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Optical Rotatory Dispersion of Nitrobenzene Derivatives. VII.[1] Application of Modified Curtius Rearrangement for Determining the Free Carboxylic Position in Some Partial Esters of 3-Nitrophthalic and 4-Nitrohemimellitic Acid

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Conclusive evidence was obtained for the position of chiral alkyl groups in the esters of 3-nitrophthalic and 4-nitrohemimellitic acid, which are key substances demonstrating interesting chiroptical property due to twisting of the nitrobenzene chromophore controlled by the remote chiral groups through *in phase* twisting of the intervening substituents. Diphenylphosphorylazide (DPPA) was used as the reagent for modified Curtius rearrangement with good success. Since it acts specifically on carboxylic acid but not on ester function, only the former is converted to amine function. The amino compounds so derived were proved to be identical with the known substances.

The method seems useful generally for determining the free carboxylic position in some partial esters of polycarboxylic acids.

l-Menthyl and *d*-bornyl esters (Ib, Ic, IIa, IIb, IVb, and IVc) show interesting chiroptical property.[3] In order to obtain conclusive evidence of their accurate structure, modified Curtius rearrangement with diphenylphosphorylazide (DPPA)[4] was attempted in success. The esters were prepared from the partial esters (Ia, III, and IVa), respectively, *via* corresponding chlorides. Migration of the methyl group during chlorination of I and II was reported.[5] Hence, the route of derivation not involving chlorination should be devised for unambiguous proof.

Compound (IIb) was also derived by methylation of IIa with diazomethane, and IIa was converted to IX by the Curtius rearrangement in high yield *via* VIa and VIb. The structure of IIb has now been confirmed conclusively, because the structure of IX is established by mild decarboxylation with acid leading to *m*-nitroaniline.[6]

Though compound (Ib) was prepared by chlorination of Ia followed by menthylation it is not identical but isomeric with IIb. Hence, the structure of Ib is also proved with certainty because no other isomers are possible.

Compound (IVb) was derived from IVa through the chloride. However, the chloride was reconverted to IVa in high yield.[3] So, the possibility of migration of the methyl groups during chlorination can be excluded. IVa was derived to VIIIb by the Curtius rearrangement in high yield via VIIIa. The structure of VIIIa was proved in two ways. (a): Partial reduction of dimethyl 3,6-dinitrophthalate (XI) gave VIIIb though in low yield. (b): Reduction of VIIIa with stannous chloride gave the diamino compound (XII), whose nuclear magnetic

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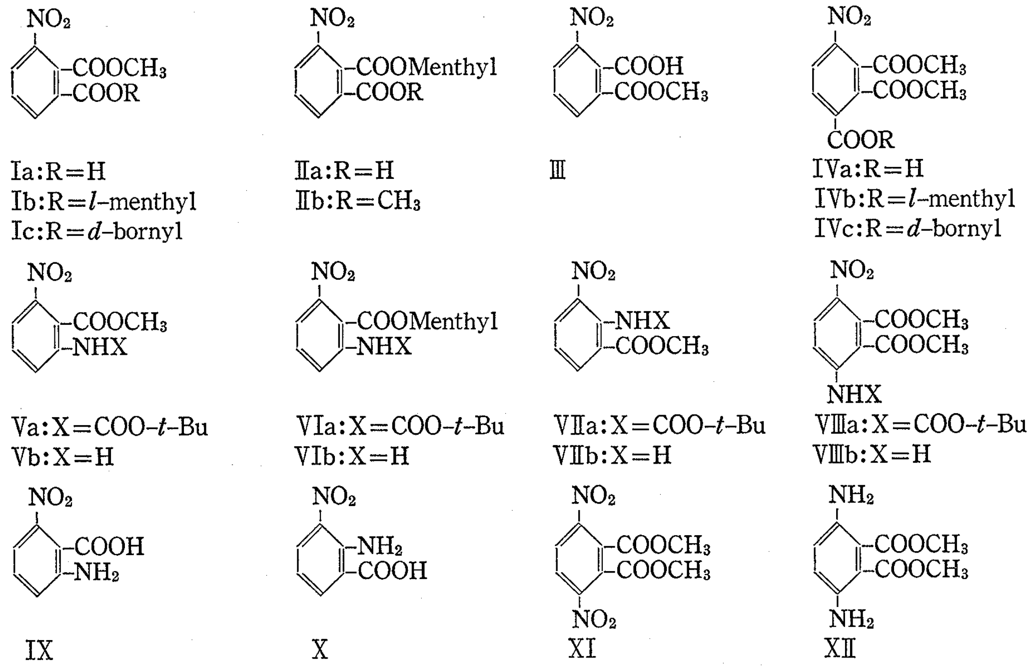
Ia: R=H
Ib: R=*l*-menthyl
Ic: R=*d*-bornyl

