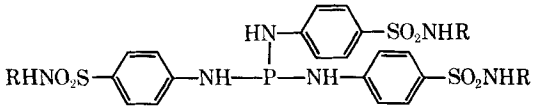
TABLE II—*N*-SUBSTITUTED DERIVATIVES OF PHOSPHORUS TRIAMIDE



R	Solvent of Crystallization[a]	M.p., °C.	Formula	Anal.,[c] % N Calcd.	N Found	S Calcd.	S Found	P Calcd.	P Found
Acetyl	C	278–280 dec.	$C_{24}H_{27}N_6O_9PS_3$	12.53	11.97	14.34	14.35	...	...
2-Thiazolyl	B	208–210[b] 260 dec.	$C_{27}H_{24}N_9O_6PS_6$	15.87	14.93	24.23	25.17	3.89	3.91
4,6-Dimethyl-2-pyrimidinyl	B	248–250[b] 270 dec.	$C_{36}H_{39}N_{12}O_6PS_3$	19.48	19.78	11.14	11.68	3.58	3.50

[a] B, absolute alcohol; C, aqueous acetic acid. [b] Liquid crystal. Melting points were performed by the capillary tube method and are uncorrected. [c] Analyses performed by Janssen Pharmaceutica, Beerse, Belgium.

Toy (8) in their work on the preparation of *N*-substituted derivatives of phenyl esters of amido and diamido phosphoric acid reported the use of pyridine–chloroform and the same mixture was later used by Cates (1). In the present investigation the pyridine–chloroform mixture (2:1) was successfully used in all the condensations.

That the phosphorus atom in the synthesized compounds is linked to the N^4 of the sulfa drug was shown qualitatively by the failure of all the condensation products to diazotize and by their solubility in dilute alkali and insolubility in dilute mineral acids.

EXPERIMENTAL

The condensation was carried out according to the following general procedure.

Phosphorus trichloride (0.01 mole), dissolved in pyridine–chloroform (25 ml.), was gradually added to the sulfa compound (0.02 mole). The mixture was refluxed for 24 hr. with all except sulfanilamide in which case refluxing for 12 hr. was sufficient. Then the solvent was distilled *in vacuo*, and the yellowish brown viscous residue was suspended in dilute hydrochloric acid, filtered, and washed with water until the washings gave a negative chloride test with silver nitrate T.S. The product, after being dried, was crystallized from the appropriate solvent. (See Tables I and II.)

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New Compounds: Synthesis of Some Sulfazopyridine Derivatives for Pharmacological Study

By H. Y. ABOU-ELENEIN, M. KHALIFA, and Y. M. ABOU-ZEID

The synthesis of some sulfazopyridine derivatives is described.

SINCE THE discovery of sulfamidochrysoidine[1] (1), a large number of sulfamoyl phenylazo dyes was made and their chemotherapeutic action was studied against various bacterial infections. In recent years combinations of sulfonamides and azo dyes are widely used as urinary disinfectants. The authors now report the synthesis of some azo dyes containing a sulfonamido moiety together with a diaminopyridyl moiety (I).

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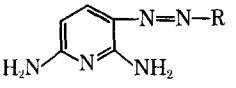
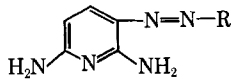
The products at present are under preliminary screening for possible antimicrobial action or any useful pharmacological activity.
[1] Prontosil.



I

Derivatives having the above general formula were synthesized by coupling diazotized sulfonamides with 2,6-diaminopyridine hydrochloride. Attempts to prepare 2,6-diaminopyridine by amination of pyridine with sodamide in the presence of solvents were unsuccessful; in the absence of solvents, a 20% yield was obtained. Two methods were applied for diazotizing the sulfa compounds: (*a*) the standard procedure and (*b*) the alternate one, which consists of dissolving the sulfonamide in sodium hydroxide first. The diazotized sulfa compound

