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SYNTHESIS OF 4-SUBSTITUTED PYRIMIDO[5,4-*C*]CINNOLINE DERIVATIVES

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ABSTRACT

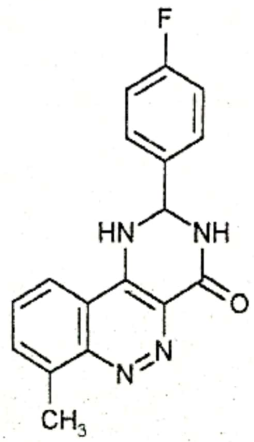
Reaction of 4-aminocinnoline-3-carboxamide or its 8-methyl derivative **1a,b** with triethyl orthoformate and acetic anhydride gave rise to the corresponding pyrimido[5,4-*c*]cinnolin-*3H*-4-ones **2a-d**. 2-Methylpyrimido derivatives **2c,d** could also be obtained via ammonolysis of 2-methyl-1,3-oxazino[5,4-*c*]cinnolin-4-ones **4a,b**. On the other hand, reaction of **1a,b** with araldehydes afforded 2-arylpyrimidocinnolines **5a-e**. Reacting compounds **2a-d** with hydrazine and different amines produced the corresponding 4-substituted amino or hydrazino derivatives **7-9**. This revealed the reactivity of the 4-position of **2** towards nucleophilic substitution. Attempts to cyclize **7a-d** to triazolopyrimidocinnolines are discussed.

INTRODUCTION

Several pyrimido[5,4-*c*]cinnolines have been reported to possess CNS[1], bactericidal[2] and anti-inflammatory[3] activity.

Pyrimido[5,4-*c*]cinnolines **2a,b** (Scheme , Table 1) are reported to be prepared in 60-80 % yield by reacting 4-aminocinnoline-3-carboxamides[4-6] **1** with formamide[5] or with a mixture of formamide and triethylorthformate[6].In this study, **2a,b** were prepared in 85 % yield using a mixture of triethyl orthoformate and acetic anhydride. 2-Methylpyrimidocinnolines **2c,d** were readily prepared by refluxing **1** in acetic anhydride only or by reacting oxazinocinnolines[7] **4** with NH_4OH. Oxazino compounds **4** in turn were prepared via cyclocondensation of aminocinnoline carboxylic acids[4] **3** with acetic anhydride.

Attempts to prepare 2-(4-fluorophenyl)-7-methylpyrimido[5,4-*c*]cinnolin-4-one **5a** by reacting **1b** with *p*-fluorobenzaldehyde in absolute ethanol containing a catalytic amount of HCl were unsuccessful. Replacing ethanol by DMF and heating for 12 hours gave rise to the tetrahydropyrimido derivative **6**. Nevertheless, this aminal intermediate was oxidized[8] to the required pyrimidocinnoline **5a** when heating was continued for 24 hours. Accordingly, overnight refluxing of **1** with the appropriate aldehyde in acidic DMF afforded 2-arylpyrimidocinnolines **5**.



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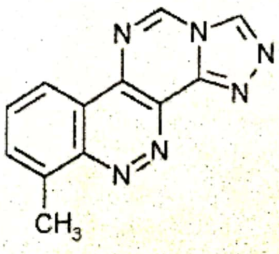
4-Hydrazinopyrimido[5,4-*c*]cinnolines **7a,b** are reported[5] to be prepared by reacting pyrimido-cinnolin-4-ones **2a,b** with $POCl_3$ and tetramethyl-ammonium chloride to give the corresponding 4-chloro derivatives which were then reacted with hydrazine. In this study, it was possible to obtain the hydrazino compounds 7 (Table 2) in 50-60 % yields by reacting pyrimidocinnolin-4-ones **2** directly with excess hydrazine in a mixture of DMF and ethanol for 20 hours. Furthermore, reacting **2** with excess benzylamine, cyclopentylamine, piperidine or weaker nucleophile; aniline afforded 50-70 % yield of the corresponding 4-substituted amino derivatives **8** and **9** (Table 2) which were isolated from unreacted 2 and excess amine and purified by crystallization from toluene. Apparently the reaction of hydrazine or an amine with **2** proceeds via an addition elimination mechanism (S_NAr). Although S_NAr reactions are not unusual in the pyrimidine nucleus, it was significant to observe that the IR (KBr) spectra of compounds **2** (and **5**) showed strong carbonyl absorption at 1720 **(2a)**, 1725 **(2b)** and 1690 **(2c,d)** cm^{-1}. It is possible that the electron-withdrawing effect of the cinnoline ring nitrogens contributes to these high carbonyl frequencies. It is also conceivable that this effect should further facilitate a nucleophilic attack at position 4 and, in addition to pyrimidine ring nitrogens, stabilize an anion intermediate. The obtainment of 4-piperidino derivatives **9** from the reaction of **2** with piperidine also indicated the steric accessibility of the 4-position.

