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# A Novel One-step Synthesis of Tricycloquinazolines

Fumio Yoneda and Katsunori Mera

*Faculty of Pharmaceutical Sciences, Kumamoto University*[1]

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Tricycloquinazoline (II) has been widely studied in chemistry[2] and biology,[3] because this compound has been shown to be carcinogenic for mouse skin by Baldwin, *et al.*[3] In an attempt to elucidate the carcinogenic activity quantum chemical considerations have been introduced and its direct interaction with DNA has been discussed.[4] In this note we will describe a novel one-step synthesis of tricycloquinazolines.

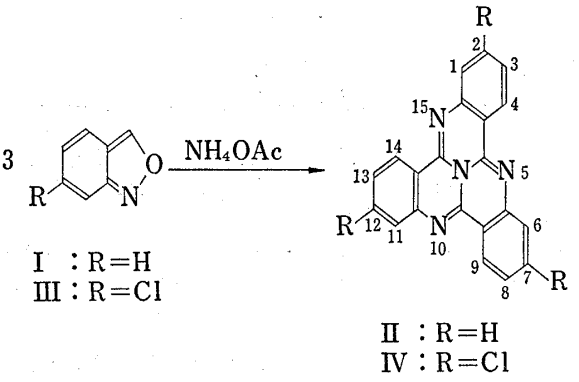



Chart 1

Treatment of anthranil (I) with excess ammonium acetate in a mixture of sulfolane and acetic acid afforded tricycloquinazoline (II) in 51% yield. Treatment of 6-chloroanthranil (III)[5] with ammonium acetate likewise gave 2,7,12-trichlorotricycloquinazoline (IV) in 43% yield. In these reactions, sulfolane seems to be a solvent of choice. The reactions in other aprotic solvents such as dimethylformamide and dimethyl sulfoxide under the same conditions did not proceed to give the desired tricycloquinazolines. Reaction of 5-nitroanthranil[5] with ammonium acetate did not give the corresponding tricycloquinazoline, but only a hydrolyzed product, 5-nitroanthranilic acid.

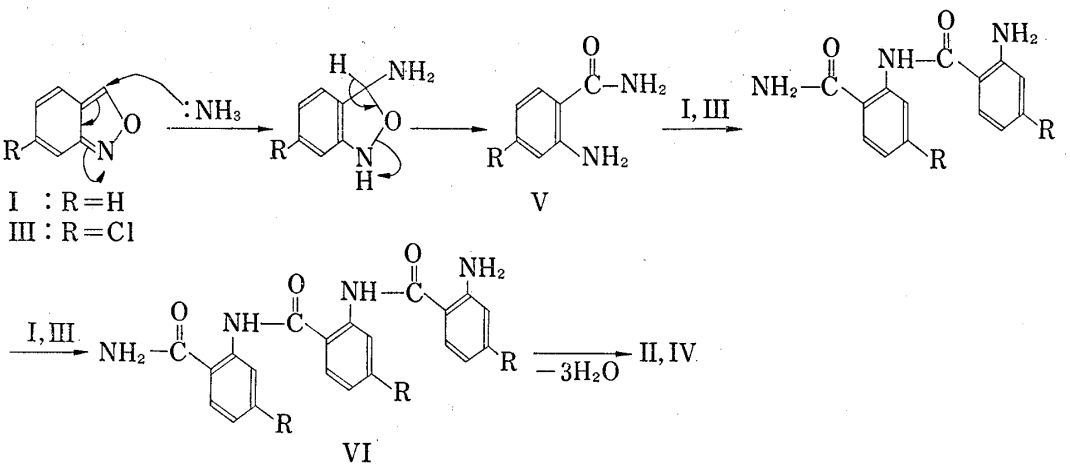
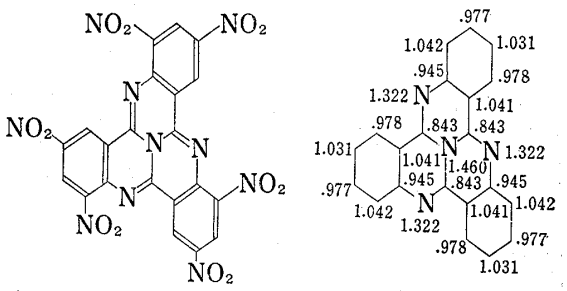



Chart 2

1) Location: *Oe-honmachi, Kumamoto.*
2) For example, K. Butler and M.W. Partridge, *J. Chem. Soc.*, **1959**, 2396.
3) For example, R.W. Baldwin, G.J. Cunnigham, and M.W. Partridge, *Brit. J. Cancer*, **13**, 94 (1959).
4) C. Nagata, M. Kodama, A. Imamura, and Y. Tagashira, *Gann.*, **57**, 75 (1966).
5) Altaf-ur-Rahman and A.J. Boulton, *Tetrahedron, Supplement*, **No. 7**, 49 (1966).

