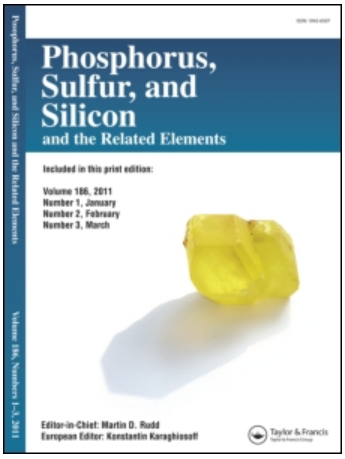

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SYNTHESIS OF SOME FUSED PYRIMIDOTETRAHYDROISOQUINOLINES

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SYNTHESIS OF SOME FUSED PYRIMIDOTETRAHYDROISOQUINOLINES*

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Treatment of 3-amino-2-methyl-1(2H)-5,6,7,8-tetrahydro-thioxoisoquinoline-4-carbonitrile(**2**) with formamide afforded pyrimidotetrahydroisoquinoline (**3**). When compound **2** was reacted with halo-compounds, *N*-alkylation occurred to give compounds **4–6**. Also, pyrimidotetrahydroisoquinolines (**8–11**) were obtained when oxazinotetrahydroisoquinoline (**7**) was treated with aminocompounds. Furthermore, base catalysed condensation of amine with aromatic aldehydes led to expected Schiff bases,[12] but additional reaction at the *N*-methyl group with formation of styryl compound **13** was observed when the reaction was carried out in acetic acid.

Key words: Tetrahydroisoquinolines; thioxoisoquinolines; pyrimidotetrahydroisoquinolines; oxazinotetrahydroisoquinolines, *N*-alkylation; Schiff bases.

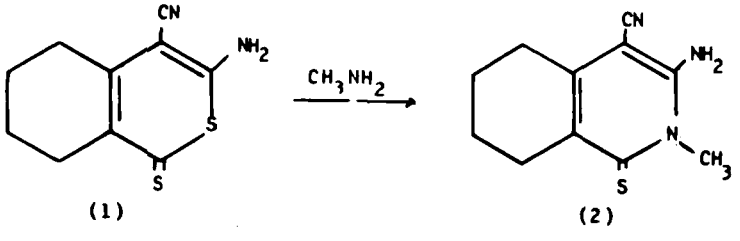
INTRODUCTION

The quinoline, isoquinoline and phenanthridine ring structures are important in medicinal plant alkaloides[1] and as a consequence have found application in chemotherapy. Thus the Cinchona alkaloids,[2] including cinchonine and quinine, useful for treatment of malaria, prompted the development of a range of antimalarials. Morphine and codeine, well known analgesics, and emetine, an antiamoebic,[3] can all be regarded as tetrahydroisoquinoline derivatives.

In the light of these biologically important application, we became interested in the synthesis of new tetrahydroisoquinolines.

RESULTS AND DISCUSSION

In the present study we used 5,6,7,8-tetrahydro-3-amino-2-methyl-1(2H) thioxoisoquinoline-4-carbonitrile[4a] (**2**) as the tetrahydroisoquinoline moiety containing starting material. This was prepared by the reaction of the corresponding thiopyranethione[4b] (**1**) with methylamine.



