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A Novel Synthesis of 6-Deoxytheophyllines and 6-Deoxy-7-deazatheophyllines[1]

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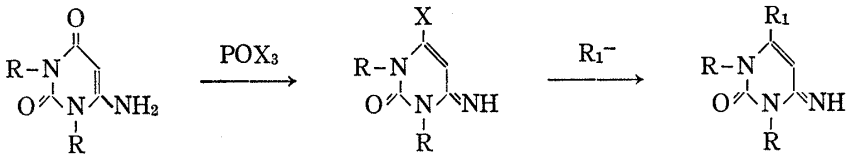
The reaction of 8-phenyl-7-deazatheophyllines (I) with phosphorus oxychloride gave 6-chloro-6-deoxy-8-phenyl-7-deazatheophyllines (II) in high yields. Compounds II served as useful starting materials for several nucleophilic reactions. The reaction of I with phosphorus oxychloride in the presence of amines has been carried out to succeed in obtaining the corresponding 6-amino-derivatives in a single step. The reaction of 8-phenyltheophylline (III) with phosphrous oxychloride gave 6-chloro-6-deoxy-8-phenyltheophylline (IV) in good yield. 6-Substituted 6-deoxy-8-phenyltheophyllines were prepared by the reaction of III with phosphorus oxychloride in the presence of amines in a single step. The reaction of I (or III) with phosphorus oxychloride essentially involves the conversion of aminoenketone (or aminoazadienketone) to iminoenchloride (or iminoazadienchloride).

The reaction of 6-amino-1,3-dialkyluracils with phosphorus oxychloride or phosphorus oxybromide was recently developed as a new route to 1,3-dialkyl-6-halogenocytosines,[3a,b] which are very convenient starting materials to undergo several nucleophilic displacements. It should be noted that in this halogenation the N-alkyl groups survive completely in spite of the considerable drastic conditions[4] and so the reaction essentially involves a conversion of the aminoenketone into the iminoenhaloengide.



R=CH_3, C_2H_5 X=Cl, Br

Chart 1

We have now attempted to extend the reaction to the bicyclic heterocycles and at first 1,3-dimethyl-6-phenyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidine (I)[5] (referred to hereafter as 8-phenyl-7-deazatheophylline) was chosen as an attractive candidate. The pyrrolo[2,3-*d*]pyrimidine (7-deazapurine) ring system has stimulated recent interest because

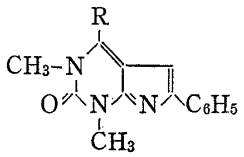
1) This work was presented at the 3rd International Congress of Heterocyclic Chemistry, Sendai, Japan, August 1971.
2) Location: *a*) *35, Shinanomachi, Shinjuku-ku, Tokyo*; *b*) *5-1, Oehonmachi, Kumamoto.*
3) *a*) K. Senga, F. Yoneda and S. Nishigaki, *J. Org. Chem.*, **36**, 1829 (1971); *b*) S. Nishigaki, K. Senga and F. Yoneda, *Chem. Pharm. Bull.* (Tokyo), **19**, 2259 (1971).
4) It is well known that the chlorination of N-methyl-azinones with phosphorus oxychloride often eliminates the N-methyl group to form the corresponding chloroazines. For example, 1-methyluracil and phosphorus oxychloride give 2,4-dichloropyrimidine as a by product: G.W. Kenner, C.B. Reese, and A.R. Todd, *J. Chem. Soc.*, **1955**, 855.
5) This compound could be prepared by the reaction of 6-amino-1,3-dimethyluracil with phenacyl bromide. This procedure is an application of the synthetic method of 7-deazatheophylline from 6-amino-1,3-dimethyluracil and chloroacetaldehyde: C.W. Noell and R.K. Robins, *J. Heterocyclic Chem.*, **1**, 34 (1964). The structural confirmation of this compound will be discussed in detail elsewhere.

of the discovery of the naturally occuring 7-deazapurine antibiotics toyokamycin,[6] tubercidin[7] and sangivamycin.[8]

