[CONTRIBUTION FROM AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

Arsenicals of the 5-Pyrazolone, 5-Isoxazolone and α-Acetoglyoxylic Acid Series

BY ROBERT F. COLES AND CLIFF S. HAMILTON

During the course of a recent investigation by the authors[1] and in conjunction with the work of Sharp and Hamilton,[2] it was decided to examine several α-acetoglyoxylate arsonophenylhydrazones, 4-(arsonophenylazo)-3-methyl-5-pyrazolones and 4-(arsonophenylazo)-3-methyl-5-isoxazolones as potential therapeutic agents.

The procedure of Sharp and Hamilton[2] for the coupling of *p*-aminobenzenearsonic acid and ethyl acetoacetate was employed to condense *o*- and *m*-aminobenzenearsonic acids and 3-nitro-4-aminobenzenearsonic acid with ethyl acetoacetate.

Chattaway and Ashworth[3] reported that acetoacetic acid evolves carbon dioxide when coupled with *p*-nitrobenzene diazonium chloride to yield pyruvaldehyde *p*-nitrophenylhydrazone. It was expected, therefore, that ethyl α-acetoglyoxylate *p*-arsonophenylhydrazone (I) when subjected to the acetoacetic ketonic hydrolysis with dilute base should yield the corresponding pyruvaldehyde *p*-arsonophenylhydrazone. However, hydrolysis with saturated barium hydroxide solution produced an insoluble barium salt which when converted to the free acid gave an analysis for α-acetoglyoxylic acid-*p*-arsonophenylhydrazone (II). Apparently a normal ester hydrolysis without decarboxylation occurred.

Experimental

Ethyl α-Acetoglyoxylate Arsonophenylhydrazone (General Procedure).—The appropriate aminobenzenearsonic acid (0.115 mole) was dissolved in a solution of sodium hydroxide (5 g., 0.125 mole) and sodium nitrite (8.1 g., 0.115 mole) in 100 ml. of water. The resulting solution was poured slowly with stirring into a solution of reagent grade hydrochloric acid (50 ml., 0.625 mole) in 300 g. of ice and water.

The solution of the diazonium salt was poured with stirring into a solution consisting of sodium acetate (55 g., 0.625 mole), ethyl acetoacetate (15 g., 0.125 mole), 95% ethanol (50 ml.) and ice and water (600 g.). The mixture was cooled in a refrigerator overnight and acidified to congo red paper in the cold with hydrochloric acid. The precipitated product was crystallized from aqueous ethanol.

α-Acetoglyoxylic Acid 4-Arsonophenylhydrazone (II).—A solution of I (8 g., 0.022 mole) in 300 ml. of a saturated solution of barium hydroxide was refluxed for two hours. The yellow precipitate was collected on a filter and washed well with water. A suspension of the solid in water was made strongly acid with hydrochloric acid; the resulting tan solid was collected and washed with water, ethanol, and ether successively. The product was purified by reprecipitating from bicarbonate solution with hydrochloric acid, yield 6 g.

4-(4-Arsonophenylazo)-3-methyl-5-pyrazolone (III).—A solution of I (5 g., 0.014 mole), in 75 ml. of water, containing sodium hydroxide (3 g., 0.075 mole), was treated with a solution of hydrazine dihydrochloride (3 g., 0.028 mole) in 50 ml. of water. The solution was warmed on a steam-bath for two hours and allowed to stand overnight. The reaction mixture was acidified to congo red paper with hydrochloric acid. The precipitated solid was collected, dissolved in hot dilute barium hydroxide solution and filtered. The filtrate was acidified with hydrochloric acid, the product collected, washed with water, ethanol and ether; yield 2 g.

The preparation of other pyrazolones was accomplished by analogous procedures.

