STUDIES ON 4-QUINAZOLINONES. PART IX[1].
RANEY NICKEL DESULPHURISATION OF 4-THIOQUINAZOLINES: ALUMINA CATALYSED HYDRATION OF 1,4- AND 3,4-DIHYDROQUINAZOLINES

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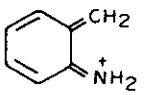
Abstract: A number of 2-substituted 3,4-dihydroquinazolines and 1,2-disubstituted 1,4-dihydroquinazolines but not the 3-mono or 2,3-disubstituted derivatives, prepared by Raney nickel desulphurisation of the corresponding 4-thioquinazolines (IV), underwent unusual alumina catalysed hydration across the C=N bond followed by ring opening through ring-chain tautomerism leading to substituted acetamide derivatives (III). A plausible mechanism has been put forward.

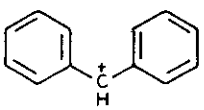
We earlier reported a few unusual and unpredictable course of reactions of 4-quinazolinones with some oxidising[1] and reducing[2-6] agents influenced by the substitution pattern and the lone pair of nitrogen. We observed, inter alia, that when the C=N of N-alkyl substituted 4-quinazolinones could be smoothly reduced, attempted metal hydride reduction of the otherwise resistant amide carbonyl under forcing condition resulted in the ring opening by cleavage at the C-N bond[4]. We now wish to record yet another type of ring opening of the 3,4-dihydroquinazolines obtained by thiolation of the amide carbonyl followed by Raney nickel desulphurisation.

We recently observed that the product of LAH reduction of 2-diphenylmethyl-4-quinazolinone (Ia) varies with the column material used. Thus, while chromatography of the crude product over silica gel afforded[5] a number of quinazoline and 3,4-dihydroquinazoline derivatives including a dimer, that over alumina furnished, besides two common products, viz. 2-(1'-hydroxydiphenylmethyl)-3,4-dihydroquinazoline (IIIa with 1'-OH) and 2-diphenylmethylquinazoline (Va), a new compound, $C_{21}H_{20}N_2O$ (M^+, m/z 316.1583), m.p. 165°C, in 19% yield. The base peak at m/z 106 (C_7H_8N, species a), and the prominent peaks at m/z 167 ($C_{13}H_{11}$, species b) and 149 ($C_8H_9N_2O$, species c) coupled with a strong IR absorption band at 1655 cm^{-1} (amide C=O) in $CHCl_3$ led us to N-(o-amino-benzyl)-diphenylacetamide (IIa) structure for the compound, corroborated by ^1H NMR spectrum (vide Exptl.).

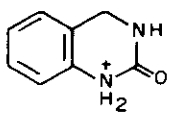
Conceivably, the ring cleaved amide (IIa) arises from the 3,4-dihydroquinazoline (IIIa). In order to ascertain the validity of this assumption as also the role of alumina surface, we required some 3,4- and 1,4-dihydroquinazolines. However, in view of the difficulty in reducing the amide function of N-alkylated 4-quinazolinones[4] and the reported[7,8] susceptibility of the dihydroquinazolines to aero-oxidation, we decided to chromatograph directly the crude products of Raney nickel desulphurisation[9] of some dihydro-4-thioquinazolines (IVa - IVg), derived[10,11] from the corresponding 4-oxo analogues (Ia - Ig).



a, m/z 106



b, m/z 167



c, m/z 149

The results shown in the Table revealed that irrespective of the column material, 1,4-dihydroquinazolines (IIIf and IIIg) could not be isolated. Nevertheless, silica gel column allowed the separation of all the 3,4-dihydroquinazolines (IIIa - IIIe) though only the N_3-substituted thiones furnished the corresponding dihydroquinazolines (IIId and IIIe) over alumina. Again, the open-chain amides (II) were obtained from the 2-alkyl/aryl substituted thiones (IV) irrespective of alkyl substitution at N-1 only when alumina was used. The formation of other products, however, depended on the N-substitution rather than the adsorbent.

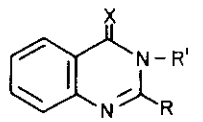
That I, II and V are derived indeed through the intermediacy of dihydroquinazolines (III) initially formed could be more clearly demonstrated as in the sequel. When pure IIIb and IIId were separately kept adsorbed on alumina for 36 hr and eluted thereafter, the former gave the amide (IIb) and quinazoline derivative (Vb) in respective yields of 20 and 60%, and the latter furnished 4-quinazolinone derivative (Id) in 75% yield as the sole isolable product.

Since the formation of open-chain amides (II) was not observed with the N_3-substituted dihydroquinazolines in which the double bond is located between N_1 and C_2, it appeared likely that a double bond between C_2 and N_3 is a prerequisite for this transformation. Presumably, the $\Delta^{2,3}$-tautomer is involved in case of the 2-substituted compounds. Furthermore, the ring opening requires

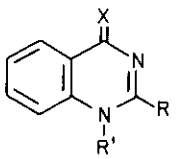
Table. Products of desulphurised 4-thioquinazolines on chromatography.

