Physical Sciences Section

Pakistan J. Sci. Ind. Res., Vol. 15, Nos. 4–5, August–October 1972

SYNTHESIS OF HETEROBICYCLIC COMPOUNDS

Part IV. Formation of 2H-1,3-Benzothiazine and 1,2,3,4-Tetrahydroquinazoline Derivatives

ASLAM BUTT and RASHEEDA PARVEEN

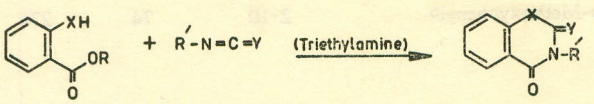
PCSIR Laboratories, Karachi 39

(Received February 28, 1972; revised May 13, 1972)

Abstract. A general route towards the formation of 2 and 3-substituted 2*H*-1,3-benzothiazine and 1,2,3,4-tetrahydroquinazoline is described.

That the reaction of salicylic acid or its esters (methyl and ethyl) with phenyl isocyanate in the presence of a catalytic amount of triethylamine leads to the formation of 3-phenyl-2*H*-1,3-benzoxazine-2,4,3*H*-dione, has been described previously.[1] It appeared capable of further extension because of the easy availability of various isocyanates and isothiocyanates on the one hand and *o*-amino- and *o*-sulphhydralbenzoic acids and its esters on the other.

The reaction could be depicted as follows:



I II III

(X could be S or N and Y=O or S; R′ is aromatic or aliphatic in nature)

When methyl anthranilate and phenyl isocyanate were reacted in the presence of triethylamine under anhydrous conditions, a product of composition $C_{14}H_{10}N_2O_2$ was found and identified as the known 2,4-dioxo-3-phenyl-1,2,3,4-tetrahydroquinazoline (III, R = Ph, X = N, and Y = O).[2,3] Similarly, methyl anthranilate and phenyl isothiocyanate in presence of triethylamine as catalyst, produced an analogous product, $C_{14}H_{10}N_2OS$, m.p. 305°C, which was characterised as 4-oxo-2-thioxo-3-phenyl-1,2,3,4-tetrahydroquinazoline,[4–6] (III, R = Ph, X = N, Y = S). Both of these compounds were obtained in almost quantitative yields. In a similar manner, it was found possible to react thiosalicyclic acid or thiosalicylates with aryl or alkyl isothiocyanates yielding the corresponding 3-substituted derivatives of 4-oxo-2-thioxo-3,4-dihydro-2*H*-1,3-benzothiazine in very good yields (Table 1).

Many workers[2–7] have prepared the products represented by formula III but the time of reaction was long, the yields were comparatively low, and the procedure was lengthy. By the present method several products could be prepared easily in better yields and in lesser time. For instance, the product mentioned above, i.e. 2,4-dioxo-3-phenyl-1,2,3,4-tetrahydroquinazoline, was first reported by Bogert and Scatchard[2] and then by Toyoshima,[3] and recently by Capuano and Zander.[4] In all those preparations, the yield was 50–75% and the time of reaction varied from 3 to 5 hr or more. In contrast, the present procedure, offers essentially quantitative yields and short reaction times.

The tetrahydroquinazoline structure of the new products (a,b,c,d,e, Table 1) unambiguously follows from the study of their IR spectra. Examination of the spectra of (a) (III, R′=*m*-bromophenyl, X=NH, Y=S), (b) (III, R′=*o*-methoxyphenyl, X=NH, Y=S) and (c) (III, R′=ethyl, X=NH, Y=S) revealed that the frequencies at 1631, 1656 (vs) and 1664 cm^{-1}, respectively in these three products, were attributable to the 4-carboxyl group, as found earlier.[8] The absorption bands at 1253 (vs), 1261 (vs) and 1261 (s) cm^{-1} in the compounds (a), (b) and (c) respectively appeared due to 2-thione group. The other bands at 1613, 1517 (vs) and 1471 cm^{-1} in (a), 1616(s), 1520(s) and 1481(s) cm^{-1} in (b) and 1616(m), 1575(vs) and 1484(s) cm^{-1} indicated tetrahydroquinazoline structure and were due to ring vibrations. Likewise, the bands at (a) 1333 (vs), (b) 1299 (w), (c) and 1332 cm^{-1} were due to C—N linkages.

