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Reaction of Biguanides and Related Compounds. IV.[1] Reaction of Arylbiguanide with Benzoylacetone in the Presence of a Small Amount of the Arylbiguanide Hydrochloride

MITSURU FURUKAWA, YOKO KOJIMA and SEIGORO HAYASHI

Faculty of Pharmaceutical Sciences, Kumamoto University[2]

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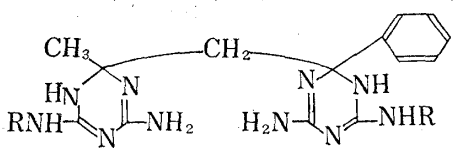
Arylbiguanide reacted with benzoylacetone in the presence of proton to give eight-membered ring compound, 4-amino-2-arylamino-6-methyl-8-phenyl-1,3,5-triazacyclo-octatetraen. *p*-Methoxyphenylbiguanide isolated exclusively two isomers, which were easily changed each other by heating. The structure of the compounds were discussed.

It is known that arylbiguanide reacts with aliphatic ketone in the presence of base to give 4-amino-6-arylamino-1,2-dihydro-*s*-triazine.[3–5] We reported in a previous paper[6] that heating of arylbiguanide free base with benzoylacetone in ethanol in the absence of any catalyst afforded 4-amino-6-arylamino-2-phenyl-2-(4'-amino-6'-arylamino-2'-methyl-1',2'-dihydro-*s*-triazinyl-2'-methyl)-1,2-dihydro-*s*-triazine (I) in low yield. When the same reaction was carried out in the presence of a small amount of the arylbiguanide hydrochloride, however, a completely different chemical behavior was observed, no same product being isolated. This paper deals with the reaction of arylbiguanide with benzoylacetone in the presence of the arylbiguanide hydrochloride.

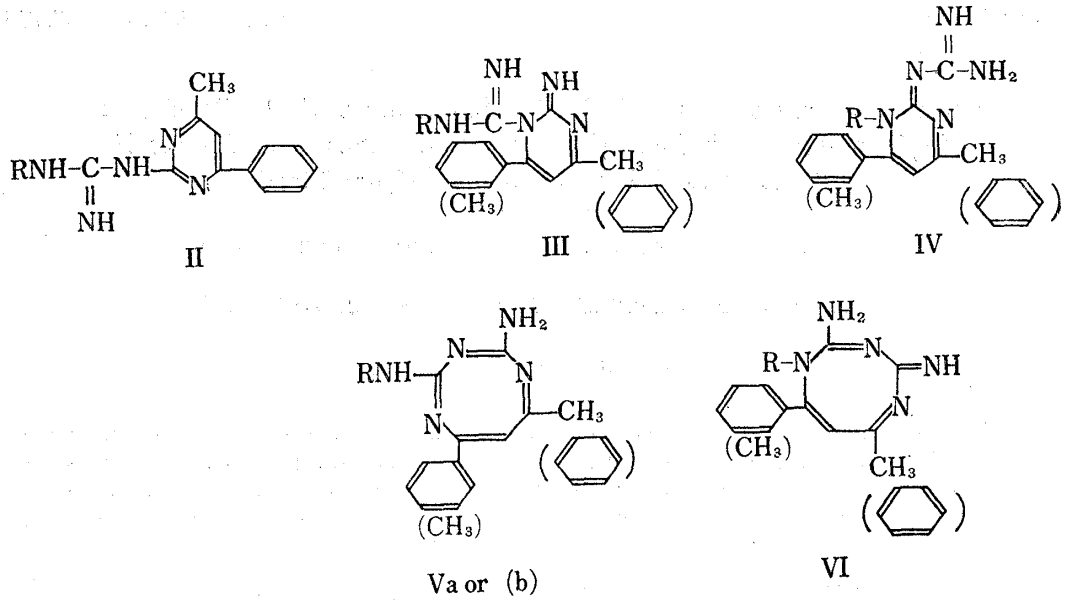


I

The reaction was effected by simple adding a small amount of arylbiguanide hydrochloride to a solution of arylbiguanide free base and benzoylacetone in ethanol. When arylbiguanide free base was heated with an equivalent amount of benzoylacetone in ethanol containing a small amount of the same arylbiguanide hydrochloride under reflux, an unexpected product was obtained in low yield, no expected compound (I) being isolated. The same result was obtained by refluxing benzoylacetone with arylbiguanide solution prepared by treating one and one-fifth mole of arylbiguanide hydrochloride with one mole of sodium ethoxide in ethanol. While the reaction of arylbiguanide hydrochloride with benzoylacetone in the absence of arylbiguanide free base was unsuccessful and the materials were quantitatively recovered. The experimental elementary analysis of the product corresponds to that of the condensation product of molecular equivalents of the arylbiguanide and benzoylacetone with loss of two molecules of water. By considering this result, the following several six-membered and eight-membered ring compounds are possible as the structure of the product.

