Chemistry of *N*-(Triphenylphosphoranylidene)sulfamoyl Chloride. 2.[1] *N*-[*N*-(Triphenylphosphoranylidene)sulfamoyl]-*N'*-alkylureas and -guanidines

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A series of *N*-[*N*-(triphenylphosphoranylidene)sulfamoyl]-*N'*-alkylureas, $Ph_3P{=}NSO_2NHC(O)NR_1R_2$ ($R_1 = R_2 = Et$; $R_1 = H$, R_2 = Me, Et, *n*-Pr, *n*-Bu), has been prepared by the reaction of ethyl *N*-[*N*-(triphenylphosphoranylidene)sulfamoyl]carbamate, $Ph_3P{=}NSO_2NHCO_2Et$, with the corresponding amine in bis(2-methoxyethyl) ether. Several sulfamoylalkylguanidines, $Ph_3P{=}NSO_2N{=}C(NH_2)NHR$ (R = Me, *n*-Pr, *n*-Bu), were prepared by the reaction of *N*-[*N*-(triphenylphosphoranylidene)sulfamoyl]-*S*-methylisothiourea, $Ph_3P{=}NSO_2N{=}C(NH_2)SMe$, with amines in bis(2-methoxyethyl) ether or triethylene glycol. The IR spectra of the guanidines contain a strong band near 1620 cm^{-1} which is attributed to the C=N group.

The synthesis of urea and guanidine derivatives of both sulfonyl and sulfamoyl chlorides has been of considerable interest because of the potential chemotherapeutic value of these compounds. Certain sulfonyl- and sulfamoylureas have been found to be effective oral hypoglycemic agents (*3–5*) and some sulfanilylguanidines possess useful bacteriostatic activity (*6*).

In continuation of the investigation of the chemistry of the novel compound *N*-(triphenylphosphoranylidene)sulfamoyl chloride, $Ph_3P{=}NSO_2Cl$ (**1**) (*1*, *2*), we initiated a program of research directed at the synthesis of alkylurea and guanidine derivatives of **1**. The title ureas were prepared by the reaction of ethyl *N*-[*N*-(triphenylphosphoranylidene)sulfamoyl]carbamate, $Ph_3P{=}NSO_2NHCO_2Et$ (**2**), with amines in bis(2-methoxyethyl) ether or triethylene glycol at elevated temperatures.

$$2 + R_1R_2NH \xrightarrow[110\text{–}120\ ^\circ C]{} \underset{\mathbf{3a\text{–}e}}{Ph_3P{=}NSO_2NHC(O)NR_1R_2} + EtOH \quad (1)$$

The carbamate **2** was prepared by the reaction of ethyl chloroformate with *N*-(triphenylphosphoranylidene)sulfamide, $Ph_3P{=}NSO_2NH_2$, in pyridine.

Alkylguanidines were obtained by the reaction of amines with *N*-[*N*-(triphenylphosphoranylidene)sulfamoyl]-*S*-methylisothiourea, $Ph_3P{=}NSO_2N{=}C(NH_2)SMe$ (**4**).

$$4 + RNH_2 \rightarrow \underset{\mathbf{5a\text{–}c}}{Ph_3P{=}NSO_2N{=}C(NH_2)NHR} + MeSH \quad (2)$$

The formation of alkylguanidines (eq 2) occurs much more slowly than the formation of the alkylureas (eq 1) and the yields are not as high. The infrared spectra of the sulfamoylalkylguanidines contain two strong bands in the region 1550–1650 cm^{-1}: for compound **5a**, the bands appear at 1560 and 1620 cm^{-1}; for **5b**, 1570 and 1616 cm^{-1}; and for **5c**, 1553 and 1627 cm^{-1}. A strong band at or very near 1550 cm^{-1} also appears in the IR spectra of the ureas and in compound **4**. However, the band near 1620 cm^{-1} is present only in compounds containing the C=N group, and we therefore assign the higher frequency band to this group. The lower frequency band may be assigned to the CNH vibration as found in N-substituted amides and ureas.

Experimental and physical data for compounds reported herein are presented in Table I.

