Chloral itself showed the expected aldehyde proton singlet at 8.96 ppm, but the chloral thiosemicarbazide showed the elusive splitting as a doublet at 7.40 ppm (J=5.4 cps).

Experimental[14]

Semicarbazones and Thiosemicarbazones——Derivatives were prepared by the usual procedures.[15] Their melting point, ultraviolet absorption, and NMR spectral data are summarized in Tables I and II.

14) All melting points are uncorrected. The NMR spectra were obtained with Hitachi H-60 spectrometer at 60 Mc and tetramethylsilane was used as an internal reference.
15) R.L. Shriner, R.C. Fuson, and D.Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed., John Wiley and Sons, Inc., New York, 1956, pp. 218—219.

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Studies on the Azasteroids and Related Compounds. IV.[1] Reactions of 1,2,3,4,6a,7,8,9,10,10a-Decahydro-6*H*-benzo[*c*]quinolizin-6-one

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In continuation of our synthetic studies on 14-azasteroids,[1,3,4] which included preparation and some reactions of B/C *trans* fused dodecahydro-6*H*-benzo[*c*]quinolizin-6-one (I), we now describe angular methylation at C-4a position of I and attempt to prepare the benzo[*c*]quinolizine derivatives with functional group at C-4 position which corresponds to C-17 position in natural steroid structure, from the compound (I).

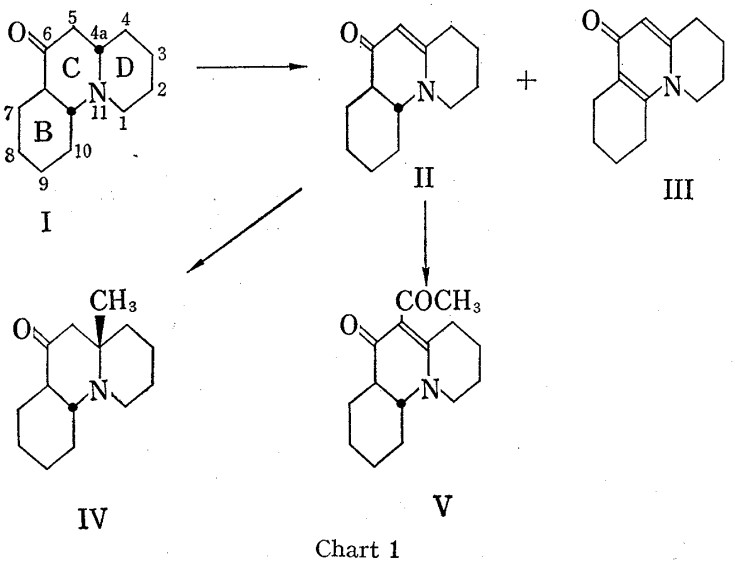


Chart 1

Dehydrogenation of the quinolizidinone (I) with mercuric acetate in 35% acetic acid solution afforded a mixture of decahydrobenzo[*c*]quinolizin-6-one (II) and the γ-pyridone (III). The former was methylated at the angular position

1) Part III: Z. Horii, K. Morikawa, C. Iwata, and I. Ninomiya, *Chem. Pharm. Bull.* (Tokyo), **16**, 1686 (1968).
2) Location: *Toneyama, Toyonaka, Osaka*; *a*) Present Address: *Kobe Women's College of Pharmacy, Nakano, Motoyama, Higashinada, Kobe.*
3) Z. Horii, K. Morikawa, and I. Ninomiya, *Chem. Pharm. Bull.* (Tokyo), **14**, 1399 (1966).
4) Z. Horii, K. Morikawa, and I. Ninomiya, *Chem. Pharm. Bull.* (Tokyo), **16**, 1472 (1968).

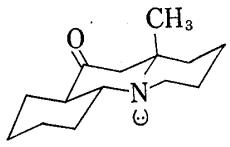
with methyl magnesium iodide in the presence of catalytic amount of the cuprous salt[5] to afford the methylquinolizidinone (IV) in 21% yield.[6]

In order to introduce a functional group at C-4 position of the vinylogous amide (II), bromination, acetoxylation or hydroxylation of II with N-bromosuccinimide, mercuric acetate or selenium dioxide were examined, but only the starting material was recovered unchanged in all cases, except acetylation of II with acetic anhydride–boron trifluoride etherate[7] yielded the C-5 acetylated product (V).

