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3-AMINOQUINAZOLINES: STRUCTURAL ASSIGNMENTS

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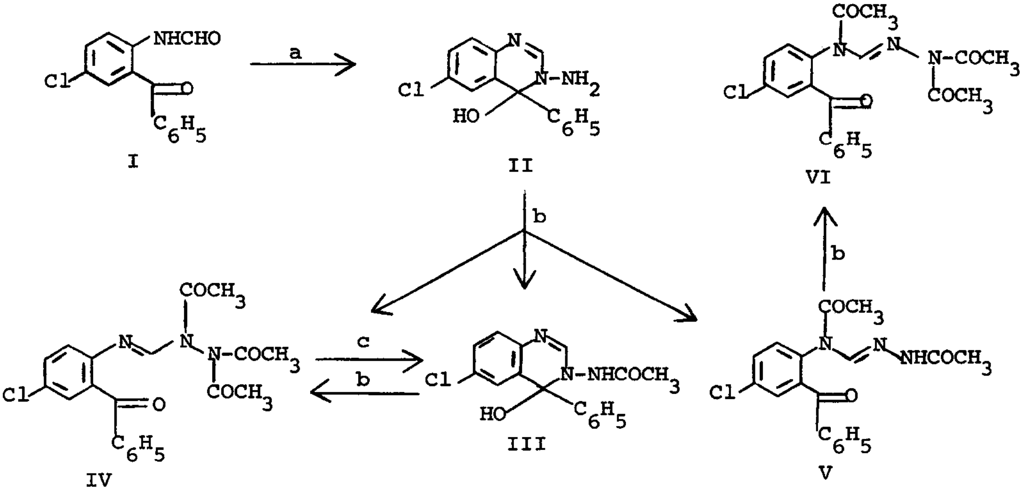
We wish to report ring-chain tautomerism of the novel 3-aminoquinazoline, II and its acetylation products. Structural assignments of the compounds were based on physico-chemical correlations with two x-ray defined structures, II and IV. Recently some of these compounds, prepared by a similar route, have been described incorrectly as 1,3,4-benzotriazepine derivatives (1).



a, hydrazine in ethanol; b, acetic anhydride in pyridine; c, KOH in methanol.

The starting material I (mp 90-91°), prepared by the formylation of 2-amino-5-chlorobenzophenone, was treated with hydrazine to afford a simple monodehydrated condensation product. That amide carbonyls are attacked by hydrazine is well known (2), but it is interesting that hydrazine appeared to have attacked initially the amide carbonyl (3). Such was suggested by the presence of 2-amino-5-chlorobenzophenone as a by-product and the absence of hydrazone derivatives in the reaction mixture. Thus, treatment of I with a slight excess of hydrazine in ethanol gave a 92% yield of II as colorless needles, mp 196-198°.

Chemical evidence was most compatible with the assignment of the quinazoline structure to II and included the conversion of II into the known (4) 6-chloro-4-phenylquinazoline (VII) by treatment with nitrous acid.

When compound II was treated with an excess of acetic anhydride in pyridine, a triacetate (IV) was obtained which had the same mp (105-7°) as, and exhibited spectral character identical with, that reported for the compound described in the literature as a triacetate of a benzotriazepine (1). The saponification of IV with methanolic potassium hydroxide gave a 79% yield of a monoacetyl derivative, mp 160-162°, to which structure III has been assigned. Compound III rapidly regenerated IV on acetylation. In addition to compound IV, the acetylation of II yielded a diacetate V, mp 164-166°. Compound V reacted slowly with acetic anhydride in pyridine to give a new triacetate VI, mp 134-136°, very similar spectrally to, but not identical with IV.

The mass spectral analyses of II and its acetates allowed classification into two fragmentation groups. Compounds II and III exhibited spectra closely related to the quinazoline VII (5), while compounds IV, V, and VI were classified as aminobenzophenones in character (6). Similarly, the uv spectra indicated II and III to belong to one class (7) while compounds IV, V and VI could be grouped in another (8).

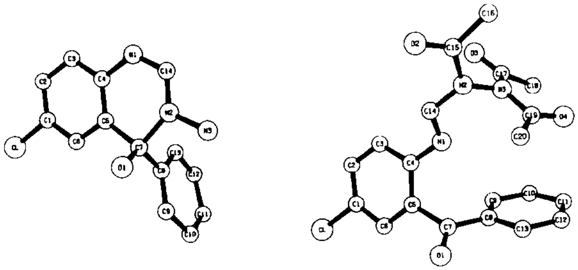
The structural correlations for II and its acetates based on the above may be readily seen. However, an unequivocal structural assignment for any one of those compounds based on purely chemical or conventional spectral data could not be envisioned. Thus, the readily available and nicely crystalline compound IV was subjected to single crystal x-ray analysis.