In 1994, Nargund et al reported[5] on the synthesis of triazolo[3`,4`:6,1]pyrimido[5,4-*c*]cinnoline **10** by refluxing 4-hydrazino derivative **7b** in excess triethyl orthoformate for 2 hours. The reported[5] δ values for H-3 and H-5 signals in DMSO-d_6 were 10.1 and 9.7 ppm respectively. This procedure was reexamined in this invistigation but gave no evidence for the formation of fused triazolo product as claimed.



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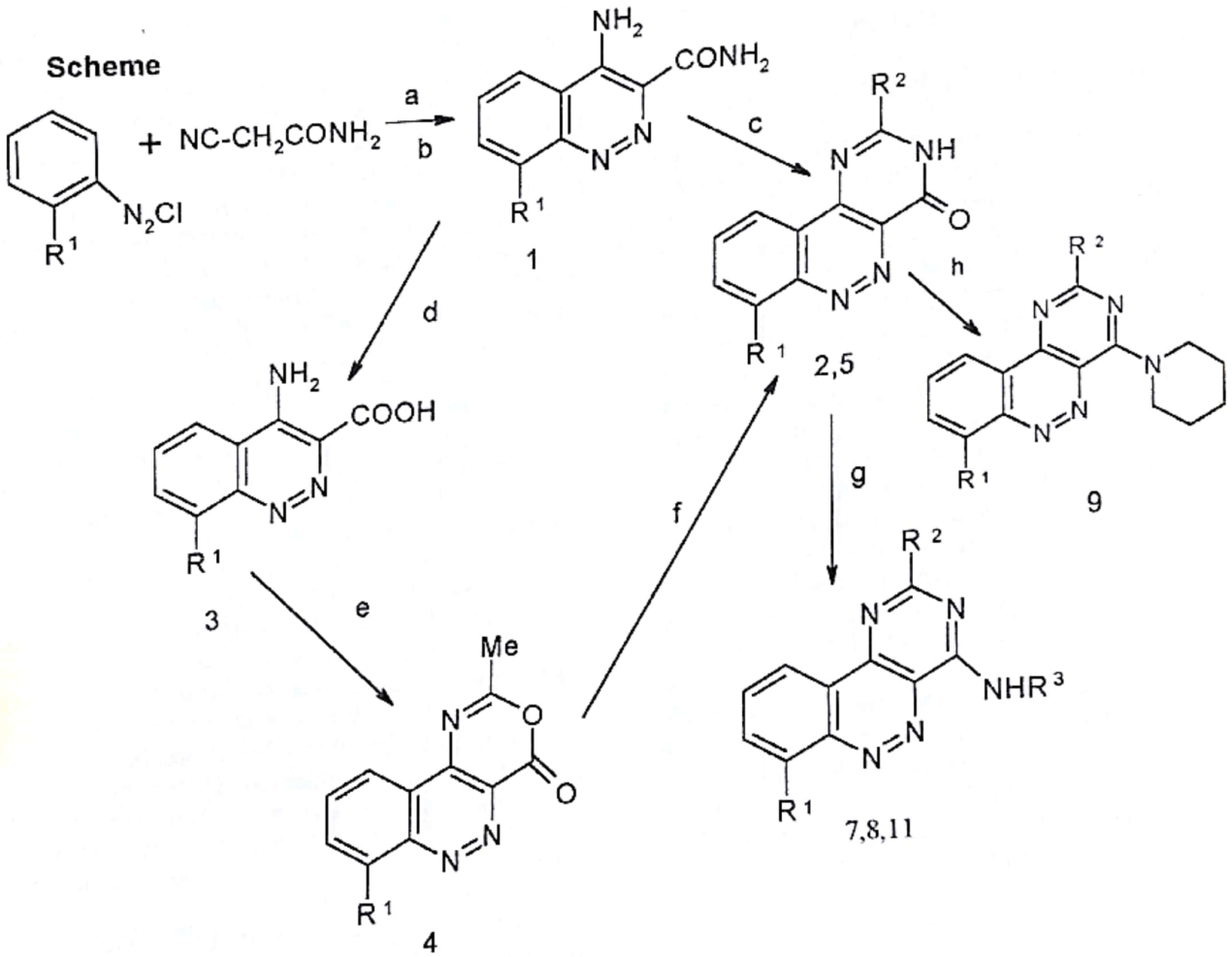
Instead, the ^{1}H-NMR of the isolated material showed that it consisted mainly of the intermediate 4-ethoxymethylidenehydrazino derivative that was expected to cyclize under the conditions of its formation. However, no cyclization was observed herein even after prolonged heating[9]. Likewise, refluxing **7c,d** with acetic anhydride up to 24 hours gave only uncyclized acyl derivative **11a,b** (table 2). Examples of unsuccessful formation of fused triazoloheterocycles from 2-hetarylhydrazine derivatives and their possible Dimorth-type isomerization by heat, acid or base have been reported[9,10]. Examination of molecular models (Dore-Smith atomic models) of triazolopyrimidocinnoline system **10** showed considerable angle and bond strain at the triazolo ring, particularly at the side of fusion (3,4 side) with the sp^3 N-4 atom intruding from the planar framework of the hetero system, which may explain the difficulty of its formation.