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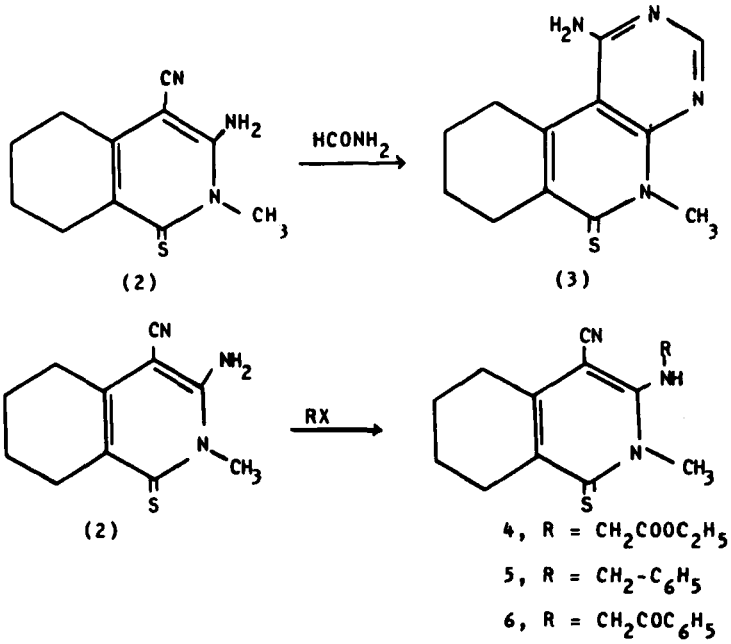
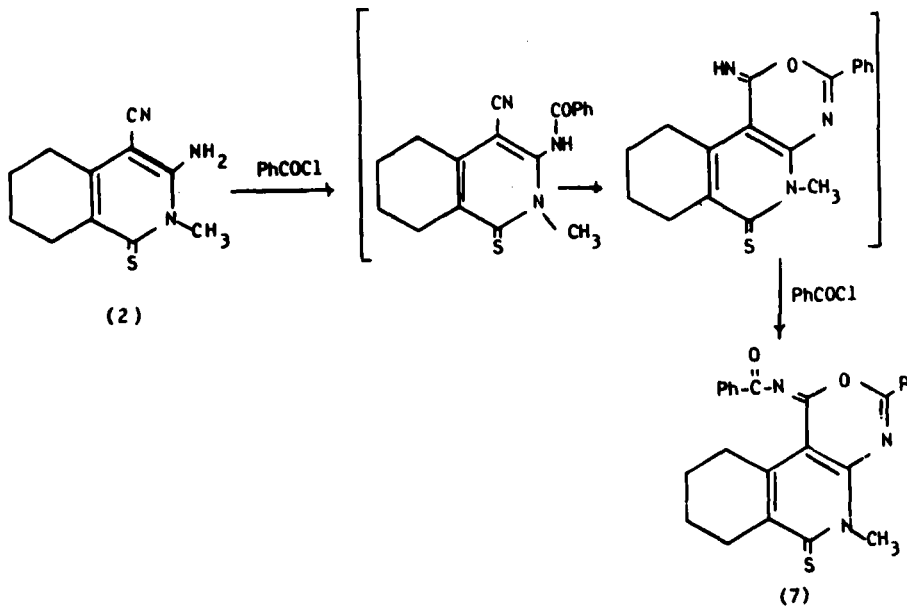
*Sixth European symposium on Organic Chemistry, Belgrade, Yugoslavia, September, 10, 1989.

