We are now extending this type of reaction to other N-oxides of heterocyclic compounds using various enamines, and the results will be reported in the future.

Institute of Pharmaceutical Sciences,
Faculty of Medicine,
Kyushu University, Katakasu, Fukuoka.

Masatomo Hamana (浜名政和)
Hiroshi Noda (野田浩司)

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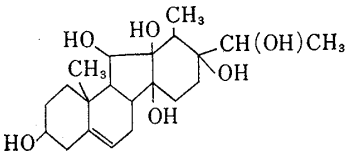
On the Structure of Metaplexigenin and Benzoylramanone

The isolation of sarcostin (I), metaplexigenin (II) and three other aglycones from the stems and leaves of *Metaplexis japonica* MAKINO (Asclepiadaceae)[1,2] and benzoylramanone (III) from the roots[3] has been reported previously.

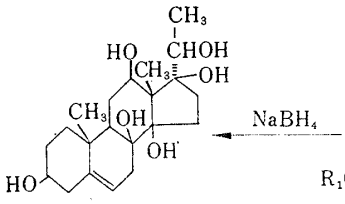
In this communication, experiments leading to the structure determination of metaplexigenin (II) and benzoylramanone (III) are described. Metaplexigenin (II), m.p. 268~275°, $C_{23}H_{34}O_7$ (*Anal.* Calcd.: C, 65.38; H, 8.11. Found: C, 65.44; H, 8.14). IR ν_{max}^{Nujol} cm^{-1}: 1745, 1720, 1240. These data suggest that II has both ester and carbonyl groups. II would not form a semicarbazone, and gave only a monooxime, m.p. 267° (decomp.), $C_{23}H_{35}O_7N$ (*Anal.* Calcd.: C, 63.14; H, 8.06; N, 3.20. Found: C, 63.31; H, 8.04; N, 2.99). Acetylation of II with acetic anhydride-pyridine afforded a monoacetate (IIa), m.p. 262~264°, $C_{25}H_{36}O_8$ (*Anal.* Calcd.: C, 64.63; H, 7.81. Found: C, 64.68; H, 7.23). Hydrolysis of II with 5% methanolic potassium hydroxide gave an acidic substance, which showed only one spot on paper chromatography (1.5*N* NH_3/BuOH) and was identified as acetic acid. As a neutral product, deacetylmetaplexigenin (IIb), m.p. 218~223°, was obtained, which was formulated as $C_{21}H_{32}O_6$ (*Anal.* Calcd.: C, 66.30; H, 8.48. Found: C, 66.32; H, 8.41). Giving the infrared absorption at 1725 and 1690 cm^{-1}. IIb afforded monooxime of m.p. 265°(decomp.), $C_{21}H_{33}O_6N$ (*Anal.* Calcd.: C, 63.77; H, 8.41; N, 3.54. Found: C, 63.81; H, 8.34; N, 3.74), which showed no absorption in carbonyl region of its infrared spectra, implying the existence of only one carbonyl group. Acetylation of IIb afforded a diacetate, m.p. 255~261°, whose identity with monoacetylmetaplexigenin (IIa) was confirmed by mixed fusion and comparison of infrared spectra. This indicates that the monoacetate of IIb is II, and no steric change had occurred during alkaline hydrolysis. II consumed one mole of lead tetraacetate (in dioxane, 164 hr.), and IIb consumed about two moles of the reagent (in dioxane, 192 hr.). I consumed about 3 moles, and VIIIa consumed 2 moles of lead tetraacetate. We are not able to reach a reasonable explanation for these results. These observations on II and IIb might be interpreted as follows: II has one carbonyl group, two secondary -OH groups (one -OH group present as an acetate). three tertiary -OH groups, and two hydroxyl groups out of the five exist as a glycol grouping. IIb was reduced by $NaBH_4$, and the product examined

1) H. Mitsuhashi, T. Nomura, Y. Shimizu, I. Takemori, E. Yamada: This Bulletin, **10**, 811 (1962). In the report, metaplexigenin was expressed as crystal 5.
2) "Rama" is the Chinese name for Metaplexis plant.
3) H. Mitsuhashi, T. Nomura, Y. Shimizu: Presented as a paper at the 82nd annual meeting of the Pharmaceutical Society of Japan, Nov. 3, 1962, Shizuoka.