In the case of benzothiazines, (d) (III, R′= *p*-bromophenyl, X = Y = S) and (e) (III, R′ = *m*-bromophenyl, X = Y = S), it was noticed that the absorption at 1689(vs) and 1673(vs) cm^{-1} were those of the carbonyl group at position 4, while the 2-thione group appeared at 1235(vs) and 1236(vs) cm^{-1} respectively. The other absorptions between 1587 –1319 cm^{-1} are due to the ring vibrations of the d and e.

Experimental

2,4-Dioxo-3-phenyl-1,2,3,4-tetrahydroquinazoline (III, R = Ph, X = Y = O). (a) Anthranilic acid (1.37 g, 0.01 mole), phenyl isocyanate (1.19 g, 0.01 mole) and triethylamine (0.2 ml) were treated together in a round-bottomed flask (250 ml) under anhydrous conditions ($CaCl_2$ tube) at room temperature (30°C). The reaction was exothermic and the contents of the flask became jelly like. On cooling, the mixture

TABLE 1. SYNTHESIS OF 2*H*-1,3-BENZOTHIAZINE AND 1,2,3,4,-TETRAHYDROQUINAZOLINE DERIVATIVES

No.	*o*-Amino sulphhydral-benzoic acids and esters (0·01 mole)	Isocyanates and isothiocyanates (0·01 mole)	4-Oxo-2-thioxo-3-substituted-1,2,3,4-tetra hydroquinazolines (III, X=NH, Y=S) R′	Yield (g)	Yield (%)	M.P. (°C)
1	Anthranilic acid (1·37 g)	PhNCS (1·35 g)	Phenyl	2·41	95	305
2	Methyl anthranilate (1·51 g)	PhNCS (1·35 g)	Phenyl	2·54	100	305
3	,,	*o*-CH_3-C_6H_4NCS (1·49 g)	*o*-Tolyl	2·01	75	275
4	,,	*m*-CH_3-C_6H_4NCS (1·49 g)	*m*-Tolyl	2·21	82	296 (Lit[6] m.p. 281)
5	,,	*p*-CH_3-C_6H_4NCS (1·49 g)	*p*-Tolyl	2·01	75	320 (Lit[3] m.p. 305)
6	,,	*p*-Cl-C_6H_4NCS (1·7 g)	*p*-Chlorophenyl	2·3	80	336 (Lit[3] m.p. 319)
7	,,	*p*-Br-C_6H_4NCS (2·14 g)	*p*-Bromophenyl	2·16	80	338 (Lit[3] m.p. 315)
8	,,	*p*-CH_3O-C_6H_4NCS (1·65 g)	*p*-Methoxyphenyl	2·27	80	312 (Lit[6] m.p. 283)
9	,,	*m*-Br-C_6H_4NCS (2·14 g)	*m*-Bromophenyl[a]	2·49	75	310
10	,,	*o*-CH_3O-C_6H_4NCS (1·65 g)	*o*-Methoxyphenyl[b]	2·10	74	278
11	,,	C_2H_5 NCS (0·87 g)	Ethyl[e]	1·85	90	250
			4-Oxo-2-thioxo-3-substituted -3, 4-dihydro-2*H*-1,3-benzo-thiazines (III, X—Y—S) R′			
12	Thiosalicylic acid (1·54 g)	C_2H_5 NCS (0·37 g)	Ethyl	2·18	98	125
13	,,	*o*-CH_3-C_6H_4NCS (1·49 g)	*o*-Tolyl	2·10	73	130
14	,,	*m*-CH_3-C_6H_4NCS (1·49 g)	*m*-Tolyl	2·14	75	149
15	,,	*p*-CH_3-C_6H_4 NCS (1·49 g)	*p*-Tolyl	2·11	73	182
16	,,	*o*-CH_3O-C_6H_4NCS (1·65 g)	*o*-Methoxyphenyl	2·22	74	184
17	,,	*p*-Methoxyphenyl *p*-CHO_3-C_6H_4NCS (1·65 g)	*p*-Methoxyphenyl	2·28	76	186
18	,,	*p*-Cl-C_6H_4NCS (1·7 g)	*p*-Chlorophenyl	2·44	30	210
19	,,	*p*-Br-C_6H_4NCS (2·14 g)	*p*-Bromophenyl[d]	2·59	74	212
20	,,	*m*-Br-C_6H_4NCS (2·14 g)	*m*-Bromophenyl[e]	2·55	73	172

a,b,c,d,e,New products.

