FORMATION OF AMINOQUINAZOLINONES FROM N-(2-AMINOBENZOYL)-N'-AROYLHYDRAZINES

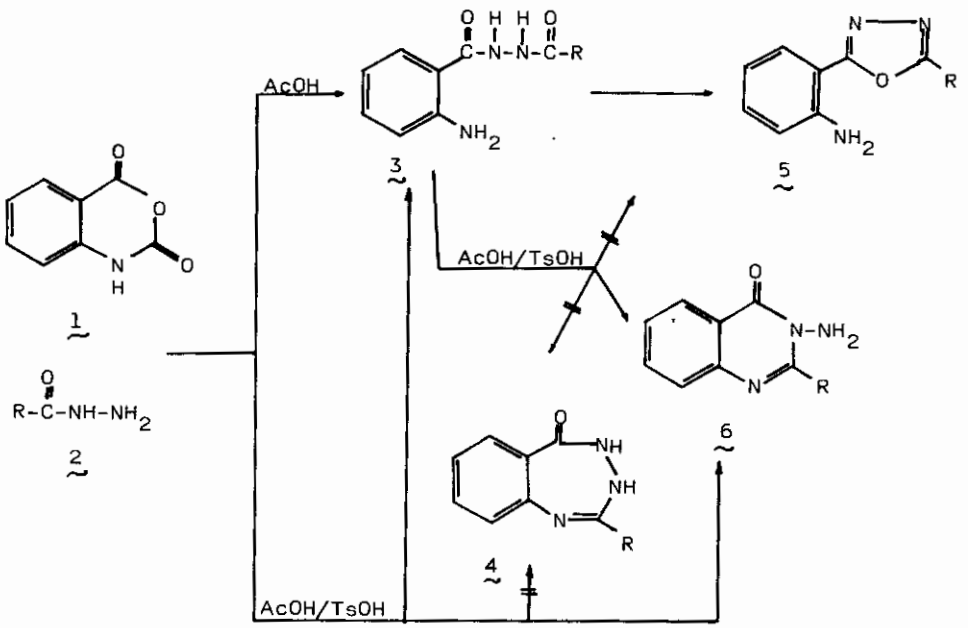
Melinda Gál*, Endre Tihanyi and Péter Dvortsák
Institute for Drug Research, Budapest, P.O.B. 82, H-1325 Hungary

Abstract - The ring closure of N-(2-aminobenzoyl)-N'-aroylhydrazines 3 in AcOH/TsOH yielded 2-aryl-3-amino-4(3H)-quinazolinones 6 instead of 2-aryl-3,4-dihydro-5H-1,3,4-benzotriazepin-5-ones 4 as reported before. The structure of the aminoquinazolinones 6 was confirmed by unambiguous synthesis.

During the last few years several papers have been published on the synthesis of 1,3,4-benzotriazepines starting with 2-aminobenzoic acid hydrazide derivatives. It is well known that hydrazide derivatives can form oxadiazole but the presence of the 2-amino group was expected to eliminate the possibility of this reaction and to favour the formation of condensed heterocycles. Later some of the early methods for the synthesis of 1,3,4-benzotriazepines proved to be inappropriate, because the products were still 1,3,4-oxadiazoles[1,2,3] or under certain conditions 3-amino-4(3H)-quinazolinones[4,5] instead of the desired compounds.

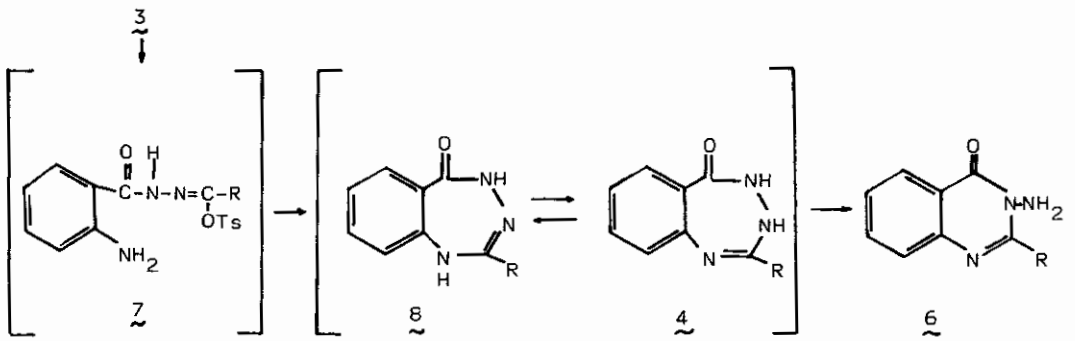
Recently a new method has been reported[6] for the preparation of 2-aryl-3,4-dihydro-5H-1,3,4-benzotriazepin-5-ones 4: isatoic anhydride 1 and aroylhydrazines 2 (R = Ph, 4-CH_3-Ph, 4-CH_3O-Ph or 4-NO_2-Ph) were refluxed in acetic acid and yielded bisacylhydrazines 3 which were subsequently heated with a catalytic amount of p-toluenesulfonic acid in acetic acid. The products of this latter reaction could also be isolated in addition to 3 when 1 was reacted with various 2 in AcOH/TsOH. The new products were assigned as benzotriazepines 4.

We felt this assignation doubtful because under these reaction conditions the formation of 3-amino-4(3H)-quinazolinones 6 can be expected[4,5] as well and it was not taken into consideration[7].



We examined the above reactions (R = Ph and 4-NO_2-Ph in 2) and isolated the compounds by the given method. All data of these samples (previously supposed to be 4)were identical with those of the corresponding 3-amino-4(3H)-quinazolinones 6[9] prepared by unambigous synthesis[10-11]. Consequently the 2-amino group of 3 really took part in the ring closure but the reaction led to the formation of the known quinazolinones 6.

