A SIMPLE SYNTHESIS OF BENZOPYRANS

Tetsuji Kametani*

Pharmaceutical Institute, Tohoku University,

Aobayama, Sendai, Japan

Kazuo Kigasawa, Mineharu Hiiragi, Haruhide Ishimaru,

Nagatoshi Wagatsuma

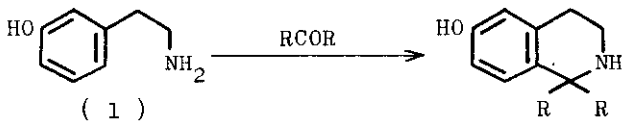
Research Laboratories, Grelan Pharmaceutical Co. Ltd.,

Sakurashinmachi, Setagayaku, Tokyo, Japan

trans-2-(3-Hydroxyphenyl)cyclohexanol (4) was converted into 1,2,3,4,4a,10b-hexahydro-6-spirocyclohexano-6H-dibenzo[b,d]pyran-9-ol (8) either by phenolic cyclisation or by acid catalysis. The corresponding 6-methyl-6-phenylbenzopyran derivative (9) was also obtained from 4 by the same methods. This type of reaction was applied to the fecile synthesis of 3,4-dihydro-6-methoxy-1-methoxycarbonyl-1-methyl-1H-2-benzopyran (11) and the hexahydro-6H-dibenzo[b,d]pyrans (18, 19, 22, and 23).

Previously, we have reported that heating 3-hydroxyphenethylamine (1) with a carbonyl compound in alcohol without acid gave

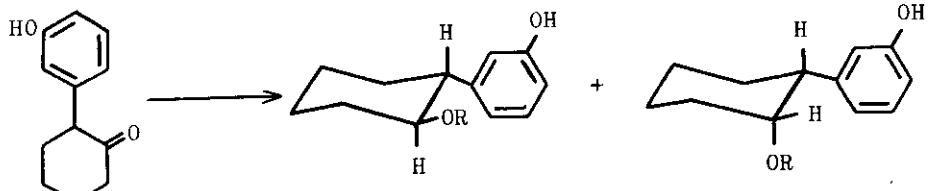
1,2,3,4-tetrahydro-6-hydroxyisoquinolines (2) with a mono- or disubstituent at the C-1 position, and proposed that this type of non-acidic reaction, especially useful for the synthesis of acid-sensitive isoquinolines, be called "Phenolic Cyclisation".[1] As an extension and modification of this reaction, we now wish to report the facile synthesis of a number of benzopyrans.



(1) (2)

Ladenburg reduction[2] of 2-(3-hydroxyphenyl)cyclohexanone (3)[3] gave a separable mixture of trans- (4), m.p. 144 - 145°, and cis-2-(3-hydroxyphenyl)cyclohexanol (6), m.p. 114°, in a ratio of 4 : 1 in 90 % yield. On the other hand, catalytic reduction of 3 over palladium-carbon afforded a mixture of 4 and 6 in a ratio of 1 : 20 in 21 % yield. Treatment of both alcohols with acetic anhydride at 100° for 3 hr gave the trans-acetate (5) [ν_{max} (liquid) 1730 and 1760 cm^{-1}; $\delta(CCl_4)$ 1.90 and 2.16)] and the cis-acetate (7) [ν_{max} (liquid) 1730 and 1760 cm^{-1}; $\delta(CCl_4)$ 1.84 and 2.16], respectively, whose stereochemistry was indicated by the following n.m.r. spectral considerations. The methine proton at the C-2 position of the trans-acetate (5) resonated at 2.3 ppm as a sextet having J

10.8, 10.8 and 3.6 Hz, and C-1 proton at 4.8 as a sextet having J 10.8, 10.8 and 4.2 Hz. Since $J_{1,2}$ is assigned 10.8 Hz, the dihedral angle for C-1 and C-2 proton is 180°. On the other hand, the C-1 and C-2 methine protons in cis-acetate (7) were observed at 5.02 as a broad signal and at 2.72 as an octet showing J 10.8, 4.0 and 2.4 Hz, respectively. On irradiation of the C-1 proton the C-2 proton showed a double doublet having J 10.8 and 4.2 Hz, and decoupling of the C-1 proton from the C-6 methylene protons at 1.83 produced a doublet for the C-1 proton with $J_{1,2}$ 2.4 Hz, indicating a dihedral angle of 60° for the C-1 and



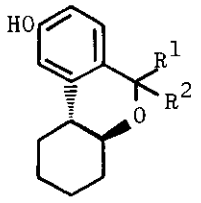
(3)

(4) R=H

(5) R=Ac

(6) R=H

(7) R=Ac



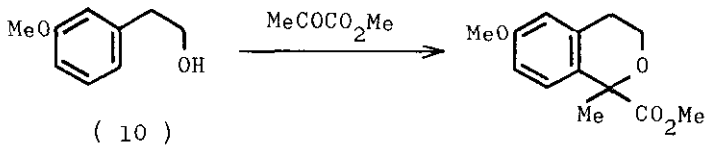
(8) $R^1+R^2=(CH_2)_5$

(9) R^1=Me, R^2=Ph

C-2 protons.

