77. **Tatsuo Ohta and Yo Mori**: Syntheses of *Py*-Benzyl-4-hydroxycarbostyrils.

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There should exist two kinds of monobenzyl- and one dibenzyl-4-hydroxycarbostyril substituted in the pyridine ring. Of these, 1-benzyl-4-hydroxycarbostyril (I) appears in Swiss and U. S. patents1) but no detail is available. 3-Benzyl-4-hydroxycarbostyril (II) was obtained by the condensation of aniline and benzylmalonic ester by Baumgarten and others.2) Lucius and Brüning3) have shown that N-methylanthranilic acid is cyclized to form 1-methyl-4-hydroxycarbostyril by boiling with acetic anhydride. Later, Lutz and others4) raised the yield of carbostyril compound employing acetic anhydride diluted with acetic acid.

Using the improved method of Lutz and others, the authors have isolated 4-acetoxy-1-benzylcarbostyril (III) as the intermediate product of a reaction between N-benzylanthranilic acid5) and the acetic anhydride-acetic acid mixture. This acetate was easily hydrolyzed to yield 1-benzyl-4-hydroxycarbostyril (I), m.p. 286°, from which the same acetate of m.p. 146~147° was again formed by treatment with acetic anhydride. (I) was also obtained by the ring closure with metallic sodium in toluene solution of methyl N-acetyl-N-benzylanthranilate (IV), $b.p_4$ 197~198°, which was prepared from methyl N-benzylanthranilate, $b.p_8$ 174°,6) and acetic anhydride.

Methyl N-(β-phenylpropionyl)anthranilate (V), $b.p_3$ 215~217°, prepared from methyl anthranilate and hydrocinnamoyl chloride in pyridine, was submitted to Camps' quinolinediol synthesis7) as in the case of (I). As the main product of this reaction, the hydrogen carbonate-insoluble crystals (A), m.p. 192~193°, were isolated. When the crystals (A) were warmed with acetic anhydride in pyridine solution or merely boiled with acetic anhydride, 4-acetoxy-3-benzylcarbostyril8) (VI), m.p. 244~245°, was obtained in a good yield. (VI) gave 3-benzyl-4-hydroxycarbostyril (II), m.p. 207~208°, on hydrolysis. Further, (II) was directly obtained by boiling the crystals (A) with conc. hydrochloric acid.

The crystals (A) corresponded to the formula of $C_{32}H_{28}O_5N_2$ and this was quite identical with the specimen obtained by the crystallization of a mixture (1:1 moles) of (II) and N-(β-phenylpropionyl)anthranilic acid (VII). Therefore, the crystals (A) are considered as a molecular compound of (II) and (VII) in the ratio of 1:1 moles, as in the case of 3-alkyl-4-hydroxycarbostyril.9)

Similarly, methyl N-benzyl-N-(β-phenylpropionyl)anthranilate, an oily liquid, was prepared from methyl N-benzylanthranilate and hydrocinnamoyl chloride, and submitted to cyclization by which 1,3-dibenzyl-4-hydroxycarbostyril (VIII) was obtained as

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1) Swiss Pat., 267,275 (1950); U. S. Pat., 2,542,850 (1951).

2) P. Baumgarten, W. Kärgel: Ber., **60**, 832 (1927). m.p. 194° (solvent free); benzoate, m.p. 256°.

3) M. Lucius, *et al.*: Chem. Zentr., **86 II**, 1034 (1915); Höchst: Ger. Pat., 287,803 (1915).

4) R. E. Lutz, *et al.*: J. Am. Chem. Soc., **68**, 1810 (1946).

5) J. Houben, W. Brassert: Ber., **39**, 3237 (1906).

6) J. van Alphen: Rec. trav. chim., **61**, 201 (1942). $b.p_{10}$ 206°.

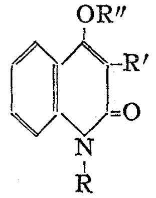
7) R. Camps: Arch. Pharm., **237**, 690 (1899); *cf.* T. Ohta: J. Pharm. Soc. Japan, **73**, 63 (1953).

8) It is presumed that the acetyl group is situated in the hydroxyl at 4-position similar to the 3-ethyl- and 3-ethyl-7,8-dimethoxy-4-hydroxycarbostyril monoacetates, respectively. *cf.* T. Ohta, T. Miyazaki, Y. Mori: Ann. Rept. Tokyo Coll. Pharm., **4**, 255 (1954).

