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# Reactions of Purine Derivatives with Phosphorus Pentaoxide and Triethylamine and Their Antitumor Effects

**H.H. Moharram and A.M. Osman**
*National Organisation For Drug Control and Research, P.O. Box 29, Cairo and Cancer Institute, Cairo University, Egypt*
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**Abstract** □ 6-Arylamino-3,7-dihydro-3,7-dimethy-2-oxo-1H-purine and 2-arylimino-6-arylamino-3,7-dihydro-3,7-dimethyl-1H-purine were obtained in a one-pot reaction when 3,7-dihydro-3,7-dimethyl-1H-purine-3,6-dione, phosphorus pentaoxide, triethylamine hydrochloride and appropriate amine amine are heated at 170°. Some derivatives were tested for their antitumor activity.

**Keywords** □ 6-Arylamino-3,7-dihydro-3,7-dimethyl-2-oxo-1H-purine, 2-arylimino-6-arylamino-3,7-dihydro-3,7-dimethyl -1H-purine, antitumor effects.

## CHEMISTRY

Purine derivatives are among the most ubiquitous of all naturally occurring heterocyclic compounds. Their vital role in many biochemical reactions and as components of nucleic acids has led to a vast and continuously expanding number of the synthesis of substituted purine derivatives. Excellent reviews are available on the subject[1-4]. In recent years much research in purine chemistry has been directed towards the preparation of potential drug, antimetabolites, and other biologically active substances. Thus, many purines and their analogoues have been claimed to posses *e.g.* antiviral[5], antitumor[6,7], antiococcidial and plant-growth regulating activity[8].

The aim of this work was to use the reagent consisted of phosphorus pentaoxide, triethylamine hydrochloride and appropriate aromatic amine, previously prepared[9], in order to aminate some 1H-purine derivatives. Mono and diamino substituted purines were obtained in one pot reaction.

Thus, 3,7-dihydro, 3,7-dimethyl, 1H-purine, 2,6-dione (**I**), was reacted with mixture of phosphorus pentaoxide, triethylamine hydrochloride and suitable amines. After decomposition of produced complex with 2N-NaOH solution, 6-arylamino-3,7-dihydro-3,7-dimethyl-2-oxo-1H-purine (**IIa-e**) and 2-arylimino-6-arylamine-3,7-dihydro-3,7-dimethyl-1H-purine (**IIIa-e**) were obtained.

## ANTITUMOR ACTIVITIY

*Evaluation of the antitumor activity of some derivatives*

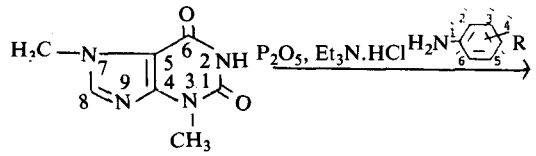
Female Swiss albino mice weighing 18-22g were supplied from the Colony of the Cancer Institute, Cairo University. Animals were maintained on standard diet and free access to water.

*Tumor*

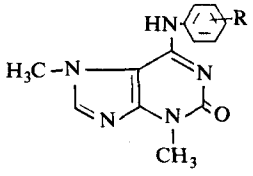
Ehrlich ascites carcinoma was used in this study. The parent line was supplied from Dr. G. Kelin Amesterdam and was maintained by Serial intraperitoneal transplantation in female Swiss albino mice. Determination of life-span of mice bearing tumor female mice were inoculated with $2.5 \times 10^6$ tumor cells from a donor mice (7 days old) and the drug in the appropriate dose was administered after 24 hr. of tumor inoculation for a total 5 injections every other day. The mice were observed for a period of two months or to the death of the last animal. The mean survival time of the treated animals were compared with that of untreated animals (Table I).

For these results we can conclude that:

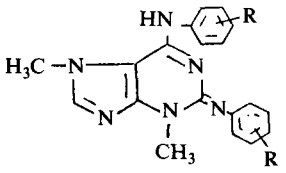
1. The 4-fluoro substituted compounds were highly active, but the disubstituted compound (**III b**) was higher activity than monosubstituted compound (**IIb**), they showed a T/Cvalues 1.8 and 1.6 respectively.



(I)



(II)



(III)

II. III R
a H
b 4-F
c 3-$CH_3$
d 4-$CH_2CH_3$
e 3,5$(CH_3)_2$

**Table I. The anticancer activity of some derivatives of purine.**

| Compound | Dose mg/kgm | No. of Doses | Mean Survival Time(days) ± S.D. | T/C |
|---|---|---|---|---|
| **IIa** | 100 | 3 | — | — |
| **b** | 100 | 2 | 18.5 ± 11 | 1.6 |
| **c** | 100 | 3 | 15.7 ± 11 | 1.36 |
| **IIIa** | 100 | 2 | 10.8 ± 11 | 0.94 |
| **b** | 100 | 2 | 20.8 ± 11 | 1.8 |
| **c** | 100 | 3 | 16.3 ± 11 | 1.42 |
| Control | — | — | 11.5 ± 3.9* | 1.0 |

* Significant different at $P<0.1$

2. The 4-methyl compounds were lower activity the 4-fluoro compounds, but the 4-methyl disubtituted compound **(IIIc)** was higher activity than 4-methyl monosubstituted compound **(IIc)**, they showed a T/C values 1.42 and 1.36 respectively.
3. The compounds types **IIa** and **IIa** were inactive, they showed a T/C values lower than 1.3.

