Staphylococcus aureus and *Escherichia coli* for their antibacterial activities and it was found that of the new compounds tested 4-hydroxycoumarins having polycyclic aromatic nucleus in the side-chains on 3-position were most active, and that the side-chains on this position are not restricted to long-chained aliphatic acyl groups in order to display high antibacterial activities of 4-hydroxycoumarins.

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234. Shigehiko Sugasawa and Hiroshi Tomisawa: Synthesis in the Benzoquinolizine Group. XVI. A Synthesis of 4',5'-Methylenedioxy-6-amino-3,4,5,6,7,8-hexahydro-(2',1': 1,2-benzoquinolizine)*

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In the earlier paper of this series the synthesis of 7-amino analog (A : R=H, R'=NH₂ or CH₂NH₂) of the compound mentioned in the title (A : R=NH₂ or CH₂NH₂, R'=H) was described.¹⁾ The objective of these synthesis exists in the preparation of those hydrobenzoquinolizine derivatives of general formula (B) for physiological assessment, which can be regarded derivable from emetine (C) and compound (D)²⁾ by the rupture of the bond of isoquinoline rings at a and b, respectively.

β -3,4-Methylenedioxyphenethyl bromide (I) was condensed with ethyl nicotinate (II), yielding the quaternary bromide (III) in a good yield. It was oxidized to the corresponding pyridone-carboxylic acid (IV)³⁾ as usual. The latter was then cyclized by boiling with phosphoryl chloride, followed by the treatment with absolute alcohol, giving carbethoxybenzoquinolizinium salt (VI'), which could be reduced to the hydrogenated product (VII), but with difficulty. The alternate route was proved to be more satisfactory.

An aqueous solution of sodium salt of (IV) was reduced catalytically by hydrogen activated upon Raney Ni, giving the corresponding piperidone (V), which was then cy-

* Part XV.: Sugasawa, Tatsuno: This Journal **72**, 248 (1952).

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1) Sugasawa, Suzuta: This Journal **71**, 1159 (1951).

2) Emetine formula, once erroneously put forward by Pyman.

3) For the constitution of this compound, see Sugasawa, et al.: Ber., **74**, 537 (1941).

clized to (VI) and reduced, one mole of hydrogen being readily absorbed yielding (VII), which was proved to be identical with the one described above.

The crude syrupy ester crystallized partially, which was separated by suctional filtration. Since the oily filtrate could not be induced to crystallize, it was converted into a hydrazide, which formed colorless needles of m.p. 224~225° from alcohol. The hydrazide of the crystalline ester formed colorless needles of m.p. 174~176° from alcohol, so they represent diastereoracemates.

The higher melting hydrazide then underwent Curtius degradation, as modified by Sugasawa and Saito⁴⁾, giving the compound (X) mentioned in the title, the dimethyl derivative of which was prepared by the conventional formic acid-formalin method.

The pure crystalline ester (VII) was hydrolyzed to the free acid (XII), which was then heated with formamide, yielding the corresponding acid amide (XIII)⁵⁾. It might be worth mentioning that other usual methods of preparing acid amide either from acid or ester were fruitless.

Lithium aluminum hydride⁶⁾ in ether converted the amide into the amine (XIV), whose dimethyl derivative (XV) was prepared as above, but the result was not quite satisfactory and further investigation upon this point is necessary.

Three above-mentioned amines (X, XI and XIV) are now being tested for their amoebicidal property.

The authors are grateful to Dr. Glenn Ulliyot and Dr. Leo J. Stevens of Smith, Kline and French Laboratories, Philadelphia, for the gift of lithium aluminum hydride. Their thanks are also due to Messrs. Huang, Sakai, and Tani and Mrs. Wu for microanalyses.

