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Photodecarboxylation of Arylacetic Acids

Kimiaki ISOBE,*,[a] Kunihiko MOHRI,[a] Jun-ichi TAGA (deceased),[a] Yuki SASAKI,[a] and Yoshisuke TSUDA[b]

Showa College of Pharmaceutical Sciences,[a] 3-3165 Higashi-tamagawagakuen, Machida, Tokyo 194, Japan and Faculty of Pharmaceutical Sciences,[b] Kanazawa University, 13-1 Takara-machi, Kanazawa 920, Japan. *Received January 31, 1992*

Arylacetic acids, when the carboxyl group is at a secondary or tertiary carbon, are decarboxylated in considerable yields on irradiation of their aqueous alkaline solutions with 254 nm light, while the corresponding free acids are not decarboxylated. Together with the simple decarboxylation reaction (type A), two other side reactions, oxidative decarboxylation (type B) and decarboxylative dimerization (type C), were observed for some compounds, particularly when >290 nm light was used. The observation of high-yield decarboxylation of angularly substituted phenanthridone derivatives suggests that the above photodecarboxylation reaction would be a useful synthetic tool, if the substrate is appropriately designed.

Keywords decarboxylation; carboxylate ion; photolysis; photodecarboxylation; arylacetic acid; oxidative decarboxylation; decarboxylative dimerization

Phenylacetic acid[1)] and 1-naphthylacetic acid[2)] were reported to lose carbon dioxide on irradiation in aqueous alkaline solution. However, the quantum yield of this reaction is only 0.01 and the yield of toluene is very low.[3a)] Pyridylacetic acids are decarboxylated with better quantum yields (0.2—0.5) to give the corresponding picolines.[4)] Irradiation of the alkaline solution of nitrophenylacetic acids caused decarboxylative dimerization to yield dinitrobibenzyls together with a small amount of nitrotoluenes.[3b)] Since the yield of the decarboxylated product is usually low, the direct photodecarboxylation reaction has been considered to be of no synthetic value.

During our synthetic studies related to isoquinoline alkaloids we observed that the isoquinoline carboxylic acid of type **1** smoothly underwent decarboxylation, on irradiation of the aqueous alkaline solution with 254 nm light to give dihydrolycoricidines (**2a** and **2b**) in high yields.[5)] This fact prompted us to investigate the structural requirement for the efficient photodecarboxylation of arylacetate anions.

Results and Discussion

On irradiation of an alkaline solution of a carboxylic acid derivative with 254 nm light, a carboxyl group at the benzylic position is efficiently removed, whether it is secondary or tertiary, to give the corresponding hydrocarbon (type A reaction) in appreciable yield. The corresponding carboxylic acid, on irradiation in an organic solutions, however, did not undergo decarboxylation and was recovered unchanged, revealing that the free acid is not decarboxylated. The results, summarized in Table I, indicate that this photodecarboxylation is characteristic of arylacetate anions. 3-Phenylpropionic, 4-phenylbutyric, and 3-phenyllactic acids were not decarboxylated on irradiation either in alkaline solution or in organic solvents.

The reaction conditions using a lamp emitting at 254 nm and ammonium hydroxide as the alkaline medium usually gave better results, compared with the conditions using a lamp emitting at >300 nm and/or sodium hydroxide solution as the alkaline medium. Under the former conditions carboxylic acids, whose carboxy group was secondary or tertiary, were decarboxylated in appreciable or high yields, though primary carboxyls were removed poorly or not at all (entries 1—6). The lactam-acids, **3** and **4**, were decarboxylated in very high yields (entries 18 and 19).

The product from this decarboxylation usually has the most stable configuration, probably because the intermediate anion (or radical, see below) has the thermodynamically most stable form and the protonation of this species is very rapid. Thus, decarboxylation of **3** and **4** (entries 18 and 19) gave the B/C-*trans* phenanthridones, **5** and **6**, respectively, and the lactam **9** (entry 17) exclusively gave the product having a *trans* stereochemistry **11**.[6)] The product from **1** (entry 20) was a mixture of the *trans* and *cis* lactams, **2a** and **2b**, in the ratio of *ca.* 1 : 1[5)] (the stability of these two compounds is almost the same).