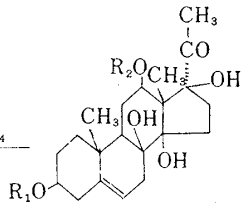
by paper partition chromatography ($CHCl_3$/formamide),[4] giving two spots. The major spot was identical with that of sarcostin (I). Trituration of the reaction products with acetone gave a pure crop of I. Sarcostin (I) has been isolated by Cornforth,[5a] and Reichstein, *et al.*,[5b] and tentatively formulated as Ia by Cornforth,[6] but recently, almost at the same time Reichstein, *et al.*,[7] Mitsuhashi and Shimizu[8] proposed the formula (Ib), independently. On the basis of the formula (Ib), the structure of metaplexigenin would be represented as II or IV. The nuclear magnetic resonance spectrum of metaplexigenin showed four singlets at 8.57 (3H), 8.05 (3H), 7.90 (3H). 7.50 (3H) τ*1 in pyridine.



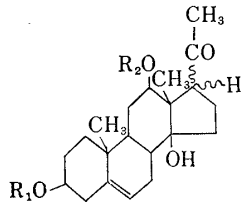
Ia



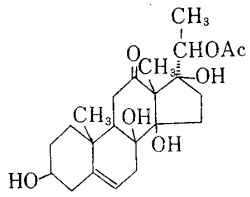
Ib



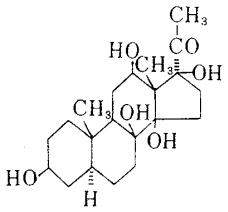
II : R_1=H, R_2=$-COCH_3$
IIa : R_1=$-COCH_3$, R_2=$-COCH_3$
IIb : R_1=R_2=H



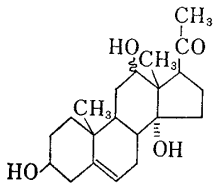
III : R_1=H, R_2=$-CO$⬡, H at C−17=α
IIIa : R_1=$-COCH_3$, R_2=$-CO$⬡
IIIb : R_1=R_2=H, H at C−17=α
IIIc : R_1=R_2=H, H at C−17=β
IIId : R_1=R_2=$-COCH_3$, H at C−17=β



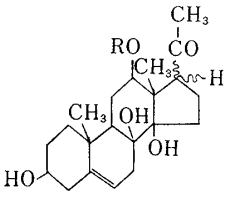
IV



V



VIa : OH at C−12=α
VIb : OH at C−12=β



VII : R=$-COCH=C(CH_3)-CH(CH_3)_2$, H at C—17=β
VIIa : R=H, H at C−17=β
VIIb : R=H, H at C−17=α

The optical rotatory dispersion curve of metaplexigenin in methanol showed a negative Cotton effect, $[\alpha]_{315}$ −756°. This curve was shifted to longer wave lengths compared to those of normal 20-keto steroids,[7~9] suggesting the presence of a α-ketol system.

*1 τ : In this communication, 10 p.p.m. value (from tetramethylsilane, used as an internal standard) is used as τ.

4) H. Mitsuhashi, Y. Shimizu, E. Yamada, I. Takemori, T. Nomura : This Bulletin, **10**, 808 (1962).
5) *a*) J. W. Cornforth, J. C. Earl : J. Chem. Soc., **1939**, 737; *b*) T. Reichstein, *et al.* : Helv. Chim. Acta, **42**, 1014 (1959).
6) J. W. Cornforth : Chem. & Ind. (London), **1959**, 602.