Experimental

N-[β -(3',4'-Methylenedioxyphenyl)-ethyl]-3-carbethoxypyridinium bromide (III). — β -3,4-Methylenedioxyphenethyl bromide (I: 8 g.), and ethyl nicotinate (II: 5 g.) and a little benzene were heated on a water bath. Yield, 12.8 g. or 96.5%. Grouped needles from alcohol, m.p. 189.5~190.5° (decomp.). *Anal.* Calcd. for C₁₇H₁₈O₄NBr: C, 53.7; H, 4.7; N, 3.7 Found: C, 53.7; H, 5.1; N, 3.5.

N-[β -(3',4'-Methylenedioxyphenyl)-ethyl]-2-pyridone-5-carboxylic acid (IV). — Alkaline potassium ferricyanide solution (K₃Fe(CN)₆ 30 g., NaOH 7 g. and H₂O 130 cc.) was added, drop by drop, to a stirred solution of the foregoing bromide (9.8 g.) in warm water (130 cc.). The mixture was kept at 40~45° for 1 hr., filtered through a wet filter and the filtrate was acidified with acetic

4) Proc. Imp. Acad. Tokyo, **20**, 137 (1940); cf. also Sugasawa, et al.: This Journal, **72**, 192 (1952).

5) Sugasawa, Lee: This Journal, **62**, 531 (1942).

6) Uffer, Schlittler: Helv. Chim. Acta, **31**, 1397 (1948).

acid, separating gray precipitate of (IV). Yield, 7 g. or 95%. Colorless pillars from much methanol, m.p. 225°. *Anal.* Calcd. for $C_{15}H_{13}O_5N$: C, 62.5; H, 4.5. Found: C, 62.7; H, 4.7.

N-(β -(3',4'-Methylenedioxyphenyl)-ethyl)-2-piperidone-5-carboxylic acid (V).—The aforementioned acid (7.3 g.), with a corresponding amount of sodium bicarbonate, was dissolved in water and reduced by hydrogen activated over Raney Ni, two moles of hydrogen being absorbed smoothly. The filtrate from the catalyst deposited white piperidone-carboxylic acid (V) on being acidified with acetic acid. Yield, 6.5 g. or 89%. Colorless scales from alcohol, m.p. 204–205°. *Anal.* Calcd. for $C_{15}H_{17}O_5N$: C 61.9; H, 5.8; N, 4.8. Found: C, 62.0; H, 5.9; N, 5.0.

4',5'-Methylenedioxy-3,4,5,6,7,8-hexahydro-9,10-dehydro-6-carbethoxy-(2',1':1,2-benzoquinolizine) (VI).—The foregoing lactam (1 g.), phosphoryl chloride (3 cc.) and pure dry toluene (2 cc.) were heated in an oil bath at 110–120° for 40 min., giving light brown clear solution. After distilling off toluene and excess of phosphoryl chloride, the residue was added with absolute alcohol (4 cc.) and the mixture was refluxed for 30 min. Alcohol was then removed by distillation and the residue was dissolved in water (10 cc.) and filtered through a wet filter. Potassium iodide was now added to the filtrate, separating yellowish brown viscous oil, which solidified after some time. Yield 1.3 g. or 88%. Yellow, grouped needles of m.p. 197° from alcohol. *Anal.* Calcd. for $C_{17}H_{20}O_4NI$: C, 47.5; H, 4.7; N, 3.3. Found: C, 47.3; H, 4.8; N, 3.0.

4',5'-Methylenedioxy-3,4-dihydro-9,10-dehydro-6-carbethoxy-(2',1':1,2-benzoquinolizinium iodide) (VI').—The above-mentioned compound (IV: 1.8 g.), phosphoryl chloride (5 cc.) and pure dry xylene (5 cc.) were heated at 120–130° for half an hour, and the product was worked up as above. Crude yield, 2.8 g. Yellow needles from alcohol, m.p. 224–225° (decomp.).

