Coupling of Diazotized *p*-Aminosalicylic Acid (PAS) with 5-(*p*-Hydroxyphenyl)-cyclohexanedione-1,3 and Related Compounds

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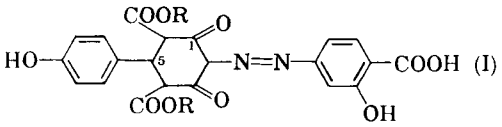
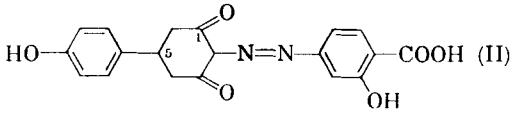
The syntheses of five derivatives of PAS are described. The compounds were prepared for study as agents having possible increased antimetabolite and/or antimicrobial properties.

IT IS KNOWN that many azo compounds are useful as dyes, diagnostic agents, indicators, staining agents for bacteria, etc. Some azo compounds depending on the radicals and functional groups involved in their structures have important physiological properties. The fact that PAS has been used with or without other drugs in the chemotherapy of tuberculosis prompted these authors to do this work, namely the synthesis of compounds (I) to (V). This report is an extension of previous work (1) and deals with the coupling of diazotized *p*-aminosalicylic acid with each of the following compounds: (*a*) 5-(*p*-hydroxyphenyl) 4,6-dicarbethoxycyclohexanedione-1,3; (*b*) 5-(*p*-hydroxyphenyl)-cyclohexanedione-1,3; (*c*) 5,5-dimethylcyclohexanedione-1,3; (*d*) 5-(2′, 3′, 4′-trimethoxyphenyl) 4,6-dicarbethoxycyclohexanedione-1,3; (*e*) trimethoxybenzene. The coupled products are represented by the formulas (I) to (V), respectively.



(I)



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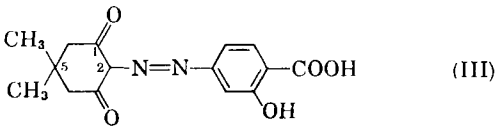

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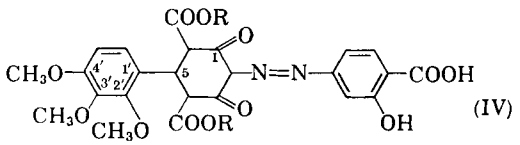
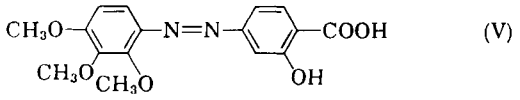
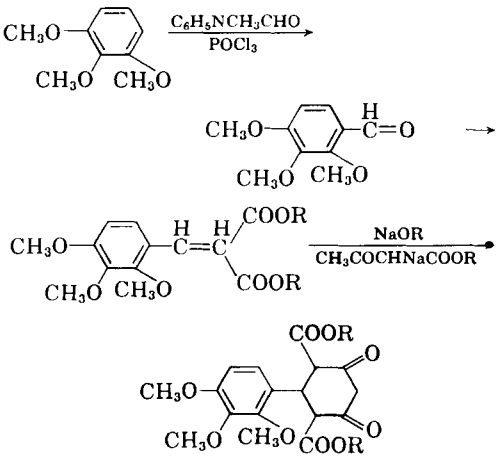


(IV)



(V)

The general methods of the preparation of compounds (*a*) and (*b*) have been previously described (2, 3). The sequence of synthesis for the preparation of compound (*d*) which is a new compound is as follows



The methods used for some of the above syntheses have been described (2, 4).

EXPERIMENTAL

In the diazotization process each of the reagents (*a*) to (*d*) was dissolved in dilute sodium hydroxide and the solution cooled to 0°. In another container an equivalent amount of the sodium salt of *p*-aminosalicylic acid was dissolved in distilled water and to this solution hydrochloric acid was added (calculated to react with: the sodium salt of PAS, the amino group of PAS, and the sodium nitrate). The calculated amount of sodium nitrite was added, a little at a time with stirring. The diazonium salt thus prepared was mixed with the sodium derivative of the respective cyclic dione. The mixture was stirred and then allowed to stand at 3° for 1 hour. Then the mixture was made acid to Congo red paper. A red-brown precipitate was formed which was filtered and washed with distilled water. Products (I) and (III) were recrystallized from 75% alcohol. Products (IV) and (V) were dissolved in ether and reprecipitated with petroleum ether. For the formation of (V) the trimethoxybenzene was dissolved in the minimum quantity of dioxane at 10° and added, with stirring, to the diazonium salt of PAS at 0°. Sodium hydroxide was added to take care of the hydrochloric acid. After stirring for 1 hour at 4° the mixture was made acid to Congo red paper, a black-red precipitate was formed which was filtered, dissolved in ether, and reprecipitated with petroleum ether. The analyses of the compounds following are given in Table I: I, N-2-[5-(*p*-hydroxyphenyl)-4,6-dicarbethoxy-cyclohexanedione-1,3]-azo-N-*p*-salicylic acid; II, N-2-[5-(*p*-hydroxyphenyl)-cyclohexanedione-1,3]-azo-N-(*p*-salicylic acid); III, N-2-[5,5-dimethyl-cyclohexanedione-1,3]-azo-N-(*p*-salicylic acid); IV, N-2-[5-(2′, 3′, 4′-trimethoxyphenyl)-4,6-dicarbethoxy-cyclohexanedione-1,3]-azo-N-(*p*-salicylic acid); V, N-1-(2,3,4-trimethoxybenzene)-azo-N-(*p*-salicylic acid).

