UDC 576.852.2.095.18:547.735

94. Shinsaku Natori, Masao Ito, and Takenari Nakagome : Antibacterial Effect of Lichen Substances and Related Compounds. VI.[1] Dibenzothiophene, Fluorene, and Carbazole Derivatives.

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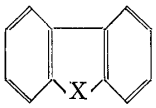
In the preceding papers,[1~3] correlation between the chemical structure and antibacterial action was examined on dibenzofuran derivatives. Of these compounds, 3-aminodibenzofuran, one of the simplest compounds of the series, showed a strong inhibitory effect on *Mycobacterium tuberculosis* A. T. C. C. No. 607. As there are many examples in which isosteric compounds[4] exhibit similar biological action[5] or show antagonism[6] between them, compounds having S, CH_2, or NH in place of oxygen atom of the dibenzofuran ring were studied, taking the 3-aminodibenzofuran as a standard. In this way, about forty kinds of dibenzothiophene, dibenzothiophene oxide, dibenzothiophene dioxide, fluorene, fluorenone, and carbazole derivatives were synthesized to examine their antibacterial action.



X=O, S, SO, SO_2, CH_2, CO, NH

Syntheses of the Derivatives

Since the chemistry of dibenzothiophene, fluorene, and carbazole was well established, almost all the compounds examined were prepared by the methods described in the literatures, which are cited in Table I. Synthetic routes are shown in Charts 1~3, and some findings to be mentioned are as follows :

2-Aminodibenzothiophene 5-Dioxide (XVIII)—A mixture of 2-bromodibenzothiophene 5-dioxide (XVII)[13](3.5 g.), Cu powder (0.2 g.), and conc. NH_4OH(70 cc.) was heated at around 200° for 7 hrs. in an autoclave. Yellow crystals, separated after cooling, were recrystallized from BuOH to colorless needles, m.p. 269~270°. Yield, 1.8 g. *Anal.* Calcd. for $C_{12}H_9O_2NS$: C, 62.34; H, 3.92; N, 6.06. Found : C, 62.59; H, 3.96; N, 6.05. The compound prepared by the reduction of 2-nitrodibenzothiophene dioxide was recorded as m.p. 270~271°[10] or m.p. 278~280°.[16]

5-Nitro-1,2,3,4-tetrahydrocarbazole (XXXII)—Condensation of *m*-nitrophenylhydrazine with cyclohexanone in the presence of HCl afforded a mixture of 5- and 7-nitro-tetrahydrocarbazole, which was submitted to chromatographic separation. 5-Nitro isomer (XXXII) thus obtained was dissolved in hot benzene and cooled rapidly or recrystallized from MeOH to red needles, m.p. 153°, which agreed well with that recorded in the literature.[21] *Anal.* Calcd. for $C_{12}H_{12}O_2N_2$: C, 66.66; H, 5.55; N, 12.96. Found : C, 66.33; H, 5.39; N, 12.57.

When the compound was dissolved in hot benzene and cooled gradually, it formed pale yellow needles of m.p. 116°, which turned readily into red needles by the above-mentioned treatment, showing dimorphism.

2-Nitrocarbazole (XXXVII)[21,22]—Dehydrogenation of the corresponding tetrahydro compound (XXXIII)[21,22] with chloranil gave the objective compound (XXXVII), which had been recorded as m.p. 165~166°, but further purification through an alumina column as benzene solution followed by recrystallization from benzene raised the m.p., giving yellow needles of m.p. 174~175°. *Anal.* Calcd. for $C_{12}H_8O_2N_2$: C, 67.92; H, 3.80; N, 13.20. Found : C, 67.67; H, 3.66; N, 12.90.