The structures of these products (II—V) were assigned from inspections of their infrared (IR) and nuclear magnetic resonance (NMR) spectra. The infrared spectrum of the compound (II) showed two peaks at 1615 and 1550 cm^{-1} which were characteristic of the vinylogous amide grouping, while its NMR spectrum exhibited a signal corresponding to an olefinic proton at C-5 as a singlet at τ 5.15. The infrared spectrum of the compound (III) showed four absorptions at 1640 (sh), 1625, 1560 and 1525 cm^{-1}, attributable to the γ-pyridone structure[8] and its NMR spectrum exhibited a singlet signal at τ 3.85 due to an olefinic proton at C-5.

The NMR spectrum of the compound (IV) showed a singlet signal at 9.05 for three protons due to an angular methyl group at C-4a, which behaved as stereochemically homogeneous and this was further proved by gas chromatographic analysis. The infrared spectrum of IV exhibited a peak corresponding to the cyclic saturated ketone at 1710 cm^{-1} and characteristic *trans*-quinolizidine bands at 2800—2755 cm^{-1} region, indicating the conformation of IV as having in IV′, and this was also rationalized by the mechanistic consideration that an attack of the Grignard reagent as a nucleophile would occur from the opposite side to the direction of lone-paired electrons on nitrogen, thus forming 4aβ-methylquinolizidine derivative. Therefore, the structure of the compound (IV) should be represented by IV′, in which the C-4a methyl group was axially oriented.

The compound (V) showed three absorptions at 1635, 1615 and 1550 cm^{-1}, attributable to the partial structure of OC–C(CO–CH_3)=C–N, in its infrared spectrum. In the NMR spectrum, the signal due to methyl protons of acetyl group appeared at τ 7.55 for three protons as a singlet, while the signal for an olefinic proton was absent. These data could suggest that the compound (II) was acetylated at C-5.[9]



IV′

Fig. 1

Experimental

Dehydrogenation of *trans*-Dodecahydro-6*H*-benzo[*c*]quinolizin-6-one (I) with $Hg(OAc)_2$——A solution of mercuric acetate (14.9 g, 47.0 mmoles) and EDTA–2Na·$2H_2O$ (17.5 g, 47.0 mmoles) in 35% AcOH (50 ml) was added to the compound (I) (10.0 g, 48.3 mmoles) in 35% AcOH (100 ml) and the mixture was warmed at 60—65° for 14 hr with stirring. After mercury formed was filtered off, the acidic filtrate was basified with 10% NaOH, and shaken with $CHCl_3$ (150 ml × 5). The combined $CHCl_3$ extracts were washed with brine and dried over anhydrous K_2CO_3. Evaporation of $CHCl_3$ gave 8.9 g of dark brown pasty residue, which was chromatographed on alumina (150 g).

The first elution with 600 ml of benzene gave 3.63 g (38%) of the starting material. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710. The second elution with 400 ml of benzene, the third elution with 1 liter of benzene–$CHCl_3$ (1:1),

5) M.S. Kharash and P.O. Towney, *J. Am. Chem. Soc.*, **63**, 2308 (1941); J. Munch-Petersen and V.K. Andersen, *Acta Chem. Scand.*, **15**, 271 (1961); H.O. House, C.D. Traficante, and R.A. Evans, *J. Org. Chem.*, **28**, 348 (1963); J.A. Sttepani, M. Torigoe, and J. Fishman, *Tetrahedron*, **21**, 3661 (1965) and references cited therein.

6) Reaction of the Grignard reagent with the vinylogous amide has been reported by A.H. Lutz and O. Schneider, *Helv. Chim. Acta*, **39**, 81 (1956), yielding β-alkylated compounds.

7) M. Gorodetsky, E. Levy, R.D. Youssefyeh, and Y. Mazur, *Tetrahedron*, **22**, 2039 (1966).

8) A.R. Katritzky and R.A. Jones, *J. Chem. Soc.*, **1960**, 2947.

9) It was reported that acetylation of the vinylogous amide, OC–C=C–N<, with acetic anhydride afforded α-acetylated product (E. Winterfeldt, H. Radunz, and P. Strehlke, *Chem. Ber.*, **99**, 3750 (1966)).

and the fourth elution with 2 liter of $CHCl_3$ gave respectively 0.47 g, 1.20 g, and 1.07 g of pale yellow semi-solids (II). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1615, 1550 and 1500. NMR in $CDCl_3$ (τ): 5.15 (–CO–CH=C<). Picrate, mp 175—177° (decomp.) (from iso-PrOH). *Anal.* Calcd. for $C_{19}H_{22}O_8N_4$: C, 52.53; H, 5.10; N, 12.90. Found: C, 52.26; H, 5.05; N, 12.89. The total yield of II was 2.74 g (30%).

