Studies on the Mechanism of Rearrangement Reaction of 2-Phenyl-4-bromotropone to 2-Phenylbenzoic Acid[1]

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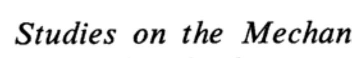
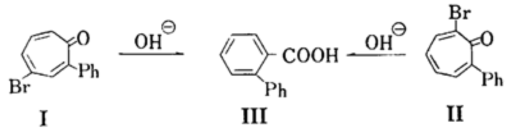
It had been found in the early period of studies on troponoid chemistry that the tropone derivatives having the halogen or methoxyl group in the 2-position undergo rearrangement to benzoic acid derivatives when treated with bases[2]. This rearrangement reaction has often been utilized for deriving unknown troponoid to known benzene derivatives to determine the position of various substituents in the seven-membered ring by the organic chemical method[2].



X = halogen, methoxyl

Two kinds of mechanism may be considered for this rearrangement reaction. One, route-A, involves the attack of the base on the carbonyl carbon (C-1), followed by ring contraction concerted with liberation of the substituent in C-2 as an anion[3]. The other, route-B, is the attack of the base on C-2 and subsequent rearrangement[4]. If the rearrangement proceeds through route-A, the carbon atom in the carboxyl group of the benzoic acid produced corresponds to the carbonyl carbon of tropone, and if the reaction goes through route-B, it will be the carbon atom at C-2 of the tropone. An investigation of the rearrangement with carbonyl-labeled 2,7-dibromo- and 2,4,7-tribromotropone proved that the modified mechanism of route-A is the correct one[5].

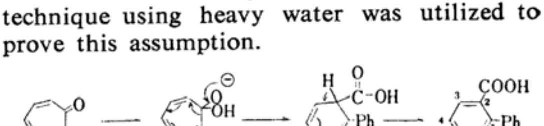
One of the authors (T. M.) found that the product obtained by treatment of 2-phenyl-4-bromotropone (I) with alkali was unexpectedly 2-phenylbenzoic acid (III), the same as the rearrangement product of 2-phenyl-7-bromotropone (II)[6].



I III II

Differing from II, I does not possess any group easily liberated as an anion at the carbon adjacent to the carbonyl group and the rearrangement product, III, no longer possesses bromine atom. Consequently, the mechanism proposed by Doering and Denney[5] cannot be applied to this rearrangement reaction.

The following mechanism was considered for this abnormal rearrangement reaction and tracer technique using heavy water was utilized to prove this assumption.



If the rearrangement proceeds through this route, the reaction carried out in a system containing deuterium as an origin of hydrogen should give a product with the carbon-bound deuterium only in the 5-position of the biphenyl formed.

A solution of I dissolved in a solution of deuterium oxide[7], sodium hydroxide-*d*, and methanol-*d*[8] was refluxed for 30 min. and 2-phenylbenzoic acid was isolated from the acid portion. To remove deuterium from the carboxyl group, the acid was converted into its methyl ester with diazomethane and the ester was hydrolyzed to deuterated 2-phenylbenzoic acid (III) of m. p. 108~110°C[9]. The

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[2] T. Nozoe, *Sci. Repts. Tohoku Univ.*, *I*, **34**, 199 (1950); T. Nozoe, *Nature*, **167**, 1055 (1951); J. W. Cook and J. D. London, *Quart. Revs.* (*London*), **5**, 99 (1951); P. L. Pauson, *Chem. Revs.*, **55**, 9 (1950).

[3] W. von E. Doering and L. H. Knox, *J. Am. Chem. Soc.*, **73**, 828 (1951); T. Nozoe. Y. Kitahara and S. Masamune, *Proc. Japan Acad.*, **27**, 649 (1951); Y. Kitahara, *Sci. Repts. Tohoku Univ.*, *I*, **39**, 250 (1956).

[4] W. von E. Doering and L. H. Knox, *J. Am. Chem. Soc.*, **74**, 5683 (1952).

[5] W. von E. Doering and D. B. Denney, ibid., **77**, 4619 (1955).

[6] T. Muroi, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **80**, 303 (1959).

[7] Norsk Hydro-electrisk; purity, 99.78%. d_4^{20} 1.10514.

