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OXIDATION OF THE 2'-NHR ANALOGUES OF 2'-OR-CHALCONES; CONVERSION OF 2'-NHR-CHALCONE EPOXIDES

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Abstract: Synthesis of 2'-NHR-chalcone epoxides and their reaction with acidic reagents are discussed.

The sequence of the oxidation of 2'-OR-chalcones with alkaline hydrogen peroxide is well-known and well-documented[1]. In case when R=H or acetyl, the Algar-Flynn-Oyamada (AFO) reaction gives - depending on the remaining substituents - 3-hydroxyflavanones, 3-hydroxyflavones and/or aurones supposedly without the intermediacy of chalcone epoxides. If the protecting groups (R) are methyl, benzyl, p-NO_2-benzyl, methoxymethyl or tosyl

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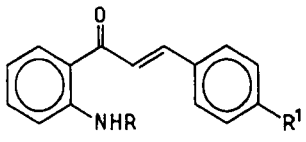
the corresponding chalcone epoxides can be prepared under the conditions of the AFO reaction. The 2'-OH and 2'-OAc chalcone epoxides are rather unstable compounds to be prepared either by peracid oxidation or from the respective chalcone dibromides. A great number of 2'-OR--chalcone epoxides have been synthesized and these proved to be valuable intermediates in flavonoid chemistry[1]. Namely, depending on the methods (reaction conditions) used for the removal of the protecting groups, and on the nature of the additional substituents various types of flavonoid derivatives with different state of oxidation can be obtained from the above epoxides.

A growing interest for the synthesis and conversion[2-7] of the analogous 2'-NHR-chalcones has been stimulated by the possibility of the transformation of such compounds into the otherwise hardly available 2-aryl-4-quinolones. The present paper deals with the oxidation of 2'-NHR-chalcones under the conditions of the AFO reaction, as well as with a few of the eventual transformations of the obtained products.

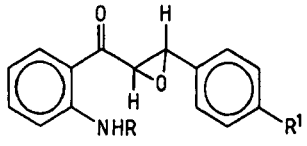
Oxidation of 2'-NHR-chalcones

For the oxidation experiments the trans-chalcones 1a-h were prepared by the condensation of the corresponding 2'-NHR-acetophenones and aromatic aldehydes under alkaline conditions. Chalcone 1h was obtained upon treatment of 1b with tosyl chloride in pyridine.

The preliminary oxidation experiments brought surprising results[4]: instead of the expected ring-closure, observed with the respective 2'-OH-chalcones, the reaction provided the epoxide 2a. The reaction of the chalcones 1a-h under the AFO conditions was examined in detail, and the stable epoxides 2a-f were obtained in excellent yield in each case.

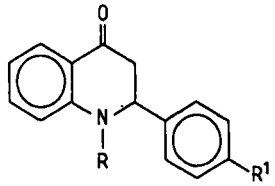


1a-h



2a-f

	R	R^1
a	H	H
b	H	OCH_3
c	$C_6H_5CH_2$	H
d	$C_6H_5CH_2$	OCH_3
e	CH_3CO	H
f	CH_3CO	OCH_3
g	$pCH_3C_6H_4SO_2$	H
h	$pCH_3C_6H_4SO_2$	OCH_3

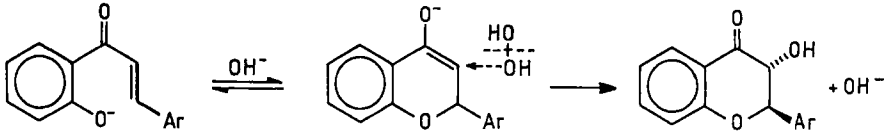


3g,h

Similar results were published by Irish authors in 1990 describing the isolation of 2a,2b,2e and the 2'-NH-$SO_2C_6H_5$ chalcone epoxides[5,6]. At the same time, the oxidation of chalcones 1g,h did not give the epoxides 2g,h only

1,2,3,4-tetrahydro-4-quinolones 3g,h were produced via cyclization. Compound 3g was prepared earlier by Diesbach et al[8] from 1g by using sodium hydroxide for the cyclization. The easy formation of 3g,h is not surprizing since the $pCH_3C_6H_4SO_2NH$ is deprotonated upon the action of the base, and - similarly to the 2'-OH-chalcone ⇌flavanone ring-closure an attack on the N-nucleophile is quite favourable. The results show that this cyclization proceeds faster that the formation of the epoxide. A similar cyclization was observed when the dibromide 1g was treated[7] with ammonia in methanol. At the same time, 1e, the 2'-$-NH_2$-5'-bromo- and the 2'-$NHCH_2C_6H_5$-5'-Br-chalcone dibromides were transformed into the corresponding aziridines.

