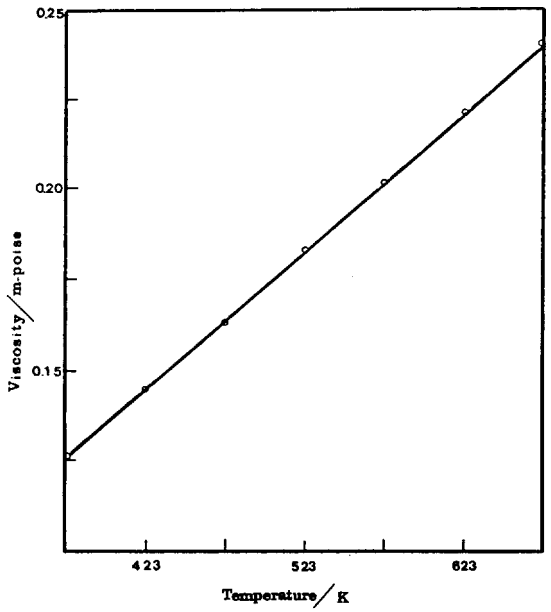


**Figure 2.** Viscosity of water vapor versus temperature Solid line; Calculated (Values of $C_p$ from Ref. 7), Open circles; Observed.

**Table 2.** The comparison of calculated and observed viscosities

| T/K | $\eta$ obs.[8] (μpoise) | $\eta$ calc. (μpoise) | Δ % |
|---|---|---|---|
| | Liquid Water | | |
| 273.15 | 17920 | 17925 | 0.03 |
| 283.15 | 13070 | 12715 | -0.03 |
| 293.15 | 10020 | 10125 | 1.05 |
| 313.15 | 6528 | 6517 | -0.17 |
| 333.15 | 4665 | 4665 | 0.00 |
| 353.15 | 3547 | 3547 | 0.00 |
| 373.15 | 2818 | 2818 | 0.00 |
| | Water Vapor | | |
| 373.15 | 125 | 125 | 0.00 |
| 423.15 | 145 | 145 | 0.00 |
| 523.15 | 183 | 183 | 0.00 |
| 573.15 | 202 | 202 | 0.00 |
| 623.15 | 222 | 221 | -0.45 |
| 673.15 | 241 | 239 | -0.83 |

viscosity near the freezing point decrease with increasing pressure and the explanation for this phenomenon is not clear until now.

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## Synthesis of Combination Compounds of Dihydropyridine and m-Blocker

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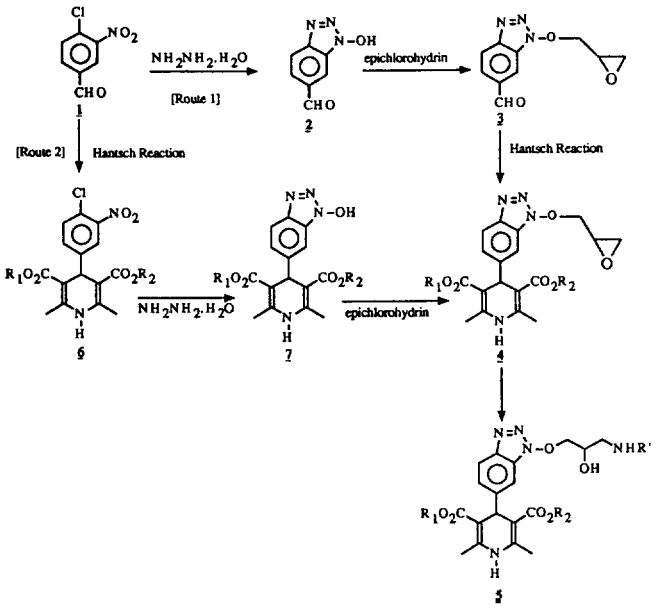
Combination of two drugs in one compound showing "dual action"[1] has been studied in searching of dual mode of action. H. A. Albrecht *et al.* of Hoffman-La Roche presented the preparation of cephalosporin linked with quinolones to find a broadened antibacterial spectrum[2]. In cardiovascular field the calcium channel blockers and the β-blockers are widely used for treatment the high blood pressure[3]. Specially the dihydropyridine derivatives (DHP)[4] in calcium channel blockers and 1-aminopropane-2,3-diol derivatives[5], such as propranolol, atenolol etc. in β-adrenergic blockers are widely used as cardiovascular drugs. By a combination of those two kinds of drugs in one molecule we would like to see the dual action of antihypertensive activities in the biological system.

