The Reaction of Benzotriazoles with 3,4-Dihydro-4*H*-pyrane and 2-Acetoxymethyl-3,4-dihydro-2*H*-pyrane

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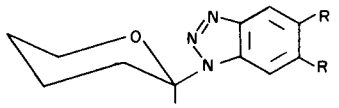
From the reaction of benzotriazoles with 2,3-dihydro-4*H*-pyrane and 2-acetoxymethyl-3,4-dihydro-2*H*-pyrane the corresponding 1-(2-tetrahydropyranyl)benzotriazole and *cis*- and *trans*-1-(6-acetoxymethyl-2-tetrahydropyranyl)benzotriazole derivatives were obtained. The structures and conformations of these compounds were confirmed by UV and NMR spectra.

Current interest in this laboratory in the synthesis of benzotriazole and *v*-triazolo[*d*]pyrimidine glycosides from glycals (1) as potential antimetabolites of purine nucleosides has led us to consider as a previous step, the reaction of benzotriazole and some of its derivatives with 3,4-dihydro-4*H*-pyrane and 2-acetoxymethyl-3,4-dihydro-2*H*-pyrane.

Since the initial work of Paul (2) it has been well known that alcohols, phenols, mercaptans, amides and a great variety of other compounds react with 3,4-dihydro-4*H*-pyrane and its derivatives to give C-2 substituted tetrahydropyranes (3). A similar reaction was shown to take place with some C-6 substituted purines by Robins *et al.* (4), who obtained 9-(tetrahydro-2-pyranyl)purines substituted at C-6 with these materials.

The heterocyclic system of benzotriazole, as well as those of its 5,6-dimethyl- and 5,6-dichloro-derivatives, could in principle react, by way of its 1 or 2 positions with either 3,4-dihydro-4*H*-pyrane or 2-acetoxymethyl-3,4-dihydro-2*H*-pyrane in a similar manner to that which takes place with purine derivatives. This is what in fact took place when ethyl acetate was used as a solvent in the presence of catalytic amounts of *p*-toluenesulfonic acid. Thus, working with 3,4-dihydro-4*H*-pyrane under these conditions led to products whose analytical data corresponded to those expected (Ia-c). In all these cases addition to the tetrahydropyrane ring took place through the nitrogen atom at position 1. This can be readily seen from their UV spectra, with maxima at 255-265 and 280-297 mμ and extinction coefficients similar to those of benzotriazoles substituted at N-1 (5). In no case could the formation of N-2 substituted products be detected.

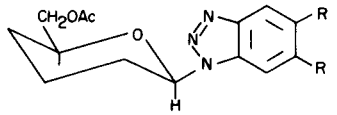


Ia, R = H
b, R = CH_3
c, R = Cl

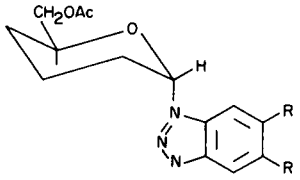
The study of the NMR spectra of these compounds also confirmed that substitution had taken place at N-1 since the protons at position 4 and 7 (in Ib and Ic), gave rise to two separate peaks, a fact indicative of their magnetic non-equivalence. In all the three cases the benzotriazole ring must occupy an equatorial position since the signal corresponding to the proton at C-2 of the tetrahydropyrane ring appears as a quartet with coupling constants of 7.5-8.4 and 2.7-3.1 cps. This suggests an axial-axial and axial-equatorial coupling with the two neighbouring protons.

Since the reactions proceed with the concomitant formation of an asymmetric carbon atom, the products obtained (Ia-c) are racemic. Up to now their resolution has not yet been attempted. The use in this reaction of racemic 2-acetoxymethyl-3,4-dihydro-4*H*-pyrane (6) entails the possibility of formation of four optically active isomeric products grouped in two pairs of racemic forms.