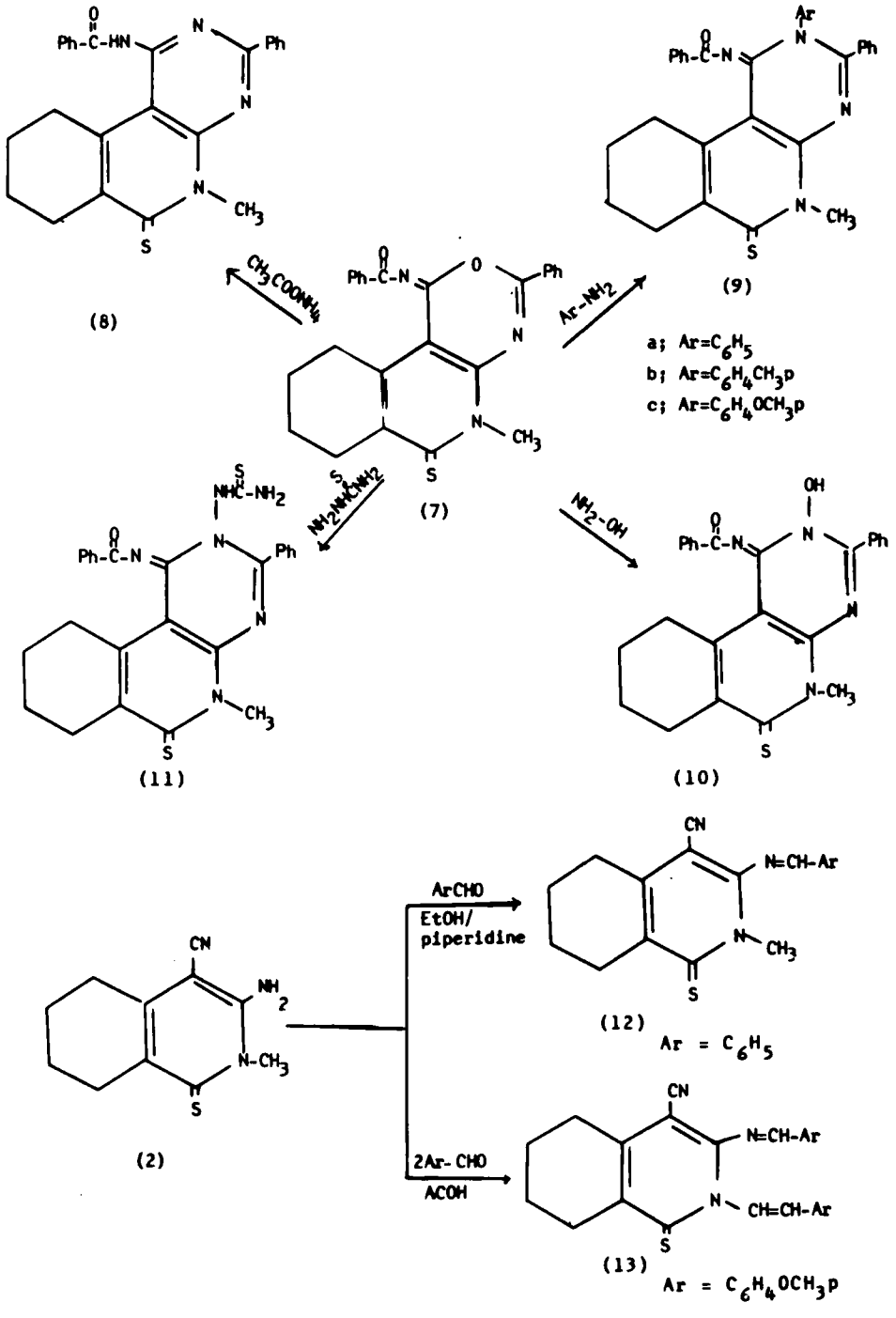


When compound (2) was refluxed with formamide the angular pyrimidotetrahydroisoquinoline (3) was obtained.

When compound (2) was treated with halo compounds such as ethyl chloroacetate, benzyl chloride or phenacyl bromide, the corresponding *N*-alkylated derivatives (4–6) were obtained.

However, benzoylation of amine (2) led to the formation of the corresponding angular oxazinotetrahydroisoquinoline (7). The reaction pathway is expected to proceed as follows:





The angular oxazinotetrahydroisoquinoline (7) reacts easily with ammonium or amino compounds, e.g., ammonium acetate, aromatic amines, hydroxylamine and thiosemicarbazide to give the corresponding pyrimidotetrahydroisoquinolines (**8–11**) in good yields (70–82%).

Finally, treatment compound (**2**) with aromatic aldehydes under basic conditions (piperidine in ethanol) gave the corresponding Schiff bases. But when the reaction was carried out in acetic acid additional condensation at the *N*-methyl group with formation of the styryl derivative (**13**) was observed.