Among these possible structures, six-membered ring structure may be denied by the following facts. 1) Infrared (IR) Spectra of the product exhibited the absorption assignable to an amino group at near 3500 cm^{-1} and no absorption due to an imino group was ob-

1) Part III: M. Furukawa, Y. Fujino, S. Yoshimatsu, Y. Kojima, and S. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 611 (1972).
2) Location: *Oe-moto-machi, Kumamoto.*
3) N.N. Crounse, *J. Org. Chem.*, **16**, 492 (1951).
4) H.C. Carringtone, A.F. Crowther and G.J. Stacey, *J. Chem. Soc.*, **1954**, 1017.
5) E.J. Modest, *J. Org. Chem.*, **21**, 1 (1956).
6) M. Furukawa, Y. Fujino and S. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **19**, 2284 (1971).



served. The absorption pattern was wholly different from 4,6-dimethyl-2-arylguanidinopyrimidine[6] which is very similar to II of the possible structure, as shown in Fig. 1. 2) The N^3 atom in biguanide is inactive and the nucleophilic attack of this nitrogen is unknown in the literature. 3) It is known that the structure of biguanide should be shown by $H_2N-\overset{NH}{\overset{\|}{C}}-N=C\langle^{NH_2}_{NH_2}$.[7] Thus, the six-membered ring structures could be excluded and the eight-membered ring structures would be more likely. Further evidence for the assignment of the structure will be also given by the results described below.

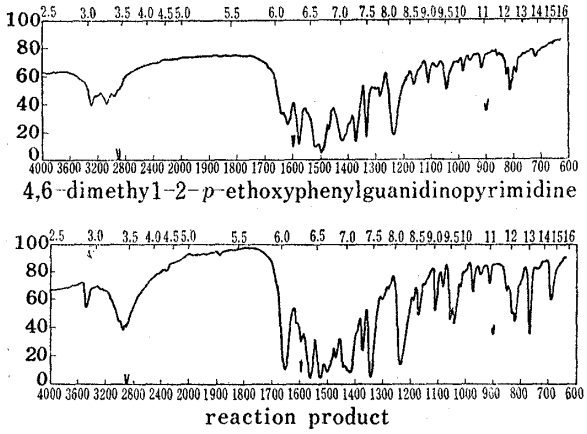


Fig. 1. IR Spectra of 4,6-Dimethyl-2-*p*-ethoxyphenylguanidinopyrimidine and the Reaction Product between *p*-Ethoxyphenylbiguanide and Benzoylacetone

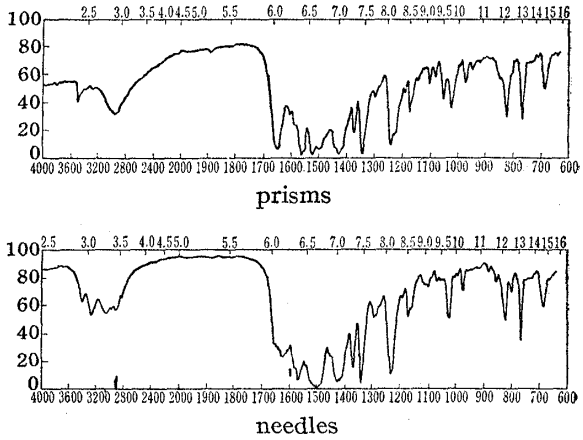


Fig. 2. IR Spectra of the Reaction Products between *p*-Methoxyphenylbiguanide and Benzoylacetone

It is particularly of interest that, in the reaction of *p*-methoxyphenylbiguanide with benzoylacetone, two isomeric products were exclusively isolated. When *p*-methoxyphenylbiguanide was heated with an equivalent amount of benzoylacetone in ethanol under reflux, a product was isolated from the concentrated reaction solution in 45% yield. Recrystallization of the product from ethanol gave needles melting at 166°, which gradually changed to

7) M. Takimoto, *J. Chem. Soc.* (Japan), **85**, 159, 172 (1964).

