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Synthesis and cytotoxicity of 1-phenyl-3,3-diacetoxy-1-propene

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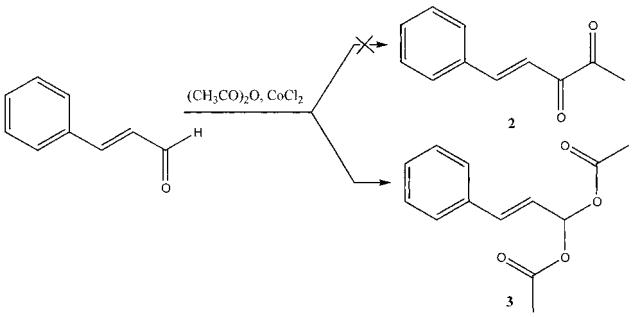
There are two purposes of this report. First, the observation is made that the reaction between cinnamaldehyde and acetic anhydride in the presence of cobalt chloride led to the formation of an acylal and not a 1,2-diketone as previously reported. Second, the cytotoxicity of a prototypic acylal towards murine P388 and L1210 leukemic cells as well as human Molt 4/C8 and CEM T-lymphocytes is described.



A number of conjugated styryl ketones have demonstrated promising cytotoxic activity [1]. These compounds were designed as thiol alkylators since α,β-unsaturated ketones possess a selective affinity for thiols in contrast to amino and hydroxy groups [2]. A promising lead compound is 4-phenyl-3-buten-2-one **1** having IC_{50} figures of 10.6 ± 1.6, 13.9 ± 4.9, 6.25 ± 2.11 and 3.49 ± 0.55 μM, respectively, against P388, L1210, Molt 4/C8 and CEM cells, respectively. In order to increase further the fractional positive charge on the carbon atom adjacent to the aryl ring of **1** (with a view to increasing thiol-alkylating properties and cytotoxicity) the formation of the analogue **2** (Scheme) was proposed. This decision was based on a consideration of the magnitude of the Taft σ* values of the different groups attached to the enone functionality. In the case of **2**, the σ* figure is 1.81 in contrast to a value of 0.00 for the methyl group of **1** [3]. Utilization of a literature procedure which described the synthesis of **2** [4] led to the isolation of a compound. However, both the ^{1}H NMR spectrum and elemental analysis (C, H) were consistent with the product being the acylal **3** and not the diketone **2**. X-ray crystallography revealed unequivocally that the compound was 1-phenyl-3,3-diacetoxy-1-propene **3**; an ORTEP II diagram [5] of **3** is portrayed in the Fig.

A review of the literature revealed that **3** had been prepared from cinnamaldehyde and acetic anhydride previously using the following catalysts, namely copper (II) trifluoromethanesulphonate [6], a perfluorinated resinsulphonic acid (nafion-H) [7], sodium phenylacetate [8], Fe^{+++}-montmorillonite [9] and concentrated sulphuric acid [10]. However the use of cobalt chloride for preparing **3** (and possibly other acylals) has not been described previously.

Compounds containing polarized ofefinic bonds are electrophiles [11] and since the σ* value of the acetoxy group

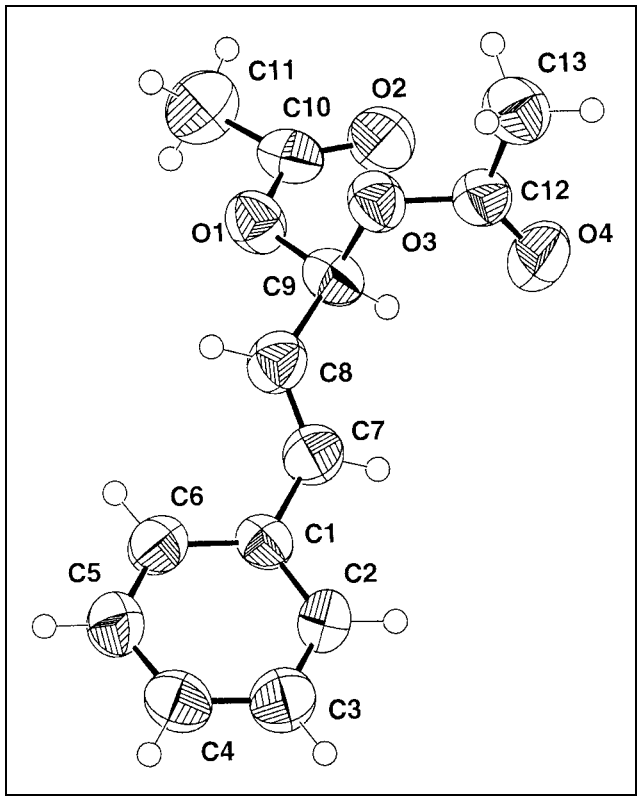


Fig.: ORTEP II drawing [5] of **3**. Displacement ellipsoids of non-hydrogen atoms are drawn at the 50% probability level. For clarity, the hydrogen atoms are drawn as small spheres of arbitrary size