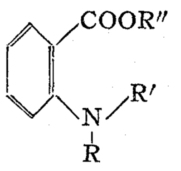
9) T. Ohta, Y. Mori: J. Pharm. Soc. Japan, **75**, 1162 (1955).

needles, m.p. 209～210°, which gave the acetate (IX) of m.p. 149～150°.

Based on the above facts and the results[9] previously obtained, the authors concluded that the presence of both -NH-CO- group and alkyl or aralkyl group such as benzyl in the 3-position of 4-hydroxycarbostyril is indispensable for the molecular compound formation noted above.



〔I〕 $R=CH_2-\phi$; $R', R''=H$
〔II〕 $R, R''=H$; $R'=CH_2-\phi$
〔III〕 $R=CH_2-\phi$; $R'=H$; $R''=COCH_3$
〔VI〕 $R=H$; $R'=CH_2-\phi$; $R''=COCH_3$
〔VIII〕 $R, R'=CH_2-\phi$; $R''=H$
〔IX〕 $R, R'=CH_2-\phi$; $R''=COCH_3$



〔IV〕 $R=CH_2-\phi$; $R'=COCH_3$; $R''=CH_3$
〔V〕 $R=H$; $R'=COCH_2CH_2-\phi$; $R''=CH_3$
〔VII〕 $R, R''=H$; $R'=COCH_2CH_2-\phi$

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Experimental*

N-Benzylanthranilic Acid—Prepared by the method of Houben and Brassert[5] from anthranilic acid and benzyl chloride. Colorless prisms (from EtOH), m.p. 176°. An ethanolic solution shows a violet fluorescence.

1-Benzyl-4-hydroxycarbostyril (I)—To 5 g. of N-benzylanthranilic acid, 12 cc. of a mixture of equal volumes of Ac_2O and 100% HOAc was added, and the mixture was heated on asbestos net for 4 hrs., cooled, and poured into ice water. After allowing the mixture to stand over night, the brownish resinous substance that separated out was collected (2.5 g.) and recrystallized from EtOH to slightly yellow plates, m.p. 143～144°. Admixture of this compound with 4-acetoxy-1-benzylcarbostyril, m.p. 146～147°, melted at 144～146°.

To 0.2 g. of these crystals, 10 cc. of 10% KOH solution was added, and the mixture was warmed on a water bath for a while. After cool, the solution was acidified with HCl, and the crystals that separated were collected. Recrystallization from EtOH yielded colorless leaflets, m.p. 286° (sintering at 282°). This compound is soluble in Na_2CO_3 and caustic alkali solutions; slightly soluble in EtOH but is soluble in this hot solvent. *Anal.* Calcd. for $C_{16}H_{13}O_2N$: C, 76.47; H, 5.22; N, 5.57. Found : C, 76.44; H, 5.43; N, 5.49.

4-Acetoxy-1-benzylcarbostyril (III)—A mixture of 0.5 g. of 1-benzyl-4-hydroxycarbostyril and 5 cc. of Ac_2O was heated on asbestos net for 1 hr., cooled, and poured into ice water. After standing over night, the separated crystals were collected, washed, and crystallized from EtOH to colorless plates, m.p. 146～147°. *Anal.* Calcd. for $C_{18}H_{15}O_3N$: C, 73.30; H, 5.15; N, 4.78. Found : C, 72.99; H, 5.16; N, 4.83.

Methyl N-Benzylanthranilate—Prepared from methyl anthranilate, benzyl chloride, and fused AcONa according to van Alphen.[6] b.p_3 174°. Yield, 62.7%.

Methyl N-Acetyl-N-benzylanthranilate (IV)—A mixture of 20 g. of methyl N-benzylanthranilate and 60 cc. of Ac_2O was warmed on a water bath for 30 mins., cooled, and poured into ice water. The oily liquid that separated was shaken with ether. The ethereal residue was distilled under diminished pressure. b.p_4 197～198°. Yield, 22 g. *Anal.* Calcd. for $C_{17}H_{17}O_3N$: C, 72.06; H, 6.05; N, 4.94. Found : C, 71.74; H, 6.11; N, 4.70.

Ring Closure of (IV) with Metallic Sodium 〔Formation of (I)〕—To a warm solution of 20 g. of methyl N-acetyl-N-benzylanthranilate dissolved in 100 cc. of toluene, 2 g. of metallic Na was added. The whole was refluxed for 3 hrs. in an oil bath. Then the reaction mixture was treated by the usual method (see below) and the crystals that precipitated from the alkaline aqueous layer with HCl were crystallized from EtOH to leaflets, m.p. 286°, from which the acetate of m.p. 146～147° was formed by boiling with Ac_2O. There was no depression on admixture with N-benzyl-4-hydroxycarbostyril and its acetate synthesized from N-benzylanthranilic acid as described above.

