SYNTHESIS OF 3,7-DIHYDRO-4H-PYRROLO[2,3-d]PYRIMIDIN-4-ONES

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Abstract - A series of 9 new 3-aryl-3,7-dihydro-2,5,6-trimethyl-7-phenylmethyl-4H-pyrrolo[2,3-d]pyrimidin-4-ones 2a-i were prepared in 44-66% yields by heating methyl 2-acetamido-4,5-dimethyl-1-phenylmethyl-1H-pyrrolo-3-carboxylate 1 in a mixture of phosphorus pentoxide, triethylamine hydrochloride and an appropriate aniline at 150°C for 25-45 min. Similar reactions of 1 with primary alkylamines can lead to formation of 7-phenylmethyl-2,5,6-trimethyl-pyrrolo[2,3-d][1,3]oxazin-4(7H)-one 3 and 3-alkyl-3,7-dihydro-2,5,6-trimethyl-7-phenylmethyl-4H-pyrrolo[2,3-d]pyrimidin-4-one 7.

INTRODUCTION

Considerable attention has been directed towards the synthesis of pyrrolo[2,3-d]pyrimidines because of their structural resemblance to purines, natural occurrence of their derivatives, and their interesting biological activity[1]. In a recent work from our laboratories, it was reported that 2-acylamino-3-cyanopyrroles react in a mixture of phosphorus pentoxide, N,N-dimethylcyclohexylamine and water to give the corresponding 2-substituted pyrrolo[2,3-d]pyrimidin-4(3H)-ones (7-deazahypoxanthines). Various biological screenings of the 7-deazahypoxanthines showed that some of the compounds were active as plant growth regulators[2].

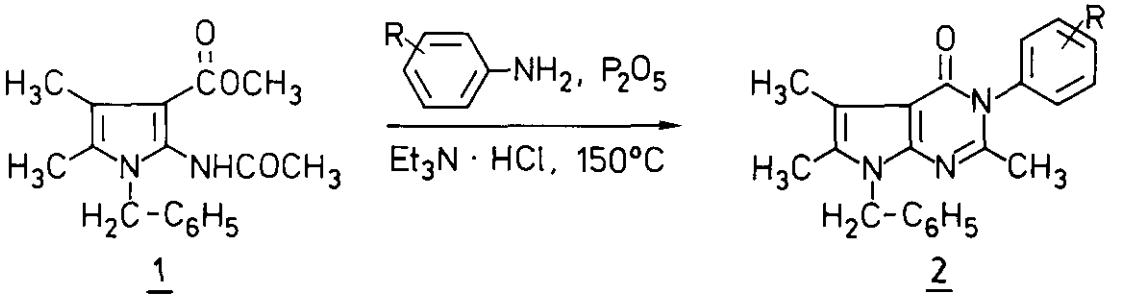
Recently, a phosphorus pentoxide-amine hydrochloride mixture was found to be a versatile ring closure reagent in the synthesis of 2,3-disubstituted 4(3H)-quinazolinones[3], 2,3-disubstituted thieno[2,3-d]pyrimidin-4(3H)-ones[4], 1,2-disubstituted hypoxanthines[5], 2,3-disubstituted pyrido[2,3-d]pyrimidin-4(3H)-ones[6], 5,6-disubstituted 1,5-dihydro-1-methyl-4H-pyrrazolo[3,4-d]pyrimidin-4-ones[7], and 5,6-disubstituted 3H-1,2,3-triazolo[4,5-d]pyrimidin-7(6H)-ones[9] from the corrosponding ortho-acylaminocarboxylates. It was therefore of interest to investigate whether that procedure could be extended to ring closure reactions of methyl 2-acetamido-4,5-dimethyl-1-phenylmethyl-1H-pyrrole-3-carboxylate 1 in order to obtain the corresponding

2,3-disubstituted 7H-pyrrolo[2,3-d]pyrimidin-4(3H)-ones 2 with potential biological activity.

RESULTS AND DISCUSSION

The starting material, methyl 2-acetamido-4,5-dimethyl-1-phenylmethyl-1H-pyrrole-3-carboxylate 1, was prepared from the corresponding 2-amino compound[9] by acetylation reaction in a mixture of acetic anhydride and acetic acid.