4-Aminocarbazole (XXXVIII)—4-Nitrocarbazole (XXXVI)[21,22](0.7 g.) in AcOH (5 cc.) was reduced with $SnCl_2 \cdot 2H_2O$(3.2 g.) in HCl(4 cc.). The separated hydrochloride was colorless powder of m.p. over 300°. Free base liberated by the action of NH_4OH, decomposing at about 230~250°, was unstable, and darkened by further purification in organic solvents. Trinitrobenzene complex formed by

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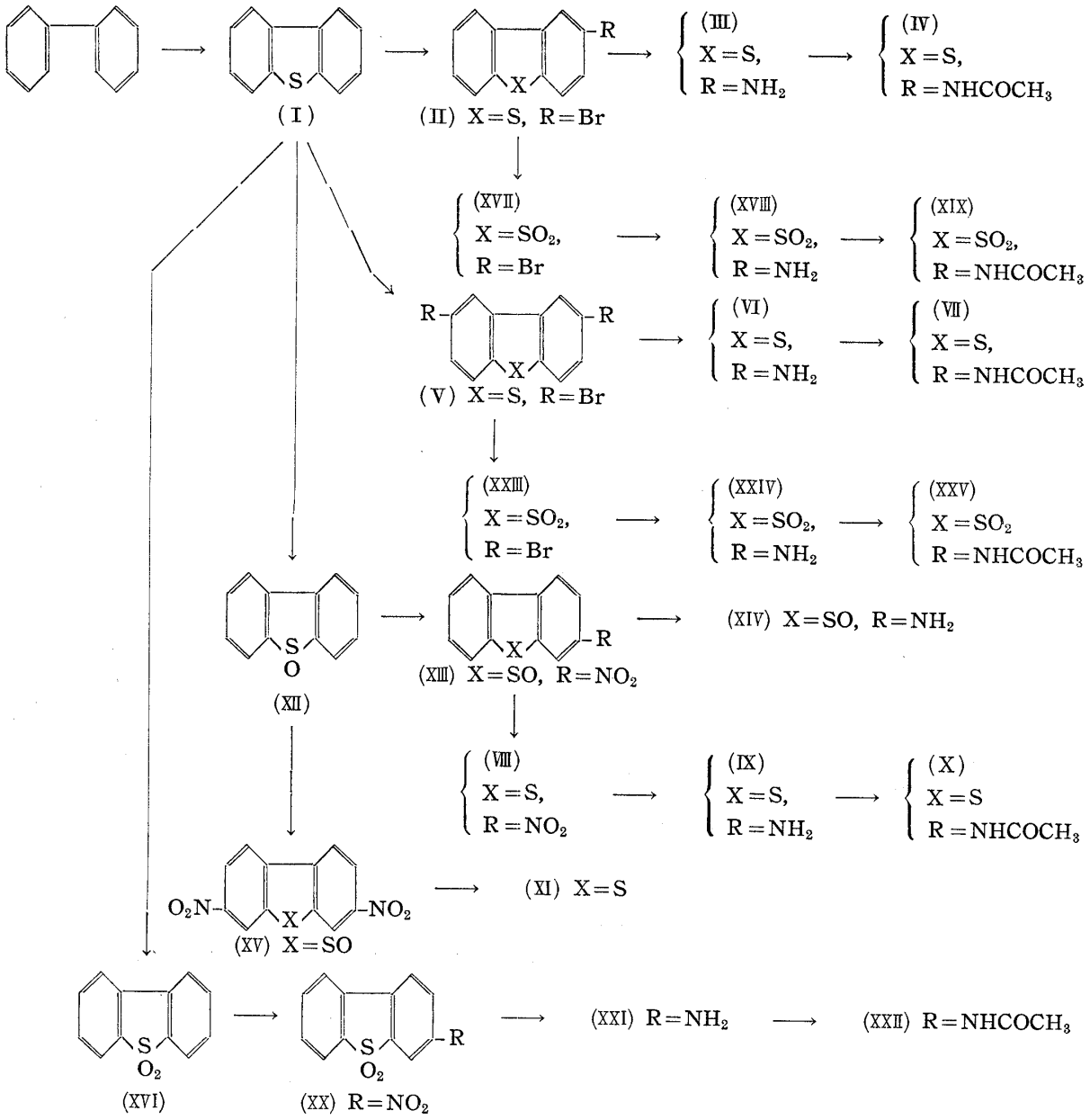