The reaction might proceed via detosylative cyclization of the proposed[6] tosylate esters 7, but the products 8 could immediately rearrange and thus 6 were isolated. As it was pointed out earlier[4,5] the formation of the smaller-sized heterocycles can be explained by thermodynamical reasons.



EXPERIMENTAL

All mps are uncorrected. IR spectra were measured using a Perkin Elmer 577 spectrometer. ^{1}H NMR spectra were obtained at 60 MHz on a Jeol 60 HL spectrometer, using TMS as internal standard. All compounds gave satisfactory microanalytical data.

6 were prepared by Reddy's procedure[6] (Method A and B) - proposed erroneously for the synthesis of 2-aryl-3,4-dihydro-5H-1,3,4-benzotriazepin-5-ones 4 - and by unambigous route[10,11] (Method C). All data of the corresponding 6 prepared by Methods A, B and C were identical[9].

3-Amino-2-aryl-4(3H)-quinazolinones 6 (General procedures)

Method A: A mixture of isatoic anhydride 1 (1.6 g, 10 mmol), aroylhydrazine 2 (10 mmol) and p-toluenesulfonic acid (0.02 g) in acetic acid (10 ml) was refluxed for 9 h. The cold solution was added slowly to water (250 ml) and extracted with chloroform (3x50 ml). The combined chloroform phases were washed with water (30 ml) and dried (Na_2SO_4). After evaporation of the solvent the residue was chromatographed over silica using benzene/ether mixture (1:1) as eluent.

6 R=Ph *Yield: 0.88 g (37 %); mp* 181-182 °C; $[M^+]$ 237; ^{1}H NMR δ (CDCl$_3$ + DMSO-d$_6$) 8.10 (d 1H, ArH-5); 7.5-7.9 (m 8H, ArH); 5.0 (bs 2H, NH_2); IR (KBr) 3300, 3210 (NH); 1660 (C=O); 1640 (C=N); 1610 (Ar) cm^{-1}.

R=4-NO_2Ph Yield: 1.12 g (39 %); mp 250-252 °C; $[M^+]$ 282; ^{1}H NMR δ (DMSO-d$_6$) 8.30 (d 2H, ArH-3'); 8.00 (d 2H, ArH-2'); 8.2 (m 1H, ArH-5); 7.4-8.0 (m 3H, ArH-6, H-7, H-8); 5.7 (bs 2H, NH_2); IR (KBr) 3300, 3220, (NH); 1670 (C=O); 1640 (C=N); 1610 (Ar); 1520, 1350 (NO_2) cm^{-1}.

Method B: A mixture of N-(2-aminobenzoyl)-N'-aroylhydrazine 3 (1 g, 3.9-3.3 mmol) and p-toluenesulfonic acid (0.02 g) in acetic acid (10 ml) was refluxed for 9 h. The reaction mixture was worked up as in Method A.

6 R=Ph Yield: 0.35 g (38 %); mp 181-182 °C

R=4-NO_2-Ph Yield: 0.38 g (41 %); mp 250-252 °C

Spectroscopic data were identical with those of 6 obtained by Method A.

Method C: A solution of 2-aryl-3,1-(4H)-benzoxazin-4-one (10 mmol) and hydrazine hydrate (72 %, 0.69 g, 10 mmol) in ethanol (30 ml) was refluxed for 1 h. After cooling the crystals were filtered off, washed with ethanol (3x5 ml)

and added to diluted acetic acid (60 %, 25 ml). The solution was heated on a steam bath for 30 min. the resulting crystals were filtered and washed with water (3x5 ml).

6 R=Ph Yield: 1.73 g (73 %); mp 182-183 °C

R=4-NO_2-Ph Yield: 1.94 g (69 %); mp 250-252 °C

Spetroscopic data were identical with those of 6 obtained by Methods A and B.

ACKNOWLEDGEMENTS

The authors wish to thank Miss R. Andersen for technical assistance.

REFERENCES AND NOTES

1. M. Takahashi, S. Onizawa and T. Satoh, Bull. Chem. Soc. Japan, 1974, 47, 2724.
2. S. Sunder, N.P. Peet and R.J. Barbuch, J. Heterocycl. Chem., 1981, 18, 1601.
3. E. Tihanyi, M. Gál and P. Dvortsák, Heterocycles, 1983, 20, 571.
4. N.P. Peet and S. Sunder, J. Org. Chem., 1975, 40, 1909.
5. N.P. Peet, S. Sunder and D.L. Trepanier, Indian J. Chem. Sect. B, 1976, 14B/9/, 701.
6. Ch.K. Reddy, P.S.N. Reddy and C.V. Ratnam, Synthesis, 1983, 842.
7. Bisacylhydrazines can be transformed to 1,3,4-oxadiazoles[8], but the possibility that 5 formed from 3 in AcOH/TsOH was excluded[6] by comparing the product (R = 4-Me-Ph) with an authentic sample of 2-(2-aminophenyl)-5-(4-methylphenyl)-1,3,4-oxadiazole synthesized from N-(2-nitrobenzoyl)-N'-(4-methylbenzoyl)-hydrazine by ring closure and reduction.
8. Houben-Weyl, 'Methoden der organischen Chemie', Georg Thieme Verlag, Stuttgart, 1967, vol. 10/2, p. 163.
9. The two other analogues (R=4-Me-Phe and 4-MeO-Phe in 6) assigned[6] as 4 also show identical physical data with the corresponding aminoquinazolinones[10].
10. L. Legrand and N. Lozac'h, Bull. Soc. Chim. Fr., 1961, 1400.
11. A.M. Abbady, M. Anwar and M.F. Abdel-Megeed, Acta Chim. Acad. Sci. Hung., 1976, 91, 341.

Received, 28th December, 1983