Tetrahedron Letters,Vol.27,No.43,pp 5255-5256,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

ON THE ISOMERIZATION OF DIALKYL INDAZOLONES TO DIHYDRO-QUINAZOLINONES

Leandro Baiocchi* and Giuseppe Picconi
Research Institute Angelini F., Viale Amelia 70, 00181 ROMA - ITALIA

Summary: 1,2-dialkyl-3-indazolones isomerize in basic medium to dihydro-4-quinazolinones. These latter, under more drastic conditions, undergo dismutation to 4(3H)-quinazolinones and anthranilamides.

Although the rearrangement of indazoles to quinazolines is described for 1-benzyl-indazole (1,2) and for 3-amino-1-benzyl-indazole (in the latter case only with a simultaneous oxidation (3)), this transformation is not general. In fact indazoles are usually resistant to the action of alkalies. 1-benzyl-3-methyl-indazole, 1-benzyl-3-methoxy-indazole, 1-benzyl-3-hydroxy-indazole and 1-benzyl-3-indazolecarboxylic acid are recovered unaltered after long boiling with NaH in toluene.

In the course of our studies on indazole derivatives oxygenated in position 3 we could observe a simple case of isomerization in basic medium from 1,2-dialkyl-indazolones 1 to dihydro-4(3H)-quinazolinones of formula 2 or 3.

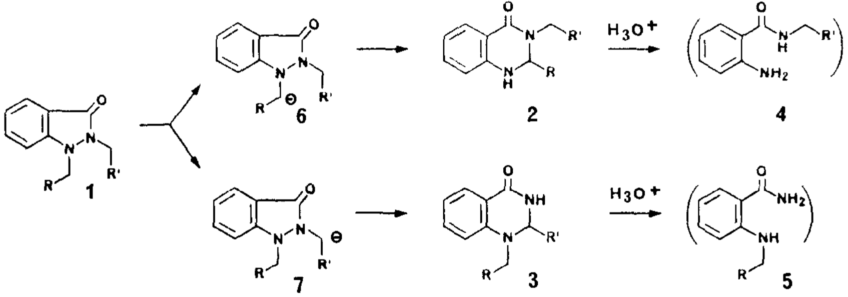


TABLE 1

STARTING INDAZOLES	R	R'	T(h)	YIELDS OF OBTAINED QUINAZOLINONES	ISOLATION TECHNIQUE	NMR (ALIPHATICS)	MASS SPECTRUM
1A[a]	Ph	H	0.25	2A[b] (88)	R	2.82: s,3H,$C\underline{H}_3$-N 5.70: s,1H,$C\underline{H}$-NH	238(6), 162(9), 161(100) 120(8), 92(8)
1B[c]	H	Ph	18	3B[d] (59)	R	2.69: s,3H,$C\underline{H}_3$-N 5.57: s,1H,$C\underline{H}$-NH	238(8), 161(100),134(15) 105(17), 104(16)
1C[e]	Ph	Ph	2.5	2C[f] (30)	C	3.63, 5.49: AX system,J=15cps $C\underline{H}_2$-Ar 5.60: s,1H,$C\underline{H}$	314(19), 237(85), 223(52) 180(16), 91(100)
				3C[g] (26)	C	4.13, 4.53: AB system,J=16cps $C\underline{H}_2$-Ar 5.71: s,1H,$C\underline{H}$	314(41), 237(66), 181(19) 180(42), 91(100)
1D[h]	Me	H	24	3D[i] (8)	C	1.17: t,3H,$C\underline{H}_3$-CH_2; 3.30: q,2H,J=6cps,$C\underline{H}_2$-CH_3; 4.55: s,2H,NH-$C\underline{H}_2$	176(61), 175 (100) 132(55), 119(32), 77(30)