AT 60°C AND ROOM TEMPERATURE RESPECTIVELY. (SOLVENT FOR CRYSTALLIZATION, METHANOL).

Molecular formula	Analysis Found C	H	N	Calculated C	H	N	UV light absorption (95% methanol) of new products λmax	log ε	IR absorption of the new products
$C_{14}H_{10}N_2OS$	66·40	3·9	11·2	66·1	3·9	11·0			
$C_{14}H_{10}N_2OS$	66·40	3·9	11·2	66·1	3·9	11·0			
$C_{15}H_{12}N_2OS$	67·5	4·7	10·4	67·2	4·5	10·4			
$C_{15}H_{12}N_2OS$	67·5	4·7	10·4	67·2	4·5	10·4			
$C_{15}H_{12}N_2OS$	67·5	4·7	10·4	67·2	4·5	10·4			
$C_{14}H_9ClN_2OS$	58·5	3·4	10·1	58·2	3·1	9·7			
$C_{14}H_9Br\ N_2OS$	50·9	2·8	8·8	50·5	2·7	8·4			
$C_{15}H_{12}N_2O_2S$	63·9	4·2	10·3	63·4	4·2	9·9			
				Requires					
$C_{14}H_9BrN_2OS$	50·8	2·9	8·8	50·5	2·7	8·4	330 290 220	3·89 4·24 4·27	3175m, 1664vs, 1616m, 1575w, 1524s, 1484m, 1332w, 1285w, 1261m, 1225s, 1198vs, 1054w, 9945w, 9076w, 8486w, 7994w, 7746s, 7612m, 7320w, 6798m.
$C_{15}H_{12}N_2O_2S$	63·71	4·2	9·5	63·4	4·4	9·9	330 290 230	3·8 4·2 4·2	3226w, 1656vs, 1616s, 1520s, 1418m, 1416vs, 1299w, 1261vs, 1235w, 1198vs, 115m, 1117w, 1040w, 8984w, 8547w, 7842, 7549s, 6873w.
$C_{10}H_{10}N_2OS$	58·4	5·1	13·8	58·3	4·9	13·6	335 290 230	2·67 4·08 4·05	3145m, 1631s, 1613s, 1517vs, 1471m, 1393m, 1361m, 1333vs, 1274w, 1235m, 1212vs, 1112s, 1091vs, 1075m, 1018m, 9615m, 8850m, 8460m 8000m, 7634s, 7407m.
				Calculated					
				C	H	N			
$C_{10}H_9NOS_2$	54·2	4·3	6·1	53·8	4·0	6·3			
$C_{15}H_{11}NOS_2$	—	—	4·6	—	—	4·9			
$C_{15}H_{11}NOS_2$	63·0	4·0	4·6	63·2	3·9	4·9			
$C_{15}H_{11}NO_2S_2$	63·1	4·1	4·5	63·2	3·9	4·9			
$C_{15}H_{11}NO_2S_2$	60·2	4·0	—	59·8	3·7	—			
$C_{15}H_{11}NO_2S_2$	60·0	4·0	—	59·80	3·7	—			
$C_{14}H_8ClNO\ S_2$	55·4	2·9	4·3	54·99	2·61	4·55			
				Requires					
				C	H	N			
$C_{14}H_8BrNOS_2$	48·4	2·5	4·4	48·00	2·3	4·00	345 270 225	2·9 4·20 4·27	3322w, 1689vs, 1P87m, 1479s 1431m, 1319s 1267m, 1253m, 1239vs, 1218w, 1122w, 1099s, 1064s, 1031s, 1015s, 8373m, 8288s, 8124s, 7868m, 7425vs, 7320s.
$C_{14}H_8BrNOS_2$	48·4	2·3	3·7	48·00	2·3	4·00	340 268 220	2·86 4·20 4·25	3152w, 1678vs 1577s 1462m, 1429m, 1323s, 1421m, 1309m, 1248m, 1236,v, 1199s, 1124, 1104s, 1065m, 1020sm, 1008w, 9946w, 8643m, 8553ms, 7840m, 7720s, 7489vs, 6906s, 6757s.

