Route of administration	Analgesia (rat tail flick)[7,8] Morphine ED_{50} mg/kg	(−) **2B** ED_{50} mg/kg (95% confid. levels)	Safety ratio (rats) LD_{50}/ED_{50}	Antagonism[8] of morphine (rats) (−) **2B** ED_{50} mg/kg	Nalorphine ED_{50} mg/kg
i.p.	4.0	2.71 (1.95–3.75)	>100		
i.m.	1.7	0.76 (0.62–0.94)	>400	1.2	0.84
p.o.	11	4.31 (3.03–6.14)	>200		

hydrolysis afforded **4B**: (free base) m.p. 172–173.5 °C/ether-hexane: PMR ($CDCl_3$) δ 2.17 (6H, s, N(CH_3), 4.05 (2H, overlapping 1H, d, J = 12 Hz - $CHN(CH_3)_2$), and 1H, m, $CHOH$) ppm:HCl salt, m.p. 241–242 °C/acetone-ethanol-hexane.

Attempts to convert **2** and **4** to a common intermediate by catalytic hydrogenolysis of the dimethylamino function were unsuccessful. However, conversion of **2B** and **4B** to their N-oxides with monoperphthalic acid followed by reductive cleavage[4] of either, using lithium in liquid ammonia, afforded the identical racemate (**6**): m.p. 93–96,5 °C/acetone-hexane. **2B** and **4B** can only differ, therefore, in the stereochemistry of the benzyl position and this was inferred from the facile Cope[5] cis-elimination of their N-oxides to give the Z and E isomers of **7** respectively in 98% stereochemical purity. Stereospecific cis-elimination dictates the geometry shown in **2** and **4**. Elimination of the amine function was observed when either N-oxide was stored over long periods, warmed in chloroform, or heated briefly above its melting point. GC-MS analysis of the elimination products was made on a 3 ft, 3% OV-17 glass column, 2 mm ID at 220 °C. The **Z-7** isomer (from **2B** N-oxide) had a retention time of 4.6 min, M^+ 204; R_f[6] 0.48 while the **E-7** isomer (M^+, 204; R_f 0.42) had a retention time of 5.7 min identical to an authentic sample of **E-7** isomer: m.p. 107–110 °C/ether-hexane prepared by acid hydrolysis followed by $NaBH_4$ reduction of 2-(3-methoxy-methoxybenzylidene)cyclohexanone.

Resolution of **2B** proceeded with an efficiency of 78% via the diastereoisomeric tartrate salts. (-) **2B** (-) tartaric acid salt: m.p. 198–200 °C/aqueous acetone; $[\alpha]_D$ −16.9°. (-) **2B** (free base): m.p. 191–193 °C/acetone-hexane; $[\alpha]_D$ −46.7°. (-) **2B**, HCl salt: m.p. 255–257 °C/acetone-methanol, $[\alpha]_D$-15.31°. (+) **2B**, HCl salt: m.p. 255–257 °C/acetone-methanol, $[\alpha]_D$+14.7°.

Biological activity. Analgesic-antagonist activity for (-) **2B** is summarized in the table. In the D'Amour-Smith rat tail flick method[7,8], i.p. route, (+) **2B** and **3B** were inactive as analgesics, the ED_{50} for **4B** was 50 mg/kg. (−) **2B** is under active clinical evaluation.

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Synthesis of N-aryl-N-glycolyl hydroxamic acids: Nonmicrosomal metabolites of nitrosoaromatics[1]

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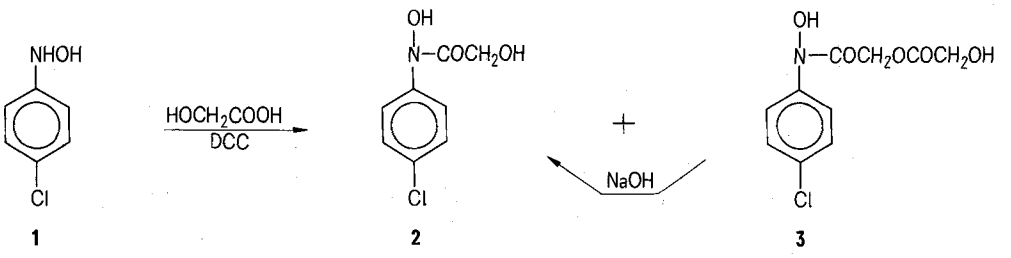
Summary. A method for the synthesis of N-aryl-N-glycolyl hydroxamic acids is described. This method consists of N-acylation of an arylhydroxylamine by glycolic acid in the presence of dicyclohexylcarbodiimide.

In previous reports it was demonstrated that nitrosoaromatic compounds are converted to N-aryl-N-glycolyl hydroxamic acids by transketolase enzymes[2,3]. This previously unknown type of hydroxamic acid derivative could be involved in the known toxicological properties of nitrosoaromatics, and their known metabolic precursors, the arylamines and nitroaromatics[4]. A further interest in these very unusual metabolites arises from the fact that they are produced by soluble enzymes, and not by microsomal enzymes[2,5].

