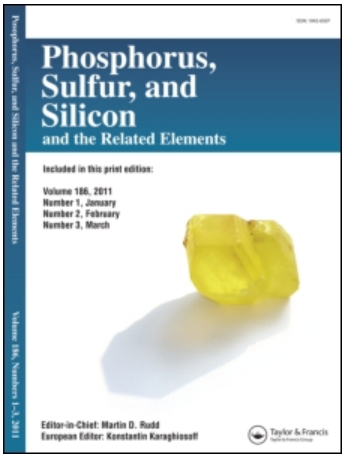

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SYNTHESIS AND REACTIONS OF SOME ISOQUINOLINE DERIVATIVES

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SYNTHESIS AND REACTIONS OF SOME ISOQUINOLINE DERIVATIVES

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Treatment of 3,4-tetramethylene-6-amino-5-cyano-thiopyran-2(1H)thione (**1**) with alkali followed by acidification with HCl afforded 1,2,5,6,7,8-hexahydro-4-cyano-3(2H)-oxoisoquinoline-1-thiol (**2**). When compound (**1**) was reacted with excess alkyl halides the corresponding O- and S-alkylated isoquinolines (**3**) were obtained. Also, α-chloroacetic acid and β-bromopropionic acid reacted with compound (**2**) to produce thiazolo and thiazinoisoquinolines (**4**) and (**5**). Furthermore, the reaction of (**2**) with one mole of phenacylbromide produced-S-phenacyl derivatives (**6**), which cyclized to give the corresponding thiazoloisoquinoline (**7**). However two moles of phenacyl bromides gave the corresponding S- and O-phenacyl derivatives (**8**). The later compounds were cyclized to give furoisoquinoline derivative (**9**).

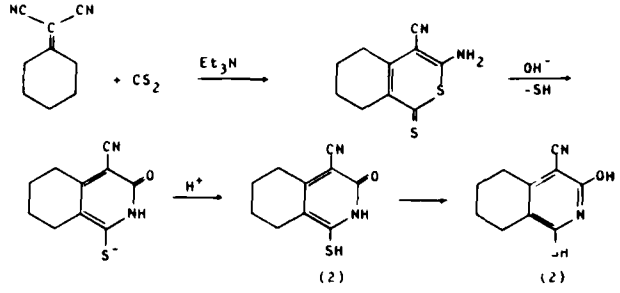
Key words: Thiopyranthione; cyclohexylidene malonitrile-, isoquinoline derivatives.

Isoquinoline derivatives were reported[1–4] to act as inhibitors of the enzyme phenylethanolamine-*N*-methyltransferase (PNMT). PNMT catalyzes the final step in the biosynthesis of epimephrine, effecting the transfer of methyl group from S-adenosylmethionine to the terminal nitrogen of norepinephrine. These compounds are of biological interest as potential therapeutic agents for disorders where specific control of adrenal epinephrine production might be beneficial.[5]

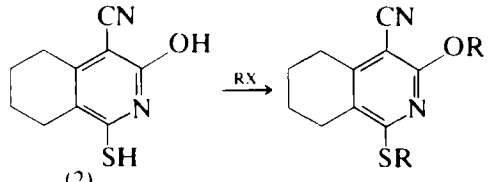
Considering the foregoing benefits we aimed to synthesize isoquinoline thiol as a starting material, then subjecting it to the reaction of different reagents to get some new heterocyclic compounds containing the isoquinoline moiety.