Since the 3-hydroxy derivative of 3g,h did not produced during the oxidation the Dean's hypothesis[9] for the conversion of 2'-hydroxychalcones in the AFO reaction, as shown below seems to be quite questionable:



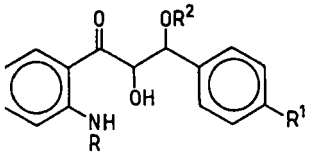
The chalcone epoxides 2a-f are as stable as the analogous 2'-OR epoxides, indicating the low nucle-

ophilicity of the nitrogen atom, and thus cyclization does not occur under the conditions of the AFO reaction.

Conversion of 2'-NHR-chalcone epoxides

Following the removal of the R protecting group of the 2'-OR-chalcone epoxides, primarily with acidic reagents (HCl or H_2SO_4 in methanol, or HCl gas in dry ether), the products are readily transformed in numerous ways. The most important of these are the conversion into α,β-substituted dihydrochalcones and, by cyclization, into 3-hydroxyflavanones. Upon cyclization with Lewis acids (i.e. $BF_3.Et_2O$) the product is either the 3-hydroxyflavanone or the corresponding isoflavone[1].

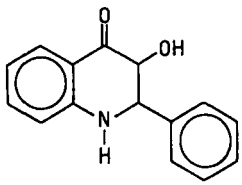
Treatment of the epoxides 2a-c,e with hydrochloric acid in methanol at room temperature resulted in the α-hydroxy-β-methoxydihydrochalcones 4a-c,e in each case. Donnelly et al[5,6] reported similar results: the reaction of 2a with hot sulfuric acid in ethanol gave 5a. When 2a was refluxed in acetic acid cyclization into cis-1,2,3,4-tetrahydro-3-hydroxy-2-phenyl-4-quinolone (6) was observed[5]. Starting from 2b only the α-hydroxy-β-acetoxydihydrochalcone 7b was obtained[6]. Under similar conditions 2'-benzyloxychalcone epoxide did not react with acetic acid, and the 4-methoxy derivative gave also the α-hydroxy-β-acetoxy derivative via opening of the oxirane ring[10].



4a-c, e ($R^2 = CH_3$)

5a ($R^2 = C_2H_5$)

7b ($R^2 = COCH_3$)



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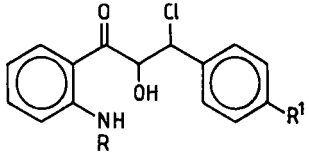

8a-f

On treatment of 2a-f with ether saturated with dry HCl only the corresponding threo chlorohydrines 8a-f were obtained independently of the reagent and the reaction time. The threo structure of these derivatives was clearly proved by ^{1}H-NMR spectroscopic data[11]. According to t.l.c. and ^{1}H-NMR examinations the reaction of the epoxides 2a-f with trifluoroacetic acid gave several unidentified products and, again, no homogeneous product could be isolated upon the application of BF_3-etherate in abs. benzene.

The above results show that the oxidation of the 2'-OR- and the analogous 2'-NHR-chalcones gives different products in many instances, and the possibilities for the conversion of the epoxides are also different. Further investigation of the similarity and variance of related reactions is in progress.

Experimental

Melting points are uncorrected. ^{1}H-NMR spectra were recorded on a Bruker WP 200 SY spectrometer at 200 MHz for

solution in $CDCl_3$ at DMSO-d_6 (internal standard TMS, δ=0.0 ppm) at room temperature. MS was obtained with a VG-7035 (UG Analytical, Manchester) type mass spectrometer.

trans-2'-NHR-chalcone (1a-f). General procedure. 2'-NHR--acetophenone (10 mmol) and 4-R^1-benzaldehyde (10 mmol) was dissolved in ethanol and sodium hydroxide (15 %, 3 cm^3) was added under stirring. After 24 h the reaction mixture was neutralized with 10 % HCl and diluted with water. The yellow product was crystallized from ethanol. 1a m.p. 72°C, lit.[2,3,5,12,13] m.p. 72°C; 1b m.p. 91°C, lit.[6] m.p. 91-92°C; 1c m.p. 81°C, lit.[7] m.p. 81°C; 1e m.p. 92°C, lit.[2,5] m.p. 92°C; 1f m.p. 130°C, lit.[6] m.p. 130°C, 1g m.p. 138°C, lit.[8] m.p. 136°C; 1d, m.p. 121-122°C, yield 50 %. ^{1}H-NMR ($CDCl_3$): 9.50 (t, 1H, NH); 7.95 (dd, 1H, H-6'); 7.70 (d, 1H, H-β); 7.60 (dd, 1H, H-3'); 7.55 (d, 1H, H-α; $J_{H\alpha,H\beta}$=12 Hz); 7.40-6.60 (m, 11H, arom.); 4.45 (d, 2H, CH_2); 3.85 (s, 3H, OCH_3).

