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The Double Smiles Rearrangement[1]

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A Smiles-type rearrangement still merits attention because of its mechanistic interest and applicability to the heterocyclic synthesis. Phillips and co-workers[3] have reported the synthesis of 1,3-diazaphenothiazines by the reaction of 2,4-disubstituted 5-bromo-6-chloropyrimidines with 2-aminothiophenol, which involves the acid-catalyzed Smiles rearrangement.

The present work was undertaken to see if the base-catalyzed Smiles rearrangement with subsequent cyclization, employing 2-substituted 4,6-dichloro-5-nitropyrimidines and 2-aminothiophenol, is efficient for the synthesis of 1,3-diazaphenothiazines.

Contrary to our expectation, we have found the occurrence of a facile double Smiles rearrangement, but no cyclization to 1,3-diazaphenothiazine. The observed rearrangement provides a first example in a Smiles-type rearrangement.

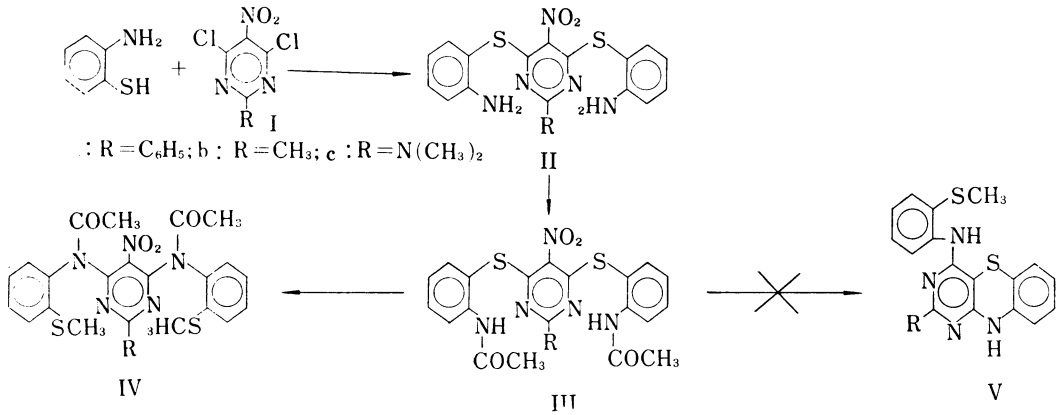

Chart 1

The reaction of 2-aminothiophenol (2 moles) with 4,6-dichloro-5-nitro-2-phenylpyrimidine (Ia) (1 mole) in ethanol containing sodium ethoxide (2 moles) at 20° for 2 hr gave 4,6-di(2-aminophenylthio)-5-nitro-2-phenylpyrimidine (IIa) in 56% yield. This compound was acetylated with pyridine–acetic anhydride to give the diacetate (IIIa). The structure of IIIa was established by infrared (IR) absorption bands at 3240 and 1660 cm^{-1}, and nuclear magnetic resonance (NMR) signals at 2.08 ppm (6H, s, -NHCOC$\underline{H}_3\times 2$) and in the aromatic proton region (13H, mult.).

When IIIa was treated with potassium hydroxide and an excess of methyl iodide in dimethylformamide (DMF) at room temperature for 20 min, the rearranged product (IVa) was obtained. The structure of IVa was confirmed by an IR absorption band at 1680 cm^{-1},

1) This paper forms part XI of Studies on the Smiles Rearrangement. Preceding paper: Y. Maki, M. Suzuki and T. Masugi, *Chem. Pharm. Bull.* (Tokyo), **16**, 559 (1968).

2) Location: *Mitahora, Gifu.*

3) A.P. Phillips, N.B. Mehta and J.Z. Strelitz, *J. Org. Chem.*, **28**, 1488 (1963).

and NMR signals at 2.03 ppm (6H, s, -NCOC$\underline{H}_3\times2$), 2.51 ppm (6H, s, -SC$\underline{H}_3\times2$) and in the aromatic proton region (13H, mult.). The rearrangement appears to be intramolecular nucleophilic displacement which occurs synchronously at both the 4 and 6 positions of the pyrimidine ring.

