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SYNTHESIS OF SOME THIENOQUINOLINE DERIVATIVES WITH EXPECTED PHARMACOLOGICAL ACTIVITY

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SUMMARY

Synthesis of some carboxamido-, hydrazido-, 1,3,4- oxadiazolino- semicarbazido-, pyrazolo-, pyrazolino-, and imidobenzamido- derivatives of 2- (7-methylthieno [2,3-b] quinoline) was described.

INTRODUCTION

It was of great interest to synthesize some thienoquinoline derivatives especially incorporated to pyrazole, pyrazoline, 1, 3, 4- oxadiazole, and 1, 2, 4- triazole moieties since some 1, 3, 4- oxadiazoles and pyrazoles were reported to exhibit antiinflamatory[1–3], antibacterial[4,5], anticonvulsant[6], and CNS depressing activities[7,8]. Also some 1, 2, 4- triazoles have significant activity against murine leukemia, while several others were found to be active against transplanted animal tumors[9].

Certain quinoline derivatives were also found active as amoebicides[10] antimalarial[11], and antibacterial agents[12]. Also, certain derivatives of hydrazone were reported to possess antitubercular and antiamoebic activities[10–13].

2–Ethoxycarbonyl-7-methylthieno [2, 3-b] quinoline (Ia) was prepared by adopting a known procedure[14] from the reaction of 2-chloro-3-formyl-7-methylquinoline with ethylthioglycolate in ethanol.

Amide derivatives (Ib, c) were produced by refluxing the ester Ia and ammonia solution or methylamine in ethanol. The key compound, the acid hydrazide, (II) was prepared through the reaction of the ester Ia and hydrazine hydrate in refluxing ethanol for 6 h., or by stirring the previous amounts in DMF at 50 °C for 2h., its structure was confirmed by correct microanalytical data and IR spectroscopy.

Treating the acid hydrazide II with the appropriate carbonyl compounds namely in ethanol at reflux temperature afforded the correspon-

ding hydrazones IIIa-d. The synthesis of 2- (2-aryl-3-acetyl-1, 3, 4-oxadiazolinyl)-7-methylthieno [2, 3-b] quinolines IVa-c was achieved by cyclization of the respective acylhydrazides IIIa-c with excess acetic anhydride.

The semicarbazide derivatives Va, b were produced from the reaction of isopropyl- and n-butyl- isocyanates with the hydrazide II.

When the hydrazide II was condensed with β-dicarbonyl reagents, namely, acetylacetone and ethyl acetoacetate 1-[2-carbo-7-methylthieno(2, 3-b)quinolino]3, 5-dimethylpyrazole VI and 1-(2-carbo-7-methylthieno(2, 3-b)quinolino]-3-methyl-3-pyrazolin-5-one VII "were obtained respectively."

In continuation of this work, we studied the action of saturated or unsaturated acid anhydrides on II, which when treated with succinic or phthalic anhydriedes in glacial acetic acid afforded the corresponding imido-derivatives VIIIa, b. The structure of all compounds were inferred from the analytical data and spectral features.

EXPERIMENTAL

The IR spectra were obtained (KBr) on a Pye Unicam Sp 1000 spectrophotometer. The ^{1}H NMR spectra were measured on a Vari. n EM 390 90 MHz in DMSO using TMS as internal standared and chemical shifts are expressed as δ ppm. Melting points are uncorrected. Microanalysis were performed by Microanalytical Lab. N.R.c. Cairo, Egypt.

