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# A CONVENIENT ONE-POT ENTRY INTO NOVEL 2-SUBSTITUTED-6,7-DIHYDRO-4H-PYRIMIDO(2,1-a) ISOQUINOLIN-4-ONES**

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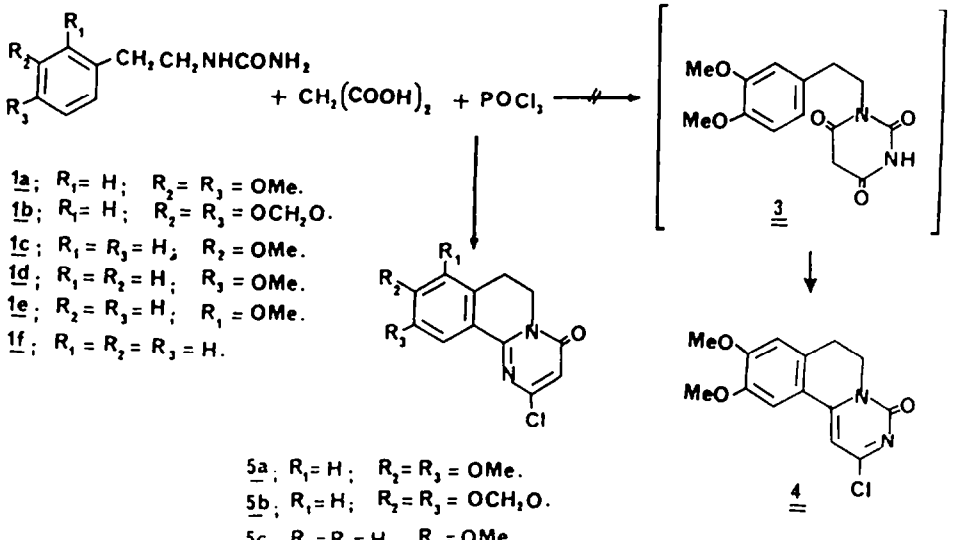
Abstract : The reaction of 1-(2-arylethyl)urea (1a - 1c) with malonic acid and phosphorus oxychloride gave 2-chloro-6,7-dihydro-4H-pyrimido(2,1-a)isoquinolin-4-ones (5a - 5c). The condensation of 6,7-dimethoxy-1-methylthio-3,4-dihydroisoquinoline (10) with 3-imino-3-morpholino-ethylpropionate (9) generated 9,10-dimethoxy-2-morpholino-6,7-dihydro-4H-pyrimido(2,1-a)isoquinolin-4-one (8).

The key intermediate 4 of pyrimido(6,1-a)isoquinolin-4-one series was synthesized in a two step sequence starting from substituted urea (1a) and diethylmalonate[1].

We envisioned to simplify further the process of obtaining compound 4 through an efficient one-pot reaction sequence (Scheme I), that would bypass isolation of barbituric acid 3.

**Scheme I**




1a; $R_1$= H; $R_2$= $R_3$ = OMe.
1b; $R_1$= H; $R_2$= $R_3$ = $OCH_2O$.
1c; $R_1$ = $R_3$ = H; $R_2$ = OMe.
1d; $R_1$ = $R_2$ = H; $R_3$ = OMe.
1e; $R_2$ = $R_3$ = H; $R_1$ = OMe.
1f; $R_1$ = $R_2$ = $R_3$ = H.

