SYNTHESIS OF *N*-(SUBSTITUTED)-*N'*-[5,5'-BIS(BROMOMETHYL)-2-OXIDO-1,3,2-DIOXAPHOSPHORINANE-2YL] UREAS

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Abstract: Synthesis of *N*-(Substituted)-*N'*-[5,5'bis(bromomethyl)-2-oxido-1,3,2-dioxaphosphorinane-2yl] ureas has been accomplished by condensation of equimolar quantities of chlorides of various carbamidophosphoric acids 3 with 2,2'-bis(bromomethyl)1,3-propanediol 4 in the presence of triethylamine in dry tetrahydrofuran at 30-40°C. Their structures were established by elemental analyses, IR ^{1}H, ^{13}C,^{31}PNMR and Mass spectral data.

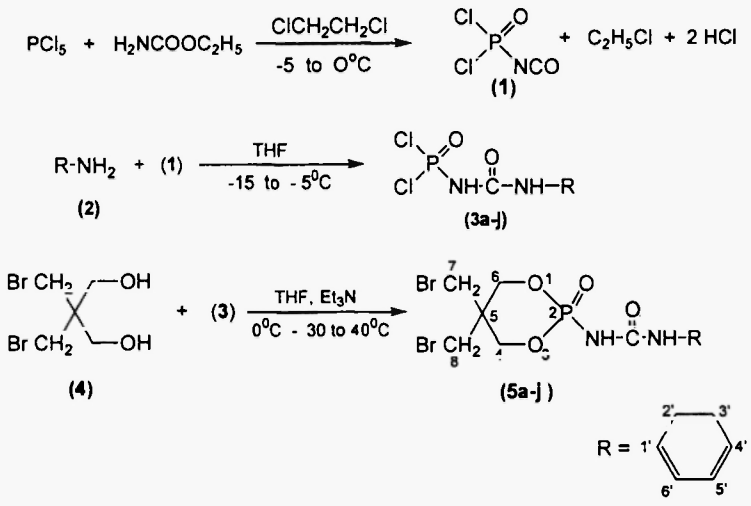
Introduction

Organophosphorus carbamates demonstrated insecticidal, bactericidal, antiviral, antitumour and anti carcinogenic activity (1-8). Synthesis of compounds containing P-N linkages has led to many interesting and for reaching developments in their application as pesticides and drugs (9-12). Several new class of substituted ureas of the type RR'P(O)NHC(O)NHR'' **5** were synthesized as our continuing research endeavor.

Results and Discussion

Addition of equivalent amount of isocyanatophosphonic dichloride 1 (2,3) to various amines 2 at –15° C in dry tetrahydrofuran led to the formation of corresponding chlorides of aryl/cyclohexyl carbamidophosphoric acids 3 (13). The powerful electron withdrawing effect of two chlorine atoms at phosphoryl group in 1 markedly enhances electrophilic character of the carbon of isocyanato group and facilitates rapid nucleophilic addition of the aryl amines to it even at low temperatures. Aromatic amines with electron donating substitutents in the ring added to 1 more effectively when compared to the aliphatic amines as indicated by their yields. These addition reactions between 1 and 2 took place in non-polar solvents at -15°C. The reaction products separated from the reaction mixture immediately after completion of the addition of amines to 1 as crystalline compounds. Further purification of carbamidophosphoric acids 3 could not be made due to their insolubility in all organic solvents and air sensitivity. Hence, they were reacted directly with 2,2'bis(bromomethyl)1,3-propanediol 4 in tetrahydrofuran in the presence of triethylamine to afford **5a-j** (Scheme-1).

Product yields, elemental analyses, IR and ^{31}P NMR data of **5a-h** are given in Table-1. Tables-2 and -3 contain their ^{1}H and ^{13}C NMR data. FAB Mass spectra data **5f** and **5g** are given in Table. 4.



Compd.	R	Compd.	R
5a	C_6H_5	5f	C_6H_3-Cl, F, (3', 4')
5b	C_6H_4-Cl (4')	5g	C_6H_3-$(CH_3)_2$ (2', 4')
5c	C_6H_4-Br (4')	5h	$C_6H_4CH_2Cl$ (2')
5d	C_6H_4-CH_3 (4')	5i	C_6H_{11}
5e	C_6H_4-OCH_3 (4')	5j	C_4H_8O

SCHEME -1

Compounds **5a-j** exhibited characteristic IR bands (14) for P=O (1223-1263 cm^{-1}), C=O (1601-1690 cm^{-1}) and P–NH (3267-3372 cm^{-1}).