Scheme



a= $NaNO_2$ / HCl ;Ac_2O for 2 c,d; ArCHO, DMF, HCl for 5; b= $AlCl_3$, PhCl c =$HC(OEt)_3$, Ac_2O for 2 a,b d=H_2SO_4

e=Ac_2O f= NH_4OH , NaOH

g= $NH_2NH_2.H_2O$ for 7, R^2NH_2 for 8 h= piperidine for 9

R^1 = H , Me

Table (1): Pyrimido[5,4-c]cinnolin-4-ones 2 and 5

No	R^1	R^2	Yield %	TLC[a] R_f	M.F. (Mol. wt.)	Microanalyses Calcd / (Found)		
						C	H	N
2a[b]	H	H	82	0.39	--	--	--	--
2b[c]	Me	H	85	0.42	--	--	--	--
2c	H	Me	85[d]	0.45	$C_{11}H_8N_4O$ (212.2)	62.25 (62.0)	3.79 (4.0)	26.40 (26.0)
2d	Me	Me	85[d]	0.50	$C_{12}H_{10}N_4O$ (226.2)	63.70 (64.0)	4.45 (4.8)	24.76 (24.4)
5a	Me	4-FC_6H_4	57	0.49	$C_{17}H_{11}FN_4O$ (306.2)	66.66 (66.7)	3.61 (3.5)	18.29 (18.3)
5b	Me	4-ClC_6H_4	54	0.41	$C_{17}H_{11}ClN_4O$ (322.7)	63.26 (63.5)	3.43 (3.2)	17.35 (17.5)
5c	Me	C_6H_5	50	0.48	$C_{17}H_{12}N_4O$ (288.3)	70.82 (71.0)	4.19 (4.6)	19.43 (19.8)
5d	H	4-ClC_6H_4	55	0.40	$C_{16}H_9ClN_4O$ (308.7)	62.24 (62.3)	2.93 (3.2)	18.14 (18.2)
5e	H	3-$NO_2C_6H_4$	55	0.39	$C_{16}H_9N_5O_3$ (319.2)	60.19 (59.9)	2.84 (3.0)	21.93 (22.0)

- [a] Silica (PhH/CCl_3H/MeOH/triethylamine, 9:1.5:3:0.1)
- [b] Reported[5] mp 359-360 °C (DMF).
- [c] Reported[5,6] mp 350-351°C (DMF).
- [d] Method A
- Compound **2d** was crystallized from DMSO; all other compounds from DMF, mp of all compounds > 300°C

