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THE REACTION OF SOME BENZHYDRYL HYDROGEN PHTHALATE ESTERS WITH THIONYL CHLORIDE:

A ONE-STEP CONVERSION TO BENZHYDRYL CHLORIDES

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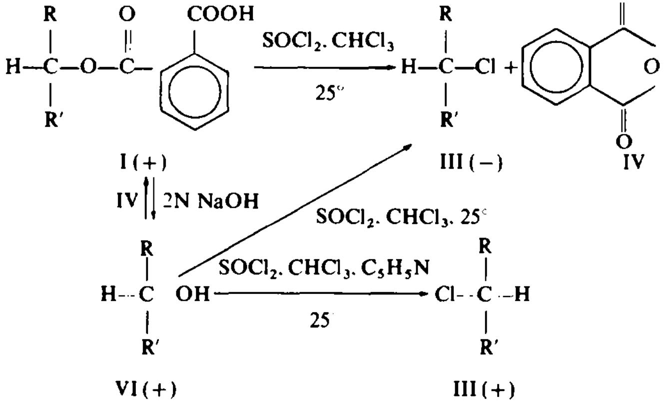
Abstract—The conversion of some benzhydryl hydrogen phthalate esters to their corresponding benzhydryl chlorides with thionyl chloride in chloroform is reported. In the case of the 4-nitro ester the reaction was found to occur with essentially complete retention of configuration.

ATTEMPTS to convert 4-nitrobenzhydryl hydrogen phthalate (I) to its acid chloride (II) by the usual $SOCl_2$-$CHCl_3$ procedure resulted in the formation of 4-nitrobenzhydryl chloride (III) and phthalic anhydride (IV) as the only isolable products in yields of 47% and 62%, respectively. Neither II nor the acid chlorosulfite V could be detected. Although the inability to isolate V is not surprising, the absence of II as the desired product of a conventional reaction is indeed intriguing as is also the isolation of III in reasonable yield.

The stereochemistry of the reaction was found to be concerted and to occur with retention of configuration about the asymmetric carbon according to Sequence 1.

SEQUENCE 1



$R = C_6H_5$

$R' = 4\text{-}NO_2\text{-}C_6H_4$

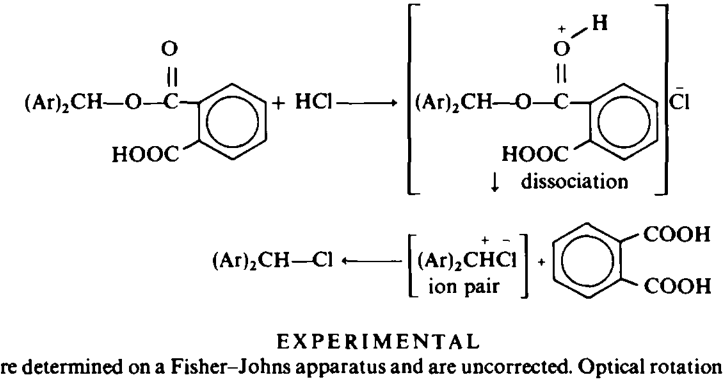
The ester I and its corresponding alcohol VI were resolved by the method of Puckowski and Ross[1] in greater than 98% optical purity($[\alpha]_D^{25}$ = +36·70° and +77·11° in $CHCl_3$, respectively). Optically active alcohol VI was converted to optically active chloride III, $[\alpha]_D^{25} = -5{\cdot}70^\circ$ (in $CHCl_3$) using stereospecific conditions (SNi) similar to those of Boozer and Lewis.[2, 3] This specific rotation compares very favourably with that obtained from optically active I under the same conditions, $[\alpha]_D^{25} = -5{\cdot}68^\circ$ (in $CHCl_3$). The enantiomer of III was obtained from optically active VI with the addition of pyridine to the reaction mixture (S_N2 conditions). The specific rotation obtained, $[\alpha]_D^{25} = +5{\cdot}85^\circ$ (in $CHCl_3$), would indicate that the conversion of optically active I to optically active III occurs stereospecifically and with essentially complete retention of configuration. It is noted that neither of the optically active enantiomers of III suffer any loss of optical activity when treated with $SOCl_2$ in $CHCl_3$ for as long as two days at 25°.

