derivatives of hydrazine have been prepared by Domagk, *et al.* (1), and tested along with other known derivatives for antitubercular activity. Among those compounds was the hydrazide of *p*-cyanobenzoic acid. This compound was reported to have significant antitubercular activity. The method of preparation of this compound has not been reported to date and is published here.

The synthesis was first attempted by reacting *p*-cyanobenzoyl chloride with 85% hydrazine hydrate or hydrazine sulfate. This method proved unsuccessful. The ethyl ester of *p*-cyanobenzoic acid was prepared and then reacted with 85% hydrazine hydrate in dioxane. This method was successful providing yields of up to 84% of *p*-cyanobenzoic acid hydrazide. If the reaction was allowed to proceed longer than 2 hours, the yield was reduced considerably with formation of substances melting above 300°. The solvent used for recrystallization was distilled water which yielded white crystals which melted at 202-203° (corrected). The reported melting point of *p*-cyanobenzoic acid hydrazide is 191°(1). A new melting point substantiated by analysis is now reported.

Uronolactone hydrazones of *p*-cyanobenzoic acid were prepared from the hydrazide in an effort to decrease the inherent toxicity of hydrazine derivatives. Sah has prepared uronic acid and uronolactone hydrazones of isonicotinic acid. These compounds were reported to be less toxic than isonicotinic acid hydrazide with no apparent loss of antitubercular activity (2).

The method of preparation of D-glucuronolactone and D-mannuronolactone *p*-cyanobenzoyl hydrazones followed the method of Sah (3) for the preparation of D-mannuronolactone and D-mannuronic acid isonicotinyl hydrazones. D-Glucuronolactone *p*-cyanobenzoyl hydrazone (III) was prepared by warming a solution of D-glucuronolactone (II) and *p*-cyanobenzoyl hydrazide (I) in absolute ethanol. The volume of the solvent was reduced and white crystals of the hydrazone crystallized from the solution.

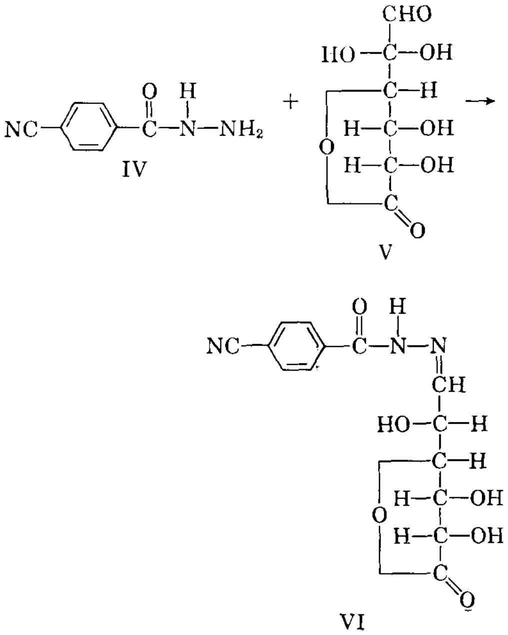
In a similar procedure to that used for the preparation of D-glucuronolactone *p*-cyanobenzoyl hydrazone, D-mannuronolactone (V) and *p*-cyano-benzoyl hydrazide (IV) were dissolved in absolute ethanol. The final concentration of the reaction



I

II

III



IV

V

VI

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TABLE I.—URONOLACTONE *p*-CYANOBENZOYL HYDRAZONES AND *p*-CYANOBENZOIC ACID HYDRAZIDE

| | Formula | Yield, % | M. p., °C. | Carbon, % | | Hydrogen, % | | Nitrogen, % | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Calcd. | Found | Calcd. | Found | Calcd. | Found |
| D-Glucuronolactone *p*-cyanobenzoyl hydrazone | $C_{14}H_{13}N_3O_6H_2O$ | 7.0.2 | 127 (decompn.) | 49.86 | 49.91 | 4.48 | 4.53 | 12.46 | 12.20 |
| D-Mannuronolactone *p*-cyanobenzoyl hydrazone | $C_{14}H_{13}N_3O_6$ | 80.8 | 169 (decompn.) | 52.66 | 52.78 | 4.10 | 4.28 | 13.17 | 13.28 |
| *p*-Cyanobenzoic acid hydrazide | $C_8H_7N_3O$ | 83.9 | 202–203 | ... | ... | ... | ... | 26.1 | 26.0 |

mixture was 0.001 mole of the reactants in approximately 220 ml. of absolute ethanol due to the relative insolubility of D-mannuronolactone in absolute ethanol. The product obtained from this dilute reaction mixture melted at 190–192°. Upon analysis, the compound was found not to be the hydrazone but possibly a product of the reaction of two moles of *p*-cyanobenzoic acid hydrazide. Regardless of the exact nature of the product formed here, it was not possible to obtain the hydrazone under such dilute reaction conditions.

