Indian Journal of Chemistry
Vol. 37B, August 1998, pp. 804 - 809

Note

Synthesis of some new spirothiazolidinone and spiroazetidinone derivatives incorporated with quinazoline

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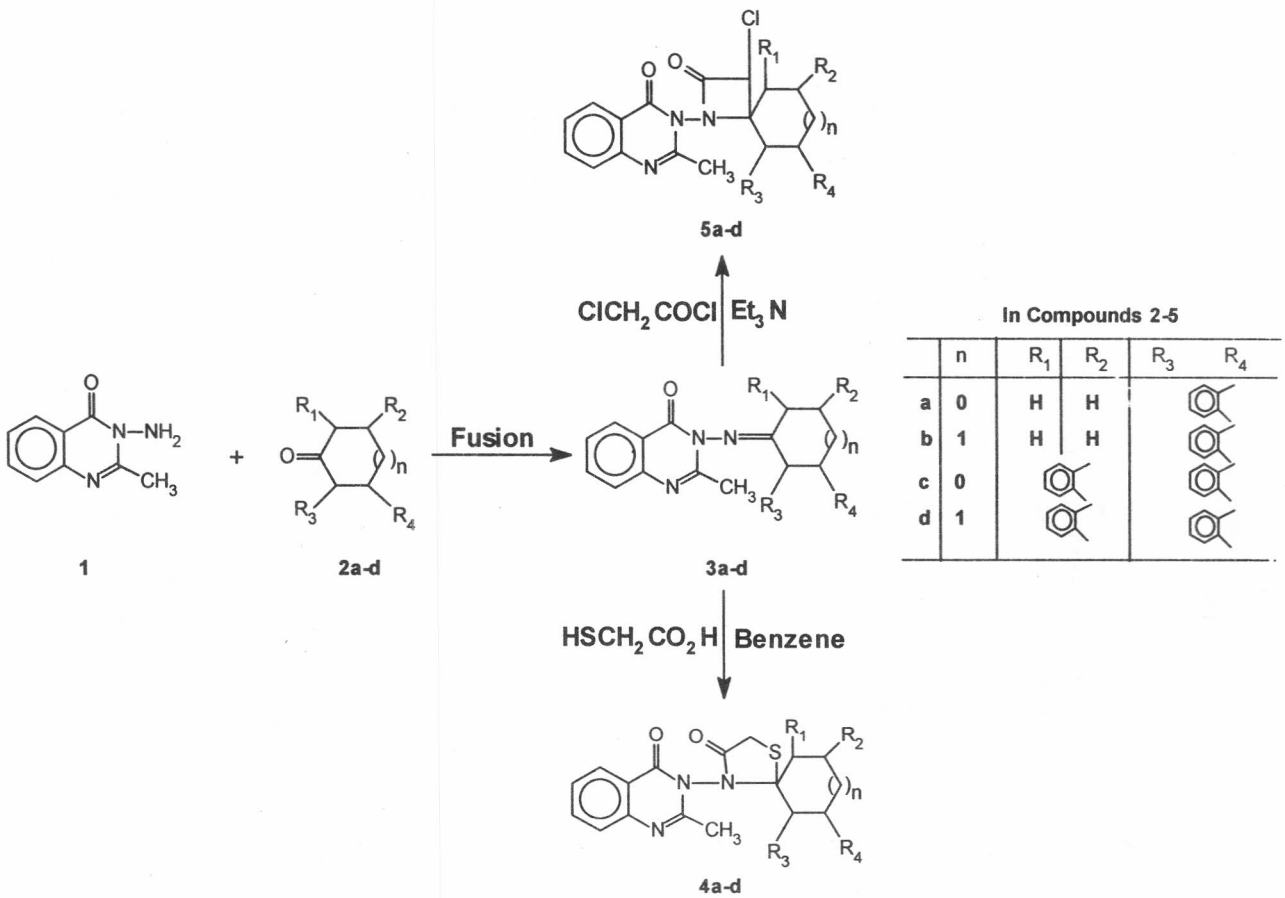
Received 2 July 1997; accepted (revised) 2 April 1998