Now we report the synthesis of the bifunctional dihydropyridines (5) linked with β-blockers via triazolyloxy group to find out the dual mode of action in the field of antihypertensive drugs. We chose the benzotriazolyloxy group as an suitable linker between DHP and aminopropane derivatives because the aromatic moiety has been known as the essential part[6] in DHP to show the antihypertensive activity and DHP with nitrogen atom at the aromatic ring generally has been accepted to show potentcy[7] in calcium channel blocking drugs. Furthermore the different ester groups were chosen aiming for the better activity[8]. In addition the hydroxyl group at the benzotriazole is the best feature to combine two drugs via oxygen which is the common atom in β-blockers[5].

Two synthetic routes which are shown below were attemted.

The first route is the synthesis of benzotriazolyl aldehyde (3) at the first which has epoxypropanoyl substitution at the aryl skeleton followed by a well known Hantsch reaction[6] with β-keto ester and amino crotonate to give the DHP derivatives (4). The second route is the synthesis of DHP skeleton (6) first and followed by cyclization of aryl substituents to give the benzotriazole (7), which is condensed with epichlorohydrin to give the compound (4). The first route gave us a low yield of DHP derivatives probably because of the less electron withdrawing power of the triazole goup. In other




hands the second route gave us a good yield of DHP derivatives (6) which were reacted further to give the benzotriazolyoxy compound (7) which were reacted with epichlorohydrin followed by the reaction with the $\beta$-blocker moiety to give the desired combination product (5).

Compound (6) is readily obtained in 80% yield from 4-chloro-3-nitrobenzaldehyde (1) by Hantsch reaction with refluxing the aldehyde, acetoacetate and 3-aminocrotonate in isopropyl alcohol for 3 hours. Benzotriazolyloxy compound (7) obtained by cyclization of compound (6) was reacted in ethanol solvent with the compound (6) and an excess of hydrazine hydrate for 24 hours refluxing. The benzotriazolyloxy compound was treated overnight with epichlorohydrin in basic media at room temperature to give the epoxy compound (4). The epoxy compound was refluxed for 2 hours with various amines in ethanol to give the desired products (5). The final combination products obtained were sent to the screening center of Korea Research Institute of Chemical Technology and were being investigated to find out the dual action of the cardiovascular activity.

## Representative Experimentals

**Ethyl 2-Methyl-2-propenyl**

**2,6-Dimethyl-4-(3′-nitro-4′-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (6).** 4-Chloro-3-nitrobenzaldehyde (7.42g, 40 mmole), ethyl 3-aminocrotonate and 2-methyl-2-propenyl acetoacetate (3.60g 40 mmole) were refluxed for 3 hours in isopropyl alcohol. The solvent was evaporated in vacuuo and the residue was column chromatographed on silica gel using toluene: ethyl acetate:methylene chloride = 25:3:3 to give an oily product (80% yield). NMR ($CDCl_3$): $\delta$ = 1.23 (t, 3H, $-CH_3$), 1.65 (s, 3H, $-CH_3$), 2.35 (bs, 6H, $2-CH_3$), 3.95 (s, 2H, $-OCH_2C-$), 4.10 (q, 2H, $-OCH_2-$), 4.75 (bs, 2H, $=CH_2$), 5.05 (bs, 1H, $-C_4-H$), 6.05 (bs, 1H, NH), 7.25-7.75 (m, 3H, aromatic). Anal. Calcd. for $C_{21}H_{23}N_2O_6Cl$: C, 57.99; H, 5.33; N, 6.44. Found: C, 58.00; H, 5.33; N, 6.48.

**Ethyl 2-Methyl-2-propenyl**

**2,6-Dimethyl-4-(1′,2′,3′-benzotriazole-1′-hydroxy)-1,4-dihydropyridine-3,5-dicarboxylate (7).** Hydrazine hydrate (1.05 m*l*, 21.56 m*l*) was added into the suspension of the above compound, Ethyl 2-Methyl-2-propenyl 2,6-Dimethyl-4-(3′-nitro-4′-chlorophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (2.5g, 5.75 mmole), in ethanol (20 m*l*) and was refluxed for 24 hours. The solvent was removed in vacuuo and the residue was dissolved in 1N-NaOH. The solution was treated with 1N-HCl until pH = 9 and was washed with methylene chloride. The aqueous solution was treated in ice bath with conc. HCl until pH = 1. The resulting solid was filtered and dried to give the desired product (59% yield). NMR (acetone-$d_6$): $\delta$ = 1.24 (t, 3H, $-CH_3$), 2.30 (bs, 6H, $2CH_3$), 4.03 (q, 2H, $-OCH_2-$), 4.38 (s, 2H, $-OCH_2-$), 4.70 (bs, 2H, $=CH_2-$), 5.15 (s, 1H, $-C_4-H$), 6.05 (bs, 2H, -OH, -NH), 7.60-8.05 (m, 3H, aromatic). Anal. Calcd. for $C_{21}H_{24}N_4O_5$: C, 61.16; H, 5.86; N, 13.58. Found: C, 61.18; H, 5.85; N, 13.56.