Mechanistically, the stereospecificity of the reaction with I can be accounted for by a concerted breakdown of either very unstable V or II, involving a 9- or 7-membered ring transition state, respectively. The latter is probably the preferred route.

The reaction would appear quite general with the benzhydryl system since the hydrogen phthalate esters of the following benzhydrols, 4-Br-4′-NO_2 (VII), 4-H (VIII), 4-CH_3 (IX), and 4-OCH_3 (X) afford the benzhydryl chlorides in yields of 91[4], 55, 61, and 36%, respectively. With the latter three, phthalic acid is a major product also (56, 68 and 47%, respectively) with IV in minor quantities (8, 14 and 17%, respectively).

The presence of phthalic acid in the case of reaction with compounds VIII, IX and X would indicate that a different mechanism is operative here. Initial reaction of $SOCl_2$ with the acid portion of the starting material would produce the acid chlorosulfite and HCl. The HCl could protonate unreacted starting material creating a reasonably good leaving group (Sequence 2). Dissociation of the protonated species to the ion pair and phthalic acid would be enhanced by the presence of electron releasing groups on the ring. Work is in progress to determine the degree of stereospecificity in this reaction path as well as the potential synthetic utility for optically active benzhydryl chlorides.

SEQUENCE 2



EXPERIMENTAL

M.ps were determined on a Fisher–Johns apparatus and are uncorrected. Optical rotation measurements were determined on a Rudolph Model 80 polarimeter equipped with a sodium lamp (λ 589 nm) using 2 dm polarimeter tubes and $CHCl_3$ as solvent. IR spectra were recorded in $CHCl_3$ with a Beckman IR-10 spectrophotometer equipped with KBr cells. Microanalysis were performed by Midwest Microlab Inc., Indianapolis, Indiana. NMR data were obtained in $CDCl_3$ with JEOL C-60 and JEOL C-60HL instruments and are reported in τ downfield from TMS as an internal standard.

4-Nitrobenzhydrol (VI) To a solution of 4-nitrobenzophenone (107·8 g, 475·0 mmole) and THF (1425 ml) in a 2-l conical flask, $NaBH_4$ (14·3 g, 380·0 mmole) was added with stirring in 0·5 g portions each dissolved in 5 ml of ice-cold H_2O. These portions were added at such a rate as to maintain the temperature below

35°. After addition was completed, the reaction mixture was stirred for 2 hr with the flask loosely stoppered, after which time it was poured slowly onto a slurry of ice and 12 N HCl. The THF was allowed to evaporate from the hydrolysed mixture over a stream of nitrogen. The yellow solid which formed was filtered and air dried. The crude alcohol (106·5 g, 97·8%), mp 71–73°, was recrystallized from a $CHCl_3$-hexane solvent pair. This gave pure alcohol, (86·0 g, 78·2%), mp 73–75° (recorded[5] 73–75·5°). The IR spectrum showed the following bands: 3610 (free OH); 3440 (bonded OH); 1600 and 1490 (Ar); 1020 (C-O); 830 and 690 (Ar) cm^{-1}. The NMR spectrum possessed the following τ 7·25 (1 H,s), (OH); 4·35 (1 H,s), (CH); 2·9–2·0 (9H,m), (Ar).