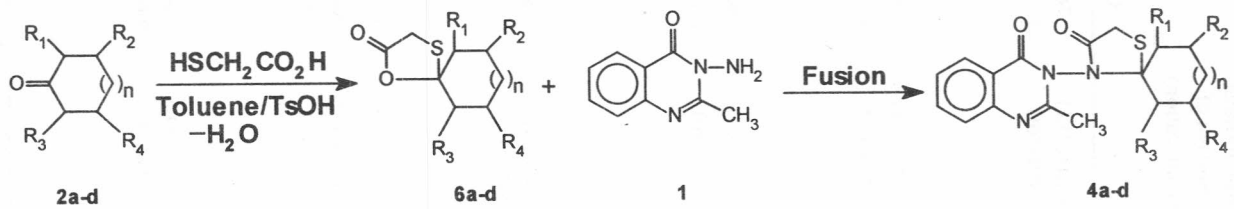
3-Amino-2-methyl-3*H*-quinazolin-4-one **1** reacts with cyclic ketones **2a-d** to afford the corresponding cycloalkylidene-3-aminoquinazolinone derivatives **3a-d**. which on treatment reacted with mercaptoacetic acid to give the spirothiazolidinones **4a-d**. Also the reaction of compounds **3a-d** with chloroacetyl chloride in the presence of triethylamine as a catalyst yield the respective spiroazetidinones **5a-d**. All the synthesized spiroheterocycle derivatives have been identified by conventional methods IR and ^{1}H NMR spectroscopy and elemental analyses.

Certain spiro compounds show anticancer[1], central nervous system activity[2], antiinflammatory activity[3] and antibiotic aranorosin[4]. Recent literature reports revealed the synthesis of spiroheterocycles which were used as intermediates for aldose reductase inhibitors[5]. Some new spiroheterocycles are found to have activity as herbicides and pesticides[6]. Also, a facile access to aphidicolane and stemodane B/C/D-ring systems have been reported[7,8], and the syntheses of some new heterobicyclic compounds containing the spiro-1,2,4-triazine moiety as potential anti HIV and anticancer agents were investigated[9] by us. The preparation of fluoran compounds for use as recording materials has also been carried out[10-12]. Also, the preparation of spiroazafuranone derivatives to be used for the treatment of neurodegenerative disorders and as anxiolytics were achieved[13,14]. Quinazoline derivatives showed divers biological activities[15-19]. Thiazolidinone derivatives have considerable commercial importance as drugs e.g. bactericidal, pesticidal, fungicidal, insecticidal, anticonvulsant, tuberculostatic, antiinflammatory, antithyroidal and potentiation of pentobarbital induced sleeping time[20,21]. Spirocycloalkylsubstituted azetidinones were used as hypocholesterolemic agents[22]. The syntheses of β-lactams using different techniques and catalysts have been accomplished[21,23,24]. The syntheses of spiro compounds containing nitrogen have gained importance because of their biological activity, but, in some cases, the preparation of these compounds required seven steps[25]. Also, the preparation of the well-known spiro derivatives, fredericamycin A, required eight steps[26]. From all of the forgoing facts it was very interesting to synthesize a new series of spirothiazolidinones and spiroazetidinones incorporated with quinazoline. We report herein a facile synthesis of some spiroquinazolineheterocycles derivatives analogous to spiro[indan-1,1'[1*H*]-3-benzenepine] derivatives[25] and fredericamycin A[26]. The advantages of our syntheses were the use of inexpensive precursors such as anthranilic acid, hydrazine hydrate, cyclic ketones and mercaptoacetic acid, facile reactions, readily available reagents and simple techniques. Our syntheses were initiated with the reaction of 3-amino-2-methyl-3H-quinazolin-4-one **1** with 1-indanone **2a**, 1-tetralone **2b**, fluorenone **2c** and anthrone **2d** to afford the corresponding cycloalkylidene-3-aminoquinazolinone derivatives **3a-d** in good yields (Scheme 1). The structure of compounds **3a-d** were established from their elemental analyses and spectroscopic data (Table 1). The IR spectrum of **3a** showed characteristic strong absorption bands at 1685 cm^{-1} corresponding to the stretching vibrations of the carbonyl group of the quinazoline ring and 1600 cm^{-1} for the C=N stretching. The ^{1}H NMR spectrum of **3a** (DMSO-d_6) showed the following signals: δ 2.59 (2H, t) for the methylene protons of the indan moiety, 3.05 (2H, t) for the benzylic methylene protons of indan residue, 3.39 (3H, s) for the methyl protons at C_2 of the quinazoline ring and 7.00-8.14 ppm (8H, m) for the aromatic protons of both quinazoline and indan rings. The ^{13}C NMR spectrum of **3a** (DMSO-d_6) showed the following signals: δ 21.88, 25.40, 35.83, 119.76, 122.84, 125.84, 126.60, 126.92, 127.06, 127.16, 133.82, 134.59, 136.64, 146.63, 155.20, 155.46, 160.08, 206.24 ppm.