Refluxing a mixture of I, sulfolane[9] and phosphorus oxychloride at 250—260° (oil-bath) for 3 hr, removal of the phosphorus oxychloride under reduced pressure and neutralization with 5% aqueous ammonia while cooling at 0—2° gave 4-chloro-1,3-dimethyl-4-deoxy-6-phenyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidine (Ia) (6-chloro-6-deoxy-8-phenyl-7-deazatheophylline) in 93% yield. The structure of Ia was ascertained on the basis of the following evidences. Compound Ia shows the presence of chlorine atom in the Beilstein test. The characteristic secondary amino absorption band at 3240 cm^{-1} of I disappeared and a new carbonyl band came out at 1690 cm^{-1}. The nuclear magnetic resonance (NMR) spectrum ($CDCl_3$) showed three singlets at 3.66 (N-CH_3), 3.75 (N-CH_3), and 6.56 ppm (C^5H), and multiplet at 7.20—8.10 ppm (benzene ring). The mass spectrometry reveals a strong parent ion (*m/e* 273) and M+2 ion, which suggests that one chlorine atom may be contained in the molecule. The assigned structure was confirmed with the information from its elemental analysis. In complete analogy with the above result, 8-(*p*-chlorophenyl)- and 8-(*p*-bromophenyl)-7-deazatheophylline were converted into 6-chloro-8-(*p*-chlorophenyl)- and 8-(*p*-bromophenyl)-6-chloro-6-deoxy-7-deazatheophylline in high yields.

These 6-chloro-6-deoxy-7-deazatheophyllines have strong reactivity and served as useful intermediates for several nucleophilic reactions. For example, even refluxing Ia in ethanol gave 6-ethoxy-6-deoxy-8-phenyl-7-deazatheophylline (Ib) in good yield. Treatment of Ia with other nucleophilic reagents gave the respective 6-substituted 6-deoxy-8-phenyl-7-deazatheophyllines. 6-Mercapto-6-deoxy-8-phenyl-7-deazatheophylline (Ie) was also obtained by the conventional thiation of I with phosphorus tentasulfide in pyridine. Catalytic reduction of Ia with palladium-on-charcoal in dioxane gave 6-deoxy-8-phenyl-7-deazatheophylline (If) (see Table I).

Table I. Preparation of 6-Substituted 6-Deoxy-8-phenyl-7-deazatheophyllines from Ia



Compound No.	R	Yield (%)	Recrystn. solvent (Appearance)	mp (°C)[a]	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
Ib	OC_2H_5	83	DMF (powder)	228—229	$C_{16}H_{17}O_2N_3$	67.82	6.05	14.83	67.79	6.24	15.02
Ic	$NHCH_3$	93	DMF (needles)	280	$C_{15}H_{16}ON_4$	66.14	6.01	20.88	66.43	6.12	20.88
Id	$N(CH_3)_2$	99	EtOH (needles)	209—210	$C_{16}H_{18}ON_4$	68.06	6.43	19.85	67.95	6.52	19.63
Ie	SH	80	EtOH (needles)	289—291	$C_{14}H_{13}ON_3S$	61.96	4.82	15.49	62.08	5.12	15.38
If	H	76	CH_3CN (prisms)	211—212	$C_{14}H_{13}ON_3$	70.27	5.48	17.56	69.97	5.45	17.58

a) All melting points were uncorrected.

The reaction of I with phosphorus oxychloride in the presence of amines has been tried to obtain the corresponding 6-amino-derivatives in a single step. Heating a mixture of I, sulfolane,[9] phosphorus oxychloride and piperidine under refluxing at 250—260° (oil-bath) for 3 hr gave 6-deoxy-8-phenyl-6-piperidino-7-deazatheophylline (Ig) in high yield. Simi-

6) H. Nishimura, K. Katagiri, K. Sato, M. Mayama and N. Shimaoka, *J. Antibiot.* (Japan), **9A**, 60 (1956).
7) K. Anzai, G. Nakamura and S. Suzuki, *J. Antibiot.* (Japan), **10A**, 201 (1957).
8) K.V. Rao and D.W. Renn, *Antimicrob. Agents Chemotherapy*, **1963**, 77.
9) Sulfolane was used as an inert, high boiling, solvent.

