IONIC HYDROGENATION OF 1-PHTHALOYL-2-p-SUBSTITUTED BENZOYLCYCLOPROPANES

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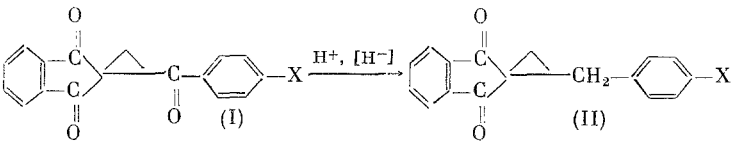
In a study of the ionic hydrogenation of 1-phthaloyl-2-p-alkylbenzoylcyclopropanes (where X = H, alkyl), we have established [1] the selective reduction of the benzoyl group to benzyl, with the preservation of the three-membered ring and the phthaloyl segment:



X = F (a), Cl (b), Br (c), CH_3O (d).

The present work is a study of the effect of the polarity of the substituent at the p-position of the benzoyl group on this reaction. The p-fluoro-, chloro-, bromo-, and methoxy-substituted benzoylcyclopropanes (Ia-d) were tested under the following conditions: substrate:CF_3COOH:Et_3SiH ratio = 1:8:10, 50°C, reaction time 2-24 h. Regardless of the substituent in Ia-d, and like the series (I) in which X = H or alkyl, only the benzoyl group is reduced, to form compounds IIa-d. The constants and spectral properties of Ia-d and IIa-d are presented in Tables 1 and 2. The structure of IIa-d is confirmed by the following: the absence of the 1680 cm^{-1} absorption band in the IR spectrum, and of the λ = 260 nm band in the UV spectrum, which are typical of the benzoyl group, and the appearance in the PMR spectrum of the benzyl proton signals with δ 2.8-3.08 ppm, while the remaining signals are retained unchanged.

For Ia-d the reaction rate depends significantly on substituent polarity; the yield after 2 h was <1% for IIa (X = F), 15% for IIb (X = Cl), and 57% for IIc (X = Br) and IId (X = MeO). Thus, as was to be expected [1], the reaction rate increases in going from an electron-accepting to an electron-donating substituent.

It is noteworthy that in contrast to other carbonyl and cyclopropane compounds, the phthaloyl and cyclopropane groups in compounds I are inert in ionic hydrogenation [2]. Thus, 2-alkyl- and 2,2-dialkyl-1,3-indandiones are reduced by ionic hydrogenation to the respective indanes [2]; this is in good agreement with the strong electron-donor effect of the cyclopropyl group, which ought to promote the hydrogenation of all carbonyl groups attached to it. In this connection the stability of the indandiol CO groups in compound I is unusual, and is due in our opinion to the following structural features: In I, the most basic segment is the benzoyl CO, because the phthaloyl CO groups are less basic due to their mutual interaction, and the basicity of the three-membered ring is weakened by the three strong electron-acceptor

TABLE 1. Physical Chemical Properties of 1-Phthaloyl-2-p-substituted Benzoylcyclopropanes

Compound	mp, °C	IR spectrum (ν, cm^{-1})	UV spectrum (λ, nm (ε))	PMR spectrum (δ, ppm)
(Ia)	183	1680, 1704, 1754	232(81000) 258(34500)	2,08(1H), 2,52(1H), 3,62(1H), 6,6–8(8H)
(Ib)	193–194	1680, 1705, 1744	232(49700) 260(25000)	2,0(1H), 2,41(1H), 3,61(1H), 6,6–7,8(8H)
(Ic)	201–202	1680, 1705, 1750	232(48000) 265(24800)	2,0(1H), 2,45(1H), 3,58(1H), 7,0–8,0(8H)
(Id)	152	1680, 1704, 1745	233(72224) 285(13704)	3,83(4H), 2,58 (1H), 2,0(1H), 6,8–8,0(8H)