Similarly, in the cases of IIIb and IIIc the double Smiles rearrangement was also observed.

On the basis of above findings, we attempted the cyclization of IIIa, b, c to 1,3-diazaphenothiazines (*e.g.* V). A solution of IIIa, b, c in DMF in the presence of potassium hydroxide was heated at about 150° for 2 hr. After addition of methyl iodide to the reaction mixture, however, the rearranged product IVa, b, c without cyclization were obtained in 60—75% yields. This fact indicates a limitation in the application of the Smiles rearrangement to the 1,3-diazaphenothiazine synthesis.

Experimental

Table I summarized synthetic and physical data of all new compounds described herein.

TABLE I

Compd.	R	mp (°C)	Recryst. solv.	Yield (%)	Appearance	Formula	Elemental analysis (%)	C	H	N
IIa	C_6H_5	223—224	benzene	56	needles	$C_{22}H_{17}O_2N_5S_2$	Calcd.	59.04	3.83	15.65
							found	58.98	3.82	15.54
IIb	CH_3	153—158[a]		83	needles	$C_{17}H_{15}O_2N_5S_2$				
IIc	$N(CH_3)_2$	216—217	acetone	56	needles	$C_{18}H_{18}O_2N_6S_2$	Calcd.	52.15	4.37	20.27
							found	52.40	4.36	20.34
IIIa	C_6H_5	244—245	acetone	77	prisms	$C_{26}H_{21}O_4N_5S_2$	Calcd.	58.74	3.98	13.17
							found	58.59	4.18	12.94
IIIb	CH_3	237—238	acetone	37	leaflets	$C_{21}H_{19}O_4N_5S_2$	Calcd.	53.71	4.07	14.91
							found	53.88	4.11	14.87
IIIc	$N(CH_3)_2$	227—228	acetone	71	prisms	$C_{22}H_{22}O_4N_6S_2$	Calcd.	52.99	4.44	16.86
							found	53.23	4.70	16.99
IVa	C_6H_5	296—297	benzene	36	needles	$C_{28}H_{25}O_4N_5S_2$	Calcd.	60.09	4.50	12.52
							found	60.33	4.75	12.49
IVb	CH_3	230—232	methanol	25	needles	$C_{23}H_{23}O_4N_5S_2$	Calcd.	55.51	4.66	14.07
							found	55.51	4.77	14.04
IVc	$N(CH_3)_2$	252—253	acetone	32	prisms	$C_{24}H_{26}O_4N_6S_2$	Calcd.	54.73	4.97	15.96
							found	54.76	5.25	15.90

a) unpurified: the structure of IIb was characterized in its acetate (IIIb)

4,6-Di(2-aminophenylthio)-5-nitro-2-substituted Pyrimidines (IIa, b, c)——To a solution of 4.0 g of 2-aminothiophenol dissolved in an ethanolic sodium ethoxide (0.9 g of sodium in 120 ml of absolute ethanol) was added 4.3 g of 4,6-dichloro-5-nitro-2-phenylpyrimidine[4] (Ia) and the mixture was allowed to stand at room temperature for 3 hr. The resulting orange precipitate was collected by filteration, wash with water, and recrystallized from benzene to give IIa as orange needles. IIb and IIc were prepared by the condensation of 2-aminothiophenol with 4,6-dichloro-2-methyl[5] (or-dimethylamino[6])-5-nitro-pyrimidine (Ib or Ic) in the same manner as described for IIa.

4,6-Di(2-acetamidophenylthio)-5-nitro-2-substituted Pyrimidines (IIIa, b, c)——To a solution of 2.0 g of IIa dissolved in 30 ml of pyridine was added 5 ml of acetic anhydride and the mixture was allowed to stand at room temperature over night. The reaction mixture was poured into water, and the yellow precipitate thus obtained was collected by filtration, throughly washed with water, and recrystallized from acetone to give the diacetate (IIIa) as yellow prisms.

IIIb and IIIc were prepared in the same manner as described for IIIa.