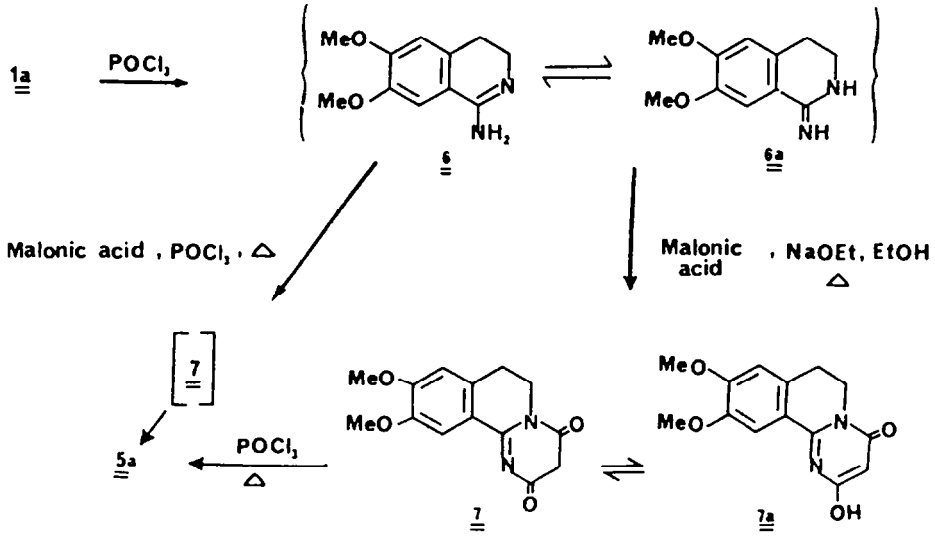
5a; $R_1$= H; $R_2$= $R_3$ = OMe.
5b; $R_1$= H; $R_2$= $R_3$ = $OCH_2O$.
5c; $R_1$ = $R_3$ = H; $R_2$ = OMe.

We believed that malonic acid will be activated[2] with $POCl_3$ and will further react with urea (1a) to form the substituted barbituric acid 3, in situ, and excess $POCl_3$ present in the reaction mixture would carry the reaction forward to the desired target compound 4. This paper describes the results of that study.

Substituted urea 1a, malonic acid and $POCl_3$ when heated together yielded a product, which was different from the authentic sample 4, as was revealed by comparison of the corresponding IR and TLC. The product showed the presence of chlorine by elemental analysis, its IR showed band at 1689 $cm^{-1}$ and $^1H$ NMR spectrum showed two triplets at $\delta$3.0 for H-7 and $\delta$4.0 for H-6 with J value 6 Hz respectively, a singlet at $\delta$6.4 for H-1 olefinic proton, its structural features indicate it to be a tricyclic system. Published data on UV spectra of pyrido(2,1-a) pyrimidines[3] and similar work by others[4] suggested the presence of carbonyl group at C-4. Combining all the data together, the structure of the compound was assigned as 2-chloro-9,10-dimethoxy-6,7-dihydro-4H-pyrimido(2,1-a)isoquinolin-4-one (5a). Similarly 1b and 1c when subjected to above set of reaction conditions gave compounds 5b and 5c respectively, however, compounds 1d, 1e and 1f failed to give the required tricyclic system, thereby pointing to the fact, that activation of the aromatic ring at the site of cyclization is a must.

A reexamination of the reacting species in Scheme I, suggests that the following pathway for the formation of 5a (Scheme II) may be followed.