2,3-Disubstituted 7H-pyrrolo[2,3-d]pyrimidin-4(3H)-ones 2 are now prepared by heating 1 in a mixture of phosphorus pentoxide, triethylamine hydrochloride and the appropriate primary aromatic amine at 150°C. In all cases investigated, the reaction proceeded smoothly and was completed within 25-45 min reaction periods affording the products 2a-i in yields ranging from 44-66% (Table 1).

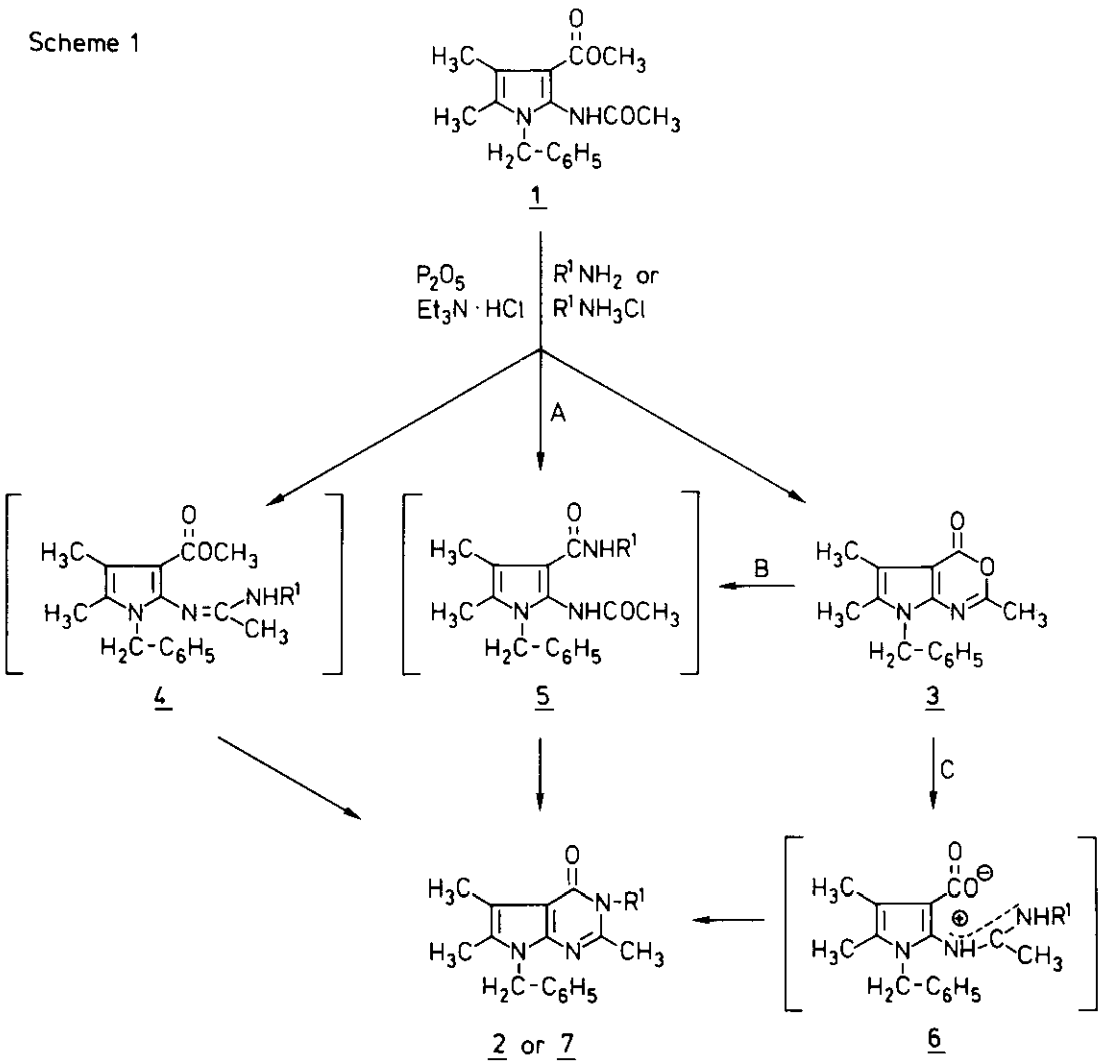


1 2

When 1 was reacted in a mixture of propylamine, phosphorus pentoxide and triethylamine hydrochloride at 150°C for 25 min, the corresponding pyrrolo[2,3-d]-[1,3]oxazin-4(7H)-one 3 was obtained in 62% yield. Reaction of 1 with ethylamine hydrochloride in the reaction mixture at 200°C for 90 min. gave 38% yield of the 3-ethyl-substituted 7H-pyrrolo[2,3-d]pyrimidin-4(3H)-one 7.

