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

Tetsuo NOZOE,* Kahei TAKASE,† Hiroaki SAITO,† Hiroshi YAMAMOTO,††
and Kimiaki IMAFUKU†††

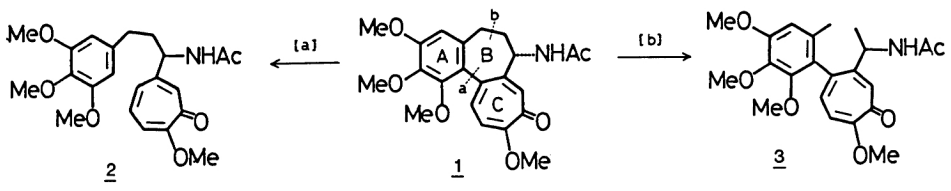
Tokyo Research Laboratories, Kao Corporation, Bunka, Sumida-ku, Tokyo 131
†Department of Chemistry, Faculty of Science, Tohoku University, Sendai 980
††Department of Chemistry, Okayama University, Tsushima, Okayama 700
†††Department of Chemistry, Kumamoto University, Kumamoto 860

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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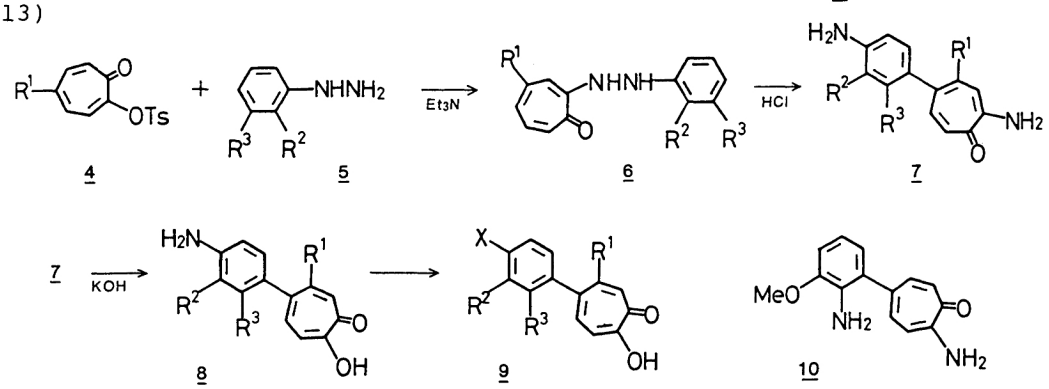
under reflux for 10 h afforded 5-(4-aminophenyl)tropolone 8a[10] as yellow needles. The 5 position of the 4-aminophenyl group was confirmed as follows: deamination of 8a by treatment with an excess of cold nitrous acid, followed by reduction with phosphinic acid, gave 5-phenyltropolone 9a (X=H, pale 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]

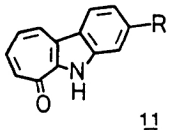


A close examination of the experimental facts observed for the rearrangement of 6 to 7 leads to the following remarks that would closely relate to the aspect

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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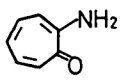

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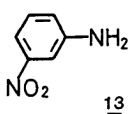

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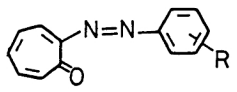

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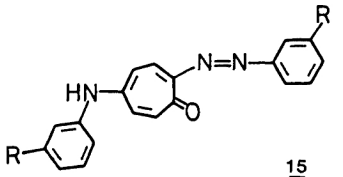

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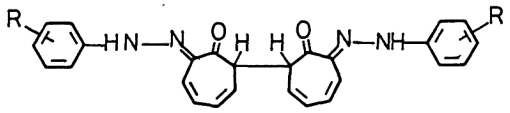

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These findings in the novel rearrangement are believed to be of value from the view point of the development of the fundamental chemistry of troponoids[7] and also to give important suggestions on further clarification of the reaction mechanism[6] 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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References

1) See B. Bhattacharyya and J. Wolff, J. Biol. Chem., 259, 11836 (1984) and references cited therein.

2) T. Nozoe, Experientia, Suppl. VII, 1957, 306; T. Nozoe, K. Takase, N. Kawabe, T. Asao, and H. Yamamoto, Bull. Chem. Soc. Jpn., 56, 3099 (1983) and references cited therein; H. Yamamoto, A. Hara, S. Inokawa, and T. Nozoe, *ibid.*, 56, 3106 (1983).

3) T. Nozoe, K. Takase, and M. Ogata, Chem. Ind., 1957, 1070; H. Yamamoto, A. Hara, A. Noguchi, H. Kawamoto, S. Inokawa, and T. Nozoe, Bull. Chem. Soc., Jpn., 55, 1594 (1982).

4) For other examples of bicyclic colchicine analogues missing B-ring, see T. J. Fritzgerald, Biochem. Pharmacol., 25, 1383 (1976); M. Rossi, J. Link, and C. Lee, Arch. Biochem. Biophys., 231, 470 (1984); C.-P. Mak and G. Buchi, J. Org. Chem., 46, 1 (1981).

5) Part of the results has been preliminarily presented: H. Saito, M. Yasunami, M. Ando, K. Takase, and T. Nozoe, 37th National Meeting of the Chemical Society of Japan, Tokyo, April 1978, Abstr. No. 2D32; H. Yamamoto, Y. Hara, T. Okazaki, Y. Hidaka, Y. Nishina, S. Inokawa, and T. Nozoe, 5th Intl. Conf. Org. Synth., Freiburg, August 1984, Abstr. No. Th30.

6) For reviews of benzidine rearrangement, see M. J. S. Dewar, "Molecular Rearrangements," ed by P. de Mayo, Interscience, New York (1963), pp. 323-344; H. J. Shine, "Mechanism of Molecular Migration," ed by B. S. Thyagarajan, Interscience, New York (1969), Vol. 2, pp. 192-247.

7) T. Nozoe, K. Takase, H. Matsumura, T. Asao, K. Kikuchi, and S. Itô, "Dai Yuki Kagaku (Comprehensive Organic Chemistry," ed by M. Kotake, Asakura, Tokyo (1960), Vol. 13, pp. 1-692; F. Pietra, Chem. Rev., 73, 293-364 (1973); D. Lloyd, "Non-benzenoid Conjugated Carbocyclic Compounds," Elsevier, Amsterdam (1984), pp. 107-125.

8) N. Kitano, S. Sugawara, Y. Kishida, F. Kondo, Y. Sugimura and N. Soma, Jpn. Kokai Tokkyo Koho 7494816 (1974); Chem. Abstr., 81, 176148r (1974).

9) N. Soma, I. Nakagawa, T. Watanabe, Y. Sato, and G. Sunagawa, Chem. Pharm. Bull., 13, 457 (1968).

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).

12) W. von E. Doering and L. H. Knox, J. Am. Chem. Soc., 75, 297 (1953); T. Ikemi, T. Nozoe, and H. Sugiyama, Chem. Ind., 1960, 932.

13) K. Takahashi, Bull. Chem. Soc. Jpn., 40, 1462 (1967).

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