Chart 1. Synthesis of Dibenzothiophene Derivatives

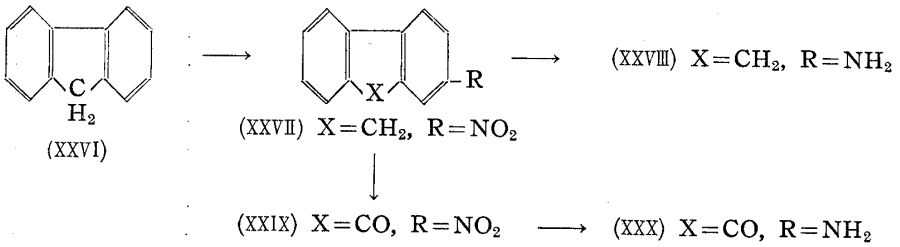

Chart 2. Synthesis of Fluorene Derivatives

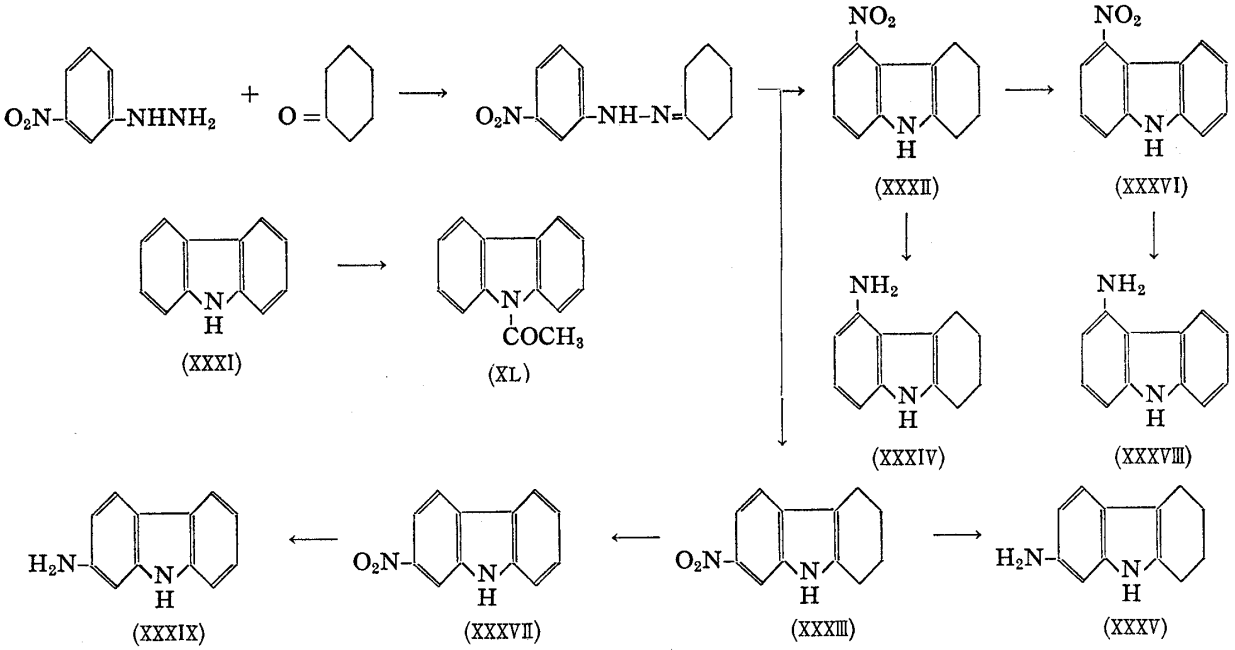

Chart 3. Synthesis of Carbazole Derivatives

the usual manner, and dark violet crystals of m.p. 216~220° separated from EtOH solution. *Anal.* Calcd. for $C_{12}H_{10}N_2 \cdot C_6H_3O_6N_3$: N, 17.72. Found : N, 16.99.

2-Aminocarbazole (XXXIX)[23]—2-Nitrocarbazole (XXXVII)(0.37 g.) in EtOH(80 cc.) was reduced catalytically with Pd-C(0.1 g.). The theoretical amount of H_2 was absorbed and evaporation of the solvent *in vacuo* afforded colorless residue of m.p. 226~238°(decomp.). Since the recrystallization from organic solvent was found to cause darkening, it was converted into trinitrobenzene complex in the usual manner, which formed dark violet needles of m.p. 186~188° by recrystallization from EtOH. *Anal.* Calcd. for $C_{12}H_{10}N_2 \cdot C_6H_3O_6N_3$: N, 17.72. Found : N, 17.41.