EXPERIMENTAL

All chemicals used were reagent grade and were purified before use. Melting points were uncorrected and were determined on Kofler melting point apparatus. Elemental analysis was performed on Perkin-Elmer 240 E Microanalyzer. IR spectra were recorded on a Pye-Unicam infrared spectrophotometer using KBr wafer technique. NMR spectra were recorded on Varian 390 E 90 MHz spectrometer in the suitable deuterated solvent using TMS as internal standard. Mass spectra were determined on Dupont 21-492 B mass spectrometer at an ionizing potential 75 *eV*, ionizing current 300 μA, and source temperature 200°C.

3-Amino-1-thioxo-2(1H)-5,6,7,8-tetrahydro-benzothiopyran-4-carbonitrile (**1**): Prepared according to lit.,[4b] m.p. 270–2°C.

3-Amino-2-methyl-1(2H)-thioxo-5,6,7,8-tetrahydro-isoquinoline-4-carbonitrile (**2**): Prepared according to lit.,[4a] m.p. 243–5°C.

Anal. Calcd for: $C_{11}H_{13}N_3S$: C, 59.45; H, 5.85; N, 18.91; S, 14.41%.
Found: C, 59.87; H, 5.47; N, 18.98; S, 14.37%.

IR, at 3400, 3300 cm^{-1} (NH_2) and at 2220 cm^{-1} (C≡N). H^1 NMR in C_5D_5N at δ 2.6 (*t*, 2H, α CH_2), δ 2.95 (*t*, 2H, α CH_2) and δ 1.6 (*m*, 4H, 2β CH_2) of cyclohexane ring, δ 4.25 (*s*, 3H, N—CH_3) and at δ 8.5 (*s*, 2H, NH_2); MS: m/z = 219 (M^+).

1-Amino-5-methyl-7,8,9,10-tetrahydro-pyrimido[4,5-c]isoquinoline-6(5H)-thione (**3**): A mixture of compound (**2**) (2.2 g, 0.01 mol) and formamide (10 ml) was refluxed for 2 hours, then allowed to cool. The solid product was filtered off and recrystallized from acetic acid to give greenish yellow needles of compound (**3**) in 80% yield, m.p. 290°C.

Anal. Calcd. for: $C_{12}H_{14}N_4S$: C, 58.53; H, 5.69; N 22.76; S, 13.00%.
Found: C, 58.23; H, 5.54; N, 22.87; S, 13.33%.

IR, at 3450, 3300 cm^{-1} 2NH and at 2225 cm^{-1} (C≡N). H^1NMR in C_5D_5N, at δ 3.0 (*m*, 4H, 2α CH_2), and δ 1.6 (*m*, 4H, 2β CH_2) of cyclohexane ring, δ 4.4 (*s*, 3H, N—CH_3), and at δ 8.1, 8.5 (2*s*, 2H 2NH), MS: m/z = 246 (M^+).

3-Ethoxycarbonylmethylamino-2-methyl-1(2H)-thioxo-5,6,7,8-tetrahydro-isoquinoline-4-carbonitrile (**4**): Chloroacetate (2.2 g, 0.01 mol) was refluxed for 4 hours, then allowed to cool. The solid product was filtered off and recrystallized from ethanol to give white crystals of compound (**4**) in 70% yield, m.p. 165–7°C.

Anal. Calcd. for: $C_{15}H_{19}N_3O_2S$: C, 59.01; H, 6.22; N, 13.77; S, 10.49%.
Found: C, 59.35; H, 6.11; N, 13.52; S, 10.72%.

IR, at 3390 cm^{-1} (NH), 2220 cm^{-1} (C≡N), 1735 cm^{-1} (C=O). H^1NMR in $CDCl_3$, at δ (*t*, 3H, CH_3 ester) δ 4.15 (*q*, 2H, CH_2 ester), δ 2.15 (*m*, 2H, α CH_2), δ 2.65 (*m*, 2H, α CH_2), and at δ 1.7 (*m*, 4H, 2β CH_2) of cyclohexane ring, δ 3.0 (*s*, 2H, N—CH_2), δ 3.9 (*s*, 3H, N—CH_3) and at δ 4.6 (*s*, 1H, NH), MS: m/z = 305 (M^+).