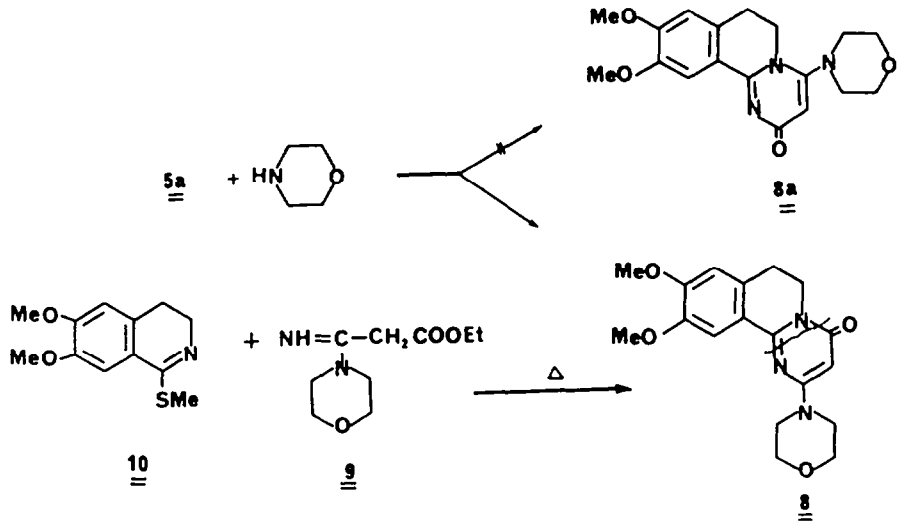
**Scheme II**



Cyclization of 1a with $POCl_3$ to 6[5] is known. Activated malonic acid (malonic acid + $POCl_3$) can attack 6 and give the tricyclic system 7, on further reaction with excess of $POCl_3$ can give 5a. In order to prove the above sequence, compound 6 was made to react with diethyl malonate in the presence of sodium ethoxide (Scheme II) to give compound 7 and/or its tautomer 7a, treatment of 7 with $POCl_3$ generated in high yield compound 5a. More directly compound 6 was heated with malonic acid and $POCl_3$ to give compound 5a, proving the proposed path was indeed followed by the above reaction.

The chloro group in compound 5a was displaced by different primary and secondary amines. The resulting morpholino compound 8 allowed further verification of the structural assignment of 5a. Morpholine could theoretically give one of the two products, compound 8 or 8a respectively, depending on the location of the chlorine atom in 5a (Scheme III).

**Scheme III**

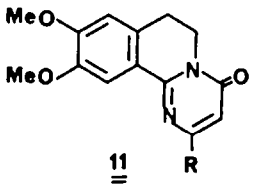



The isolated compound was assigned structure 8, based on spectral data. The final confirmation of the structure 8 came through its unambiguous synthesis. Retrosynthetic analysis of the structure 8 (Scheme III) reveals that this compound can be synthesized from compounds 9 and 10[11], the former being synthesized unambiguously by reacting ethyl-3-imino-3-methoxy-propionate hydrochloride[7] with one equivalent of morpholine. Fusion reaction between 9 and 10 gave a compound which was identical in all respects to 8, proving that morpholine in 8 and chloro in 5a are at C-2[8] of the pyrimido(2,1-a)isoquinolin-4-one skeleton.

Condensation of compound 5a with different amines gave compounds 11a - 11f (Table I).

Table I

A few representative compounds of 2-substituted-9,10-dimethoxy-6,7-dihydro-4H-pyrimido (2,1-a)isoquinolin-4-ones (11).




11 R

| Compound No. | R |
|---|---|
| 11a | isobutylamino |
| 11b | 1,1-dimethylhydrazino |
| 11c | amino |
| 11d | 4'-methoxybenzylamino |
| 11e | N-Carbethoxyhydrazino |
| 11f | phenylethylamino |

Conclusions : (i) Activated arylethylurea, malonic acid and $POCl_3$ on heating give the tricyclic pyrimido(2,1-a)isoquinolin-4-ones.
(ii) Mechanism for the one-pot synthesis of 5a is suggested.
(iii) An alternative method to synthesise 2-morpholino-6,7-dihydro-8,9-dimethoxy-4H-pyrimido (2,1-a)isoquinolin-4-one is found.

## EXPERIMENTAL

Melting points were obtained on a Kofler hot stage apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 157 spectrophotometer using KBr disks. $^1H$ NMR spectra were recorded on a Varian T-60 spectrophotometer using tetramethylsilane as an internal standard. Chemical shifts are reported in δppm. UV spectra were recorded on a Carl Zeiss specord spectrophotometer.

Compounds 1a, 1c - 1f[9], 6, 9 were synthesized by literature methods.