Table (2): 4-Substitutedaminopyrimido[5,4-c]cinnolines 7-9 and 11

No	R^1	R^2	R^3	Yield %	Mp °C (Cryst. solvent	M.F.	Microanalyses Calcd /(Found)		
							C	H	N
7a[a]	H	H	NH_2	60	260-62 (DMF)	--	--	--	--
7b[b]	Me	H	NH_2	62	267-70 (DMF)	--	--	--	--
7c	H	Me	NH_2	50	277-80 (MeCN)	$C_{11}H_{10}N_6$ (226.2)	58.39 (58.0)	4.45 (4.5)	37.14 (37.4)
7d	Me	Me	NH_2	56	292-95 (DMF)	$C_{12}H_{12}N_6$ (240.2)	59.98 (59.9)	5.03 (4.7)	34.97 (34.7)
8a	H	Me	Bn	68	240-43 (PhMe)	$C_{17}H_{13}N_5$ (287.3)	71.06 (71.4)	4.56 (4.8)	24.37 (24.6)
8b	Me	Me	Bn	70	228-30 (PhMe)	$C_{19}H_{17}N_5$ (315.3)	72.36 (72.0)	5.43 (5.2)	22.20 (22.2)
8c	Me	H	Cyclopentyl	59	282-84 (PhMe)	$C_{16}H_{17}N_5$ (279.3)	68.79 (68.9)	6.13 (6.5)	25.07 (25.2)
8d	H	H	Ph	56	268-70 (PhMe)	$C_{16}H_{11}N_5$ (273.2)	70.31 (70.1)	4.05 (4.2)	25.62 (25.5)
8e	Me	Me	Ph	50	260-63 (PhMe)	$C_{18}H_{15}N_5$ (301.3)	71.74 (71.7)	5.01 (4.6)	23.23 (23.2)
9a	H	H		55	280-82 (PhMe)	$C_{15}H_{15}N_5$ (265.3)	67.90 (68.0)	5.69 (5.6)	26.39 (26.0)

Table (2): *continued*

9b	Me	H		57	282-84 (PhMe)	$C_{16}H_{17}N_5$ (279.3)	68.79 (68.6)	6.13 (6.4)	25.07 (24.9)
9c	H	Me		69	275-76 (PhMe)	$C_{16}H_{17}N_5$ (279.3)	68.79 (68.9)	6.13 (6.4)	25.07 (25.3)
9d	Me	Me		64	266-68 (PhMe)	$C_{17}H_{19}N_5$ (293.3)	69.60 (69.2)	6.52 (6.5)	23.87 (24.0)
11a	H	Me	NHAc	85	>300 (DMF)	$C_{13}H_{12}N_6O$ (268.2)	58.20 (57.8)	4.50 (4.6)	31.32 (30.8)
11b	Me	Me	NHAc	87	>300 (EtOH/H_2O)	$C_{14}H_{14}N_6O$ (282.3)	59.56 (59.4)	4.99 (5.0)	29.76 (29.8)

[a] Reported mp 260-262 °C (DMF). [b] Reported mp 265-266 °C (DMF).

EXPERIMENTAL

Mp (uncorrected) : Griffin apparatus. IR: Shimadzu-IR 435. ^{1}H-NMR: Jeol FXQ-90, Jeol EX-270 or Varian-200, using tetramethylsilane as internal standard. EIMS: Hewlett Packard 5988 or Finnigan SSQ 7000. TLC: UV-fluorescent plastic-backed sheets with silica (Merck 60 F254); solvent system: PhH: $CHCl_3$: MeOH: triethylamine (9: 1.5: 3: 0.1). Elemental analyses were carried out at the Microanalytical Center, Cairo University, Cairo, Egypt.