is 2.56 [12], one would anticipate that the unsaturated carbon atom adjacent to the phenyl ring in **3** would have a high affinity for cellular electrophiles. The IC_{50} figures for **3** against P388, L1210, Molt 4/C8 and CEM cells were 5.70 ± 0.2, 43.6 ± 0.6, 37.8 ± 3.0 and 32.1 ± 1.4 μM, respectively. Comparable data using these four cell lines for a reference drug melphalan, which is an antineoplastic alkylating agent, were 0.22 ± 0.01, 2.13 ± 0.02, 3.24 ± 0.56 and 2.47 ± 0.21 μM, respectively. While compound **3** is less potent than melphalan, there are two reasons at least for developing analogues of **3** as candidate cytotoxic and anticancer agents. First, a prototypic member of this series namely **3** displayed activity towards four neoplastic cell lines particularly against P388 cells. Second, the two ester groups in **3** are capable of facile hydrolysis in vivo leading to polar molecules thereby exemplifying the soft drug principle [13].

Thus **3** is a novel template for subsequent molecular modification with a view to preparing new cytotoxic and anticancer agents.

Experimental

1. Chemistry

Employment of a literature method [4] led to a product which was crystallized from petroleum ether bp 40–60 °C/C_6H_6 to give **3**, m.p. 72–74 °C (lit. [8] m.p. 85 °C) in 52% yield: ^{1}H NMR (500 MHz, $CDCl_3$): δ: 2.10 (s, 6 H, $2 \times CH_3$), 6.19 [q, IH, $CH(OCOCH_3)_2$], 6.85 (d, IH, $C_6H_5CH{=}CH$, J = 16.05 Hz), 7.24–7.42 (m, 6 H, $C_6\underline{H}_5C\underline{H}{=}CH$). Calcd. for $C_{13}H_{14}O_4$: C, 66.65, H, 6.02. Found C, 66.75; H, 6.31. For the X-ray crystallographic determination of **3**, the compound was recrystallized from CH_3OH by slow evaporation. Details of the physical parameters of the X-ray crystallographic structure may be obtained from the authors.

2. Cytotoxicity evaluations

Compound **3** was examined against P388 cells using a literature method [14]. The assays using L1210, Molt 4/C8 and CEM cell lines were undertaken by a reported procedure [15].

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References

1 Dimmock, J. R.; Kumar, P.; Quail, J. W.; Pugazhenthi, U.; Yang, J.; Chen, M.; Reid, R. S.; Allen, T. M.; Kao, G. Y.; Cole, S. P. C.; Batist, G.; Balzarini, J.; De Clercq, E.: Eur. J. Med. Chem. **30**, 209 (1995)
2 Dimmock, J. R.; Raghavan, S. K.; Logan, B. M.; Bigam, G. E.: Eur. J. Med. Chem. **18**, 248 (1983)
3 Perrin, D. D.; Dempsey, B.; Serjeant, E. P.: pK_a Prediction for Organic Acids and Bases, pp. 113, 111, Chapman and Hall, London, 1981
4 Ahmad, S.; Iqbal, J.: J. Chem. Soc., Chem. Commun. 692 (1987)
5 Johnson, C. K.: Ortep II Report ORNL-5138, Oak Ridge National Laboratory, TN, USA, 1976
6 Chandra, K. L.; Saravanan, P.; Singh, V. K.: Syn. Lett. 359 (2000)
7 Olah, G. A.; Mehrotra, A. K.: Synthesis, 962 (1982)
8 Thiele, R.; Meisenheimer, J.: Justus Liebigs Ann. Chem. **306**, 247 (1899)
9 Li, T.-S.; Zhang, Z.-H.; Gao, Y.-T.: Synth. Commun. **28**, 4665 (1998)
10 Hill, A. J.; Nason, E. H.: J. Amer. Chem. Soc. **46**, 2240 (1924)
11 Stenlake, J. B.: Foundations of Molecular Pharmacology, Volume 1, p. 82, The Athlone Press, London 1979
12 Perrin, D. D.; Dempsey, B.; Serjeant, E. P.: pK_a Prediction for Organic Acids and Bases, p. 114, Chapman and Hall, London 1981
13 Bodor, N.: Advances in Drug Research, Volume 13, p. 255, Academic Press, London 1984
14 Phillips, O. A.; Nelson, L. A.; Knaus, E. E.; Allen, T. M.; Fathi-Afsar, R.: Drug Design Del. **4**, 121 (1989)
15 Balzarini, J.; De Clercq, E.; Mertes, M. P.; Shugar, D.; Torrence, P. F.: Biochem. Pharmacol. **31**, 3673 (1982)