[8] D. H. Hill, B. Stewart, S. W. Kantor, W. A. Judge and C. R. Hauser, *J. Am. Chem. Soc.*, **76**, 5129 (1954).

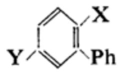
[9] Under this rearrangement condition, 2-phenylbenzoic acid was proved to be free from secondary deuteration on aromatic nucleus, since the infrared absorption spectrum of the product obtained by treatment of 2-phenylbenzoic acid under the same conditions as for rearrangement of I was identical with that of the original substance. D. J. G. Ives (*J. Chem. Soc.*, **1938**, 81) also reported that deuteration did not take place on the benzene ring when benzoic acid was treated in a deuterium oxide-sodium hydroxide-*d* system.

TABLE I. COMPARISON OF INFRARED ABSORPTION BANDS OF DEUTERATED COMPOUNDS AND CORRESPONDING NON-DEUTERATED COMPOUNDS*

III′	III	IV′	IV	V′	V
3070	3065	3370	3370	3275	3270
3030		3175	3175	3230	3215
2890	2920	3055		3020	3010
2655	2670				
2520	2525				
	2280				
1949	1955				
1692	1695	1692	1692	1658	1658
1601	1597	1640	1640		1598
	1502	1619	1618	1587	1583
1483	1481	1602	1594	1533	1530
1456	1450	1582	1578	1497	
1445			1498	1477	1473
1408	1412	1482	1477	1453	1444
	1400	1455		1437	
1290	1282	1442	1447		1403
1260	1252		1418	1372	1370
1180	1182	1400		1303	1303
1164			1383		1287
1139	1143	1150	1150	1254	1248
	1110	1112	1111	1157	1154
1094		1075	1074		1125
1073	1073	1010	1005	1112	
1047	1049	957		1073	1073
1007	1003		905	1047	1051
929			860	1010	1004
910	908	841		975	975
	884	800	800	941	
	856	778	774	922	916
694	694	743	751		904
673	673		725		832
654	651	696	696	776	772
			670	756	
				742	740
				705	701
				662	655

* IR spectra are measured using a Perkin-Elmer Model 21 double beam spectrophotometer in KBr pellet.

infrared absorption spectrum of III (Table I.) was different from that of III′[10], and this fact indicated that it contained the deuterium atom.



III: $X=COOH$, $Y=D$
IV: $X=CONH_2$, $Y=D$
V: $X=NHCOCH_3$, $Y=D$
VI: $X=NHCOCH_3$, $Y=Br$
III′: $X=COOH$, $Y=H$
IV′: $X=CONH_2$, $Y=H$
V′: $X=NHCOCH_3$, $Y=H$

In order to determine the position of the deuterium atom in III, the following reaction was carried out. III was allowed to react with thionyl chloride at room temperature and the resulting acid chloride, treated with ammonia water, gave the amide (IV), m. p. 172.5~173°C. The Hofmann reaction of IV by the method of Graebe[11] yielded the corresponding amine and the product was acetylated to give deuterated 2-acetamidobiphenyl (V), m. p. 113~114°C. The infrared absorption spectra of IV and V so obtained (Table I) and determination of deuterium by mass analysis (cf. Experimental) indicated that the deuterium atom has remained during the series of these reaction steps.

Bromination of V and V′ with 1 mol. of bromine in glacial acetic acid gives the known 2-acetamido-5-bromobiphenyl (VI)[12] of m. p. 127.5~128.5°C in a quantitative yield from both. The infrared absorption spectra of VI derived from both V and V′ were entirely identical, indicating that the deuterium atom in V had been substituted with a bromine atom in this bromination procedure. VI is a known substance and the position of its bromine atom has already been determined. These facts have proved that the deuterium atom in II, IV and V is in 5-position in the biphenyl ring and, consequently, the reaction mechanism assumed for this abnormal rearrangement might be proved to be correct.