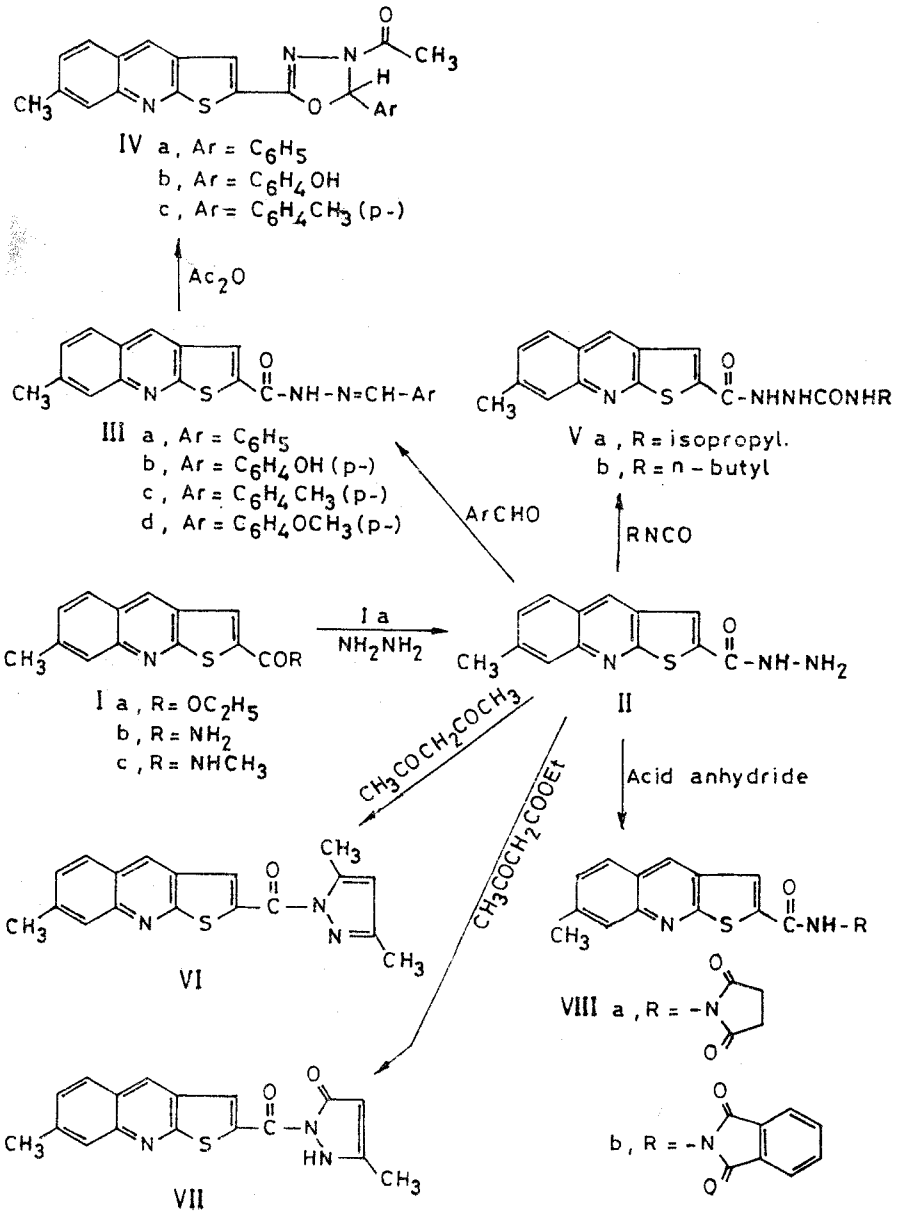
2- Ethoxycarbonly-7-methylthienlo[2, 3-b]quinoline Ia:

2- Chloro-3-formyl-7-methylquinoline[15] (2.05g; 10 mmole), ethylthioglycolate (2.4 g; 20 mmole) and sodium carbonate anhydrous (1.06 g; 10 mmole) in ethanol (15 ml) were refluxed for 6h. and then poured onto ice, a precipitate was deposited (2.35 g; 87 %). Recrystallisation from ethyl acetate / light petroleum gave the product as crystals m.p. 170–172 °C; found: C, 66.05; H, 4.87; N, 4.80 ($C_{15}H_{13}NO_2S$) requires C, 66.39; H, 4.82; H, 5.16; % IR: 1705 cm^{-1} (C=O).

2- Amido-7-methylthieno[2, 3-b]quinoline Ia,b:

General procedure:

The ester Ia (10 mmole) was refluxed with slight excess of ammonia solution or methylamine solution for 1–6 h. The solvent was concentrated


IV a, Ar = C6H5
b, Ar = C6H4OH
c, Ar = C6H4CH3 (p-)
Ac2O
III a, Ar = C6H5
b, Ar = C6H4OH (p-)
c, Ar = C6H4CH3 (p-)
d, Ar = C6H4OCH3 (p-)
V a, R = isopropyl.
b, R = n-butyl
ArCHO
RNCO
I a, R = OC2H5
b, R = NH2
c, R = NHCH3
I a
NH2NH2
II
CH3COCH2COCH3
CH3COCH2COOEt
Acid anhydride
VI
VII
VIII a, R =
b, R =

and on cooling a precepitate formed was filtered off then recrystallised to produce the amide derivative, (Ia, b).