Two mechanisms have been suggested for this decarboxylation: one is ejection of a solvated electron from the carboxylate ion to give the carboxylate radical, which breaks

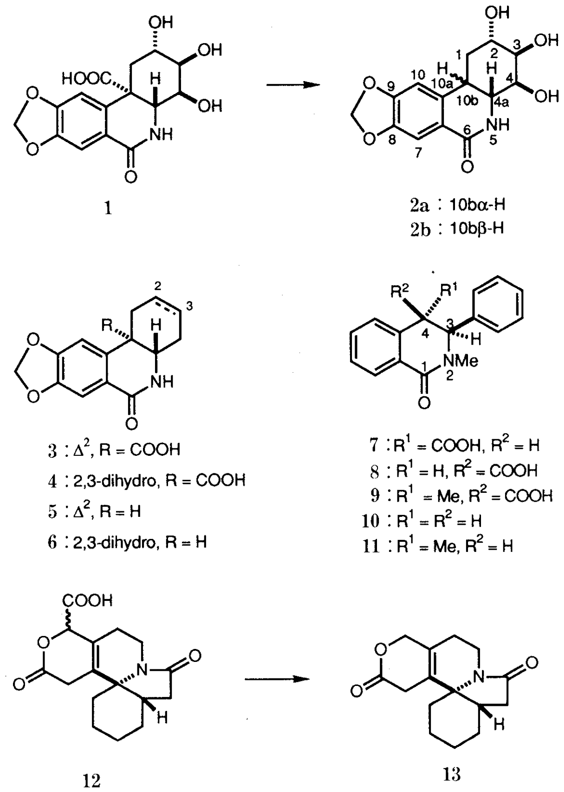

Chart 1

Table I. Photodecarboxylation of Arylacetic Acids in Alkaline Solution[a]

Entry	Acid	Product	Yield (%)[b]	Recovery (%)[b]
1	Phenylacetic	Toluene	Trace	14
2	3,4-Dimethoxyphenylacetic	3,4-Dimethoxytoluene	Nil	53
3	4-Fluorophenylacetic	*p*-Fluorotoluene	Nil	
4	4-Chlorophenylacetic	*p*-Chlorotoluene	Nil	
5	4-Bromophenylacetic	*p*-Bromotoluene	Nil	
6	Homophthalic	*o*-Toluic acid[c]	7	64
7	2-(3,4-Dimethoxyphenyl)propionic	3,4-Dimethoxyethylbenzene	23	
8	*dl*-*O*-Acetylmandelic	Benzyl alcohol	41	—
9	*dl*-α-Aminophenylacetic	Benzylamine	78	—
10	9-Fluorenecarboxylic	Fluorene[d]	11	79
11	9-Fluorenecarboxylic[e]	Fluorene	40	48
12	Diphenylacetic	Diphenylmethane	91	
13	2-(2-Carboxyphenyl)propionic	2-Ethylbenzoic acid[c]	46—60	6
14	2-(2-Carboxyphenyl)-2-methylpropionic[f]	2-Isopropylbenzoic acid[c]	40	6
15	Cushman's lactam (*trans*) **7**[7]	The carbostyril **10**[7]	71	20
16	Cushman's lactam (*cis*) **8**[7]	The carbostyril **10**	18	77
17	The lactam **9**	The carbostyril **11**	47	45
18	The lactam **3**[g]	The phenanthridone **5**	96	—
19	The lactam **4**[g]	The phenanthridone **6**	97	—
20	The lactam **1**[g]	The phenanthridones (**2a**+**2b**)	*ca.* 100	—
21	The lactone **12**	The lactone **13**[8]	18	—

a) See Experimental. *b*) Isolated yield. *c*) Isolated as a methyl ester. *d*) Contaminated with *ca.* 10% fluorenone. *e*) Equimolar $NaBH_4$ was added to the reaction medium. *f*) Hydrolysate of the dimethyl ester with 3 N NaOH was diluted with H_2O to *ca.* 0.1 N solution and directly irradiated. *g*) An 0.1 N NaOH solution was irradiated with a 20 W medium-pressure mercury lamp (pencil-type) for 0.5 h at 20 °C.

