# Synthesis of 3-(*o*-Chlorophenyl)-4-methylsydnone

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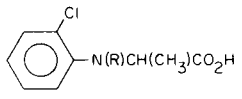
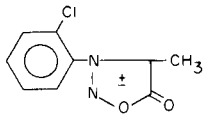
The reported failure of *N*-(*o*-chlorophenyl)-*N*-nitrosoalanine (Ib) to undergo cyclodehydration to the corresponding sydnone II has been attributed to the bulk of the *ortho*-chloro substituent (1,2). Although a number of unsuccessful attempts to prepare sydnones have been recorded in the literature, such cases have involved invariably, either the inability to obtain the requisite *N*-nitroso precursor, or the intervention of other reactions competing with sydnone formation (3,4). In addition, the purely steric rationale offered for this sole exception (1), would appear to be unlikely in view of the successful preparations of 4-methyl-3-*o*-tolyl- and 4-methyl-3-(2,6-xylyl)sydnones (5) in which the steric demands of the *ortho*-methyl substituents are, at least, of comparable magnitude (6).

Since no experimental or physical data were available for Ib, *N*-(*o*-chlorophenyl)alanine (Ia) was nitrosated under standard conditions to yield a compound (positive Liebermann nitroso test) whose nmr spectrum was consistent with the desired *N*-nitroso structure Ib. Although no difficulty was encountered in preparing an analytically pure sample of Ib, the compound was somewhat unstable. It discolored in strong light and decomposed completely on attempted recrystallization from carbon tetrachloride. Because of this heat lability, attempted cyclization of Ib to II was carried out with the more powerful dehydrating agent, trifluoroacetic anhydride (7), rather than hot acetic anhydride. The bicarbonate-insoluble product (negative Liebermann nitroso test) was shown to be the desired sydnone II by elemental analysis and standard spectroscopic data (ir, uv, and nmr). The structure of II was further established by hydrolyzing it with mineral acid (3) to yield *o*-chlorophenylhydrazine hydrochloride. The identity of the latter compound was confirmed by comparison (m.p., ir, and uv) with an authentic sample (8).




Ia, R = H
b, R = NO




II

The phenomenon of multiple infrared bands in the carbonyl region of sydnones (3) was observed for II. When examined both as a chloroform solution and as a Nujol mull, two intense bands appeared at 1740 and 1775 $cm^{-1}$. In the case of the Nujol mull spectrum, a third medium-intensity band was found at still higher frequency (1820 $cm^{-1}$), however, in chloroform solution (*ca.* 10%) this band was considerably weaker, essentially collapsing to a shoulder on the 1775 $cm^{-1}$ band.

## EXPERIMENTAL

Melting points (Thomas-Hoover capillary apparatus) are uncorrected. Ir, uv, and nmr spectra were determined, respectively, with a Perkin-Elmer Model 137, a Cary Model 14, and a Varian Model T-60 spectrometer. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan.

*N*-(*o*-Chlorophenyl)alanine (Ia).

The procedure described by Miller and Sharp (1) for the preparation of authentic Ia was found to be unsatisfactory. The yield of Ia was 17% (*vs.* 75%) and 84% of the starting *o*-chloroaniline was recovered. Following the general method of Eade and Earl (9), a mixture of *o*-chloroaniline (0.2 mole), ethyl 2-bromopropionate (0.2 mole), sodium acetate trihydrate (0.2 mole), and 5 ml. of ethanol was stirred and refluxed at 130 ± 3° for 20 hours. After cooling and diluting with 80 ml. of water, the mixture was extracted with ether (3 x 100 ml.), and the combined extracts were evaporated *in vacuo*. The residual oil was refluxed with 160 ml. of 10% aqueous sodium hydroxide for 2 hours, cooled and the mixture washed with ether (3 x 50 ml.). The aqueous layer was cooled (ice-bath) and the solution brought to *p*H 3 by the slow addition of concentrated hydrochloric acid. The resulting suspension was stored in the refrigerator for several hours, filtered, washed with cold water and dried: crude yield, 22.8 g. (57%) of a white solid, m.p. 146-148°. After recrystallization from chloroform (80% recovery) the m.p. was unchanged, [lit. m.p. 148.5-149.5° (1), m.p. 150° (10)].

*N*-(*o*-Chlorophenyl)-*N*-nitrosoalanine (Ib).

