Recently, open-ring triazolobenzodiazepine derivatives were reported to exhibit significants CNS activity.[13] Our results indicated that a novel series of peptido-aminobenzophenones are potentially useful CNS agents with excellent pharmacological characteristics and are interesting as novel water-soluble derivatives of 1,4-benzodiazepines[14] (Table II).

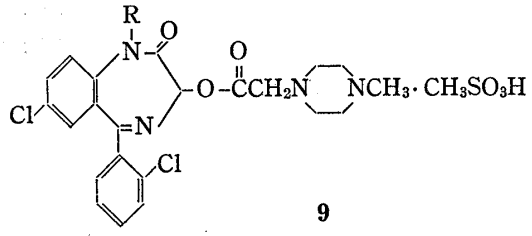
Acknowledgment The authors wish to thank to Dr. H. Otsuka, Director of this Laboratory, for his encouragement and permission for publication of this work. Thanks are also due to Drs. W. Nagata, T. Sugasawa, and K. Yamamoto of this Laboratory for their helpful advice throughout this work.

Shionogi Research Laboratory,
Shionogi & Co., Ltd.
Fukushima-ku, Osaka 553, Japan

Kentaro Hirai*
Teruyuki Ishiba
Hirohiko Sugimoto
Kazuyuki Sasakura
Toshio Fujishita
Yuji Tsukinoki
Katsumi Hirose

Received March 22, 1978

13) M. Gall, J.B. Hester, Jr., A.D. Rudzik, and R.A. Lahti, *J. Med. Chem.*, **19**, 1057 (1976).
14) As one of recent efforts to get water-soluble-derivatives of 3-hydroxy-1,4-benzodiazepines, methanesulfonic acid salts of amino ester derivatives (**9**) have been prepared (A.Nudelman, R.J. McCaully, and S.C. Bell, *J. Pharm. Sci.*, 63, 1880 (1974).



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[Chem. Pharm. Bull. 26(6)1950—1953(1978)]

UDC 547.838.1.04.09 : 615.277.4.011.5.076.7

Synthesis and Mutagenicity of 10-Azabenzo[*a*]pyrene-4,5-oxide and Other Pentacyclic Aza-arene Oxides

Aza-arene oxides, dibenz[*a,j*]acridine-5,6-oxide, dibenz[*a,h*]acridine-12,13-oxide, dibenz[*c,h*]acridine-5,6-oxide, and 10-azabenzo[*a*]pyrene-4,5-oxide were synthesized and their mutagenic activity to *Salmonella typhimurium* strains TA 98 and TA 100 was tested.

Keywords——arene oxide; aza-arene oxide; 10-azabenzo[*a*]pyrene; 10-azabenzo-[*a*]pyrene-4,5-oxide; dibenzacridine oxide; mutagenicity.

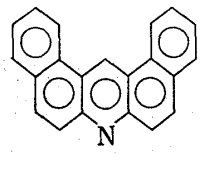
Chemical and biological interests on arene oxides have been focussed, and the rapid progress on the study of polycyclic arene oxides is remarkable.[1] However only a little attention has been paid on the chemistry and biochemistry of aza-arene oxides which are possible metabolic intermediates and activated form of carcinogenic aza-arenes.[2] Many aza-arenes have been known to be carcinogenic, and some of them have quite high activity.[3] They were also

1) D.M. Jerina and J.W. Daly, *Science*, **185**, 573 (1974).
2) Y. Kitahara, K. Shudo and T. Okamoto, *Heterocycles*, **8**, 363 (1977).
3) A. Dipple, "Polynuclear Aromatic Carcinogens, in Chemical Carcinogens (ACS Monograph 173)", ed. by C.E. Searle, American Chemical Society, 1976, p. 245—314.

found in tar,[4] urban atmosphere,[5] and tobacco smoke.[6] The present communication describes the synthesis and mutagenic activity of several pentacyclic aza-arene oxides (**5**—**8**) which were prepared from aza-arenes, dibenz[*a*, *j*]acridine (**1**), dibenz[*a*,*h*]acridine (**2**), dibenz[*c*,*h*]acridine (**3**), and 10-azabenzo[*a*]pyrene (phenaleno[1,9-*g*,*h*]quinoline, or pyrenoline, **4**).[7]