3-Benzylamino-2-methyl-1(2H) thioxo-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (**5**): A mixture of compound (**2**) (2.2 g, 0.01 mol) and benzyl chloride (5 ml) was refluxed for 2 hours, then allowed to cool. The reaction product was triturated with pet. ether for several times, then separated by filtration and recrystallized from ethanol to give yellow crystals of compound (**5**) in 68% yield, m.p. 155–7°C.

Anal. Calcd. for: $C_{18}H_{19}N_3S$: C, 69.90; H, 8.79; N, 13.59; S, 10.53%.
Found: C, 70.22; H, 8.85; N, 13.37; S, 10.12%.

IR, at 3390 cm^{-1} (NH), and at 2220 cm^{-1} (C=N). H^1NMR in $CDCl_3$, at δ 2.7 (*m*, 4H, 2α CH_2) and at δ 1.85 (*m*, 4H, 2α CH_2) and at δ 1.85 (*m*, 4H, 2β CH_2) of cyclohexane ring, δ 4.3 (*s*, 3H, N—CH_3), δ 4.65 (*s*, 2H, N—CH_2), δ 5.3 (*s*, 1H, NH), and at δ 7.15 (*m*, 5H, C_6H_5).

2-Methyl-3-phenacylamino-1(2H)-thioxo-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (**6**): A mixture of compound (**2**) (2.2 g, 0.01 mol) and phenacyl bromide (2 g, 0.01 mol) in 30 ml ethanol was refluxed for 6 hours on a water bath, then allowed to cool and poured into water. The solid product was separated by filtration and recrystallized from ethanol to give yellowish brown crystals of compound (**6**) in 65% yield, m.p. 185°C.

Anal. Calcd. for: $C_{19}H_{19}N_3OS$: C, 67.65; H, 5.63; N, 12.46; S, 9.49%.
Found: C, 67.93; H, 5.88; N, 12.13; S, 9.18%.

IR, at 3400 cm^{-1} (NH), 2220 cm^{-1} (C═N), and at 1730 cm^{-1} (C═O).
H^1NMR in $CDCl_3$, at δ 2.15 (*m*, 2H, α CH_2), δ 2.5 (*m*, 2H, α CH_2), and at δ 1.75 (*m*, 4H, 2β CH_2) of cyclohexane ring, δ 2.7 (*s*, 2H, N—CH_2), δ 4.2 (*s*, 3H, N—CH_3), and at δ 7.7 (*m*, 5H, C_6H_5).

*1-Benzoylimino-5-methyl-3-phenyl-1H-[1,3]-7,8,9,10=tetrahydrooxazino[4,3-c]*isoquinoline-6(5H)-thione (**7**): A mixture of compound (**2**) (2.2 g, 0.01 mol) and benzoyl chloride (5 ml) was refluxed for 1 hour, then allowed to cool, and treated with pet. ether (50 ml). Pet. ether was decanted, and the solid product was triturated with pet. ether for several times and then recrystallized from ethanol to give orange crystals of compound (**7**) in 75% yield, m.p. 265°C.

Anal. Calcd. for: $C_{25}H_{21}N_3O_2S$: C, 70.25; H, 4.91; N, 9.83; S, 7.49%.
Found: C, 70.22; H, 5.15; N, 10.02; S, 7.52%.

IR, at 1700 cm^{-1} (C═O), also revealed the disappearance of bands characteristic of (NH_2) and (C═N) groups.
H^1NMR in $CDCl_3$, at δ 2.73 (*m*, 2H, α CH_2), δ 3.15 (*m*, 2H, α CH_2), and at δ 1.75 (*m*, 4H, 2β CH_2) of cyclohexane ring, δ 4.3 (*s*, 3H, N CH_3) and at δ 7.2–8.2 (*m*, 10H, $2C_6H_5$), MS: m/z = 427 (M^+).