The 5,5'-bis(bromomethyl) protons signal **5a-j** appeared as two separate singlets at δ 3.57-3.94 and 3.24-3.51 due to their non-equivalence and orientation as *axial* and *equatorial*. The upfield signal is attributed to the *equatorial* bromomethylene and the deshielded signal to the *axial* bromomethylene group (15). The 4 and 6 dimethylene groups displayed multiplets in the region 4.36-4.76 ppm. The aryl/cyclohexyl protons appeared at expected region (16). The signal of phosphoryl amidic proton P(O)NH appeared at extreme down field at δ 9.32-10.10 when compared to their carbamidic proton C(O)NH which occurred at δ 8.40 - 9.10. Both the NH proton signals were confirmed by D_2O exchange experiments.

Table-1: Physical, IR and ^{31}P NMR spectral data of 5a-j

Compd	Mp (°C)	Yield (%)	Molecular formula	Elemental analysis Found(Calcd)%			IR(cm^{-1})			^{31}P NMR (ppm)
				C	H	N	P=O	C=O	P-NH	
5a	190-191	68	$C_{12}H_{15}Br_2O_4PN_2$	32.60 (32.46	3.41 3.28	6.33 6.26)	1252	1642	3301	-6.20
5b	178-179	62	$C_{12}H_{14}Br_2O_4PN_2Cl$	30.25 (30.09	2.96 2.78	5.87 5.66)	1242	1601	3276	-6.85
5c	201-202	70	$C_{12}H_{14}Br_3O_4PN_2$	27.66 (27.48	2.70 2.57	5.37 5.26)	1249	1652	3289	-3.51
5d	210-211	66	$C_{13}H_{17}Br_2O_4PN_2$	34.23 (34.08	3.75 3.58	6.14 6.02)	1248	1623	3267	-5.50
5e	164 -165	60	$C_{13}H_{17}Br_2O_5PN_2$	33.07 (32.86	3.75 3.54	5.93 5.76)	1249	1619	3303	-6.44
5f	178-179	67	$C_{12}H_{13}Br_2O_4PN_2FCl$	29.15 (28.80	2.65 2.49	5.66 5.50)	1263	1670	3313	-2.66
5g	198-199	62	$C_{14}H_{19}Br_2O_4PN_2$	35.77 (35.59	4.07 3.94	5.95 5.79)	1258	1662	3292	-3.00
5h	194-195	69	$C_{15}H_{16}Br_2O_4PN_2Cl$	35.01 (34.50	3.13 2.92	5.44 5.24)	1225	1621	3318	-5.54
5i	180-182	52	$C_{12}H_{21}Br_2O_4PN_2$	31.84 (31.68	4.67 4.48	6.18 5.89)	1251	1629	3325	-5.40
5j	190-192	46	$C_{10}H_{18}Br_2O_5PN_2$	27.47 (27.24	4.15 4.06	6.40 6.29)	1231	1638	3319	-5.52