Ozonization of **1** in methylene chloride at −30——50° followed by treatment with potassium iodide, gave dialdehyde (**9**, 24%) and tetra-aldehyde (**10**, 11%). Treatment of **9** with hexamethylphosphorous triamide[8] gave dibenz[*a*, *j*]acridine-5,6-oxide (**5**), mp 252—254°, in 60% yield. Acid treatment gave a phenol (**11**), which yielded a chelate complex with copper sulfate.[2] Dibenz[*a*, *h*]acridine-12,13-oxide (**6**), mp 164—165° was prepared by oxidation of **2** with *m*-chloroperbenzoic acid in a heterogeneous solution of methylene chloride and aqueous sodium bicarbonate.[9] Acid-catalyzed isomerization of **6** gave a phenol.[10] Since this phenol did not form a chelate complex with copper sulfate,[2] the alternative structure was eliminated. Oxidation of dibenz[*c*, *h*]acridine (**3**) by *m*-chloroperbenzoic acid in chloroform at 60° gave dibenz[*c*, *h*]acridine-5,6-oxide (**7**), mp 179—180°, in 37% yield. In the presence of aqueous sodium bicarbonate, the reaction yielded the N-oxide (**12**) of **7**.

10-Azabenzo[*a*]pyrene (**4**) was oxidized by OsO_4 to a diol (**13**), mp 208—210°. Since the ultraviolet (UV) spectrum of **13** is close to that of chrysene, but not to that of benz[*a*]-anthracene, the diol group locates at the 4,5-position. The diol was treated with orthoacetic



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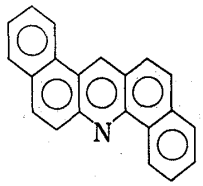

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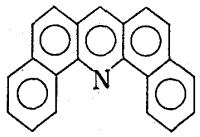

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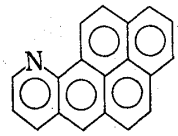

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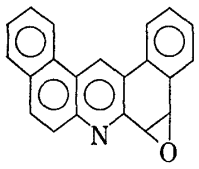

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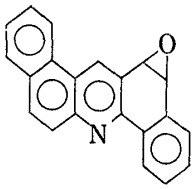

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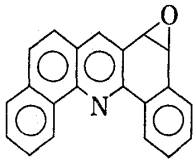

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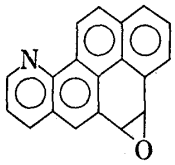

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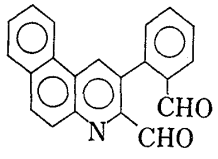

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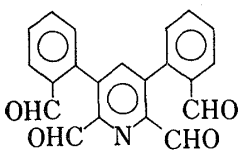

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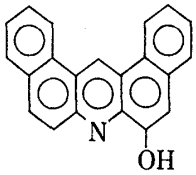

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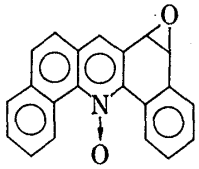

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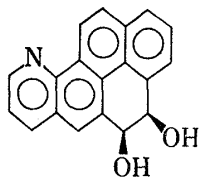

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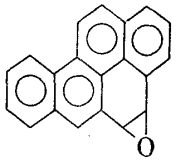

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4) E. Sawicki, J.E. Meeker and M.J. Morgan, *Int. J. Air Wat. Poll.*, **9**, 291 (1965).
5) E. Sawicki, S.P. McPherson, T.W. Stanley, J. Meeker and W.C. Elbert, *Int. J. Air Wat. Poll.*, **9**, 515 (1965).
6) B.L. van Duuren, J.A. Bilbao and C.A. Joseph, *J. Natl. Cancer Inst.*, **25**, 53 (1965).
7) All the new compounds were analyzed and characterized by infrared, nuclear magnetic resonance and mass spectra.
8) M.S. Newman and S. Blum, *J. Am. Chem. Soc.*, **86**, 5598 (1964).
9) K. Ishikawa, H.C. Charles and G.W. Griffin, *Tetrahedron Lett.*, **1977**, 427.
10) The position of hydroxy group is not established.

ester-trimethylsilyl chloride[11] to give **8**, which was purified on an alumina column and recrystallized from ether–tetrahydrofuran to give pale yellow needles, mp 181—183°. The UV spectrum of **8** is similar to that of benzo[*a*]pyrene-4,5-oxide (**14**).