The possible synthetic routes leading to 2, 3 or 7 are shown in Scheme 1. In the synthesis of 2 a gas was evolved shortly after addition of 1 to the reaction mixture. This observation can rationalize the formation of 5 by which the ethoxy group is split off from the ester group of 1. In similar reactions with the thiophene analogue of 1 an intermediate similar to 5 was actually isolated[4]. A possible route to 2 via the amidine intermediate 4 cannot be totally excluded, since it is known that amidines are formed by reactions of carboxamides with the

Scheme 1



2: R^1 = Aryl

7: R^1 = Alkyl

phosphorus pentoxide reagent[10]. The oxazinone 3 can also be suggested as an intermediate in the two possible alternative pathways B and C for formation of 2. In the preparation of 2c, the reaction mixture was examined by TLC shortly after

Table 1: Preparation of 3-aryl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-ones 2.

2	R	Reaction Time[min]	Yield [%]	Mp[°C] (solvent)	Formula (Mol Wt)	Microanalysis[%] Found/Calcd. C	H	N
a	H	30	56	175-176 (MeOH)	$C_{22}H_{21}N_3O$ (343.4)	77.37 / 76.94	6.18 / 6.16	12.16 / 12.24
b	2-CH_3	40	44	162-163 (MeOH)	$C_{23}H_{23}N_3O$ (357.5)	77.34 / 77.28	6.51 / 6.49	11.87 / 11.76
c	4-CH_3	30	56	173-174 (MeOH)	$C_{23}H_{23}N_3O$ (357.5)	77.38 / 77.28	6.51 / 6.49	11.56 / 11.76
d	4-CH_2CH_3	25	56	168-169 (MeOH)	$C_{24}H_{25}N_3O$ (371.5)	77.75 / 77.60	6.79 / 6.78	11.28 / 11.31
e	2-Cl	45	50	186-187 (MeOH)	$C_{22}H_{20}ClN_3O$ (377.9)	69.71 / 69.93	5.35 / 5.34	10.94 / 11.12
f	4-Cl	30	46	187-188 (MeOH)	$C_{22}H_{20}ClN_3O$ (377.9)	69.84 / 69.93	5.35 / 5.34	11.02 / 11.12
g	2-F	30	57	188-189 (MeOH)	$C_{22}H_{20}FN_3O$ (361.4)	73.22 / 73.11	5.60 / 5.58	11.55 / 11.63
h	3-F	30	55	156-157 (70% MeOH)	$C_{22}H_{20}FN_3O$ (361.4)	73.55 / 73.11	5.62 / 5.58	11.63 / 11.63
i	4-F	35	66	208-210 (MeOH)	$C_{22}H_{20}FN_3O$ (361.4)	73.27 / 73.11	5.58 / 5.58	11.43 / 11.63

Table 2: Spectral properties of 2.

2	IR(KBr)[a] [cm^{-1}]	MS[m/z] (% Intensity)	^{1}H-NMR ($CDCl_3$)[b] [δ]
a	1680	343 (M^+,100)	2.12 (3H,s), 2.18 (3H,s), 2.35 (3H,s)
		252 (60)	5.37 (2H,s), 7.00-7.63 (10H,m)
		118 (42)	
b	1685	357 (M^+,100)	2.12 (9H,s), 2.37 (3H,s), 5.33 (2H,s)
		266 (56)	7.00-7.43 (9H,m)
		132 (38)	
c	1690	357 (M^+,100)	2.08 (3H,s), 2.17 (3H,s), 2.33 (3H,s)
		266 (68)	2.40 (3H,s), 5.32 (2H,s), 6.90-7.43
		132 (51)	(9H,m)
d	1685	371 (M^+,100)	1.10 (3H,t,7), 2.10 (3H,s), 2.18 (3H,
		280 (40)	s), 2.35 (3H,s), 2.73 (2H,q,7),
		146 (26)	5.31 (2H,s), 6.93-7.43 (9H,m)
e	1690	377 (M^+,100)	2.13 (3H,s), 2.17 (3H,s), 2.36 (3H,s)
		286 (54)	5.34 (2H,s), 7.02-7.67 (9H,m)
		152 (46)	
f	1685	377 (M^+,100)	2.10 (3H,s), 2.17 (3H,s), 2.35 (3H,s)
		286 (61)	5.33 (2H,s), 6.97-7.58 (9H,m)
		152 (45)	
g	1683	361 (M^+,100)	2.12 (3H,s), 2.22 (3H,s), 2.37 (3H,s)
		270 (43)	5.37 (2H,s), 7.00-7.50 (9H,m)
		136 (26)	
h	1685	361 (M^+,100)	2.12 (3H,s), 2.20 (3H,s), 2.35 (3H,s)
		270 (56)	5.37 (2H,s), 6.95-7.57 (9H,m)
		136 (45)	
i	1685	361 (M^+,100)	2.11 (3H,s), 2.17 (3H,s), 2.35 (3H,s)
		270 (55)	5.35 (2H,s), 6.97-7.42 (9H,m)
		136 (37)	

