THE SYNTHESIS OF 9H-IMIDAZO[1,2-a][1,3]DIAZEPINES

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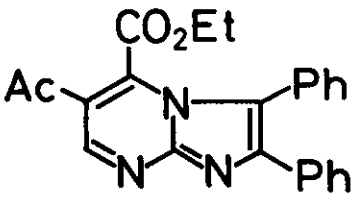
Abstract —— Ethyl 7-acetyl-2,3-diphenyl-9H-imidazo[1,2-a][1,3]-diazepine-5-carboxylate (8) and its acetate (7) were synthesized via the ring-expansion reaction of ethyl 5a-acetyl-4a,5a-dihydro-2,3-diphenyl-5H-cyclopropa[4a,5a]imidazo[1,2-a]pyrimidine-4a-carboxylate (2).

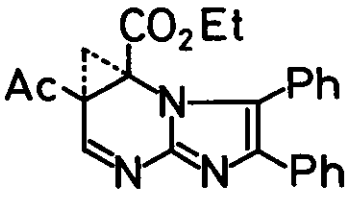
Relatively little work has been carried out on 1,3-diazepines with a benzene ring fused to the diazepine system[1]. A few derivatives of pyrimido[2,1-b][1,3]-diazepine have been prepared[2]. The synthesis of bicyclic guanidines such as 5,6,7,8-tetrahydro-[3] or 2,3,5,6,7,8-hexahydro-1H-imidazo[1,2-a][1,3]diazepine[4] derivatives, some of which showed the anticonvulsant and hypoglycemic activity, has also been reported. However, to our knowledge, 9H-imidazo[1,2-a][1,3]diazepines have not hitherto been reported. In this communication, we report the synthesis of the title compounds via the ring-expansion of cyclopropaimidazopyrimidine (2).

Recently, we reported[5] the synthesis and ring transformation reaction of 6H-cyclopropa[5a,6a]pyrazolo[1,5-a]pyrimidines, which were readily obtained by the reaction of 6-acetyl-7-ethoxycarbonylpyrazolo[1,5-a]pyrimidine-3-carbonitrile with diazomethane under ice-cooling. Thus, we selected ethyl 6-acetyl-2,3-diphenyl-imidazo[1,2-a]pyrimidine-5-carboxylate (1) as a starting material for the synthesis of the title compounds. The compound 1 was synthesized by condensation of ethyl 3-ethoxymethylene-2,4-dioxovalerate with 2-amino-4,5-diphenylimidazole[6] in refluxing ethanol in 86 % yield. Treatment of 1 with a large excess of diazomethane under ice-cooling gave ethyl 5a-acetyl-4a,5a-dihydro-2,3-diphenyl-5H-cyclopropa-[4a,5a]imidazo[1,2-a]pyrimidine-4a-carboxylate (2) [mp 193-195°; ν max. (KBr) cm^{-1}: 1750, 1720, 1660; δ (DMSO-d_6) : 0.85 (3H, t, J=7 Hz, $CH_2\underline{CH}_3$), 1.85 and 2.75 (each 1H, each d, J=6 Hz, CH_2), 2.39 (3H, s, $COCH_3$), 3.20-3.70 (2H, m, $\underline{CH}_2CH_3$), 7.10-7.60 (10H, m, Ar-H), 8.61 (1H, s, C_6-H)] in 73 % yield.

