

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

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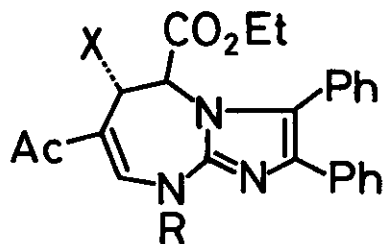
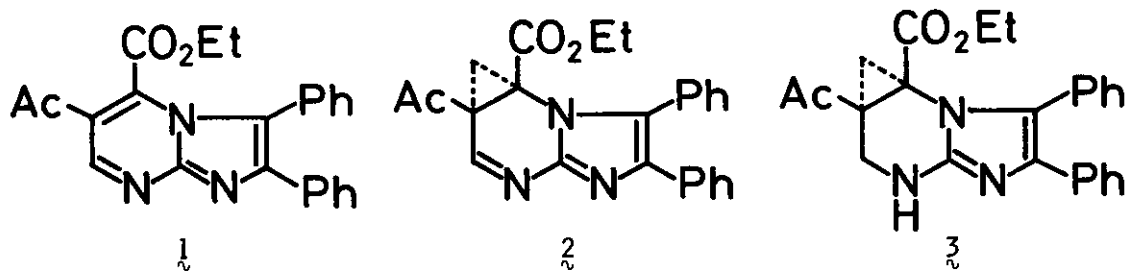
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Abstract — Ethyl 7-acetyl-2,3-diphenyl-9H-imidazo[1,2-a][1,3]-diazepine-5-carboxylate (**8**) and its acetate (**7**) were synthesized via the ring-expansion reaction of ethyl 5a-acetyl-4a,5a-dihydro-2,3-diphenyl-5H-cyclopropa[4a,5a]imidazo[1,2-a]pyrimidine-4a-carboxylate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

Relatively little work has been carried out on 1,3-diazepines with a benzene ring fused to the diazepine system¹). A few derivatives of pyrimido[2,1-b][1,3]-diazepine have been prepared²). 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]diazepine⁴) 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 reported⁵) 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-diphenylimidazole⁶) 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, \underline{J} =7 Hz, CH_2CH_3), 1.85 and 2.75 (each 1H, each d, \underline{J} =6 Hz, CH_2), 2.39 (3H, s, COCH_3), 3.20-3.70 (2H, m, CH_2CH_3), 7.10-7.60 (10H, m, Ar-H), 8.61 (1H, s, C_6 -H)] in 73 % yield.

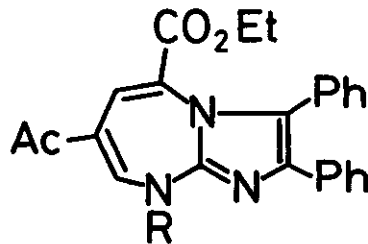
Next, hydrogenolytic ring-expansion reaction of **2** was examined. Catalytic hydrogenation of **2** over PtO₂ under atmospheric pressure in dioxane gave 6,7-dihydro compound (**3**), mp 247-249° (CH₃CN). The NMR spectrum (DMSO-d₆) of **3** showed the presence of cyclopropane ring protons at δ 1.92 and 2.36 (each 1H, each d, $\underline{J}=6$ 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. C₂₄H₂₃N₃O₃ 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-d₆) : 1.13 (3H, t, $\underline{J}=7$ Hz, CH₂CH₃), 1.78 (3H, s, COCH₃), 2.45 (1H, br d, $\underline{J}=15$ Hz, C₆-H), 3.90 (1H, d d, $\underline{J}=15$, 6 Hz, C₆-H), 3.90-4.30 (2H, m, CH₂CH₃), 4.90 (d d, $\underline{J}=3$, 6 Hz, C₅-H), 6.76 (1H, br s, C₈-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 8.28⁷⁾ as singlet assignable to C₈-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 CCl₄ 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 C₅- and C₆-protons as two sets of doublets at δ 4.97 and 5.81 with a coupling constant of 5 Hz⁸⁾, 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 DBU⁹⁾ 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 Al₂O₃ in refluxing benzene, underwent hydrolysis of N-acetyl group to give **8** as red crystals, mp 303-305° (CH₃CN) (Found : C, 71.99; H, 5.31; N, 10.54. C₂₄H₂₁N₃O₃ requires C, 72.16; H, 5.30; N, 10.52) in 40 % yield. The structure



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 ₃ CN) (log ϵ) nm	δ (DMSO-d ₆)					Mass (m/z)
			CO ₂ CH ₂ CH ₃ (J=7 Hz)	COCH ₃	C ₆ -H	Ar-H	C ₈ -H	
7	1720	238 (4.47)	0.96 (3H, t)	2.48	*	7.10-7.50	8.00	441 (M ⁺)
	1700	278 (4.27)	3.65 (2H, q)	2.50		(11H, m)		
	1680	348 (3.16)						
8	3200-2600	248 (4.26)	0.84 (3H, t)	2.55	6.92	7.00-7.60	*	399 (M ⁺)
	1710	292 (4.23)	3.55 (2H, q)			(11H, m)		
	1650	427 (2.97)						

* Overlapped with benzene ring protons

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References and Notes

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