a) Only $\nu_{C=O}$ are indicated.

b) No. of protons, multipicities and coupling constants (Hz) in parantheses.

Table 3: ^{13}C NMR data of 2[13].

C	2a	2b	2c	2d	2e	2f	2g	2h	2i
2	151.5	151.5	151.7	151.8	151.1	151.1	151.4	151.0	151.5
4	159.9	159.3	159.9	160.0	159.0	159.8	159.3	159.6	160.0
4a	104.2	104.3	104.1	104.3	104.0	104.2	104.0	104.2	104.2
5	110.8	110.9	110.6	110.7	110.9	110.8	111.0	110.9	110.9
6	127.4	127.7	127.6	127.5	127.3	127.5	127.8	127.1	127.6
7a	146.0	146.1	145.8	145.9	146.0	145.8	146.0	145.9	145.9
1'	138.5	135.5	135.7	135.9	136.2	137.0	125.3(d)	140.0(d)	134.4(d)
							J=11Hz	J=10Hz	J=4Hz
2'	128.2	137.5	127.8	128.0	132.6	129.6	157.7(d)	115.6(d)	130.1(d)
							J=250Hz	J=21Hz	J=9Hz
3'	129.4	130.9	130.0	128.9	130.2	129.6	116.6(d)	162.9(d)	116.5(d)
							J=20Hz	J=249Hz	J=23Hz
4'	128.4	128.7	138.2	144.5	130.0	134.4	130.6(d)	116.1(d)	162.3(d)
							J=7Hz	J=23Hz	J=249Hz
5'		127.0			127.8		124.8(d)	130.5(d)	
							J=4Hz	J=10Hz	
6'		128.2			130.0		130.4	124.3(d)	
								J=3Hz	
1"	137.6	137.7	137.5	137.6	137.4	137.4	137.6	137.5	137.6
2"	126.3	126.4	126.2	126.3	126.4	126.3	126.4	126.4	126.4
3"	128.4	128.4	128.3	128.4	128.4	128.4	128.5	128.5	128.5
4"	127.0	127.0	126.9	127.0	127.0	127.1	127.2	127.1	127.2
N-CH_2-	44.9	45.0	44.8	44.9	45.0	45.0	45.1	45.0	45.0
2-CH_3	24.1	23.4	24.0	24.1	23.1	24.0	23.3	23.8	24.1
5-CH_3	9.5	9.5	9.4	9.4	9.4	9.4	9.5	9.4	9.5
6-CH_3	9.5	9.5	9.4	9.4	9.4	9.4	9.5	9.4	9.5
2'-CH_3		17.2							
4'-CH_3			20.9						
4'-$CH_2\underline{C}H_3$				15.2					
4'-$\underline{C}H_2CH_3$				28.3					

addition of 1. Using 1 and 3 as references, it was found that only spots corresponding to 1 and 2c could be detected. Although the intermediates 3-6 were not detected in the reaction mixture, it is believed that reactions of 1 with anilines follow pathway A, in which 5 immediately are converted to 2 by cyclodehydration in the phosphorus pentoxide-amine mixture.

