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SYNTHESES AND REACTIONS OF DEUTERATED TROPONOIDS

Shô Itô, Josuke Tsunetsugu, Takeshi Kanno, Hiroshi Sugiyama
and Hitoshi Takeshita
Department of Chemistry, Tohoku University,
Sendai, Japan

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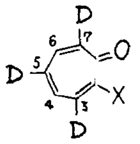
As the result of the extensive study by Nozoe and his coworkers[1], a large number of nucleophilic reagents has been found to react with reactive troponoids[2] which carry either halogens, methoxyl or tosyloxyl groups at 2-position to give various substituted troponoids or condensed-ring compounds. The site of attack by the reagents in these reactions has always been determined using the compounds with alkyl or halogen substituents at proper positions, and was summarized[1] as follows: 2-Methoxytropones react at 2-position (attack at 2), 2-halotropones at 7-position (attack at 7), and 2-tosyloxytropones both at 2- and 7-positions. However, these reactions are very much depend on nature and position of the substituent on tropone nucleus, and reagents and the solvents used[3]. It is, therefore, inadequate and sometimes dangerous to make any assumption on reacting site of the unsubstituted compounds on the basis of the result on substituted counterparts[4]. In order to clarify this point with unsubstituted reactive troponoids, we have synthesized deuteriotroponoids and carried out their several typical nucleophilic reactions; the result is reported in this paper.



I X=OH

II X=OMe

III X=OTs

IV X=Cl

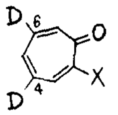
V X=NH_2

VIII X=NHMe

XI X=NMe_2

XV X=$NHNH_2$

XVI X=Br

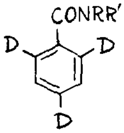


VI X=NH_2

IX X=$NHCH_3$

XII X=NMe_2

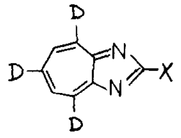
XIV X=OH



VII R=R'$_4$=H

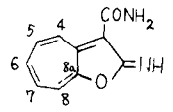
X R=Me, R'=H

XIII R=R'=Me



XVII X=SH

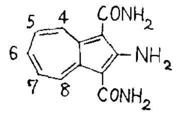
XVIII X=H



XIXa

XIXb 4,6,8-$\underline{d}_3$

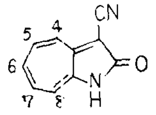
XIXc 5,7-$\underline{d}_2$



XXa

XXb 4,6,8-$\underline{d}_3$

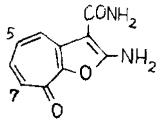
XXc 5,7-$\underline{d}_2$



XXIa

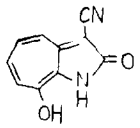
XXIb 4,6,8-$\underline{d}_3$

XXIc 5,7-$\underline{d}_2$



XXIIa

XXIIb 5,7-$\underline{d}_2$



XXIII

Catalytic hydrogenation (Pd-C) of 3,5,7-tribromotropolone with deuterium in dioxane-deuterium oxide in the presence of triethylamine furnishes tropolone-3,5,7-$\underline{d}_3$ I, m.p. 49-50°[5,6], in 10% yield without contamination due to random exchange of hydrogens[7]. 2-methoxytropone-3,5,7-$\underline{d}_3$ II, b.p. 90°/3 mm Hg, can be prepared by the similar way (sodium acetate was used in place of triethylamine) in almost quantitative yield. The second method for preparation of I, comprizing acid-catalyzed deuterium exchange of tropolone will be reported later[8] together with the rate study. I can be converted to its methyl ether

II[9,10], identical with the one obtained by catalytic reduction, and to tosylate III, m.p. 161°[11]. The 2-chlorotropone-3,5,7-$\underline{d}_3$ IV, m.p. 64-65°, was obtained directly from I[12](attack at 2).

Reactive troponoids, II, III, IV, thus prepared were subjected to the reaction with amines. The result of the product analysis, shown in Table I, revealed the complexity of the reactions.

Table I. Reaction of Amines with Reactive Troponoids.

Reagent	Reacting Site	Product	Yield of Product from		
			II	III	IV
Ammonia[9,13]	2	V	98%	47%	-
	7	VI	-	53%	15%
	1	VII	-	-	85%
Methylamine[3,15]	2	VIII	99%	46%	40%
	7	IX	-	19%	23%
	1	X	-	21%	29%
Dimethylamine[15]	2	XI	99%	86%	83%
	7	XII	-	-	11%
	1	XIII	-	-	-

Alkaline hydrolysis[13] of 2-aminotropone-4,6-$\underline{d}_2$, m.p. 104-105°, yielded tropolone-4,6-$\underline{d}_2$ XIV, m.p. 48-49° (attack at 2). Furthermore, II was converted to the corresponding 2-hydrazino- XV[6] and then to 2-bromotropone XVI[16,17], m.p. 59-60°, *via* attacks at 2. Reaction of thiourea with II in alkaline medium[18] was also found to occur at 1 and 2, affording 2-mercapto-1,3-diazaazulene-4,6,8-$\underline{d}_3$ XVII, m.p. >300° (84.4%). Hydrogen peroxide oxidation of XVII gave 1,3-diazaazulene-4,6,8-$\underline{d}_3$ XVIII, m.p. 119°.

