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A Convenient Synthesis of 5-Aryltropolones via Novel Benzidine Type Rearrangement of 2-(2-Arylhydrazino)tropones

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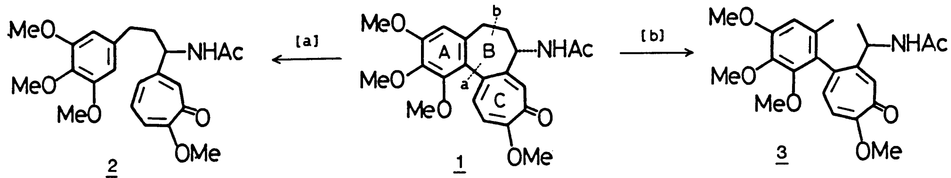
Treatment of a wide variety of 2-(2-arylhydrazino)tropones with ethanolic acid at 50-80 °C readily gave the benzidine type rearrangement products, i.e. 2-amino-5-(4-aminoaryl)tropones, which in turn were conveniently led to the corresponding 5-aryltropolones that can be utilized for synthesizing B-ring-open analogues of colchicine.

In view of highly important biological activity of colchicine (1),[1)] we have reported[2)] a convenient synthesis of the B-ring-open analogues (2) of 1 (in which a bond is disconnected at [a]) starting from 4-acetyltropolone.[3)] We now wish to describe in this communication a convenient synthesis of 5-aryltropolones which can be led to another, potentially useful B-ring-open analogues[4)] (3) of 1 (a bond being disconnected at [b]) from 2-(2-arylhydrazino)tropones via a new type of benzidine rearrangement.[5,6)]

Although the tropolone nucleus is well known to susceptible to many electrophilic substitutions, it does not undergo the Friedel-Crafts type alkylation or acylation, and the reaction of organolithium and magnesium reagents with troponoids affords C-3 and C-7 substitution products.[7)] Thus, virtually no efficient synthetic scheme has been established so far for the preparation of 5-aryltropolones. Meanwhile, it was found by Sankyo Research group[8)] that some 2-(2-arylhydazino)tropones (6) showed interesting physiological activity but were very unstable towards acid. We have carried out the following systematic experiments and established a general, convenient method of preparing 5-aryltropolones which are expected to be readily led to colchicine analogues of type 3 having a similar conformation as that of 1.

Thus, the treatment of compound 6a[9)] with 2 M hydrochloric acid in ethanol under reflux for 3.5 h gave yellow needles which were identified to be 2-amino-5-(4-aminophenyl)tropone (7a).[10,11)] Alkaline hydrolysis of 7a in ethanolic 2 M KOH



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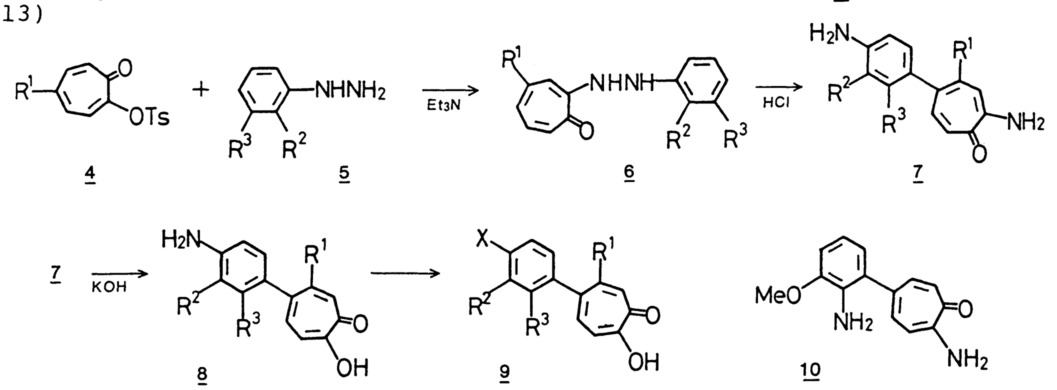
under reflux for 10 h afforded 5-(4-aminophenyl)tropolone 8a[10] as yellow needles. The 5 position of the 4-aminophenyl group was confirmed as follows: deamination of 8a by treatment with an excess of cold nitrous acid, followed by reduction with phosphinic acid, gave 5-phenyltropolone 9a (X=H, pale yellow needles, 30% yield), previously obtained via different routes from phenylcycloheptatriene in extremely low yields.[12]

We have then prepared a wide variety of 2-(2-arylhydrazino)tropone derivatives 6 by the reaction of reactive troponoids 4 (a: R^1=H, b: R^1=iPr, c: R^1=isopropenyl) with arylhydrazines 5 in the presence of an equivalent amount of triethylamine in relatively good yields. These arylhydrazinotropones 6 have been found similarly to undergo the rearrangement of the benzidine type, giving the diamino compounds 7, which have been led to 5-aryltropolones 8; the yields and melting points of these products (6, 7, and 8b-l, as representative examples)[10] are summarized in Tables 1 and 2. The conversion of the 4-amino group on the benzene ring of 8 into 4-methoxy derivative 9 (X=OMe) is exemplified by treatment of 8a with $NaNO_2$-HCl in aq. MeOH to give phenol 9 (X=OH)[10] which is methylated with diazomethane [to afford 2-methoxy-5-(4-methoxyphenyl)tropone, mp 148-149.5 °C],[10] and then hydrolyzed with dilute alkali to yield tropolone 9 (X=OMe), mp 155-157 °C).[13]