4-(3-Arsonophenylazo)-3-methyl-5-isoxazolone (IV).—A solution of ethyl α-acetoglyoxylate 3-arsonophenylhydrazone (5 g., 0.014 mole) in 75 ml. of water, containing

TABLE I

ARSENICALS

Compound	Crystn. solvent	Yield, %	M. p., °C.	Formula	Analyses, % As Calcd.	Found
Ethyl α-acetoglyoxylate-*o*-Arsonophenylhydrazone	30% Ethanol	90	182.5–183.5	$C_{12}H_{15}AsN_2O_6$	20.92	21.09
m-Arsonophenylhydrazone	50% Ethanol	92	197–198	$C_{12}H_{15}AsN_2O_6$	20.92	21.11
4-Arsono-2-nitrophenylhydrazone	Aq. ethanol	84	251–252 dec.	$C_{12}H_{14}AsN_3O_8$	18.58	18.56
Acid α-acetoglyoxylic-4-Arsonophenylhydrazone (II)	[a]	82	240–241 dec.	$C_{10}H_{11}AsN_2O_6$	22.69	22.67
3-Methyl-5-pyrazolone-4-(2-Arsonophenylazo)	Aq. ethanol	22	268–269 dec.	$C_{10}H_{11}AsN_4O_4$	22.97	22.90
4-(3-Arsonophenylazo)	[b]	65	>250	$C_{10}H_{11}AsN_4O_4$	22.97	22.91
4-(4-Arsonophenylazo) (III)	[b]	44	>250	$C_{10}H_{11}AsN_4O_4$	22.97	22.70
4-(2-Nitro-4-arsonophenylazo)	[b]	32	>250	$C_{10}H_{10}AsN_5O_6$	20.18	19.99
3 Methyl-5-isoxazolone-4-(2-Arsonophenylazo)	Aq. ethanol	28	232–233	$C_{10}H_{10}AsN_3O_5$	22.90	22.67
4-(3-Arsonophenylazo) (IV)	Aq. ethanol	55	>250	$C_{10}H_{10}AsN_3O_5$	22.90	22.86

[a] Purified by reprecipitation from sodium bicarbonate solution by the addition of hydrochloric acid. [b] Purified by reprecipitation from barium hydroxide solution by the addition of hydrochloric acid. [c] Method of Cislak and Hamilton, THIS JOURNAL, 52, 638 (1930).

The arsonophenylhydrazones of ethyl α-acetoglyoxylate when treated with hydrazine or hydroxylamine in basic solution yielded the corresponding 4-(arsonophenylazo)-3-methyl-5-pyrazolones or 5-isoxazolones.

(1) Coles and Hamilton, THIS JOURNAL, **68**, 1799 (1946).
(2) Sharp and Hamilton, *ibid.*, **68**, 588 (1946).
(3) Chattaway and Ashworth, *J. Chem. Soc.*, 475 (1933).

sodium bicarbonate (2.36 g., 0.028 mole), was treated with hydroxylamine hydrochloride (1.5 g., 0.022 mole) in 25 ml. of water. The precipitated solid was redissolved by the addition of solid sodium bicarbonate and the solution warmed for two hours. An additional 2 g. of sodium bicarbonate was added and the heating continued for two more hours. The reaction mixture was acidified to congo red paper with hydrochloric acid, filtered, and the solid washed with water, ethanol, and ether. Crystallization was effected from aqueous ethanol; yield 2.5 g.

Other isoxazolones were prepared by similar procedures.

Summary

1. Several aminobenzenearsonic acids have been diazotized and coupled with ethyl acetoacetate.

2. The products from (I) have been treated with hydrazine or hydroxylamine in the presence of base to give the corresponding 4-(arsonophenylazo)-3-methyl-5-pyrazolones or 5-isoxazolones.

3. The barium hydroxide hydrolysis of ethyl α-acetoglyoxylate-4-arsonophenylhydrazone produced normal ester hydrolysis rather than the expected acetoacetic ketonic hydrolysis.