Anal. Calcd. for $C_{23}H_{21}NO_2$: N, 4.08, Found: N, 4.06.

trans-2'-Tosylamido-4-methoxychalcone (1h). 2.5 g (10 mmol) of 1b and 1.9 g (10 mmol) of p-toluenesulfonyl chloride in abs. pyridine (35 cm^3) gave 1.6 g (40 %) of 1h, m.p. 159°C (from ethanol). ^{1}H-NMR ($CDCl_3$): 11.1 (s, 1H, NH); 7.85-6.90 (m, 14H, arom.); 3.80 (s, 3H, OCH_3); 2.20 (s, 3H, CH_3).

Anal. Calcd. for $C_{23}H_{21}NO_4S$: N, 3.43, S, 7.87, Found: N, 3.40, S, 7.82

Epoxidation of 2'-NHR-chalcones (1a-d, g,h). General procedure. 3.5 mmol of 2'-NHR-chalcones was dissolved in methanol (200 cm^3) containing 10 % NaOH (1.4 cm^3) and 30 % H_2O_2 (2.1 cm^3) was added under stirring at room temperature. After 24 h the mixture was neutralized with diluted acetic acid. Slightly yellow product was obtained. 2a m.p. 160°C, lit.[5] m.p. 153-155°C; 2b m.p. 146°C, lit.[6] m.p. 146-148°C.

trans-2'-Benzylaminochalcone epoxide (2c) 0.9 g (80 %), m.p. 116°C. ^{1}H NMR ($CDCl_3$): 9.26 (t, 1H, NH); 7.75 (dd, 1H, H-6'); 7.40-7.20 (m, 11H, arom.); 6.70 (dd, 1H, H-3'); 6.55 (m, 1H, H-5'); 4.45 (d, 2H, CH_2); 4.30 (d, 1H, H-β); 4.05 (d, 1H, H-α; J_{H_α,H_β} = 2 Hz).

Anal. Calcd. for $C_{22}H_{19}NO_2$: N, 4.25, Found: N, 4.19.

trans-2'-Benzylamino-4-methoxychalcone epoxide (2d) 0.6 g (50 %) m.p. 74°C. ^{1}H-NMR ($CDCl_3$): 9.25 (t, 1H, NH); 7.30-6.55 (m, 13H, arom.); 4.45 (d, 2H, CH_2); 4.30 (d, 1H, H-β); 4.0 (d, 1H, H-α; J_{H_α,H_β}=2 Hz); 3.80 (s, 3H, OCH_3).

Anal. Calcd. for $C_{23}H_{21}NO_3$: N, 3.89, Found: N, 3.85.

1-Tosyl-2,3-dihydro-2-phenyl-4(1H)-quinolone (3g) m.p. 136°C, lit.[8] m.p. 138°C. ^{1}H-NMR ($CDCl_3$): 7.90-7.10 (m, 13H, arom.); 5.90 (dd, 1H, H-2; $J_{2,3e}$=3 Hz, $J_{2,3a}$=8 Hz); 3.0 (dd, 1H, H-3a); 2.60 (dd, 1H, H-3e); 2.40 (s, 3H, CH_3). MS: m/z=377 (M^+).

1-Tosyl-2,3-dihydro-2-(4'-methoxyphenyl)-4(1H)-quinolone (3h) M.p. 118-120°C. ^{1}H-NMR ($CDCl_3$): 7.80-7.10 (m, 12H, arom.);

5.85 (dd, 1H, H-2; $J_{2,3e}$=2.5 Hz, $J_{2,3a}$=8 Hz); 3.80 (s, 3H, OCH_3); 3.20 (m, 2H, H-3e, 3a); 2.35 (s, 3H, CH_3). MS: m/z=407 (M^+).

Epoxidation of 2'-acetamidochalcones (1e,f). 3 mmol of 2'-acetamidochalcone (1e,1f) was dissolved in methanol (100 cm^3) containing 27 % NH_3 solution (1.2 cm^3) and 30 % hydrogen peroxide (3 cm^3) was added under stirring at room temperature. After 24 h the solvent was evaporated and the residue was crystallized from ethanol.

trans-2'-Acetamidochalcone epoxide (2e): 0.7 g (83 %), m.p.: 143°C (lit.[5] m.p. 140-141°C). ^{1}H-NMR ($CDCl_3$): 11.38 (bs, 1H, NH); 8.75 (dd, 1H, H-6'); 7.90 (dd, 1H, H-3'); 7.60 (m, 1H, H-5'); 7.50-7.35 (m, 5H, arom.); 7.10 (m, 1H, H-4'); 4.30 (d, 1H, H-β); 4.10 (d, 1H, H-α; J_{H_α,H_β}=2 Hz); 2.15 (s. 3H, CH_3).