2- Carboxamido-7-methylthineo[2, 3-b]quinoline Ia:

The reaction mixture was refluxed for 6 h., to produce 2.29 g; 95 % of amide, m.p. 286–87 °C from ethanol / water; found, C, 63.95; H, 4.56; N, 11.23 ($C_{13}H_{10}N_2OS$) requires C, 64.43; H, 4.16; N. 11.56. IR, 3350, 3180 (NH_2); 1650 (C=O); 1590 cm^{-1} (δNH).

2-N-Methylamido-7-methylthieno[2, 3-b]quinoline Ib:

The reaction mixture was refluxed for 1 h. to produce 2.3 g; 90 % of amide derivative m.p. 237 °C from ethanol, found: C, 65.86; H, 4.99; N, 11.04 ($C_{14}H_{12}N_2OS$) requires C, 65.59; H. 4.72; N. 10.93 IR, 3430, 3240 (NH_2); 1655 (C=O) and 1610 cm^{-1} (δNH). ^1H NMR, δ2.58 (s, quinoline-CH_3), δ 2.9 (d, amide-CH_3), δ 7.58 (dd, H-6), δ 7.97 (d, H-5), δ 8.1 (d, H-8), δ 8.2 (s, H-4), δ 9. |3 (s, olifinic cH).

2-Carbohynrazido-7-methylthieno[2, 3-b]quinoline II:

A mixture of thienoquinoline ester Ia (2.7 g; 10 mmole) and hydrazine hydrate (2 ml) in 50 ml ethanol was refluxed for 6 hr. The separated solid was filtered off and recrystallised from n-butanol to produce the hydrazide derivative 2.5 g in a quantitative yield, m.p. 278 °C decompn.

It can be prepared also in the same yield in DMF by stirring the same amounts at 50 °C for 2 hr. and pouring the mixture onto ice-cold water. Found, C, 60.29; H, 4.53; N, 16.10 ($C_{13}H_{11}N_3OS$) requires C, 60.67; H, 4.31; N, 16.33. IR: multiple bands (broad) at 3320–3020 (NH_2 & NH), 1610 cm^{-1} (C=O). ^1H NMR: δ 2.59 (s, CH_3), δ 4.67 (broad, NH_2), δ 7.52 (dd, H–6), δ 7.9 (s, H–8), δ 8.09 (d, H–5), δ 8.17 (s, H–4), δ 8.98 (s, olifinic CH).

2- Arylhydrazono-7-methylthieno[2, 3-b]quinoline III a-d

General procedure:

A mixture of the hydrazide II (10 mmole) and the respective aldehyde (20 mmole) in ethanol (30 ml) was heated under reflux for 4 hr. The reaction mixture was cooled, the solid was filtered off, washed with aqueous ethanol and recrystallised from n-butanol to produce the hydrazone derivatives (III a-d).

2-Phenylhydrazono-7-methylthieno[2,3-b]quinoline IIIa:

was produced in 81 % yield, m.p. 267–78 °C. Found, C, 69.54; H, 4.53; N, 11.89 ($C_{20}H_{15}N_3OS$) requires C, 69.54; H, 4.37; N, 12.16. IR: 3520–3440 NH; 1650 cm^{-1} (C=O).

2-p-Hydroxyphenylhydrazon-7-methylthieno[2,3-b]quinoline IIIb,

was produced in 91 % yield, m.p.: 325–27 °C. Found, C, 66.48; H, 4.56; N, 11.24 ($C_{20}H_{15}N_3O_2S$) requires, C, 66.46; H, 4.18; N, 11.62. IR, 3320 (NH); 1620 (C=O) and 1580 cm^{-1} (C=N).

2-p-Tollylhydrazono-7-methyl thieno[2,3-b]quinoline IIIc,

was produced in 86 % yield m.p. 297 °C. Found, C. 69.92; H, 4.62; N, 11.26 ($C_{21}H_{17}N_3OS$) requires, C. 70.17; H, 4.76; N, 11.69; IR, 3480–3395 (NH), 1650 (C=O) and 1605 cm^{-1} (C=N).

2-Methoxyphenylhydrazono-7-methylthieno[2,3-b]quinoline IIId;

was produced in 85 % yield, m.p. 274–76 °C. Found, C, 67.60; H, 4.38; N, 10.81 ($C_{21}H_{17}N_3O_2S$) requires, C, 67.187; H, 4.56; N, 11.19. IR, 3540–3400 NH, 1650 (C=O) and 1605 cm^{-1} (C=N).

