Rearrangement of 3-Amino-1-benzylindazole to 4-Amino-2-phenylquinazoline

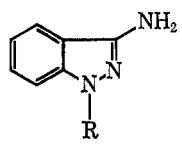
NEVILLE FINCH* AND HEINZ W. GSCHWEND

Research Department, CIBA Pharmaceutical Company, Summit, New Jersey 07901

Received October 23, 1970

Attempts to prepare 3-amino-1-benzylindazole (4) by cyclization of *o*-(1-benzylhydrazino)benzonitrile (2) yielded instead a rearranged and oxidized product 4-amino-2-phenylquinazoline (3). A mechanism for this transformation is proposed. The intermediates postulated have been synthesized and subjected to rearrangement conditions. Some comments are made about the chemistry of dihydroquinazolines.

3-Aminoindazoles 1 (R = H) have been obtained by various routes.[1-4] The preparation of specifically 1-substituted 3-aminoindazoles (R ≠ H) seemed trivial in view of the literature reports[1,3] on the ease of cyclizing *o*-hydrazinobenzonitriles. Since we were interested in



1

such compounds, we decided to synthesize the undescribed 3-amino-1-benzylindazole (4) by this approach.

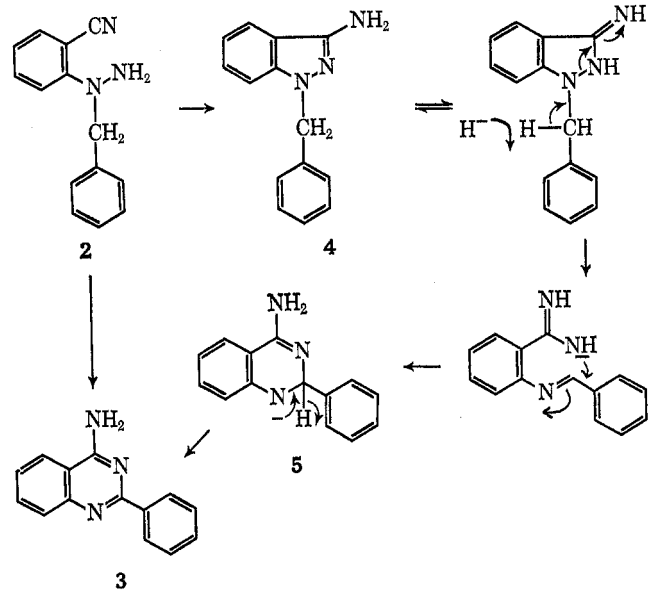
o-(1-Benzylhydrazino)benzonitrile (2) was prepared by nitrosation and subsequent reduction of *N*-benzylanthranilonitrile. However, compound 2 resisted all our numerous attempts to effect cyclization (NaOEt–EtOH, HCl, $SnCl_4$, pyrolysis), only starting material being recovered. Complete transformation of the starting material was achieved by strenuous basic conditions, namely NaH in refluxing diethylene glycol dimethyl ether. To our surprise, however, the product (32% isolated yield) was the known 4-amino-2-phenylquinazoline[5] (3). The identity of our product was confirmed by melting point, mixture melting point, and spectral comparison with a sample prepared by the literature procedure.[5] A mechanism could be proposed for this process (Scheme I) but it seemed desirable to provide further experimental support for it.

The desired 3-amino-1-benzylindazole (4) was prepared unambiguously by Curtius degradation of the known 1-benzylindazole-3-carboxylic acid.[6]

When this indazole 4 was subjected to the cyclization conditions, *i.e.*, NaH–refluxing diethylene glycol dimethyl ether, 4-amino-2-phenylquinazoline (3) could be isolated in 68% yield. This yield thus precludes a disproportionation type mechanism for the oxidation process involved in product formation. It also provides support for the contention that 4 is on the reaction pathway from 2 to 3 (Scheme I).