RESULTS AND DISCUSSION

Treatment of cyclohexanone with malononitrile and CS_2 afforded 3,4-tetramethylene-6-amino-5-cyano-2(1H)-thiopyranethione(**1**). When (**1**) was subjected to the effect of alkali followed by acidification, the corresponding tetrahydro isoquinoline thiol (**2**) was obtained. When compound (**2**) was treated



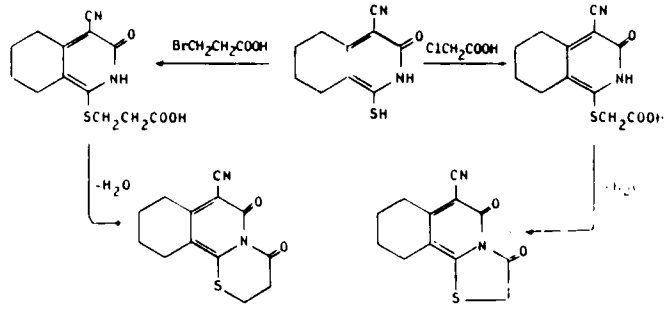
with methyl and/or ethyl iodide, alkylation occurred at both oxygen and sulphur and the dialkyl derivatives (**3a–b**) were obtained



(2)

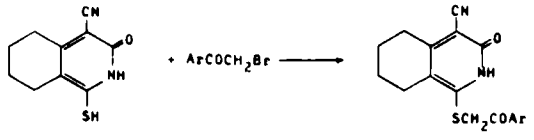
3a, R = CH_3
3b, R = CH_3CH_2

Beside its easy alkylation, compound (**2**) was considered as a versatile intermediate for building up a third angular ring to produce some interesting tricyclic compounds. Thus, when (**2**) was treated with chloroacetic and/or β-bromopropionic acid in refluxing ethanol and sodium acetate, 2,3,7,8,9,10-hexahydro-3,5-dioxo-5H-thiazolo[2,3-a]-isoquinoline-6-carbonitrile(**4**), and 3,4,8,9,10,11-hexahydro-4,6-dioxo-2H,6H[1,3]thiazino[2,3-a]isoquinoline-7-carbonitrile(**5**) were obtained respectively. The reaction pathway is expected to proceed as follows:



(5) (4)

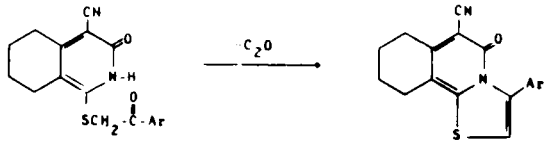
The formation of compounds (**4**) and (**5**) indicates that compound (**2**) is preferentially S-alkylated than O-alkylated if there is enough alkylating agent. Evidence in support of this behavior comes from the reaction of compound (**2**) with phenacyl bromide derivatives. Thus when compound (**2**) was treated with one mole of phenacyl bromide derivatives, the S-alkylation product, 2,3,5,6,7,8-hexahydro-1-aroylmethylthio-3-oxoisoquinoline-4-carbonitrile(**6a–c**) were obtained.



(6) a; Ar=C_6H_5
b; Ar=C_6H_4Cl
c; Ar=C_6H_4Br

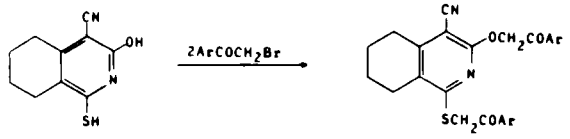
The produced compound (**6a**) was readily dehydrated upon treatment with acetic anhydride or heating over its melting point to give the corresponding

thiazoloisoquinoline derivatives (7) as follows:



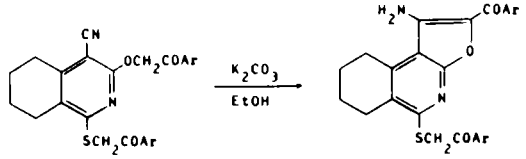
(6) (7)

However when compound (**2**) was reacted with two moles of phenacyl bromide, both S- and O-alkylation occurred and the corresponding dialkylation products (**8a–c**) were obtained.



(8) a; Ar=C_6H_5
b; Ar=C_6H_4ClP
c; Ar=C_6H_4BrP

O-alkylation of (**2**) was confirmed by refluxing an ethanol solution of compound (8a) in presence of K_2CO_3 where cycloaddition on the cyano group has occurred to produce the corresponding furoisoquinoline (**9**).