Compounds **3a-d** reacted with mercaptoacetic



Scheme I



Scheme II

acid in dry benzene to give the target products **4a-d** in good yields (Table 1, Scheme 1). The structures of compounds **4a-d** were confirmed on the basis of their elemental analyses and spectroscopic data (Table I). The ^{1}H NMR spectrum of **4a** (DMSO-d_6) showed the following signals: δ 2.43 (2H, t) for the methylene protons of the indan ring, 2.59 (2H, t) for the benzylic methylene protons of the indan residue, 2.92 (2H, s) for the methylene protons of thiazolidine ring, 3.40 (3H, s) for methyl protons at C_2 of quinazoline ring, 7.39-8.34 ppm (8H, m) for the aromatic protons of

Table I—Physical Data of -3-aminoquinazolinones **(3a-d)**, spirothiazolidinones **(4a-d)** and spiroazetidinones **(5a-d)**

Compd	Yield (%)	m.p. (°C)	Mol. formula (Solvent of crystallization)	Found (%) (Calc.)					^{1}H NMR (DMSO-d_6), (δ, TMS) ppm	^{13}C NMR (DMSO-d_6), (δ, TMS) ppm
				C	H	N	S	Cl		
3a	70	98-100	$C_{18}H_{15}N_3O$ (ethanol)	74.60 (74.74)	5.10 (5.19)	14.41 (14.53)	—	—	2.95 (2H, t), 3.05 (2H, t), 3.39 (3H, s), 7.00-8.14 (8H, m)	21. 88, 25.40, 35.83, 119.76, 122.84, 125.84, 126.60, 126.92, 127.06, 127.16, 133.82, 134.53, 136.64, 146.63, 155.20, 155.46, 160.00, 206.24
3b	73	102-104	$C_{19}H_{17}N_3O$ (ethanol)	75.15 (75.24)	5.50 (5.61)	13.75 (13.86)	—	—	2.50 (2H, m), 2.65 (2H, t), 2.90 (2H, t), 3.39 (3H, s), 7.06-8.19 (8H, m)	21.86, 24.59, 25.45, 35.86, 119.76, 122.84, 125.85, 126.60, 126.92, 127.06, 127.16, 133.80, 134.50, 136.62, 146.59, 155.10, 155.50, 160.06, 205.20
3c	70	94-96	$C_{22}H_{15}N_3O$ (ethanol)	78.25 (78.33)	4.35 (4.45)	12.40 (12.46)	—	—	3.37 (3H, s), 7.00-8.20 (12H, m)	35.85, 119.70, 120.80, 121.70, 122.80, 124.70, 125.80, 126.50, 126.90, 127.05, 127.16, 130.70, 132.75, 133.80, 134.50, 135.70, 136.50, 136.62, 146.59, 155.60, 160.00, 206.30
3d	68	260-262	$C_{23}H_{17}N_3O$ (ethanol)	78.60 (78.63)	4.80 (4.84)	11.92 (11.96)	—	—	2.95 (2H, s), 3.39 (3H, s), 7.00-8.20 (12H, m)	26.40, 35.85, 119.70, 120.80, 121.70, 122.80, 123.90, 125.75, 126.50, 126.89, 127.00, 127.16, 130.70, 132.75, 133.80, 134.50, 135.70, 136. 50, 136.62, 146.59, 155.60, 160.00, 206.30
4a	60	116-118	$C_{20}H_{17}N_3O_2S$ (ethanol)	66.05 (66.11)	4.60 (4.68)	11.45 (11.57)	8.70 (8.81)	—	2.43 (2H, t), 2.59 (2H, t), 2.92 (2H, s), 3.40 (3H, s), 7.39-8.34 (8H, m)	22.79, 27.84, 28.81, 119.67, 120.49, 125.83, 126.42, 126.56, 128.29, 132.06, 133.82, 142.25, 144.60, 146.66, 152.85, 155.46, 155.79, 159.99, 174.67, 197.45
4b	61	90-92	$C_{21}H_{19}N_3O_2S$ (ethanol)	66.80 (66.84)	5.00 (5.03)	11.10 (11.14)	8.48 (8.50)	—	2.03 (2H, m), 2.43 (2H, t), 2.59 (2H, t), 2.92 (2H, s), 3.40 (3H, s), 7.10-8.34 (8H, m)	21.82, 22.79, 27.84, 28.81, 119.67, 120.49, 125.88, 126.16, 126.42, 126.56, 126.92, 133.35, 133.82, 142.25, 146.66, 152.85, 155.46, 155.79, 159.99, 174.67, 197.45