In the three cases studies, as before, it was possible to prove the exclusive formation of N-1 substituted benzotriazoles. The UV spectra of the compounds obtained were similar to those of 1-alkyl-benzotriazoles (5). In addition,



IIa, R = H
b, R = CH_3
c, R = Cl



IIIa, R = H
b, R = CH_3
c, R = Cl

two different signals were observed for the aromatic protons in C-4 and C-7 in the cases of the 5,6-dimethylbenzotriazole and 5,6-dichloro-benzotriazole. Furthermore it was possible to separate the mixtures of racemates (IIb + IIIb and IIc + IIIc) formed into the individual racemic forms, *cis* (IIb,c) and *trans* (IIIb,c). This separation was accomplished by column chromatography on silica gel. No attempt was made to separate these racemic forms into the corresponding optically active compounds.

The mixture obtained in the reaction with benzotriazole itself could also be separated by preparative t.l.c. once the acetyl group had been removed by treatment with alcoholic ammonia. In this case no attempt was made to separate the racemic forms of the acetyl derivatives because the components (IIa + IIIa) of the liquid mixture were thermally unstable and underwent a facile interconversion upon heating.

A similar treatment of the remaining acetyl derivatives, *cis* (IIb,c) and *trans* (IIIb,c), with alcoholic ammonia at room temperature gave the corresponding alcohols.

The structures and conformations of the *cis* and *trans* isomers were inferred basically from their NMR spectra. In the case of the acetylated products (II, III) the acetoxymethyl group at C-6 must be in both racemic forms, *cis* and *trans*, in an equatorial position for this would avoid 1,3-diaxial interactions with hydrogen atoms. Another argument in favour of this conformation was the well known fact (7) that a reverse anomeric effect is induced by the acetoxymethyl group. In the racemic forms of the *cis* isomers (II) the benzotriazole moiety is equatorial and the proton at C-2 of the tetrahydropyrane ring is axial since the signal corresponding to this proton in their NMR spectra appears as a quartet with coupling constants within the usual range for axial-axial and axial-equatorial couplings. (See Experimental).

On the other hand the NMR spectra obtained from the *trans* racemic forms show a broad band, half-height with Δ_{ν}^{m} 6-6.7 cps, corresponding to the anomeric proton that, in these cases, must be equatorial.

It must be emphasized also, in support of these assignments, that the chemical shifts of the anomeric proton differ by 0.2-0.3 τ for all pairs of *cis-trans* isomers studied. This is in agreement with the fact observed with various pairs of α- and β-nucleosides (8) as well as with tetrahydropyrane derivatives (9). In all these cases the axial anomeric protons appear a field higher than that for their corresponding equatorial counterparts.

EXPERIMENTAL

Melting points are uncorrected. The NMR spectra were recorded on a Perkin-Elmer R-10 spectrometer in deuteriochloroform with TMS as an internal standard. The UV spectra were recorded with a Perkin-Elmer 350 spectrophotometer. Thin layer plates were made of silica gel, Merck GF_{254} (0.25 mm.), using a mixture of cyclohexane-ethyl acetate (1:1) as the developing system; spots were made visible with UV light (254 mμ).

Reactions with 3,4-dihydro-4*H*-pyrane.

In all cases the following experimental conditions were employed. To 3,4-dihydro-4*H*-pyrane (12.6 g., 0.15 mole) and a small amount of *p*-toluenesulfonic acid were added benzotriazole (0.1 mole) or one of its derivatives dissolved in ethyl acetate (70 ml.). The mixture was heated under reflux for four hours. The solution was cooled, washed with a 5% solution of sodium bicarbonate in water and dried over sodium sulfate. Only, two spots were observed by thin layer chromatography, one of which was benzotriazole or the corresponding derivative.

After removal of the solvent *in vacuo* the product separated as a solid or thick oil that crystallized on scratching.

1-(2-Tetrahydropyranyl)benzotriazole (Ia).

This compound was obtained in 70% yield, b.p. 144-146°/0.7 mm., m.p. 52-53° (petroleum ether); UV λ max (ethanol), 255 (ϵ, 6,780), 260 (ϵ, 6,390), 280 mμ (ϵ, 4,355); NMR spectrum (deuteriochloroform, τ), 4.04 quartet ($J_{a,a}$ 8.4 cps, $J_{a,e}$ 3.1 cps), 1.7-2.9 multiplet (5H, aromatic).

