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BASE CATALYSED RING EXPANSION OF AN 2-AZABICYCLO[3.2.0]HEPTANE-3,4-DIONE TO A DIHYDROAZATROPOLONE: A NEW ROUTE TO AZATROPOLONES[1]

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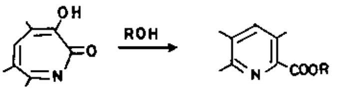
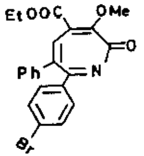
The syntheses of azatropolones, new nonbenzenoid aromatic compounds, are described. Base catalysed ring expansion of an 2-azabicyclo[3.2.0]-heptane-3,4-dione gave a dihydroazatropolone, which was dehydrogenated with DDQ oxidation to give an azatropolone.

Recent synthesis of the azatropolones (**4**) and (**5**) revealed that this new heterocycle (**A**), in spite of an aromaticity expected for its nucleus, was reactive to protic solvents affording a pyridine-2-carboxylate (**B**)[2]. *X*-Ray crystallography of the methyl ether (**1**) also indicated nonplanarity of the azatropolone nucleus[1].

In order to investigate these unexpected characters of azatropolone nucleus in detail, we planned to prepare further examples of the compound with different substitution patterns.



A **B**



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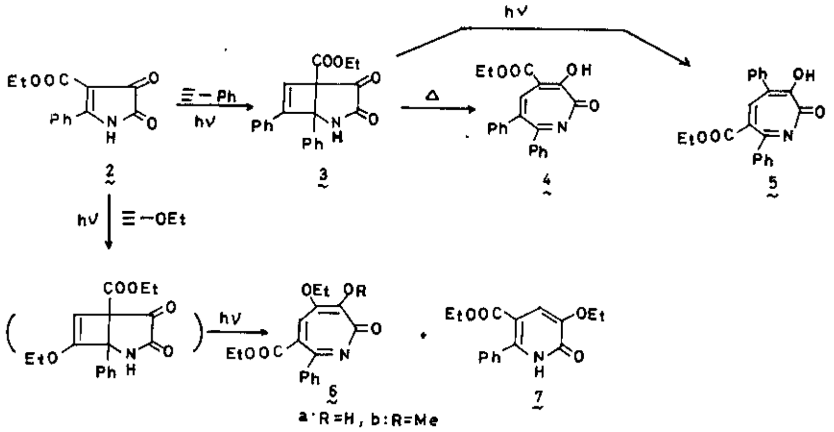
The method used in the synthesis of **4**, thermal ring expansion of the photocycloadduct (**3**), has a serious limitation for the present purpose, since the reaction of a Δ^2-pyrroline-4,5-dione (**2**) and acetylenic compounds does not always give the desired cycloadduct of type (**3**), instead frequently gives the rearranged product of type (**5**) directly. For example, the photocycloaddition reaction (300W Hg lamp, 45 min. in 1,2-dimethoxyethane at 0°C) of **2** with ethoxyacetylene afforded the azatropolone (6a)[3] in 20% yield accompanied with the pyridone (7)[4] (20% yield).



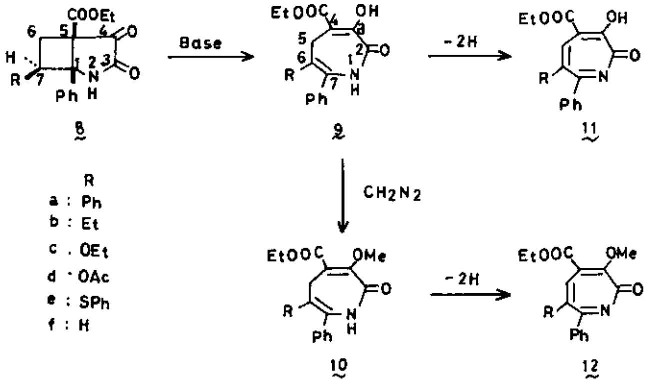
Therefore, we intended stepwise synthesis of azatropolones in a clearcut way: ring expansion of 8, which was easily prepared and well established[5-6], to a dihydroazatropolone (9) followed by dehydrogenation to an azatropolone (11).