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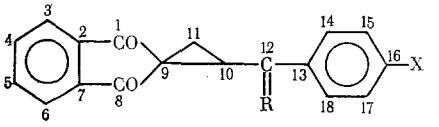
TABLE 2. Physical Chemical and Spectral Properties of 1-Phthaloyl-2-p-substituted Benzylcyclopropanes

Compound	Yield, % (time, h)	mp, °C	IR spectrum (ν, cm^{-1})	UV spectrum (λ, nm (ε))	PMR spectrum (δ, ppm)
(IIa)	57(24)	72	1704 1745	229(50200)	1,63(2H), 2,41(1H), 3,08(2H), 6,7–8,0(8H)
(IIb)	78(6)	87–88	1705 1740	230(51600)	1,91(2H), 2,38(1H), 2,81(2H), 6,5–7,8(8H)
(IIc)	62(6)	108	1705 1740	229(51700)	1,9(2H), 2,4(1H) 3,05(2H), 6,9–8,0(8H)
(IId)	57(2)	87	1704 1750	229(83621)	2,0(2H), 2,5(1H) 3,1(2H), 3,83(3H) 6,9–8,1 (8H)

TABLE 3. Chemical Shifts of C Atoms of Compounds I and II in $CDCl_3$ and CF_3COOH



X	R	^{13}C NMR spectrum (δ, ppm)										
		C^1, C^6	C^2, C^7	C^3, C^6	C^4, C^5	C^9	C^{10}	C^{11}	C^{12}	C^{13}	$C^{14, 15}$ $C^{17, 18}$	C^{16}
In $CDCl_3$												
CH_3	O	195,1 197,4	142,0 143,3	135,6 135,9	123,4 123,6	43,1	38,3	22,1	190,6	134,7	129,0 130,0	145,0
C_2H_5	O	195,2 197,6	142,0 143,3	135,6 136,0	123,4 123,6	41,4	38,3	21,5	190,6	134,9	128,8 129,1	151,2
n-C_3H_7	O	195,2 197,7	142,0 143,2	135,6 136,0	123,4 123,6	41,4	38,6	21,5	190,6	134,8	128,0 129,4	149,7
CH_3	H_2	198,9 199,4	140,5 141,6	135,2 135,3	122,7 122,9	40,5	39,1	26,6	32,6	137,5	128,7 129,8	136,2
C_2H_5	H_2	199,0 199,3	142,1 143,2	135,2	122,8 122,9	40,5	38,8	26,6	32,7	137,8	128,6 128,8	142,7
n-C_3H_7	H_2	198,7 199,1	142,1 143,2	135,1	122,7 122,9	40,5	38,8	26,5	32,7	138,0	128,7 129,1	141,0
In CF_3COOH												
H	O	197,4 199,6	142,0 143,1	136,2 136,4	124,5	42,7	39,6	23,0	201,1	137,8	129,8 129,9	137,8
CH_3	O	197,1 199,8	142,1 143,2	137,5 137,8	124,5	42,7	39,7	23,0	201,2	133,9	130,0 130,6	148,7
C_2H_5	O	197,4 200,1	142,1 143,3	137,7 137,9	122,6 124,6	42,8	39,9	23,1	201,5	134,0	129,5 130,2	155,2
n-C_3H_7	O	196,8 199,4	142,1 143,2	137,4 137,6	124,4	42,7	39,6	22,8	200,8	134,2	130,0	153,1
n-C_4H_9	O	196,8 199,4	142,0 143,2	137,3 137,6	124,4	42,6	39,6	22,9	200,9	134,1	129,9 130,0	153,4
n-C_5H_{11}	O	197,2 199,9	142,1 143,2	137,6 137,8	124,5	42,8	39,9	22,8	201,3	134,0	130,0	153,8
C_2H_5	H_2	203,9 204,6	142,9 144,0	136,9 137,1	123,8 124,0	42,5	43,4	28,6	33,1	–	128,8 128,9	141,7

groups. Therefore, the benzoyl segment is hydrogenated to benzyl. In the benzyl derivatives (II), the three-membered ring is attached to only two electron-acceptor substituents; this increases its basicity in comparison with I, and leads to protonation. The protonated cyclopropane segment reacts with the phthaloyl carbonyls, and the positive charge is delocalized in such a way that the fraction thereof on the CO C atoms and the three-membered ring is insufficient for the addition of a hydride ion.

