containing ^{14}C -labeled ethyl malonate. In his experiment using the lichen thallus packed with the solution of diethyl malonate- ^{14}C in a glass cylinder, incorporation of radioactivity into the depside was not observed.

National Institute of Radiological Sciences,
9-1, Anagawa, 4-chome,
Chiba-shi

Mikio Yamazaki (山崎幹夫)
Mitsuyoshi Matsuo (松尾光芳)

Faculty of Pharmaceutical Sciences,
University of Tokyo,
Hongo, Tokyo

Shoji Shibata (柴田承二)

Received April 22, 1965

[Chem. Pharm. Bull.]
13(8)1017~1019(1965)]

UDC 547.857.7.07

The Synthesis of 1-Alkoxy-, 1-Alkoxy-9-alkyl-, and 9-Alkyladenines

Much interest in the recently discovered preferential alkylation of adenine (IV) on the 3-position¹⁻⁴⁾ and of its N-substituted derivatives at the same^{*1,1,5,7)} or other position^{1,4,6-9)} stimulated us to investigate the site of alkylation of adenine 1-oxide (I)^{10,11)} in connection with our current research program. Now we report the synthesis of 9-alkyladenines (VIIa, b, c)¹²⁾ from IV, as shown in Chart 1, through the use of the easily removable alkoxy group at the 1-position to orient to the 9-position on alkylation.

Treatment of I with methyl, ethyl iodide, and benzyl bromide in N,N-dimethylacetamide at room temperature furnished the corresponding 1-alkoxyadenine salt (II) as the major product (60~80%): 1-methoxyadenine hydriodide (IIa: X=I), m.p. 222° (decomp.); 1-ethoxyadenine hydriodide (IIb: X=I), m.p. 208° (decomp.); 1-benzyloxyadenine hydrobromide (IIc: X=Br), m.p. 214~219° (decomp.). The salts were readily converted in good yields to the corresponding free bases (III) by the use of Amberlite IR-45 or basification to pH 7.5 (for IIc): IIIa, m.p. 255~257° (decomp.); IIIb, m.p. 219° (decomp.); IIIc, m.p. 164~166° (decomp.). The 1-alkoxy structure was assignable by the successful catalytic hydrogenolysis of the free bases (IIIa, b, c) to adenine (IV) (84~90%

*1 In the case of benzylation on N'-benzoyladenine with benzyl bromide, instead of the chloride (Ref. 7), in dimethylacetamide at 90° for 8 hr., we also obtained 3-benzyl-N'-benzoyladenine hydrobromide of m.p. 257~259° (decomp.) in a yield of 57%, which gave (78%) 3-benzyladenine on mild alkaline hydrolysis. A similar observation has been made by B. Shimizu and M. Miyaki (Tetrahedron Letters, No. 25, 2059 (1965)).

- 1) N. J. Leonard, T. Fujii: J. Am. Chem. Soc., **85**, 3719 (1963). (See earlier references cited therein.).
- 2) C. J. Abshire, L. Berlinguet: Can. J. Chem., **42**, 1599 (1964).
- 3) N. J. Leonard, R. A. Laursen: Biochemistry, **4**, 354 (1965).
- 4) M. Asai, M. Miyaki, B. Shimizu: Agr. Biol. Chem., **29**, 170 (1965).
- 5) B. C. Pal, C. A. Horton: J. Chem. Soc., **1964**, 400.
- 6) J. A. Montgomery, H. J. Thomas: J. Am. Chem. Soc., **85**, 2672 (1963).
- 7) *Idem*: J. Heterocyclic Chem., **1**, 115 (1964).
- 8) J. W. Jones, R. K. Robins: J. Am. Chem. Soc., **85**, 193 (1963).
- 9) N. J. Leonard, T. Fujii: Proc. Natl. Acad. Sci. U.S., **51**, 73 (1964). (See earlier references cited therein.).
- 10) M. A. Stevens, D. I. Magrath, H. W. Smith, G. B. Brown: J. Am. Chem. Soc., **80**, 2755 (1958).
- 11) M. A. Stevens, G. B. Brown: *Ibid.*, **80**, 2759 (1958).
- 12) T. C. Myers, L. Zeleznick: J. Org. Chem., **28**, 2087 (1963), and references therein.

Chart 1.*2

yield), with uptake of one equivalent mole of hydrogen, in the presence of Raney nickel catalyst. Interestingly, the 1-alkoxyadenines (III) had similar ultraviolet absorption spectra (*e.g.*, IIIa : $\lambda_{\text{max}}^{0.1N \text{ HCl}}$ 258 $\text{m}\mu$ (ϵ 11,600), λ_{min} 229 (2,700); $\lambda_{\text{max}}^{0.1N \text{ NaOH}}$ 269 (14,300), λ_{min} 240 (4,100)) to those of 1-alkyladenines.^{8,9)}