larly, 6-morpholino-6-deoxy-8-phenyl-7-deazatheophylline (Ih) was obtained. This procedure offers a convenient synthetic method for preparation of 6-amino-derivatives. Furthermore, this method could be applicable to other heterocycles. The reaction of I with phosphorus oxychloride in excess N,N-dimethylaniline gave interestingly 6-(*p*-N,N-dimethylaminophenyl)-6-deoxy-8-phenyl-7-deazatheophylline (Ii) in 65% yield. The latter was assigned on the basis of elemental analysis, molecular weight determination by mass spectrometry, and in particular the NMR spectrum (CF_3COOH) (6H singlet at 3.61 ppm ($N(CH_3)_2$), two 3H singlets at 3.75 ($N\text{-}CH_3$) and 4.15 ppm ($N\text{-}CH_3$), 1H singlet at 6.50 ppm (C^7H), and 9H multiplet at 7.40—8.20 ppm (benzene ring). The compounds thus prepared are listed in Table II.

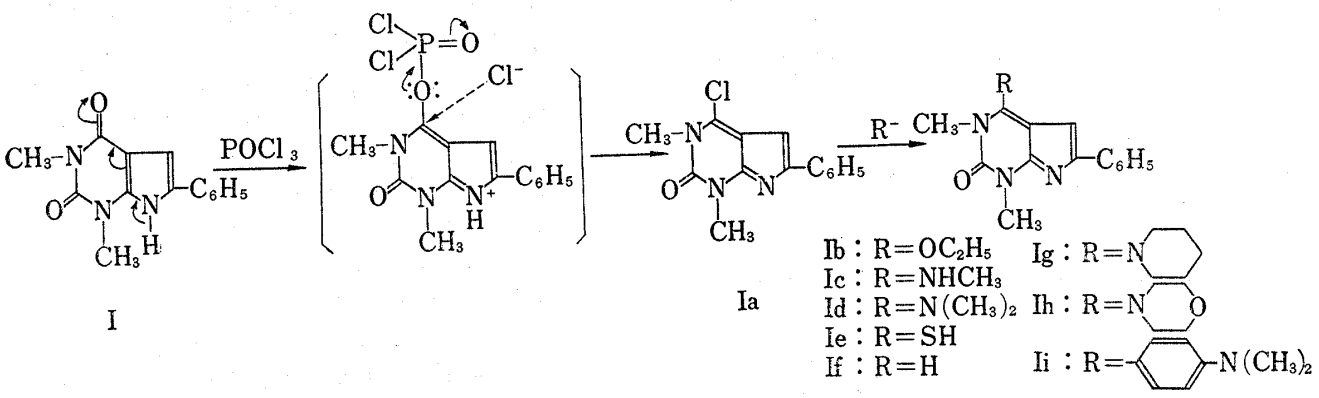


Chart 2

Table II. One Step Synthesis of 6-Substituted 6-Deoxy-8-phenyl-7-deazatheophyllines from I

Reactant	Product	Yield (%)	Recrystn. solvent (Appearance)	mp (°C)[a]	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
Piperidine	Ig	82	EtOH (needles)	198—200	$C_{19}H_{22}ON_4$	70.78	6.88	17.38	71.01	6.72	17.28
Morpholine	Ih	88	EtOH (needles)	210	$C_{18}H_{20}O_2N_4$	66.65	6.22	17.27	66.39	6.13	17.04
N,N-Dimethyl-aniline	Ii	65	CH_3-CN (needles)	209	$C_{22}H_{22}ON_4$	73.72	6.19	15.63	73.70	6.29	15.62

a) All melting points were uncorrected.

Next, the reaction of theophyllines with phosphorus oxychloride has been tried in order to get the corresponding 6-chloro-6-deoxytheophyllines, which serves as useful intermediates for several nucleophilic reactions. It is interesting to note that these 6-deoxytheophylline derivatives belong to a new class of purines and that the reaction is essentially a conversion of the aminoazadienketone into the iminoazadienchloride.