Table II. Side Reactions

Entry	Acid[a]	Base	Conditions[b]	Products (%)			
				Type A	Type B	Type C	Recovery
22	*dl*-Mandelic	3 N NH_4OH	A	72[c]	—	—	26
23	*dl*-Mandelic	3 N NH_4OH	B	—	6[d]	—	82
24	Benzilic	0.1 N Na_2CO_3	A	22[e]	—	25[f]	50
25	Benzilic	0.1 N $Na_2CO_3+NaBH_4$[g]	A	16[e]	—	3[f]	72
26	Benzilic	3 N NH_4OH	A	17[e]	—	8[f]	70
27	Benzilic	3 N NH_4OH	B	—	4[h]	—	88
28	4-Nitrophenylacetic	0.1 N NaOH	C	—	—	93[i]	—
29	4-Nitrophenylacetic	0.1 N NaOH + $NaBH_4$[g]	C	—	—	85[i]	—

a) The amount of acid used was 5 mmol. *b*) A, a 100 W mercury lamp without a Pyrex filter for 5 h at 20 °C; B, a 100 W mercury lamp with a Pyrex filter for 5 h at 20 °C; C, The acid (0.5 mmol) solution was irradiated with a 20 W medium-pressure mercury lamp (pencil-type) for 2 h at 5—20 °C. *c*) Benzyl alcohol. *d*) Benzaldehyde, isolated as the 2,4-dinitrophenylhydrazone. *e*) Benzhydrol. *f*) Benzopinacol. *g*) The amount of $NaBH_4$ added was 0.5 mmol. *h*) Benzophenone. *i*) 4,4′-Dinitrobibenzyl.

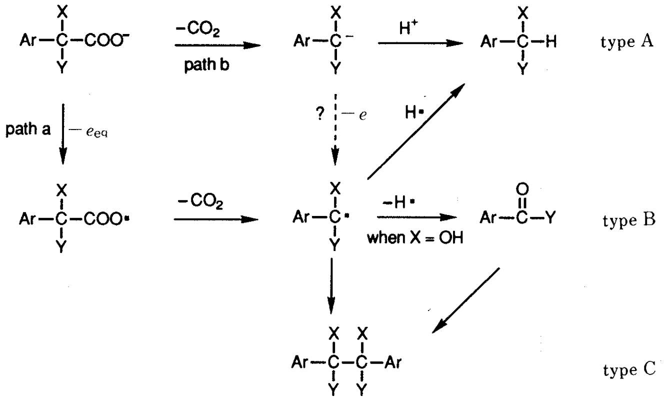

Chart 2

down, giving rise to carbon dioxide and benzyl radical (path a),[1] and the other is direct breakdown of the excited carboxylate ion to the benzyl anion (path b).[3] Although no evidence for the mechanism was available from our results, we tentatively assume that both mechanisms may be operating, as shown in Chart 2, depending on the substrates and reaction conditions.

Beside the above simple decarboxylation reaction, two other side reactions, oxidative decarboxylation (type **B** reaction) and decarboxylative dimerization (type **C** reaction) were observed. Type **B** reaction is evident for the compounds bearing a hydroxy group at the benzylic position and appears to increase when >290 nm light is used (entries 23 and 27). The formation of fluorenone from 9-fluorenecarboxylic acid (entry 10), that formally falls into the type **B** reaction category, suggests the possible participation of aerial oxygen,[9] which was completely inhibited by addition of sodium borohydride to the reaction medium (entry 11).