As an alternate method, distilled water was used as a solvent for the reaction and an identical procedure followed. The white crystalline product obtained was analyzed to be D-mannuronolactone *p*-cyanobenzoyl hydrazone (VI) (See Table I).

## EXPERIMENTAL

**Infrared Data.**—Infrared spectra were obtained using a Beckman IR-4 infrared recording spectrophotometer. All of the compounds prepared exhibited the characteristic cyano band in the range 2240-2210 cm.$^{-1}$. The spectra of D-glucuronolactone *p*-cyanobenzoyl hydrazone and D-mannuronolactone *p*-cyanobenzoyl hydrazone were found to be identical. This would seem to indicate the two compounds have identical structures except for the position of the hydroxyl on $C_5$, which apparently does not influence the infrared spectra. The spectra of the hydrazones contain a strong band of 1780–1760 cm.$^{-1}$, which is indicative of a C=O stretching vibration of a gamma lactone reported as 1780–1760 cm.$^{-1}$ by Bellamy (4). Supporting evidence that the hydrazones exist in the uronolactone and not the uronic acid form is the absence of the carboxylic acid OH stretching vibrations, which usually occur as broad bands with a series of minor peaks over the range 3000–2500 cm.$^{-1}$ (5).

**Preparation of Uronolactone *p*-Cyanobenzoyl Hydrazones Ethyl *p*-Cyanobenzoate.**—*p*-Cyanobenzoyl chloride (0.09 mole) was placed in a 100-ml. beaker and 10 ml. of absolute ethanol added. The mixture was heated gently on a steam bath and the reaction proceeded as evidenced by the formation of hydrochloride gas.

Upon completion of the reaction after approximately 10 minutes of gentle heating, the reaction mixture was neutralized with a solution of sodium bicarbonate. Upon neutralization, crystals of ethyl *p*-cyanobenzoate formed and were filtered from the solution. The product was recrystallized from ethanol and water; yield, 81.6%, m.p. 53–54° (lit. 54°).

***p*-Cyanobenzoic Acid Hydrazide.**—Three grams (0.017 mole) of ethyl *p*-cyanobenzoate was placed in a 100-ml. round-bottomed flask equipped with a reflux condenser and 25 ml. of *p*-dioxane added. Five milliliters of 85% hydrazine hydrate was added and the mixture refluxed for 1.5 hours. The reaction mixture was allowed to cool to room temperature and the solvent evaporated under a jet of air in an evaporating dish. The resulting crystals were dried at room temperature and recrystallized from hot distilled water.

**D-Glucuronolactone *p*-Cyanobenzoyl Hydrazone.**—*p*-Cyanobenzoic acid hydrazide, 5.0 Gm. (0.031 mole) was dissolved in 50 ml. of hot absolute ethanol. D-Glucuronolactone (Eastman), 5.3 Gm. (0.031 mole), was dissolved separately in 50 ml. of hot absolute ethanol. The solutions were mixed and heated to 50–60° on a steam bath for 15 minutes.

After cooling to room temperature, the solution was concentrated under a jet of air to 25 ml. It was placed in a freezer and white crystals formed within 1 hour. The white crystals were filtered from the solution and recrystallized from absolute ethanol.

**D-Mannuronolactone *p*-Cyanobenzoyl Hydrazone.**—*p*-Cyanobenzoic acid hydrazide, 0.5 Gm. (0.0031 mole) was dissolved in 75 ml. of hot distilled water. D-Mannuronolactone (Kelco No. 2065), 0.53 Gm. (0.0031 mole), was dissolved separately in 5 ml. of hot distilled water. The solutions were mixed and heated between 50 and 60° on a steam bath for 15 minutes. The solution was allowed to cool to room temperature, filtered, and placed in a refrigerator.

The white crystals which formed overnight were filtered from the solution and washed with cold distilled water. The product was recrystallized from distilled water.

## SUMMARY

1. Two new hydrazone derivatives were prepared: D-glucuronolactone and D-mannuronolactone *p*-cyanobenzoyl hydrazones.

2. A new melting point for *p*-cyanobenzoyl hydrazide is reported.

3. Infrared studies supporting evidence that the hydrazones exist in the uronolactone and not in the uronic acid form is reported.

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(5) *Ibid.*, p. 163.