

## Effect of UV Irradiation and Tritiation on Hydroxyzine

**Keyphrases** □ Hydroxyzine—decomposition by UV irradiation, tritiation, degradation products □ Tranquilizers, minor—hydroxyzine, UV photodecomposition, tritiation, degradation products □ Chlorobenzophenone—degradation product of hydroxyzine following UV irradiation

## To the Editor:

Hydroxyzine, a diphenylmethane minor tranquilizer, is commercially available as a tablet, syrup, suspension, and solution. It is an effective antianxiety agent (1) and is particularly useful in its ability to render disturbed patients more approachable and amenable to psychotherapy. Recently, it was shown to be more effective than cyproheptadine in pruritus treatment (2).

An aqueous hydroxyzine solution turned dark brown in the air (3), and hydroxyzine was photodegraded by UV light to give three spots on TLC (4). During the purification of tritiated hydroxyzine for the metabolic study (5), the tritiated hydroxyzine solution gradually turned dark brown in the air under room light. Therefore, hydroxyzine susceptibility to oxidative deterioration in the presence of light is apparent. Since the nature of the degradative products of hydroxyzine is still unknown, the effect of UV irradiation on hydroxyzine was studied. In a preliminary experiment, the aqueous hydroxyzine solution turned slightly brown in the dark and >90% of the hydroxyzine remained unchanged.

Three grams of hydroxyzine hydrochloride was dissolved in 20 ml of distilled water and irradiated under a UV lamp (3660 Å, 100 w) at a distance of 20 cm for 3 days. The reaction mixture, which was white material in the brown solution, was extracted three times with two volumes of cyclohexane. The combined extracts were dehydrated over anhydrous sodium sulfate and filtered through 10 g of activated magnesium silicate in a Büchner funnel. The solvent was evaporated *in vacuo*, and the colorless residue was sublimed at 70° at 5 mm Hg pressure to give white crystals.

The product was soluble in organic solvent and insoluble in water. It was negative to Dragendorff and iodoplatinate reagents, indicating the absence of a piperazine ring. It was positive to the 2,4-dinitrophenylhydrazine test, and its IR spectrum showed a strong peak at 6.1 μm attributable to a ketone group. It gave a positive Beilstein test, indicating the presence of a chloride atom. It fluoresced strongly under UV light, implicating a highly conjugated system in the structure. The information suggested that the product was *p*-chlorobenzophenone.

*Anal.*—Calc. for C<sub>13</sub>H<sub>9</sub>ClO: C, 72.07; H, 4.7. Found: C, 71.96; H, 4.24.

Moreover, the product had TLC behavior, UV (UV<sub>max</sub> 211 and 261 in ethanol) and IR spectra, and a melting point (77–78° uncorrected) identical to those of authentic *p*-chlorobenzophenone. Therefore, the product was identified as *p*-chlorobenzophenone. The yield was ~13%. The

mother liquor of the reaction mixture was yellowish brown and became darker on standing in the air at room temperature. The mixture contained at least four yellowish Dragendorff-positive compounds separable by silica gel TLC in chloroform containing 2% methanol. Characterization of the products was not attempted further.

This finding prompted us to identify the tritiation degradation products of hydroxyzine. Hydroxyzine (1 g) was tritiated<sup>1</sup> according to Wilzbach's method (6) by exposing it to 3 Ci of tritium gas at 250 mm Hg pressure at 26° for 2 weeks. The unpurified product gave five distinct dark spots on the fluorogram (7) of the silica gel sheet<sup>2</sup>, developed in cyclohexane–benzene–diethylamine (75:15:10), with *R<sub>f</sub>* values and percentages of radioactivity as follows: 0, 16%; 0.24, 12%; 0.46, 19%; 0.70, 8%; and 0.88, 45%.

The silica gel zones with *R<sub>f</sub>* 0.46 and 0.88 were scraped off, purified, chromatographed in other solvent systems, and identified as hydroxyzine and *p*-chlorobenzophenone, respectively. The tritiated product was purified according to Wilzbach (8). The specific activities of the tritiated hydroxyzine before and after purification were 154 and 16.3 μCi/mg, respectively. The decrease in specific activity after purification indicated that contaminants with high specific activities formed during the tritiation procedure were removed.

This study indicates that hydroxyzine in aqueous solution is very unstable on UV irradiation and that hydroxyzine is also vulnerable to tritiation. In either case, *p*-chlorobenzophenone was a main decomposition product.

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