Communications to the Editor

[Chem. Pharm. Bull. 34(4)1840—1842(1986)]

NEW DEGRADATION PRODUCTS IN AN AQUEOUS SOLUTION OF HYDRALAZINE HYDROCHLORIDE WITH CIMETIDINE

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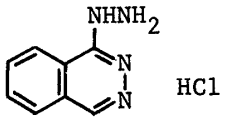
Hydralazine hydrochloride was found to undergo hitherto unknown degradation with cimetidine in aqueous solution to give 1,1-di(phthalazin-3-yl)amine, 1,1-di(phthalazin-3-yl)hydrazine, 1-amino-1,2,2-tri(phthalazin-3-yl)hydrazine, and 1,1,2-tri(phthalazin-3-yl)hydrazine.

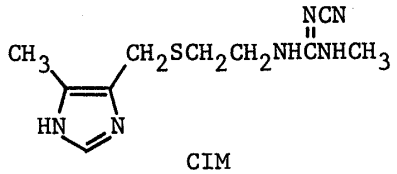
KEYWORDS — hydralazine hydrochloride; cimetidine; degradation; 1,1-di(phthalazin-3-yl)amine; 1,1-di(phthalazin-3-yl)hydrazine; 1-amino-1,2,2-tri(phthalazin-3-yl)hydrazine; 1,1,2-tri(phthalazin-3-yl)-hydrazine; MS; IR; ^{1}H-NMR

Hydralazine hydrochloride (HYD), a potent peripheral vasodilator for treating essential hypertension, undergoes several pharmaceutically undesirable reactions such as chelation with metal ions, formation of Schiff bases with aldehydes and ketones, oxidation, and pH-dependent decomposition.[1] Most of these reactions are apparently due to the highly reactive hydrazino group, and they often cause discoloration. During the storage of a prescription admixture of pulverized HYD with cimetidine (CIM), a histamine H_2-receptor antagonist for duodenal ulcer, the initially uncolored admixture gradually turns to pale yellow. On the basis of this finding, we investigated the reaction of HYD with CIM in aqueous solution, and found that the HYD undergoes hitherto unknown degradation accompanied with discoloration.

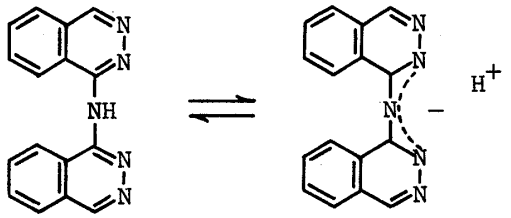
A mixture of HYD (0.006 mol)[2] and CIM (0.004 mol)[2] in sterile purified water (50 ml) stirred at room temperature led to the gradual formation of yellow precipitates. After stirring for 14 days, the precipitates were filtered off to give yellow crystals (58 mg), which exhibited at least four new spots (Rf 0.28, 0.63, 0.73, and 0.79) on TLC (Silicagel 70FM plate-Wako: CH_3CN:MeOH=7:3). In order to isolate these products, the resulting crystals were chromatographed through activated alumina[3] successively with EtOAc and MeOH. The first eluent from EtOAc was evaporated in vacuo and recrystallized from EtOH to give fine yellow needles (F-1: 30 mg). Analogous treatment of the second eluent from EtOAc and the last eluent from MeOH afforded pale orange amorphous (F-2: trace) and fine deep yellow needles (F-3: 15 mg).



HYD



CIM



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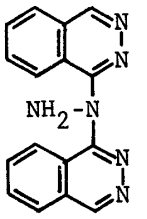

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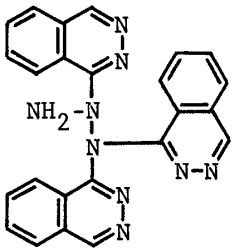

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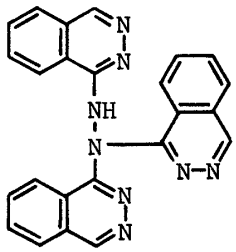

