

PREPARATION OF CHLORO- α -TRUXILLIC ACIDS VIA 3-METHYL-4-NITRO-5-STYRYL-ISOXAZOLE PHOTODIMERS

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Abstract — Chloro- α -truxillic acids (3b-e) were prepared by oxidation of the photodimers (2b-e) of 3-methyl-4-nitro-5-chlorostyrylisoxazoles (1b-e).

INTRODUCTION

The photodimerisation of solid organic compounds has been studied thoroughly in order to correlate the photoproducts with the crystal structures of the reagents in the solid state.¹ Many compounds give the expected photoproducts according to the topochemical postulate,² whereas in a few cases the "wrong" photoproducts were obtained.^{3,4}

Apart from the crystal structure correlations between reagents and photoproducts, solid state photoreactivity is an important tool for preparative purposes because in many cases the photoreactions led to one photoproduct with high yield. However, this feature is a strong limitation when the interest is for other photoisomers which then become inaccessible by this route.

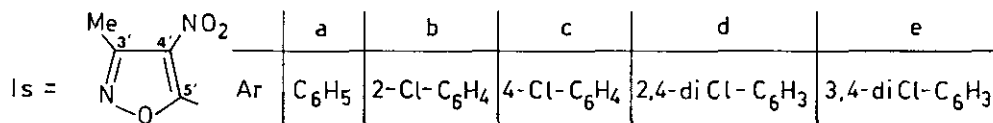
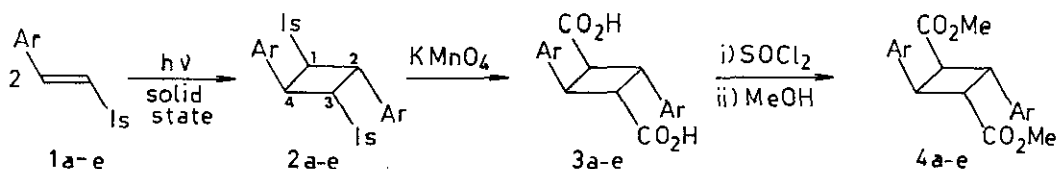
In light of this it is noteworthy to remember that all the *trans*-chlorocinnamic acids have β -structures⁵ and they photoreact in the solid state to give β -truxinic acids; therefore chloro- α -truxillic acids were not obtained directly by this method, even if some derivatives were prepared. In fact, the dimethyl 4,4'-dichloro- α -truxillate was prepared *via* irradiation of solid 4-chlorocinnamide followed by methanolysis.⁶ Other products as 2,2',4,4'-tetrachloro- α -truxillic

and 3,3',4,4'-tetrachloro- α -truxillic acids were synthesized by ozonolysis of dimers obtained from irradiated solutions of *trans*-1-(2,4-dichlorophenyl)-2-(2-thienyl)ethene and *trans*-1-(3,4-dichlorophenyl)-2-(thienyl)ethene respectively.⁷ In addition the irradiation of octadecyl-4-chlorocinnamate led to dioctadecyl-4,4'-dichloro- α -truxillate.⁸

In previous research it was found that 3-methyl-4-nitro-5-styrylisoxazole gave the centrosymmetric dimer upon irradiation in the solid state,⁹ whereas in solution the photoreaction led to the same dimer together with δ -truxinic and ϵ -truxillic type dimers.¹⁰ Alkaline hydrolysis of the isoxazole rings of these dimers led to α -truxillic, ϵ -truxillic, δ -truxinic¹⁰ and γ -truxillic¹¹ acids. As an extension of the above results we now report a study on the photobehaviour of some chloro-substituted styrylisoxazoles which gave the centrosymmetric dimers upon irradiation in the solid state. The photoproducts were then oxidized to the corresponding chloro- α -truxillic acids. As many diarylcyclobutane derivatives may be converted into α -truxillic acids, this new route could also be of some importance for the preparation of reference compounds.