**Ethyl 2-Methyl-2-propenyl**

**2,6-Dimethyl-4-[1,2-epoxy-3-(1′,2′,3′-benzotriazole-1′-oxy)-propanolyl]-1,4-dihydropyridine-3,5-dicarboxylate (4).** Epichlorohydrin (1.99 m*l*, 25.2 mmole) in dioxane (5 m*l*) was added into the aqueous sodium hydroxide solution (NaOH 0.12 g in 3.9 m*l* of water) dissolving the above hydroxy compound Ethyl 2-Methyl-2-propenyl 2,6-Dimethyl-4-(1′,2′,3′-benzotriazole-1′-hydroxy)-1,4-dihydropyridine-3,5-dicarboxylate (1.24 g, 3 mmole) and stirred overnight at room temperature. The reaction mixture was extracted with methylene chloride and the organic layer was washed with brine and water and dried over sodium sulfate. After evaporation of the solvent the residue was column chromatographed on silica gel eluted with toluene/ethyl acetate = 1:4 to give an oily product (69% yield). NMR (acetone-$d_6$): $\delta$ = 1.25 (q, 3H, $-CH_3$), 1.65 (s, 3H, $-CH_3$), 2.35 (s, 6H, $2-CH_3$), 3.75-3.83 (m, 4H, $-OCH_2-$, $-CH_2-$), 3.95 (bs, 1H, -CH-), 4.07 (q, 2H, $-OCH_2-$), 4.05-4.10 (d, 2H, $-OCH_2-$), 4.83 (s, 2H, $-OCH_2-$), 5.20 (bs, 2H, $=CH_2$), 5.51 (s, 1H, $C_4-H$), 7.25-8.25 (m, 3H, aromatic), 8.75 (bs, 1H, -NH). Anal. Calcd. for $C_{24}H_{29}N_4O_6$: C, 61.40; H, 6.23; N, 11.93. Found: C, 61.42; H, 6.21; N, 11.92.

**Ethyl 2-Methyl-2-propenyl**

**2,6-Dimethyl-4-[1-tert-butylamino-3-(1′,2′,3′-benzotriazole-1′-oxy)- propanolyl]-1,4-dihydropyridine-3,5-dicarboxylate (5).** Tert-butylamine (1.53 m*l*, 14.5 mmole) was added into the suspension of the above epoxide compound Ethyl 2-Methyl- 2-propenyl 2,6-Dimethyl-4-[1,2-epoxy-3-(1′,2′,3′-benzo ria ole-1′-oxy)-propanolyl]-1,4-dihydropyridine-3,5-dicarboxylate (1.36 g, 2.9 mmole) in ethanol (5 m*l*) and was refluxed for 2 hours. The solvent was evaporated and column chromatographed on silica gel using ethyl acetate/methanol = 2:1 as an eluent to give the desired final product (60% yield). NMR ($CDCl_3$): $\delta$ = 1.27 (q, 3H, $-CH_3$), 1.38-1.40 (m, 9H, $3-CH_3$), 1.45 (s, 3H, $-CH_3$), 2.12 (m, 6H, $2-CH_3$), 3.78- 3.87 (m, 4H, -CH-, $-CH_2-$, -NH), 4.05-4.15 (m, 2H, $-OCH_2-$), 4.45 (s, 2H, $-OCH_2$), 4.55 (m, 2H, $-OCH_2$), 4.83-5.05 (m, 2H, $=CH_2$), 5.20 (s, 1H, $-C_4-H$), 7.40-8.37 (m, 3H, aromatic), 8.90 (bs, 1H, -NH). Anal. Calcd. for $C_{24}H_{40}N_5O_6$: C, 59.14; H, 7.09; N, 16.88. Found: C, 59.14; H, 7.07; N, 16.86.

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## Photo-Sensitized Mutarotation of α-(D)-Glucose in Dimethyl Sulfoxide (DMSO)


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Mutarotation of glucose in aqueous solvent has been extensively investigated, but in nonaqueous, aprotic solvent, effort to study both thermal and photochemical mutarotations have been severely limited because of poor solubility of glucose in the solvents.

We have first reported[1] the kinetics of photo-mutarotation of α-(D)-glucose including thermodynamic parameters and temperature dependence of quantum yields. In the previous paper, however, the photons and the photochemical effect of DMSO on the photo-mutarotation were not mentioned in detail.