4-*Nitrobenzhydryl hydrogen phthalate* (I). A solution of 4-nitrobenzhydrol (19·0 g, 82·0 mmole), phthalic anhydride (16·4 g, 111·0 mmole) and pyridine (100 ml) was added to a 500-ml conical flask. With rapid stirring, NaH (6·0 g, 125·0 mmole of a 50% dispersion in mineral oil) was added at such a rate to maintain the temperature of the reaction below 35°. After addition, stirring was maintained for 4 hr with the flask loosely stoppered. The mixture was poured slowly onto a slurry of ice (3 kg) and 1 N HCl (100 ml). The solution was made acidic to pH 5. The organic material was extracted with 1 l of $CHCl_3$ which was then washed with several 100-ml portions of 0·5 N HCl followed by several washings with H_2O. The $CHCl_3$ solution was dried over anhydrous Na_2SO_4, filtered, and the solvent removed. The yellow solid which remained was recrystallized from a $CHCl_3$-hexane yielding pale yellow crystals (23·3 g, 75·4%), mp 157–159° (recorded[1] 158°). The IR spectrum showed the following bands: 3500–2500 (OH and CH); 1730 and 1700 (C═O); 1600 and 1490 (Ar); 1515 and 1345 (NO_2); 1280 and 1250 (C—O); 830 and 690 (Ar). The NMR spectrum showed: τ 2·8 (1H,s), (CH); 2·7–1·7 (13H,m), (Ar); −1·9 (1H,s), (COOH). (Calcd for $C_{21}H_{15}NO_6$: C, 66·84; H, 4·01. Found: C, 66·77; H, 4·11%).

(+)-4-*Nitrobenzhydryl hydrogen phthalate* (I). The racemic ester (106 g, 281·0 mmole) was dissolved in 99% EtOH (1 l) in a 2-l flask. Quinine (90·4 g, 279·0 mmole) was added in small portions to the warmed and stirring solution. The resulting solution was filtered and stored in a sealed 2-l flask. White crystals formed within a week (68 g), mp 124–127°. These were removed by filtration, redissolved in 99% EtOH and after standing one week, the colorless crystals that formed were removed by filtration (51 g, 26%), mp 126–128°, $[\alpha]_D^{25}$ −61·15° (c = 1·00). The quinine salt (28·1 g, 40·0 mmole) was dissolved in 95% EtOH (1 l). This solution was added quickly to rapidly stirring, ice-cold 0·2 N HCl (1120 ml). The white solid that formed was collected by filtration and was dried (13·2 g, 87·5%), mp 127–130°. After recrystallization from C_6H_6, the solid melted at 129–131°, $[\alpha]_D^{25}$ +36·70° (c = 2·00), (recorded[1] 131–132°, $[\alpha]_D^{20}$ +37·2°). The IR and NMR spectra were similar to those of the racemic ester. (Calcd for $C_{21}H_{15}NO_6$: C, 66·84; H, 4·01. Found: C, 67·05; H, 4·15%).

(+)-4-*Nitrobenzhydrol* (VI). A solution of (+)-4-nitrobenzhydryl hydrogen phthalate (4·0 g, 10·7 mmole) in THF (60 ml) was poured into ice-cold 2 N NaOH (1 l) which was stirred rapidly. N_2 was bubbled through the aqueous solution until no odor of THF remained. The pale yellow solid which formed was collected by filtration and was dried *in vacuo* (2·05 g, 84·4%). Recrystallization from C_6H_6 yielded yellow crystals, mp 79–80·5° (recorded[1] 80–81°), $[\alpha]_D^{25}$ +77·11° (c = 1·99), (recorded[1] $[\alpha]_D^{19}$ +78·2°). The IR and NMR spectra were identical to those of the racemic alcohol. (Calcd for $C_{13}H_{11}NO_3$: C, 68·11; H, 4·84. Found: C, 68·22; H, 4·94%).

Conversion of (+)-4-*Nitrobenzhydrol* (VI) *to* (−)-4-*nitrobenzhydryl chloride* (III).—(+)-4-Nitrobenzhydrol (0·5 g, 2·2 mmole) was dissolved in $CHCl_3$ (3 ml) in a 25-ml round bottom flask equipped with a condenser and a $CaCl_2$ drying tube. $SOCl_2$ (0·39 g, 3·3 mmole) was added dropwise to the solution. The reaction mixture was allowed to stir for 24 hr at room temperature after which time TLC analysis (silica gel GF, C_6H_6) showed only a trace of alcohol. The volatile materials were removed *in vacuo* and the remaining oil distilled, bp 148–149° (30 μ). The IR spectrum was identical to that of an authentic sample of *dl*-4-nitrobenzhydryl chloride and showed: 3010 (Ar); 2920 and 2850 (CH); 1600 and 1490 (Ar); 1520 and 1350 (NO_2); 820 and 690 (Ar) cm^{-1}. The NMR spectrum showed: τ 4·0 (1H,s), (CH); 2·85–1·95 (9H,m), (Ar). The yield of optically active chloride was 55·1% (0·3 g), $[\alpha]_D^{25}$ −5·70° (c = 1·00), n_D^{20} 1.6124 (recorded for racemic chloride[6] n_D^{20} 1·6171). (Calcd for $C_{13}H_{10}ClNO_2$: C, 63·04; H, 4·07. Found: C, 63·05; H, 4·15%).