4',5'-Methylenedioxy-3,4,5,6,7,8-hexahydro-6-carbethoxy-(2',1':1,2-benzoquinolizine) (VII).—The compound (VI: 28 g.) was converted to the corresponding chloride and the latter was reduced catalytically over Adams' Pt, 1 mole of hydrogen being readily absorbed. From the filtrate alcohol was distilled off and the residue was dissolved in water, basified with sodium bicarbonate and the liberated base was taken up in benzene, dried and the solution was filtered through an alumina column and evaporated, leaving syrupy residue, yield, 14 g. or 70%. This solidified partially on being triturated with a little alcohol. Six g. of crystalline substance was thus collected on a filter, forming colorless needles of m.p. 97–98° when purified from benzin. *Anal.* Calcd. for $C_{17}H_{21}O_4N$: C, 67.3; H, 6.9; N, 4.6. Found: C, 67.8; H, 7.4; N, 4.6.

4',5'-Methylenedioxy-3,4,5,6,7,8-hexahydro-(2',1':1,2-benzoquinolizine)-6-carboxylic acid hydrazide (VIII).—A mixture of the syrupy ester (VII: 3 g.), separated from the crystalline ester by filtration, an equivalent amount of hydrazine hydrate and a little absolute alcohol were heated on a steam bath for a few hrs. and cooled, separating the crystalline hydrazide, which forms colorless needles from alcohol, m.p. 224–225°. Yield, 2 g.

From the crystalline ester of m.p. 97–98° the hydrazide was prepared similarly, which separated in colorless needles of m.p. 174–176° from alcohol. The results of analyses show that these two esters are diastereoracemates. *Anal.* Calcd. for $C_{15}H_{19}O_3N_3$: C, 62.3; H, 6.6; N, 14.5. Found in substance of m.p. 174–176°: C, 62.0; H, 6.7; N, 14.5. Found in substance of m.p. 224–225°: C, 62.1; H, 6.7; N, 14.

4',5'-Methylenedioxy-3,4,5,6,7,8-hexahydro-6-dimethylamino-(2',1':1,2-benzoquinolizine) (XI).—The higher melting hydrazide mentioned above was converted to the 6-amino derivative as has been described in the previous paper⁷⁾. The dihydrochloride of this amino compound (0.6 g.), sodium formate (0.35 g), formic acid (1.05 g. of 80%) and formalin (1.15 g. of 30%) were heated in an oil bath at 95–100° for 8 hrs. To the reaction mixture hydrochloric acid (8 cc. of 10%) was then added and the whole evaporated in vac., the residue was dissolved in water, filtered through a wet filter and the filtrate was then basified with sodium carbonate and the liberated base was extracted with benzene. To the dried benzene solution dry hydrogen chloride in benzene was added, separating the hydrochloride of (XI) as crystalline solid, yield, 0.45 g. or 75%. Purified from alcohol, forming colorless plates of m.p. 176–177°. *Anal.* Calcd. for $C_{16}H_{22}O_2N_2HCl \cdot H_2O$: C, 58.45; H, 7.6; N, 8.5; Cl, 10.8. Found: C, 58.5; H, 7.45; N, 8.6; Cl, 11.2.

The dihydrochloride forms colorless needles from alcohol, m.p. 261° (decomp.).

4',5'-Methylenedioxy-3,4,5,6,7,8-hexahydro-(2',1':1,2-benzoquinolizine)-6-carboxylic acid (XII).—The above mentioned compound (VII: 1 g. of m.p. 97–98°) was hydrolyzed by heating with alcoholic potassium hydroxide for 1 hr., alcohol was then evaporated and the residue was acidified with hydrochloric acid. On keeping the mixture in the cold the hydrochloride of the acid (XII) separated out, which was collected and dried. Yield, 1 g. or nearly theoretical. Forms colorless needles from water, m.p. 249–250°. *Anal.* Calcd. for $C_{15}H_{17}ON \cdot HCl$: C, 57.7; H, 5.8; N, 4.5. Found: C, 57.5; H, 5.75; N, 4.3).

4',5'-Methylenedioxy-3,4,5,6,7,8-hexahydro-6-carbamyl-(2',1':1,2-benzoquinolizine) (XIII).—The foregoing acid (0.5 g.) and formamide (1 g.) were heated in an oil bath at 170–175° for about 10 hrs. To the reaction mixture a little water was added, basified and the basic substance separated

7) Sugawara, et al.: This Journal, 72, 192 (1952).

was extracted with chloroform, dried and evaporated, yielding crude acid amide. Yield, 0.4 g. or 90%. Comes in colorless grouped needles from benzene, m.p. 237~238°. *Anal.* Calcd. for $C_{15}H_{18}O_3N_2$: N, 10.2. Found: N, 10.7.