4-Thio-quinazolines	Adsor-bent*	Dihydro-quinazolines(%)	Amides (%)	Quinazolines (%)	4-Quinazoli-nones (%)
IVa	S	IIIa(11)	-	Va(26)	-
	A	-	IIa(7.5)	(31)	-
IVb	S	IIIb(10)	-	Vb(44)	-
	A	-	IIb(7.7)	(29)	-
IVc	S	IIIc(Unstable)**	-	Vc**	-
	A	-	IIc(7.3)	(33)	-
IVd	S	IIId(29)	-	-	Id(21)
	A	(10)	-	-	(22)
IVe	S	IIIe(6)	-	-	Ie(30)
	A	(28)	-	-	(22)
IVf	S	-	-	-	If(50)
	A	-	IIf(7.4)	-	(21)
IVg	S	-	-	-	Ig(48)
	A	-	IIg(7.7)	-	(20)

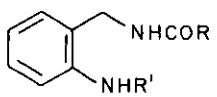
* S = silica gel, A = alumina ** Even during crystallisation, IIIc was partially converted to Vc. As such the yields could not be accurately estimated.



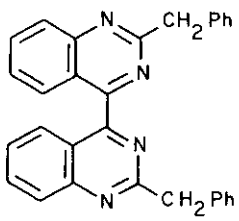
I a-e, X = O
IV a-e, X = S



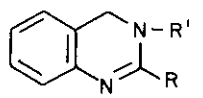
I f,g, X = O
IV f, g, X = S



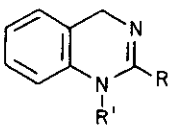
II a-c, f, g



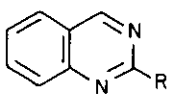
VI



III a-e



III f, g



V a-c

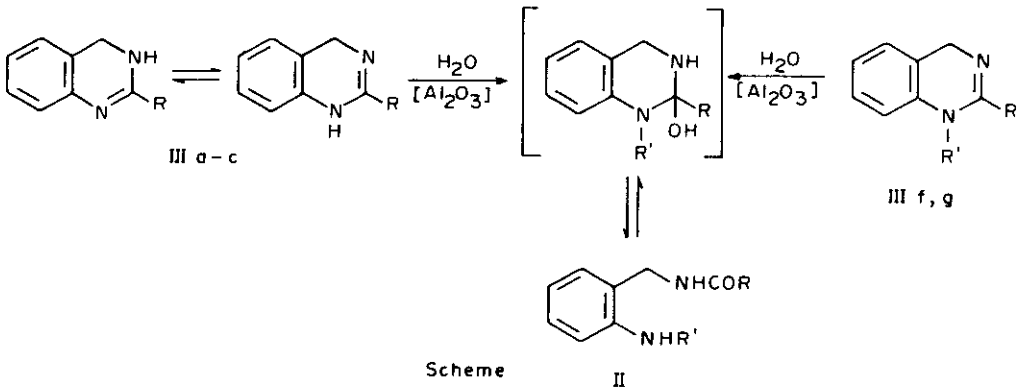
a R = $CHPh_2$, R' = H; b: R = CH_2Ph, R' = H; c: R = CH_3, R' = H; d: R = CH_2Ph, R' = CH_3
e R = H, R' = Ph; f: R = R' = CH_3; g: R = CH_2Ph, R' = CH_3

a ring-chain tautomerism of an intermediate carbinolamine that necessitates hydration at the C_2–N_3 double bond (Scheme). As the open-chain amide was not obtained by chromatography through silica gel or by acid/base treatment of the dihydro derivative, obviously the hydration must have been induced by alumina which is known[12-15] to cause a variety of surface catalysed secondary reactions.

The conversion of dihydroquinazolines to quinazolines evidently requires an available hydrogen at N_3 for elimination since quinazolinones were obtained instead when either of the nitrogen atoms was substituted.

The oxidation of the reactive methylene group at C-4 conceivably involves a free

radical mechanism[16] plausibly through a hydroperoxide intermediate[3,5]. The isolation of a hitherto unknown dimer, m.p. 180°C, characterised as 2,2'-dibenzyl-4,4'-biquinazolinyl (VI) by spectral analysis (vide Experimental), on



Scheme II

chromatography of desulphurised product of 2-benzyl-3,4-dihydro-4-thioquinazoline (IVb) over silica gel supports this contention. None of the other products, viz. quinazoline (Vb) or the dihydroquinazoline (IIIb) yielded the dimer on being refluxed with deactivated Raney nickel in alcoholic solution. It is, therefore, unlikely that mere adsorption of the 3,4-dihydroquinazolines on alumina would trigger radical reaction though the facile aero-oxidation[7,8] appear to be peculiar to this system.

EXPERIMENTAL

Alumina (according to Brockmann; S. Merck, India) and silica gel (60-120 mesh; B. D. H., India) were used for chromatography. The ir (ν_{max} in cm^{-1}) and ^1H nmr (δ ppm from TMS) spectra were taken in nujol mull and $CDCl_3$ respectively.