TABLE I—SULFAZOPYRIDINE DERIVATIVES



M.p.,[b] °C.	Yield, %	Solvent of Crystallization[a]	Method of Diazotization	Formula	Anal.,[c] % Calcd. N	Calcd. S	Found N	Found S
R = N-(2-Phenyl-3-pyrazolyl)-p-sulfamoyl Phenyl								
134–135	95	B	(*a*)	$C_{20}H_{18}N_8O_2S$	25.77	7.36	25.16	7.14
R = N-(2,4-Dimethyl-6-pyrimidinyl)-p-sulfamoyl Phenyl								
250	89–92	B	(*a*)	$C_{17}H_{18}N_8O_2S$	28.1	8.04	28.66	8.20
R = N-(3,4-Dimethyl-5-isoxazolyl)-p-sulfamoyl Phenyl								
250	90	A	(*a*)	$C_{16}H_{17}N_7O_3S$	25.31	8.53	25.12	8.55
R = N-(2,4-Dimethoxy-6-pyrimidinyl)-p-sulfamoyl Phenyl								
220	89	A	(*a*)	$C_{17}H_{18}N_8O_4S$	26.04	7.44	25.99	7.29
R = N-(3,4-Dimethylbenzoyl)-p-sulfamoyl Phenyl								
210	88	A	(*b*)	$C_{20}H_{20}N_6O_3S$	19.82	7.55	19.52	7.57
R = N-(6-Methoxy-3-pyridazinyl)-p-sulfamoyl Phenyl								
180	90	A	(*b*)	$C_{16}H_{16}N_8O_3S$	27.98	8.00	27.82	8.48

[a] A, aqueous ethanol; B, absolute ethanol. [b] All melt with decomposition. [c] Analyses were performed by Janssen Pharmaceutica, Beerse, Belgium.

thus obtained was then coupled with 2,6-diaminopyridine hydrochloride and in all cases the azo dye was isolated by adjusting the pH of the reaction mixture to 6.5–7.

EXPERIMENTAL[2]

2,6-Diaminopyridine—Sodium amide was obtained by dissolving freshly cut sodium (27.6 Gm.) in anhydrous liquid ammonia (600 ml.) in the presence of 0.5 Gm. ferric nitrate as catalyst. The flask containing the suspension of sodium amide was fitted with a dropping funnel containing 39.4 Gm. of dry pyridine which was added cautiously while the ammonia was allowed to escape through the soda-lime tube. After all the ammonia was driven out (by removal of the dry ice–ether bath) and after the temperature of the apparatus reached the laboratory temperature, the dry ice condenser was replaced by a vertical condenser protected by a calcium chloride tube, and the funnel was replaced by a thermometer which dipped into the reaction mixture. The flask was heated in an oil bath, the temperature of the reaction mixture being maintained at 170° until hydrogen ceased to evolve (9–10 hr.). The solid cake which separated on cooling was treated with 10% sodium hydroxide solution until the vigorous decomposition stopped and then with water to complete the hydrolysis of the sodium salt. The product which was obtained in 20% yield (10 Gm.) melted at 120–122° as reported (2) after one crystallization from benzene.

Diazotization Procedures—(*a*) The sulfonamide (0.01 mole) was dissolved in 20 ml. of 25% hydrochloric acid by gentle warming, diluted with 100 ml. of water, and cooled to 0–5°. This solution was diazotized by the dropwise addition of a cold solution of 0.012 mole sodium nitrite in water. It was set aside for 15 min. at a temperature not exceeding 5° after complete addition of the nitrite.

(*b*) The sulfonamide (0.01 mole) was dissolved in 20 ml. of 25% sodium hydroxide solution, 0.012 mole of sodium nitrite was added with continuous stirring and then acidified by the dropwise addition of 25 ml. of hydrochloric acid. It was left for 10 min. after complete addition of the acid, the temperature being maintained at 0–5° during the diazotization.

Coupling Procedure—The diazonium salt solution prepared above was gradually added with continuous stirring to a solution of 2,6-diaminopyridine (0.01 mole) dissolved in 10% hydrochloric acid (temperature should not exceed 5° during the addition), and left aside for 15 min. for complete reaction. The pH of the medium was then adjusted to about 6.5–7 by the addition of dilute sodium hydroxide solution with stirring. The azo dye which precipitated was filtered at the pump and crystallized either from aqueous ethanol or absolute ethanol. (See Table I.)

[2] Melting points were performed by the capillary tube method and are uncorrected.

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