2-Chloro-9,10-dimethoxy-6,7-dihydro-4H-pyrimido(2,1-a)isoquinolin-4-one (5a) Method A :

A mixture of 1- 2-(3,4-dimethoxyphenyl)ethyl urea (1a; 60.0 g, 0.268 mol), malonic acid (35.0 g, 0.336 mol) and excess of $POCl_3$ (750 ml) was stirred at room temperature for 15 min, then heated at 105-110°C for 3 hours. Excess of $POCl_3$ was removed under reduced pressure. The residue was poured directly onto crushed ice when a solid separated out. It was extracted with chloroform. The organic layer was washed with water and dried ($Na_2SO_4$). The solvent was removed under reduced pressure to give a residue. The residue was purified by flash chromatography using 20% ethyl acetate - pet. ether as eluant. Evaporation of the solvent gave the product, which was crystallised from dichloromethane - pet. ether. Yield 35.0 g (45%), mp 188-189°C; IR : 1600, 1666 $cm^{-1}$; UV (Methanol): λmax ( ε ) 208 (31435), 235 (17995) 260 (8200), 338 (20956) nm; $^1H$ NMR ($CDCl_3$) : δ3.00 (t, 2H, J 6 Hz, H-7), 4.00 (s, 6H, 2 X $OCH_3$), 4.10 (t, 2H, J 6 Hz, H-6), 6.40 (s, 1H, H-3), 6.70 (s, 1H, H-8), 7.72 (s, 1H, H-11); (Found : C, 57.54; H, 4.39; N, 9.73; Cl, 11.74. $C_{14}H_{13}ClN_2O_3$ requires C, 57.44; H, 4.48; N, 9.57; Cl, 12.11).

Method B : Compound 7 (1.0 g, 0.003 mol) and an excess of $POCl_3$ kept at 100°C for 3 hours and worked up as described above, yield 100%. The product was identical to compound 5a.

Method C : A solution of 1-amino-6,7-dimethoxy-3,4-dihydro-isoquinoline[6] (6, 0.50 g, 2.5 mmol) and malonic acid (0.312 g, 3 mmol) in $POCl_3$ (3 ml) was refluxed for 2 hours. The resulting violet reaction mixture was cooled and excess of $POCl_3$ was distilled off under reduced pressure. The residue was worked up as described in method A, yield 0.128 g (25%), mp 188-189°C, mmp with the compound 5a was undepressed. The tlc and spectral data were also identical to 5a.

1- 2-(3,4-methylenedioxy phenyl)ethyl urea (1b). This was prepared through conventional method[10] from 2-(3,4-methylenedioxy phenyl)ethyl amine and KCNO, yield 70%, mp 145-147°C; $^1H$ NMR (DMSO-$d_6$) : δ2.67 (t, 2H, J 6 Hz), 3.00 - 3.50 (m, 4H), 5.33 (bs, 1H, exchanges with $D_2O$), 6.00 (s, 2H), 6.53 - 7.00 (m, 3H); (Found : C, 55.54; H, 5.69. $C_{10}H_{12}N_2O_3$ 0.5 $H_2O$ requires C, 55.23; H, 6.03).

2-Chloro-9,10-methylenedioxy-6,7-dihydro-4H-pyrimido(2,1-a)isoquinolin-4-one (5b)
Compound 5b was synthesized as described in method A, yield 23%, mp 148-149°C; IR : 1700 $cm^{-1}$; UV (Methanol) : λmax ( ε ) 208 (21319), 235 (14710), 241 (15236), 260 (5330), 338 (15350) nm; $^1H$ NMR ($CDCl_3$) : δ3.00 (t, 2H, J 7 Hz, H-7), 4.30 (t, 2H, J 7 Hz, H-6), 6.20 (s, 2H, $OCH_2O$), 6.50 (s, 1H, H-3), 6.80 (s, 1H, H-8), 7.80 (s, 1H, H-11); (Found : C, 54.22; H, 3.72; N, 10.11 $C_{13}H_9ClN_2O_3.0.5H_2O$ requires C, 54.65; H, 3.50; N, 9.80).