When a mixture of 8-phenyltheophylline (II),[10] sulfolane[9] and phosphorus oxychloride was treated as described for the preparation of Ia, 6-chloro-6-deoxy-8-phenyltheophylline (IIa) was obtained in 84% yield. The formation of IIa was indicated from the following evidences. The characteristic secondary amino stretching absorption band at 3160 cm^{-1} of II disappeared and a new carbonyl band came out at 1690 cm^{-1}. The mass spectrometry reveals the parent ion (*m/e* 274) and M+2 ion. In complete analogy with the above result, reaction of 8-(*p*-chlorophenyl)-, 8-(*p*-methoxyphenyl)-, 8-(*p*-N,N-dimethylaminophenyl)-, 8-

10) E.C. Taylor and E.E. Garcia, *J. Am. Chem. Soc.*, **86**, 4722 (1964).

(*p*-bromophenyl)- and 8-ethyltheophylline with phosphorus oxychloride gave the corresponding 8-substituted 6-chloro-6-deoxytheophyllines in high yields. These compounds are extremely unstable and undergo ready hydrolysis even by moisture in air at elevated temperature to afford the starting materials, therefore their purification was unsuccessful by any methods. Furthermore, in several nucleophilic reactions, these compounds underwent hydrolysis predominantly to give only hydrolyzed starting materials.

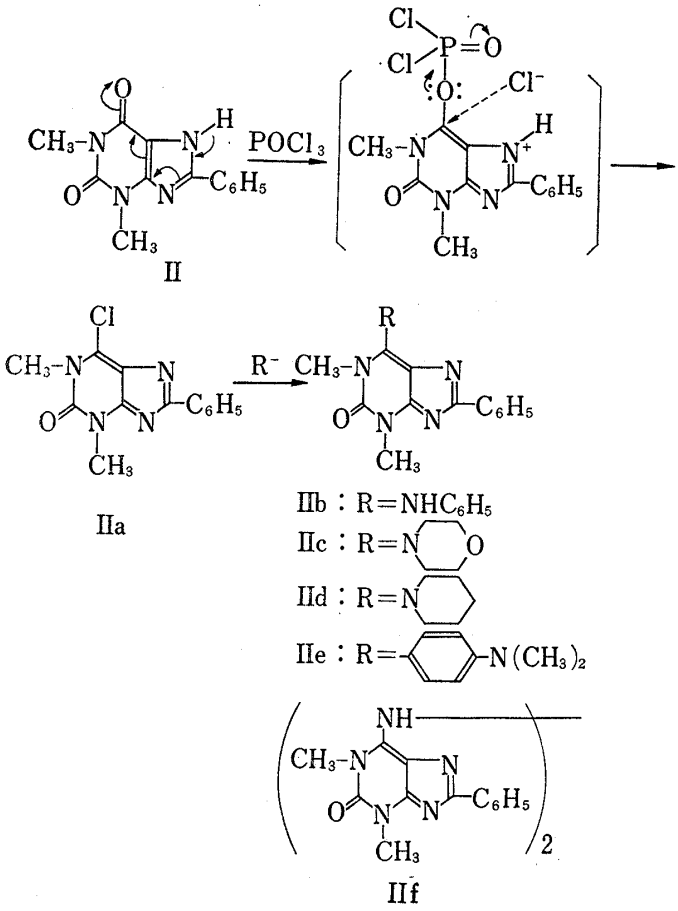


Chart 3

In order to avoid such hydrolyses as described above in the nucleophilic reactions, the reaction of the theophyllines with phosphorus oxychloride in the presence of nucleophilic reagents has been carried out to succeed in obtaining the expected 6-substituted 6-deoxytheophyllines. For example, refluxing a mixture of II,[10] sulfolane,[9] phosphorus oxychloride and aniline at 250—260° (oil-bath) for 3 hr gave 6-anilino-6-deoxy-8-phenyltheophylline (IIb) in quantitative yield. In the same manner, 6-morpholino- (IIc) and 6-piperidino-derivative (IId) were prepared. The reaction of II[10] with phosphorus oxychloride in excess N,N-dimethylaniline gave 6-(*p*-N,N-dimethylaminophenyl)-6-deoxy-8-phenyltheophylline (IIe) in good yield (see Table III). Its structure was assigned on the basis of elemental analysis, molecular weight determination by mass spectrometry, and the NMR spectrum (CF_3COOH) (6H singlet at 3.70 ppm ($N(CH_3)_2$), two 3H singlets at 3.79 ($N\text{-}CH_3$) and 4.25 ppm ($N\text{-}CH_3$), and 9H multiplet at 7.85—8.45 ppm (benzene ring). On using hydrazine monohydrochloride as nucleophilic reagent, 6,6′-bis-(6-deoxy-8-phenyltheophyllinyl)-hydrazine (IIf) was obtained in 70% yield.