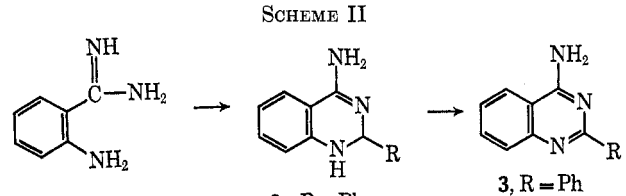
4-Amino-1,2-dihydroquinazolines are mentioned only once in the literature,[7] and the work by Carrington describes only 2,2-dimethyl compounds which are

SCHEME I



thus blocked to aromatization. Nevertheless, his procedure worked well to provide 4-amino-2-phenyl-1,2-dihydroquinazoline (6a) by condensation of *o*-aminobenzamidine with benzaldehyde (Scheme II).

SCHEME II



6a, R = Ph
b, R = CH_2Ph

3, R = Ph
7a, R = CH_2Ph
7b, R = H

Reaction of this new substance 6a with NaH in refluxing diethylene glycol dimethyl ether again gave a good yield (70%) of 4-amino-2-phenylquinazoline (3) thus providing additional support for our mechanistic scheme (Scheme I) which involves the anion derived from 6a, namely 5, as an intermediate in the rearrangement.

The chemistry of 1,2-dihydroquinazolines has had only limited attention. A precedent for the ease of aromatization can be cited, though, in the aerial oxidation (or by potassium ferricyanide) of 2-aminoalkyl-4-aryl-1,2-dihydroquinazolines.[8] However, it is important to emphasize that oxidation of 6a to 3 occurs with sodium hydride in an aprotic solvent under nitrogen and in 70% yield. This attests to a special type of reactivity in this system, imparted by the stability of

(1) (a) M. A. Aron and J. A. Elvidge, *Chem. Ind. (London)*, 1234 (1958); (b) F. C. Cooper, *J. Chem. Soc.*, 4212 (1958).

(2) (a) E. W. Parnell, *ibid.*, 4930 (1961); (b) M. W. Partridge and M. F. G. Stevens, *ibid.*, 3663 (1964).

(3) J. J. Lafferty, D. H. Tedeschi, and C. L. Zirkle, U. S. Patent 3,133,081 (1964); *Chem. Abstr.*, **61**, 4364 (1964).

(4) G. Beck, E. Degener, and H. Heitzer, *Justus Liebigs Ann. Chem.*, **716**, 47 (1968).

(5) H. Meerwein, P. Laasch, R. Mersch, and I. Spille, *Chem. Ber.*, **89**, 224 (1956).

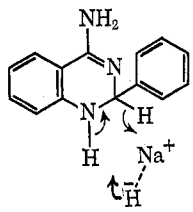
(6) K. v. Auwers and W. Schaich, *ibid.*, **54**, 1756 (1921).

(7) H. C. Carrington, *J. Chem. Soc.*, 2527 (1955).

(8) A. Marxer, U. Salzmann, and F. Hofer, *Helv. Chim. Acta*, **52**, 2351 (1969).

the radical anion or perhaps the ability of the C_2 hydrogen to leave as hydride (Scheme III).

SCHEME III



A recent publication by Pakrashi[9] describes a surprising transformation which bears on this point. Reduction of 2-benzyl-3-methyl-4-quinazolinone with sodium borohydride in methanol yields 3-methyl-4-quinazolinone, *i.e.*, borohydride effects debenzylation from carbon! Viewed in terms of the mechanism of Scheme III, this suggests that a 1,2-dihydroquinazoline anion given a choice between expelling hydride or benzyl anion, chooses, not unreasonably, the latter. (Of course, a radical mechanism cannot be excluded.) To confirm this point to our satisfaction, 4-amino-2-benzyl-1,2-dihydroquinazoline (**6b**), prepared from *o*-aminobenzamidine and phenylacetaldehyde dimethyl acetal, was reacted with sodium hydride in refluxing diethylene glycol dimethyl ether. The known 4-aminoquinazoline[10] (**7b**) was the sole isolable product in 43% yield. A mass spectrum of the mother liquors indicated trace amounts of 4-amino-2-benzylquinazoline (**7a**) suggesting that hydride loss is still present as a minor pathway.