Table-2: ^{1}H NMR Chemical Shift data of **5a-h**

Compd	CH_2(4&6)	Br-CH_2 a	Br-CH_2 e	Ar-H	Cyclohexyl/ CH_2-Ph	Ar-CH_3	P(O)NHC(O)	C(O)NHR
5a	4.38 – 4.46 (m,4H)	3.82 (s,2H)	3.24 (s 2H)	6.96 - 7.42 (m,5H)	–	–	9.42 (brs)	8.66 (brs)
5b	4.40 – 4.54 (m,4H)	3.75 (s, 2H)	3.35 (s 2H)	6.92 – 7.46 (m,5H)	–	–	9.92 (brs)	8.77 (brs)
5c	4.38 – 4.51 (m, 4H)	3.78 (s,2H)	3.35 (s,2H)	6.94 – 7.51 (m, 4H)	–	–	10.10 (brs)	9.10 (brs)
5d	4.24 – 4.46 (m,4H)	3.79 (s,2H)	3.36 (s,2H)	6.98 – 7.62 (m,4H)	–	2.30 (s,3H)	9.80 (brs)	8.71 (brs)
5e	4.20 – 4.42 (m,4H)	3.92 (s,2H)	3.36 (s,2H)	6.83 – 7.45 (m,4H)	–	3.50 (s,3H)	9.32 (brs)	8.72 (brs)
5f	4.32 – 4.77 (m,4H)	3.72 (s,2H)	3.42 (s,2H)	6.73 – 7.75 (m,4H)	–	–	9.32 (brs)	8.72 (brs)
5g	4.13 –4.40 (m,4H)	3.57 (m,2H)	3.25 (s,2H)	6.65 –7.84 (m,3H)	–	2.15(s 3H) 2.21(s,3H)	9.34 (brs)	8.90 (brs)
5h	4.30 – 4.52 (m,4H)	3.93 (s,2H)	3.34 (s,2H)	6.62 – 7.58 (m,4H)	3.96 (m,2H)	–	10.3 (brs)	7.86 (brs)
5i	4.13 – 4.42 (m,4H)	3.96 (s,2H)	3.51 (s,2H)	–	1.19 – 1.74 (m,11H)	–	9.81 (brs)	8.40 (brs)
5j	4.24 – 4.46 (m,4H)	3.94 (s,2H)	3.38 (s,2H)	–	3.39 – 3.68 (m,8H,CH_2)	–	9.70 (brs)	8.90 (brs)

Table-3: ^{13}C NMR Chemical Shift[a] of some members of 5

Compd	Chemical shifts (in ppm)
5c	71.4 (s, 2C,C-4&6), 38.2 (s, 1C,C-5), 34.1 (s, 1C, C-7), 35.2(s, 1C, C-8),154.4 (s, 1C, C=O), 138.4 (s, 1C, C-1′),118.6 (s, 1C, C-2′), 130.9 (s, 1C, C-3′), 124.2 (s, 1C, C-4′),130.9(s, 1C, C-5′),118.6(s, 1C, C-6′).
5d	72.6 (s, 2C,C-4&6), 38.6 (s, 1C,C-5), 33.4 (s, 1C, C-7), 34.2(s, 1C, C-8),156.4 (s, 1C, C=O), 136.2 (s, 1C, C-1′),118.0 (s, 1C, C-2′), 129.6 (s, 1C, C-3′), 131.8 (s, 1C, C-4′),129.6 (s, 1C, C-5′),118.0(s, 1C, C-6′).20.1(s,3H,CH_3).
5g	70.6 (s, 2C,C-4&6), 38.9 (s, 1C,C-5), 34.1 (s, 1C, C-7), 35.4(s, 1C, C-8),151.7 (s, 1C, C=O), 133.6 (s, 1C, C-1′),122.0 (s, 1C, C-2′), 130.8 (s, 1C, C-3′), 128.7 (s, 1C, C-4′),126.6 (s, 1C, C-5′),114.3(s, 1C, C-6′).20.1(s,3H,CH_3), 17.6(s,3H,CH_3).
5i	76.2 (s, 2C,C-4&6), 39.5 (s, 1C,C-5), 34.0 (s, 1C, C-7), 35.6(s, 1C, C-8),154.2 (s, 1C, C=O), 55.0 (s, 1C, C-1′),32.0 (s, 1C, C-2′), 25.6 (s, 1C, C-3′), 25.0 (s, 1C, C-4′),25.6 (s, 1C, C-5′),32.8(s, 1C, C-6′).