(9); Ar=C_6H_5

EXPERIMENTAL

All chemicals used were reagent grade and were purified prior to use. Melting points were determined on kofler melting point apparatus and are uncorrected. Elemental analysis was performed on Perkin–Elmer 240E Microanalyzer. IR spectra were recorded on a Pye-Unicam infrared spectrophotometer using KBr wafer technique. NMR spectra were recorded on NT-200 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.

3,4-Tetramethylene-6-amino-5-cyano-2(1H)thiopyranethione(**1**). To a mixture of 6.6 gm (0.1 mole)-malononitrile, 10 ml cyclohexanone (0.1 mole), 20 ml carbondisulphide, 30 ml methanol, and 5 ml dimethylformamide, 6 ml of triethylamine was added dropwise. The mixture was stirred at room temperature until the product starts to precipitate. The reaction mixture was allowed to stand for 24 hours. The solid product was then filtered off, washed well with alcohol and recrystallized from propanol, m.p. 270–2°C, Lit 272°C.[6]

Anal. Cacd: $C_{10}H_{10}N_2S_2$: C, 54.05; H, 4.50; N; 12.61; S, 28.82%. Found: C, 54.45; H, 4.22; N, 12.32; S, 28.93%.

2,3,5,6,7,8-Hexahydro-4-cyano-3-oxoisoquinoline-1-thiol(**2**). A sample of compound(**1**) (2.2 gm, 0.01 mole) was refluxed with 50 ml 1N NaOH for 4 hours, then the reaction mixture was allowed to

cool and acidified with conc. HCl, the solid product was separated by filtration, washed well with water and recrystallized from benzene-ethanol mixture to give white crystals of compound(**2**) in 80% yield, m.p. > 300°C.

Anal. Calcd: $C_{10}H_{10}N_2OS$: C, 58.25; H, 4.85; N, 13.59; S, 15.53% Found: C, 58.38; H, 5.02; N, 13.38; S, 15.42%. IR, at 3120 cm^{-1} (NH), 2500–2400 cm^{-1} (SH), 2220 cm^{-1} (C≡N) and at 1700–1650 cm^{-1} (C=O).

H^1 NMR in DMSO-d_6 at δ 1.3–1.8 (m, 4H, 2βCH_2) and δ 2.3–2.6 (m, 4H, 2αCH_2) of cyclohexane ring, δ 4.7 proad peak (1H, SH) and 7.4 (s, 1H, NH), MS: m/z = 206 (M^+).

5,6,7,8-Tetrahydro-3-alkoxy-1-alkylthioisoquinoline-4-carbonitrile(**3**). General procedure: A mixture of compound(**2**) (2 gm, 0.01 mole) alkyliodide (0.02 mole) and sodium acetate (2.00 gm) in 30 ml ethanol was refluxed for 4 hours, then allowed to cool, and poured into water. The solid product was filtered off and recrystallized from ethanol to give compounds (3_a) and (3_b).

3a, R = CH_3, produced in 70% yield m.p. 93–94°C.

Anal. Calcd.: $C_{12}H_{14}N_2OS$: C, 61.53; H, 5.98; N, 11.96; S, 13.67%. Found: C, 61.64; H, 6.21; N, 11.87; S, 13.57%. H^1 NMR in $CDCl_3$ at δ 1.4–18 (m) (4H, 2βCH_2), δ 2.2–2.4 (m, 2H, αCH_2) and 2.7–2.9 (m, 2H, αCH_2) of cyclohexane) at 2.5 (s, 3H, SCH_3) and at 3.9 (s, 3H, OCH_3). MS: m/z = 234(M^+).

3b, R = C_2H_6 produced in 65% yield, m.p. 262°C.

Anal. Calcd.: $C_{14}H_{18}N_2OS$: C, 64.12; H, 6.8; N, 10.68; S, 12.21%. Found: C, 64.32; H, 7.02; N, 10.58; S, 12.00%.