In order to clarify the synthetic route to 7, the reaction of 1 with ethylamine hydrochloride was followed by TLC. The reaction progress showed that the oxazinone 3 was the main intermediate from which 7 can be formed via 5 (route B) or 6 (route C). Although the intermediates 5 and 6 were not detected in the reaction mixture, these intermediates are plausible, since analogous compounds have already been isolated in the synthesis of 4(3H)-quinazolinones from 4H-3,1-benzoxazin-4-ones and primary amines [11,12]. Dealing with the latter compounds, it was found that reactions of the analogues to 5 required heating above 250°C before thermal cyclodehydration took place, whereas the quinazolone analogues to 7 could be achieved at much lower temperatures by reactions between primary amines and the oxazinones[12]. In view of these findings, it is believed that route C via the intermediate 6 is the one operating in the synthesis of 7.

EXPERIMENTAL

Microanalyses were carried out at NOVO A/S Copenhagen. IR spectra were recorded on a Perkin-Elmer 580 (potassium bromide used in all cases). Mass spectra were obtained on a Varian MAT 311A and a Varian MAT CH7A. ^{1}H NMR spectra were recorded in $CDCl_3$ (TMS as internal standard δ = 0) on a Jeol JNM-PMX 60 spectrometer. ^{13}C NMR spectra were recorded in $CDCl_3$ on a Jeol FX 60Q spectrometer (the solvent as internal standard). Melting points were obtained on a Büchi-apparatus (uncorrected). Yields refer to analytical pure compounds.

Methyl 2-Acetamidopyrrole-3-carboxylate 1.

Methyl 2-amino-4,5-dimethyl-1-phenylmethylpyrrole-3-carboxylate[9] (77.5 g, 0.3 mol) was dissolved in the least possible amount of glacial acetic acid, acetic anhydride (76.5 g, 0.75 mol) was added, and the mixture was stirred for 3 h. The reaction mixture was poured on to crushed ice (900 g). The precipitate was collected by filtration, washed several times with water, dried and recrystallized from 50% aqueous methanol to afford 72.1 g (80%) of the title compound. Mp 143-144°C. IR (KBr) 1705, 1680 cm^{-1}. MS m/z 300 (M^+), 258, 167, 135, 91 (100%). ^{1}H NMR ($CDCl_3$) δ

2.03 (6H,s), 2.18 (3H,s), 3.78 (3H,s), 5.03 (2H,s), 6.80-7.43 (5H,m), 7.93 (1H,br s). ^{13}C NMR ($CDCl_3$) δ 9.4 (CH_3), 10.8 (CH_3), 22.8 ($CO\underline{C}H_3$), 47.1 (CH_2), 50.3 (OCH_3), 104.7 (C-3), 115.0 (C-4), 123.5 (C-5), 125.7 (o-phenyl C), 127.0 (p-phenyl C), 128.4 (m-phenyl C), 130.3 (C-2), 137.1 (i-phenyl C), 165.5 (COO), 170.7 (NHCO). Found: C, 68.23; H, 6.76; N, 9.22. Calcd. for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33.

Preparation of 3-Aryl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-ones 2.

General Procedure:

The reagent was prepared by mixing phosphorus pentoxide (8.5 g, 60 mmol), triethylamine hydrochloride (8.3 g, 60 mmol), and the aniline (60 mmol) in a 250 ml 3-necked flask fitted with a mechanical stirrer and a reflux condenser with a drying tube (calcium chloride). The mixture was heated in an oil bath at 180°C (oil bath temperature) until a homogeneous mixture was achieved (~0.5 h). The oil bath temperature was adjusted to 150°C, and 1 (4.5 g, 15 mmol) was added and reacted for the specified reaction time (Table 1). The required reaction time was obtained by following the disappearance of the starting material 1. At 10 min intervals, a small sample was taken out from the reaction mixture, dissolved in a 2M sodium hydroxide solution and extracted with dichloromethane. The extract was subjected to aluminium oxide TLC (ether) using 1 as reference. When 1 was not present in the extract, the flask was removed from the oil bath and allowed to cool to about 100°C, and 30 ml of water was added. The hydrolyzed reaction mixture was adjusted to pH = 12 with a 2M sodium hydroxide solution and extracted with dichloromethane (4 x 50 ml). The combined organic phases were dried over sodium sulphate and filtered. The solvent was removed under reduced pressure leaving the crude product which was dissolved in 50 ml of methanol, acidified with 30 ml of a 4M hydrochloric acid solution and precipitated by adding water (20-40 ml). The precipitate was filtered off, dried and recrystallized.

Pyrrolo[2,3-d][1,3]oxazin-4(7H)-one 3.

