New Compounds: *N*-Arylglyoxylohydroxamyl Derivatives of Nitrogen Mustard

By JOSEPH P. LAROCCA and COY AVERY GIBSON

The synthesis and physical properties of some *N,N*-bis(2-chloroethyl)arylglyoxylohydroxamamides are described.

Compounds having antineoplastic activity have been classified in the following types (1, 2): alkylating agents, antimetabolites, hormones and steroids, antibiotics, and miscellaneous. Of these types, the alkylating agents and the antimetabolites are represented by the greatest number of clinically useful antineoplastic drugs. The common alkylating agents are derivatives of bis(2-chloroethyl)-amine (nitrogen mustard), ethylenimines, methane sulfonates, and epoxides. These compounds react spontaneously with electron-rich centers of biologically important material. The first alkylating agent to be used was methyl bis(2-chloroethyl)amine which was also the first drug to be used systemically against cancer (2). Its high toxicity led to the development of other nitrogen mustards (1) of the general type, $R—N(CH_2CH_2Cl)_2$, in an effort to reduce the toxicity. In many cases the nitrogen mustard has been attached to a "carrier moiety" in an effort to permit the nitrogen mustard to be more specific or localized in its effect (3). Recently, the work of Popp (4, 5), Wiley and Irick (6), and Sen and Shirley (7) has shown that less toxic and more effective compounds can be developed through this concept. This "carrier moiety" theory led to the synthesis and testing of benzimidazole, quinacrine, chloroquine, and amino acid mustards (3).

The synthesis and reduction of various arylglyoxylohydroxamides and chlorides have been studied (8). The unreduced chlorides have slight antineoplastic activity (9) probably due to the chemical reactivity of the chlorine (10) resulting in a monoalkylating-like action.

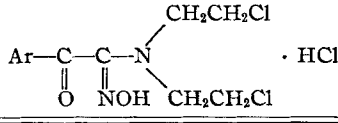
EXPERIMENTAL

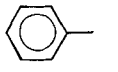
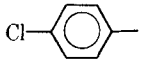
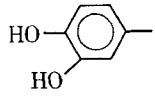
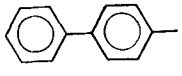
Preparation of Intermediates—*Arylglyoxylohydroxyamyl Chlorides*—These compounds were prepared by previously described procedures (8, 10).

Bis(2-chloroethyl)amine—Bis(2-chloroethyl)amine hydrochloride was prepared according to the method of Ward (11). The free amine was obtained by the method employed by Friedmann and Seligman (12).

Synthesis of Arylglyoxylohydroxamamides—A solution of 0.04 mole of arylglyoxylohydroxamyl chloride in 50 ml. of anhydrous ether was treated dropwise with 0.071 mole of bis(2-chloroethyl)amine in a benzene–chloroform mixture (4:1). The solution became warm and bis(2-chloroethyl)-amine hydrochloride precipitated as the addition was continued. After the addition of the amine was completed, the flask was stoppered tightly and allowed to stand overnight in the refrigerator.

Table I—*N,N*-Bis(2-chloroethyl)arylglyoxylohydroxamamide Hydrochlorides



No.	Ar	M.p.,[a] °C.	% Yield	Anal. Cl Calcd.	Cl Found[c]	N Calcd.	N Found[c]
1		101–103.5	47.3	32.40	31.30 32.00	8.64	7.86 7.64
2		124–126	50.5	39.38	38.24 39.00	7.79	7.30 7.55
3		125–127	43.4[b]	29.78	27.87 26.99	7.85	7.10 7.14
4		145–147	24.0	26.44	25.84 25.79	6.99	6.55 6.55

[a] All melting points were uncorrected and taken with a Thomas-Hoover capillary melting point apparatus. [b] Allowed to stand under refrigeration for 6 days before crystallization occurred. [c] Analyses performed in this laboratory. Chlorine determined by the Parr peroxide bomb method and nitrogen by the Henegar method of Kjeldahl's analysis.