The desired C_1-C_5 bond cleavage was achieved as follows. Treatment of 8 with triethylamine or DBU (DBU was more effective) in benzene afforded the dihydroazatropolones (9) (4-ethoxycarbonyl-3-hydroxy-7-phenyl-6-substituted-1,5-dihydro-2H-azepin-2-one) in satisfactory yield. They were smoothly methylated with diazomethane to the corresponding methyl ethers (10). Results are given in Table 1.

Desulfurization of 8e with Raney Ni (W-2) in abs. EtOH gave, with concomitant ring opening, directly 9f in 60% yield. However, the SPh substituent of 9e could not be removed with Raney Ni in similar conditions.

The NMR and UV spectra (Table 2) of 9a-f and 10a-f are consistent with their assigned structures. In the NMR spectra, 9a-e and 10a-e exhibited C_5-methylene proton signal around δ 3.2-3.3, as a singlet, and 9f showed C_5-methylene protons at δ 3.05 (d, J=7Hz) and C_6-olefinic proton at δ 5.95 (t, J=7Hz).

The conversion of 9 to the azatropolones (11) was successfully carried out, in several cases, by oxidation with DDQ. The mixture of 9 and DDQ (1.5 mol eq) in benzene was heated in a sealed tube at 100° for 5-45 min. and the resulted product was purified by rapid chromatography over SiO_2. 9c and 9f smoothly gave the desired azatropolone (11c) and (11f) respectively, while dehydrogenation of 9a, 9b, 9d and 9e proceeded very slowly under the similar condition. Forced conditions (higher temp. and longer reaction time) produced only extensive decomposition[7].



On the contrary, dehydrogenation of the methyl ethers (10) was easily accomplished under the similar condition, though the reactions were much slower. The resulting azatropolone methyl ethers (12), except 12f, were easily purified by SiO_2 chromatography. The methyl ether (12f) could not be obtained in a pure form, since it was rapidly hydrolysed during chromatographic separation over SiO_2 to regenerate the azatropolone (11f). The results are summarized in Table 3.

The UV spectra of these azatropolones (11) and their methyl ethers (12) (Table 4) supported the assigned structures, and the methyl ether (12a) was identical with the compound reported in the previous paper[2].

Table 1. *Ring Opening of 8 with Base.*

Starting Material	R	Reaction Condition Base	Temp.(°C)	Time (hr)	Dihydroazatropolone	Yield (%)
8a	Ph	NEt$_3$*[2]	reflux	8	9a	50
		DBU*[3]	r.t.	24	9a	86
8b	Et	DBU	reflux	2	9b	63
8c	OEt	DBU	"	3	9c	70
8d	OAc	DBU	"	3	9d	71
8e*[1]	SPh	NEt$_3$*[4]	"	6	9e	92
8e	"	Raney Ni	r.t.	20	9f	60

*[1] The stereoisomeric mixture at C_7 was used as a starting material.

*[2] No solvent was used.

*[3] DBU was used as a 2% benzene solution.

*[4] NEt$_3$ was used as a 10% benzene solution.

Table 2. *UV Spectra of Dihydroazatropolones (9) and Their Methyl Ethers (10).*

Compound	R	m.p.	λ_{max} nm (ε) in dioxane
9a	Ph	226-236°	226(19,200), 269(17,600)
9b	Et	140-145°	227(13,000), 263(13,500)
9c	OEt	173-178°	220(13,600), 262(17,400)
9d	OAc	192-194°	220(14,000), 258(15,400)
9e	SPh	178-180°	220(20,300), 263(18,200)
9f	H	194-197°	220(14,000), 257(14,600)
10a	Ph	178-179°	228(18,800), 300sh (10,000)
10b	Et	116-118°	222(13,300), 252(12,200)
10c	OEt	gum	225(9,200), 252(10,900)
10d	OAc	136-138°	222(14,000), 253(13,400)
10e	SPh	136-141°	220(21,600), 260sh (15,400), 315sh (7,500)
10f	H	130-131°	222(14,750), 249(12,800)