IIa: R=H
IIb: R=CH_3

III

IVa: R=H
IVb: R=*l*-menthyl
IVc: R=*d*-bornyl

Va: X=COO-*t*-Bu
Vb: X=H

VIa: X=COO-*t*-Bu
VIb: X=H

VIIa: X=COO-*t*-Bu
VIIb: X=H

VIIIa: X=COO-*t*-Bu
VIIIb: X=H

IX

X

XI

XII

Chart 1

resonance (NMR) spectrum showed a single peak due to aromatic protons, indicating symmetric arrangement of the substituents. These results confirmed the previously described structure and also indicate that no significant migration occurred during chlorination except the case of Ia. Fig. 1 represents the NMR patterns of aromatic protons of the two series of derivatives to show the clear difference between them.

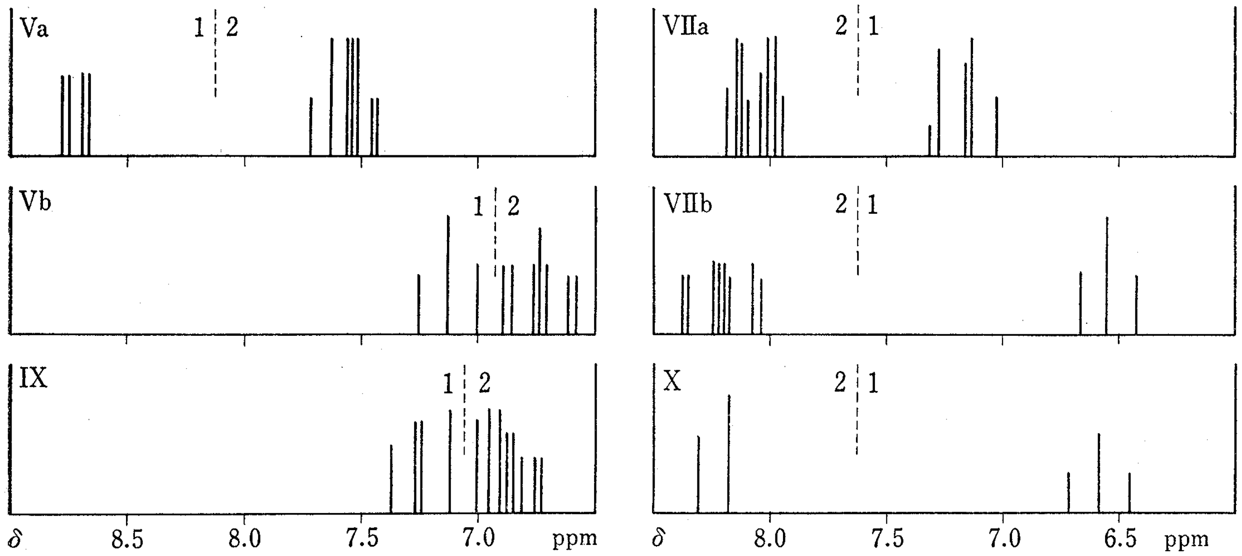

Fig. 1. NMR-Patterns of Aromatic Protons of Compounds Va, Vb, VIIa, VIIb, IX and X

Line positions and relative intensities are roughly reproduced. Numerals pinching the dotted line indicate the ratio of integrated peak areas on the respective side.