To verify this proposal concerning ionic hydrogenation, we used a number of 1,3-phthaloyl-2-alkylcyclopropanes, III, in which the basicity of the three-membered ring is reduced by the presence of four attached CO groups. It might be expected that the cyclopropyl group would not protonate at all in these compounds, so that there would be no CO stabilization. That in turn should cause the phthaloyl CO groups to be hydrogenated. Actually under the conditions of ionic hydrogenation, as we have shown, both CO groups of III are reduced [3].

To test the validity of the proposed sequence in the ionic hydrogenation of I, we studied the ^{13}C NMR spectra of compounds I-III in $CDCl_3$ and CF_3COOH. Signals were assigned on the basis of the monoresonance spectra given by the ^{13}C chemical shifts of 1,3-indandione and p-alkylacetophenones [4-6]. Table 3 presents the results. In going from $CDCl_3$ to CF_3COOH the shielding of the carbonyl carbon of the p-alkylbenzoyl segment of I decreases by 11 ppm, whereas for the carbons of the phthaloyl CO groups and the three-membered ring this change is no more than 2 ppm. This agrees with the original protonation of the benzoyl CO group. After the reduction of benzoyl to benzyl, the signals of the CO carbons and the three-membered ring of II in CF_3COOH are shifted 5 ppm downfield as compared with the same signals in $CDCl_3$. Comparison of the spectra of III in the two solvents show that the carbonyl carbon signals in CF_3COOH are shifted 5 ppm downfield, whereas the chemical shifts of the three-membered-ring C atoms do not change in going from $CDCl_3$ to CF_3COOH. This indicates that in III, in contrast to II, the CO groups are protonated, but the cyclopropyl group is not.

Thus, the ^{13}C NMR spectra of these compounds agree with the proposed sequence of protonation of 1-phthaloyl-2-p-substituted benzoylcyclopropanes under conditions of ionic hydrogenation, and with the reason proposed for the stability of the phthaloyl CO groups and the three-membered ring toward triethylsilane and trifluoroacetic acid.

EXPERIMENTAL

IR spectra were obtained on a UR-20 apparatus in KBr. Melting points were determined in a Kofler apparatus. PMR spectra were obtained on a Varian DA-601 L apparatus relative to HMDS in $CDCl_3$. UV spectra were obtained in a Specord UV-VIS apparatus in C_2H_5OH. ^{13}C NMR spectra were obtained in a Bruker WP-80 pulse Fourier spectrometer at 20.116 MHz, with wide-band isolation from protons for 30% solutions in CF_3COOH and $CDCl_3$. The internal standard was cyclohexane (δ 27.5 ppm). Chemical shifts were converted to the δ scale.

Compounds Ia-d were synthesized by the method of [7]. During the synthesis 1,3-dibromo-1-phthaloyl-3-p-methoxybenzoylpropane was obtained by the following modified procedure:

1,3-Dibromo-1-phthaloyl-3-p-methoxybenzoylpropane. A sample of 1.5 g of 1-phthaloyl-3-p-methoxybenzoylpropane was dissolved with heating in a small amount of CCl_4. Then 0.2 ml of Br_2 was added to the solution with heating and several grains of benzoyl peroxide were added while the reaction mixture was irradiated with a quartz lamp. After the solution decolorized the reaction mixture was cooled, the solvent was distilled off, and the residue was crystallized from CH_3COOH. The yield of dibromide was 72%, mp 145°C.

Ionic Hydrogenation of 1-Phthaloyl-2-p-Substituted Benzoylcyclopropanes Ia-d. The reaction was carried out by the procedure of [8] at a substrate:Et_3SiH:CF_3COOH molar ratio of 1:8:10 (2-24 h, 50°C).