[a] *J* (Hz) given in parenthesis

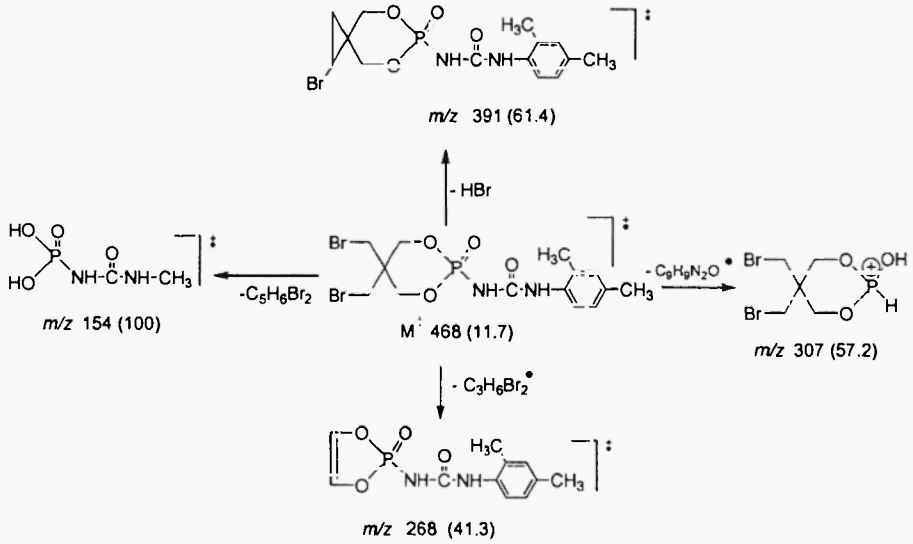
Table -4: Mass Spectral data of some members of 5

Compd	m/z (% relative abundance)
5f	491[(2.1) M+1],493 [(12.7) M+2], 495 [(5.3) M+4], 497 [(4.2) M+6], 486(18),460(12.4),442 (3.6),391(100),359(19.1), 325(8.3),316(18.7), 307(92.6),289(74.8),279(27.0),255(33.2),209(29.1),188(24.9),167(39.5), 120(41.6),107(73.5).
5g	468 [(11.7) M+],470 [(21.2) M+2], 472[(10.6) M+4], 460(6.3),414(11.6), 391(61.4),307(57.2),289(33.9),268(41.3),209(10.6),167(17.0).154(100), 149(59.3),136(100),120(17.0), 107(27.5).

The C-4 and C-6 carbon resonated as doublets at δ 70.6-72.6. The low intensity doublet at δ 38.2-39.5 is attributed to the tertiary C-5. Appearance of doublets for this carbon suggests it long range coupling with phosphorus (17-18). The two bromomethylene C-7 &8 attached to C-5 gave two signals one at δ 33.4-34.1 and 34.2-35.6 due to their non-equivalence and presence as axial and equatorial conformation. The C=O carbon gave signal at δ 151.7-156.4.

^{31} P NMR resonances (19) of these compounds **5a-i** appeared in the range of –2.66 to – 6.85 ppm

The FAB mass spectra of **5g** is rationalized in the scheme-2 as a representative of the series. Presences of M+1, M^+, [M- 2,4-dimethylphenyl urea] and [M-3,3'-bis(bromomethyl)-cyclopenten] ions conformed their assigned structure. Compound **5f** also exhibited similar fragmentation (Scheme-2).



SCHEME-2

Experimental

The melting points were determined on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by the Central Drug Research Institute, Lucknow, India. All IR spectra were recorded as KBr pellets on a Perkin – Elmer 1430 unit. ^{1}H and ^{13}C NMR spectra were recorded on AMX 400 MHz spectrometer operating at 400 MHz for ^{1}H, 100 MHz for ^{13}C and 161.9 for ^{31}P. Compounds were dissolved in $CDCl_3$ and DMSO-d_6. The chemical shifts (δ) were referenced to TMS (^{1}H and ^{13} C) and 85% H_3PO_4 (^{31}P).FAB Mass spectra were recorded on a JOEL DK, 102/DA/600 system using Argon/Xenon at 6kV, 10mA.

2,2′-Bis(bromomethyl)1,3-propanediol **4** was procured from Aldrich Chemical Company inc. USA and was used without further recrystallization.

Preparation of 2,4-dimethylphenyl carbamidophosphoric acid dichloride 3g.

A solution of 2,4-dimethyl aniline (**2c**, 0.24 g, 2.0 mmol) in dry tetrahydrofuran (25ml) was added drop wise to a cold solution (-15°C) of isocyanatophosphonic dichloride (**1**, 0.32 g, 2.0 mmol) in dry tetrahydrofuran during 20 mints. After the addition the temperature of the reaction mixture was maintained between –15°C to –5°C for 30-40 mints. Later, the temperature was raised to room temperature with stirring for 30-40 mints. 2,4,dimethyl phenyl carbamidophosphoric acid dichloride being insoluble in tetrahydrofuran separated out. It was collected by filtration and dried under reduced pressure (15).