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TABLE I.—ANALYSIS OF COMPOUNDS

No.	M.P., °C.	Empirical Formulas	Analysis: Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
I	...	$C_{26}H_{24}N_2O_{10}\cdot 2H_2O$	54.74	5.11	5.11	54.91	5.58	5.11 5.28
II	d. 186	$C_{19}H_{10}O_6N_2\cdot{}^1/_2H_2O$	60.48	4.61	...	60.78	4.88	...
III	d. 235	$C_{15}H_{16}N_2O_5\cdot H_2O$	55.89	4.96	...	55.87	4.78	...
IV	232	$C_{28}H_{30}N_2O_{12}\cdot H_2O$	55.62	5.29	...	55.66	5.37	...
V	...	$C_{16}H_{16}N_2O_6\cdot H_2O$	...	...	8.00	...	...	7.89

REFERENCES

(1) Papadakis, P. E., Scigliano, J., Chin, C., and Adrian, A., *J. Am. Chem. Soc.*, **72**, 4256(1950).
(2) Papadakis, P. E., *ibid.*, **67**, 1799(1945).
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(4) Papadakis, P. E., and Boand, W., *J. Org. Chem.*, **26**, 2075(1961).

Communications

New Alkaline-Stable Species for Selected Members of the Tetracycline Family

Sir:

We have recently observed a new modification of selected members of the tetracycline family which shows greatly enhanced stability under alkaline conditions. This derivative is a complex having the following general formula: (tetracycline - group - antibiotic) - $(aluminum)_a$-$(calcium)_b$-(gluconic acid)$_c$ where a, b, and c are the molar ratios of the respective constituents. Although the molar ratios a, b, and c can vary over a wide range in this derivative, greatly enhanced alkaline stability occurs only when the molar ratios of aluminum and calcium are three or greater. The molar ratio of gluconic acid does not appear to contribute significantly to the alkaline stability, but appears to play an important role in solubilizing the derivative.

In measuring the alkaline stability of derivatives in this series, extensive use has been made of half-life determinations, as reported by McCormick, *et al.* (1). Half-life values have been determined in 0.1 *N* sodium hydroxide at 90–100° by following the time change in (*a*) ultraviolet absorbance at 365 mμ and (*b*) the microbiological activity of the antibiotic.[1] Table I *demonstrates* the enhanced alkaline stability of selected members of the tetracycline family in this series of derivatives.

[1] Microbiological assays were performed under the direction of Dr. J. J. Corbett, Biological Assay Development Laboratory.

TABLE I.—RELATIVE ALKALINE STABILITY OF VARIOUS DERIVATIVES OF 6-DEMETHYLCHLORTETRACYCLINE (DMCTC),[a] CHLORTETRACYCLINE (CTC),[a] 6-DEMETHYLTETRACYCLINE (DMTC), TETRACYCLINE (TC),[a] AND 6-DEOXY-6-DEMETHYLTETRACYCLINE (DODMTC)

	Half-Life, min., in 0.1 *N* NaOH at 90–100°: Spectrophotometric Determination	Half-Life, min., in 0.1 *N* NaOH at 90–100°: Microbiological Determination
DMCTC·HCl	40	60
DMCTC-aluminum-gluconate (1:4:6.6)	95	..
DMCTC-aluminum-calcium-gluconate (1:4:1:12)	1,120	..
DMCTC-aluminum-calcium-gluconate (1:4:2:12)	3,000	..
DMCTC-aluminum-calcium-gluconate (1:4:3:12)	Very long[b]	..
DMCTC-aluminum-calcium-gluconate (1:4:5:12)	Very long[b]	Very long[b]
CTC·HCl	4	..
CTC-aluminum-calcium-gluconate (1:4:5:12)	12	..
CTC-aluminum-calcium-gluconate (1:4:7:12)	26	..
DMTC·HCl	32	..
DMTC-aluminum-calcium-gluconate (1:4:5:12)	Very long[b]	..
TC·HCl	7	..
TC-aluminum-calcium-gluconate (1:4:5:12)	Very long[b]	..
DODMTC·HCl	200	..
DODMTC-aluminum-calcium-gluconate (1:4:5:12)	Very long[b]	..

[a] The trademarks of the American Cyanamid Co. for 6-demethylchlortetracycline, chlortetracycline, and tetracycline are Declomycin, Aureomycin, and Achromycin, respectively.
[b] No change observed after 4 to 6 hours in 0.1 *N* sodium hydroxide at 90–100°.