General procedure for desulphurisation: An alcoholic solution of the 4-thioquinazoline was treated with excess Raney nickel (activity W2), heated under reflux till tlc indicated disappearance of the starting material. After usual work-up, the crude mixture was chromatographed. The physical data of the products are given below:

IIa: m.p. 165°C; ir 1615 (1655 in $CHCl_3$); ^1H nmr 4.27 (2H, d, J = 6Hz, $ArCH_2NHCO$), 4.57 (2H, s, $ArNH_2$), 4.95 (1H, s, $CHPh_2$), 6.3-7.4 (14H, m, ArH); MS m/z 316 (M^+), 167, 165, 152, 149, 121, 106 (100%), 77.

IIb: m.p. 119°C; ir 1623; ^1H nmr 3.53 (2H, s, $COCH_2Ph$), 4.25 (2H, br, $ArNH_2$),

4.32 (2H, d, J = 6Hz, $ArCH_2NHCO$), 5.75 (1H, br, NHCO), 6.50-7.30 (9H, m, ArH); MS m/z 240 (M^+), 149, 121, 106 (100%), 91, 77.

IIc: m.p. 114°C (Lit.[18] m.p. 113.5°C); ir 1658, 1641, 1615; ^1H nmr 2.00 (3H, s, $COCH_3$), 4.30 (2H, br, $ArNH_2$), 4.38 (2H, d, J = 6Hz, $ArCH_2NHCO$), 5.82 (1H, br, NHCO), 6.66-7.34 (4H, m, ArH); MS m/z 164 (M^+), 149, 121 (100%), 106, 76, 43.

IIf: m.p. 101°C; ^1H nmr 2.01 (3H, s, $COCH_3$), 2.79 (3H, s, $NHCH_3$), 4.39 (2H, d, J = 6Hz, $ArCH_2NHCO$), 5.73 (1H, br, NHCO), 6.45-7.35 (4H, m, ArH); MS m/z 178 (M^+, 100%), 135, 120, 119, 118, 91.

IIg: m.p. 91-93°C; ir 1653; ^1H nmr 2.78 (3H, s, $NHCH_3$), 3.56 (2H, s, $COCH_2Ph$), 4.33 (2H, d, J = 6Hz, $ArCH_2NHCO$), 4.90 (1H, br, ArNH), 5.65 (1H, br, NHCO), 6.00-7.30 (9H, m, ArH); MS m/z 254 (M^+), 163, 135, 120, 119, 118 (100%), 91, 77.

IIIa: m.p. 171°C; ir 1650, 1618; ^1H nmr 4.61 (2H, s, $ArCH_2N$), 5.13 (1H, s, $CHPh_2$), 6.66-7.50 (14H, m, ArH); MS m/z 298 (M^+), 297 (100%), 219, 193, 167, 165, 152, 131, 105, 104, 77.

IIIb: m.p. 213°C (dec.); ir (KCl) 1660, 1640, 1630; ^1H nmr 4.05 (2H, s, $ArCH_2Ph$), 4.65 (2H, s, $ArCH_2NH$), 6.80-8.00 (9H, m, ArH); MS m/z 222 (M^+), 221 (100%), 194, 143, 131, 105, 104, 91, 77.

IIId: m.p. 245-247°C (dec.); ir 1658, 1638; ^1H nmr 3.14 (3H, s, NCH_3), 4.45 (2H, s, $ArCH_2Ph$), 4.73 (2H, s, $ArCH_2N$), 6.80-7.80 (9H, m, ArH); MS m/z 236 (M^+), 235, 220, 219 (100%), 91, 77.

IIIe: m.p. 122°C (Lit.[19] m.p. 119°C); ir 1617; ^1H nmr 4.96 (2H, s, $ArCH_2N$), 8.16 (1H, s, C_2-H), 6.92-8.48 (9H, m, ArH); MS m/z 208 (M^+), 207, 130, 77.

Vb: m.p. 70°C (Lit.[20] m.p. 59-60°C); ir 1620; ^1H nmr 4.43 (2H, s, $ArCH_2Ph$), 7.20-8.00 (9H, m, ArH), 9.29 (1H, s, C_4-H); MS m/z 220 (M^+, 100%), 219, 193, 166, 130, 117, 103, 91, 77, 76.

Vc: Oil (Lit.[21] b.p. 255°C/atm); ir 1619; ^1H nmr 2.95 (3H, s, $ArCH_3$), 7.54-8.18 (4H, m, ArH), 9.38 (1H, s, C_4-H); MS m/z 144 (M^+, 100%), 143, 129, 117, 103, 102, 76.

VI: m.p. 180°C; ir 1616; ^1H nmr 4.51 (4H, s, 2 x $ArCH_2Ph$), 7.20-8.20 (18H, m, ArH); MS m/z 438 (M^+, 100%), 437, 256, 219, 218, 91.

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