**Table II. Physicochemical data of purine derivatives.**

| Com-pound | Reaction time(h) | Yield % | M.P. °C | Formula (MW) | (MS, *m/z*) % | Elemental analysis % Calcd. C | H | N | Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **IIa** | 3.5 | 39 | 217 | $C_{13}H_{13}N_5O$ (255.58) | 255($M^+$, 100) | 61.17 | 5.13 | 27.43 | 61.21 | 5.12 | 27.55 |
| **IIIa** | 3.5 | 19 | 130 | $C_{19}H_{19}N_6$ (331.29) | 331($M^+$, 100) | 69.07 | 5.59 | 25.44 | 68.83 | 5.45 | 25.59 |
| **IIb** | 3.5 | 41 | 227 | $C_{13}H_{12}N_5OF$ (273.27) | 273($M^+$, 100) | 57.14 | 4.43 | 25.63 | 57.29 | 4.41 | 25.80 |
| **IIIb** | 3.5 | 17 | 212 | $C_{19}H_{17}N_6F_2$ (367.38) | 367($M^+$, 100) | 62.29 | 4.40 | 22.94 | 62.38 | 4.34 | 22.75 |
| **IIc** | 3.5 | 52 | 209 | $C_{14}H_{15}N_5O$ (269.31) | 269($M^+$, 100) | 62.44 | 5.61 | 26.00 | 62.67 | 5.61 | 26.28 |
| **IIIc** | 3.5 | 13 | 180 | $C_{21}H_{23}N_6$ (359.42) | 359($M^+$, 17) | 70.37 | 6.19 | 23.45 | 70.53 | 6.23 | 23.53 |
| **IId** | 3.0 | 61 | 222 | $C_{15}H_{17}N_5O$ (283.33) | 283($M^+$, 100) | 61.63 | 6.21 | 23.95 | 61.91 | 6.91 | 23.44 |
| **IIId** | 3.0 | 17 | 205 | $C_{23}H_{26}N_6$ (386.49) | 386($M^+$, 76) | 71.48 | 6.78 | 21.74 | 71.62 | 6.53 | 21.87 |
| **IIe** | 3.0 | 52 | 220 | $C_{15}H_{17}N_5O$ (283.33) | 283($M^+$, 100) | 63.59 | 6.09 | 24.72 | 63.56 | 6.06 | 24.50 |
| **IIIe** | 3.0 | 22 | 195 | $C_{23}H_{26}N_6$ (386.49) | 386($M^+$, 100) | 74.97 | 6.82 | 18.21 | 74.73 | 6.64 | 18.52 |

**Table III. Spectral properties of compound II and III.**

| Compound | $N_7$-H | IR $cm^{-1}$ N-H | $H^1$ NMR in DMSO-$d_6$ |
|---|---|---|---|
| **IIa** | 3250 | 3250 | 2.37(s, 3H), 2.32(s, 3H), 6.36(s, 1H), 6.81-7.84(m, 6H). |
| **IIIa** | 3250 | 3245 | 2.35(s, 3H), 2.37(s, 3H), 6.34(s, 1H), 6.81-7.82(b, m, 10H, 10.04(s, 1H). |
| **IIb** | 3240 | 3245 | 2.37(b, s, 6H), 6.38(s, 1H), 7.08-7.86(m, 5H). |
| **IIIb** | 3245 | 3250 | 2.35(s, 3H), 2.36(s, 3H), 6.34(s, 1H), 6.83-7.72(b, m, 8H), 10.04(s, 1H). |
| **IIc** | 3230 | 3245 | 2.32(s, 3H), 2.38(b,s,6H), 6.35(s, 1H), 6.64(m, 4H), 7.35(s, 1H). |
| **IIIc** | 3250 | 3250 | 2.34(2, 3H), 2.36(b, s, 6H), 2.38(s, 3H), 6.34(2, 1H), 6.58-7.52(b, m, 9H). |
| **IId** | 3240 | 3240 | 2.28(s, 3H), 2.36(s, 3H), 3.21(s, 5H), 6.38(s, 1H), 6.78-7.62(s, 5H). |
| **IIId** | 3250 | 3240 | 2.27(s, 3H), 2.34(s, 3H), 3.24(b, s, 10H), 6.74-7.52(s, 10H). |
| **IIe** | 3245 | 3245 | 2.29(s, 3H), 2.33(s, 3H), 2.36(b, s, 6H), 6.38(s, 1H), 6.90-7.76(m, 4H). |
| **IIIe** | 3240 | 3250 | 2.26(s, 3H), 2.34(s, 3H), 3.24(b, s, 12H), 6.72-7.74(b, s, 8H). |

