Notes

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Kazuo Sugimoto*1 and Sadao Ohki*2 : Potential Anticancer Agents. Synthesis of Aromatic Nitrogen Mustards containing Azo Group.

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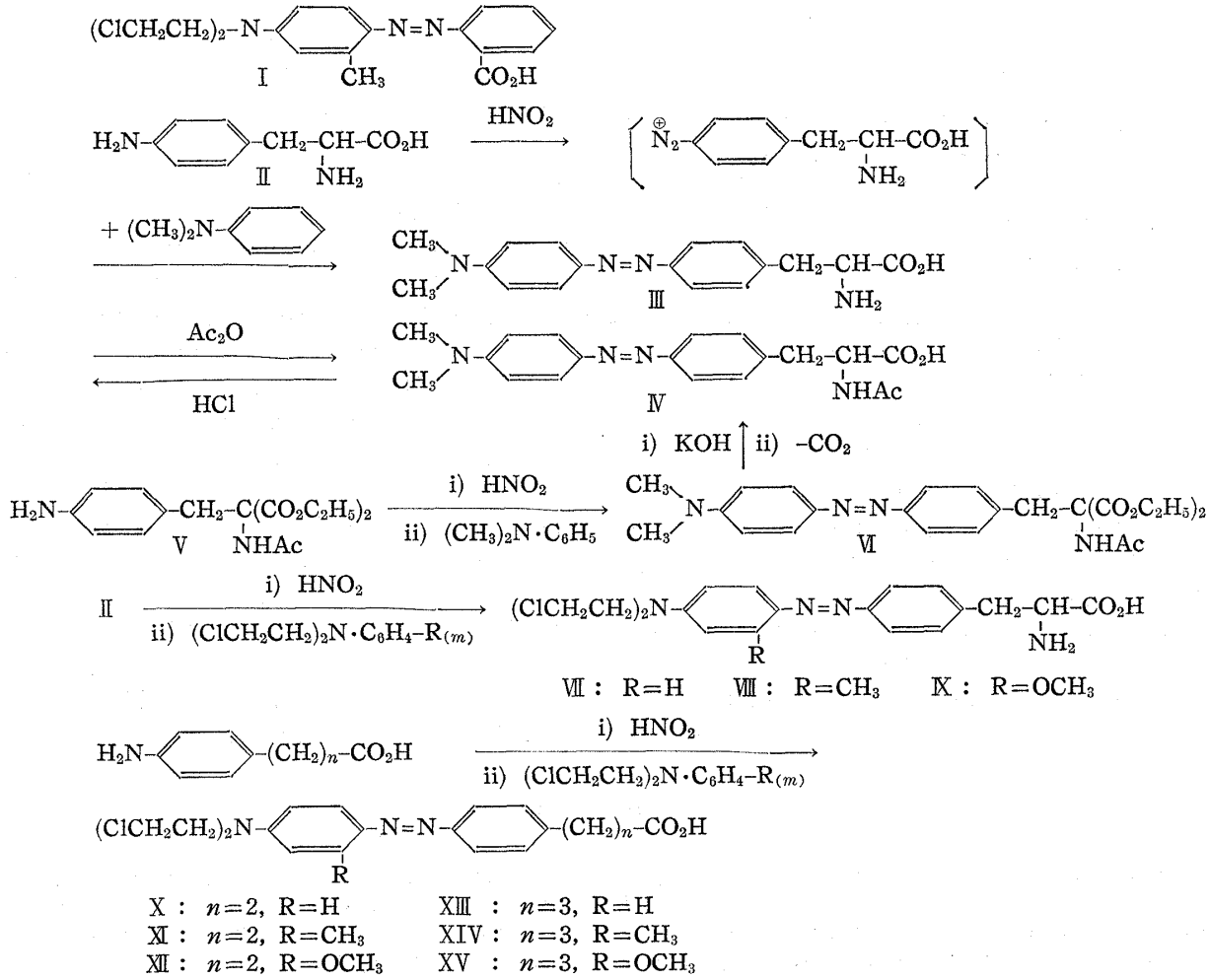
In 1958, Bergel[1] has summarized the relationship between the structure and activity of nitrogen mustards and he has shown evidences for the hypothesis that the so-called alkylating agents consist of a carrier group and an alkylating group, and that the differences in effects and side effects on tumors might be related to the differences in the carrier group. And he disclosed that phenylalanine and 4-phenylbutyric acid are good carriers for the alkylating group. On the other hand, Ross, *et al.*[2] have reported that 4-bis(2-chloroethyl)aminoazobenzene derivatives such as I inhibit the growth of the carcinome especially when carboxyl or methyl group is attached at *ortho* position of azo-linkage.