1-Benzoylamino-5-methyl-3-phenyl-7,8,9,10-tetrahydro-pyrimido-[4,5-c]-isoquinoline-6(5H)-thione (**8**): A mixture of compound (**7**) (2.1 g, 0.005 mol) and ammonium acetate (3.85 g, 0.05 mol) in acetic acid (20 ml) was refluxed for 5 hours, then allowed to cool and poured into water. The solid product was filtered off and recrystallized from acetic acid to give yellow crystals of compound (**8**) in 82% yield, m.p. 25°C.

Anal. Calcd. for: $C_{25}H_{22}NOS$: C, 70.42; H, 5.16; N, 13.14; S, 7.51%.
Found: C, 70.50; H, 5.32; N, 13.08; S, 7.38%.
MS: m/z = 426 (M^+).

2-Aryl-1-benzoylimino-5-methyl-3-phenyl-7,8,9,10-tetrahydropyrimido[4,5-c]-isoquinoline-6(5H)-thiones (**9a–c**):

General procedure
A mixture of compound (**7**) (2.1 g, 0.005 mol) and aromatic amine (0.005 mol) in ethanol was refluxed for 6 hours, then allowed to cool. The solid product was filtered off and recrystallized from acetic acid to give yellow crystals of the compounds (**9a–c**).

(**9a**), Ar = C_6H_5, produced in 78% yield, m.p. 255–7°C.
Anal. Calcd. for: $C_{31}H_{26}N_4OS$: C, 74.10; H, 5.17; N, 11.50; S, 6.37%.
Found: 73.92; H, 5.32; N, 11.28; S, 6.22%.

IR, at 1700 cm^{-1} (C═O).
H^1NMR in $CDCl_3$, at δ 2.95 (*m*, 4H, 2α CH_2) and at δ 1.85 (*m*, 4H, 2β CH_2) of cyclohexane ring, δ 4.3 (*s*, 3H, N—CH_3) and at δ 7.2–8.2 (*m*, 15H, 3 C_6H_5).

(**9b**), Ar = $C_6H_4CH_3$-*p*, produced in 82% yield, m.p. 208°C.
Anal. Calcd. for: $C_{32}H_{28}N_4OS$: C, 74.41; H, 5.42; N, 10.85; S, 6.20%.
Found: C, 74.85; H, 5.43; N, 11.08; S, 6.32%.

IR, at 1700 cm^{-1} (C═O).

(**9c**), Ar = $C_6H_4OCH_3$-*p*, produced in 75% yield, m.p. 25°C.
Anal. Calcd. for: $C_{32}H_{28}N_4O_2S$: C, 72.18; H, 5.26; N, 10.52; S, 6.01%.
Found: C, 72.01; H, 5.32; N, 10.72; S, 6.27%.

IR, at 1700 cm^{-1} (C═O).

*1-Benzoylimino-2-hydroxy-5-methyl-3-phenyl-7,8,9,10-tetrahydropyrimido[4,5-c]*isoquinoline-6(5H)-thione (**10**): A mixture of compound (**7**) (2.1 g, 0.005 mol), hydroxylamine hydrochloride (2 g) and a solution

of sodium acetate (2 g in 2 ml H_2O) in 30 ml ethanol was refluxed for 5 hours, then allowed to cool, and poured into water. The solid product was filtered off and recrystallized from ethanol to give yellow crystals of compound (**10**) in 70% yield, m.p. 190°C.

Anal. Calcd. for: $C_{25}H_{22}N_4O_2S$: C, 67.87; H, 4.97; N, 12.66; S, 7.23%.
Found: C, 68.08; H, 5.15; N, 12.52; S, 7.11%.