Reaction of (IIIa, b, c) with KOH in the Presence of Methyl Iodide——To a solution of 0.8 g of IIIa dissolved in 30 ml of DMF was added 1 ml of methyl iodide and to this further added aq. KOH solution (0.4 g

4) J.A. Hendry and R.F. homer, *J. Chem. Soc.*, **1952**, 328.
5) J. Baddiley and A. Tophan, *J. Chem. Soc.*, **1944**, 678.
6) W.R. Boon, *J. Chem. Soc.*, **1957**, 2146.

of KOH in 20 ml of water). The reaction mixture was allowed to stand at room temperature for 20 min and then poured into water. The resulting precipitate was chromatographed on silica gel (solvent: $CHCl_3$). The rearranged product (IVa) thus obtained was recrystallized from benzene to give colorless needles.

The similar treatment of IIIb and IIIc with KOH gave the rearranged products, IVb and IVc, respectively.

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Synthesis of β-(Pyrazolyl-N)-DL-alanine

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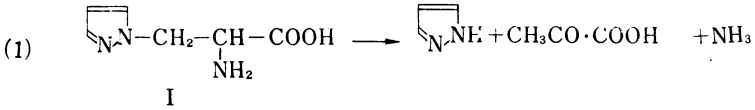
β-(Pyrazolyl-N)-L-alanine(I) is so far the only naturally-occurring amino acid containing a pyrazole ring; it is also unusual in possessing an alanine side chain directly to a nitrogen atom of the heterocyclic nucleus.

β-(Pyrazolyl-N)-L-alanine was first isolated from the pressed juice[2] and seed of watermelon(*Citrullus vulgaris*)[3] and has subsequently been found in several other plants.[3]

The correct chemical structure was proposed by Noe and Fowden[3] on the basis of its nuclear magnetic resonance spectrum and other properties. The structure has been confirmed as α-amino-β-(pyrazolyl-N)-propionic acid by comparison of the natural amino acid with the L-isomer obtained from synthetic material.[4,5] Additional supporting evidence was provided by the stoichiometric conversion of I to pyrazole, pyruvic acid and ammonia (reaction 1) by a pyrazolealaninase enzyme obtained from a strain of *Pseudomonas cruciviae*, grown in a medium in which β-(pyrazolyl-N)-L-alanine provided the carbon and nitrogen sources.[5]

(1) 

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Murakoshi, Kuramoto, Haginiwa, and Fowden (1972) reported that β-(pyrazolyl-N)-alanine(I) was synthesized from pyrazole and O-acetylserine by an enzyme from watermelon seedlings (*Citrullus vulgaris*); no activity was detected when either serine or O-phosphoserine replaced serine as a substrate for the enzyme (serine was incorporated into β-(pyrazolyl-N)-alanine if acetyl-CoA was added to enzymic incubation mixture).[6] The synthesis was presumed to involve the formation of an enzyme-bound α-aminoacrylate moiety, following an intramolecular elimination of acetate: other reactions such as enzymic synthesis of tryptophan from indol and serine,[7] of mimosine from 3,4-dihydroxypyridine and O-acetylserine,[6] and

1) Location: *Yayoi-cho, Chiba.*
2) S. Shinano and T. Kaya, *J. Agric. Chem. Soc. Japan*, **31**, 759 (1957).
3) F.F. Noe and L. Fowden, *Biochem. J.*, **77**, 543 (1960).
4) N. Sugimoto, H. Watanabe, and A. Ide, *Tetrahedron*, **11**, 231 (1960).
5) M. Takeshita, Y. Nishizuka, and O. Hayaishi, *J. Biol. Chem.*, **238**, 660 (1963).
6) I. Murakoshi, H. Kuramoto, J. Haginiwa, and L. Fowden, *Phytochem.*, **11**, 177 (1972).
7) J.B. Greenberg and A.W. Galston, *Plant Physiol.*, **34**, 489 (1959); P. Madhusdanan Nair and C.S. Vaidyanathan, *Arch. Biochem. Biophys.*, **104**, 405 (1964); U. Schiewer, N. Erdmann and E. Libbert, *Physiologia Plantarum*, **23**, 473 (1970).