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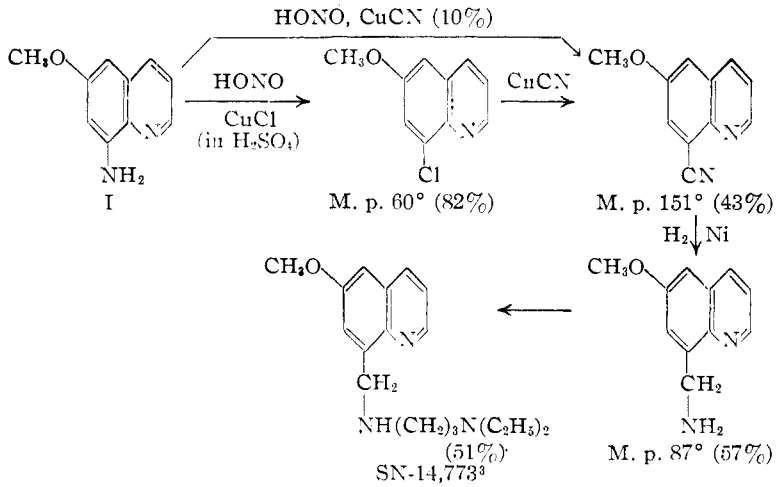
Methylene and *p*-Phenylene Analogs of Plasmocid[1]

BY CHARLES C. PRICE,[2] H. R. SNYDER AND EARLE M. VAN HEYNINGEN

In order to evaluate the effect of interposing a methylene or phenylene residue between the amino side chain and the nucleus in the 8-aminoquinoline series, two analogs of 6-methoxy-8-(diethylaminopropylamino)-quinoline, sometimes referred to as Plasmocid, have been prepared.

The synthesis of both compounds started from 6-methoxy-8-aminoquinoline. The methylene analog was prepared by replacement of the amino group with cyano, preferably through the chloro compound by treatment with cuprous cyanide. The 8-cyano compound was reduced catalytically and then treated with 3-diethylaminopropyl chloride.



The *p*-phenylene analog was prepared by three similar procedures: (1) The amino group of I was diazotized and the product coupled directly with nitrobenzene. (2) The amino group was acetylated, nitrosated and coupled with nitrobenzene. (3) The salt of diazotized I with 1,5-naphthalenedisulfonic acid was isolated and coupled with nitrobenzene. The last was the most convenient procedure.

Experimental[4]

8-Cyano-6-methoxyquinoline by the Sandmeyer Reaction.—To 3 g. (0.017 mole) of 8-amino-6-methoxyquinoline was added a solution of 1.1 ml. (0.02 mole) of concentrated sulfuric acid (sp. gr. 1.84) in 50 ml. of water. The mixture was heated to dissolve the yellow sulfate that formed, and then cooled rapidly an in ice-bath to reprecipitate the sulfate in fine needles. The cooled suspension was diluted with a solution of 3.3 ml. (0.06 mole) of sulfuric acid in 50 ml. of water and then diazotized at a temperature below 5° with a 5 *N* sodium nitrite solution to a starch-iodide end-point. A deep red solid formed during the course of the diazotization and this was filtered from the diazotization mixture. The filtrate was made neutral to red litmus paper with cold 30% sodium hydroxide by gradual addition such that the temperature of the mixture did not rise above 5°. A pink precipitate formed. This neutral suspension was poured slowly with stirring into 23 ml. of 1 *N* sodium cuprous cyanide cooled in an ice-bath. No visible change occurred so the mixture was stirred overnight, thus slowly coming to room temperature. Then the solid in the mixture was collected and extracted with 50 ml. of boiling 95% ethanol. The alcohol extract was evaporated to dryness on a steam-bath and the dark residue dissolved by heating in a minimum amount of 20% acetic acid. The hot acetic acid solution was treated with a small amount of Darco and filtered. The white crystals that formed on cooling were 8-cyano-6-methoxyquinoline, m. p. 147–150° (9.5%).

Replacing the sulfuric acid by phosphoric or hydrochloric acid did not change the yield. Addition of the acidic diazonium solution to a solution of sodium cuprous cyanide and excess sodium cyanide at either 50 or 100° gave none of the desired 8-cyano-6-methoxyquinoline.

(1) The work reported was carried out under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

(2) Present address: University of Notre Dame, Notre Dame, Indiana.

(3) The Survey Number, designated SN-, refers to the number assigned by the Survey of Antimalarial Drugs. The activity of such compounds will be compiled in a forthcoming monograph.

(4) Analyses were performed by Misses T. Spoor and L. Hruda.