(Contd)

Table I—Physical Data of -3-aminoquinazolinones **(3a-d)**, spirothiazolidinones **(4a-d)** and spiroazetidinones **(5a-d)**—*Contd*

Compd	Yield (%)	m.p. (°C)	Mol. formula (Solvent of crystallization)	Found (%) (Calc.)					^{1}H NMR (DMSO-d_6), (δ, TMS) ppm	^{13}C NMR (DMSO-d_6), (δ, TMS) ppm
				C	H	N	S	Cl		
4c	61	64-66	$C_{24}H_{17}N_3O_2S$ (ethanol)	70.00 (70.07)	4.00 (4.13)	10.10 (10.21)	7.70 (7.78)	—	2.90 (2H, s), 3.40 (3H, s), 7.00-8.35 (12H, m)	27.70, 28.85, 119.67, 120.67, 120.49, 125.83, 126.16, 126.42, 126.56, 126.92, 127.40, 133.35, 133.82, 142.25, 142.50, 144.60, 146.66, 146.54, 152.85, 155.46, 155.79, 159.99, 174.67, 197.45
4d	58	190-192	$C_{25}H_{19}N_3O_2S$ (ethanol)	70.50 (70.58)	4.40 (4.47)	9.80 (9.88)	7.49 (7.52)	—	2.85 (2H, s), 2.90 (2H, s), 3.40 (3H, s), 7.10-8.40 (12H, m)	26.70, 27.60, 28.85, 119.67, 120.67, 121.40, 125.83, 126.16, 126.42, 126.50, 126.92, 127.40, 133.35, 133.82, 142.25, 142.50, 144.60, 146.66, 146.54, 152.85, 155.46, 155.79, 159.99, 174.67, 197.45
5a	58	220-222	$C_{20}H_{16}N_3O_2Cl$ (benzene)	65.70 (65.75)	4.35 (4.38)	11.40 (11.50)	—	9.50 (9.58)	2.43 (2H, t), 2.59 (2H, t), 3.39 (3H, s), 5.82 (1H, s), 7.00-8.14 (8H, m)	22.60, 25.84, 28.81, 119.67, 120.49, 125.83, 126.42, 126.56, 128.29, 132.06, 133.82, 142.25, 144.60, 146.66, 152.85, 155.46, 155.79, 159.99, 174.67, 197.40
5b	56	250-252	$C_{21}H_{18}N_3O_2Cl$ (benzene)	66.40 (66.49)	4.70 (4.74)	11.00 (11.08)	—	9.10 (9.23)	2.03 (2H, m), 2.43 (2H, t), 2.57 (2H, t), 3.40 (3H, s), 5.70 (1H, s), 7.00-8.30 (8H, m)	21.82, 22.79, 27.84, 28.81, 119.76, 120.49, 125.83, 126.42, 126.56, 128.29, 132.06, 133.82, 142.25, 144.60, 146.66, 152.85, 155.46, 155.79, 159.99, 174.67, 197.40
5c	55	230-232	$C_{24}H_{16}N_3O_2Cl$ (benzene)	69.70 (69.73)	3.80 (3.87)	10.10 (10.16)	—	8.40 (8.47)	3.40 (3H, s), 5.52 (1H, s), 7.00-8.34 (12H, m)	28.70, 119.67, 120.49, 121.30, 121.50, 122.64, 122.70, 123.40, 125.89, 126.42, 126.56, 128.29, 132.06, 132.60, 133.82, 142.25, 144.60, 146.66, 152.85, 155.46, 155.79, 159.99, 174.67, 197.40
5d	54	245-247	$C_{25}H_{18}N_3O_2Cl$ (benzene)	70.20 (70.25)	4.15 (4.21)	9.80 (9.83)	—	8.10 (8.19)	2.90 (2H, s), 3.40 (3H, s), 5.52 (1H, s), 7.00-8.29 (12H, m)	27.80, 28.70, 119.67, 120.49, 121.30, 121.50, 122.64, 122.70, 123.40, 125.83, 126.42, 126.56, 128.29, 132.06, 133.82, 142.25, 144.60, 146.66, 152.85, 155.46, 155.79, 159.99, 174.67, 197.40