Reaction of 4-amino-2-benzyl-1,2-dihydroquinazoline (**6b**) with sodium carbonate and potassium ferricyanide in aqueous ethanol at room temperature also gave 4-aminoquinazoline (45%) as the only isolable product. Further work is required to clarify the actual nature of the bond-breaking process at C_2 to determine whether it is homolytic or heterolytic.

Experimental Section[11]

***o*-(1-Benzylhydrazino)benzonitrile (2).**—Anthranilonitrile (10.8 g, 91.5 mmol), 12 g of $NaHCO_3$, and 10.9 ml of benzyl bromide (91.5 mmol) were refluxed in ethylene glycol dimethyl ether for 44 hr. The solvent was evaporated, and the residue was taken up in methylene chloride, washed with water, and dried over Na_2SO_4. After removal of the solvent the residue was crystallized from benzene to give a total of 10 g of analytically pure *N*-benzylanthranilonitrile (mp 114–116°).[12]

This anthranilonitrile (5.2 g, 25 mmol) was stirred at 0° in 300 ml of 6 *N* hydrochloric acid. Over a period of 3 hr, 2 g of $NaNO_2$ in 100 ml of water was added. Stirring was continued for an additional 2 hr. The precipitate was then filtered, washed successively with water, and dried *in vacuo* to give 5.8 g (97.5%) of pure *N*-nitroso-*N*-benzylanthranilonitrile (mp 69–71°; ν_{max}^{Nujol} 2230, 1490, 1435, 1060 cm^{-1}).

Anal. Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 71.27; H, 4.56; N, 17.57.

N-Nitrosoamine (2.7 g, 11.4 mmol) was stirred in 30 ml of water under an atmosphere of nitrogen. Then 2.34 g of zinc dust and dropwise 3.9 ml of acetic acid were added. The temperature was then raised to 60–65° and maintained at this level for 0.5 hr. After cooling, the aqueous solution was made basic with sodium carbonate and the product extracted into methylene chloride. After drying and evaporating the solvent, 2.4 g of solid was obtained. A part thereof was recrystallized from ether to give an analytically pure sample of *o*-(1-benzylhydrazino)-benzonitrile (2) (mp 109–111°; $\nu_{max}^{CH_2Cl_2}$ 3440, 3370, 3200, 2230, 2210, 1605, 1575, 1530, 1490 cm^{-1}).

Anal. Calcd for $C_{14}H_{13}N_3$: C, 75.31; H, 5.87; N, 18.82. Found: C, 75.43; H, 5.77; N, 18.67.

3-Amino-1-benzylindazole (4).—1-Benzylindazole-3-carboxylic acid[6] (22 g, 87 mmol) was refluxed for 1.5 hr in 150 ml of thionyl chloride. The excess reagent was then removed *in vacuo* and the residue dissolved in 200 ml of acetone. Then a solution of 42 g of NaN_3 in 200 ml of water was added to the cold solution of the acid chloride. The precipitated azide was stirred for 2 hr. Crushed ice was then added and after 1.5 hr more the product was filtered and dried at room temperature *in vacuo*. The azide was then dissolved in 700 ml of ethanol and refluxed for 20 hr to give the corresponding urethane (mp 114–116°; ν_{max}^{Nujol} 3200, 1730, 1715 cm^{-1}), which did not have to be isolated for the next step. The ethanolic solution was reduced to about half its volume and then refluxed for 20 hr with 200 ml of 30% aqueous KOH. The ethanol was then distilled off, and the aqueous solution was cooled and diluted with water to precipitate the amine. The product was filtered off, washed with water, and dried to yield 17.4 g (mp 114–116°) or 90% overall from the acid.