RESULTS AND DISCUSSION

The 3-methyl-4-nitro-5-styrylisoxazoles (1a-e), prepared according to the literature,^{12,13} gave the corresponding photodimers (2a-e) upon irradiation as reported in the following scheme:



As in the case of solid state photoreactivity of 3-methyl-4-nitro-5-styrylisoxazole,^{9,10} in the above photoreactions only one dimer was obtained as the main product. The blue-shifts of UV spectra of photoproducts **2b-e** (Table 1) with respect to those of monomers **1b-e** are in agreement for cyclobutane ring photoformation through the ethylenic bonds of two molecules of compounds **1b-e**. The configuration of the photodimers **2b-e** was elucidated by convergent results obtained from spectroscopic analysis (MS, NMR) and chemical reactions. Mass

spectra show peaks attributable to the molecular ions of dimers of 1b-e thus confirming the dimeric structure of photoproducts 2b-e. In addition only peaks with m/z corresponding to the $M/2$ fragments $IsCHCHAR^+$ and not to the fragments $ArCHCHAR^+$ were found.

TABLE 1. Photodimers 2a-e by solid state irradiation of styrylisoxazoles 1a-e

compd.	irradiation time, h	yield, %	mp, °C	UV(MeOH) λ_{max}, nm (log ϵ)
2a ^a	1.5	90	201-202	269 (4.06)
2b	0.5	89	234-235(a)	273 (4.06)
2c	4.0	86	214-215(a)	268 (4.04)
2d	0.5	84	205-207(a)	272 (4.05)
2e	1.0	95	231-232(a)	272 (4.05)

^aRecrystallized from ethanol-acetone

These results are in agreement for each of the five truxillic type structures for 2b-e, but no conclusive choice among them was possible by this technique, as previously reported in the case of compound 2a.⁹ However, the *trans* configuration of 1a-d¹³ and 1e, allowed us to rule out the *peri*-, γ -, and *epi*-type structures and to consider only the α - or ϵ -type structures deriving from *trans-trans* (2+2) photocycloadditions. The same considerations may be drawn from the ¹³C-NMR spectra of compounds 2a-e; in fact compound 2a shows only ten signals as expected on the basis of symmetry considerations for α - or ϵ -truxillic structures; thus excluding on an experimental basis dimers from *trans-cis* photocycloadditions. Similar conclusions are obtained also for compounds 2b-e. The assignments based on chemical shifts considerations are reported on Table 2. The distinction between C-3' and C-5' of the isoxazole system was confirmed by the coupled spectra which showed a quartet ($J = 6.8-7.2$ Hz) for the signals at 154.9-155.85 ppm due to the C-3' carbon atoms. Additional information to solve the structural problem was obtained from ¹H-NMR of compounds 2b-e. In fact the data reported in Table 2 showed that the two 3-methyl groups of the isoxazole rings give only one signal for each dimer as expected for α - or ϵ -type structures. The methyl proton chemical shifts were found in the range 2.39-2.47 ppm, which is very close to the value 2.33 ppm for the same groups in compound 2a having α -truxillic type structure.¹⁰ Because it has been reported¹⁰ that the above methyl groups appeared at 2.51 ppm in the photoisomers of 2a having δ -

truxinic or ϵ -truxillic type structures, the above findings, taking into account substituent effects, strongly suggest an α -truxillic type structure also for compounds 2b-e in which the aryl portions facing the alkyl groups are responsible for a shielding effect on the methyl groups which appeared at higher fields with reference to compounds where such effect is not operating. A similar "facing effect" was already evidenced^{10,6} and used⁶ to distinguish between dimethyl α -truxillates and dimethyl β -truxinates. In order to confirm the above assignments and taking into account the possibility of obtaining chloro- α -truxillic acids, we achieved these results by oxidizing dimers 2b-e with potassium permanganate. The same reaction was extended also to compound 2a.

TABLE 2. ^1H - and ^{13}C -NMR data of photodimers 2a-e^a

compd	^1H -NMR δ			^{13}C -NMR δ
	3'-CH ₃	Ring protons ^b	Aromatic protons	
2a	2.33	5.18	7.21	43.0(C-1), 41.5(C-2), 155.5(C-3'), 129.8(C-4'), 171.9(C-5'), 11.1(3'-CH ₃), 136.2s, 128.65d, 127.8d, 127.0d
2b	2.39	5.46	7.15-7.65	42.2(C-1), 38.4(C-2), 155.45(C-3'), 129.85(C-4'), 170.7(C-5'), 11.4(3'-CH ₃), 133.7s, 133.5s, 129.7d, 129.3d, 127.3d
2c	2.39	5.14	7.15-7.30	42.6(C-1), 41.6(C-2), 154.9(C-3'), 130.1(C-4'), 171.2(C-5'), 11.2(3'-CH ₃), 134.6s, 134.0s, 129.0d, 128.4d
2d	2.47	5.45	7.30-7.60	41.9(C-1), 38.2(C-2), 155.6(C-3'), 130.4(C-4'), 170.1(C-5'), 11.4(3'-CH ₃), 134.7s, 134.4s, 132.0s, 129.6d, 128.2d, 127.7d
2e	2.47	5.12	7.00-7.50	42.45(C-1), 41.35(C-2), 155.85(C-3'), 130.3(C-4'), 170.5(C-5'), 11.2(3'-CH ₃), 136.1s, 133.1s, 132.4s, 130.8d, 129.1d, 126.3d