2-Chloro-9-methoxy-6,7-dihydro-4H-pyrimido(2,1-a)isoquinolin-4-one (5c). Compound 5c was synthesized through method A, yield 22.5%, mp 148-149°C. IR : 1670, 1615 and 1600 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) : δ3.02 (t, 2H, J 5 Hz, H-7), 3.88 (s, 3H, $OCH_3$), 4.24 (t, 2H, J 5 Hz, H-6),

6.32 (s, 1H, H-3), 6.72 (d, 1H, J 2 Hz, H-8), 6.88 (dd, 1H, J 2 & 7 Hz, H-10), 8.20 (d, 1H, J 7 Hz, H-11); (Found : C, 59.36; H, 4.35; N, 10.50; Cl, 13.58. $C_{13}H_{11}ClN_2O_2$ requires C, 59.43; H, 4.22; N, 10.67; Cl, 13.50).

9,10-Dimethoxy-3,4,6,7-tetrahydro-2H-pyrimido(2,1-a)isoquinolin-2,4-dione (7 and/or 7a). Sodium metal (0.6 g, 0.026 mol) and abs. ethanol (50 ml) were made to react. 1-Amino-3,4-dihydro-5,6-dimethoxyisoquinoline hydrochloride (1.0 g, 0.003 mol) was added and the reaction mixture refluxed for 15 min, followed by addition of diethyl malonate (1.055 g, 0.007 mol). The reaction mixture was further refluxed for 24 hours, excess of solvent was removed under reduced pressure and the residue treated with water and extracted with ethyl acetate. The basic aqueous layer was made acidic by dil. HCl and the separated solid was filtered, washed with water, dried and crystallised from ethanol, yield 0.7 g (85%), mp 220-221°C; IR : 3400, 1670 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$):$\delta$2.83 (t, 2H, J 7 Hz, H-7), 3.63 and 3.70 (s each, 6H, 2 X $OCH_3$), 3.90 (t, 2H, J 7 Hz, H-6), 5.17 (s, 1H, H-3), 6.66 and 7.30 (s each, 2H, H-8, H-11); (Found: C, 58.46; H, 5.05; N, 9.31. $C_{14}H_{14}N_2O_4.0.75H_2O$ requires C, 58.42; H, 5.42; N, 9.73).

Ethyl-3-imino-3-morpholino-propionate (9). Ethyl-3-imino-3-methoxy propionate hydrochloride (9.0 g, 0.05 mol) and morpholine (14.0 g, 0.16 mol) in methanol (25 ml) were left at room temperature for 14 hours. Excess of solvent was removed under reduced pressure and the excess of morpholine was dissolved in a minimum amount of water and treated with 30% NaOH (ice cold condition). The product was extracted with ethyl acetate. The organic layer was washed with water and dried over $Na_2SO_4$. Evaporation of the solvent under reduced pressure gave a mobile liquid. Trace impurities were removed by passage through an alumina column using ethyl acetate – pet. ether (7:3) as eluant, yield 5.46 g (55%); $^1H$ NMR ($CDCl_3$) : $\delta$ 1.26 (t, 3H, J 7 Hz), 3.23 (m, 4H), 3.70 (m, 4H), 4.06 (q, 2H, J 7 Hz), 4.06 (s, 2H); (Found : C, 54.01; H, 8.23; N, 13.75. $C_9H_{16}N_2O_3$ requires C, 53.98; H, 8.05; N, 13.99).

9,10-Dimethoxy-2-morpholino-6,7-dihydro-4H-pyrimido(2,1-a)isoquinolin-4-one (8).