The following compounds were prepared according to reported methods: 4-aminocinnoline-3-carboxamide[4] **(1a),** 4-amino-8-methylcinnoline-3-carboxamide[4,5] **(1b),** 4-aminocinnoline-3-carboxylic acid[4] **(3a),** 4-amino-8-methylcinnoline-3-carboxylic acid[4] **(3b),** 2-methyl-1,3-oxazino[5,4-c]cinnolin-4-one[7] **(4a),** 2,7-dimethyl-1,3-oxazino[5,4-c]cinnolin-4-one[7] **(4b).**

Pyrimido[5,4-*c*]cinnolin-3*H*-4-one[5,6] (2a)and 7-Methylpyrimido[5,4-*c*]cinnolin-3*H*-4-one[5] (2b).

A mixture of **1a** or **1b** (0.01 mol), acetic anhydride (0.1 mol) and triethyl orthoformate (0.09 mol) was refluxed for 4 h. The mixture was cooled, filtered and the precipitate was purified by crystallization (Table 1):
2a: IR (KBr) 3500, 3100-2700, 1720, 1680, 1600 cm^{-1}.
2b: IR (KBr) 3600-2800, 3450, 1725-1710, 1680, 1600 cm^{-1}.
^{1}H-NMR (DMSO-d_6) **(2b):** δ 8.58 (d, 1H, ArH), 8.51 (s, 1H,H-2), 7.96 (m, 2H, ArH), 3.00 (s, 3H, CH_3) ppm.

2-Methylpyrimido[5,4-*c*]cinnolin-3*H*-4-one (2c)and 2,7-Dimethylpyrimido[5,4-*c*]cinnolin-3*H*-4-one[5] (2d).

Method A:

A mixture of **1a** or **1b** (0.01 mol) and acetic anhydride (25 ml, 0.26 mol) was refluxed for 4 h. The mixture was cooled, filtered and the precipitate was crystallized (Table 1).

Method B:

A suspension of **4a** or **4b** (0.01 mol) in ammonium hydroxide solution (50%, 50 ml) was stirred at ambient temperature for an overnight. A solution of sodium hydroxide (10%, 30 ml) was added and the mixture was refluxed for 1h, cooled and acidified with acetic acid. The separated solid was washed with ice-cold water, dried and crystallized from DMF **(2c)** or DMSO **(2d)** (Table 1) in 70 and 65 % yield, respectively.
2c: IR (KBr) 3450, 3200-2700, 1690, 1620 cm^{-1}.
2d: IR (KBr) 3600-2700, 3400,3300, 1690-1660, 1600 cm^{-1}.
EIMS *m/z* 226 $(M)^+$ (100%), 185 $(M\text{-}CH_3CN)^+$ (4%).

2-Arylpyrimido[5,4-*c*]cinnolin-3*H*-4-ones (5a-e).

A mixture of **1a** or **1b** (0.01 mol) and the appropriate aromatic aldehyde (0.03 mol) in dry DMF (25ml) containing HCl (0.2 ml) was refluxed for 24 h. The mixture was concentrated, cooled and filtered. The precipitate was washed with hot benzene, dried and recrystallized (Table 1).
5a: IR (KBr) 3400,1725 cm^{-1};^{1}H-NMR (DMSO-d_6) δ 13.28 (br, 1H, NH, D_2O exchangeable), 8.40 (d, 2H, ArH), 7.95-7.92 (m, 2H, ArH), 7.72-7.59 (m, 3H, ArH), 3.01 (s, 3H, CH_3) ppm.
5b: IR (KBr) 3400,1690, 1600 cm^{-1};^{1}H-NMR (DMSO-d_6) δ 13.3 (br, 1H, NH, D_2O exchangeable), 8.59 (m, 1H, ArH), 8.31 (d, 2H, ArH), 7.80 (m, 2H, ArH), 7.63 (d, 2H, ArH), 2.94 (s, 3H, CH_3) ppm.
5c: IR (KBr) 3300, 1710,1610 cm^{-1}; EIMS *m/z* 288 $(M)^+$ (100%) .
5d: IR (KBr) 3230,1705,1600 cm^{-1}; EIMS *m/z* 310 $(M+2)^+$ (35.2%), 308 $(M)^+$ (100%), 280 $(M\text{-}N_2)^+$ (28.4%).
5e: IR (KBr) 3400,1710 cm^{-1}.

2-(4-Fluorophenyl)-7-methyl-1,2,3,4-tetrahydropyrimido[5,4-*c*]cinnolin-4-one (6).