A 300-mg sample was recrystallized from ethanol to give shiny needles: mp 115–116°; nmr ($CDCl_3$) δ 4.18 (singlet, 2 H), 5.3 (singlet, 2 H), 6.8–7.6 (multiplet, 9 H); $\lambda_{max}^{CH_3OH}$ 232 mμ (ϵ 16,770), 318 (4800); ν_{max}^{Nujol} 3440, 3305, 3200, 1623, 1606, 1572, 1535 cm^{-1}.

Anal. Calcd for $C_{14}H_{13}N_3$: C, 75.31; H, 5.87; N, 18.82. Found: C, 75.44; H, 5.74; N, 18.85.

4-Amino-2-phenylquinazoline (3). A.—*o*-(1-Benzylhydrazino)-benzonitrile (5.9 g, 26.5 mmol) and 1.55 g of 55% NaH (washed three times with anhydrous ether, 1.2 equiv) were dissolved and refluxed under nitrogen in 120 ml of dry diethylene glycol dimethyl ether for a period of 16 hr. The solvent was then removed *in vacuo*, water was added, and excess base was neutralized with 2 *N* HCl to a pH of 8. The product was extracted into CH_2Cl_2. After drying and removing all solvent, the dark residue was dissolved in ether and treated with charcoal. From ether–hexane 1.9 g of quinazoline was obtained (mp 140–143). Recrystallization from ether gave an analytically pure sample (mp 143–145°).

B. 3-Amino-1-benzylindazole (1.0 g, 4.5 mmol) and 260 mg of 55% NaH (washed three times with ether) was refluxed as described in A in 20 ml of dry diethylene glycol dimethyl ether. After the work-up procedure (as described in A), a total of 680 mg of quinazoline were obtained (68%). Recrystallization from ether–hexane gave 530 mg of a pure sample (mp 144.5–145.5°). The products from A and B showed identical analytical and spectroscopic properties (ir, uv, nmr, mass spectrum).

C.—4-Amino-2-phenyl-1,2-dihydroquinazoline hydrochloride (1.3 g, 5 mmol) was worked up to the free base using sodium carbonate and dichloromethane. The organic layer was dried over Na_2SO_4 and the solvent removed to complete dryness. The gummy residue was dissolved in 20 ml of dry diglyme and refluxed together with 260 mg of NaH (55%, washed three times with dry ether) for 16 hr under a nitrogen atmosphere. The solvent was then removed *in vacuo* (water aspirator), ice and water were added to the residue, and the mixture was transferred into a separating funnel using methylene chloride. The aqueous phase was made neutral with 2 *N* HCl and then basic with dilute sodium carbonate solution and the product extracted into methylene chloride. After drying over Na_2SO_4 and removal of the solvent *in vacuo*, 1 g of solid material was obtained. Recrystallization from ether–hexane gave 330 mg (mp 144–145°) as a first crop and 400 mg (mp 138–142°) as a second crop (70%). The material was identical in all respects (analysis, melting point, ir, uv, mass spectrum) with the 4-amino-2-phenylquinazoline obtained under A and B.

4-Amino-2-phenyl-1,2-dihydroquinazoline (6a).—*o*-Aminobenzamidine dihydrochloride[7] (10.4 g, 50 mmol) and 5 ml of benzaldehyde (50 mmol) were refluxed for 1 hr in 180 ml of ethanol under an atmosphere of nitrogen. The warm solution was filtered to remove a small amount of insoluble material. After concentrating the reaction mixture to about one-half of its original volume, ether was added until the solution turned very slightly turbid. The product crystallized as a monohydrochloride (8.8 g, mp 211–215°). Analytically pure material was ob-

(9) S. C. Pakrashi and A. K. Chakravarti, *Chem. Commun.*, 1443 (1969).

(10) J. S. Morley and J. C. E. Simpson, *J. Chem. Soc.*, 1354 (1959).

(11) Melting points were obtained in a Thomas-Hoover melting point apparatus and are uncorrected. Nmr spectra were obtained on a Varian A-60 instrument.