Thus the structure of metaplexigenin is represented as II. If metaplexigenin has formula (IV), the nuclear magnetic resonance should show the doublet from coupling of the 21-CH_3 with the 20-hydrogen. For example, I shows clear doublet at 8.53 τ (in pyridine). But the nuclear magnetic resonance spectrum of II lacks a signal in this region. Therefore, the formula (IV) for metaplexigenin is excluded. Recently, Reichstein, *et al.* obtained from an African Asclepiadaceae plant, *Gongronema taylorii* (Schltr, et Rendle) Bullock a compound very similar to metaplexigenin (II), and named tayloron, $C_{21}H_{34}O_6$. The reduction of this compound with $NaBH_4$ gave dihydrosarcostin, and from this result structure (V) was proposed.[7]

Benzoylramanone (III), m.p. 222~226°, $C_{28}H_{36}O_5$ (*Anal.* Calcd.: C, 74.30; H, 8.02. Found: C, 74.28; H, 8.11), UV λ_{max}^{EtOH} mμ(log ε): 233(4.11), 276(3.18), IR ν_{max}^{Nujol} cm^{-1}: 3600, 3500, 1720, 1690, 1600, 1580, 1270, 715 cm^{-1}. These data strongly suggest that III is a monobenzoate. III gave a monooxime, m.p. 286~291°, $C_{28}H_{37}O_5N$ (*Anal.* Calcd.: C, 71.92; H, 7.98; N, 3.00. Found: C, 71.72; H, 7.89; N, 3.11). Acetylation of III afforded a monoacetate (IIIa), m.p. 224~226°, $C_{30}H_{38}O_6$ (*Anal.* Calcd.: C, 72.85; H, 7.44. Found: C, 72.81; H, 7.85), IR: ν_{max}^{Nujol} 3500 cm^{-1}. These results suggest that III has one carbonyl group, two secondary -OH groups (one as a benzoate), and one tertiary -OH group. Hydrolysis of III with 5% methanolic potassium hydroxide gave an acidic substance, and this acid was identified as benzoic acid by paper partition chromatography (1.5*N* NH_3/BuOH) and by mixed melting point. The neutral fraction was a mixture of two substances. By means of partition chromatography (Celite, benzene+BuOH/H_2O), isoramanone (IIIb) and ramanone (IIIc) were obtained. Isoramanone (IIIb), m.p. 220~234°, $C_{21}H_{32}O_4$ (*Anal.* Calcd.: C, 72.38; H, 9.26. Found: C, 71.94; H, 9.23), IR ν_{max}^{Nujol} cm^{-1}: 3500, 1680. Ramanone (IIIc), m.p. 184~196°, $C_{21}H_{32}O_4$ (*Anal.* Calcd.: C, 72.38; H, 9.26. Found: C, 72.31; H, 9.22), IR ν_{max}^{Nujol} cm^{-1}: 3500, 1680. The ratio of IIIb to IIIc is about 1:4. IIIc gave a monooxime, $C_{21}H_{33}O_4N$, m.p. 274~278°, and a diacetate (IIId), $C_{25}H_{36}O_6$, m.p. 199~202°.

Tschesche, *et al.* isolated a glycoside from the leaves of *Digitalis purpurea*,[10] and obtained digipurpurogenin-I, and digipurpurogenin-II as the genins. The structure of these compounds was represented as VIa and VIb.[11,12] IIIb and IIIc are very similar to digipurpurogenin-II and isodigipurpurogenin-II,[13] respectively, the latter of which was obtained by the treatment of VIb with alkali.

The identity of isoramanone (IIIb) with digipurpurogenin-II, and ramanone (IIIc) with isodigipurogenin-II was confirmed by the mixed fusion with the authentic samples kindly sent from Prof. Tschesche.*[2] The optical rotatory dispersion curve of IIIc showed a negative Cotton effect, trough $[\alpha]_{301}$ −1306°, peak $[\alpha]_{260}$ +1238° in methanol, and IIIb showed a positive Cotton effect, peak $[\alpha]_{305}$ +895°, trough $[\alpha]_{265}$ −659°, in methanol. The optical rotatory dispersion curve of III, peak $[\alpha]_{305}$ +532°, trough $[\alpha]_{270}$ −680°, in MeOH, is very similar to IIIb, so it appears that both compounds have the same configuration.*[3] IIIc was refluxed 5 hours with 5% methanolic potassium hydroxide, and the resulting mixture was examined by paper partition chromatography ($CHCl_3$/formamide). The results indicated that IIIc is the main product, and IIIb a minor product. The same experiment with IIIb showed that IIIc is the major and IIIb is the minor product. Thus, there is an equilibrium between IIIc and IIIb in alkaline solution.