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Nitraminanaloges Ibuprofen

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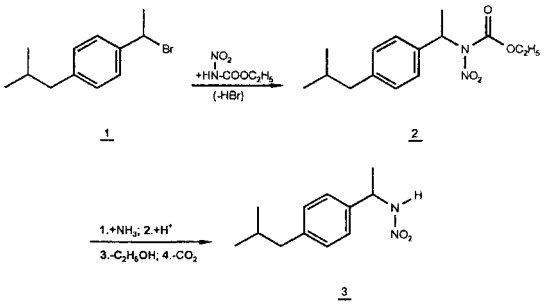
Häufiges Ziel einer Veränderung acider Wirkstoffe ist der bioisostere Ersatz von Carboxylfunktionen durch Sulfonsäure- und Phosphonsäuregruppen sowie durch Stickstoff-Heterocyclen [1]. Auch die primäre Nitraminfunktion besitzt eine der Carboxylgruppe vergleichbare NH-Acidität mit ähnlicher Raumerfüllung. Es war daher von Interesse, im Rahmen unserer Untersuchungen an N-Nitroaminen die Carboxylgruppe im Ibuprofen durch die Nitraminfunktion zu ersetzen. Versuche zur Herstellung des nitraminanalogen Ibuprofens **3** verliefen erfolgreich über **2**, ausgehend von 1-(4′-Isobutylphenyl)-1-brom-ethan (**1**) und *N*-Nitrourethan (Schema) [2]. Valenti et al. hatten bereits 1983 das gut wirksame Tetrazolanalogon beschrieben [3].

Schema



3 wurde 1. auf die Hemmung der Cyclooxygenase/Thromboxan-Synthase von Rinderblut- Thrombozyten durch Bestimmung der 12-Hydroxy-heptadecatriensäure (12-HHT) und 2. auf die Hemmung der 5-Lipoxygenase von Rinderblut-Granulozyten durch Bestimmung des Leukotriens B_4 (LTB_4) getestet [4]. Die Ergebnisse sind der Tabelle zu entnehmen.

Tabelle: Prozentuale Hemmung von Cyclooxygenase-Synthetase und 5-Lipoxygenase

Verbdg.	Konz. (μmol)	Hemmung (%)	
		12-HHT	LTB_4
Ibuprofen	10	100,0	40,3
	3,3	100,0	
	1,0	63,1	
Nitramin **3**	10	100,0	19,5
	3,3	49,6	
	1,0	11,2	

Experimenteller Teil

Schmp. (unkorr.) werden mit dem Kofler-Heiztischmikroskop der Fa. Reichert bestimmt, Elementaranalysen mit dem CHN-Analyser 240 Perkin-Elmer und dem CHNO-Rapid- Analyser Heraeus durchgeführt. Die Ergebnisse entsprachen den üblichen Grenzen der Theorie. NMR-Messungen (^1H,^{13}C) erfolgten am Gemini 200-Gerät Varian, Massenspektren wurden mit dem MAT 44S Finnigan aufgenommen.

1. 1-(4′-Isobutylphenyl)-1-brom-ethan (**1**)

5,3 g (0,03 mol) 1-(4′-Isobutylphenyl)-1-ethanol ($Sdp._{1,0}$: 117 °C) [2] werden mit 10,2 g (0,06 mol) 48 proz. HBr-Lsg. versetzt und 3 h lang rückflusserhitzt. Nach dem Erkalten gibt man 30 ml Et_2O hinzu, trennt ab, wäscht mit