(12) A. M. Simonov, B. K. Martsokha, and F. T. Pozharskii, *Zh. Obshch. Khim.*, **32**, 2388 (1962).

tained by recrystallizing a sample from ethanol-ether: mp 216–219°; $\nu_{cm^{-1}}^{Nujol}$ 1660, 1626, 1605; $\lambda_{max}^{CH_3OH}$ 228 mμ (ε 37,300,)258 (7540), 348 (2080), 370 (3280).

Anal. Calcd for $C_{14}H_{13}N_3 \cdot HCl$: C, 64.75; H, 5.43; N, 16.18. Found: C, 64.54; H, 5.73; N, 16.18.

4-Amino-2-benzyl-1,2-dihydroquinazoline (6b).—*o*-Aminobenzamidine hydrochloride[7] (8.4 g, 40 mmol) and 6.65 g of phenylacetaldehyde dimethyl acetal (40 mmol) were refluxed for 3 hr in 170 ml of ethanol. After cooling the reaction mixture, the ethanol was evaporated *in vacuo*, the residue taken up in methylene chloride and washed with an aqueous sodium carbonate solution under an atmosphere of N_2, and the organic layer dried over Na_2SO_4. The solvent was then removed and the residue dissolved in hot benzene. Upon cooling 5.6 g (59%) of product was obtained which after recrystallization from benzene showed mp 145–147°; $\nu_{cm^{-1}}^{Nujol}$ 3455, 3370, 1660, 1620, 1605; $\lambda_{max}^{CH_3OH}$ 232 mμ (ε 50,800), 261 (9100), 359 (2200); nmr (DMSO-d_6) δ 6.4–7.5 (m, 9 H), 5.9 (s, 1 H exchange), 5.4 (s, 2 H exchange), 4.92 (t, J = 6 Hz, 1 H), 3.91 (d, J = 6 Hz, 2 H).

Anal. Calcd for $C_{15}H_{15}N_3$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.97; H, 6.50; N, 17.43.

4-Amino-2-benzyl-1,2-dihydroquinazoline (6b) → 4-Aminoquinazoline (7b). A.—4-Amino-2-benzyl-1,2-dihydroquinazoline (480 mg, 2 mmol) and 120 mg of NaH (55%, washed three times with anhydrous ether) were refluxed under an atmosphere of N_2 in 12 ml of dry diethylene glycol dimethyl ether for a period of 16 hr. After cooling, the reaction mixture was diluted with CH_2Cl_2, washed with dilute $NaHCO_3$ solution, and dried over Na_2SO_4. After removal of the solvent the residue (170 mg) was crystallized from CH_2Cl_2–ether to give 120 mg of 4-aminoquinazoline (**7b**): mp 258–260° (lit.[10] 259–260° and 267°); mass spectrum *m/e* 145 (Calcd for $C_8H_7N_3$: 145.064. Found: 145.063.).

B.—4-Amino-2-benzyl-1,2-dihydroquinazoline (480 mg, 2 mmol) were stirred at room temperature in 20 ml of ethanol with a solution of 3 g of $K_3Fe(CN)_6$ and 1.7 g of K_2CO_3 in 22 ml of water for 2 hr. The solvent was then partially removed and, after the addition of 4 ml of 10 *N* NaOH solution, the mixture was extracted with CH_2Cl_2. From the residue (170 mg), 130 mg of 4-aminoquinazoline (**7b**), mp 257–260°, was obtained (45%).

Registry No.—**2**, 28519-76-8; **3**, 1022-44-2; **4**, 28519-78-0; **4**, 28519-78-0; **6a** HCl, 28607-64-9; **6b**, 28519-79-1; *N*-nitroso-*N*-benzylanthranilonitrile, 28519-75-7.

Acknowledgment.—We wish to acknowledge the support and encouragement of Dr. George deStevens, the technical assistance of Mr. Ali Hamdan, and helpful discussions with Mr. L. Dorfman, whose staff we thank for microanalyses and spectra.