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* All melting points are uncorrected.

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Methyl N-(β-Phenylpropionyl)anthranilate (V)—First, hydrocinnamoyl chloride was prepared from hydrocinnamic acid and $SOCl_2$ by the usual manner. To 15 g. of methyl anthranilate dissolved in 10 cc. of pyridine, the crude hydrocinnamoyl chloride was added dropwise under ice cooling. The reaction mixture was poured onto crushed ice and the separating oily liquid was taken up in ether. The ethereal layer was washed with $NaHCO_3$ solution and water successively, dried, and evaporated. The ethereal residue (25 g.) was distilled under reduced pressure. b.p$_8$ 215∼217°. *Anal.* Calcd. for $C_{17}H_{17}O_3N$: C, 72.06; H, 6.05; N, 4.94. Found : C, 71.61; H, 5.62; N, 5.06.

Ring Closure of (V) with Metallic Sodium [Formation of the Molecular Compound (A)]—A solution of 14.2 g. (0.1 mole) of methyl N-(β-phenylpropionyl)anthranilate dissolved in 100 cc. of toluene was heated at 60∼65° in an oil bath. To this was added 1.5 g. of metallic Na in small pieces, and the mixture refluxed for 1.5 hrs. After dissolving the remaining Na by addition of EtOH, the content was poured into water and the aqueous layer was separated. The aqueous solution was combined with aqueous washings from toluene layer, acidified with HCl, and the crystals that separated out were collected. The crystals were treated with $NaHCO_3$ solution, and the insoluble substance (8.7 g.) was recrystallized from EtOH with charcoal to colorless needles, m.p. 192∼193°. It dissolves in caustic alkali solution but precipitates out on acidification with inorganic acid; it is more soluble than 3-benzyl-4-hydroxycarbostyril in EtOH. *Anal.* Calcd. for $C_{32}H_{28}O_5N_2$: C, 73.83; H, 5.42; N, 5.38. Found : C, 73.46; H, 5.44; N, 5.62.

In certain circumstances, 3-benzyl-4-hydroxycarbostyril (1.4 g. from 0.1 mole of the ester) was directly obtained from the less soluble fraction in EtOH by crystallization of the bicarbonate-insoluble substance.

The bicarbonate-soluble portion was acidified with HCl, and from which the free acid of the starting material (N-(β-phenylpropionyl)anthranilic acid (Ⅶ)) was obtained. Colorless needles (from dil. EtOH), m.p. 141∼142°. *Anal.* Calcd. for $C_{16}H_{15}O_3N$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.61; H, 5.36; N, 5.10.

Boiling of the Molecular Compound (A) with Acetic Anhydride [Obtaining of 4-Acetoxy-3-benzylcarbostyril (VI)]—0.5 g. of the molecular compound, m.p. 192∼193°, was boiled with Ac_2O (10 cc.) on asbestos net for 1 hr., and the mixture was poured into ice water. The separating crystals were recrystallized from EtOH to colorless silky needles, m.p. 244∼245°. Yield, 0.2 g. When mixed with 4-acetoxy-3-benzylcarbostyril (Ⅲ), there was no depression of the melting point. *Anal.* Calcd. for $C_{18}H_{15}O_3N$: C, 73.70; H, 5.15; N, 4.78. Found : C, 73.57; H, 5.16; N, 4.79.

Treatment of the Molecular Compound (A) with Acetic Anhydride in Pyridine—A mixture of 0.2 g. of the molecular compound (A) dissolved in 2 cc. of pyridine and 2 cc. of Ac_2O was warmed on a water bath for 30 mins., poured into ice water, and the separating crystals were crystallized from EtOH to colorless needles, m.p. 244∼245°. No depression of the melting point occurred on admixture with the compound (Ⅲ).

Hydrolysis of the Acetate obtained from the Molecular Compound (A)—The acetate was warmed with 10% KOH solution on a water bath. The mixture went into solution before long and from which 3-benzyl-4-hydroxycarbostyril was precipitated by addition of HCl. The crystals thus obtained were quite identical with the substance separated from the molecular compound (A) by boiling with conc. HCl.