became hard. On trituration with ether, it formed a white powder which was crystallised from methanol to give 2,4-dioxo-3-phenyl-1,2,3,4-tetrahydroquinazoline (1.92 g, 81%), m.p. 280°C, undepressed by an authentic sample prepared by the method of refs. 2 and 3. (Found: C, 70.6; H, 4.2; N, 11.80%. Calc. for $C_{14}H_{10}N_2O_2$: C, 70.4; H, 4.3; N, 11.80%).

(b) Similarly, methyl and ethyl anthranilate (0.01 mole) when treated with phenyl isocyanate (0.01 mole) respectively in the presence of triethylamine (0.2 ml) gave 2,4-dioxo-3-phenyl-1,2,3,4-tetrahydroquinazoline (III, R = Ph, X = Y = O 99%), m.p. 280°C, identical in all respects with the above products.

All the other 1,2,3,4-tetrahydroquinazolines listed in Table 1 (1–11) were prepared as mentioned in method (a).

4-Oxo-2-thioxo-3-phenyl-3,4-dihydro-2 H-1,3-benzothiazine (*III, R Ph,=X=Y=S*). (a) Thiosalicylic acid (1.54 g, 0.01 mole), phenyl isothiocyanate (1.35 g, 0.01 mole) and triethylamine (0.2 ml) were mixed together in a R.B. flask under anhydrous conditions. The contents on heating gently at 60°C dissolved to give a jelly-like mass, which on trituration with petroleum ether gave a yellow product 4-oxo-2-thioxo-3-phenyl-3,4-dihydro-2*H*-1,3-benzothiazine (III, R = Ph, X = Y = S) (2.35 g, 87%) upon crystallising from methanol. It melted at 159°C, undepressed by a mixture with an authentic sample prepared by the method of Lilly *et al.*[4] (Found: C, 61.9; H, 3.3; N, 5.5. Calc. for $C_{14}H_9NOS_2$:C, 61.6; H, 3.3; N, 5.2%).

(b) Similarly methyl thiosalicylate (1.68 g, 0.01 mole), phenyl isothiocyanate (1.35 g, 0.01 mole) and triethylamine (0.2 ml) were mixed together in a round-bottomed flask under anhydrous conditions at room temperature (30°C), affording a yellow solid in 15 min. On trituration with petroleum ether it gave 4-oxo-2-thioxo-3-phenyl-3,4-dihydro-2H-1,3-benzothiazine (2.41 g, 89%) which upon recrystallisation from methanol melted at 159°C. The product was identical in all respect with the above.

All the remaining benzothiazines listed in Table 1 (12–20) were prepared as mentioned in method (a).

Acknowledgement. The technical help of M. Aslam, Laboratory Assistant, is greatly appreciated.

References

1. A. Butt, A.M. Khan and R. Parveen, Pakistan J. Sci. Ind. Res., **14,** 192 (1971).
2. M.T. Bogert and G. Scatchard, J. Am. Chem. Soc., **41,** 2052(1919).
3. S. Toyoshima and K. Shimada, J. Pharm. Soc. Japan, **85,** 502 (1965); Chem. Abstr., **63,** 7009g (1965).
4. L. Capuano and M. Zander, Chem. Ber., **99,** 3085 (1966); Chem. Abstr., **66,** 10899 (1967).
5. K. Lampert and G. Doleschall, Monatsh., **95,** 950(1964); Chem. Abstr., **61,** 11993e (1964).
6. H.B. Constintin Analele stiint. Univ. A.I. Cuza Iasi Sect. I, **14,** 65(1968); Chem. Abstr. **70,** 106470p (1969).
7. G. Wagner and P. Rickter, Pharmazie, **22,** 911 (1967); Chem. Abstr., **69,** 106639e (1968).
8. H. Culbertson, J.C. Decius and D.T. Chreotensen, J. Am. Chem. Soc., **74,** 4834 (1952).
9. R. Mecke Jr. and R. Mecke, Chem. Ber., **89,** 343(1956).