Experimental[13]

Rearrangement Reaction of 2-Phenyl-4-bromotropone (I) in Heavy Water System.—To a solution of sodium (1.38 g.) dissolved in methanol-*d* (35 ml.), deuterium oxide (25 ml.) and I (4.9 g.) were added and the mixture, provided with a calcium chloride tube, was refluxed for 30 min. on a water bath. Methanol was evaporated in a reduced pressure, the residue was diluted with 10 ml. of water, and extracted with chloroform to remove the neutral portion. The aqueous layer was acidified with hydrochloric acid to Congo red, the precipitated acid portion was extracted with chloroform, and the extract was washed with water. After drying over magnesium sulfate, chloroform was evaporated from the extract and the residue was sublimed in reduced pressure, from which 2.3 g. of crude crystals, m. p. 99~104°C, was obtained.

Without further purification, this product was dissolved in ether and ether solution of diazomethane was added to effect esterification. The residue obtained on evaporation of ether was dissolved in ethanol (30 ml.), 2 N sodium hydroxide (10 ml.) was added, and the mixture was refluxed

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[10] The same reaction was carried out in parallel, using 2-phenylbenzoic acid synthesized from fluorene[11]. The compounds not containing deuterium are represented by the same compound number as the corresponding deuterated compounds but with a prime.

[11] C. Graebe and A. S. Rateanu, *Ann.*, 279, 257 (1894).

[12] H. A. Scarborough and W. A. Waters, *J. Chem. Soc.*, 1927, 89.

[13] All melting points are uncorrected.

for 2.5 hr. to effect hydrolysis. Ethanol was evaporated, the residue was acidified with diluted hydrochloric acid extracted with chloroform. The crystals obtained from this extract were sublimed in reduced pressure and afforded 2.15 g. (61.6%) of crystals melting at 95~103°C. Recrystallization from cyclohexane gave III m. p. 108~110°C.

Found: D, 8.93. Calcd. for $C_{13}H_9DO_2$: D, 10.00 atom%.

2-Carbamoylbiphenyl-5-*d* (IV).—The addition of thionyl chloride (2 ml.) to III (1.9 g.) resulted in vigorous reaction with evolution of hydrogen chloride. The mixture was allowed to stand at room temperature for 1.5 hr., excess thionyl chloride was distilled off in reduced pressure, and the oily residue was added to 28% ammonia water under ice-cooling, by which white precipitates formed at once. The precipitates were collected and the crude amide (1.8 g) of m. p. 145~158°C so obtained was recrystallized from hydrous ethanol to IV, m. p. 172.5~173°C.

Found: D, 8.37. Calcd. for $C_{13}H_{10}DNO$: D, 9.08 atom%.

2-Acetamidobiphenyl-5-*d* (V).—IV (1.75 g.) was triturated with water (10 ml.) in a mortar and transferred to a beaker. A solution of sodium hypobromide, prepared from bromine (1.75 g.), sodium hydroxide (3.5 g.), and water (22 ml.) at 0°C, was added into the beaker with ice-cooling and the mixture was stirred for 1 hr. A trace of insoluble matter was removed by filtration, the filtate was heated at 50~55°C for 1 hr., and submitted to steam distillation. The distillate was extracted with chloroform, the extract was washed with water, dried, and chloroform was evaporated. The residue (1 g.) was dissolved in dehydrated pyridine (3 ml.) and acetyl chloride (0.7 g.) was added dropwise under ice-cooling. The mixture was allowed to stand for 30 min. and poured into 2 N hydrochloric acid containing cracked ice. The crystals that separated out were collected by filtration (1.1 g.), m. p. 104~108°C. Recrystallization from hydrous ethanol gave V, m. p. 113~114°C.

Found: D, 6.60. Calcd. for $C_{14}H_{12}DNO$: D, 7.70 atom%.

2-Acetamido-5-bromobiphenyl (VI).—A solution of bromine (390 mg.) in glacial acetic acid (2 ml.) was added to a solution of V (500 mg.) dissolved in glacial acetic acid (3 ml.), with stirring, and the mixture was allowed to stand overnight. The mixture was then poured into ice-water, and crude crystals (750 mg.) of m. p. 115~118°C were sublimed in reduced pressure. Recrystallization of the sublimate from hydrous ethanol gave V as colorless needles m. p. 127.5~128.5°C.

Found: C, 57.64; H, 4.40; N, 4.37. Calcd. for $C_{14}H_{12}ONBr$: C, 57.93; H, 4.17; N, 4.83%.

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