Conversion of dl-4-Nitrobenzhydryl hydrogen phthalate (I) *to dl-4-nitrobenzhydryl chloride* (III) *with thionyl chloride*. The racemic ester (1·885 g, 5·0 mmole) was dissolved in $CHCl_3$ (15 ml). To this solution, $SOCl_2$ (1·07 g, 9·0 mmole) was added with stirring. The reaction mixture was allowed to stir 4·5 days at 25° after which TLC analysis (silica gel GF, C_6H_6) showed complete reaction. Volatile materials were removed *in vacuo*. The yellow gum which remained was dissolved in 125 ml of hot petroleum ether (bp 65–110°). Crystals of pure phthalic anhydride which formed were removed by filtration (0·46 g, 62·1%) and the remainin solvent was removed *in vacuo* from the filtrate. The last traces of phthalic anhydride were removed by sublimation at 40–45 (50 μ) for 10 hr. The remaining oil was distilled twice at 132–134 (35 μ). This yielded pure 4-nitrobenzhydryl chloride (0·573 g, 46·5%), n_D^{20} 1·6160. The IR spectrum was identical to that of the chloride obtained from reaction of the alcohol with $SOCl_2$.

Preparation of hydrogen phthalate esters VII, VIII, IX *and* X. These esters were prepared in excellent yields (> 75%) according to the procedure described for I.

Reaction of VII, VIII, IX *and* X *with* $SOCl_2$. According to the procedure outlined for the conversion of I to III, the above esters were converted to the corresponding benzhydryl chlorides in yields of 91[4], 55, 61 and 36%, respectively. The last three chlorides exhibited physical properties which compared favourably with those reported.[7-9] Yields of phthalic anhydride obtained were 95[4], 8, 14 and 17%, respectively, while yields of phthalic acid were 0, 56, 68 and 47%, respectively.

Conversion of (+)I *to* (−)III *with* $SOCl_2$. The procedure previously described for the conversion of *dl*-I to *dl*-III was modified in that the reaction was allowed to proceed for 52 hr at 25°. From 0·21 g (0·55 mmole) of optically active I, a yield of 46% of optically active III was obtained, bp 138–140° (20 μ), n_D^{20} 1·6147, $[\alpha]_D^{25}$ −5·68° (c = 1·00). The IR spectrum was identical to that of *dl*-III and TLC analysis showed only one component. (Calcd. for $C_{13}H_{10}ClNO_2$: C, 63·04; H, 4·07. Found: C, 62·96; H, 4·36%).

Conversion of (+)VI *to* (+)III *with* $SOCl_2$ *and pyridine.* (+)-4-Nitrobenzhydrol (0·125 g, 0·55 mmole) was dissolved in $CHCl_3$ (2 ml). Pyridine (0·043 g, 0·55 mmole) was added with stirring and $SOCl_2$ (0·12 g, 1·0 mmole) was added dropwise. The reaction mixture was allowed to stir for 2 hr at 25° at which time TLC analysis showed complete reaction. Volatile materials were removed *in vacuo*. The gum which remained was extracted with 40 ml of petroleum ether (bp 65–110°) leaving a yellow solid residue. The petroleum ether was removed *in vacuo* leaving crude III as an oil which was purified by distillation (0·10 g, 70%), bp 154–156° (50 μ), n_D^{20} 1·6154, $[\alpha]_D^{25}$ +5·85° (c = 1·00). TLC analysis showed only one component. The IR spectrum was identical to that of *dl*-III. (Calcd for $C_{13}H_{10}ClNO_2$: C, 63·04; H, 4·07. Found: C, 62·73; H, 4·22%).

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