Method i : A mixture of 2-Chloro-9,10-dimethoxy-6,7-dihydro-4H-pyrimido(2,1-a)isoquinolin-4-one (5a) (1.0 g, 0.003 mol) and an excess of morpholine (10 ml) were heated and stirred at 110-120°C for 24 hours. Excess of the morpholine was removed under reduced pressure, the residue was diluted with water and extracted with ethyl acetate. The organic layer was washed with water, dried ($Na_2SO_4$). The solvent was distilled off under reduced pressure, the product was crystallised from methanol, yield 0.70 g (60%), m.p. 244-246°C; IR : 1665 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) : $\delta$2.47 (t, 2H, J 7 Hz, H-7), 3.47 (m, 4H, $-CH_2-N-CH_2$), 3.57 (m, 4H, $-CH_2-O-CH_2$) 3.77 (s, 6H, 2 X $OCH_3$), 4.03 (t, 2H, J 7 Hz, H-6), 5.20 (s, 1H, H-3), 6.38 (s, 1H, H-8), 7.33 (s, 1H, H-11); (Found : C, 62.75; H, 5.83; N, 11.98. $C_{18}H_{21}N_3O_4$ requires C, 62.96; H, 6.16; N, 12.23).

Method ii : 6,7-Dimethoxy-1-methylthio-3,4-dihydroisoquinoline[11] (10, 41 mg, 1.7 mmol) and 9 (115 mg, 5.5 mmol) were heated together at 110°C for 1 hour. The reaction mixture was diluted

with water, extracted with ethyl acetate and washed with dil. HCl. The acidic portion was made basic and again extracted with ethyl acetate, washed with water, dried ($Na_2SO_4$) and the solvent removed under reduced pressure. The residue was chromatographed on alumina column using 2% methanol - chloroform as eluant. Evaporation of the eluant gave pure 8, yield 35 mg (50%). The compound was identical in all respects with 8 from method i.

9,10-Dimethoxy-2-isobutylamino-6,7-dihydro-4H-pyrimido(2,1-a)isoquinolin-4-one (11a). Compound 11a was synthesized through method i, yield 80%, mp of the hydrochloride 173-176°C. IR : 3125, 3030, 1695 and 1680 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) : $\delta$1.03 (d, 6H, J 6 Hz, $CH\underline{Me}_2$), 1.93 (m, 1H, $C\underline{H}Me_2$), 2.83 (m, 2H, $NHC\underline{H}_2$-$CHMe_2$), 3.08 (t, 2H, J 6 Hz, H-7), 3.50 (s, 3H, $OCH_3$), 3.93 (s, 3H, $OCH_3$), 4.10 (t, 2H, J 6 Hz, H-6), 5.03 (s, 1H, H-2), 6.53 (s, 1H, H-8), 8.06 (s, 1H, H-11), 8.33 (br, 1H, NH); (Found : C, 58.91; H, 6.01; N, 11.42; Cl, 9.38. $C_{18}H_{24}ClN_3O_3$ requires C, 59.25; H, 6.35; N, 11.51; Cl, 9.71).

9,10-Dimethoxy-2-(1,1-dimethylhydrazino)-6,7-dihydro-4H-pyrimido(2,1-a)isoquinolin-4-one (11b). The compound 11b was synthesized through method i, yield 37%, mp of the hydrochloride 188-192°C. IR : 1666 and 1639 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) : $\delta$2.81 (t, 2H, J 6 Hz, H-7), 3.0 (s, 6H, $NMe_2$), 3.80 (s, 6H, 2 X $OCH_3$), 4.05 (t, 2H, J 6 Hz, H-6), 5.10 (s, 1H, H-2), 6.43 (s, 1H, H-8), 7.46 (s, 1H, H-11); (Found : C, 54.22; H, 5.83; N, 15.67; Cl, 9.76. $C_{16}H_{21}ClN_4O_3$ requires C, 54.46; H, 5.99; N, 15.88; Cl, 10.04).