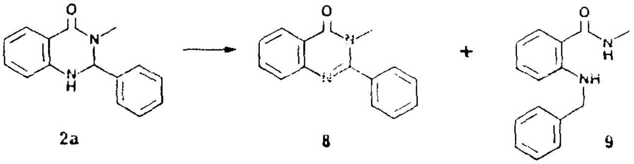
a) H. Milrath, Monatsh. Chem. 29, 927 (1908); b) m.p. 164-5°C (Lit. 165°C, H. Böhne, H. Böing, Arch. Pharm. 293, 1011 (1960)); c) m.p. 90-1°C, from sodium salt of 1-methyl-3-indazolol and benzyl chloride in ethanol; d) m.p. 206-8°C (Lit. 206-207°C, H. Gurien, B.B. Brown, J. Pharm. Sci. 52, 1102 (1963)); e) m.p. 147-9°C, from 1-benzyl-3-indazolol sodium salt and benzyl chloride; f) m.p. 157-160°C (Lit. 163-5°C, H.L. Yale, M. Kalkstein, J. Med. Chem. 10, 334 (1967)); g) m.p. 127-29°C (V. Bhaskar Rao, C.V. Ratnam, Indian J. Chem. Sect. B 16B(2), 144 (1978)); h) m.p. 76-8°C, from 1-ethyl-3-indazolol sodium salt and methyl iodide; i) m.p. 110-12°C (Lit. 112-13°C, G. Pala, A. Mantegani, Gazz. Chim. Ital. 94, 595 (1964)).

All the reactions were carried out in a 0.5 M toluenic solution at 80°C with an equivalent of sodium hydride at the times reported in Table 1. The products were purified by crystallization (R) or separated by column chromatography and then recrystallized (C). Partial transformations were obtained also by refluxing the product of formula 1 in an alcoholic solution of sodium alcoholate or in a two-phase medium using NaOH aqueous solutions.

The structure of all the compounds of type 2 or 3 thus obtained was confirmed by both NMR and Mass spectrometry and by comparison with substances already described in the literature and also by using Gas/Mass spectrometry for the detection in the mixtures of acidic hydrolysis of the corresponding 4 or 5 substituted anthranilamides (Table 2).

As emerges from the results reported in Table 1, the formation of the derivatives of type 2 or 3 clearly depends on the tendency of the substrate to form one of the two possible carbanions 6 or 7, which respectively depend on the nature of R and R'. As regards positions, position 1 seems to be slightly more reactive than position 2.

Furthermore as the presence of traces of secondary products was noticed in the gaschromatographic analysis of some reaction raw mixtures, an investigation on their origin and nature was also carried out. Finch and Gschwend (3) had already noticed the formation of quinazolines from dihydroquinazolines by proton abstraction and had excluded that the quinazolines could form by dismutation. On the contrary we found by long heating (50 hours) of a 3% toluenic solution of 2a under nitrogen stream, in the presence of sodium hydride (0.5 mol.), the formation of equimolecular amounts of 3-methyl-2-phenyl-4(3H)-quinazolinone 8 (4) and of N-benzylanthranilic acid methylamide 9 (5).



The correlation between this dismutation and that of Cannizzaro is singular, even though a further research is required on the reaction mechanism of the former.

TABLE 2

PRODUCT	MASS SPECTRUM
4A[a]	150(100), 120 (99), 119 (59), 92 (52), 65 (29)
4C[b]	226 (34), 120 (34), 106(100), 91 (21)
5C[c]	226 (56), 209 (38), 181 (38), 180(100), 91 (47)

a) A. Weddige, J.Prakt. Chem. (2) 36, 150 (1887); b) O.C.Denner, J.King, J.Org. Chem. 8, 168 (1943); c) W.L.F. Armarego, J. Chem. Soc. 2697 (1961).

References

1) B. A. Tertov, P.P. Onishchenko,V. V. Bessonov, Khim. Geterotsikl. Soedin. 1410 (1974).
2) A. M. Simonov, B.K. Martsokha, F. T. Pozharskii, Zh. Obshch. Khim. 32, 2388 (1962).
3) N. Finch, H.W. Gschwend, J. Org. Chem. 36, 1463 (1971).
4) M. Körner, J. Prakt. Chem. (2) 36, 162 (1887).
5) S. C. Pakrashi, A. K. Chakravarty, J. Org. Chem. 37, 3143 (1972).

(Received in UK 4 September 1986)