Boiling of the Molecular Compound (A) with conc. HCl (Separation of 3-Benzyl-4-hydroxycarbostyril)—1.0 g. of the molecular compound (A) was boiled with 20 cc. of conc. HCl for 2 hrs. The crystals dissolved gradually through an oily liquid. After cool, the solution was neutrallized with $NaHCO_3$, and the separating crystals were collected, washed, and crystallized from EtOH to colorless transparent plates or needles containing one mole of EtOH of crystallization. The crystals hereby obtained melt at 207∼208°. It effloresces rapidly in the air to white opaque crystals. The melting point of the solvent-free compound is just the same as the EtOH-containing one. *Anal.* Calcd. for $C_{16}H_{13}O_2N \cdot C_2H_5OH$: C, 72.70; H, 6.44; N, 4.71. Found : C, 72.09; H, 6.20; N, 4.72. Calcd. for $C_{16}H_{13}O_2N$ (solvent free) : C, 76.47; H, 5.22; N, 5.57. Found: C, 76.39; H, 5.22; N, 5.66. Calcd. for $C_{16}H_{13}O_2N \cdot C_2H_5OH$ (after heating at 110°/3 mm. for 2 hrs.): EtOH, 15.48. Found : EtOH, 15.43.

4-Acetoxy-3-benzylcarbostyril (VI)—Prepared from (Ⅱ) by boiling with Ac_2O. Colorless needles (from EtOH). m.p. 244∼245°.

4-Benzoyloxy-3-benzylcarbostyril—Prepared from 3-benzyl compound and BzCl in pyridine. Colorless silky needles (from EtOH), m.p. 256∼257°. *Anal.* Calcd. for $C_{23}H_{17}O_3N$: N, 3.94. Found : N, 3.94.

Synthesis of the Molecular Compound (A)—A mixture of 3-benzyl-4-hydroxycarbostyril (0.1 g.) and N-(β-phenylpropionyl)anthranilic acid (0.1 g.) was recrystallized from EtOH to colorless needles of m.p. 192∼193°. This compound showed no depression of the melting point when mixed with the molecular compound produced from methyl N-(β-phenylpropionyl)anthranilate

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with metallic Na.

Methyl N-Benzyl-N-(β-phenylpropionyl)anthranilate—To 8 g. of methyl N-benzylanthranilate dissolved in 10 cc. of pyridine, an equivalent quantity of hydrocinnamoyl chloride (prepared from 5 g. of hydrocinnamic acid) was added in small portions with chilling, and then the mixture was warmed on a water bath for a while to complete the reaction. After cool, the content was poured onto crushed ice, and the separating oily liquid was taken up in ether. The ethereal layer was washed first with $NaHCO_3$ solution, then with water, dried, and the solvent was distilled off. The residue thus obtained was distilled in high vacuum at 160~180°(bath temp.), 2×10^{-4} mm. Hg. Slightly yellowish viscous oil. *Anal.* Calcd. for $C_{24}H_{23}O_3N$: C, 77.19; H, 6.21; N, 3.75. Found: C, 76.66; H, 6.49; N, 3.35.

Ring Closure of Methyl N-Benzyl-N-(β-phenylpropionyl)anthranilate with Metallic Sodium [Formation of 1,3-Dibenzyl-4-hydroxycarbostyril (VIII)]—To 7 g. of the sample dissolved in 30 cc. of toluene, 0.7 g. of metallic Na was added, and this was treated exactly in the same way as for N-benzyl-4-hydroxycarbostyril. Yield, 4.7 g. Colorless needles (from EtOH), m.p. 209~210°. *Anal.* Calcd. for $C_{23}H_{19}O_2N$: C, 80.91; H, 5.61; N, 4.10. Found: C, 81.35; H, 5.80; N, 4.03.

4-Acetoxy-1,3-dibenzylcarbostyril (IX)—Prepared from 1,3-dibenzyl-4-hydroxycarbostyril by boiling with Ac_2O. Colorless microprisms (from EtOH), m.p. 149~150°. *Anal.* Calcd. for $C_{25}H_{21}O_3N$: C, 78.31; H, 5.52; N, 3.65. Found: C, 78.19; H, 5.63; N, 3.48.

Summary

1-Benzyl-, 3-benzyl-, and 1,3-dibenzyl-4-hydroxycarbostyril were obtained by the method of Camps' quinolinediol synthesis. In the case of 3-benzyl compound, the molecular compound of 3-benzyl-4-hydroxycarbostyril with N-(β-phenylpropionyl)-anthranilic acid was isolated as the main reaction product. 1-Benzyl compound was also prepared according to Lutz's method.

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