Phosphorus pentoxide (11.4 g, 80 mmol), triethylamine hydrochloride (11.0 g, 80 mmol), and n-propylamine (4.7 g, 80 mmol) were mixed at 180°C according to the general procedure. The temperature was adjusted to 150°C, and 1 (6.0 g, 20 mmol) was added and reacted for 25 min. The reaction mixture was worked up as described in the general procedure. The crude product was recrystallized from methanol to give 3.3 g

(62%) of the title compound. Mp 131-132°C. IR (KBr) 1760 cm^{-1}. MS m/z 268 (M^+), 91 (100%). ^1H NMR ($CDCl_3$) δ 2.08 (3H,s), 2.28 (3H,s), 2.42 (3H,s), 5.25 (2H,s), 6.90-7.42 (5H,m). ^{13}C NMR ($CDCl_3$) δ 9.4 (CH_3), 9.5 (CH_3), 21.1 (CH_3), 45.5 (CH_2), 98.8 (C-4a), 112.0 (C-5), 126.3 (o-phenyl C), 127.4 (p-phenyl C), 127.5 (C-6), 128.6 (m-phenyl C), 136.6 (i-phenyl C), 145.2 (C-7a), 157.3 (C-4), 161.3 (C-2). Found: C, 71.64; H, 6.04; N, 10.47. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44.

3-Ethyl-3,7-dihydro-4H-pyrrolo[2,3-d]pyrimidin-4-one 7.

Phosphorus pentoxide (11.4 g, 80 mmol), triethylamine hydrochloride (11.0 g, 80 mmol), and ethylamine hydrochloride (6.5 g, 80 mmol) were mixed at 180°C according to the general procedure. The temperature was adjusted to 200°C, and 1 (6.0 g, 20 mmol) was added. Small samples of the reaction mixture were collected at convenient intervals, hydrolyzed and extracted with dichloromethane. After 90 min reaction time, TLC (aluminium oxide, dichloromethane) showed that the reference compound 3 was not present in the extract. The flask was removed from the oil bath and cooled to about 100°C, and 30 ml of water was added. The mixture was made alkaline with a 2M sodium hydroxide solution (pH = 12) and extracted with dichloromethane (4 x 50 ml). The combined organic phases were dried over sodium sulphate and filtered. Evaporation of the solvent under reduced pressure left a crude oily product which was dissolved in 40 ml of boiling toluene and poured, while still hot, in 250 ml of petroleum ether (65-70°C) under vigorous stirring. The incipient precipitate was filtered off and discarded. The filtrate was left overnight, and then the precipitate was filtered off and recrystallized from toluene/ligroin (80-100°C) to give 2.3 g (38%) of the title compound. Mp 128-129°C. IR (KBr) 1680 cm^{-1}. MS m/z 295 (M^+, 100%), 204, 91, 42. ^1H NMR ($CDCl_3$) δ 1.33 (3H,t,J = 7Hz), 2.08 (3H,s), 2.37 (3H,s), 2.57 (3H,s), 4.13 (2H,q,J = 7Hz), 5.27 (2H,s), 6.88-7.40 (5H,m). ^{13}C NMR ($CDCl_3$) δ 9.3 (CH_3), 9.5 (CH_3), 13.9 ($CH_2\underline{C}H_3$), 22.7 (CH_3), 38.4 ($\underline{C}H_2CH_3$), 45.5 (CH_2), 104.3 (C-4a), 110.2 (C-5), 126.3 (o-phenyl C), 127.0 (p-phenyl C), 127.2 (C-6), 128.4 (m-phenyl C), 137.8 (i-phenyl C), 145.9 (C-7a), 151.1 (C-2), 159.3 (C-4). Found: C, 73.05; H, 7.17; N, 14.17. Calcd. for $C_{18}H_{21}N_3O$: C, 73.19; H, 7.17; N, 14.22.

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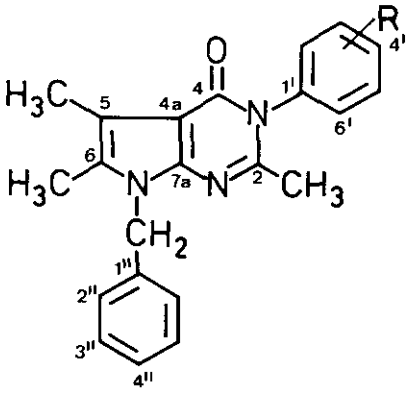

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