Table 3. *DDQ oxidation of 9 and 10.*

Starting Material	R	Temp. (°C)	Time	Product	m.p.	Yield (%)
9a	Ph	100°	45 min			2[*1]
9b	Et	100°	45 min			17[*1]
9c	OEt	100°	25 min	11c	92-95°	65
9d	OAc	100°	45 min			5[*1]
9e	SPh	100°	45 min			5[*1]
9f	H	100°	5 min	11f	187-189°	50
10a	Ph	120°	2 hr	12a	131-133°	40
10b	Et	120°	1.5 hr	12b	yellow gum	45
10c	OEt	100°	20 min	12c	"	50
10d	OAc	120°	1.5 hr	12d	"	40
10e	SPh	110°	2 hr	12e	"	68
10f	H	100°	3 min	12f[*2]		50[*3]

[*1] The reaction mixture was treated with methanol and the yield of the azatropolone was calculated from the weight of the methyl pyridine-2-carboxylate, the rearranged product of the azatropolone.

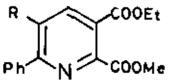
[*2] 12f was not isolated in a pure form.

[*3] Yield was calculated from the weight of 11f.

Table 4. *UV Spectral Data of Azatropolones and Their Methyl Ethers.*

	R	λ_{max} nm (ε) in dioxane
6a		265sh (11,800), 312 (8,500), 380 (6,200)
11c	OEt	251sh (7,900), 320 (6,600), 385 (7,900)
11f	H	241 (10,800), 290sh (8,900), 357 (6,500)
6b		254 (14,000), 290sh (8,900), 357 (6,500)
12a[2]	Ph	253 (17,000), 300 (12,300)
12b	Et	220 (12,300), 262 (12,800), 345sh (3,300)
12c	OEt	260 (13,500), 360 (3,400)
12d	OAc	263 (9,900), 287 (9,000), 355sh (4,000)
12e	SPh	222 (16,400), 250 (16,300), 345sh (5,800)

All azatropolones prepared above were proved to be unstable, like **4** and **5**, in protic solvents^2. Treatment of **11c**, **11f**, and **6a** with methanol in the presence of catalytic amount of sodium acetate afforded the methyl pyridine-2-carboxylates (**13c**), (**13f**), and (**14**) in quantitative yield, respectively. Similarly **13a**, **b**, **d**, **e** were isolated from the oxidation products of **9a**, **b**, **d**, **e** after treatment with methanol. [**13a**: m.p. 103-105°^{2}. **13b**: m.p. 88-89°. **13c**: m.p. 96-97°. **13d**: m.p. 62-64°. **13e**: m.p. 78-82°. **13f**: m.p. 135-140°. **14**: m.p. 82-84°.]



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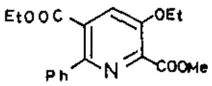

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2. T. Sano, Y. Horiguchi and Y. Tsuda, *Heterocycles*, **9**, 731 (1978).
3. Pale yellow needles, m.p. 179-181°. The structure was deduced from the UV spectra of **6a** and its methyl ether (**6b**), m.p. 60-63°, which were different from the isomers (**11c**) and (**12c**), respectively.
4. **7** was identical with the pyridone reported in a previous paper. [T. Sano, Y. Horiguchi, Y. Tsuda and Y. Itatani, *Heterocycles*, **9**, 161 (1978).]
5. T. Sano and Y. Tsuda, *Heterocycles*, **4**, 1229 (1976).
6. T. Sano , Y. Tsuda, H. Ogura, K. Furuhata and Y. Iitaka, *Heterocycles*, **4**, 1233 (1976).
7. Though a spot assumed to be the azatropolone was recognizable among many other spots on TLC of the reaction mixture, its chromatographic separation over SiO_2 was failed because of its solvolytic unstability.

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