2,3,7,8,9,10-Hexahydro-3,5-dioxo-5H-thiazolo[2,3-a]isoquinoline-6-carbonitrile(**4**). A mixture of compound(**2**) (2 gm, 0.01 mole), chloroacetic acid (1 gm, 0.01 mole) and fused sodium acetate (1.7 gm, 0.02 mole) in 30 ml ethanol was refluxed for 12 hours, then the reaction mixture was allowed to cool and poured into water. The solid product was filtered off and recrystallized from ethanol to give white crystals of (**4**) in 87% yield m.p. 198–200°C.

Anal. Calcd.: $C_{12}H_{10}N_2O_2S$: C, 58.78; H, 4.06; N, 11.38; S, 13.00%. Found: C, 58.78; H, 4.18; N, 11.22; S, 12.96%. IR, at 2220 cm^{-1} (CN), 1720 cm^{-1} (C=O) and at 1660 cm^{-1} (C=O) H^1 NMR in DMSO-d_6, at δ 1.5–1.9 (m, 4H, 2βCH_2), δ 2.1–2.3 (m, 2H, αCH_2), and 2.6–2.8 (m, 2H, αCH_2) of cyclohexane and at 4.00 (s, 2H, CH_2) of thiazol ring. MS: m/z = 246(M^+).

3,4,8,9,10,11-Hexahydro-4,6-dioxo-2H,6H[1,3]*thiazino*[2,3-*a*]-*7-carbonitrile*(**5**). A mixture of compound(**2**) (2 gm, 0.01 mole), β-bromopropionic acid (1.5 gm, 0.01 mole) and fused sodium acetate (1.7 gm, 0.02 mole) in 30 ml ethanol was refluxed for 12 hours, then the reaction mixture was allowed to cool and poured into water. The solid product was separated by filtration and recrystallized from ethanol to give white crystals of compound(5) in 70% yield, m.p. 226–28°C.

Anal. Calcd.: $C_{13}H_{12}N_2O_2S$: C, 60.00; H, 4.61; N, 10.72; S, 12.30%. Found: C, 60.28; H, 4.81; N, 10.59; S, 12.28%. IR, 2220 cm^{-1} (C≡N), 1720 cm^{-1} (C=O), and 1670 cm^{-1} (C=O). MS: m/z = 260(M^+).

2,3,5,6,7,8-Hexahydro-1-aroylmethylthio-3-oxoisoquinoline-4-carbonitrile(**6**). General procedure: A mixture of compound(**2**) (2 gm, 0.01 mole) and phenacyl bromide or any of its derivatives in 30 ml ethanol was refluxed for 4 hours, then the reaction mixture was allowed to cool. The solid product was filtered off and recrystallized from ethanol to produce compounds (**6a–c**).

6a, Ar=C_6H_5 produced in 78% yield, m.p. 160°C.

Anal. Calcd.: $C_{18}H_{16}N_2O_2S$: 66.66; H, 4.93; N, 8.64; S, 9.87%. Found: C, 66.88; H, 5.08; N, 8.52; S, 9.96%. IR, at 3430 cm^{-1} (NH), 2200 cm^{-1} (C≡N), and 1700–1650 cm^{-1} (C=O) H^1 NMR in $CDCl_3$ at δ 1.5–1.8 (m, 4H, 2βCH_2), δ 2.2–2.4 (m, 2H, αCH_2), δ 2.7–2.9 (m, 2H, αCH_2) of cyclohexane, δ 4.5 (s, 2H, S-CH_2), δ 7.5 (s, 1H, NH) and δ 6.9–7.4, (m, 5H, Ar–H). MS: m/z = 324(M^+).

6b, Ar=C_6H_4Cl produced in 70% yield, m.p. 233–35°C.

Anal. Calcd.: $C_{18}H_{15}ClNO_2S$: C, 60.25; H, 4.18; Cl, 9.90; N, 7.81; S, 8.92%. Found: C, 60.38; H, 4.33; Cl, 9.87; N, 7.62; S, 9.12%.

6c, Ar=C_6H_4Br, produced in 50% yield, m.p. 180°C).