2-[2-aryl3-acetyl-1, 3, 4-oxadiazoline]-7-methylthieno[2, 3-b]quinolines IVa-c:

General procedure:

A mixture of the hydrazone derivatives IIIa-c (10 mmole) and acetic anhydride (20 ml) was refluxed for 3 h. The excess acetic anhydride and acetic acid were removed in vacuo and the solid residue was filtered off, washed with water, aqueous ethanol and recrystallised from benzene-pet ether mixture to give the oxadiazole derivatives IVa-c.

2-[2-phenyl-3-acetyl-1,3,4-oxadiazoline]-7-methylthieno[2,3-b]-quinoline

IVa, was produced in 85 % yield, m.p. 215 °C. Found, C, 68.78; H, 4.65; N, 10.43 ($C_{22}H_{17}N_3O_2S$) requires, C, 68.19; H, 4.42; N, 10.84; IR, 1650 (C=O), 1590 (C=N), 1150 cm^{-1} (C-O-C). ^1H NMR, δ 2.3 (s, CH_3–C=O), δ 2.59 (s, CH_3), δ 7.3 (s, oxadiazoline proton), δ 7.49-8.1 (m, aromatic protons), δ 8.88 (s, olifinic proton).

2-[2-p-hydroxyphenyl-3-acetyl-1,3,4-oxadiazoline]-7-methylthieno[2,3-b] quinoline IVb, was produced in 90 % yield, m.p. 312–14 °C. Found, C, 65.64; H, 4.59; N, 10.69 ($C_{22}H_{17}N_3O_3S$) requires, C, 65.49; H, 4.25; N, 10.41 IR, 3450 broad band (OH), 1650 (C=O), and 1190 cm^{-1} (C-O-C).

2-[2-p-methylphenyl-3-acetyl-1,3,4-oxodiazoline]-7-methylthineo-[2, 3-b] quinoline IVc, was produced in 88 % yield, m.p. 208 °C. Found, C, 65.64; H, 4.59; N, 10.69 ($C_{23}H_{19}N_3O_2S$), requires, C, 65.49; H, 4.25; N, 10.41. IR, 1670 (C=O) and 1595 cm^{-1} (C=N).

2-Alkylsemicarbazido-7-methylthieno[2,3-b]quionline V:

General procedure:

A mixture of the hydrazide II (10 mmole), and the alkyl isocyanate (12 mmole) in dry benzene (50 ml) was refluxed for 6 h. The solvent was then evaporated, and the formed solid washed with water, filtered off, then recrystallised from methanol to produce the semicarbazide derivatives.

2-isopropyl-semicarbazido-7-methylthieno[2,3-b]quinoline Va,

was produced in 86 % yield, m.p. 308 °C decompn. Found, C. 60.69; H, 5.56; N, 15.70 ($C_{17}H_{18}N_4O_2S$) requires, C. 59.62; H, 5.29; N, 16.36. IR, 3320 (NH) and 1650 cm^{-1} (C=O).

2-n-Butyl-semicarbazido-7-methylthieno[2,3-b]quinoline Vb,

was produced in 85 % yield, m.p. 320 °C. Found, C, 61.06; H, 4.99; N, 15.19 ($C_{18}H_{20}N_4O_2S$) requires, C, 60.65; H, 5.65; N, 15.71. IR, 3320 (NH) and 1650 cm^{-1} (C=O).

1-[2-Carbo-7-methylthieno[2,3-b]quinolino]3,5-dimethyl pyrazole VI:

A mixture of the hydrazide II (0.51 g; 2 mmole) and excess freshly distilled acetylacetone (5 ml) was heated on water bath for 3 h. The formed solid was filtered off and recrystallised from ethanol to produce 0.51 g in 80 % yield and m.p. 205 °C decompn. Found, C, 67.51; H, 4.77; N, 12.73 ($C_{18}H_{15}N_3OS$) requires, C, 67.26; H, 4.70; N, 13.07. IR, 1610 cm^{-1} (C=O). ^1H NMR, δ 1.95 and δ 2.15 (2s of 3 and 5 methyl protons of pyrazole ring), δ 2.55 (s, CH_3), δ 6.7 (s, CH_2 of pyrazole);

δ 7.45 (dd, H-6); 87.9 (s, H-8); δ 8.05 (d, H-5); δ 8.43 (s, H-4) and δ 8.95 (s, olifinic CH of thiophene ring).