The fifth elution with 1.4 liter of $CHCl_3$–EtOH (20:1) and the sixth elution with EtOH (500 ml) gave respectively 0.99 g and 0.48 g of a brown semi-solid (III). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1640 (sh), 1625, 1560, and 1525. NMR in $CDCl_3$ (τ): 3.85 (–CO–CH=C<, 1H, singlet). Picrate, yellow needles from EtOH–acetone, mp 225—228° (decomp.). *Anal.* Calcd. for $C_{19}H_{20}O_8N_4$: C, 52.78; H, 4.66; N, 12.96. Found: C, 52.65; H, 4.79; N, 12.65. The total yield of III was 1.57 g (16%).

4a-Methyldodecahydro-6*H*-benzo[*c*]quinolizin-6-one (IV)——To the Grignard reagent prepared from Mg (219 mg, 9.0 matoms), CH_3I (1.28 g, 9.0 mmoles) and anhydrous ether (20 ml) was added Cu_2Br_2 (140 mg, 0.97 mmole) in one portion. A solution of the compound (II) (370 mg, 1.8 mmoles) in anhydrous ether (20 ml) was added dropwise to the above mixture at R.T. and then refluxed with stirring for 1.5 hr. The reaction mixture was decomposed with aq. saturated NH_4Cl solution under ice-cooling. The ethereal layer was separated and the aq. layer was shaken with ether (30 ml × 4). The combined ether extracts were washed with brine and dried over anhydrous K_2CO_3. Evaporation of ether gave a brown oil (300 mg), which was chromatographed on alumina (15 g). The first elution with 300 ml of benzene gave a pale yellow oil (IV) (80 mg, 21%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2800, 2755 and 1710. NMR in $CDCl_3$ (τ): 9.05 (3H, singlet, >C–CH_3). Picrate, yellow needles from acetone, mp 219—220° (decomp.). *Anal.* Calcd. for $C_{20}H_{26}O_8N_4$: C, 53.33; H, 5.82; N, 12.44. Found: C, 53.19; H, 5.70; N, 12.51.

The second elution with 500 ml of $CHCl_3$ gave the starting material (200 mg, 54%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1615 and 1550.

5-Acetyl-1,2,3,4,6a,7,8,9,10,10a-decahydro-6*H*-benzo[*c*]-quinolizin-6-one (V)——A solution of the compound (II) (560 mg) in Ac_2O (10 ml) in the presence of BF_3·ether (2.5 ml) was refluxed for 1.5 hr. After cooling, the reaction mixture was poured into ice-water, basified with 20% NaOH and shaken with $CHCl_3$ (50 ml × 5). The combined extracts were washed with H_2O and dried over anhydrous K_2CO_3. Evaporation of $CHCl_3$ afforded a dark brown solid (570 mg), which was chromatographed on alumina (30 g). The first elution with 300 ml of benzene gave the starting material (70 mg, 13%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1615 and 1550.

The second elution with 200 ml of benzene–$CHCl_3$ (1:1), and the third elution with 350 ml of $CHCl_3$ gave respectively 45 mg and 315 mg of a pale pink colored solid (V), which was recrystallized from *n*-hexane–benzene (4:1) to give pink colorled needles, mp 119—120° (decomp.). *Anal.* Calcd. for $C_{15}H_{21}O_2N$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.74; H, 8.42; N, 5.66. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1635, 1615, 1550. NMR in $CDCl_3$ (τ): 7.55 (3H, singlet, >C–CO–CH_3). The total yield of V was 360 mg (54%).

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Antitumor Activity of Psychotropic Drugs and Their Synergic Action with Cyclophosphamide

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It has been reported that chlorpromazine has weak antitumor activity on Walker 256[2] and Sarcoma 37,[3,4] and also some other phenothiazine derivatives have the same effect on

1) Location: *Tsukiji 5-chome, Chuo-ku, Tokyo.*
2) F. Paulesu and L. Vargiu, *Georn. Ital. Chemiother.*, **2**, 70 (1955).
3) M. Belkin and W.G. Hardy, *Science*, **125**, 233 (1957).
4) E. Hirschberg, *Cancer Res.*, suppl., **23**, 521 (1963).