**Table IV. $^{13}C$ NMR Spectra (in DMSO-$d_6$) of compound II and III**

| Com-ound. | C-2 | C-6 | C-5 | C-4 | C-8 | 3-$CH_3$ | 7-$CH_3$ | C-1' | C-2' | C-3' | C-4' | C-5' | C-6' | R |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **IIa** | 158.6 | 153.8 | 102.0 | 151.4 | 127.4 | 25.0 | 28.7 | 140.2 | 119.7 | 127.6 | 121.1 | — | — | — |
| **IIIa** | 157.3 | 153.6 | 102.1 | 151.3 | 127.2 | 25.3 | 28.6 | 140.2 | 119.6 | 127.4 | 121.2 | — | — | — |
| **IIb** | 158.5 | 152.5 | 106.2 | 151.6 | 127.3 | 24.5 | 28.7 | 141.8 | 132.5 | 129.1 | 123.3 | — | — | — |
| **IIIb** | 157.3 | 153.0 | 106.4 | 151.4 | 127.5 | 24.2 | 28.8 | 141.9 | 132.4 | 128.7 | 123.5 | — | — | — |
| **IIc** | 158.4 | 153.7 | 102.2 | 151.4 | 127.4 | 25.0 | 28.6 | 138.2 | 118.7 | 130.2 | 123.3 | 125.8 | 123.4 | 17.3 |
| **IIIc** | 157.5 | 153.7 | 102.3 | 151.3 | 127.2 | 25.1 | 28.4 | 138.2 | 118.6 | 130.5 | 123.7 | 125.7 | 123.4 | 17.5 |
| **IId** | 158.3 | 153.9 | 102.5 | 151.6 | 127.5 | 24.8 | 28.5 | 138.4 | 118.9 | 130.2 | 123.1 | 125.6 | 123.6 | 17.7 |
| **IIId** | 157.4 | 153.5 | 102.2 | 151.7 | 127.4 | 24.7 | 28.3 | 138.5 | 118.6 | 130.4 | 123.0 | 125.4 | 123.7 | 17.3 |
| **IIe** | 157.4 | 153.3 | 101.2 | 151.1 | 126.7 | 25.2 | 28.6 | 135.5 | 118.5 | 129.7 | 131.6 | 125.6 | 123.5 | 19.7 |
| **IIIe** | 157.8 | 153.2 | 101.0 | 151.3 | 126.9 | 25.3 | 28.4 | 135.4 | 118.4 | 129.7 | 131.6 | 125.5 | 123.6 | 17.8 |

The structures assigned to the products **IIa-e** and **IIa-e** were based on analytical data of IR, MS, $^1H$-NMR and $^{13}C$ NMR spectra.

## EXPERIMENTAL

IR (KBr) spectra were recorded on Perkin-Elmer 580. $^1H$ NMR and $^{13}C$ NMR spectra were recorded on a Jeol Fx60Q (DMSO-d6/TMS) at temperature specified in (Table I, II). Mass spectra were obtained on a varian MAT 311A. Microanalyses were carried out at NOVO A/S Copenhagen. Melting points were obtained on a Büchi apparatus (uncorrected). Thin layer chromatography (TLC) was performed on aluminium plates precoated with Merck's Silica gel 60 F254.

***6-Arylamino-3,7-dihydro-3,7-dimethyl-2-oxo-1H-purine and 2-arylamino-6-arylimino-3,7-dihydro-3,7-dimethyl-1H-purine***

The reagent was prepared by mixing $P_2O_5$ (14.2gm; 0.1mol), $Et_3N{\cdot}HCl$ (13.2gm; 0.1mol) and the aromatic amine (0.1mol) in a 250ml 3-necked flask protected with the drying tube. The mixture was heated in an oil bath of 170°C (oil bath temperature) until a clear homogeneous mixture was achieved (0.5-1h). The oil-bath temperature was adjusted to 170° and 3,7-dihydro-3,7-dimethyl-1H-purine-2,6-dione (**I**) (0.018 mol) was added. The reaction progress was followed by taking a sample (50 mg) from the reaction mixture at 0.5 hr periods. The sample was treated with a 2M NaOH solution until alkaline reaction (pH 9-10) and extracted with $CH_2Cl_2$. The extract was subjected to TLC with ethyl acetate/ether (6:1) as eluent. The disappearance of the starting material **I** and the product **II** and **III** were monitored using **I** as reference. Heating and stirring was continued for the reaction periods given in Table I. The flask was removed from the oil-bath and allowed to cool to about

100 °C, then a 2M NaOH solution and added (1500 m*l*) till alkaline reaction (pH 10-11). The mixture was stirred at room temperature until the reaction cake was digested (0.5 h). The solid precipitate was filtered off, washed with water (1500 m*l*) and ethanol, to give **IIa-e**, the filtrate added to (350 m*l*) ether till completely precipitate, the precipitate was filtered off, washed with water (1500m*l*), ethanol and ether, to give **IIIa-e**, (Table II, III and IV).

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