SYNTHESIS OF PYRAZOLONE DERIVATIVES. XXXII[1]. STUDIES ON (5S,8R)-8,9,9-TRIMETHYL-5,6,7,8-TETRAHYDRO-5,8-METHANO-1,2,3-BENZOTRIAZINE

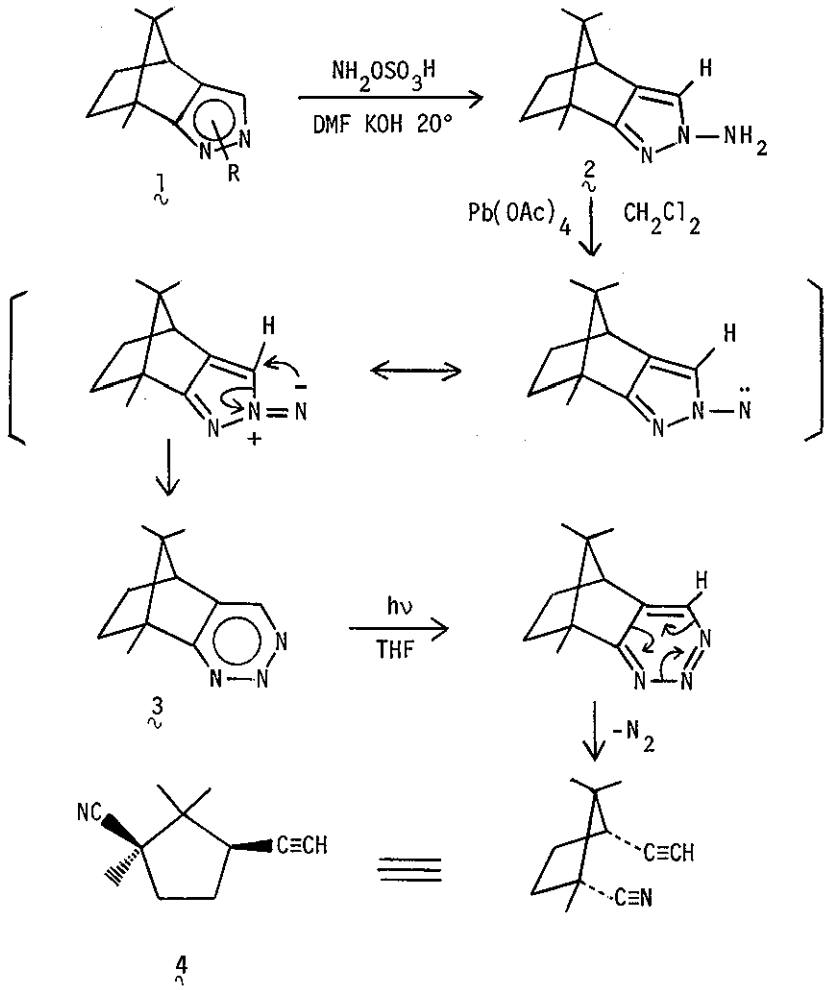
Isoo Ito*, Noriichi Oda, Shin-ichi Nagai and Yoshihisa Kudo
Faculty of Pharmaceutical Sciences, Nagoya City University
Tanabe-dori, Mizuho-ku, Nagoya, Japan

Oxidation of 2-amino-4,7-methanoindazole (2) resulted in ring expansion to afford 5,8-methano-1,2,3-benzotriazine (3) which showed prominent central stimulation in mice. Irradiation of 3 provided 3-ethynylcyclopentanecarbonitrile (4).

We have recently synthesized a series of (4S,7R)-1- or 2-substituted-7,8,8-trimethyl-4,5,6,7-tetrahydro-4,7-methano-1- or 2H-indazoles (1) and the related compounds[2] in order to examine their pharmacological properties. In this paper we wish to report the oxidation of 2-amino-4,7-methanoindazole (2) and the photochemical reaction of the oxidation product (3). In addition, its pharmacological screening was examined.