4',5'-Methylenedioxy-3,4,5,6,7,8-hexahydro-6-aminomethyl-(2',1':1,2-benzoquinolizine) (XIV)—In the thimble of a Soxhlet apparatus the foregoing amide (0.5 g.) was placed and was reduced with lithium aluminum hydride (0.2 g.) by boiling with absolute ether. About 40 hrs. was necessary before all the amide was dissolved. The unreacted $LiAlH_4$ was decomposed by adding water and then acidified with dil. sulfuric acid. The aqueous layer was now basified and extracted with benzene. To the dried benzene solution dry hydrogen chloride was added, separating the hydrochloride of the base. Yield, 0.3 g. or 47%. Forms colorless grouped needles from aqueous alcohol-acetone, m.p. 255~256°. *Anal.* Calcd. for $C_{15}H_{20}O_2N_2 \cdot 2HCl$: C, 54.05; H, 6.6; N, 8.4. Found: C, 54.2; H, 6.55; N, 8.4.

Pt salt: Minute needles of m.p. 245~246° (decomp.) from dil. hydrochloric acid.

4',5'-Methylenedioxy-3,4,5,6,7,8-hexahydro-6-dimethylaminomethyl (2',1':1,2-benzoquinolizine) (XVI?)—The foregoing amine hydrochloride (0.3 g.), sodium formate (0.2 g.), formic acid (1 g. of 80%) and formalin (1 g. of 30%) were heated in an oil bath at 95~100° for 8 hrs., light brown, clear solution being obtained. Hydrochloric acid (10 cc. of 5%) was now added and the mixture was evaporated to dryness in vacuum. The residue was dissolved in water, filtered and basified. The liberated base was collected in benzene, dried and dry hydrogen chloride in benzene was added. Since no crystalline hydrochloride separated, the whole was evaporated in vac., leaving faint yellow solid mass (0.2 g. or 67%), which, however, was not induced to crystallize. The Pt salt separated in crystalline powder from dil. hydrochloric acid, but did not analyze correctly. Further investigation will be made.

Summary

Synthesis of 4',5'-methylenedioxy-3,4,5,6,7,8-hexahydro-6-amino-(2',1':1,2-benzoquinolizine) and some of its derivatives, starting from β -(3,4-methylenedioxyphenyl)-ethyl bromide and ethyl nicotinate, is described. Their amoebicidal activities are now being examined.

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235. Hiroshi Watanabe: On the Structure of Sclerotiorine. I.

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From the mycelium of *Penicillium multicolor* G. M. P.*** grown on the Czapek-Dox medium, the author obtained an orange coloring matter, m.p. 206~207° (corr.), $[\alpha]_D^{20} + 483^\circ$ (alcohol).

From the properties of this pigment, it was suggested that it might be identical with sclerotiorine, a pigment obtained by Curtin and Reilley¹⁾ from *Penicillium sclerotiorum* van Beyma. Therefore, a direct comparison by a mixed fusion with the authentic specimen was attempted and the identity of both pigments was established.

Although the previous workers had forwarded alternative empirical formulae, $C_{20}H_{19}O_5Cl$ or $C_{20}H_{21}O_5Cl$, for sclerotiorine, the results of the present study showed that a formula, $C_{21}H_{23}O_5Cl$ (I), would be more probable than the former to represent the pigment.

Sclerotiorine is characterized by its instability in air, gradually absorbing oxygen,

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*** The culture was determined and kindly supplied by Dr. Y. Abe of the Agricultural Chemical Institute, University of Tokyo.

1) T. P. Curtin J. Reilley: *Biochem. J.*, **34**, 1419 (1940); *Nature*, **146**, 335 (1940).