prisms melting at 166° on standing at room temperature for a couple of days in recrystallization solvent without isolation. Further recrystallization of the prisms from ethanol precipitated needles at first, which gradually changed again to the same prisms. The IR spectra of these two crystals were thoroughly different as shown in Fig. 2. This exhibits that there is not only difference in the crystal form, but also in the molecular structure of the crystals. The prisms would be probably isomerized to the needles of the unstable isomer by heating on recrystallization and then to the prisms of the stable isomer on standing at room temperature. The IR absorption pattern of the compound obtained by the reaction of another arylbiguanide with benzoylacetone was similar to that of the prisms of the stable isomer. The nuclear magnetic resonance (NMR) spectra of the both crystals exhibited two singlets at 7.56 τ and 6.20 τ assigned to the methyl group in the heterocyclic ring and the methoxy group in the benzene ring, respectively, and complex multiplets in the region of 3.27—1.93 τ, as shown in Fig. 3. It should be noted that the NMR spectra of the both crystals were completely same, though, in order to avoid migration to the stable isomer, the measurement was carried out immediately after the crystals were dissolved in the solvent. This fact suggests that the structures of these two crystals are extremely analogous. The high resolution mass spectra exhibited almost same fragmentation pattern, establishing the empirical formula $C_{19}H_{19}ON_5$ with a molecular ion at *m/e* 333.158 for the needles and *m/e* 333.156 for the prisms. This requires the removal of two water molecules from the molecular equivalents of the both reactants, *p*-methoxyphenylbiguanide and benzoylacetone. The ion at mass 211 was observed and the suggested composition corresponds to loss of a *p*-methoxyphenylamino radical from the molecular ion. This suggests that *p*-methoxyphenylamino group substitutes in the molecule. By these results, it is presumed that the structure V of the possible eight-membered ring structure would be more likely as the structure of the stable isomer.

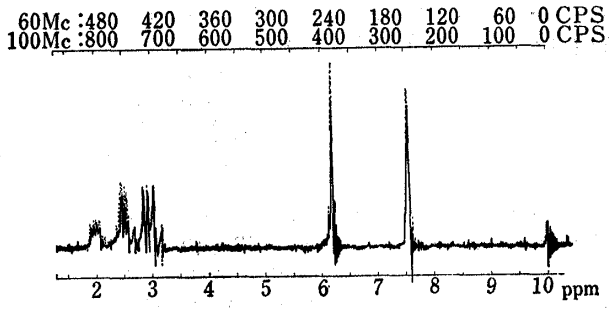
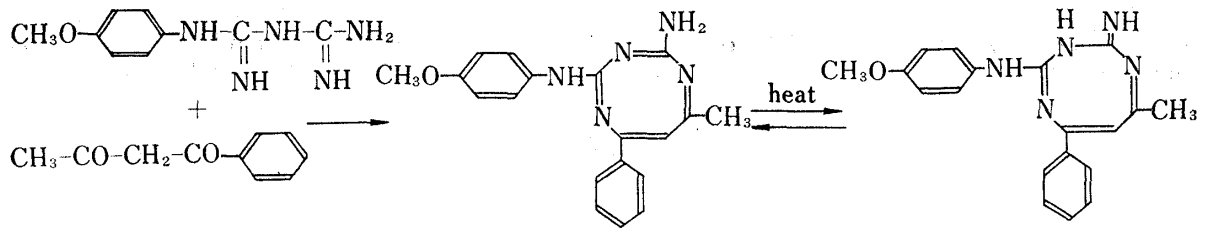


Fig. 3. NMR Spectra of the Reaction Products between *p*-Methoxyphenylbiguanide with Benzoylacetone

——: prisms ----: needles



Though the spectral data does not allow an unequivocal choice between Va and Vb, chemical intuition suggests that Va would be more appropriate rather than Vb, because the carbonyl reactivity of the acetyl group in benzoylacetone is stronger than that of the benzoyl group. Additionally, it is reasonable to presume that the unstable isomer would be the tautomeric type of the stable isomer, because the IR spectrum of the compound exhibited the absorption assignable to an amino and imino group at 3400 cm^{-1} and 3272 cm^{-1}, respectively. Acid catalyzed hydrolysis of the amino or imino group in V to carbonyl group resulted in failure and polymerization product was obtained. V was, on the other hand, stable for alkaline hydrolysis.