Anal. Calcd. for $C_{11}H_{13}N_3O$: C, 65.02; H, 6.40; N, 20.67. Found: C, 64.88; H, 6.54; N, 20.74.

1-(2-Tetrahydropyranyl)-5,6-dimethylbenzotriazole (Ib).

This compound was obtained in 73% yield, m.p. 92-93° (cyclohexane); UV λ max (ethanol), 261 (ϵ, 7,430), 268 (ϵ, 6,970), 287 mμ (ϵ, 4,650); NMR spectrum (deuteriochloroform, τ), 4.09 quartet ($J_{a,a}$ 7.5 cps, $J_{a,e}$ 2.8 cps), 2.27 and 2.55 singlets (2H, aromatic), 7.67 singlet (6H, methyl groups).

Anal. Calcd. for $C_{13}H_{17}N_3O$: C, 67.53; H, 7.40; N, 18.22. Found: C, 67.54; H, 7.57; N, 17.97.

1-(2-Tetrahydropyranyl)-5,6-dichlorobenzotriazole (Ic).

This compound was obtained in 60% yield, m.p. 125-126° (cyclohexane); UV λ max (ethanol), 265 (ϵ, 5,700), 271 (ϵ, 5,670), 297 mμ (ϵ, 4,145); NMR spectrum (deuteriochloroform, τ), 4.01 quartet ($J_{a,a}$ 7.5 cps, $J_{a,e}$ 2.7 cps), 1.86 and 2.12 singlets (2H, aromatic).

Anal. Calcd. for $C_{11}H_{11}Cl_2N_3O$: C, 48.52; H, 4.04; N, 15.44. Found: C, 48.82; H, 4.17; N, 15.19.

Reactions with 2-acetoxymethyl-3,4-dihydro-2*H*-pyrane.

The experimental conditions used here were essentially the same as above. Benzotriazole (0.02 mole) or one of its derivatives dissolved in ethyl acetate (50 ml.) was heated with 2-acetoxymethyl-3,4-dihydro-2*H*-pyrane (3.9 g., 0.025 mole) and a small amount of *p*-toluenesulfonic acid. After heating for five hours, the solution was cooled, washed with 5% aqueous sodium bicarbonate and dried over sodium sulfate. Three spots were observed on thin layer chromatography, one of which corresponded to the benzotriazole employed. The solvent was evaporated and the residue was treated in the manner described in each case.

cis- and *trans*-1-(6-Acetoxymethyl-2-tetrahydropyranyl)-5,6-dimethylbenzotriazole (IIb, IIIb).

The crude product (5.8 g.) which was obtained as a thick oil was chromatographed on silica gel. Elution with a mixture of ethyl acetate-petroleum ether (1:1) gave two separate products. The first product was a thick oil (1.44 g.) that solidified on standing, m.p. 84-85° (ethanol-water); UV λ max (ethanol), 263 (ε, 7,882), 287 mμ (ε, 5,489); NMR spectrum (deuteriochloroform, τ), 3.80 broad band ($\Delta_\nu^m \sim 6.6$ cps), 2.20 and 2.43 singlets (2H, aromatic), 8.03 singlet (3H, acetyl group), 7.61 singlet (6H, methyl groups). This was the *trans* isomer (IIIb).

Anal. Calcd. for $C_{16}H_{21}N_3O_3$: C, 63.36; H, 6.93; N, 13.86. Found: C, 63.64; H, 7.22; N, 13.60.

The second product was a white solid (2.3 g.), m.p. 104-105° (benzene-petroleum ether); UV λ max (ethanol), 261 (ε, 7,350), 267 (ε, 6,910), 290 mμ (ε, 4,420); NMR spectrum (deuteriochloroform, τ), 4.04 quartet ($J_{a,a}$ 6.9 cps, $J_{a,e}$ 3.6 cps), 2.24 and 2.55 singlets (2H, aromatic), 7.95 singlet (3H, acetyl group), 7.62 singlet (6H, methyl groups). This was the *cis* isomer (IIb).