Table I. Mutagenicity of Pentacyclic Aza-arene Oxides

Compounds	His$^+$/plate/μg			
	TA 98		TA 100	
	+S-9	−S-9	+S-9	−S-9
1	2.4	0	16	0
5	0.4	0	2.8	0
2	2.3	0	39	0
6	1.4	0	13	1.8
3	11	0	95	0
7	0.7	0	8.5	0
12	1.8	0	4.8	0.8
4	32	0	80	0
8	12	2200	15	1100
BP[a)]	86	0	80	0
14	0	900	0	1100

a) Benzo[*a*]pyrene.

Mutagenicity of these epoxides and the parent aza-arenes was tested in *Salmonella typhimurium* strains TA 98 and TA 100[12] with and without rat liver microsome S-9 induced by PCB as reported earlier.[13] The result was shown in Table I. All the parent aza-arenes were inactive without S-9 Mix. The presence of S-9 Mix, however, activated these compounds. In particular dibenz[*c*, *h*]acridine (**3**) and 10-azabenzo[*a*]pyrene (**4**) were as active as benzo[*a*]-pyrene to TA 100, though they were somewhat weaker to TA 98 than benzo[*a*]pyrene.

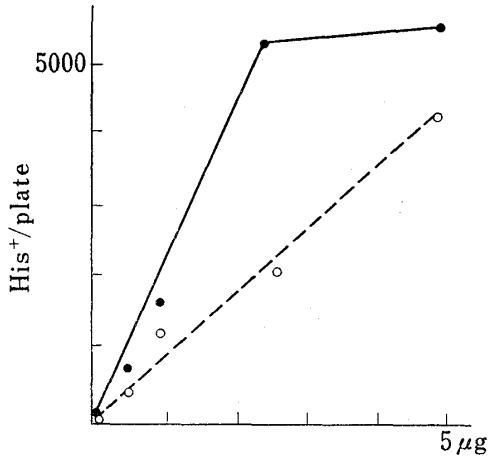

Fig. 1. Dose Response Curves of **8** and **14** to TA 98

—●— **8**, ---○--- **14**.

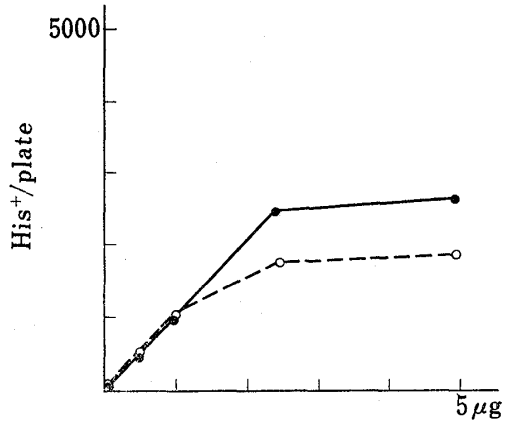

Fig. 2. Dose Response Curves of **8** and **14** to TA 100

—●— **8**, ---○--- **14**.

The epoxide (**5**) was only weakly active in the presence of S-9 Mix, and inactive without S-9 Mix. Therefore, **5** is not the activated form of **1**, The epoxide (**6**) was weakly active to TA 100 without S-9 Mix, and may be an activated metabolite though it is not the important

11) P. Dansette and D.M. Jerina, *J. Am. Chem. Soc.*, **96**, 1224 (1974).
12) J. McCann, N.E. Spingarn, J. Kobori and B.N. Ames, *Proc. Natl. Acad. Sci.* (*U. S. A.*), **72**, 979 (1975).
13) M. Nagao, T. Yahagi, Y. Seino, T. Sugimura, and N. Ito, *Mutation Res.*, **42**, 335 (1977).