Anal. Calcd. for $C_{17}H_{15}NO_3$: N, 4.98, Found: N, 4.97.

trans-2'-Acetamido-4-methoxychalcone epoxide (2f): 0.5 g (53 %), m.p. 135°C. ^{1}H-NMR ($CDCl_3$): 11.4 (bs, 1H, NH); 8.80 (dd, 1H, H-6'); 7.85 (dd, 1H, H-3'); 7.60 (m, 1H, H-5'); 7.35-7.10 (m, 5H, arom.); 4.35 (d, 1H, H-β); 4.0 (d, 1H, H-α; J_{H_α,H_β}=2 Hz); 3.80 (s, 3H, OCH_3); 2.25 (s, 3H, $COCH_3$).

Anal. Calcd. for $C_{18}H_{17}NO_4$: N, 4.50, Found: N, 4.45.

Methanolysis of 2'-NHR-chalcone epoxides. 0.25 mmol of 2'-NHR-chalcone epoxide (2a-c,e) was dissolved in methanol (10 cm^3) containing 0.1 cm^3 of cc. HCl. The mixture was

stirred for 24 h at room temperature. After evaporation the residue was dissolved in chloroform, washed with $NaHCO_3$ solution and water. The organic phase was dried and evaporated. The crude products were purified by column chromatography using Kieselgel-40 and hexane-acetone (7:3) as eluent.

erythro-2-Hydroxy-3-methoxy-1-(2'-aminophenyl)-3-phenyl--propan-1-one (4a) orange oil (55 %). ^{1}H-NMR ($CDCl_3$) 7.65 (dd, 1H, H-6'); 7.40-6.60 (m, 8H, arom.); 6.10 (bs, 2H, NH_2); 5.40 (d, 1H, H-β); 4.50 (d, 1H, H-α; J_{H_α,H_β}=5 Hz); 3.80 (bs, 1H, OH); 3.30 (s, 3H, OCH_3). MS: m/z=271 (M^+).

erythro-2-Hydroxy-3-methoxy-1-(2'-aminophenyl)-3-(4--methoxyphenyl)-propan-1-one (4b) orange oil (60 %). ^{1}H-NMR ($CDCl_3$): 7.60-6.60 (m, 8H, arom.), 6.15 (bs, 2H, NH_2); 5.60 (d, 1H, H-β); 4.60 (d, 1H, H-α; J_{H_α,H_β}=5 Hz); 3.85 (s, 3H, OCH_3); 3.80 (bs, 1H, OH); 3.30 (s, 3H, OCH_3). MS: m/z=301 (M^+).

erythro-2-Hydroxy-3-methoxy-1-(2'-benzylaminophenyl)-3--phenylpropan-1-one (4c) orange oil (52 %). ^{1}H-NMR ($CDCl_3$): 9.20 (t, 1H, NH); 7.30-6.70 (m, 14H, arom.); 5.55 (d, 2H, CH_2); 5.40 (d, 1H, H-β); 4.60 (d, 1H, H-α, J_{H_α,H_β} =5 Hz); 3.90 (bs, 1H, OH); 3.35 (s, 3H, OCH_3). MS: m/z=361 (M^+).

erythro-2-Hydroxy-3-methoxy-1-(2'-acetamidophenyl)-3--phenylpropan-1-one (4e) orange oil (50 %). ^{1}H-NMR ($CDCl_3$): 11.2 (bs, 1H, NH); 8.85-7.50 (m, 9H, arom.); 5.45

(d, 1H, H-β); 4.60 (d, 1H, H-α; J_{H_α,H_β}=5 Hz); 3.85 (s, 1H, OH); 3.40 (s, 3H, OCH_3); 2.20 (s, 3H, $COCH_3$). MS: m/z=313 (M^+).