Synthesis of *N*-(2,4-dimethylaniline)-*N'*-[5,5′-bis(bromomethyl)-2-oxido-1,3,2-dioxaphosphorinane-2yi] urea (5g)

To a cooled solution of 2,2′-bis(bromomethyl)1,3-propanediol (**1** ,0.52 g, 2.0 mmol) and triethylamine (0.40 g. 4.0 mmol) in 20 ml of dry tetrahydrofuran was added drop wise, a solution of 2,4-dimethylphenyl carbamidophosphoric acid dichloride (**3** 0.56g, 2.0 mmol) in 40ml of dry tetrahydrofuran during 20 mints at 0°C. After the addition, the temperature of the reaction mixture was raised to 30 to 40°C and stirred for 5 hours. The progress of the reaction was monitored by the TLC in the 1:3 mixture of ethyl acetate and hexane as mobile solvent and silica gel as adsorbent. Triethylamine hydrochloride was separated by filtration and the solvent from the filtrate was evaporated under reduced pressure. The residue obtained after washing with water was triturated with 2-propanol to afford 0.58 g (62%), m.p.194-195°C.

Compounds **5a-j** were synthesized by adopting the same procedure.

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Reference

1. M.Kuranari, Japan Patent, 26819 (1965); *Chem Abstr.* **64**, 9737h (1966).
2. Z.B.Papanastassiou and T.J.Bardos, *J.Med Chem.* **5**, 1000 (1962).
3. R.I.Zhadanov,W.A.Buina, N.A.Kapitanova and I.A.Nuretdinov, *Synthesis* 269 (1979).
4. H.Zimmer and A.Sill, *Prog. Drug.Res.* **5**, 150 (1964).
5. O.M.Friedman, Z.B. Papanastassiou and R.S.Levi, *J.Med.Chem.* **6**, 82 (1963).
6. H.Arnold, F.Bourseaux and N.Brock, *Arzeimittel Frosch* **11**, 143 (1961).
7. T.L.Lemke and D.Boring, *J. Heterocyclic Chem.* **17**, 1455 (1980).
8. P.Hsu, I.S.Kao, J.S.Tsai, C.H.Chou, M.C.Liu, M.L.Sheu, T.Y.Meug, Y.F.Jen, R.C.Pan and S.W.Li, *Sci Sinica (Peking).* **13**, 789 (1964).
9. R.J.W.Cremlyn and D.H.Wakeford, *Topics in Phosphorus Chemistry*, John Wiley & Sons, New York, Vol. 8, 1976.
10. M.Venugopal, B.Sankar Reddy, C.Devendranath Reddy and K.D.Berlin, *J. Heterocycl. Chem.* **38**, 275 (2001).
11. A.R.Kartizky, C.W.Rees and E.F.V.Scriven, *Comprehensive Heterocyclic Chemistry II*, Pergmon Press, Oxford, U.K. (1996).
12. P.Vasu Govardhana Reddy, Y.Hari Babu, C.Suresh Reddy and D. Srinivasulu, *Hetero Atom. Chem.* **13**, 340 (2002).
13. L.N.Rao, C.D.Reddy and B.Sankar Reddy, *Indian. J. Chem.* **40B**, 817 (2001).
14. L.C.Thomas, *The Interpretation of the Infrared Spectra of Organophosphorus Compounds,* Heydon, London (1974).
15. K.V.Raghu and C.D.Reddy, *Indian. J. Chem.* **35B**, 1228 (1996).
16. R.M.Silverstein and F.X.Webster, *Spectrometric Identification of Organic Compounds,* 6th edition, Wiley, New York (1998).
17. G. W. Buchanan, R. H. Whitman and M. Malajandi, *Org. Mang. Reson.* **19**, 98 (1982).
18. C. D. Reddy, R. Suryanarayana Reddy, M. S. Reddy, M. Krishnaiah , K. Darrell Berlin and P. Sunthankar, *Phosphorus Sulfur and Silicon* **1**, 62 (1991).
19. L. D. Quin and J. G. Verkade, *Phosphorus-31 NMR Spectral Properties in Compound Characterization and Structural Analysis* VCH, Publishers, Inc., New York (1994).

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