IR, at 3400 cm^{-1} (OH), and at 1680 cm^{-1} (C=O).
H¹NMR in $CDCl_3$, at δ 2.95 (*m*, 4H, 2α CH_2) and at δ 1.85 (*m*, 4H, 2α CH_2) and at δ 1.85 (*m*, 4H, 2β CH_2) of cyclohexane ring, δ 4.3 (*s*, N—CH_3), and at δ 7.2–8.2 (*m*, 10H, 2 C_6H_5).

*1-Benzoylimino-5-methyl-3-phenyl-7,8,9,10-tetrahydro-2-thiouridopyrimido[4,5-c]*isoquinoline-6(5H)-thione (**11**): A mixture of compound (**7**) (2.1 g, 0.005 mol) and thiosemicarbazide (0.5 g, 0.005 mol) in ethanol (30 ml) was refluxed for 6 hours, and allowed to cool. The solid product was filtered off and recrystallized from ethanol to give yellow crystals of compound (**11**) in 78% yield, m.p. 255–7°C.

Anal. Calcd. for: $C_{26}H_{24}N_6OS_2$: C, 62.40; H, 4.80; N, 16.80; S, 12.80%.
Found: C, 62.52; H, 4.96; N, 16.57; S, 12.62%.

IR, 3500–3350 cm^{-1} (NH_2, NH) and 1700 cm^{-1} (C=O)

3-Benzylideneamino-2-methyl-1(2H)-thioxo-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (**12**): A mixture of compound (**2**) (2.2 g, 0.01 mol) and benzaldehyde (1.06 g, 0.01 mol) in ethanol was refluxed in presence of few drops of piperidine for 8 hours, then allowed to cool. The solid product was filtered off and recrystallized from acetic acid to give yellow crystals of compound (**12**) in 70% yield, m.p. > 300°C.

Anal. Calcd. for: $C_{18}H_{17}N_3S$: C, 70.53; H, 5.53; N, 13.68; S, 10.42%.
Found: C, 70.52; H, 5.69; N, 13.54; S, 10.38%

IR, at 2220 cm^{-1} (C≡N), 1620 cm^{-1} (C=N) and revealed the disappearance of bands characteristic of (NH_2) group.
H¹NMR in $CDCl_3$, at δ 2.9 (*m*, 4, 2α CH_2) and at δ 1.8 (*m*, 4H, 2β CH_2) of cyclohexane ring, δ 4.0 (*s*, 3H N—CH_3), δ 7.3 (*m*, 3H, C_6H_5), δ 7.8 (*m*, 2H, C_6H_5) and at δ 8.6 (*s*, 1H, —CH=N—).

3-(4-Methoxybenzylidine-amino)-2-(4-methoxystyryl)-1(2H)-thioxo-5,6,7,8-tetrahydro-isoquinoline-4-carbonitrile (**13**): A mixture of compound (**2**) (2.2 g, 0.01 mol) and *p*-anisaldehyde (2.72 g, 0.02 mol) in acetic acid was refluxed for 6 hours and allowed to cool. The solid product was filtered off and recrystallized from acetic acid to give yellow crystals of compound (**13**) in 80% yield, m.p. 255–7°C.

Anal. Calcd. for: $C_{27}H_{25}N_3O_2S$: C, 71.20; H, 5.49; N, 9.23, S, 7.03%.
Found: C, 71.42; H, 5.56; N, 9.10; S, 7.00%.

IR, at 2220 cm^{-1} (C≡N) 1630 cm^{-1} (C=N) and revealed the disappearance of bands characteristic of (NH_2) group. H¹NMR in $CDCl_3$, at δ 2.7 (*m*, 4H, 2α CH_2) and at δ 1.8 (*m*, 4H, 2β CH_2) of cyclohexane ring, δ 3.8, 3.9 (2*s*, 6H, 2OCH_3), δ 5.8 (2*d*, 2H, CH=CH), δ 7.3 (*m*, 8H, Ar—H) and at δ 8.7 (*s*, 1H, CH=N—).

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