1-[2-Carbo-7-methylhieno[2,3-b]quinolino]3-methyl-3- pyrazolin-5-one VII:

A mixture of the hydrazide II (0.51 g, 2 mmole) and excess ethyl acetoacetate (5 ml) was heated on water bath for 3 h. The formed solid was filtered off and recrystallised from ethanol to yield 0.55 g, in 85 % yield and m.p. over 270 °C. Found, C, 63.11; H, 4.35; N, 12.54 ($C_{17}H_{13}N_3O_2S$) requires, C, 63.14; H, 4.05; N. 12.99. IR, 3170 (NH), 1720 and 1650 cm^{-1} (C=O bands).

2[7-methylthieno[2,3-b]quinoline] -N- imidobenzamide derivatives. VIII a,b:

General procedure:

A mixture of the hydrazide II (I mmole) and the appropriate acid anhydride (1 mmole) in glacial acetic acid (10 ml) was refluxed for 3 h. The solvent was concentrated, then poured upon ice-cold water, filtered off and recrytallised.

2-[7-methylthieno[2,3-b]quinoline]-N-imidosuccinamide VIIIa;

was produced in 80 % yield and m.p. 293 °C. Found, C, H, 4.32; N, 12.58 ($C_{17}H_{13}N_3O_3S$) requires, C, 60.16; H, 3.86; N, 12.38. IR, 3370 (NH), 1725 and 1670 cm^{-1} (C=O) groups. ^1H NMR, δ 2.65 (s, CH_3); δ 2.9 (s, CH_2-CH_2); δ 7.59 (dd, H-6); δ 7.95 (s, H-8); δ 8.17 (d, H-5), δ 8.45 (s, H-4) and δ 9.13 (s, CH of thiophene ring).

2-[7-methylthieno[2,3-b]quinoline]-N-imidophthalimide VIIIb,

was produced in 95 % yield and m.p. 343 °C. Found, C, 65.5; H, 3.89; N, 10.33 ($C_{21}H_{13}N_3O_3S$) requires C, 65.1; H, 3.38; N, 10.85. IR, 3350 (NH), 1725 and 1690 cm^{-1} (C=O) groups. ^1H NMR; δ 2.56 (s, CH_3), δ 7.55 (dd, H-6), δ 7.92–8.19 (m, aromatic protons), δ 8.46 (s, H-4) and δ 9.1 (s, CH, olifinic proton).

REFERENCES

1. GEORGE, T.; MEHTA, D.V.; TAHILRAMANI, R; DAVID, J. and TALWALKER, P.K.; J. Med. Chem., 14 (4) 335 (1971).

2. MAZZONE, G.; BONINA, F. AND ARRIGO REINA, R. (1st Chim. Farm. Tossical., Univ. Catana, Catania, Italy). Farmaco, Ed. Sci. 1980, 35 (1), 31–40; C.A., 92, 181094b (1980).

3. MUECKTER, H. (Chemie Gruenenthal G.m.b.H.); Ger. Offen, 2. 533, 926 (Cl. A 61K31 / 41) (1977), C.A., 86, 133786 h (1977).

4. SHERMAN, W.R.; J. Org. Chem. 26, 88 (1961).

5. GUPTA, A.K.S., GARG, M. and CHANDRA, U.; J. India Chem. Soc., 56, 1230 (1979).

6. G. MAFFII, E. TESTA & R. FUSCO, R.; Farmaco (pavia) Ed. Sci. 13, 629–38 (1958); C.A.: 53, 20552 (1959).

7. VINCENT, M., MAILLARD, J. and BENARD, M.; Bull. Soc. Chem. France, 1580 (1962).

8. Societe d'exploitation des Laboratoires.; LOGEAIS, J., Fr. M1324, June, 19 (1962); C.A., 58, 1468 (1963).

9. OLESON, J.J.; SLOBODA, A.; TROY, W.P.; HALLIDAY, S.L.; LANDES, J.M. et al.; J. Am. Chem. Soc., 77, 6713 (1955).

10. MISRA, V.S. and AGARWAL (Km) S.; J. Indian Chem. Soc., 56, 175 (1979).

11. NASR, M., NABIH, I., and BRUCKHALTER, J.H.; J. Med. Chem., 21, 295 (1978).

12. VON OETTIGER, "The Therapeutic Agents on the Quinoline Groups", Chemical Cat. Co. New York (1933).

13. BARKOVIC, D., and MOVRIN, M.; Acta Pharm, Jugoslav., II, 39–45 (1961), C.A., 57, 2338 (1962).

14. METH-COHN, O.; NARINE, B. et al., J. Chem. Soc., Perkin trans I, 2509 (1981).

15. METH-COHN, O.; NARINE, B. and TARNOWSKI, B.; Tetrahedron Lett., 33, 3111 (1979).