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1) F. Bergel : N.Y. Acad. Sci., **68**, 1238 (1958).
2) W.C.J. Ross, G.P. Warwich : J. Chem. Soc., **1956**, 1364.

This paper discribes the synthesis of aromatic nitrogen mustards (Ⅶ～XV) which possess phenylalanine, 3-phenylpropionic, or 4-phenylbutyric acid as a carrier group and an azo group as the masking group.

3-[*p*-(*p*-Dimethylaminophenylazo)phenyl]alanine (Ⅲ) was first prepared as a model compound to establish the synthetic route of the objective compounds. Gram, *et al.*[3] reported that diazotization of the *p*-amino group in Ⅱ usually proceeds much more rapidly than that of *α*-amino acid. Following his procedure, Ⅱ was selectively diazotized and the resulting diazonium salt was coupled with N,N-dimethylaniline to afford Ⅲ in a good yield. Since the purification of Ⅲ was very difficult, Ⅲ was acetylated to give Ⅳ. m.p. 198～200°. The structure of Ⅲ was further proved by the synthesis from Ⅴ. Diethyl acetamido(*p*-amino-benzyl)malonate (Ⅴ) was diazotized and coupled with N,N-dimethylaniline to afford Ⅵ. Hydrolysis and decarboxylation of Ⅵ gave Ⅳ in a good yield, which gave Ⅲ on hydrolysis. The compound (Ⅳ) obtained by the both methods was proved to be identical on admixture. The ultraviolet spectrum of Ⅲ (Fig. 1) was similar to that of 4-(dimethylamino)-azobenzene.

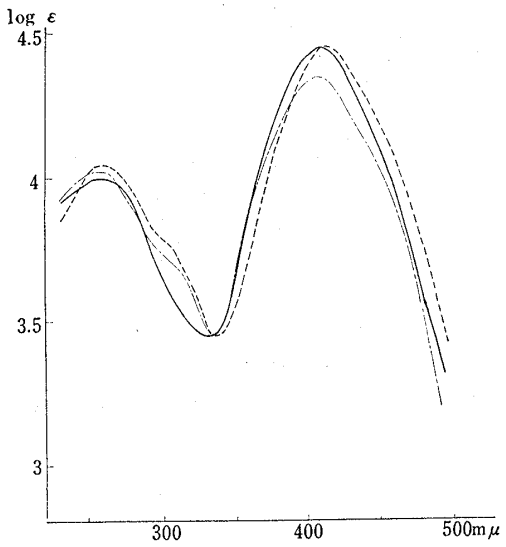
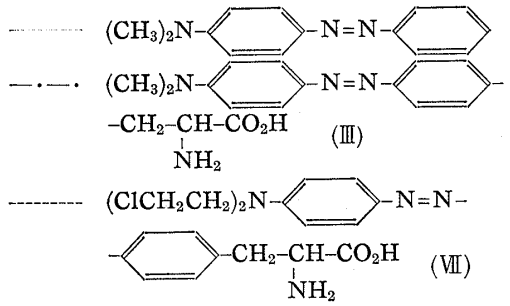


Fig. 1. Ultraviolet Spectra (in EtOH)



Thus one step synthesis of Ⅲ is established, 3-{*p*-[*p*-bis-(2-chloroethyl)aminophenylazo]phenyl}alanine (Ⅶ) and *ortho* substituted derivatives (Ⅷ and Ⅸ) were then prepared by the coupling of *p*-diazonium phenylalanine with corresponding N,N-bis(2-chloroethyl)aniline: (Table I). Ultraviolet spectrum of Ⅶ is shown in Fig. 1.

By the same procedure aromatic nitrogen mustards having 3-phenylpropionic (X, Ⅺ and Ⅻ) and 4-phenylbutyric acid (XIII, XIV and XV) as the carrier group were prepared. The properties and analytical data of these compounds were summarized in Table I. The compounds, X, XIII and XV could not be purified sufficiently, so they were converted to the corresponding ethyl esters (X′, XIII′ and XV′) by allowing the ethanolic solution of these acids to stand for several days in a refrigerator. The esters thus obtained were easily purified by recrystallization.

Pharmacological and biological properties of these compounds against Ehrlich ascites tumor were examined, but none of them proved to be of outstanding promise.