Anal. Calcd. for $C_{16}H_{21}N_3O_3$: C, 63.36; H, 6.93; N, 13.86. Found: C, 63.60; H, 6.67; N, 13.66.

cis- and *trans*-1-(6-Acetoxymethyl-2-tetrahydropyranyl)-5,6-dichlorobenzotriazole (IIc, IIIc).

The thick crude oil (7.7 g.) which crystallized on standing was dissolved in benzene and added to a silica gel column moistened with a mixture of ethyl acetate-cyclohexane (1:1). Elution was carried out with the same mixture giving, first, 1.32 g. of a white solid, m.p. 130-131° (methanol); UV λ max (ethanol), 264 (ε, 6,170). 278 (ε, 6,050), 296 mμ (ε, 4,120); NMR spectrum (deuteriochloroform, τ), 3.76 broad band ($\Delta_\nu^m \sim 6.0$ cps), 1.91 and 1.99 singlets (2H, aromatic), 7.94 singlet (3H, acetyl group). This product was the *trans* isomer (IIIc).

Anal. Calcd. for $C_{14}H_{15}Cl_2N_3O_3$: C, 48.83; H, 4.36; N, 12.20. Found: C, 48.58; H, 4.45; N, 12.42.

Continued elution afforded another solid product (3.3 g.), m.p. 110-111° (methanol); UV λ max (ethanol), 264 (ε, 6,030), 271 (ε, 5,810), 293 mμ (ε, 4,170); NMR spectrum (deuteriochloroform, τ), 4.00 quartet ($J_{a,a}$ 8.1 cps, $J_{a,e}$ 4.6 cps), 1.85 and 2.08 singlets (2H, aromatic), 7.89 singlet (3H, acetyl group). These data indicate that the second product was the *cis* isomer (IIc).

Anal. Calcd. for $C_{14}H_{15}Cl_2N_3O_3$: C, 48.83; H, 4.36; N, 12.20. Found: C, 48.72; H, 4.21; N, 11.95.

Deacetylation of the 6-Acetoxymethyl Derivatives.

In all cases the acetylated product was dissolved in dry methanolic ammonia and kept at room temperature for 30 hours. After removal of the methanol the product was recrystallized as indicated in each case.

cis- and *trans*-1-(6-Hydroxymethyl-2-tetrahydropyranyl)benzotriazole.

The crude product obtained (IIa + IIIa) from the reaction of 2-acetoxymethyl-3,4-dihydro-2*H*-pyrane with benzotriazole was treated with methanolic ammonia as indicated above. A sample (1.4 g.) of the residue obtained after removal of the methanol was dissolved in chloroform and the solution was applied to five preparative t.l.c. plates (20 x 20 cm., and 2 mm. thickness silica gel, Merck PF_{254}). The plates were developed in a mixture of ether-petroleum ether (1:2) allowing the solvent to run the total length of the plates and dried. This procedure was repeated several times resulting in the separation of the two major components which were detected by a UV lamp (254 mμ).

The band with smaller R_f gave 0.35 g. of a white solid, m.p. 77-78° (benzene-petroleum ether); UV λ max (ethanol), 255.5 (ε, 6,380), 261.5 (ε, 6,100), 280 mμ (ε, 3,860); NMR spectrum (deuteriochloroform, τ), 3.73 broad band ($\Delta_\nu^m \sim 6.7$ cps), 1.7-2.9 multiplet (4H, aromatic). This product was the *trans* isomer.

The second band gave 0.21 g. of a thick oil; NMR spectrum (deuteriochloroform, τ), 4.06 quartet ($J_{a,a}$ 9.7 cps, $J_{a,e}$ 3.3 cps), 1.8-3.0 multiplet (4H, aromatic). This compound was the *cis* isomer.

cis-1-(6-Hydroxymethyl-2-tetrahydropyranyl)-5,6-dimethylbenzotriazole.

This compound was obtained as a white solid, m.p. 109-110° (ethyl acetate-cyclohexane); UV λ max (ethanol), 260 (ε, 7,646), 287 mμ (ε, 4,805); NMR spectrum (deuteriochloroform, τ), 4.08 quartet ($J_{a,a}$ 8.5 cps, $J_{a,e}$ 3.0 cps), 2.29 and 2.61 singlets (2H, aromatic), 7.65 singlet (6H, methyl groups).