A mixture of **1b** (1.9 g, 0.01mol) and 4-fluorobenzalaldehyde (3.1 ml, 0.028 mol) in dry DMF (25 ml) containing HCl (0.2 ml) was refluxed for 12 h. The reaction mixture was cooled, filtered and the precipitate was crystallized from DMF to give 1.4 g(45%) of 6: mp 294-296°C ; R_f 0.44; IR (KBr) 3400, 3100, 1690 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 13.31 (s,1H, NH, D_2O exchangeable), 8.64 (m, 1H, H-2), 8.36 (m,

2H, ArH), 7.96-7.82 (m, 2H, ArH), 7.70-7.58 (m, 3H, ArH) and 2.96 (s, 3H, CH_3) ppm.
Anal Caled for $C_{17}H_{13}FN_4O$ (308.3): C, 66.22; H, 4.24; N, 18.17.
Found: C, 66.5; H, 3.9; N, 18.3.

4-Hydrazinopyrimido[5,4-c]cinnolines (7a-d).

A mixture of the appropriate pyrimidocinnoline **2a-d** (0.01 mol), hydrazine monohydrate (99%) (10 ml, 0.20 mol), absolute ethanol (10ml) and dry DMF (5 ml) was refluxed for 18 h. The mixture was evaporated, cooled and the separated solid was purified by crystallization (Table 2).
7b[5]: IR (KBr) 3400, 3350-3170, 1670, 1640-1620 cm^{-1}.
7c: IR (KBr) 3350, 3300,3150-3050,1660, 1625 cm^{-1}; EIMS m/z 226 $(M)^+$ (4.5%), 199 $(M-HCN)^+$ (5.5%), 185 $(M-MeCN)^+$ (15%), 171 $(M-HCN, N_2)^+$ (11.5 %), 130 $(M-HCN, N_2, MeCN)^+$ (4.7%).
7d: IR (KBr) 3400, 3350,3320, 3270, 1670, 1640-1620 cm^{-1};^{1}H-NMR(DMSO-d_6) δ 10.13 (br, 1H, NH, D_2O exchangeable), 8.23 (d, 1H, ArH), 7.84 (m, 2H, ArH), 4.58(s, 2H, NH_2, D_2O exchangeable), 3.31 (s, 3H, 2-CH_3), 2.85(s, 3H, 7-CH_3) ppm; EIMS *m/z* 240 $(M)^+$ (1.6 %), 199 $(M-MeCN)^+$ (1 %), 157 $(M-C_3H_5N_3)^+$ (2.7 %).

4-Benzylaminopyrimido[5,4-c]cinnoline (8a) and 4-benzylamino-2,7-dimethylpyrimido[5,4-c]cinnoline (8b).

To an ethanolic solution of benzylamine (50 %) (15 ml, 0.068 mol), was added pyrimidocinnolin-4-one **2a** or **2d** (0.01 mol) and the solution was refluxed for 20 h. The mixture was evaporated, the residue was washed repeatedly with pet ether (40-60°C), and the remaining solid was crystallized from toluene (Table 2):
8a: IR (KBr) 3400, 1610 cm^{-1}.
8b: IR (KBr) 3400,1600 cm^{-1};^{1}H-NMR($CDCl_3$-d_6) δ 8.78 (m, 1H, ArH), 8.01 (br, 1H, D_2O exchangeable), 7.82 (m, 2H, ArH), 7.48-7.26 (m, 5H, ArH), 4.97 (m, 2H, CH_2Ph), 3.09 (s, 3H, 2-CH_3), 2.78 (s, 3H, 7-CH_3) ppm; EIMS *m/z* $(M)^+$ (100%), 300 $(M-CH_3)^+$ (5.3%), 224 $(M-CH_2Ph)^+$ (4.5%), 211 $(M-NHCH_2Ph)^+$ (9.9%).

4-Substitutedaminopyrimido[5,4-c]cinnolines (8c-e) and (9a-d).