Table III. One Step Synthesis of 6-Deoxy-8-phenyltheophyllines from II

Reactant	Product	Yield (%)	Recrystn. solvent (Appearance)	mp (°C)[a]	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
Aniline	IIb	100	EtOH (needles)	232—233	$C_{19}H_{17}ON_5$	68.86	5.17	21.14	68.58	5.23	21.30
Morpholine	IIc	78	EtOH (needles)	196—197	$C_{17}H_{19}O_2N_5$	62.75	5.89	21.53	62.58	5.89	21.52
Piperidine	IId	84	MeOH–H_2O (needles)	170	$C_{18}H_{21}ON_5$	66.85	6.55	21.66	66.76	6.75	21.93
N,N-Dimethyl-aniline	IIe	73	CH_3CN (needles)	243—244	$C_{21}H_{21}ON_5$	70.17	6.89	19.49	70.15	6.94	19.53

a) All melting points were uncorrected.

Experimental[11]

6-Chloro-6-deoxy-8-phenyl-7-deazatheophylline (Ia)——A mixture of 0.51 g (0.002 mole) of 8-phenyl-7-deazatheophylline (I), 5 ml of $POCl_3$ and 1 ml of sulfolane was refluxed at 250—260° for 3 hr. After the excess of $POCl_3$ was evaporated under reduced pressure, 30 ml of 5% aq. NH_3 was added to the residue under cooling (0—2°). After standing for 1 hr, the insoluble materials were collected by filtration, washed with H_2O and dried (P_2O_5 desiccator) to give 0.51 g (93%) of yellow powder. Recrystallization from EtOAc gave yellow needles, mp 181—182°. *Anal.* Calcd. for $C_{14}H_{12}ON_3Cl$: C, 61.43; H, 4.79; N, 15.35. Found: C, 61.28; H, 4.78; N, 15.43.

Under the same conditions, 8-(*p*-chlorophenyl)- and 8-(*p*-bromophenyl)-7-deazatheophylline were converted into 6-chloro-8-(*p*-chlorophenyl)-6-deoxy-7-deazatheophylline [mp >300°, *Anal.* Calcd. for $C_{14}H_{11}ON_3Cl_2$: C, 54.56; H, 3.60; N, 13.64. Found: C, 54.72; H, 3.54; N, 13.59] and 6-chloro-8-(*p*-bromophenyl)-6-deoxy-7-deazatheophylline [mp >300°. *Anal.* Calcd. for $C_{14}H_{11}ON_3BrCl$: C, 47.68; H, 3.14; N, 11.92. Found: C, 47.51; H, 3.11; N, 12.03], respectively.

6-Ethoxy-6-deoxy-8-phenyl-7-deazatheophylline (Ib)——A mixture of 0.55 g (0.002 mole) of Ia and 10 ml of EtOH was refluxed for 5 min. After EtOH was removed, 30 ml of H_2O was added to the residue. The insoluble materials were collected by filtration, and dried to give 0.58 g of pale yellow crystals.

6-Methylamino-6-deoxy-8-phenyl-7-deazatheophylline (Ic)——A mixture of 0.55 g (0.002 mole) of Ia and 10 ml of 40% aq. NH_2CH_3 was stirred for 1 hr at room temperature. The resulting clear solution was evaporated under reduced pressure, and 30 ml of H_2O was added to the residue. The separated crystals were collected by filtration, and dried to give 0.5 g of yellow powder.

6-Dimethylamino-6-deoxy-8-phenyl-7-deazatheophylline (Id)——A mixture of 0.55 g (0.002 mole) of Ia and 0.28 g (0.002 mole) of 40% aq. $NH(CH_3)_2$ was stirred for 30 min at room temperature. The resulting solution was treated as described in the preparation of Ic to give 0.56 g of yellow powder.