7) K.A. Jaeggi, E.K. Weiss, T. Reichstein: Helv. Chim. Acta, **46**, 694 (1963).
8) The paper was presented on March 13th, 1963 by Yuzuru Shimizu and submitted to the Graduate School, Hokkaido University in partial fulfilment of requirements for the degree of Doctor of Philosophy; "Steroids," **2**, September (1963).
9) C. Djerassi: Optical Rotatory Dispersion Application to Organic Chemistry, McGraw-Hill Book Co., New York (1960); E.W. Foltz, A.E. Lipman, C. Djerassi: J. Am. Chem. Soc., **77**, 4359 (1955); C. Djerassi, R. Riniker, B. Riniker: Bull. Soc. Chim. France, **1957**, 741; C. Djerassi, O. Halpern, V. Halpern, O. Schindler, Ch. Tamm: Helv. Chim. Acta. **41**, 250 (1958).

These observation suggest that IIIb and IIIc are epimeric at C-17. If we assume that ramanone and isoramanone have a C/D trans juncture, the stable form upon alkaline hydrolysis is 17α-H-type.[14] This type of compound should show a strong positive Cotton effect.[9]

Ramanone is the main product upon alkaline hydrolysis, so must be the more stable form. This assumption is inconsistent with the optical rotatory dispersion results. Cynanchogenin (VII) has a C/D *cis* ring juncture, and upon alkaline hydrolysis, deacylcynanchogenin (VIIa) and isodeacylcynanchogenin (VIIb) are obtained in about the ratio of 7:3.[8,15] VIIa has a negative Cotton effect, and VIIb has a positive Cotton effect.[8] Sondheimer, *et al.*[16] reported that the 17-β-H-type is stable form in C/D *cis* steroids, and conversion from 17α-H to 17β-H causes a remarkable shift of $[\alpha]_D$ to negative side.

Since, sarcostin has been isolated from the same plant, and shown to have a *cis* C/D juncture, biogenetic analogy would favor this configuration in the other steroidal constituents. The above evidences lead to the possible structures (IIIc) for ramanone (=isodigipurpurogenin-II), IIIb to isoramanone (=digipurpurogenin-II), and III for benzoylramanone.

Faculty of Pharmaceutical Sciences,
Hokkaido University,
Sapporo, Hokkaido.

Hiroshi Mitsuhashi (三橋 博)
Taro Nomura (野村太郎)

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*2 We wish to thank Prof. Dr. R. Tshesche for sending us the valuable samples.
*3 We are indebted to Dr. K. Takeda, Director of Shionogi Research Laboratory, Osaka for these measurements.

10) R. Tschesche, G. Grimmer: Ber., 88, 1569 (1955).
11) R. Tschesche, G. Brügmann, H.W. Marquardt, H. Machleidt: Ann., **648**, 185 (1961).
12) R. Tschesche: Angew. Chem., **73**, 727 (1961).
13) Prof. Tschesche has noted in private communication, that in 11), 12) he adopted cyclo acetal form for isodigipurpurogenin-II, but now suggests that the product is an epimer at C-17 from the results of $[M]_D$, and studies in alkaline solution, showing that isodigipurpurogenin-II and VIb are in equilibrium.
14) A. Butenandt, G. Fleischer: Ber., **70**, 96 (1937); R.E. Marker, *et al.*: J. Am. Chem. Soc., **61**, 1333 (1939).
15) H. Mitsuhashi, Y. Shimizu, T. Nomura, T. Yamada, E. Yamada: This Bulletin, **11**, 1198 (1963).
16) N. Danieli, Y. Mazur, F. Sondheimer: J. Am. Chem. Soc., **84**, 875 (1962).