Anal. Calcd. for $C_{14}H_{19}N_3O_2$: C, 64.36; H, 7.27; N, 16.09. Found: C, 64.28; H, 7.54; N, 15.83.

trans-1-(6-Hydroxymethyl-2-tetrahydro-pyranyl-5,6-dimethylbenzotriazole.

This was obtained as a thick liquid; NMR spectrum (deuteriochloroform, τ), 3.88 broad band ($\Delta_\nu^m \sim 6.6$ cps), 2.37 and 2.47 singlets (2H, aromatic), 7.72 singlet (6H, methyl groups).

cis-1-(6-Hydroxymethyl-2-tetrahydropyranyl)-5,6-dichlorobenzotriazole.

This compound was obtained as a white solid, m.p. 158-159° (benzene); UV λ max (ethanol), 264 (ε, 6,180), 270.7 (ε, 5,940), 296 mμ (ε, 4,270); NMR spectrum (deuteriochloroform, τ), 4.05 quartet ($J_{a,a}$ 7.6 cps, $J_{a,e}$ 4.5 cps), 1.96 and 2.22 singlets (2H, aromatic).

Anal. Calcd. for $C_{12}H_{13}Cl_2N_3O_2$: C, 47.68; H, 4.30; N, 13.90. Found: C, 47.95; H, 4.59; N, 14.17.

trans-1-(6-Hydroxymethyl-2-tetrahydropyranyl)-5,6-dichlorobenzotriazole.

This was obtained as a white solid, m.p. 149-150° (benzene); UV λ max (ethanol), 265.5 (ε, 6.250), 272 (ε, 6,150), 296 mμ (ε, 3,620); NMR spectrum (deuteriochloroform, τ), 3.75 broad band ($\Delta_\nu^m \sim 6.4$ cps), 1.88 and 2.03 singlets (2H, aromatic).

Anal. Calcd. for $C_{12}H_{13}Cl_2N_3O_2$: C, 47.68; H, 4.30; N, 13.90. Found: C, 47.62; H, 4.15; N, 14.04.

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REFERENCES

(1) M. Fuertes, G. García-Muñoz, M. Lora-Tamayo, R. Madroñero, and M. Stud, *Tetrahedron Letters,* 4089 (1968).

(2) R. Paul, *Bull. Soc. Chim. France,* 1, 973 (1934).

(3) W. E. Perham and D. Delaitsch, *J. Am. Chem. Soc.,* 70, 4187 (1948); W. E. Perham and E. L. Anderson, *ibid.,* 76, 4962 (1954); A. J. Speziale, K. W. Ratts, and G. J. Merco, *J. Org. Chem.,* 26, 4311 (1961).

(4) R. K. Robins, E. F. Godefroi, E. C. Taylor, L. R. Lewis, and A. Jackson, *J. Am. Chem. Soc.,* 83, 2574 (1961); L. R. Lewis, F. H. Schneider, and R. K. Robins, *J. Org. Chem.,* 26, 3837 (1961); W. A. Bowles, F. H. Schneider, L. R. Lewis, and R. K. Robins, *J. Med. Chem.,* 6, 471 (1963).

(5) R. H. Wiley, N. R. Smith, D. M. Johnson, and J. Moffat, *J. Am. Chem. Soc.,* 76, 4933 (1954).

(6) R. Zelinski, A. Verbiscar and H. Eichel, *J. Org. Chem.,* 23, 184 (1958).

(7) B. Coxon, *Tetrahedron,* 22, 2281 (1966).

(8) T. Nishimura and B. Shimizo, *Chem. Pharm. Bull* (Japan), 13, 803 (1965); K. I. Imai, A. Nohara, and M. Honjo, *ibid.,* 14, 1377 (1966); E. E. Leutzinger, W. A. Bowles, R. K. Robins, and L. B. Townsend, *J. Am. Chem. Soc.,* 90, 127 (1968).

(9) U. E. Diner and R. K. Brown, *Can. J. Chem.,* 45, 2547 (1967).

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