Antibacterial Action of the Derivatives

Methods were entirely the same as described in the preceding paper.[1] Results are shown in Table I by the highest inhibitory dilution.

Table I. Antibacterial Activity of Dibenzothiophene, Fluorene, and Carbazole Derivatives

Compound		Ref. for Synth.	Highest dilution for complete inhibition ($\times 10^4$) *St. aureus* Terashima	*E. coli communior*	*Mycobac. tuberc.* A.T.C.C. No. 607	*Mycobac. tuberc.* $H_{37}Rv$	
			Nutrient broth	Nutrient broth	Lockemann-Bloch	Sauton	Kirchner
3-Aminodibenzofuran		3)	4	2	256~512	256*	4
2-Aminodibenzofuran		3)	1	1	64	64*	4
p,p'-Diaminodiphenyl sulfone			—	—	32	—	—
Dibenzothiophene	(I)	7)	<0.5	<0.5	—	—	—
2-Bromo-	(II)	8)	<0.5	<0.5	—	—	—
2-Amino-	(III)	7)	0.5	<0.5	64	128*	<4
2-Acetamido-	(IV)	7)	<0.5	<0.5	—	—	—
2,8-Dibromo-	(V)	9)	<0.5	<0.5	—	—	—
2,8-Diamino-	(VI)	9)	0.5	0.5	2	—	—
2,8-Diacetamido-	(VII)	9)	2	<0.5	—	—	—
3-Nitro-	(VIII)	10)	<0.5	<0.5	—	—	—
3-Amino-	(IX)	11)	1	0.5	64	256*	<4
3-Acetamido-	(X)	12)	<0.5	<0.5	—	—	—
3,7-Dinitro-	(XI)	10)	<0.5	<0.5	—	—	—
Dibenzothiophene 5-oxide	(XII)	11)	<0.5	<0.5	—	—	—
3-Nitro-	(XIII)	11)	2	<0.5	2	—	—
3-Amino-	(XIV)	11)	0.5	0.5	4	—	—
3,7-Dinitro-	(XV)	10)	16	<0.5	1	—	—

Dibenzothiophene 5-dioxide	(XVI)	12)	<0.5	<0.5	—	—	—
2-Bromo-	(XVII)	13)	<0.5	<0.5	—	—	—
2-Amino-	(XVIII)		<0.5	<0.5	<1	—	—
2-Acetamido-	(XIX)	10)	<0.5	<0.5	—	—	—
3-Nitro-	(XX)	14)	<0.5	<0.5	—	—	—
3-Amino-	(XXI)	14)	<0.5	<0.5	<1	<4	<4
3-Acetamido-	(XXII)	12)	<0.5	<0.5	—	—	—
2,8-Dibromo-	(XXIII)	9, 15)	<0.5	<0.5	—	—	—
2,8-Diamino-	(XXIV)	9)	0.5	<0.5	<1	<2	<2
2,8-Diacetamido-	(XXV)	16)	<0.5	<0.5	—	—	—
Fluorene	(XXVI)		<0.5	<0.5	—	—	—
2-Nitro-	(XXVII)	17)	<0.5	<0.5	—	—	—
2-Amino-	(XXVIII)	17)	2	2	16	32*	<4
Fluorenone							
2-Nitro	(XXIX)	18)	<0.5	<0.5	—	—	—
2-Amino-	(XXX)	19)	1	0.5	4	32*	<4
Carbazole	(XXXI)		<0.5	<0.5	—	—	—
5-Nitro-1,2,3,4-tetrahydro-	(XXXII)	20, 21)	<0.5	<0.5	<1	—	—
7-Nitro- 〃	(XXXIII)	20, 21)	<0.5	<0.5	<1	—	—
5-Amino- 〃	(XXXIV)[a]	22)	<0.5	<0.5	<1	—	—
7-Amino- 〃	(XXXV)[a]	22)	8	0.5	1	—	—
4-Nitro-	(XXXVI)	21, 22)	<0.5	<0.5	<1	—	—
2-Nitro-	(XXXVII)	21, 22)	<0.5	<0.5	<1	—	—
4-Amino-	(XXXVIII)[a]		<0.5	<0.5	1	—	—
2-Amino-	(XXXIX)[a]	23)	1	0.5	2	16	2
9-Acetyl-	(XL)	24)	0.5	<0.5	—	—	—

*) See the note in Table I (p. 545) of the preceding paper.[1]

a) Purificaion of the amine was unsuccessful and a crude product was submitted to antibacterial tests.