For the formation of benzopinacol from benzilic acid (entries 24 and 26) (type **C** reaction), we can exclude the possibility of intermediary formation of benzophenone (type **B** reaction), since it is well known that irradiation of benzophenone gives benzopinacol with high quantum yield.[10] Addition of sodium borohydride to the medium markedly, though not completely, suppressed the formation of benzopinacol (entry 25).

Formation of 4,4′-dinitrobibenzyl from 4-nitrophenylacetic acid (entry 28) may also be classified into the type C reaction category. Formation of this compound was not affected by addition of sodium borohydride (entry 29). However, we wonder if it was really produced by a pure photochemical process, because the yield of 4,4′-dinitrobibenzyl was high only when NaOH was used as the medium, and it has been reported that the action of a strong base on 4-nitrotoluene produces 4,4′-dinitrobibenzyl.[11]

In conclusion, the direct photodecarboxylation of arylacetic acids in ammonium hydroxide solution with 254 nm light can be a useful synthetic method in the case of secondary or tertiary carboxyls. In particular, quantitative removal of a carboxy group from the lactam acids **3** and **4**, potential intermediates to various alkaloids, illustrates the utility of this method, when the substrate is appropriately designed. Photodecarboxylation[8] of the allylacetic acid **12** to **13** (entry 21) should also fall into this reaction category.

Experimental

Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. Infrared (IR) spectra were taken in KBr disks, recorded on a Jasco IR-810 spectrophotometer, and are given in cm^{-1}. ^{1}H-Nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a JEOL FX-100 in $CDCl_3$ with tetramethylsilane as an internal standard and are given in δ. High-resolution mass spectra (HRMS) were determined with a JEOL JMS D-300 spectrometer.

General Procedure for Photodecarboxylation of Arylacetic Acids A stirred solution of carboxylic acid (0.5—5 mmol) in 3 N NH_4OH (15—150 ml) was irradiated with a 100 W high-pressure mercury lamp (Riko-Kagaku Sangyo Co. Ltd., quartzlamp) without a Pyrex filter for 2—5 h at 20 °C. The progress of the reaction and the product ratio were checked by high performance liquid chromatography (HPLC). Isolations of the product and the starting material are described below. Yields are shown in Table I. Identities were confirmed by HPLC, thin layer chromatography (TLC), and spectroscopic comparisons with authentic specimens.

i) For Monocarboxylic Acid: The aqueous solution after the reaction was extracted with ether or an appropriate solvent. Concentration of the extract gave the decarboxylated product, which was purified by passing it through a short silica gel column. Acidification of the aqueous solution with 10% HCl, followed by extraction with $CHCl_3$ recovered the starting material.

ii) For Dicarboxylic Acid: The reaction mixture was evaporated to dryness *in vacuo*, and the residue was neutralized with 10% HCl, then esterified with CH_2N_2 in CH_3OH–Et_2O. The resulting product was chromatographed to isolate the decarboxylated product and the starting material as their methyl esters (entries 6, 13, and 14).

Decarboxylation of the Lactam Acid (3) The lactam acid (**3**)[12] (56 mg) in 0.1 N NaOH (10 ml) was irradiated with a 20 W medium-pressure mercury lamp (pencil-type) for 30 min at 5 °C. The precipitate was extracted with $CHCl_3$ to give the *trans*-phenanthridone (**5**) (45 mg, 96%), mp >300 °C. IR (Nujol) cm^{-1}: 3200, 1678, 1622. ^{1}H-NMR (DMSO-d_6) δ: 7.33, 6.88 (each 1H, s, ArH), 6.06 (2H, s, OCH_2O), 5.74 (2H, br s, olefinic H). MS *m/z*: 243 (M^+), 189 ($M^+ - 54$, base peak). HRMS *m/z*: Calcd for $C_{14}H_{13}NO_3$: 243.0895. Found: 243.0892.