Experimental

Diethyl Acetamido[*p*-(*p*-dimethylaminophenylazo)benzyl]malonate (VI)——Diethyl acetamido(*p*-amino-benzyl)malonate[4] (Ⅴ) (6.2 g., 0.02 mole) was dissolved in conc. HCl (5 ml.) and H_2O (10 ml.) and diazotized with $NaNO_2$ (1.4 g., 0.02 mole) under ice-cooling. To this solution was added N,N-dimethylaniline (3.6 g., 0.03 mole) under stirring and resulted precipitates were collected. Recrystallization of the precipitates from 50% EtOH gave red crystals (6.0 g., 66%), m.p. 153～155°. *Anal.* Calcd. for $C_{24}H_{30}O_5N_4$: C, 63.44; H, 6.60; N, 12.33. Found : C, 63.65; H, 6.96; N, 12.07.

3) H. F. Gram, C. W. Mosher, B. R. Baker : J. Am. Chem. Soc., **81**, 3103 (1959).
4) D. F. Elliott, C. Harington : J. Chem. Soc., **1949**, 1374.

TABLE I. $(ClCH_2CH_2)_2N$-C$_6$H$_3$(R_1)-N=N-C$_6$H$_4$-$(CH_2)_n$CH(R_2)-COO-R_3

Compound No.	Substituent				m.p. (°C)	Recryst. solvent	Appearance
	n	R_1	R_2	R_3			
VII	1	H	NH_2	H	173~175	A	Y
VIII	1	CH_3	〃	〃	181~185	B	Y
IX	1	OCH_3	〃	〃	173~174	C	Z
X′	1	H	H	C_2H_5	124~126	A	X
XI	1	CH_3	〃	H	130~135	〃	Y
XII	1	OCH_3	〃	〃	148~151	B	X
XIII′	2	H	〃	C_2H_5	64~ 71	〃	〃
XIV	2	CH_3	〃	H	128~132	〃	〃
XV′	2	〃	〃	C_2H_5	73~ 76	〃	〃

Compound No.	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Yield (%)
VII	$C_{19}H_{22}O_2N_4Cl_2$	55.74	5.38	13.69	56.01	5.74	13.86	95
VIII	$C_{20}H_{24}O_2N_4Cl_2$	56.73	5.67	—	56.30	5.78	—	98
IX	$C_{20}H_{24}O_3N_4Cl_2 \cdot \frac{1}{2}H_2O$	53.57	5.58	12.50	53.10	5.87	12.24	59
X′	$C_{21}H_{25}O_2N_3Cl_2$	59.71	5.97	9.95	59.57	5.88	10.14	39
XI	$C_{20}H_{23}O_2N_3Cl_2$	58.82	5.63	10.29	58.89	5.89	10.47	81
XII	$C_{20}H_{23}O_3N_3Cl_2$	56.60	5.42	9.90	56.40	5.17	10.13	98
XIII′	$C_{22}H_{27}O_2N_3Cl_2$	60.55	6.19	9.64	60.62	6.30	9.88	66
XIV	$C_{21}H_{25}O_2N_3Cl_2$	59.71	5.92	9.95	60.04	6.03	9.92	62
XV′	$C_{23}H_{29}O_2N_3Cl_2$	61.33	6.44	9.33	61.55	6.44	9.77	68

A: EtOH B: EtOH-H_2O C: H_2O X: orange yellow Y: red Z: brown red

N-Acetyl-3-[*p*-(*p*-dimethylaminophenylazo)phenyl]alanine (IV)——a) A solution of VI (4.5 g., 0.01 mole) in 5% KOH-EtOH (27 ml.) was refluxed for 1 hr. and the separated crystals were collected. The crystals were dissolved in H_2O (20 ml.) and acidified with AcOH (4 ml.) and heated for 1 hr. on a water bath. After cool separated crystals were collected and recrystallized from dil. EtOH to afford red powder (3.0 g., 84.7%), m.p. 198~200°. *Anal.* Calcd. for $C_{19}H_{22}O_3N_4$: C, 64.40; H, 6.21; N, 15.81. Found: C, 64.41; H, 5.92; N, 15.85.

b) A mixture of III (*vide infra*) (0.5 g.) and Ac_2O (3 ml.) was heated on a water bath for 3 min. After cool the mixture was diluted with H_2O and kept for 12 hr., and the separated crystals were collected and was recrystallized from dil. EtOH to afford red powder (0.5 g., 89%), m.p. 198~200°. This was identical with the sample obtained above on admixture. *Anal.* Calcd. for $C_{19}H_{22}O_3N_4$: C, 64.40; H, 6.21. Found: C, 64.08; H, 6.38.