Cleavage of the oxirane ring with HCl in abs. ether. Synthesis of threo-ethylene chlorohydrins (8). 0.5 mmol of 2'-NHR-chalcone epoxide was dissolved in abs. ether (10 cm^3) saturated with dry HCl. After 48 h in refrigerator the product precipitated was filtered off and crystallized from hexane or purified using column chromatography.

threo-1-(2'-aminobenzoyl)-2-phenylethylene chlorohydrin (8a) Yield 65 %, m.p. 106-108°C. ^{1}H-NMR ($CDCl_3$): 7.70-6.70 (m, 9H, arom.); 6.05 (bs, 2H, NH_2); 5.50 (d, 1H, H-β); 5.30 (d, 1H, H-α; J_{H_α,H_β}=2 Hz); 3.80 (d, 1H, OH). IR (KBr): 3440, 3330, (νNH, OH), 1635 cm^{-1} (νC=O).

Anal. Calcd. for $C_{15}H_{14}ClNO_2$: Cl, 12.85, N, 5.07, Found: Cl, 12.91, N, 5.24.

threo-1-(2'-aminobenzoyl)-2-(4-methoxyphenyl)-ethylene chlorohydrin (8b). Yellow oil (70 %). ^{1}H-NMR (DMSO-d_6): 7.70-6.70 (m, 8H, arom.); 6.70 (d, 1H, H-β); 6.10 (d, 1H, H-α; J_{H_α,H_β}=1.5 Hz); 5.0-5.50 (d, deuterable NH_2, OH); 3.60 (d, 3H, CH_3). MS: m/z=305 (M^+).

threo-1-(2'-benzylaminobenzoyl)-2-phenylethylene chlorohydrin (8c). Yellow oil (68 %). ^{1}H-NMR ($CDCl_3$): 8.90 (t, 1H, NH); 7.70-6.60 (m, 14H, arom.); 5.60 (d, 1H, H-β); 5.35 (d, 1H, H-α; J_{H_α,H_β}=2 Hz); 4.40 (d, 2H, CH_2); 3.85 (d, 1H, OH). MS: m/z=365 (M^+).

threo-1-(2'-acetamidobenzoyl)-2-phenylethylene chlorohydrin (8e). Yield 75 % m.p. 134-136°C. ^{1}H-NMR ($CDCl_3$): 10.45 (s, 1H, NH); 8.65-7.10 (m, 9H, arom.); 5.60 (s, 1H, H-β); 5.20 (d, 1H, H-α; J_{H_α,H_β}=2 Hz); 3.75 (bs, 1H, OH); 2.10 (s, 3H, $COCH_3$). IR(KBr): 3500, 3370 (νNH, OH), 1695 (νCH_3CO), 1665 (νC=O).

Anal. Calcd. for $C_{17}H_{16}ClNO_3$: Cl, 11.15, N, 4.40. Found: Cl, 11.13, N, 4.29.

threo-1-(2'-acetamidobenzoyl)-2-(4-methoxyphenyl)--ethylene chlorohydrin (8f). Yellow oil (60 %). ^{1}H-NMR (DMSO-d_6): 7.80-6.60 (m, 8H, arom.); 6.70 (d, 1H, H-β); 6.10 (d, 1H, H-α; J_{H_α,H_β}=2.5 Hz); 5.40 (s, 1H, OH); 4.60 (bs, 1H, NH); 3.80 (s, 3H, OCH_3); 3.65 (s, 3H, $COCH_3$). MS: m/z=347 (M^+).

References

1. Litkei, Gy., Chalcone Epoxides in Flavonoid Chemistry in Recent Developments in the Chemistry of Natural Products. Vol. 9. p. 293. Budapest, 1979.
2. Janzsó, G., Topics in Flavonoid Chemistry and Biochemistry. Ed. L. Farkas, M. Gábor, F. Kállay, Akad. Kiadó Budapest, 1975, p. 144.
3. Tőkés, A.L., Szilágyi, L., Synth. Commun. 17, 1235 (1987).
4. Tőkés, A.L., Janzsó, G., Synth. Commun. 19, 3159 (1989).

5. Donnelly, J.A., Farrell, D.F., J. Org. Chem. 55, 1757 (1990).

6. Donnely, J.A., Farrell, D.F., Tetrahedron 46, 885 (1990).

7. Tőkés, A.L., Litkei, Gy., Janzsó, G., Synth. Commun. 20, 1905 (1990).

8. Diesbach, H., Kramer, H., Helv. Chim. Acta 28, 1399 (1945).

9. Dean, F.M., Podimnang, V., J. Chem. Soc. 1965, 3978.

10. Bognár, R., Litkei, Gy. Acta Chim. Acad. Sci. Hung. 67, 83 (1971).

11. Reichel, L, Neubauer, A., Z. Chem. 8, 423 (1968).

12. Engler, C., Dorant, K., Ber. 28, 2497 (1895).

13. Mannich, C., Dannehl, M., Ber. 71, 1899 (1938).

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