Table I. Data for *N*-[*N*-(Triphenylphosphoranylidene)sulfamoyl]-*N'*-alkylureas and -guanidines

compound	% yield[a]	mp,[b] °C	crystn solvent
2	79.3	183.2–184.0	EtOH
3a, $R_1 = H$, $R_2 = Me$	80.5	202.5–204.2	EtOH
3b, $R_1 = H$, $R_2 = Et$	53.5	201.8–202.4	EtOH
3c, $R_1 = H$, $R_2 = n$-Pr	87.5	202.0–203.0	$CHCl_3$/EtOH
3d, $R_1 = H$, $R_2 = n$-Bu	91.2	204.8–205.4	$CHCl_3$/EtOH
3e, $R_1 = R_2 = Et$	65.7	191.8–192.8	$CHCl_3$/PhH[c]
4	92.8	155.2–155.8	PhH/C_6H_{14}
5a, R = Me	58.7	207.8–208.8	$CHCl_3$/PhH
5b, R = *n*-Pr	26.8	184.0–185.5	CH_2Cl_2/PhH
5c, R = *n*-Bu	53.5	188.2–189.2	CH_2Cl_2/PhH

[a] Crude yield. [b] All compounds decompose with bubbling. [c] An attempt to recrystallize this compound from EtOH resulted in the loss of the diethylamino group and the formation of **2** in 82.5% yield.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 337 grating IR spectrophotometer and on a Perkin-Elmer Model 283 spectrophotometer with printer. Solid samples were run as KBr pellets. Melting points were determined with a Hoover melting point apparatus in open capillaries and are uncorrected. Elemental analyses (C, H, N) in agreement with theoretical values (±0.4%) were obtained for all new compounds.

Ethyl N-[N-(Triphenylphosphoranylidene)sulfamoyl]carbamate (2). Pyridene (300 mL) from a freshly opened bottle and *N*-(triphenylphosphoranylidene)sulfamide (128 g, 0.36 mol) were added to a three-necked flask (2000 mL) fitted with a mechanical stirrer, pressure-equalizing dropping funnel, and stopper. The addition of $EtCO_2Cl$ (125 mL, ca. 1.56 mol) to the vigorously stirred mixture over a period of 4 h gave a brown, homogeneous solution. The reaction was exothermic and gas was evolved during the addition of the chloroformate. After all of the chloroformate had been added, the dropping funnel was replaced with a thermometer and the mixture was heated with a mantle to 45–50 °C for 2 h. The solution was cooled and, with continued stirring, concentrated HCl (300 mL) was added from a dropping funnel; the temperature was kept at 30 °C by cooling with ice and controlling the rate of addition.

Without adding additional water, the solid which precipitated was filtered and then stirred for 1 h at room temperature with excess 1.0 M NaOH. Filtration of this mixture gave unreacted sulfamide (33.4 g, 26.3%) and a greenish filtrate which yielded 90 g of white, powdery **2** (79.3%) upon acidification with concentrated HCl (85 mL). Compound **2** is not appreciably soluble in aqueous carbonate solutions and its separation from

[†] Taken in part from the MS Thesis of J.A.M., Virgina Commonwealth University, 1976.

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0021-9568/78/1723-0353$01.00/0

unreacted sulfamide is best accomplished using alkali metal hydroxides.

***N*-[*N*-(*Triphenylphosphoranylidene*)*sulfamoyl*]-*N'*-*alkylureas* (*3a–e*).** Bis(2-methoxyethyl) ether (100 mL of practical grade), **2** (20.6 g, 0.048 mol), and the appropriate amine (ca. 0.110 mol) were added to a two-necked flask (300 mL) fitted with a mechanical stirrer and reflux condenser. The heterogeneous mixture was stirred for 10 min at room temperature and then heated to 112 °C (oil bath temperature) at which point the solid had dissolved to give a yellow solution. After 10 min at 112 °C, a white solid precipitated. Heating was continued for 1 h and then the mixture was cooled and suction filtered and the white solid washed with water and dried in vacuo. Recrystallization from suitable solvents gave analytically pure material (Table I). In the case of gaseous amines, the amine was passed directly into the reaction mixture until precipitation of the derivative occurred.

***N*-[*N*-(*Triphenylphosphoranylidene*)*sulfamoyl*]-*S*-*methylisothiourea* (*4*).** An intimate mixture of **1** (66.5 g, 0.177 equiv) and *S*-methylisothiourea hydrogen sulfate (37.0 g, 0.266 equiv) was added in portions and with vigorous stirring to saturated aqueous potassium carbonate (250 mL) contained in a two-necked flask (1000 mL) equipped with a mechanical stirrer. After stirring for 45 min, acetone (250 mL) was added and the mixture stirred at room temperature for 27 h. Analysis of the mixture by TLC indicated the absence of **1**. Water (200 mL) was added and the mixture stirred for a short time. Filtration of the mixture, followed by drying of the solid in vacuo gave 70.1 g of **4** (92.8%).