6-Mercapto-6-deoxy-8-phenyl-7-deazatheophylline (Ie)——Method A: A mixture of 0.55 g (0.002 mole) of Ia and 0.28 g (0.002 mole) of 40% aq. NaSH is 15 ml of H_2O was heated for 1 hr on the water bath. After cooling, the separated crystals were filtered off, washed with H_2O and dried to give 0.45 g of yellow powder.

Method B: A mixture of 0.51 g (0.002 mole) of I and 0.44 g (0.002 mole) of P_2S_5 in 10 ml of pyridine was refluxed for 3 hr. After pyridine was removed under reduced pressure, 50 ml of H_2O was added to the yellow residue. After standing overnight at room temperature, the separated precipitates were collected by filtration, washed with H_2O and dried to give 0.5 g (93%) of pale yellow powder, which was identical with the product obtained in Method A.

6-Deoxy-8-phenyl-7-deazatheophylline (If)——A solution of 0.82 g (0.003 mole) of Ia in 200 ml of dioxane containing 0.4 g of 10% Pd-C was hydrogenated at room temperature and under atmospheric pressure. Hydrogenation was stopped when the theoretical volume (67 ml) of hydrogen was consumed. The solution was filtered and evaporated to dryness. To the residue, 10 ml of 5% aq. NH_3 was added and maintained for few hours. The separated crystals were collected by filtration, washed with H_2O and dried to give 0.55 g of yellow powder. NMR (DMSO-d_6) ppm: 3.80 (3H, singlet, N-CH_3). 3.93 (3H, singlet, N-CH_3), 7.11 (1H, singlet, C^7 H), 7.50—8.35 (5H, multiplet, C_6H_5), 8.63 (1H, singlet, C^6H).

General Procedure for One-step Synthesis of 6-Substituted 6-Deoxy-8-phenyl-7-deazatheophyllines (Ig—i)——A mixture of 0.003 mole of I, 8 ml of $POCl_3$, 1.5 ml of sulfolane and 0.009 mole of nucleophilic reagent was refluxed for 3 hr at 250—260°. After excess of $POCl_3$ was removed under reduced pressure, the resulting residue was treated as described in the preparation of Ia. The crystals thus obtained were recrystallized from an appropriate solvent.

6-Chloro-6-deoxy-8-phenyltheophylline (IIa)——A mixture of 0.51 g (0.002 mole) of II, 5 ml of $POCl_3$ and 1.5 ml of sulfolane was refluxed for 3 hr at 250—260°. After excess of $POCl_3$ was removed under reduced pressure, the resulting residue was treated as described in the preparation of Ia to give 0.46 g (84%) of yellow powder.

General Procedure for One-step Synthesis of 6-Substituted 6-Deoxy-8-phenyltheophyllines (IIb—e)——A mixture of 0.003 mole of II, 8 ml of $POCl_3$ 3 ml of sulfolane and 0.009 mole of nucleophilic reagent was refluxed for 3 hr at 250—260°. After excess of $POCl_3$ was removed under reduced pressure, the resulting residue was treated as described in the preparation of Ia. The crystals thus obtained were recrystallized from an appropriate solvent.

6,6′-Bis-(6-deoxy-8-phenyltheophyllinyl)-hydrazine (IIf)——A mixture of 0.77 g (0.003 mole) of II, 0.62 g (0.009 mole) of hydrazine-HCl, 8 ml of $POCl_3$ and 2.5 ml of sulfolane was refluxed for 3 hr at 250°. After excess of $POCl_3$ was removed under reduced pressure, the resulting residue was treated as described in the preparation of Ia to give 0.53 g (70%) of pale yellow powder. Recrystallization from DMF gave colorless

11) All melting points are uncorrected. NMR spectra were taken at 60 Mc with a Hitachi, Perkin-Elmer Co., Ltd. Model R-20A or a Japan Electron Optics Lab. Co., Ltd. Model JNM-3H60 spectrometer using tetramethylsilane as the internal reference.

powder, mp >360°. *Anal.* Calcd. for $C_{26}H_{24}O_2N_{10}$: C, 61.40; H, 4.76; N, 27.56. Found: C, 61.43; H, 4.91; N, 27.59.

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