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Relationship between Chemical Structure and Antibacterial Action

Following the preceding work,[1] relationship between chemical structure and antibacterial activity was observed in about forty kinds of dibenzothiophene, fluorene, and carbazole derivatives, in which O atom of dibenzofuran ring was replaced with S, CH_2, or NH group, comparing with the corresponding dibenzofuran derivatives.

None of these compounds inhibited the growth of *Staph. aureus* and *E. coli* with the exception of fair effectiveness of 3,7-dinitrodibenzothiophene 5-dioxide (XV) and 7-aminotetrahydrocarbazole (XXXV) on *Staph. aureus*.

Replacement of O atom of 2- and 3-aminodibenzofuran with S atom gave 2- and 3-aminodibenzothiophene (III and IX) which retained the original inhibitory action against

both strains of Mycobacterium; (IX) being less inhibitory against No. 607 strain than the original 3-aminodibenzofuran but equally effective on $H_{37}Rv$ strain, and (III) being inhibitory in almost the same dilution as that of 2-aminodibenzofuran.

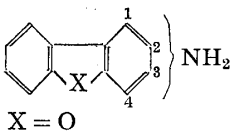
2-Aminofluorene (XXVIII), an isosteric compound of 3-aminodibenzofuran, also showed antibacterial action against the organism, though the activity was weaker than (IX). When similar replacement was made with NH group to give a carbazole, the compound (XXXIX) was less effective or, rather, ineffective.

It would be deduced from the ineffectiveness of (XIV), (XXI), and (XXX) that oxidation of S atom to SO or SO_2 and of CH_2 to CO caused the decrease of activity.

The fact that 2,8-diaminodibenzothiophene 5-dioxide (XXIV) was entirely devoid of antitubercular action is rather interesting, because the compound has similar disposition of substituents as in *p,p'*-diaminodiphenyl sulfone.

Based on the rather small examples mentioned here, it may be said that an isosterism exists in antibacterial activity of these series of compounds, for which 3-aminodibenzofuran is a standard effective compound. Comparison of antibacterial activity of amino compounds against *Mycobac. tuberc.* A.T.C.C. No. 607 is shown in Table II.

Table II. Comparison of Antibacterial Activity of Amino Derivatives against *Mycobacterium tuberculosis* A.T.C.C. No. 607

Compound	Highest dilution for complete inhibition ($\times 10^4$)			
	Position of amino group			
	1	2	3	4
				
X = O	<1	64	256~512	16
O (tetrahydro)	—	—	32	—
S	—	64	64	—
SO	—	—	4	—
SO_2	—	<1	<1	—
CH_2	—	—	16	—
CO	—	—	4	—
NH	1	—	2	—
NH (tetrahydro)	<1	—	1	—

Similarly as observed in the dibenzofuran derivatives, the reversal of antibacterial activity occurred when Kirchner's medium was employed and the antagonism shown by serum was assumed to be inevitable for these series of compounds.

The authors express their deep gratitude to Prof. S. Shibata for his unfailing guidance. Thanks are also due to Dr. M. Tsuruoka and Mr. Y. Ashikari, Department of Bacteriology, for their kind cooperation in a part of antibacterial tests (*Mycobac. tuberc.* $H_{37}Rv$). They are indebted to Yawata Iron & Steel Co., Ltd. for supply of the materials for research and to the members of the analytical laboratory of this Institute for carrying out microanalyses.

Summary

About forty kinds of dibenzothiophene, fluorene, and carbazole derivatives were synthesized and the relationship between chemical structure and antibacterial action, especially against *Mycobac. tuberc.* A.T.C.C. No. 607, was elucidated in comparison with these of dibenzofuran derivatives.

(Received July 8, 1957)