^a Spectra recorded in CDCl₃ with Me₄Si as internal standard

^b The values of cyclobutane ring protons refer to mid-points of AA'BB' systems

Even if the 3-methyl-4-nitroisoxazol-5-yl group may be hydrolysed to give the carboxylic group,¹³ we decided to use the oxidation method to obtain the corresponding α -truxillic acids because the above alkaline hydrolysis of 2a, followed by acidification, led to α -truxillic¹⁰ and γ -truxillic¹¹ acids, whereas the

oxidation method allowed us to prepare α -truxillic and chloro- α -truxillic acids only.

Table 3. Yields and melting points of compounds 3a-e and 4a-e

compd	yield, %	mp ($^{\circ}$ C)	lit. mp ($^{\circ}$ C)	
3a	82	274-75 dec.	15	274-78 dec.
4a	--	174	16	174
3b	87	279-80 dec.	-	-
4b	--	102-03	-	-
3c	87	309-10 dec.	14	278-80
4c	--	163-64	6	162-63
3d	86	316-17 dec.	7	>290
4d	--	175-76	7	175-76
3e	62	280-82 dec.	-	-
4e	--	188-90	7	191-3

However, the melting points of chloro- α -truxillic acids obtained by oxidation (Table 3), were not diagnostic for confirming the above structures. In fact 2,2',4,4'-tetrachloro- α -truxillic acid was described as having mp >290 $^{\circ}$ C while that of 3,3',4,4'-tetrachloro- α -truxillic acid was not reported.⁷ 4,4'-Dichloro- α -truxillic acid (mp 278-280 $^{\circ}$ C¹⁴) was obtained from 4,4'-dinitro- α -truxillic acid whose structure was later questioned.⁵ 13 C-NMR spectra taken on the crude acids obtained by oxidation, showed the presence of only one type of truxillic acid. Therefore no isomerisation occurred during the above reaction. Again the number of signals for 3a-e reported in Table 3, were in agreement for α - or ϵ -type structures. It can also be noted that the chemical shift values of carboxylic carbons (Table 4) are very close to those of the C-5' in the 3-methyl-4-nitroisoxazol-5-yl groups. Comparison of 13 C-NMR spectra of compounds 2a-e with those of 3a-e allowed us to attribute the signals at lower field (in the region 38.1-46.45 ppm; doublets in off-resonance spectra) to the cyclobutane ring carbons bonded to the carboxylic groups or 3-methyl-4-nitroisoxazol-5-yl groups and aryl moieties, respectively. In particular on going from compounds 2a-e to compounds 3a-e the C-1 and C-3 atoms show a downfield shift, whereas C-2 and C-4 atoms appeared at higher field (2a, 2c, 2e) or remained unaltered. Acids 3a-e were then converted into the corresponding dimethyl esters 4a-e which showed only one signal in the 1 H-NMR spectra (Table 4) for two identical methyl groups in the range 3.28-3.38 ppm. The δ values and the melting points for compounds 4a,¹⁶ 4c,⁶ and 4d-e⁷ are in agreement with those reported in the literature for

esters with the corresponding substituents for which α -truxillic configurations were demonstrated. Similarly 4b showed a signal at 3.34 ppm due to two equivalent methyl groups.

Table 4. ^1H - and ^{13}C -NMR data of compounds 3a-e and 4a-e

compd	^1H -NMR δ^a			^{13}C -NMR δ^a			
	O-CH ₃	Ring Protons ^b	Aromatics	C-1	C-2	C=O	Aromatics
3a	-	4.08	7.20-7.50	46.45	41.35	173.2	139.7s, 128.4d, 127.8d, 126.9d
4a	3.28	4.25	7.32				
3b	-	4.30	7.20-7.70	44.4	38.4	172.4	136.3s, 133.6s, 129.1d, 128.5d, 128.0d, 127.2d
4b	3.34	4.50	7.10-7.60				
3c	-	4.07	7.35-7.55	45.95	40.3	172.6	138.3s, 131.35s, 129.5d, 128.0d
4c	3.37	4.16	7.00-7.60				
3d	-	4.30	7.40-7.90	44.3	38.1	172.2	135.5s, 134.7s, 132.3s, 129.5d, 128.6d, 127.3d
4d	3.38	4.38	7.30-7.50				
3e	-	4.12	7.25-7.80	45.75	40.1	172.4	140.5s, 130.9s, 130.2d, 129.8, 129.5s, 128.1d
4e	3.38	4.08	7.00-7.45				

