94. Shinsaku Natori, Masao Ito, and Takenari Nakagome: Antibacterial Effect of Lichen Substances and Related Compounds. VI. \(^1\)
Dibenzo thiophene, Fluorene, and Carbazole Derivatives.

(Pharmaceutical Institute, Medical Faculty, University of Tokyo\(^*\))

In the preceding papers,\(^1\) correlation between the chemical structure and antibacterial action was examined on dibenzofuran derivatives. Of these compounds, 3-aminodibenzo furan, one of the simplest compounds of the series, showed a strong inhibitory effect on \textit{Mycobacterium tuberculosis} A.T.C.C. No. 607. As there are many examples in which isosteric compounds\(^0\) 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-aminodibenzo furan as a standard. In this way, about forty kinds of dibenzo thiophene, dibenzo thiophene oxide, dibenzo thiophene dioxide, fluorene, fluorenone, and carbazole derivatives were synthesized to examine their antibacterial action.

\[
X = O, S, SO_2, CH_2, CO, NH
\]

**Syntheses of the Derivatives**

Since the chemistry of dibenzo thiophene, 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-Aminodibenzo thiophene 5-Dioxide (XVIII)**—A mixture of 2-bromodibenzo thiophene 5-dioxide (XVII)(3.8 g), Cu powder (0.2 g), and conc. \(NH_2OH\)(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\(^\circ\). Yield, 1.8 g. \textit{Anal.} Calcld. for \(C_{12}H_8O_2NS\): 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-nitrodibenzo thiophene dioxide was recorded as m.p. 270–271\(^\circ\)\(^{10}\) or m.p. 278–280\(^\circ\)\(^{10}\).

**5-Nitro-1,2,3,4-tetrahydro carbazole (XXXII)**—Condensation of \(m\)-nitrophenyldihydrazine with cyclohexanone in the presence of HCl afforded a mixture of 5- and 7-nitro-tetrahydro carbazole, which was submitted to chromatographic separation. 5-Nitro isomer (XXXI) thus obtained was dissolved in hot benzene and cooled rapidly or recrystallized from \(MeOH\) to red needles, m.p. 153\(^\circ\), which agreed well with that recorded in the literature.\(^{21}\) \textit{Anal.} Calcld. for \(C_{15}H_{15}O_2NS\): 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\(^\circ\), which turned readily into red needles by the above-mentioned treatment, showing dimorphism.

**2-Nitroc arbazole (XXXIV)**—Dehydrogenation of the corresponding tetrahydro compound (XXXIII)\(^{21,22}\) with chloranil gave the objective compound (XXXV), which had been recorded as m.p. 165–166\(^\circ\), 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\(^\circ\). \textit{Anal.} Calcld. for \(C_{15}H_{15}O_2NS\): C, 67.92; H, 3.80; N, 13.20. Found: C, 67.67; H, 3.66; N, 13.90.

**4-Aminoc arbazole (XXXVIII)**—4-Nitroc arbazole (XXXVII)\(^{21,25}\)(0.7 g) in \(AcOH\) (5 cc) was reduced with \(SnCl_2\cdot2H_2O\)(3.2 g) in \(HCl\)(4 cc). The separated hydrochloride was colorless powder of m.p. over 300\(^\circ\). Free base liberated by the action of \(NH_2OH\), decomposing at about 230–250\(^\circ\), was unstable, and darkened by further purification in organic solvents. Trinitrobenzen complex formed by

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* Hongo, Tokyo (名取信一, 伊藤昌男, 中村孟也).
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_{18}H_{16}N_{2}·C_{6}H_{4}O_{2}N_{3}: N, 17.72. Found: N, 16.99.

**2-Amino-3-carbazole (XXVII)**—2-Nitrocavazol (XXVII)(0.37 g.) in EtOH(80 cc.) was reduced catalytically with Pd-C(0.1 g.). The theoretical amount of H₂ 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_{18}H_{16}N_{2}·C_{6}H_{4}O_{2}N_{3}: N, 17.72. Found: N, 17.41.