2-Amino-9,10-dimethoxy-6,7-dihydro-4H-pyrimido(2,1-a)isoquinolin-4-one (11c). The compound 11c was synthesized as described in method i, yield 77%, mp 273-274°C; IR : 3450, 3333, 1666 and 1639 $cm^{-1}$; $^1H$ NMR ($CDCl_3$ + DMSO-$d_6$) :$\delta$3.00(t, 2H, J 6 Hz, H-7),3.96 (bs, 6H, 2 X $OCH_3$), 4.25 (t, 2H, J 6 Hz, H-6), 5.30 (s, 1H, H-2), 6.13 (bs, 2H, $NH_2$), 6.93 (s, 1H, H-8), 7.80 (s, 1H, H-11); (Found : C, 61.47; H, 5.79; N, 15.61. $C_{14}H_{15}N_3O_3$ requires C, 61.52; H, 5.54; N, 15.37).

9,10-Dimethoxy-2-(4-methoxybenzylamino)6,7-dihydro-4H-pyrimido(2,1-a)isoquinolin-4-one (11d) Compound 11d was synthesized through method i, yield 49%, mp of the hydrochloride 163-166°C. IR : 1695 and 1680 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) : $\delta$2.86 (t, 2H, J 6 Hz, H-7), 3.77 and 3.88 (s each, 6H, 2 X $OCH_3$). 4.20 (t, 2H, J 6 Hz, H-6), 4.25 (d, 2H, J 5 Hz, NH-$C\underline{H}_2$), 5.26 (s, 1H, H-2), 5.26 (bs, 1H, NH), 6.62 (s, 1H, H-8), 6.77 (d, 2H, J 9 Hz, ArH-3',5'), 7.17 (d, 2H, J 9 Hz, ArH-2',6'), 7.63 (s, 1H, H-11); (Found : C, 60.77; H, 6.08; N, 9.60; Cl, 8.10. $C_{22}H_{24}ClN_3O_4$ requires C, 61.43; H, 5.64; N, 9.77; Cl, 8.25).

2-(N-Carbethoxyhydrazino)9,10-dimethoxy-6,7-dihydro-4H-pyrimido(2,1-a)isoquinolin-4-one (11e) The compound 11e was synthesized as described in method i, yield 81%, mp of hydrochloride 162-166°C. IR : 3279, 2989, 1754, 1686 and 1661 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) : $\delta$1.61 (t, 3H, J 7 Hz, $CH_2C\underline{H}_3$), 2.58 (bs, 1H, NH-NHCO), 2.93 (t, 2H, J 6 Hz, H-7), 3.93 (s, 6H, 2 X $OCH_3$), 4.13 (m, 4H, $C\underline{H}_2$-$CH_3$ and H-6), 5.56 (s, 1H, H-2), 6.63 (s, 1H, H-8), 7.43 (bs, 1H, NH-$N\underline{H}$CO), 7.63

(s, 1H, H-11); (Found : C, 51.86; H, 5.52; N, 14.26; Cl, 9.11. $C_{17}H_{21}ClN_4O_5$ requires C, 51.44; H, 5.34; N, 14.12; Cl, 8.93).

9,10-Dimethoxy-2-(phenylethylamino)-6,7-dihydro-4H-pyrimido(2,1-a)isoquinolin-4-one (11f). Compound 11f was synthesized as described in method i, yield 54%, mp of hydrochloride 174-175°C. IR : 3333, 1666 and 1639 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) : $\delta$2.91 (t, 4H, J 6 Hz, $PhCH_2$- and H-7), 3.38 (m, 2H, $NHCH_2$-$CH_2$), 3.90 (s, 6H, 2 X $OCH_3$), 4.20 (t, 2H, J 6 Hz, H-6), 4.86 (bs, 1H, NH), 5.26 (s, 1H, H-2), 6.60 (s, 1H, H-8), 7.16 (s, 5H, ArH), 7.60 (s, 1H, H-11); (Found : C, 63.56; H, 5.92; N, 10.52; N, 10.52; Cl, 8.22. $C_{22}H_{24}ClN_3O_3$ requires C, 63.83; H, 5.85; N, 10.15; Cl, 8.56).

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## REFERENCES AND NOTES

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