one. The K-region oxide (**7**) is not the major activated form of the potent mutagenic parent compound (**3**). Interestingly the N-oxide (**12**) was weakly mutagenic to TA 100 without S-9 Mix. Contrary to those K-region oxides of dibenzacridines, the K-region oxide (**8**) of **4** was quite strongly active to TA 98 and TA 100 without S-9 Mix. Therefore **8** seems to be one of the important ultimate mutagens of **4**. The dose response curves of **8** and benzo[*a*]-pyrene-4,5-oxide (**14**) without S-9 Mix were shown in Fig. 1 and 2. The result suggests that **8** is more stronger than **14** to TA 98 in the present assay system. A further metabolism by S-9 Mix is detoxificative as the case of **14**. We are trying to synthesize a potent arene oxide of **3**, and to identify the metabolites of **4**.

Faculty of Pharmaceutical Sciences,
University of Tokyo
Hongo, Bunkyo-ku, Tokyo, 113, Japan,

Yoshiyasu Kitahara
Haruhiro Okuda
Koichi Shudo
Toshihiko Okamoto

National Cancer Center Research Institute
Tsukiji, Chuo-ku, Tokyo, 104, Japan

Minako Nagao
Yuko Seino
Takashi Sugimura

Received March 27, 1978

[Chem. Pharm. Bull. 26(6)1953—1954(1978)]

UDC 547.787.3.04 : 547.551.42.04

Electrolytic Intramolecular Cyclization of N-Alkyl-carboxanilides to Benzoxazolium

Anodic oxidation of N-alkylcarboxanilides in methanol at controlled potentials resulted in the formation of N-alkylbenzoxazolium perchlorate *via* nucleophilic attack of the carbonyl oxygen to the phenyl ring.

Keywords——N-alkylcarboxanilides; intramolecular cyclization; benzoxazolium; anodic oxidation; controlled potential electrolysis; cyclic voltammetry;

Oxidations of alkyl- and aryl-thioanilides have long been known as a method to prepare benzothiazoles.[1] However, oxidations of carboxamides usually caused C-C or C-N bond fisssion, and/or substitution reactions.[2] There seems to be no publication on the oxidation of carboxanilides to form benzoxazoles,[3] though a few papers have reported intramolecular oxidative cyclization with carboxamide oxygen: the formation of benzocoumarines as trace or minor products *via* amidyl radicals in the persulphate oxidation of *o*-phenylbenzamides,[4] and the electrochemical oxidation of phloretylglycine to give a dienone lactone.[5]

1) *a*) P. Jacobson, *Chem. Ber.*, **19**, 1067 (1886); b) Y.Mizuno and K. Watanabe, *Yakugaku Zasshi*, **70**, 540 (1950); *c*) Y. Mizuno and K. Adachi, *Ann. Rept. Fac. Pharm. Kanazawa Univ.*, **1**, 8 (1951); *d*) B.S Thyagatajan, *Chem. Rev.*, **58**, 439 (1958); *e*) T. Hisano and Y. Yabuta, *Yakugaku Zasshi*, **93**, 1356 (1973).
2) B.C. Challis and J.A. Challis, "The Chemistry of Amides," ed. by J. Zabicky, Interscience Publishers, Inc., New York and London, 1970, p. 787; N.L. Weinberg and H.R. Weinberg, *Chem. Rev.*, **68**, 449 (1968); N.L. Weinberg, "Technique of Electroorganic Synthesis," ed. by N.L. Weinberg, John Wiley and Sons, Inc., New York and London, 1974, p. 452.
3) On oxidation of acetoanilide according to the method for benzothiazole formation (ref. 1) *b*)), corresponding benzoxazole was not formed.
4) A.R. Forrester, A.S. Ingram, and R.H. Thomson, *J. Chem. Soc. Perkin I*, 2847 (1972); R.H. Thomson, *Chem. Ind.* (London), 936 (1976).
5) H. Iwasaki, L.A. Cohen, and B.Witcop, *J. Am. Chem. Soc.*, **85**, 3701 (1963).