**Table 1.** Change of Specific Rotations of α-(D)-Glucose on Irradiation at 350 nm. (temp: 34 ± 2 °C)

| Time (min.) | Specific Rotations | | | | | |
|---|---|---|---|---|---|---|
| | $[\alpha]^W$ | $[\alpha]^D$ | $[\alpha]^a$ | $[\alpha]^{ac}$ | $[\alpha]^b$ | $[\alpha]^{bc}$ |
| 0 | 106.9 | 106.9 | 105.6 | 105.6 | 105.8 | 105.8 |
| 514 | 106.9 | 106.9 | 102.5 | 101.1 | 101.7 | 100.6 |
| 1224 | 105.0 | 105.0 | 96.9 | 97.3 | 93.9 | 94.2 |
| 1562 | 102.8 | 102.8 | 87.2 | 91.5 | 86.1 | 89.3 |
| 2752 | 84.4 | 84.4 | 63.3 | 84.7 | 62.2 | 83.3 |
| 7200 | 54.0 | 54.0 | 53.9 | 53.9 | 54.4 | 54.0 |

$^W$wrapped. $^D$DMSO only. $^a$acetophenone and DMSO. $^b$benzophenone and DMSO. $^{ac}$acetophenone effect only (corrected for the thermal effect). $^{bc}$benzophenone effect only (corrected for the thermal effect).

In this paper, we wish to discuss the photochemical mechanism including the roles of DMSO, benzophenone and acetophenone.

Since the glucose molecule does not have any UV absorbing chromophores, the photo-mutarotations were not expected. However, irradiation of α-(D)-glucose in DMSO at 254 nm caused glucose molecule to mutarotate. To investigate the roles of DMSO, some classical sensitizers such as benzophenone and acetophenone were chosen for the sensitized mutarotations.

Irradiation[2] of α-(D)-glucose in DMSO with benzophenone or acetophenone at 350 nm showed mutarotations and the reaction mixtures reached equilibrium at the optical rotation, $[\alpha] = 53.9°$.

The phosphorescence of benzophenone and acetophenone were quenched efficiently by glucose molecules and showed linear Stern-Volmer relations (Table 2 and Figure 1).

**Table 2.** Stern-Volmer Quenching of the Sensitizer's Phosphorescence by Glucose

| Sensitizer | $k_q\tau$ | $\tau$ (sec)[3] | $k_q$ |
|---|---|---|---|
| Benzophenone | 0.409 | $4.7 \times 10^{-3}$ | $0.1 \times 10^{10}$ |
| Acetophenone | 0.037 | $2.3 \times 10^{-3}$ | $1.6 \times 10^{10}$ |

[3]V. L. Ermolaev, Soviet Physics, p. 333 (1963).

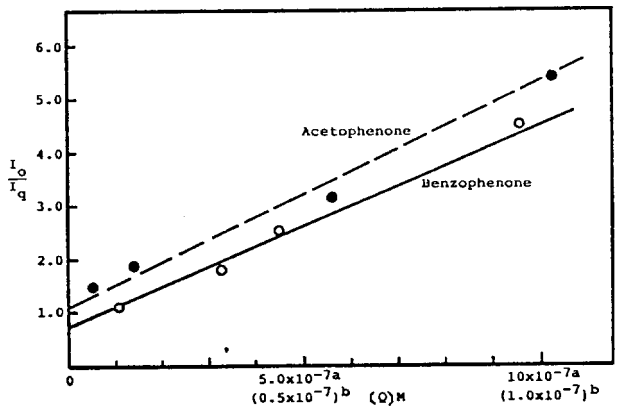


**Figure 1.** Stern-Volmer Quenching of Acetophenone and Benzophenone Phosphorescence by Glucose. ($I_q$ and $I_o$ represent the phosphorescence intensity with and without quencher respectively. *a* and *b* represent the Concentration of Quencher for Benzophenone and Acetophenone respectively).

Irradiation of α-(D)-glucose in DMSO without benzophenone or acetophenone at 350 nm showed no mutarotation (Table 1), however, irradiation at 254 and 300 nm caused an efficient mutarotation (Table 3).

The mutarotation at 254 nm in DMSO is not an unexpected result since DMSO molecule has a chromophore absorbing at 250-260 nm.

α-(D)-Glucose in water did not mutarotate at any wavelength of irradiation. This is an understandable fact considering the absence of UV-absorbing chromophores both in water and glucose. α-(D)-Glucose in DMSO, however, showed a chromophores absorbing at 285-290 nm, which would be