Pharmaceutical Institute,
Tohoku University
Aobayama, Sendai

TETSUJI KAMETANI
MASATAKA IHARA
KEIICHI TAKAHASHI

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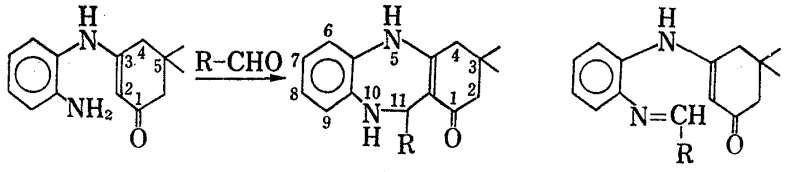
UDC

Synthesis of 3,3-Dimethyl-2,3,4,5,10,11-hexahydro-11-phenyl-1H-dibenzo[*b*,*e*][1,4]diazepin-1-one, a New Tricyclic System

Recent development of seven-membered ring compound as psychopharmacological agents including benzodiazepine[1-2] and dibenzodiazepine[3] led us to attempt the synthesis of a series of linearly fused tricyclic compounds in which one of the six-membered rings is partly saturated. In the present paper we wish to report a simple and convenient synthesis of the title compound (II), a new 6-7-6 ring system.



I II III

R=H,CH_3,C_2H_5,C_6H_5,C_6H_4Cl (*p*)

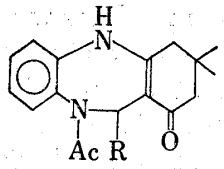
Our method consists of interaction of an aldehyde with 3-(*o*-aminoanilino)-5,5-dimethyl-2-cyclohexen-1-one (I) and the cyclization is brought about by loss of water. I is readily available by condensation of *o*-phenylenediamine with dimedone.

It is remarkable that the reaction is complete by simply allowing the reactants at room temperature with a small amount of acid catalyst such as acetic acid and hydrochloric acid. The high reactivity of I with an aldehyde can be attributable to enaminone structure involved in I in which α-position is particularly reactive to electrophilic reagents.[4-7]

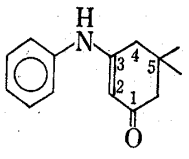
Apparently the ring closure, I→II, is a variation of Mannich reaction. To our knowledge this is the first example of formation of diazepine ring system by Mannich type cyclization.

The structure II (R=C_6H_5) is supported by infrared (IR) and nuclear magnetic resonance (NMR) spectra, the other possible structure III (R=C_6H_5) being ruled out. The IR spectrum ($CHCl_3$) showed absorptions at 3412, 3340, 1610, 1587, 1515 cm^{-1} (vinylogous amide)[8] and

1) G.A. Archer and L.H. Sternbach, *Chem. Rev.*, **68**, 747 (1968).
2) L.H. Sternbach, L.O. Randall and S.R. Gustafson, "1,4-Benzodiazepines," in M. Gordon (ed.) "Psychopharmacological Agents," Vol. I, Academic Press, New York and London, 1964, p. 35.
3) C. Kaiser and C.L. Zirke, "Antidepressant Drugs," in A. Burger (ed.) "Medicinal Chemistry," Part II, Wiley-Interscience, New York, 1970 p. 1481.
4) F. Zymalkowski and H.-J. Rimak, *Arch. Pharm.*, **294**, 759 (1961).
5) G.H. Alt and A.J. Speziale, *J. Org. Chem.*, **29**, 794 (1964).
6) H.J. Teuber and R. Braun, *Chem. Ber.*, **100**, 1353 (1967); H.J. Teuber, E. Worbs and D. Cornelius, *ibid.*, **101**, 3918 (1968).
7) C. Ruangsiyanand, H.-J. Rimak and F. Zymalkowski, *Chem. Ber.*, **103**, 2403 (1970).
8) K. Kotera, *Yakugaku Zasshi*, **80**, 1275 (1960)



IV



V

3310 cm^{-1} (secondary amine). The NMR spectrum (DMSO-d_6) had signals at τ 1.13 (1H, s, O=C-C=C-NH), 2.81 (5H, s, C_6H_5), 2.85—3.40 (4H, Ar), 3.76 (1H, d, NH), 4.16 (1H, d, N-C<u>H</u>-C_6H_5), 7.38 (2H, s, CH_2), 7.80, 7.83 (2H, CH_2), 8.90, 8.95 (2×3H, s, gem CH_3), two (1.13, 3.76) of which were removed and one (4.16) of which changed to a singlet by D_2O.

The ready formation of 10-acetyl derivative (IV) also supported the structure II. Imino group at 5-position of II or 3-position of III is of vinylogous amide character and reluctant to acetylation. Our attempts to acetylate vinylogous imino group of 3-anilino-5,5-dimethyl-2-cyclohexen-1-one (V) also failed.

The synthesis just outlined is of quite general application since several analogs of II (R=H, CH_3,[9] C_2H_5, and $C_6H_4Cl(p)$) could be prepared with great ease. It also features simple manipulation, ready availability of starting material and excellent yields.

The following procedure for the preparation of II (R=C_6H_5) is illustrative: To a solution of 2.3 g (0.01 mole) of I in 10 ml of ethanol was added 1.06 g (0.01 mole) of benzaldehyde and one drop of acetic acid and the resulting mixture was allowed to stand at room temperature for 1 hr. The deposited crystalline was collected as nearly pure light-yellow plates, mp 258—259°. Yield was 3 g (94.3%). The melting point raised to 258.5—259.5° after one recrystallization from ethanol. *Anal.* Calcd. for $C_{21}H_{22}ON_2$: C, 79.21; H, 6.96; N, 8.80. Found: C, 79.06; H, 6.96; N, 8.86.

Faculty of Pharmaceutical Sciences,
Fukuoka University
Nanakuma, Fukuoka

Seiji Miyano
Nobuhiro Abe

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9) Acetaldehyde diethylacetal was employed as an aldehyde component instead of acetaldehyde.

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The Reaction of 4-Cyanoisoquinolines with the Grignard Reagent and Carbanions

Recently, we reported[1] the photochemical reaction of 4-cyanoisoquinoline and its 1-alkyl derivatives (**1**) in alcohols, esters, ethers, and amides, which was found to result in unusually facile addition of these solvents to C-1 position of **1** from the carbon atom adjacent to the hetero-atoms (Z), giving rise to **2**.

We now wish to describe the chemical behavior of **1** toward the Grignard reagent and also other carbanions mainly affording 1-substituted derivatives (**3**) without any interaction with the cyano function (Table I, Chart 1 and 2). Structure of the products is readily recognized from infrared (IR), ultraviolet (UV), and nuclear magnetic resonance (NMR) spectra, and an example of these data is shown beside the formula of **3h**. There have been a few

1) M. Natsume and M. Wada, *Tetrahedron Letters*, **1971**, 4503.