We have developed an efficient method for the synthesis of this new class of hydroxamic acids, which we now describe for N-(4-chlorophenyl)-N-glycolylhydroxamic acid (**2**). Standard methods which employ acid chlorides or anhydrides for the synthesis of hydroxamic acids[6] could not be employed in the preparation of **2** and related compounds. A previous report on the coupling of carboxylic acids with hydroxylamine by employing dicyclohexylcarbodiimide (DCC)[7] suggested the method which we developed. Critical to the success of this procedure is the saponification of the crude product to convert **3** to **2** before the final isolation is attempted.

To 2.9 g (0.02 moles) of 4-chlorophenylhydroxylamine (**1**) in 50 ml of anhyd. ether at 0 °C was added 8.3 g (0.04 moles) of DCC in 20 ml of anhyd. ether. With stirring and continued cooling was added to this solution 3.0 g (0.04 moles) of glycolic acid in 10 ml of DMF in the course of 15 min. The resulting mixture was stirred with cooling for 15 min, then filtered to remove dicyclohexylurea, which was washed with 20 ml of ether. The ether solution was stirred with 1.6 g (0.04 moles) of NaOH in 30 ml of H_2O for 15 min at 0 °C. This mixture was transferred to a separatory funnel and the 2 phases separated. The ether layer was washed with 10 ml of H_2O, which was then combined with



the previous H_2O layer. The aqueous solution was washed with 20 ml of Et_2O, and the pH adjusted to 5 with 5% HCl. After saturating with NaCl, the aqueous phase was extracted twice with 50 ml of ethyl acetate. The combined ethyl acetate extracts were dried (Na_2SO_4) and evaporated to give an oil which solidified upon stirring with 40 ml of H_2O.

Recrystallization of the solid from aqueous ethanol gave 2.2 g (55%) of the product **2** as a white crystalline powder (m.p. 124–125 °C). Elemental analysis, NMR and IR data confirmed that the product was the hydroxamic acid **2.**

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Degradation of 2,3,7,8-tetrachlorodibenzo-p-dioxin in organic solvents by gamma ray irradiation

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Summary. The effect of gamma ray irradiation on 2,3,7,8 tetrachlorodibenzo-p-dioxin (TCDD) dissolved in organic solvents is described; TCDD is degradated with the loss of 1 or more chlorine atoms.

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is recognized as one of the most potent low mol. wt toxins known. TCDD has a number of toxic effects[1-6], such as teratogenicity, mutagenicity, immunosuppression and carcinogenicity; furthermore, it is a chemically and metabolically inert compound with a very long half-life both in the environment[7-10] and in living systems[11-19]. Therefore the possibility of TCDD accumulation in the food chain represents a serious health hazard.

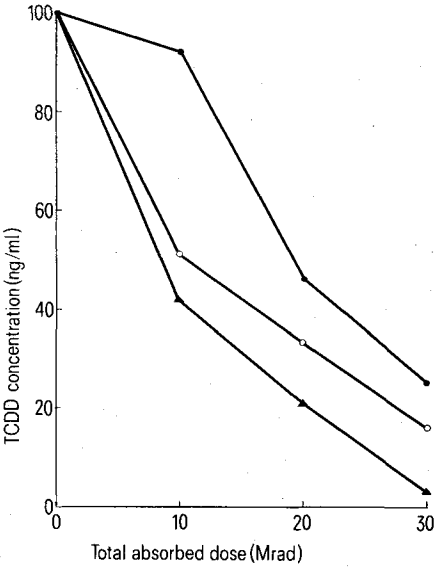
The most serious case of environmental contamination by TCDD occurred about 2 years ago near the Italian town of Seveso, when a large, densely populated area was contaminated as a consequence of an explosion in a reactor producing 2,4,5-trichlorophenol[20]. Since the population is still living in the contaminated areas, the problem of decontamination must be solved urgently, in order to reduce the possibility of adverse biological effects due to chronic exposure.

So far the only known methods of degrading the TCDD molecule are photoreduction by UV rays in organic solvents[21,22] and incineration at a temperature above 750 °C[23]. These methods are now under investigation with a view to their practical application to the situation in Seveso.

As an attempt to contribute to solving this problem, we report the outcome of preliminary experiments on the effects of gamma rays on TCDD dissolved in organic solvents.

All irradiations were accomplished with an experimental irradiator (BC-27 model) containing a 10,000-Ci ^{60}Co source. The dose rate was 10^6 rad/h. The changes caused by gamma ray irradiation were studied varying the total dose of radiation absorbed by solutions of TCDD in dioxane, acetone or ethanol at a concentration of 100 ng/ml. Aliquots of 0.5 ml were put into glass screw-capped vials which were then submitted to irradiation at room temperature.

The irradiated solutions were directly analyzed for TCDD content and compared with control samples prepared and



Effect of gamma ray irradiation on TCDD concentration. TCDD was dissolved in ethanol (▲), acetone (○) and dioxane (●) at a concentration of 100 ng/ml. Solutions were irradiated at a dose rate of 10^6 rad/h and their TCDD concentration was measured after 10,20 and 30 h.