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F-1 was assigned to 1,1-di(phthalazin-3-yl)amine (1)[3] by the presence of an NH group in the IR (3320 cm^{-1}) and ^{1}H-NMR (δ 9.86) and by the expected M^+ ion and fragment ions common to HYD in the MS. However, the existence of an absorption at 2230 cm^{-1}, which is characteristic of carbodiimides, suggested that 1 might exist as an equilibrium mixture with the zwitterionic form (1') in the solid state. F-2 was characterized by MS since the fraction showed two spots on TLC. The MS chromatogram revealed two well resolved peaks. One of the peaks, which exhibited an M^+ ion at m/z 288, was assumed to be 1,1-di(phthalazin-3-yl)-hydrazine (2)[4] because of the occurrence of intense fragment ions at m/z 272 (M^+-NH_2) and 171, both of which were observed in 1. The other peak exhibited an M^+ ion at m/z 431 was presumed to be 1-amino-1,2,2-tri(phthalazin-3-yl)hydrazine (3)[5] based on strong fragment ions at m/z 415 (M^+-NH_2) and 272. F-3 was assigned to 1,1,2-tri(phthalazin-3-yl)hydrazine (4)[6] based on an NH group in the IR (3350 cm^{-1}) and ^{1}H-NMR (δ 12.13) and on an MS fragmentation pattern similar to 3.

The mechanism of this reaction and the formation of other degradation products resulting from the counterpart are under study and will be reported elsewhere.[7]

ACKNOWLEDGMENTS Thanks are due to Dr. Katsuhiko Nagahara of Kitasato University for ^{1}H-NMR, and to Dr. Syunichi Manabe and Mr. Hajime Yamanaka of this school for the MS. We also express appreciation to Dr. Misuzu Ichiba for helpful discussions.

REFERENCES AND NOTES

1) Z.H. Israili and P.G. Dayton, Drug Metab. Rev., 6, 283 (1977) and references cited therein.

2) Hydralazine hydrochloride (Lot No. 7003239) and cimetidine (Lot No. 89507) were generously supplied by Ciba-Geigy (Japan) Ltd. and Smith-Klein Fujisawa Co., Ltd., respectively.

3) Compound 1; mp 219-222°C. IR (Nujol) cm^{-1}: 1020, 1080, 1160, 1260, 1300, 1470, 1520, 1580, 1600, 1620, 2230, 3320. MS m/z (%): 273 (23.9), 272 (29.2), 245 (6.2), 172 (11.4), 171 (100), 103 (30.4), 89 (21.4), 76 (14.0). ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.84-8.50 (10H, m, aromatic protons), 9.86 (1H, s, NH, D_2O exchangeable). UV ($CHCl_3$) λmax nm (log ε): 848 (4.07), 813sh (3.84), 393 (4.37), 288 (4.17), 280 (4.15), 258 (4.13). Anal. Calcd for $C_{16}H_{11}N_5$: C, 70.32; H, 4.06; N, 25.63. Found: C, 70.49; H, 4.10; N, 25.85.

4) Compound 2; MS m/z (%): 288 (62.8), 273 (19.8), 272 (100), 258 (20), 172 (11.8), 171 (94.7), 144 (21.6), 129 (12.2), 103 (29.3), 89 (17.9), 76 (17.6).

5) Compound 3; MS m/z (%): 431 (45.4), 416 (26.6), 415 (91.6), 386 (59.2), 273 (22.2), 272 (92.1), 145 (36.1), 144 (35.9), 130 (100), 129 (66), 103 (63.6), 89 (41.8), 76 (26.4).

6) Compound 4; mp >300°C. IR (Nujol) cm^{-1}: 1050, 1140, 1530, 1580, 1600, 1620, 3080, 3350. MS m/z (%): 416 (15.8), 415 (33.4), 273 (19.3), 272 (100), 145 (27.4), 144 (16.6), 130 (41.7), 129 (29.3), 103 (33.9), 89 (23.4), 76 (13.3). ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.61-9.09 (15H, m, aromatic protons), 12.13 (1H, s, NH, D_2O exchangeable). UV ($CHCl_3$) λmax nm (log ε): 836 (4.14), 812sh (4.05), 378 (4.72), 272sh (4.84), 252 (5.04). Anal. Calcd for $C_{24}H_{16}N_8$ 1/5 H_2O: C, 68.63; H, 3.94; N, 26.68. Found: C, 68.65; H, 3.81; N, 26.80.

7) The absence of cimetidine did not give the degradation products described herein.

(Received February 17, 1986)