Anal. Calcd.: $C_{18}H_{15}BrN_2O_2S$: C, 53.59; H, 3.72; Br, 19.85; N, 6.94; S, 7.94%.
Found: C, 53.72; H, 3.18; Br, 19.75. N, 6.87; S, 8.08%.

7,8,9,10-Tetrahydro-5-oxo-3-phenyl-5H-thiazolo[2,3-a]isoquinoline-6-carbonitrile(**7**). A sample of **6a** was heated over its melting point for 1 hour, then allowed to cool, ethanol (30 ml) was added and refluxed for 2 hours. The solid product was separated by filtration and recrystallized from acetic acid to give pale yellow crystals of compound(**7**) in 70% yield, m.p. 185°C.

Anal. Calcd.: $C_{18}H_{14}N_2OS$: C, 70.58; H, 4.57; N, 9.15; S, 10.45%. Found: C, 70.34; H, 4.52; N, 9.22; S, 10.18%. IR, 2200 cm^{-1} (C≡N), 1670 cm^{-1} (C=O).

5,6,7,8-Tetrahydro-3-aroylmethoxy-1-aroylmethylthioisoquinoline-4-carbonitrile(**8**). General procedure: A mixture of compound(**2**) (2 gm, 0.01 mole), phenacyl bromide or any of its derivatives (0.02 mole) and fused sodium acetate (0.02 mole) was refluxed in 30 ml ethanol for 6 hours, the solid product was filtered off washed well with water and recrystallized from ethanol to produce compounds **8a–c**.

8a Ar=C_6H_5 produced in 70% yield, m.p. 213–15°C.

Anal. Calcd.: $C_{26}H_{22}N_2O_3S$: C, 70.58; H, 4.97; N, 6.33; S, 7.23%. Found: C, 70.82; H, 4.89; N, 6.12; S, 7.54%. IR at 220 cm^{-1} (C≡N), 1720 cm^{-1} and at 1690 cm^{-1} (2CO).

H^1 NMR in $CDCl_3$ at δ 1.5–1.8 (m, 4H, $2\beta CH_2$), δ 2.2–2.4 (m, 2H, αCH_2) and δ 2.6–2.8(m, 2H, αCH_2) of cyclohexane ring, δ 4.3 (s, 2H, SCH_2), 5.4 (s, 2H, OCH_2) and δ 7–7.5 (m) (10H, ArH). MS: m/z = 442(M^+).

8b, Ar=C_6H_4Cl produced in 70% yield, m.p. 185–87°C.

Anal. Calcd.: $C_{26}H_{20}Cl_2N_2O_3S$: C, 61.17; H, 3.92; Cl, 13.72; N, 5.49; S, 6.27%. Found: C, 61.33; H, 4.08, Cl, 13.58, N, 5.62, S, 6.34%.

8c, Ar=C_6H_4Br, produced in 65% yield, m.p. > 300°C.

Anal. Calcd.: $C_{26}H_{20}Br_2N_2O_3S$: C, 52.00; H, 3.33; Br, 26.66; N, 4.66; S, 5.33%. Found: C, 52.28; H, 3.52; Br, 26.48; N, 4.48; S, 5.22%.

4,5,6,7-Tetrahydro-8-amino-3-benzoylmethylthio-9-benzoylfuro[2,3-b]isoquinoline(**9**). A mixture of **8a** (0.9 gm, 0.002 mole) and potassium carbonate (2 gm) in 30 ml ethanol was refluxed for 8 hours then allowed to cool and poured into water. The solid product was filtered off and recrystallized from ethanol as yellow crystals in 70% yield m.p. 248–50°C.

Anal. Calcd.: $C_{26}H_{22}N_2O_3S$: C, 70.58; H, 4.97; N, 6.33; S, 7.23%. Found: C, 70.83; H, 5.18; N, 6.12; S, 7.08%.

IR, 3300, 3200 cm^{-1} (NH_2), 1680 cm^{-1} (CO).

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