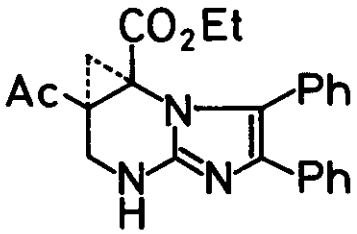
Next, hydrogenolytic ring-expansion reaction of 2 was examined. Catalytic hydrogenation of 2 over PtO_2 under atmospheric pressure in dioxane gave 6,7-dihydro compound (3), mp 247-249° (CH_3CN). The NMR spectrum (DMSO-d_6) of 3 showed the presence of cyclopropane ring protons at δ 1.92 and 2.36 (each 1H, each d, J=6 Hz). On the other hand, when catalytic hydrogenation of 2 was carried out over 5 % Pd-C under the same condition, ethyl 7-acetyl-5,6-dihydro-2,3-diphenyl-9H-imidazo[1,2-a][1,3]diazepine-5-carboxylate (4), mp 216-218° (EtOH) (Found : C, 72.08; H, 5.71; N, 10.51. $C_{24}H_{23}N_3O_3$ requires C, 71.80; H, 5.78; N, 10.47), was interestingly obtained in 66.3 % yield. The spectral data [ν max. (KBr) cm^{-1} : 3200-2600, 1750, 1610; λ max. (EtOH) nm (log ε) : 248 (4.19), 332 (4.26); δ (DMSO-d_6) : 1.13 (3H, t, J=7 Hz, CH_2CH_3), 1.78 (3H, s, $COCH_3$), 2.45 (1H, br d, J=15 Hz, C_6-H), 3.90 (1H, d d, J=15, 6 Hz, C_6-H), 3.90-4.30 (2H, m, CH_2CH_3), 4.90 (d d, J=3, 6 Hz, C_5-H), 6.76 (1H, br s, C_8-H), 7.10-7.50 (10H, m, Ar-H), 12.55 (1H, br s, NH)] established its structure. An attempt to direct preparation of ethyl 7-acetyl-2,3-diphenyl-9H-imidazo[1,2-a][1,3]diazepine-5-carboxylate (8) from 4 with DDQ oxidation was unsuccessful, only a tarry mixture being obtained. Thus, compound 4 was acetylated with acetic anhydride and pyridine to obtain 5, mp 158-160°. The fact that an attractive signal was seen in its NMR spectrum at δ 8.28[7] as singlet assignable to C_8-proton shifted downfield by the effect of N-acetyl group would strongly support the structure of 4. The acetate reacted with 1.2 equivalent moles of NBS in CCl_4 in the presence of benzoyl peroxide to give ethyl 6-bromo-7,9-diacetyl-5,6-dihydro-2,3-diphenyl-9H-imidazo[1,2-a][1,3]-diazepine-5-carboxylate (6), mp 150-154° (benzene-ligroin), in a quantitative yield. Since the NMR spectrum of 6 revealed C_5- and C_6-protons as two sets of doublets at δ 4.97 and 5.81 with a coupling constant of 5 Hz[8], the configuration of 6 was characterized as trans. Treatment of 6 with triethylamine in refluxing benzene afforded ethyl 7,9-diacetyl-2,3-diphenyl-9H-imidazo[1,2-a][1,3]diazepine-5-carboxylate (7) as pale yellow crystals, mp 206-208°(EtOH), in 47.3 % yield. Dehydrobromination of 6 with DBU[9] to 7 was achieved more readily. Thus, a mixture of 6 and an equimolar amount of DBU in benzene was stirred at room temperature for 10 min, and 7 was isolated in 73 % yield. Compound 7, on treatment with basic Al_2O_3 in refluxing benzene, underwent hydrolysis of N-acetyl group to give 8 as red crystals, mp 303-305° (CH_3CN) (Found : C, 71.99; H, 5.31; N, 10.54. $C_{24}H_{21}N_3O_3$ requires C, 72.16; H, 5.30; N, 10.52) in 40 % yield. The structure



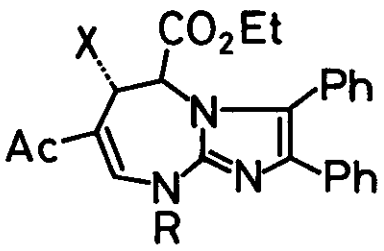
1



2



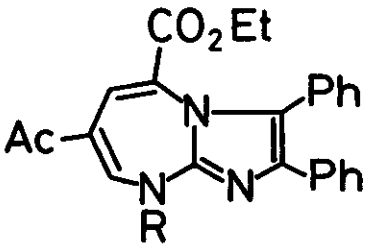
3



4 : R = X = H

5 : R = Ac ; X = H

6 : R = Ac ; X = Br



7 : R = Ac

8 : R = H

determination of 7 and 8 were performed on the basis of spectral data as summarized in Table.

Spectral Data of 9H-Imidazo[1,2-a][1,3]diazepines (7 and 8)

Compd. No.	ν max.(KBr) cm^{-1}	λ max.(CH_3CN) (log ε) nm	δ (DMSO-d_6) $CO_2CH_2CH_3$ (J=7 Hz)	$COCH_3$	C_6-H	Ar-H	C_8-H	Mass (m/z)
7	1720 1700 1680	238 (4.47) 278 (4.27) 348 (3.16)	0.96(3H, t) 2.48 3.65(2H, q) 2.50	*		7.10-7.50 (11H, m)	8.00	441 (M^+)
8	3200-2600 1710 1650	248 (4.26) 292 (4.23) 427 (2.97)	0.84(3H, t) 2.55 3.55(2H, q)	6.92		7.00-7.60 (11H, m)	*	399 (M^+)

* Overlapped with benzene ring protons

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References and Notes

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