Compound Ia (39.9 g., 0.2 mole) was added gradually with stirring to 250 ml. of cold (5-10°) concentrated hydrochloric acid. The colorless solution was further cooled to -5° and, with continuous stirring, 15.2 g. (0.22 mole) of solid sodium nitrite was added at -3 to -6° during 0.5 hour. The product gradually precipitated during this addition and on subsequent stirring for 3.5 hours in the same temperature range. The suspension was poured onto 270 g. of cracked ice, cooled for an additional 1.5 hours and the solid filtered, washed thoroughly with cold water and dried *in vacuo*

over potassium hydroxide: crude yield, 39.3 g. (86%) of a yellow solid, m.p. 93-94° dec. Compound Ib was recrystallized by dissolving it in 275 ml. of anhydrous ether, adding 1.5 g. of Norit, filtering, and concentrating the light yellow filtrate at 25-30° to 200 ml. with a stream of nitrogen. After adding *n*-pentane (*ca.* 400 ml.) to the point of faint turbidity and scratching, crystallization was allowed to proceed in the freezer (*ca.* -20°) overnight: yield, 32.9 g. (84% recovery), m.p. 96-97° dec. Two additional recrystallizations provided the analytical sample as pale yellow prisms, m.p. unchanged; ir (Nujol) 1755 $cm^{-1}$ (carboxyl); nmr (deuteriochloroform-TMS) $\delta$ 1.41 (d, 3H, $J$ = 7 Hz, $CH_3$), 4.92 (q, 1H, $J$ = 7 Hz, CH), 7.60 (m, 4H, aromatic), and 12.2 ppm (s, 1H, $CO_2H$).

*Anal.* Calcd. for $C_9H_9ClN_2O_3$: C, 47.28; H, 3.97; N, 12.25. Found: C, 47.17; H, 4.05; N, 12.39.

3-(*o*-Chlorophenyl)-4-methylsydnone (II).

A stirred solution of 22.9 g. (0.1 mole) of freshly recrystallized Ib in 250 ml. of anhydrous ether was maintained at -15 to -20° while 18 ml. (0.13 mole) of redistilled trifluoroacetic anhydride was added dropwise during 0.5 hour. Stirring was continued for 0.5 hour at -15 to -20°, for 1.5 hours in an ice-bath, and finally for 4 hours at room temperature. The ether was evaporated *in vacuo* and the dark orange oil was treated gradually with an excess (*ca.* 900 ml.) of cold 5% aqueous sodium bicarbonate with cooling and swirling to maintain the temperature at $< 0°$. The orange oil which remained insoluble was scratched to initiate crystallization, and after cooling for 2 hours (ice-bath) to insure complete solidification, the product was filtered, washed thoroughly with cold water and dried *in vacuo* over phosphorus pentoxide: crude yield, 17.0 g. (81%) of an orange, slightly sticky solid, m.p. 70-72°. Compound II was recrystallized by dissolving it in the minimum amount (*ca.* 1 g./12 ml.) of carbon tetrachloride at 25-27°, filtering, and concentrating the filtrate at 25-27° to *ca.* 8-10 ml. by bubbling nitrogen through the solution. The latter was cooled (-15 to -20°), scratched to initiate crystallization, and stored in the freezer (-15 to -20°) overnight: yield, 13.6 g. (80% recovery) of a light orange crystalline solid, m.p. 71-72°. A cream-colored sample of II could be obtained after repeated recrystallizations from carbon tetrachloride, however, the m.p. was unchanged; ir (Nujol) 1740, 1775, and 1820 $cm^{-1}$ (sydnone carbonyl); uv max (MeOH) 306 m$\mu$ ($\epsilon$, 7,670); nmr (deuteriochloroform-TMS) $\delta$ 2.07 (s, 3H, $CH_3$) and 7.80 ppm (m, 4H, aromatic).

*Anal.* Calcd. for $C_9H_7ClN_2O_2$: C, 51.32; H, 3.35; N, 13.30. Found: C, 51.24; H, 3.38; N, 13.35.

A suspension of 530 mg. (2.5 mmoles) of II in 5 ml. of 6*N* hydrochloric acid was heated on the steam bath. The sydnone gradually dissolved with gas evolution and after 1.5 hours, the solution was cooled, filtered, and the product (80% yield) recrystallized from 2-propanol; colorless flakes, m.p. 198-199° dec. The latter was identified as *o*-chlorophenylhydrazine hydrochloride by comparison (m.p., ir, and uv) with an authentic sample (8).

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