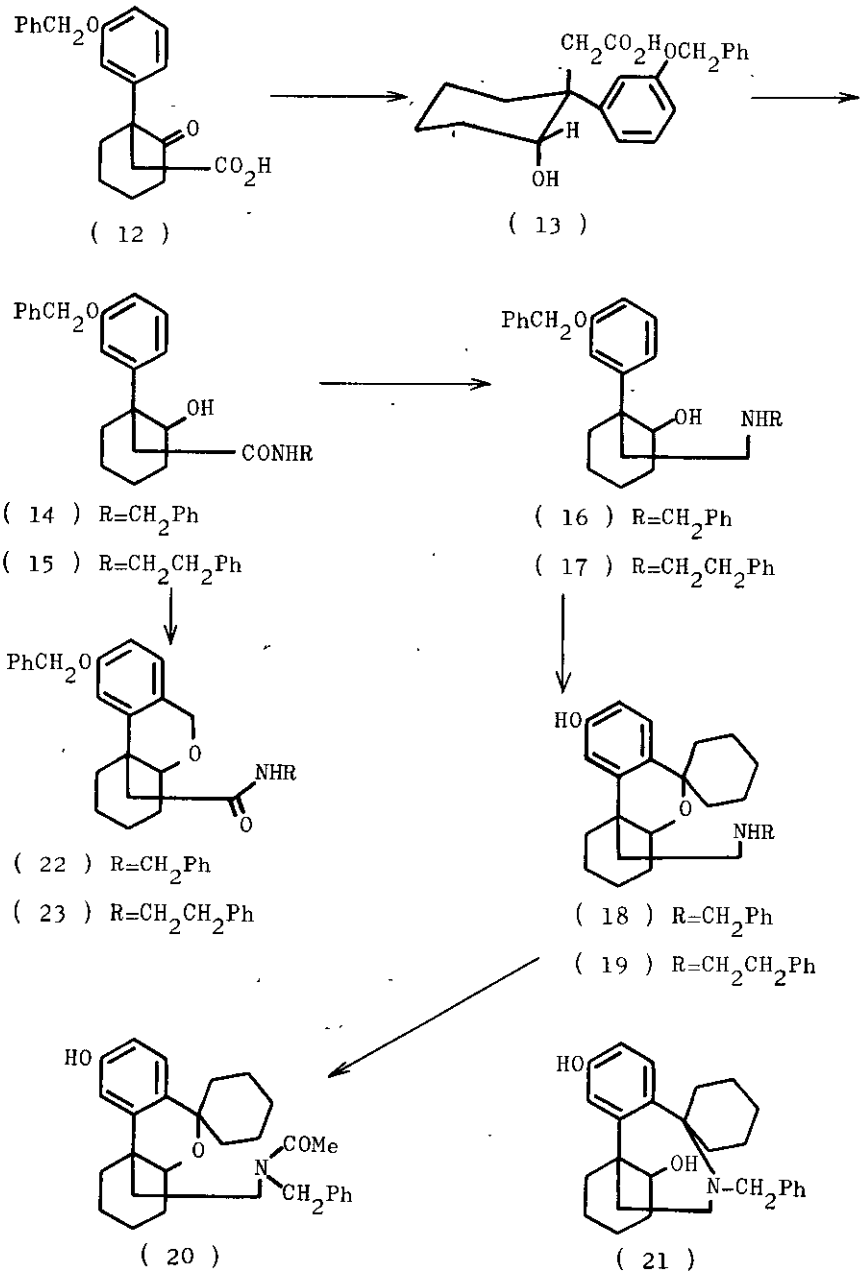
Heating trans-alcohol (4) with cyclohexanone in ethanol in a sealed tube for 15 hr without acidic catalyst gave in 28 % yield 1,2,3,4,4a,10b-hexahydro-6-spirocyclohexano-6H-dibenzo-[b,d]pyran-9-ol (8), m.p. 179 - 180° [δ(DMSO-d_6) 6.65 (1H, dd, J 8.3 and 2.3 Hz, C_8-H), 6.75 (1H, d, J 2.3 Hz, C_{10} - H), and 6.95 (1H, d, J 8.3 Hz, C_7 - H)], which was also obtained in 85.1 % yield by condensation of 4 with cyclohexanone in the presence of concentrated hydrochloric acid. Similarly, the reaction of trans-alcohol (4) with acetophenone afforded 6-methyl-6-phenylbenzopyran analogue (9), m.p. 128 - 130° [δ (DMSO-d_6) 6.83 (1H, dd, J 8.3 and 2.3 Hz), 6.93 (1H, d, J 2.3 Hz) and 7.15 (1H, d, J 8.3 Hz)].