A feasible pathway for this one-step synthesis of tricycloquinazolines is as follows. The nucleophilic attack of ammonia liberated from ammonium acetate at C-3 of anthranils with subsequent oxygen-nitrogen bond cleavage forms anthranilamides (V). The amino group of benzene nucleus of V attacks at C-3 of anthranils and the repetition of this process may give VI, which is cyclized with elimination of three moles of water to form tricycloquinazolines (see Chart 2). This mechanism was partially supported by the formation of II in the reaction of I with anthranilamide in a mixture of sulfolane and acetic acid. Moreover it is known that treatment of VI (R=H) prepared in several steps with phosphorus pentoxide give II.[2)]

Butler and Partridge[2)] described that nitration of tricycloquinazoline yielded a dinitroderivative. However we observed that the nitration using fuming nitric acid in sulfuric acid yielded 1,3,6,8,11,13-hexanitrotricycloquinazoline (VII) in high yield. The structure of VII was assigned on the basis of the following evidence. Its infrared spectrum has a simple pattern which depends upon its molecular symmetricity (Fig. 1). The nuclear magnetic resonance (NMR) spectrum (aceton-$d_6$) of VII shows only two doublets at 9.23 ($C_{4,9,14}$ H, $J$=3 Hz) and 9.45 ppm ($C_{2,7,12}$ H, $J$=3 Hz). The mass spectrometry reveals a strong parent ion at *m/e* 590. It is noted that the experimental result is in accord with the electrophilic reactivity predicted from the electron densities (VIII)[4)] of II.




VII VIII

Chart 3

## Experimental[6)]

**Tricycloquinazoline (II)**——Anthranil (I) (2.38 g, 0.02 mole) and ammonium acetate (3.08 g, 0.04 mole) were added to a mixture of sulfolane (15 ml) and AcOH (5 ml) and the mixture was heated under stirring at 170° for 10 hr. After cooling, the precipitated crystals were collected by filtration and washed with EtOH. Recrystallization from benzene gave yellow needles (1.09 g, 51%), mp 323°, which were in all respects identical with an authentic sample.[2)]

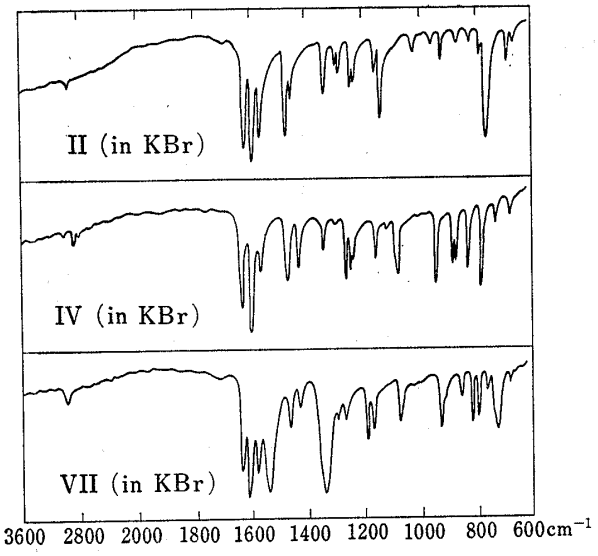



Fig. 1.

**2,7,12-Trichlorotricycloquinazoline (IV)**——6-Chloroanthranil (III) (0.2 g, 0.0013 mole) and ammonium acetate (0.5 g, 0.0065 mole) were added to a mixture of sulfolane (5 ml) and AcOH (2 ml) and the mixture was heated under stirring at 140—150° for 7 hr. After cooling, the resulting crystals were collected by filtration and recrystallized from toluene to give pale yellowish green needles (0.08 g, 43.4%), mp 365° (dec.). *Anal.* Calcd. for $C_{21}H_9N_4Cl_3$: C, 59.53; H, 2.14; N, 13.22. Found: C, 59.60; H, 2.21; N, 13.09.

**1,3,6,8,11,13-Hexanitrotricycloquinazoline (VII)**——Tricycloquinazoline (II) (0.2 g, 0.00063 mole) in conc. $H_2SO_4$ (10 ml) was heated with fuming $HNO_3$ (5 ml) at 120° for 2 hr. The reaction mixture was poured into ice water, and the precipitated crystals were filtered off and washed with $H_2O$. Recrystallization from nitrobenzene gave orange crystals (0.3 g, 81.3%), mp>380°. *Anal.* Calcd. for $C_{21}H_6O_{12}N_{10}$: C, 42.72; H, 1.03; N, 23.73. Found: C, 42.49; H, 1.10; N, 23.52.

6) Melting points are uncorrected. Infrared spectra were obtained on a Hitachi infrared spectrophotometer model EPI-2. NMR spectra were taken at 60 Mc with a Hitachi, Perkin-Elmer Co., Ltd. Model R-20A spectrometer using tetramethylsilane as the internal reference.