Decarboxylation of the Dihydro-lactam Acid (4) The dihydro-lactam acid (**4**)[13] (60 mg) in 0.1 N NaOH (10 ml) was irradiated as above for 15 min. The reaction mixture was neutralized with 10% HCl, and extracted with $CHCl_3$–CH_3OH to give the decarboxylated product, which on crystallization from CH_3OH–$CHCl_3$, gave the *trans*-phenanthridone (**6**)[14] (49 mg, 97%), as colorless prisms, mp 302—305 °C. IR (Nujol) cm^{-1}: 3180, 1675, 1618. ^{1}H-NMR (DMSO-d_6–$CDCl_3$) δ: 7.35, 6.83 (each 1H, s, ArH), 6.05 (2H, s, OCH_2O). MS *m/z*: 245 (M^+, base peak). HRMS *m/z*: Calcd for $C_{14}H_{15}NO_3$: 245.1051. Found: 245.1051.

Decarboxylation of Cushman's Lactam (*trans*-7) Cushman's lactam (*trans*-**7**)[7] (112 mg) in 5% NH_4OH (150 ml) was irradiated with a 100 W high-pressure mercury lamp for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was extracted with $CHCl_3$ to give the decarboxylated product **10** (67 mg, 71%), mp 117—118 °C (lit. mp 118—119 °C).[7a] IR: 1645, 1605. ^{1}H-NMR δ: 8.19—8.09 (1H, m, ArH), 7.43—6.94 (8H, m, ArH), 4.76 (1H, dd, $J=7$, 3 Hz, H-3), 3.67 (1H, dd, $J=16$, 7 Hz, H-4), 3.10 (3H, s, NCH_3), 3.02 (1H, dd, $J=16$, 3 Hz, H-4).

Decarboxylation of Cushman's Lactam (*cis*-8) Cushman's lactam (*cis*-**8**) (112 mg, 0.4 mmol) in 5% NH_4OH was irradiated and worked up as above to give the decarboxylated product **10** (17 mg, 18%), which was identical with compound **10** obtained above.

The Lactam (9) Preparation of **9** was done by Cushman's method.[7] A mixture of α-methylhomophthalic anhydride[15] (1.76 g) and *N*-benzylidenemethylamine (1.31 g) in benzene (20 ml) was stirred for 3 h at room temperature to give the lactam **9** (2.74 g, 93%), as colorless prisms, mp 255 °C (dec). IR: 3425, 1720, 1630. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ: 8.1 (1H, m, ArH), 7.5—6.8 (8H, m, ArH), 5.02 (1H, s, H-3), 3.03 (3H, s, NCH_3), 1.41 (3H, s, C_4-Me). HRMS *m/z*: Calcd for $C_{18}H_{17}NO_3$: 295.1209. Found: 295.1212.

Decarboxylation of the Lactam (9) The lactam **9** (103 mg) in 5% NH_4OH (150 ml) was irradiated as above for 2 h. After concentration of the reaction mixture under reduced pressure, the residue was extracted with $CHCl_3$ and the product was purified by silica gel chromatography (AcOEt : hexane = 2 : 1) to give the decarboxylated product **11** (41 mg, 47%), mp 130—135 °C. IR: 1650, 1605. ^{1}H-NMR δ: 8.23—8.13 (1H, m, ArH), 7.47—6.82 (8H, m, ArH), 4.45 (1H, d, $J=7$ Hz, H-3), 3.80 (1H, quintet like, $J=7$ Hz, H-4), 3.07 (3H, s, NCH_3), 1.19 (3H, d, $J=7$ Hz, CH_3). HRMS *m/z*: Calcd for $C_{17}H_{17}NO$: 251.1310. Found: 251.1325.

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13) The dihydro-lactam acid (**4**) was prepared as follows. The corresponding methyl ester[12] was hydrogenated to the dihydro derivative, mp 289—291 °C, and then hydrolyzed with 40% KOH–MeOH to the acid **4**, 263—265 °C.
14) We thank Profs. I. Ninomiya and T. Naito, Kobe Women's University, for the authentic sample of **6**.
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