CONCLUSIONS

1. 1-Phthaloyl-2-p-X-substituted benzoylcyclopropanes (where X = F, Cl, Br, OCH_3), regardless of the substituent, are selectively reduced by ionic hydrogenation to 1-phthaloyl-2-p-substituted benzylcyclopropanes. As the electronegativity of the substituent decreases, the reduction rate increases.

2. The stability of the phthaloyl CO groups and the three-membered ring in this reaction is attributed to their mutual interaction; this agrees well with experimental data and with the ^{13}C NMR spectra of the compounds.

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BIS(OXAZOLYL)ALKYLAMINES IN DIENE SYNTHESIS

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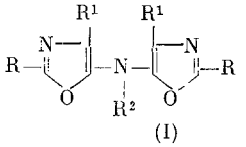
The condensation of 2-R-4-R^1-5-R_2^2N-oxazoles with maleimide in benzene, ether, or acetic acid can proceed by two distinct routes, the competition between which is determined by the nature of the substituents R, R^1, and R^2: 1) 1,4-cycloaddition leading to the formation of endoxopiperidines and β-aminopyridines, and 2) 1,3-addition, giving substituted β-pyrrolines [1]. The specific effect of the 5-amino group on the reactivity of the oxazole ring disappears in the case of the 5-Ph_2N derivatives.

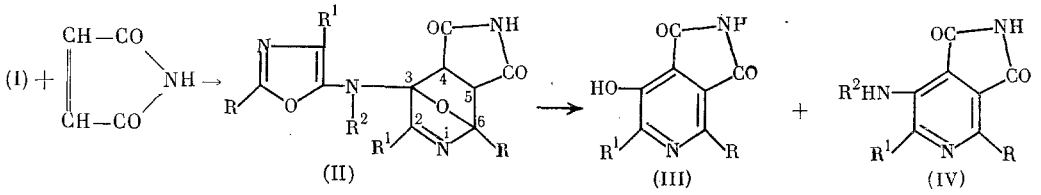
We here report a study of the reaction of maleimide with bis-2,2'-R_2-4,4'-R_2^1(H)-5,5'-oxazolylalkylamines (Ia-e), which are structurally analogous to 5-R_2N-oxazoles



(I)

R, R^1, R^2 = Me, Me, Me (Ia); Me, Me, *n*-Pr (Ib); Me, Et, *n*-Pr (Ic); Me, H, Me (Id); Me, H, Et (Ie).

It has been shown experimentally (Table 1) that (I) react under all conditions solely as conjugated azadienes to form endoxopiperidines (II) or pyridines (III) and (IV), which are derived from (II)



(II) (III) (IV)

R, R^1, R^3=Me, Me, Me (IIa); Me, Me, Pr (IIb); Me, Et, Pr (IIc); R, R^1=Me, Me (IIIa); Me, Et (IIIb); Me, H (IIIc); R, R^1, R^3=Me, Me, Me (IVa); Me, Me, Pr (IVb); Me, Et, Pr (IVc); Me, H, Me (IVd); Me, H, Et (IVe).

In aprotic solvents, the bis(oxazolyl)amines (Ia-c) react with maleimide to give exclusively the (oxazolylaklylamino)endoxopiperidines (II), changes in the solvent or temperature having no effect on the mode of reactivity of (I), nor on the yields of the 1,4-addition product (in contrast to 5-Alk_2N-oxazoles and 5-PhAlkN-oxazoles [1]). In their physicochemical properties, the piperidines (II) are reminiscent of the corresponding adducts of 5-Ph_2N-oxazoles, being relatively stable crystalline compounds which are of low solubility in ether, water, and benzene. The course of the reaction is independent of the molar ratio of (I): maleimide (1:1-3). The inertness of the second oxazole ring is evidently due to the complexity of the spatial geometry of (I), which following addition of one mole of the imide increase to such an extent that the second oxazole moiety becomes inaccessible. This steric hindrance is

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