^aSpectra recorded in DMSO-d₆ for compounds 3a-e and in CDCl₃ for 4a-e, with Me₄Si as internal standard. ^bThe values of cyclobutane ring protons refer to mid-points of AA'BB' systems

Therefore from the above results combined with the mass spectral data and taking into consideration only the dimer structures deriving from *trans-trans* monomer cycloadditions, while we confirm that compound 2a is *trans*-1,3-di-(3-methyl-4-nitroisoxazol-5-yl)-*trans*-2, *cis*-4-diphenylcyclobutane (α -truxillic type structure), we now assign the same configuration also to compounds 2b-e.

The high yields of the photodimers 2b-e and the easy preparation of the requisite 1b-e renders the above described route particularly suitable for the preparation of di- and tetrachloro- α -truxillic acids.

EXPERIMENTAL

Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 283 apparatus in KBr pellets. Proton and Carbon-13 NMR spectra were recorded on a Perkin-Elmer R32 and on a Varian FT 80-A spectrometers, respectively. All chemical shifts were reported in ppm downfield from tetramethylsilane as internal standard. Mass spectra of 2a-e taken by direct inlet (D.E.I.) of samples in a VG 70-70 EQ spectrometer showed, among others, peaks corresponding to M and M/2. UV spectra were registered (methanol) with a Cary-14 spectrophotometer. Thin-layer chromatography (TLC) was carried out with Merck silica gel 60 F₂₅₄ precoated plates (benzene as eluent) and mineral light lamp (model UV SL-58) was used for revealing spots. Dimers have lower R_f with respect to monomers. Compounds 1e, 2b-e, 3b-e, and 4b gave satisfactory analytical results.

General procedure for the preparation of compounds 1a-e

Compounds 1a-e were prepared according to the literature.^{12,13} TLC of mother liquors showed also minor products as spots with lower R_f than those of 1a-e. The new compound 1e (yield 80%) crystallized from ethanol-chloroform, is a yellow solid: mp 226-227°C; IR: 1630, 1570, 1375, 980, and 820 cm⁻¹; UV λ_{\max} (log ϵ): 248 (4.19), 262 (4.10), 267 (4.10), 350 (4.32); UV spectral data for 1a-d are tabulated in ref.13. ¹H-NMR (CDCl₃) δ : 2.61 (s, 3H, CH₃), 7.26-7.80 (m, 5H, ethylenic and aromatic). The configuration of 1e was not attributable through the above NMR data; however the trans configuration was assigned on the basis of similarity of the UV spectrum with that of 1d.¹³ Compound 1d was found to have mp 169-170°C, that is higher than that previously reported.¹³

Solid state irradiation of compounds 1a-e

Solid 1a-e, deposited between two glasses by evaporation of saturated benzene solutions, were irradiated with a 250 W (G.E.C.) mercury lamp as reported in ref.10 for 1a; yields, irradiation times and crystallisation solvents of compounds 2a-e are reported in Table 1.

General procedure for oxidation of compounds 2a-e

Potassium permanganate (30 mmoles) dissolved in 350 ml of acetone-water (2.5: 1 v/v), was added dropwise under stirring at room temperature to the dimers (5 mmoles) dissolved in acetone (200 ml). The mixture was stirred for 2-3 h and then the excess of potassium permanganate and manganese dioxide was reduced by

treatment with sodium sulphite and hydrochloric acid. Removal of acetone left the expected acids 3a-e which were filtered off and crystallized from ethanol.

Preparation of compounds 4a-e

The acids 3a-e (300 mg) were refluxed with thionyl chloride (4 ml) for 1h. Evaporation of the excess of thionyl chloride under reduced pressure left the solid diacyl dichlorides which were refluxed with methanol (10 ml) for 15 min. Concentration of the methanolic solutions afforded the expected diesters 4a-e which were crystallized from methanol.

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