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The amine hydrochloride was removed by filtration and the clear supernatant liquid treated for 10 min. with dry hydrogen chloride gas by bubbling the gas continuously through the solution. A viscous oily semisolid separated which crystallized after standing under refrigeration for 48 hr. The crystals were collected by filtration, washed with anhydrous ether, and dried in a vacuum desiccator. All compounds were found to be hygroscopic. The results are summarized in Table I.

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New Compounds: Preparation and Hydrogenation of Azomethines Derived from 2,4-Dihydroxyphenyl Benzyl Ketones

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Reaction of 2,4-dihydroxyphenyl benzyl ketones with primary amines and subsequent catalytic hydrogenation with platinum catalyst has afforded a series of polyphenolic amines derived from resorcinol.

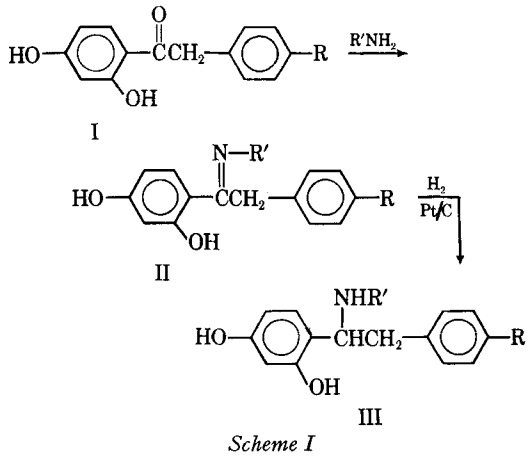
IT HAS BEEN alleged that quinine and mepacrine may exert their antimalarial activity by inhibition of the phosphorylation of glucose (1, 2). Because a number of polyphenolic compounds have been demonstrated to be inhibitors of oxidative phosphorylation (3–6), a number of polyphenolic amines derived from resorcinol have been synthesized in this laboratory as potential antimalarial agents.

The synthetic method is shown in Scheme I. Data on the compounds with structures II and III are presented in Tables I and II, respectively. All the compounds of structure III were isolated and characterized as the hydrochlorides.

Hydrogenation of the azomethines (Table I), where R′ = 2,4-dichlorobenzyl and 3,4-dichlorobenzyl, and subsequent treatment with hydrogen chloride gave a mixture of hydrochloride salts. 2,4-Dichlorobenzylamine hydrochloride was isolated from the former and 3,4-dichlorobenzylamine hydrochloride from the latter. Elemental analyses of the desired secondary amine salts indicated incomplete removal of the primary amine hydrochlorides (based on the calculation of the desired secondary amine salts).

EXPERIMENTAL[1]

The ketones (I), where R = H and R = Cl, were prepared by the method of Chapman and Stephen (7). The ketones (I), where R = OCH_3, was prepared as described by Klarmann (8).



Scheme I

N - (2,4 - Dihydroxyphenyl - p - methoxybenzylmethylene)benzylamine—A solution of 10.3 Gm. (0.04 mole) of 2,4-dihydroxyphenyl-*p*-methoxybenzyl ketone and 4.3 Gm. (0.04 mole) of benzylamine in 350 ml. of dry toluene was refluxed for 24 hr. until the theoretical amount of water was collected in a Dean-Stark apparatus. The solution was concentrated *in vacuo* and the residue on recrystallization from toluene gave 14.0 Gm. (quantitative yield) of yellow crystalline product, m.p. 177–179°. An analytical sample was obtained after an additional recrystallization from toluene, m.p. 180–181°. (See Table I.)

N - (2,4 - Dihydroxyphenyl - p - chlorobenzylmethyl)veratrylamine Hydrochloride—A solution of *N*-(2,4-dihydroxyphenyl-*p*-chlorobenzylmethylene)veratrylamine (4.1 Gm., 0.01 mole) in 150 ml. of acetone was hydrogenated at a pressure of 30 p.s.i. and room temperature, using 1.0 Gm. of 5% platinum-on-charcoal as the catalyst. After 90 min. the theoretical uptake of hydrogen was observed and the catalyst and solvent removed. The waxy residue was dissolved in 50 ml. of anhydrous

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[1] All melting points (corrected) were taken on a Thomas-Hoover melting point apparatus.