**Antibacterial Action of the Derivatives**

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

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

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ref. for Synth.</th>
<th>St. aureus</th>
<th>E. coli communior</th>
<th>Mycobac. tuberc.</th>
<th>A.T.C.C. No. 607</th>
<th>H₂Rv</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-Aminodibenzoferan</td>
<td>3)</td>
<td>4</td>
<td>2</td>
<td>256—512</td>
<td>256*</td>
<td>4</td>
</tr>
<tr>
<td>2-Aminodibenzoferan</td>
<td>3)</td>
<td>1</td>
<td>1</td>
<td>64</td>
<td>64*</td>
<td>4</td>
</tr>
<tr>
<td>p,p'-Diaminodiphenyl sulfone</td>
<td></td>
<td>—</td>
<td>—</td>
<td>32</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Dibenzothiophene</td>
<td>(I)</td>
<td>7</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2-Bromo-</td>
<td>(II)</td>
<td>8</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2-Amino-</td>
<td>(III)</td>
<td>7</td>
<td>0.5</td>
<td>&lt;0.5</td>
<td>64</td>
<td>128*</td>
</tr>
<tr>
<td>2-Acetamido-</td>
<td>(IV)</td>
<td>7</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2,8-Dibromo-</td>
<td>(V)</td>
<td>9</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2,8-Diamino-</td>
<td>(VI)</td>
<td>9</td>
<td>0.5</td>
<td>0.5</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>2,8-Diacetamido-</td>
<td>(VII)</td>
<td>9</td>
<td>2</td>
<td>&lt;0.5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3-Nitro-</td>
<td>(VIII)</td>
<td>10</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3-Amino-</td>
<td>(IX)</td>
<td>11</td>
<td>0.5</td>
<td>0.5</td>
<td>64</td>
<td>256*</td>
</tr>
<tr>
<td>3-Acetamido-</td>
<td>(X)</td>
<td>12</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3,7-Dinitro-</td>
<td>(XI)</td>
<td>10</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Dibenzothiophene 5-oxide</td>
<td>(XII)</td>
<td>11</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3-Nitro-</td>
<td>(XIII)</td>
<td>11</td>
<td>2</td>
<td>&lt;0.5</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>3-Amino-</td>
<td>(XIV)</td>
<td>11</td>
<td>0.5</td>
<td>0.5</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>3,7-Dinitro-</td>
<td>(XV)</td>
<td>10</td>
<td>16</td>
<td>&lt;0.5</td>
<td>1</td>
<td>—</td>
</tr>
</tbody>
</table>

NII-Electronic Library Service
<table>
<thead>
<tr>
<th>Substance</th>
<th>Formula</th>
</tr>
</thead>
</table>
| Dibenzothiophene 5-dioxide | (XVI) 12| \(<0.5\)  
| 2-Bromo-                  | (XVII) 13 | \(<0.5\)  
| 2-Amino-                  | (XVII) | \(<0.5\)  
| 2-Acetamido-              | (XIX) 10 | \(<0.5\)  
| 3-Nitro-                  | (XI) 14 | \(<0.5\)  
| 3-Amino-                  | (XI) 14 | \(<0.5\)  
| 3-Acetamido-              | (XXI) 15 | \(<0.5\)  
| 2,8-Dibromo-              | (XXII) 9 | \(<0.5\)  
| 2,8-Diamino-              | (XXIV) 9 | \(<0.5\)  
| 2,8-Diacetamido-          | (XXV) 16 | \(<0.5\)  
| Fluorene                  | (XXVI) | \(<0.5\)  
| 2-Nitro-                  | (XXVII) 17 | \(<0.5\)  
| 2-Amino-                  | (XXVII) 17 | 2  
| Fluorenone                | (XXX) 19 | 0.5  
| 2-Nitro-                  | (XXXI) 18 | \(<0.5\)  
| 2-Amino-                  | (XXXI) 19 | 4  
| Carbazole                 | (XXXI) | \(<0.5\)  
| 5-Nitro-1,2,3,4-tetrahydro-| (XXXII) 21 | \(<0.5\)  
| 7-Nitro-                  | (XXXII) 20 | \(<0.5\)  
| 5-Amino-                  | (XXXIV) 22 | \(<0.5\)  
| 7-Amino-                  | (XXXV) 22 | 0.5  
| 4-Nitro-                  | (XXXVI) 22 | \(<0.5\)  
| 2-Nitro-                  | (XXXVI) 21 | \(<0.5\)  
| 4-Amino-                  | (XXXVII) 22 | \(<0.5\)  
| 2-Amino-                  | (XXXVII) 23 | 1  
| 9-Acetyl-                 | (X) 24 | \(<0.5\)  

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

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

22) S. G. P. Plant:  Ibid., 1936, 899.

**Relationship between Chemical Structure and Antibacterial Action**

Following the preceding work, a 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, CH₂, 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-aminothetrahydrocarbazole (XXXV) on *Staph. aureus*.

Replacement of O atom of 2- and 3-aminodibenzo-derivates 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-aminodibenzoferan but equally effective on H₂Rv strain, and (III) being inhibitory in almost the same dilution as that of 2-aminodibenzoferan.

2-Aminofluorene (XXVIII), an isosteric compound of 3-aminodibenzoferan, 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 SO₂ and of CH₂ 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 isostericism exists in antibacterial activity of these series of compounds, for which 3-aminodibenzoferan 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**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Highest dilution for complete inhibition (×10⁴)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X = O</td>
<td>Position of amino group</td>
</tr>
<tr>
<td>O (tetrahydro)</td>
<td>1</td>
</tr>
<tr>
<td>S</td>
<td>&lt;1</td>
</tr>
<tr>
<td>SO</td>
<td>64</td>
</tr>
<tr>
<td>SO₂</td>
<td>&lt;1</td>
</tr>
<tr>
<td>CH₃</td>
<td>16</td>
</tr>
<tr>
<td>CO</td>
<td>4</td>
</tr>
<tr>
<td>NH</td>
<td>2</td>
</tr>
<tr>
<td>NH (tetrahydro)</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

Similarly as observed in the dibenzoferan 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. H₂Rv). 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 dibenzoferan derivatives.

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