quinazoline and indan rings. The ^{13}C NMR spectrum of **4a** (DMSO-d_6) showed the following signals: δ 22.79, 27.84, 28.81, 119.67, 120.49,125.83, 126.42, 126.56, 128.29, 132.06, 133.82, 142.25, 144.60, 146.66, 152.85, 155.46, 155.79, 159.99, 174.67, 197.45. For the rigid identification of compounds **4a-d**, an unequivocal syntheses for **4a-d** were established by the reaction of cyclic ketones namely 1-indanone **2a**, 1-tetralone **2b**, fluorenone **2c** and anthrone **2d** with mercaptoacetic acid in the presence of *p*-toluenesulfonic acid in toluene to afford the spiroheterocyclic derivatives **6a-d** in good yields[27] (Scheme II), which were subsequently reacted with 3-amino-2-methyl-3*H*-quinazolin-4-one **1** to afford the target compounds **4a-d**. For the synthesis of the new spiroazetidinone derivatives **5a-d**, compounds **3a-d** reacted with chloroacetyl chloride in benzene in the presence of triethylamine as a catalyst to give the corresponding spiroazetidinone derivatives **5a-d** in good yields (Scheme I). The structures of compounds **5a-d** were elaborated on the basis of their elemental analyses and spectroscopic data (Table I). The IR spectrum of compound **5a** showed characteristic strong absorption bands at 1730 cm^{-1}, 1700 cm^{-1} corresponding to the stretching vibrations of the carbonyl group of the azetidinone ring and the quinazoline ring respectively, and at 790 cm^{-1} for C-Cl stretching vibration. The ^1H NMR spectrum of **5a** (DMSO-d_6) showed the following signals: δ 2.43 (2H, t) for the methylene protons of the indan moiety, 2.59 (2H, t) for the benzylic methylene protons of the indan residue, 3.39 (3H, s) for methyl at C_2 of the quinazoline ring, 5.82 (1H, s) the proton at C_3 of the azetidinone ring, 7.00-8.4 ppm (8H, m) for the aromatic protons of the quinazoline and indan rings. The ^{13}C NMR spectrum of **5a** (DMSO-d_6) showed the following signals: δ 22.60, 25.84, 28.81, 119.67, 120.49, 125.83, 126.2, 126.56, 128.29, 132.06, 133.82, 142.25, 144.60, 146.66, 152.85, 155.46, 155.79, 159.99, 174.67, 197.40 ppm.

Experimental Section

The time required for completion of each reaction was monitored by TLC. Melting points are uncorrected. ^1H NMR (δ, ppm) spectra were measured on an EM-360 90-MHz spectrophotometer using TMS as internal standard. A Varian FT-80 was used to obtain all ^{13}C NMR (δ, ppm) spectra. IR (ν, cm^{-1}) spectra were recorded on a Pye-Unicam SP 200-G spectrophotometer. Elemental analyses were determined on a Perkin-Elmer 240 C microanalyser.

Synthesis of 3-amino-2-methyl-3H-quinazolin-4-one 1. This compound was prepared according to the reported method[28].

Synthesis of cycloalkylidene-3-aminoquinazolin-4-one derivatives (3a-d): General Procedure. Each compound **2a-d** (0.01 mole) was fused with compound **1** (0.01 mole) for 1/2 hr, then 25 mL of absolute ethanol was added to the reaction mixture. The reaction mixture was refluxed for 6 hr, cooled to room temperature whereby compounds **3a-d** were precipitated, filtered off and dried. Yields, melting points and spectral analyses are depicted in Table I.

Synthesis of spirothiazolidinone derivatives 4a-d: General procedure. Each compound **3a-d** (0.001 mole) was dissolved in 25 mL of dry benzene and to this solution, mercaptoacetic acid (0.001 mole) was added. Then the reaction mixture was refluxed for 8 hr. At the end of the refluxing time, the solvent was removed by distillation and the residue was poured into 50 mL of 20% sodium carbonate solution, whereby compounds **4a-d** were precipitated, filtered off and dried. The results are given in Table I.

Synthesis of spiroazetidinone derivatives 5a-d: General Procedure. Each compound **3a-d** (0.001 mole) was dissolved in 25 mL of dry benzene and to this solution, chloroacetyl chloride (0.001 mole) and triethylamine (0.001 mole) were added. Then the reaction mixture was stirred at room temperature for 10 hr. At the end of stirring time, the solvent was removed by distillation and the residue was poured into 25 mL of iced water, whereby compounds **5a-d** were precipitated, filtered off and dried. Results are shown in Table I.

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