(4S,7R)-7,8,8-Trimethyl-4,5,6,7-tetrahydro-4,7-methano-2H-indazole [(1: R=H), mp 153-155°; NMR ($CDCl_3$) δ 7.08 (1H, s, C(3)-H)] and hydroxylamine-O-sulfonic acid was allowed to react in the presence of KOH at 20° to give 82.9% yield of (4S,7R)-7,8,8-trimethyl-

2-amino-4,5,6,7-tetrahydro-4,7-methano-2H-indazole [(2), bp_3 123-125°; $[\alpha]_D^{25}$ +21.9° (c=1.90, EtOH); IR (film) cm^{-1} 3320 and 3220 (NH_2); NMR ($CDCl_3$) δ 6.76 (1H, s, C(3)-H), 5.32 (2H, b.s, NH_2); M^+ 191; UV λ_{max}^{EtOH} nm (log ε) 236 (3.90)]. Although the formation of 1-amino isomer is considered, the structure of 2 was confirmed on the basis of spectral data, in particular the NMR spectrum, which indicates the chemical shift of aromatic proton upfield by 0.32 ppm relative to that of 1.



This suggests that the aromatic proton is adjacent to the amino group and consequently in the shielding area of the nitrogen. Gas liquid chromatography examination (3% Silicon SE-30) of compound 2 showed the existence of only one isomer.

The oxidation of compound 2 with lead tetraacetate provided pale yellow needles in 75.5% yield after separation on silica gel column. The product was formulated $C_{11}H_{15}N_3$ and assigned to (5S,8R)-8,9,9-trimethyl-5,6,7,8-tetrahydro-5,8-methano-1,2,3-benzotriazine [(3), mp 108-110°; $[\alpha]_D^{25}$ +6.8° (c=0.95, EtOH); NMR ($CDCl_3$) δ 8.84 (1H, s, C(4)-H); UV λ_{max}^{EtOH} nm (log ε) 223 (3.46), 295 (2.45); M^+ 189, M^+-N_2 161]. IR spectrum of 3 had no band in the NH_2 region. Analytical data and other spectral data are in full agreement with the postulated structure. The mechanism of the reaction involved nitrene formation and subsequent expansion of the pyrazole ring by intramolecular rearrangement[3] to give compound 3. Despite of several attempts to trap a nitrene intermediate, we were unable to do because of the rapid transformation of the intermediate to 3.

5,8-Methano-1,2,3-benzotriazine (3) dissolved in physiological saline was injected into mice (ddY strain, male 25-35 g) intraperitoneally, intravenously or orally. The behavior of the animal was observed and scored according to the Irwin's method after the administration. Abnormal gait could be seen about 3 min after the intraperitoneal administration of the sample in a dose of 10 mg/kg, then clonic convulsions occurred. The animal recovered almost completely within 30 min. Immediately after receiving a dose of 20 mg/kg (i.p.) animal showed tremor and twitches, and then clonic and tonic convulsions developed. The animal died with a tonic

extension within 2 min after the administration. Those results suggest that the LD_{50} value of the sample for the intraperitoneal administration may be between 10 and 20 mg/kg. When a dose of 65 mg/kg was administered orally, straub trail, salivation and urination could be observed at the beginning, and then clonic and tonic convulsion occurred. The animal died with a tonic extension within 5 min after the administration. The animal received intraveous injection of the sample in a dose of 10 mg/kg showed vigorous convulsion and died almost instantaneously.

Those effects of 5,8-methano-1,2,3-benzotriazine ($\underset{\sim}{3}$) seem to be similar to those of pentylenetetrazol, a central nervous system stimulant.

Irradiation (100W, high pressure mercury lamp, Pyrex) of $\underset{\sim}{3}$ in tetrahydrofuran resulted in the loss of nitrogen to provide a new substance in quantitative yield. This substance showed a one proton doublet at δ 2.18 ppm assigned to acetylenic proton. The IR spectrum showed absorption at 3270 and 2240 cm^{-1} consistent with the presence of acetylenic and cyano groups, respectively. On the basis of these data, the structure of the new substance was determined as (1R,3S)-3-ethynyl-1,2,2-trimethylcyclopentanecarbonitrile [($\underset{\sim}{4}$), mp 75-77°; $[\alpha]_D^{23}$ +51.7° (c=0.236, EtOH); NMR ($CDCl_3$) δ 2.18 (1H, d, J=2.3 Hz, C≡C<u>H</u>); M^+ 161]. This photochemical reaction may be considered to proceed by a concerted mechanism.

ACKNOWLEDGEMENT We thank Professor Emeritus S. Sugasawa for his encouragement throughout this work.

REFERENCES

1 Part XXXI: I. Ito, T. Ueda, T. Asano and N. Oda, Chem. Pharm. Bull. (Tokyo), "submitted".

2 I. Ito, N. Oda and S. Nagai, Yakugaku Zasshi, "submitted".

3 H. E. Baumgarten, P. L. Creger and R. L. Zey, J. Am. Chem. Soc., 82 3977 (1960).

Received, 5th August, 1977