***N*-[*N*-(*Triphenylphosphoranylidene*)*sulfamoyl*]-*N'*-*methylguanidine* (*5a*).** Powdered, crude **4** (20.0 g, 0.047 mol) and triethylene glycol (205 mL, purified grade) were placed in a two-necked flask (500 mL) equipped with a magnetic stirrer, reflux condenser, and a gas dispersion tube connected via a trap and three-way stopcock to a lecture bottle of methylamine (Matheson). The mixture was stirred and heated in an oil bath to a bath temperature of 120 °C, effecting nearly complete dissolution of **4**. Methylamine, in a current of nitrogen, was then added at a moderate rate until the evolution of methyl mercaptan had ceased (about 2 h), as indicated by lead acetate paper; the solution was pale green at this point. Stirring was stopped and the solution, which turned yellow upon cooling, was decanted from a small amount of insoluble residue and added to water (700 mL) with vigorous stirring. A fine, white powder separated which gave, after filtering and drying in vacuo over P_2O_5, 11.3 g (58.7%) of **5a**. The other alkylguanidines were prepared similarly except that bis(2-methoxyethyl) ether was used as solvent.

Acknowledgment

We thank Mr. Malcolm Stone of A. H. Robins Co. for the elemental analyses.

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Received for review March 20, 1978. Accepted May 31, 1978.

Synthesis of Potentially Estrogenic Carcinogens: 7,12-Dimethylbenz[*a*]anthracene-3,9-diol

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Previously no diphenolic derivatives of the powerful mammary carcinogen, 7,12-dimethylbenz[*a*]anthracene have been reported. The present report concerns the synthesis of 7,12-dimethylbenz[*a*]anthracene-3,9-diol from 4-methoxyphthalic anhydride and 6-methoxy-2-bromonaphthalene. This compound has the potential to behave both as an estrogen and as a carcinogen.

7,12-Dimethylbenz[*a*]anthracene (DMBA) has been employed for many years as a useful tool in the induction of mammary tumors in rodents (*1*). The susceptibility of these tumors to hormonal influences, particularly by estrogens, prompted this laboratory to investigate the properties of polycyclic hydrocarbon diols, the hydroxy groups of which are superimposable with those of the potent experimental carcinogenic estrogen diethylstilbestrol and the naturally occurring estrogen 17β-estradiol.

This laboratory first prepared benz[*a*]anthracene-3,9-diol (BA-3,9-diol) (*2*) as a model compound with which to pursue the concept that polycyclic hydrocarbon diols of proper architecture will behave as estrogens. The compound BA-3,9-diol did indeed display estrogenic activity as evidenced by bioassay. The compound also inhibited the binding of 17β-estradiol to the 8S binding protein of rat uterine cytosol at an intensity similar to that of the known estrogen inhibitor, Nafoxidine hydrochloride (*3*).

The present report concerns the synthesis of 7,12-dimethylbenz[*a*]anthracene-3,9-diol. The scheme outlined for the acquisition of this compound (Scheme I) is similar to that used previously for the preparation of methyl-substituted derivatives (*4*) and hydroxy-substituted derivatives (*5*) of DMBA. The reaction of 4-methoxyphthalic anhydride with the Grignard reagent prepared from 6-methoxy-2-bromonaphthalene gave the isomeric acids 2-(6-methoxy-2-naphthoyl)-4-methoxybenzoic acid (**1**) and 2-(6-methoxy-2-naphthoyl)-5-methoxybenzoic acid (**1a**). The structure of acid **1** was established by decarboxylation to 3-methoxyphenyl 6-methoxy-2-naphthyl ketone (**7**) which was reduced by sodium borohydride to 2-(6-methoxy-2-naphthyl)-3-methoxybenzyl alcohol (**8**). The alcohol **8** was also synthesized from 3-methoxybenzaldehyde and the Gringnard reagent prepared from 2-bromo-6-methoxynaphthalene (Scheme II)

The keto acid **1** reacted with methylmagnesium iodide to give the lactone 3-methyl-3-(6-methoxy-2-naphthyl)-5-methoxyphthalide (**2**) which was reduced with Zn(Cu) in base to the acid 2-[2-(6-methoxy-2-naphthyl)ethyl]-4-methoxybenzoic acid (**3**). Cyclization of the acid **3** in HF gave 3,9-dimethoxy-7-methylbenz[*a*]anthr-12-one (**4**). Reaction of the ketone **4** with me-

0021-9568/78/1723-0354$01.00/0