On the other hand, the reaction of 2-(3-methoxyphenyl)ethanol (10) with methyl pyruvate required an acidic catalyst and in the presence of a catalytic amount of p-toluenesulphonic acid afforded 3,4-dihydro-6-methoxy-1-methoxycarbonyl-1-methyl-1H-2-benzopyran (11) [ν_{max} (liquid) 1730 cm^{-1}; δ (CCl_4) 1.60 (3H, s, >C-Me), 6.5 - 6.9 (2H, m, ArH) and 7.26 (1H, d, J 8.3 Hz,



(10) (11)

Chart 4


PhCH2O
O
CO2H
(12)
CH2CO2H
OCH2Ph
H
OH
(13)
PhCH2O
OH
CONHR
(14) R=CH2Ph
(15) R=CH2CH2Ph
PhCH2O
OH
NHR
(16) R=CH2Ph
(17) R=CH2CH2Ph
PhCH2O
O
NHR
O
(22) R=CH2Ph
(23) R=CH2CH2Ph
HO
O
NHR
(18) R=CH2Ph
(19) R=CH2CH2Ph
HO
O
N
COMe
CH2Ph
(20)
HO
OH
N-CH2Ph
(21)

C_8 - H)] in 80 % yield. This suggests that this type of reaction is a kind of phenolic cyclisation.

As an extension of this method, the amino alcohols (16 and 17) and amido alcohols (14 and 15) were readily transformed to yield a number of novel bonzopyrans. Sodium borohydride reduction of ketocarboxylic acid (12)[4] gave in quantitative yield the alcohol (13), m.p. 138 - 139°, whose stereochemistry was indicated by n.m.r. spectroscopy (δ in $CDCl_3$) which showed the methine proton at 3.96 as a triplet having J 3 Hz. Condensation of this alcohol with benzylamine and phenethylamine afforded the amides (14 and 15), whose reduction with lithium aluminium hydride gave the amines (16) (hydrochloride, m.p. 197 - 199°) and (17) (m.p. 115 - 116°). Reaction of 16 with cyclohexanone in the presence of hydrochloric acid then furnished in 30 % yield the benzopyran (18), m.p. 203 - 204°, ν_{max} (KBr) 3300 cm^{-1} (OH or NH), whose n.m.r. spectrum showed an ABX pattern [δ($CDCl_3$) 6.58 (1H, dd, J 8.5 and 2.0 Hz, C_8-H), 6.73 (1H, d, J 2.0 Hz, C_{10}-H), and 6.98 (1H, d, J 8.5 Hz, C_7-H)] for the three aromatic protons. The alternate benzazocine (21) was excluded since an amide (20) [ν_{max} (KBr) 1620 cm^{-1}] was formed by the usual acetylation. Similarly, the amino alcohol (17) could be converted into the benzopyran derivative (19), m.p. 218 - 219°, ν_{max} (KBr) 3250 cm^{-1}, in 27 % yield.

Moreover by reaction with formalin and hydrochloric acid the amido alcohol (14) was trnasformed into the benzopyran

(22), m.p. 127 - 128°, ν_{max} (KBr) 1650 cm^{-1} in 55 % yield, whose structure was indicated since no acetylation occurred and by an n.m.r. AB pattern at 4.80 and 5.12 (J 13 Hz) for the C-5 methylene protons. The second amido alcohol (15) also gave the benzopyrans (23), m.p. 156 - 157° [ν_{max} (KBr) 1660 cm^{-1} (-CON<), $\delta(CDCl_3)$ 4.12 and 4.60 (each 1H, each d, J 15 Hz, C_6-H_2)] in 62 % yield.

Thus, in contrast to the standard methods,[5,6] we have developed a new and simple synthetic method of benzopyrans.

REFERENCES

1 T. Kametani, K. Fukumoto, K. Kigasawa, M. Hiiragi, and H. Ishimaru, Heterocycles, 1975, 3, 311.

2 R. Cornubert, G. Barraud, M. Cormier, M. Descharmes, and H. G. Eggert, Bull. Soc. chim. France, 1957, 407.

3 T. Kametani, K. Fukumoto, K. Kigasawa, M. Hiiragi, H. Ishimaru and K. Wakisaka, J. Chem. Soc. (C), 1971, 1805.

4 T. Kametani, K. Kigasawa, M. Hiiragi, N. Wagatsuma, K. Wakisaka, F. Satoh, and S. Saito, J. Medicin. Chem., 1970, 13, 1064.

5 H. H. Warren, G. Dougkerty, and E. S. Wallis, J. Amer. Chem. Soc., 1957, 79, 3812.

6 S. Siegel and S. Coburn, J. Amer. Chem. Soc., 1951, 73, 5494.

Received, 12th April, 1975