Compound IV crystallized from ethanol as well-formed prisms with cell parameters $\underline{a}$ = 8.289(2), $\underline{b}$ = 8.953(2), $\underline{c}$ = 27.004(5), Å, $\underline{\beta}$ = 96.40(2)°, $\underline{D}_m$ = 1.33 g. cm^{-3}, $\underline{D}_c$ = 1.33 g. cm^{-3} for $C_{20}H_{18}ClN_3O_4$ with $\underline{Z}$ = 4. The space group is $P2_1/c$. The intensity data were measured by the moving crystal-moving counter method on a Hilger-Watts γ290 four-circle diffractometer with Ni-filtered Cu $\underline{K}_\alpha$ radiation. Of the 2684 unique reflections with $2\theta \leq 114°$, 1499 were significantly above back-ground. The structure was solved by Patterson and Fourier methods and was refined by full-matrix least squares to a R value of 10.5% for the observed data and isotropic thermal parameters. The molecular structure is shown in Figure I(b). Once the structure of IV was established. the structures of V and VI then logically followed.

Unfortunately, a structural correlation between compounds II and IV could not be drawn and it was necessary to carry out an x-ray single crystal determination of compound II. The x-ray analysis of II was achieved in spite of the small size (0.025 mm diameter) of its acicular crystals. The crystal data for II was found to be $\underline{a} = 7.232(4)$, $\underline{b} = 20.33(1)$, $\underline{c} = 9.492(5)$ Å, $\underline{\beta} = 111.68(5)°$; $\underline{D}_m = 1.42$ g. cm^{-3} , $\underline{D}_c = 1.40$ g. cm^{-3} for $C_{14}H_{12}ClN_3O$ with $\underline{Z} = 4$. The non-centrosymmetric space group Aa was confirmed by the structure analysis. The 883 reflections (511 unobservably weak) were measured as described for compound IV ($2\theta \leq 96.5°$). The structure was solved by Patterson and Fourier methods and refined by full-matrix least squares to an R value of 8.4%. The molecular structure of compound II is shown in Figure I(a). From the structure of compound II, the structure shown for compound III was assigned.

Figure I

The molecular structures of compounds II(a) and IV(b)



a b

Acknowledgement: We are grateful to Professor George Buchi for helpful discussions and the members of our Physical Chemistry Department directed by Dr. P. Bommer.

References:
1) C. Podesva, G. Kohan and K. Vagi, <u>Can. J. Chem.</u>, <u>47</u>, 489 (1969).
2) See for example, M. Ohno and C.B. Anfinsen, <u>J. Amer. Chem. Soc.</u>, <u>89</u>, 5994 (1967).
3) Podesva, et.al., see ref. 1, perhaps due to their incorrect structural assignment, postulated that hydrazine attacked 2-(2',2'-bis-carboethoxyvinylamino)-5-chlorobenzophenone at the ketone carbonyl to give a carbinolhydrazine intermediate. It is much more likely that attack of the ketone is the ring closure step and that the initial attack of hydrazine is Michael-like at the carboethoxyvinyl moiety.
4) S.C. Bell and P.H.L. Wei, <u>J. Org. Chem.</u> <u>30</u>, 3576 (1965).
5) The 70 eV mass spectrum of VII, m/e 240 (rel. intensity 72), 239 (100), 205 (95) was quite characteristic and even the minor fragments of VII were present in the spectra of II, m/e 273 (rel. intensity 15), 254 (90), 240 (64),

239 (100), 205 (99) and III, m/e 315 (rel. intensity 2), 297 (35), 282 (36), 254 (70), 240 (33), 239 (55), 220 (100), 205 (44).

6) The mass spectra of V, m/e 357 (rel. intensity 5), 315 (12), 273 (42), 242 (50), 231 (100), 230 (69), 105 (50); VI, m/e 399 (rel. intensity 3), 357 (14), 315 (17), 298 (20), 273 (34), 242 (43), 231 (100), 230 (50), 105 (24), and IV, m/e 399 (rel. intensity 18), 357 (22), 315 (29), 298 (57), 273 (70), 242 (86), 231 (100), 230 (80), 105 (55) were clearly related to each other.

7) The spectra of II, uv max (isopropanol) 237, 283 mμ (ε 13,500, 11,550) and III were very similar. All of the compounds II, III, IV, V and VI exhibited the chromophore at 292-6 mμ (ε 10,400-11,700) when treated with 1N KOH.

8) The uv spectra of compounds IV, V and VI were as follows: IV, uv max (isopropanol) 202, 232, 252 mμ (ε 36,900, 21,400, 22,000), V, 212 sh, 252 mμ (ε 30,000, 30,900), and VI, 217, 249 mμ (ε 36,000, 21,200).