Formation of azulene derivatives from the reactive troponoids trideuterated compounds using cyanoacetamide as active methylene compound, ratio of troponoids, cyanoacetamide and sodium ethoxide being set to 1:2:2. The reactions were carried out at 0° for 12 hrs. in absolute ethanol. Under this condition, II gave 2-iminocyclohepta-[b]-furan-3-carbamide-4,6,8-$\underline{d}_3$ XIXb, m.p. 187-188°, in 49% yield and 2-aminoazulene-1,3-dicarbamide-4,6,8-$\underline{d}_3$ XXb, m.p. > 300°, in 11% yield through attack at 2[20)]. With another mole of cyanoacetamide under the similar condition, XIXb was converted to XXb (9%) and 3-cyanocyclohepta-[b]-pyrol-2-one-4,6,8-$\underline{d}_3$ XXIb, m.p. > 300°, (71%) through the attacks at 8a. In the cases of III and IV, attack of the reagent occured at 7-position: The product from the reaction of IV was XIXc, m.p. 187-188° (53.1%), XXc, m.p. > 300°, (21.7%), and XXIc, m.p. > 300°, (24.2%)[19)], and that from III was XIXc (43.5%), XXc (trace), and 2-amino-3-carbamidofuro[2,3-b]tropone-5,7-$\underline{d}_2$ XXIIb, m.p. > 300°, (50.4%)[21)].

Although the reason for the complexity of these reactions is not yet clear, study on reaction of reactive deuterated troponoid with the other nucleophilic reagents is in progress.

We are deeply indebted to Professor Tetsuo Nozoe for his generousity of letting us to use the unpublished results of his group. Thanks are also due to Sankyo Co. Ltd. for their gift of tropolone.

REFERENCES AND FOOTNOTES

1) For general reference, see (a) T. Nozoe *et al.*, *Daiyukikagaku*, (Ed. M. Kotake), Vol. 13, p. 181. Asakura Publ., Tokyo (1960), (b) T. Nozoe *Progr. Org. Chem.* (Ed. J.W. Cook), Vol. 5, p. 132. Academic Press (1961), T. Nozoe, *Non-Benzenoid Aromatic Compounds*, (Ed. D. Ginsburg), p. 339. Interscience Publ., New York (1959).

2) This general name was proposed by Nozoe in 1960[1a)].

3) For example, 2-chloro-5-methyltropone gives 2-amino-4-methyltropone with ammonia in methanol, but the same compound forms 2-methylamino-5-methyltropone with methylamine under the same condition; T. Sato, *J. Chem. Soc. Japan, Pure Chem. Sec.*, **80**, 1167 (1959); 2-methoxy-5-chlorotropone yields 6-chloro-3-methoxycarbonyl-cyclohepta-[b]-furan-2-one with dimethyl malonate in alkaline condition in benzene, while it gives 7-chloro-3-methoxycarbonyl-cyclohepta-[b]-furan-2-one in methanol. T. Nozoe, S. Seto, T. Sato and H. Takeshita, to be published.

4) The Grignard reaction of 2-methoxytropone is the only reaction in

which the attacking site of the reagents is so far established (attack at 7). Y. Kitahara and M. Funamizu, to be published.

5) The compound was first obtained by Ikegami, but neither number nor position of deuterium was established. Y. Ikegami, Bull. Chem. Soc. Japan, 34, 94 (1961).

6) All of the deuterated compounds showed the correct molecular ion in their mass spectra. Location of deuterium was established by NMR spectroscopy. The analysis of spectra of troponoids will be reported elsewhere by S. Itô, H. Sugiyama, J. Tsunetsugu and T. Nozoe.

7) Tropolone itself is recovered unchanged under the same condition.

8) S. Itô, H. Takeshita, J. Tsunetsugu and T. Kanno, to be published.

9) W.von E. Doering and L.H. Knox, J. Amer. Chem. Soc., 73, 828 (1951).

10) J.W. Cook, A.R. Gibb, R.A. Raphael, A.R. Sommervill, J. Chem. Soc., 503 (1951).

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12) R.A. Abadir, J.W. Cook, J.D. Loudon and D.K.V. Steel, J. Chem. Soc., 2350 (1952).

13) T. Nozoe, S. Seto, H. Takeda, S. Morosawa and K. Matsumoto, Proc. Japan Acad., 27, 556 (1951).

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15) T. Sato, J. Chem. Soc. Japan, Pure Chem. Sec., 80, 1056 (1959).

16) T. Nozoe, S. Seto, H. Takeda, S. Morosawa and K. Matsumoto, Sci. Repts. Tohoku Univ., Ser. I, 36, 126 (1952).

17) During this conversion which requires heating in hydrobromic acid, 30% of deuterium at 7-position is exchanged with hydrogen.

18) T. Nozoe, T. Mukai and I. Murata, J. Amer. Chem. Soc., 76, 3352 (1954).

19) T. Nozoe, S. Seto, S. Matsumura and T. Asano, Proc. Japan Acad., 32, 339 (1956), T. Nozoe, S. Seto, S. Matsumura and Y. Murase, Bull. Chem. Soc. Japan, 35, 1179 (1962), T. Nozoe, S. Seto, K. Takase, S. Matsumura and T. Nakazawa, J. Chem. Soc. Japan, Pure Chem. Sec., 86, 346 (1965).

20) Of these two compounds, only XXa was isolated by Nozoe et al. (Proc. Japan Acad., 32, 472 (1956)) together with XXIa which we failed to identify.

21) In the same reaction, Kato has obtained XXa, XXIIa and 3-cyano-8-hydroxy-2-ketocyclohepta-[b]-pyrole, XXIII (PhD Thesis, Tohoku University, 1965).