3-[*p*-(*p*-Dimethylaminophenylazo)phenyl]alanine (III)——a) A solution of IV (1.0 g.) in conc. HCl (2 ml.) was heated on a water bath for 1 hr. After cool the mixture was made alkaline with 10% Na_2CO_3, and the separated crystals were collected and recrystallized from dil. EtOH to afford red crystals (0.6 g., 68%), m.p. 192~195°. *Anal.* Calcd. for $C_{17}H_{20}O_2N_4$: C, 65.36; H, 6.45; N, 17.94. Found: C, 64.68; H, 6.03; N, 17.60.

b) 3-(*p*-Aminophenyl)alanine (5.0 g., 0.025 mole) was dissolved in 4*N* HCl (17 ml.) and diazotized with $NaNO_2$ (1.8 g., 0.026 mole) in H_2O (3 ml.) under ice-cooling. To this mixture was added dimethylaniline (3.1 g., 0.025 mole) with stirring. After 1 hr. the mixture was made alkaline with 10% Na_2CO_3 and the separated crystals were collected and recrystallized from dil. EtOH to afford red crystals (1.2 g., 80%), m.p. 193~196°. This was identical with the sample obtained above on admixture. *Anal.* Calcd. for $C_{17}H_{20}O_2N_4$: C, 65.36; H, 6.45; N, 17.94. Found: C, 64.70; H, 6.11; N, 17.68.

Preparation of Bis(2-chloroethyl)aminoazobenzene Derivatives (VII~XV)——Aminobenzene derivatives (0.05 mole) was dissolved in 4*N* HCl and diazotized with $NaNO_2$ (0.05 mole) in H_2O (100 ml.) under cooling

in an ice bath. To this solution was added bis(chloroethyl)amine derivative (0.05 mole) in EtOH, and the mixture was kept at 0° for 3~7 days. The separated crystals were collected and recrystallized from appropriate solvent (see Table I).

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Summary

Aromatic nitrogen mustards containing an azo group (Ⅶ~XV), a nitrogen mustard with a carrier and masking group, were synthesized in one step starting from *p*-amino-phenylalanine or aliphatic *p*-amino-phenyl acid.

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Yoshio Ban and Masako Seo: The Synthesis of β-Carboline Derivatives. V.*1 A Synthesis of 1-Methyl-1,2,3,4,7,8-hexahydro-13*H*-benz[*g*]indolo[2,3-*a*]quinolizinium Salts.

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In the preceding paper*1, the total synthesis of alstoniline (I), an alkaloid of *Alstonia constricta* F. MUELL was described. In the course of this work, the intermediate, 5-methyl-5,6,7,8-tetrahydro-3(2*H*)isoquinolone (Ⅱ) was brominated with phosphoryl bromide in a sealed tube to afford the fully aromatized compound, 3-bromo-5-bromomethyl-isoquinoline (Ⅲ). Also, when the similar bromination was carried out in an open vessel, there was obtained a mixture of 3-bromo-5-methylisoquinoline (Ⅳ) and the above dibromo-base (Ⅲ).*1

It is described in this paper that the same intermediate (Ⅱ) was subjected to chlorination with phosphoryl chloride to afford the partially aromatized product, 3-chloro-5-methyl-5,6,7,8-tetrahydroisoquinoline (Va), in contrast to the foregoing bromination reactions, from which compound (Va) 1-methyl-1,2,3,4,7,8-hexahydro-13*H*-benz[*g*]indolo[2,3-*a*]quinolizinium salts (Ⅷa and b) were synthesized.

The results of the above halogenation reactions are parallel to those briefly described by Swan who halogenated 5,6,7,8-tetrahydro-3(2*H*)isoquinolone with phosphoryl chloride and with phosphoryl bromide.[1] The structures of the products were readily distinguished by their ultraviolet absorption spectra as are shown in Fig. 1. The spectrum of Ⅴ is similar to that of 2-chloropyridine which is quite different from those of Ⅲ and Ⅳ. As for the latters, reference was made to 3-fluoroisoquinoline.[2]

Meanwhile, it has been already reported that Vb was condensed with Ⅵ to afford Ⅶb, which was cyclized with phosphoryl chloride or aluminum chloride to furnish Ⅷc,

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*1 Part Ⅳ: This Bulletin, **12**, 1296 (1964).

*2 Kita-12-jo, Nishi-5-chome, Sapporo, Hokkaido (伴 義雄, 瀬尾雅子).

1) G. A. Swan: J. Chem. Soc., **1958**, 2038.

2) S. B. Knight, W. K. Miller, A. Roe: J. Am. Chem. Soc., **74**, 1599 (1952).