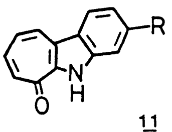


A close examination of the experimental facts observed for the rearrangement of 6 to 7 leads to the following remarks that would closely relate to the aspect

Table 1. Synthesis of 2-(2-arylhydrazino)tropones (6)

Starting material	Product	R^1	R^2	R^3	Yield/%	Mp θm/°C
4a	6a	H	H	H	66	168
"	b	H	Me	H	82	90-91
"	c	H	H	Me	72	148
"	d	H	OMe	H	56	119
"	e	H	H	OMe	80	148-150
"	f	H	Cl	H	64	91-93
"	g	H	H	Cl	80	159-161
"	h	H	NO_2	H	21	178-179
"	i	H	H	NO_2	62	188-190
4b	j	iPr	H	H	40	153-154
4c	k	$C(=CH_2)Me$	H	H	63	176-178
"	l	"	Me	H	55	141-142

of the reaction mechanism. i) The presence of electron-donating substituents on the benzene ring greatly accelerates the rearrangement, whereas that of electron-withdrawing group markedly suppresses the reaction. ii) The rearrangement products of the benzidine type 7 are available even if an isopropyl or isopropenyl group is present on C-4 of the tropone ring of 6. iii) Besides 7, formation of various by-products is usually observed: the representative products isolated[10] are diphenyline type 10 (4% from 6e as diacetate), indolotropones 11 (5, 10, 20, 17, and 5% from 6a, 6c, 6e, 6g, and 6i, respectively), 2-aminotropone 12 (19% from 6d), m-nitroaniline 13 (6% from 6h), arylazotropones 14 (a few % from various 6), and 5-anilino-2-arylazotropones 15 (1.5 and 1% from 6a and 6g, respectively); no rearrangement products of o-benzidine or o- and p-semidine type have been isolated so far from any kinds of 6. iv) A small amount of dimers 16 are produced from 6, when the preparation or the acid-catalyzed rearrangement is carried out without protection from oxygen.



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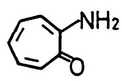

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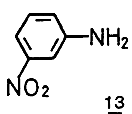

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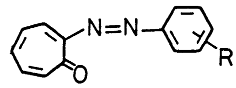

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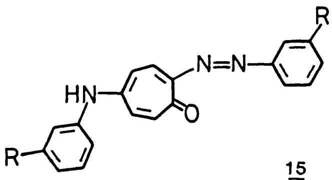

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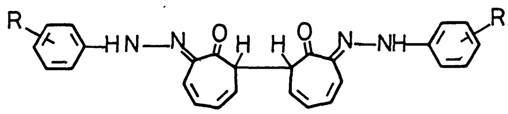

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These findings in the novel rearrangement are believed to be of value from the view point of the development of the fundamental chemistry of troponoids[7] and also to give important suggestions on further clarification of the reaction mechanism[6] of benzidine rearrangement. Moreover, present work demonstrates an effective way for preparation of various 5-aryltropolones which can be led to colchicine analogues.

Table 2. Synthesis of 2-amino-5-aryltropones (7) and 5-aryltropolones (8)

Compd	R^1	R^2	R^3	Yield/%	Mp θm/°C	Compd	Yield/%	Mp θm/°C
7a	H	H	H	91	203-204	8a	96	185-186
b	H	Me	H	89	204	b	95	157-158
c	H	H	Me	87	153-155	c	98	115-117
d	H	OMe	H	48	185	d	87	155-157
e	H	H	OMe	77	185-187	e	90	167-169
f	H	Cl	H	77	230 dec	f	97	136-138
g	H	H	Cl	79	161-162	g	96	161-163
h	H	NO_2	H	39	253-254	h	50	272-275
i	H	H	NO_2	49	246-247	i	71	250-253
j	iPr	H	H	a)		j b)	92	250 dec
k	$C(=CH_2)Me$	H	H	a)		k b)	62	119-121
l	"	Me	H	a)		l b)	79	85 dec

a) The product was susceptible to gradual air oxidation. Thus it was subjected to the alkaline hydrolysis to convert into the 5-aryltropolone derivatives (8). b) 5-(4-Acetamidophenyl)tropolones.

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10) ^{1}H NMR (100 or 200 MHz), ^{13}C NMR (for some compounds), MS (high-resolution EI), and IR data were in agreement with the structures of the products described in this paper. Experimental detail will be published soon.

11) 7a: yellow crystals; MS m/z 212 (M^+); ^{1}H NMR (DMSO-d_6) δ=5.2 (2H, brs, NH2), 6.70 (2H, brd, J=8.5 Hz, H-3', 5'), 7.4 (2H, brd, J=8.5 Hz, H-2',6'), 7.0-7.9 (4H, m. H-3,4,6,7), and 7.5 (2H, m, NH_2); ^{13}C NMR (DMSO-d_6) δ=113.0 (C-3), 114.5 (C-3',5'), 127.9 (C-2',6'), 129.3 (C-7), 129.9 (C-1'), 133.9 (C-4), 136.0 (C-5,6), 148.2 (C-4'), 156.7 (C-2), and 174.6 (C-1).

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