A mixture of **2a-d** (0.01 mol) and the appropriate amine (0.2 mol) was heated under reflux for 48 h. Toluene (75 ml) was added and the reflux was continued for another 15 min. The mixture was filtered, the filtrate was concentrated, cooled and the separated solid was collected, dried and crystallized from toluene (Table 2):

8c: IR (KBr) 3450-3100,1660,1620 cm^{-1}; EIMS m/z 280 $(M+1)^+$ (4.2%), 265 $(M-CH_3)^+$ (2%).
8d: IR (KBr) 3500-3100,1660, 1610 cm^{-1}.
8e: IR (KBr) 3350,1640, 1605 cm^{-1};^{1}H-NMR($CDCl_3$-d_6) δ 9.77 (s, 1H, NH), 8.82 (m, 1H, ArH), 8.04 (m, 2H, ArH), 7.85 (m, 2H, ArH), 7.47(m, 2H, ArH), 7.20 (m, 1H, ArH), 3.13 (s, 3H, 2-CH_3), 2.85(s, 3H, 7-CH_3) ppm; EIMS *m/z* 302 $(M+1)^+$ (33%), $(M)^+$ (14.1%), 300$(M-1)^+$ (45.3%), 286 $(M-CH_3)^+$ (9.5%), 69 (100%).
EIMS **(9a)** *m/z* 264 $(M-1)^+$ (28.2%), 194 $(M-C_5H_{10}N)^+$ (1.4%).
9b: IR (KBr) 1590 cm^{-1}
9c: IR (KBr) 1590 cm^{-1}
9d: IR (KBr) 1580 cm^{-1}

4-Acetylhydrazinopyrimido[5,4-c]cinnolines (11a,b)

A mixture of **7c** or **7d** (0.02 mol) and acetic anhydride (0.2 mol) was refluxed for 4 h. The mixture was cooled, filtered and the solid was purified by crystallization (Table 2):
11a: IR (KBr) 3470, 3400, 1720-1700 cm^{-1}
11b: IR (KBr) 3500-3400, 1740-1715 cm^{-1}
^{1}H-NMR(DMSO-d_6) ***(11b)*** δ 8.62 (d, 1H, ArH, 7.99 (m, 2H, ArH), 3.02 (s, 3H, 2-CH_3), 2.65 (s, 3H, 7-CH_3), 2.51 (s, overlaps with DMSO-d_6 absorption, $COCH_3$) ppm.

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تشييد مشتقات البيريميدو[٥، ٤-ج]سينولين المستبدلة في الوضع ٤

خديجة منصور غنيم، محمد يسري حافظ عيسوى، سلوى السيد محمد المليجى ،

علياء محمد كمال

قسم الكيمياء العضوية ، كلية الصيدلة ، جامعة القاهرة

قصر العيني ١١٥٦٢، القاهرة، جمهورية مصر العربية

تـــم في هذا البحث تفاعل ٤-أمينوسينولين-٣-كربوكساميد (١أ،ب) مع ثلاثي ايثيل الأورثوفورمات و أنهيدريد حمـــض الخليك لتكوين مركبات البيريميدو (٢أ،ب)، و ٢-ميثيل بيريميدو [٥، ٤ج]سينولين-٤-اوكسو (٢ج،د). و قد أمكن الحصول علي مركبات ٢ج، د أيضا بتفاعل الأمونيوم هيدروكسيد مع ٢-ميثيل-١، ٣-أوكسازينو [٥، ٤ ج]ســـينولين-٤-اوكســـو(٤). كذلـــك تـــم تشـــييد مركبات ٢-أريل بريميدو سينولين (٥) بتفاعل الأمينوسينولين كربوكساميد ١أ،ب مع مختلف الارالديهيدات.

و قد أظهرت النتائج فاعلية مجموعة الكربونيل في الموقع ٤ في مركبات البيريمدوسينولين ٢ حيث تم تفاعلها مـــع الهيدرازين و أمينات مختلفة لتكون مشتقات ال٤-هيدرازينو (مركبات ٧) و الالكيل/أريل أمينوبريميدوسينولين (٨ ، ٩). وقد تم تفسير هذه الفاعلية لقرب هذا الموقع لذرات النتروجين في حلقة السينولين. و يناقش البحث أيضا محاولات حلقنة مشتقات الـــ٤-هيدرازينو إلى مشتقات ترايازوليه.