Experimental

Reaction of *p*-Methoxyphenylbiguanide with Benzoylacetone in the Presence of a Small Amount of the Hydrochloride——To a solution of 2.07 g (0.01 mole) of *p*-methoxyphenylbiguanide and 0.2 g (0.001 mole) of *p*-methoxyphenylbiguanide hydrochloride in 50 ml of EtOH was added 1.62 g (0.01 mole) of benzoylacetone and the solution was heated for 10 hr under reflux. After the solution was concentrated the oily residue was poured into H_2O and repeatedly washed with H_2O. Resulting solidified mass was collected by filtration and dissolved into EtOH by heating for recrystallization. On standing overnight at room temperature, 1.5 g (45%) of a mixture of needles and prisms was isolated. The mixture was dissolved into a suitable amount of EtOH by heating and after standing for 2 hr at room temperature, needles deposited were collected by filtration. The melting point was 166°. *Anal.* Calcd. for $C_{19}H_{19}O\,N_5$: C, 68.45; H, 5.74; N, 21.01. Found: C, 68.31; H, 5.67; N, 20.98. IR ν_{max}^{KBr} cm^{-1}: 3400 (NH), 3270 (=NH). NMR ($CDCl_3$) τ: 7.56 (3H, singlet, CH_3), 6.20 (3H, singlet, CH_3O), 3.72—1.93 (13H, multiplet, aromatic and amino hydrogen). Mass Spectrum *m/e*: 333 (M^+). The needles were dissolved into a suitable amount of EtOH and the solution was stood for a couple of days at room temperature. The deposited prisms melting at 166° were collected by filtration. A small amount of needles deposited accompaying with prisms was completely changed to prisms on standing for a few days. *Anal.* Calcd. for $C_{19}H_{19}O\,N_5$: C, 68.45; H, 5.74; N, 21.01. Found: C, 68.36; H, 5.81; N, 21.12. IR ν_{max}^{KBr} cm^{-1}: 3498, 1657 (NH_2). NMR ($CDCl_3$) τ: 7.56 (3H, singlet, CH_3), 6.20 (3H, singlet, CH_3O), 3.72—1.93 (13H, multiplet, aromatic and amino hydrogen). Mass Spectrum *m/e*: 333 (M^+).

Reaction of *p*-Ethoxyphenylbiguanide with Benzoylacetone in the Presence of Proton——To a solution of 1.10 g (0.005 mole) of *p*-ethoxyphenylbiguanide and 0.11 g (0.0005 mole) of *p*-ethoxyphenylbiguanide hydrochloride in 50 ml of EtOH was added 0.81 g (0.005 mole) of benzoylacetone and the solution was heated for 10 hr under reflux. After concentrated, the oily residue was poured into H_2O and washed with cold H_2O. Resulting solidified mass was filtered and recrystallized from EtOH to give 0.25 g (14.5%) of colorless prisms melting at 185°. *Anal.* Calcd. for $C_{20}H_{21}ON_5$: C, 69.14; H, 6.09; N, 20.16. Found: C, 69.15; H, 6.05; N, 19.94. IR ν_{max}^{KBr} cm^{-1}: 3498, 1661 (NH_2).

Reaction of *p*-Chlorophenylbiguanide with Benzoylacetone in the Presence of Proton——To a solution of sodium ethoxide (prepared from 0.115 g of Na) in 50 ml of EtOH was added 1.49 g (0.006 mole) of *p*-chlorophenylbiguanide hydrochloride with stirring under heating. NaCl deposited was filtered off and to the filtrate was added 0.81 g (0.005 mole) of benzoylacetone. The solution was heated for 10 hr under reflux and then concentrated. The oily residue was poured into H_2O and repeatedly washed with cold H_2O. Resulting solidified mass was recrystallized from EtOH to give 0.31 g (15.3%) of colorless prims melting at 175—177.5°. *Anal.* Calcd. for $C_{18}H_{16}N_5Cl$: C, 64.00, H, 4.77; N, 20.73. Found: C, 64.16; H, 4.89; N, 20.52. IR ν_{max}^{KBr} cm^{-1}: 3457, 1663 (NH_2).

Attempted Condensation of *p*-Methoxyphenylbiguanide Hydrochloride with Benzoylacetone——A mixture of 2.44 g (0.01 mole) of *p*-methoxyphenylbiguanide hydrochloride and 1.62 g (0.01 mole) of benzoylacetone in 100 ml of EtOH was heated for 24 hr under reflux. After the solution was concentrated, precipitates deposited on cooling were collected by filtration and recrystallized from EtOH to give 2.01 g of unchanged *p*-methoxyphenylbiguanide.

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