The second alkylation occurred at the 9-position when the 1-alkoxyadenines (IIIa, b, c) were treated again with methyl, ethyl iodide, and benzyl bromide in *N,N*-dimethylacetamide at room temperature, resulting in the formation (52~70%) of the corresponding 1-alkoxy-9-alkyladenine salts (V): 1-methoxy-9-methyladenine hydriodide (Va : X=I), m.p. 214~215° (decomp.); 1-ethoxy-9-ethyladenine hydriodide (Vb : X=I), m.p. 186° (decomp.); 1-benzyloxy-9-benzyladenine hydrobromide (Vc : X=Br), m.p. 218° (decomp.). The salts thus obtained had similar ultraviolet absorption spectra (*e.g.*, Va : $\lambda_{\text{max}}^{0.1N \text{ HCl}}$ 260 $\text{m}\mu$ (ϵ 12,200), λ_{min} 243 (7,400); $\lambda_{\text{max}}^{0.1N \text{ NaOH}}$ 257 (12,400), $\lambda_{\text{shoulder}}$ 264 (11,200), λ_{min} 243 (8,900)) which resemble to those of 1,9-dialkyladenine salts.^{8,9)} The location of the second alkyl group was established by hydrogenolysis, using hydrogen and Raney nickel, of the corresponding free bases (VIa, b, c), which led to the formation (67~74%) of 9-alkyladenines (VIIa, b, c) with uptake of one equivalent mole of hydrogen: VIIa, m.p. 303~305°⁹⁾; VIIb, m.p. 193~195°¹³⁾; VIIc, m.p. 233~236°.¹⁾ The directivity of the

*2 We prefer not to commit ourselves as to tautomeric forms by the designations of structure employed herein, except for those which have been customarily used.

13) J. A. Montgomery, C. Temple, Jr. : J. Am. Chem. Soc., **79**, 5238 (1957).

1-alkoxy substituent in the alkylation described above is parallel to that of the 1-alkyl group reported by Leonard and Fujii.⁹⁾

Further interest in the first alkylation stems from the conversion (57%) of I to 9-benzyladenine 1-oxide hydrobromide (VIII), m.p. 240~243° (decomp.), by the reaction with two mole equivalents of benzyl bromide at an elevated temperature (120°) for 3 hrs. The free base of m.p. 285° (decomp.) obtained from VIII was deoxygenated with hydrogen and Raney nickel to give (95% yield) 9-benzyladenine (VIIc), which was obtained also by heating the salt (VIII) in N,N-dimethylacetamide*³ under reflux for 1 hr.

We are grateful to the Matsunaga Science Foundation for a grant in support of this work, and to Prof. Nelson J. Leonard of University of Illinois for his warm encouragement.

Faculty of Pharmaceutical Sciences,
University of Tokyo,
Bunkyo-ku, Tokyo

Tozo Fujii (藤井澄三)
Taisuke Itaya (板谷泰助)
Shun-ichi Yamada (山田俊一)

Received May 10, 1965

*³ The recently proposed mechanism by E.C. Taylor and E.E. Garcia (J. Am. Chem. Soc., 86, 4721 (1964)) for the deoxygenation of the 7-N-oxide group of 8-substituted theophyllines in DMF seems not to be applicable to our case.

[Chem. Pharm. Bull.]
13(8)1019~1023(1965)

UDC 574.597.02.07

Conversion of Enmein to (–)-Kaurane. The Absolute Stereochemistry of Enmein

In the joint paper with several research groups,¹⁾ we have reported the chemical structure of enmein, a diterpene bitter substance from *Isodon trichocarpus* KUDO, is to be formulated as I and this result was ascertained by our X-ray diffraction study.²⁾ The absolute configuration of enmein has been proposed¹⁾ on the basis of the optical rotatory dispersion data and the conformational analysis and hence enmein was biogenetically considered to be a diterpene homolog of (–)-kaurene. In the present communication, we wish to describe the transformation of enmein into (–)-kaurane (α -dihydro(–)-kaurene)^{3,4)} through multi-step chemical reactions, which confirms the absolute configuration of enmein with antipodal A/B stereochemistry to steroids.*¹

Diketolactone methyl ester (III), m.p. 212~212.5°, $\nu_{\text{max}}^{\text{KBr}}$ cm^{–1}: 1761, 1714 (Anal. Calcd. for C₂₁H₂₈O₆: C, 67.00; H, 7.50. Found: C, 67.27; H, 7.47), derived from dihydroenmein (II) by a series of reactions mainly described by Kubota, *et al.*,⁵⁾ was treated with ethanedithiol at room temperature in the presence of boron trifluoride etherate

*¹ The recent X-ray study using the anomalous dispersion method has also confirmed this absolute configuration. cf. Y. Iitaka, M. Natsume: Acta Cryst., in press.

1) T. Kubota, T. Matsuura, T. Tsutsui, S. Uyeo, M. Takahashi, H. Irie, A. Numata, T. Fujita, T. Okamoto, M. Natsume, Y. Kawazoe, K. Shudo, T. Ikeda, M. Tomoeda, S. Kanatomo, T. Kosuge, K. Adachi: Tetrahedron Letters, No. 20, 1243 (1964).

2) Y. Iitaka, M. Natsume: *Ibid.*, No. 20, 1257 (1964).

3) L.H. Briggs, R.W. Cawley: J. Chem. Soc., 1948, 1888.

4) L.H. Briggs, B.F. Cain, R.C.C. Ambie, B.R. Davis, P.S. Rutledge, J.K. Wilmshurst: *Ibid.*, 1963, 1345.

5) T. Kubota, T. Matsuura, T. Tsutsui, K. Naya: Nippon Kagaku Kaishi, 84, 353 (1963).