Quinazolines and 1,4-Benzodiazepines. LII.[1] Rearrangement of 1-Alkyl-7-chloro-1,3-dihydro-3-acetoxy-3-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-ones with Base

A. WALSER,* G. SILVERMAN, J. BLOUNT, R. IAN FRYER, AND L. H. STERNBACH

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

Received October 22, 1970

The preparation and rearrangement of the title compounds (**2a,b**) to 2,5-epoxy-1,4-benzodiazepin-3-ones (**3a,b**) are described. The further rearrangement of the 2,5-epoxy compound **3a** to the corresponding 3-hydroxy-1,4-benzodiazepin-2-one **4a** is shown, and the possible mechanisms involved in these conversions are discussed. The determination of the structure of **3a** by single X-ray diffraction analysis is also presented.

Although considerable attention has been devoted to 3-substituted 1,4-benzodiazepines, 3-hydroxy-3-methyl derivatives are not reported in the literature. Bell and coworkers[2] attempted the preparation of 7-chloro-1,3-dihydro-3-hydroxy-3-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one by hydrolysis of the corresponding 3-acetoxy derivative. Using either acid or base, they obtained only 2-acetyl-6-chloro-4-phenylquinazoline.

Since 1,4-benzodiazepines bearing an alkyl substituent in the 1 position cannot undergo a similar rearrangement to quinazolines, we were able to prepare 7-chloro-1,3-dihydro-1,3-dimethyl-3-hydroxy-5-phenyl-2*H*-1,4-benzodiazepin-2-one (**4a**) by acid hydrolysis of the corresponding acetate **2a** (Scheme I).

The benzodiazepine structure assigned to **4a** is based on spectroscopic data which would not satisfy the alternate 2-acetyl-2-hydroxy-1,2-dihydroquinazoline structure (intermediate A in Schemes II and III). The uv spectra of **4a** and **2a** do not differ from those of other related benzodiazepine derivatives. The intermediate A would be expected to show the uv characteristics of compound **7**, the hydrochloride of which has a strong maximum at 450–454 mμ.[3] An absorption of this kind is not observed for compound **4a** in 0.1 *N* hydrochloric acid. The carbonyl band at 1660 cm^{-1} in the ir spectrum of **4a** certainly speaks for the benzodiazepine structure. The same argument holds for the chemical shift of the methyl group which is not compatible with an acetyl group free of unusual shielding. The conformational equilibrium observed in dimethyl sulfoxide solution gives additional support to the assigned structure, for such conformational equilibria have been found with other benzodiazepines.[4]

Surprisingly, the use of sodium methoxide in methanol did not lead to the 3-hydroxybenzodiazepine **4a** but to compound **3a**. The same reagent also effected the conversion of **4a** to **3a**. A plausible mechanism for these rearrangements is shown in Scheme II. If R represents hydrogen, the intermediate A would convert readily to 2-acetyl-6-chloro-4-phenylquinazoline (**6**) by dehydration.

We were able to reverse this rearrangement and obtained the 3-hydroxy-3-methylbenzodiazepine **4a** by treatment of compound **3a** with hydrogen chloride in ethanol. The proposed mechanism is shown in Scheme III and is envisioned as proceeding through the same intermediate A.

We also looked into the possible formation of 7-chloro-1,3-dihydro-3-hydroxy-3-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one by controlled acid-catalyzed ethanolysis of the 1-methoxymethyl derivative **2b**. While mild ethanolysis allowed the preparation of com-

(1) Paper LI: N. W. Gilman and L. H. Sternbach, *J. Heterocycl. Chem.*, **8**, 297 (1971).

(2) S. C. Bell, *et al.*, *ibid.*, **33**, 457 (1968).

(3) Compare G. F. Field, *Chem. Commun.*, 886 (1969).

(4) P. Linscheid and J. M. Lehn, *Bull. Soc. Chim. Fr.*, 992 (1967).