It may be noteworthy that a small amount of the amine was formed during the formation of the *t*-butyl carbonates in all cases. Whether it is due to slight excess of the acid reactant or thermal decomposition is not certain. CD-spectra of compounds (VIa) and (VIb), which are derivative of *l*-menthyl *o*-nitrobenzoate, both show a negative Cotton effect near 330 nm due to twisted nitrobenzene moiety indicating the general validity of the rule we proposed in the previous papers.[3]

Experimental

Melting point in capillary were measured with YAMATO Model MP-21 and mp on hot plate with Yanaco MP. Melting point are uncorrected. Infrared (IR)-spectra were measured with JASCO IRA-1 grating infrared spectrophotometer. NMR-spectra were measured with Hitachi R-24 60 MHz High Resolution NMR spectrophotometer. CD-spectra and $[\alpha]_D$ were measured with JASCO J-20 Automatic Recording Spectropolarimeter. Merck TLC and PLC silica gel 60 F_{254} were used for analytical and preparative layer chromatography, respectively.

_l_-Menthyl N-_t_-Butoxycarbonyl-6-nitroanthranilate (VIa)——144 mg of DPPA was weighed in a 5 ml-flask. 171 mg of Ia was added to the flask. Finally, 53 mg of NEt_3 dissolved in 510 ml of dry *t*-BuOH was added to the flask. The mixture was refluxed for 24 hr in an oil-bath maintained at 100±10°. The reaction mixture was then rotoevaporated to dryness. The residue was dissolved in ether, washed with 1/2N HCl and 5%-$NaHCO_3$ aq. successively, and dried over Na_2SO_4. On evaporation of ether 175 mg of yellow oil was obtained (crude yield 85%). A portion (48 mg) of the crude product was separated by chromatography on a silica plate developing with $CHCl_3$. From the higher band (ultraviolet (UV)-absorbing) 39 mg of crystals were obtained. Massive crystals from hexane had mp 124—125°. TLC $Rf=0.80$ ($CHCl_3$). UV λ_{max}^{MeOH} nm (ε): 324 (2000), 235 (17200), 217 (17400). IR λ_{max}^{KBr} cm^{-1}: 3450 (amino), 3100, 2960, 2080, 1740 (ester CO), 1720 (urethane CO), 1540, 1360 (nitro). PMR ($CDCl_3$) δ ppm: 0.76—0.98 (5 sharp peaks due to Me-groups in *l*-Menthyl residue), 1.50 (9H, singlet), 5.00 (1H, multiplet due to $OCHR_2$), near 7.50 (2H, multiplet), 8.45 (1H, quartet). $[\alpha]_D=-1.82°$ ($c=0.073$ in MeOH). CD ($c=7.14\times10^{-5}$ mole/liter in MeOH) $[\theta]_{410}=0$, $[\theta]_{346}=-9500$ (max), $[\theta]_{246}=-15400$ (max), $[\theta]_{223}=-19000$ (max). *Anal.* Found: C, 62.85; H, 7.68; N, 6.42. Calcd. for $C_{22}H_{32}O_6N_2$: C, 62.84; H, 7.67; N, 6.66%. From the lower band (yellow) 5.0 mg of yellow crystals were obtained. This substance was identical with IVb.

_l_-Menthyl 6-Nitroanthranilate (VIb)——116 mg of the remaining portion of the above crude product was treated with 1.0 ml of trifluroacetic acid (TFA) at room temp. under stirring for 0.5 hr. The reaction mixture was rotoevaporated to dryness. A few drops of NEt_3 was added to make the amine product free and rotoevaporated again. The residue was separated by chromatography on silica gel plates. Extraction of the main band (yellow) with EtOAc afforded 87 mg of yellowish crystals (yield: 98%). mp 101—106° (Kofler). TLC $Rf=0.65$ ($CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3150, 3480, 3380 (amino), 1710 (ester), 1620, 1600 (arom. C=C), 1530, 1360 (nitro). PMR ($CDCl_3$) δ ppm: 0.70—2.20 (18H, due to *l*-menthyl residue); 4.70 (1H, multiplet, $-OCHR_2$); 5.40 (2H, broad singlet, NH_2); 6.6—6.8 (2H, complex multiplet); 7.10 (1H, triplet, 8 Hz). $[\alpha]_D^{28}=-224°$ ($c=0.105$ in MeOH). CD ($c=1.038\times10^{-4}$ mole/liter in MeOH): $[\theta]_{420}=0$, $[\theta]_{336}=-4300$ (max), $[\theta]_{333}=-1900$ (min), $[\theta]_{262}=-10300$ (max), $[\theta]_{241}=-1860$ (min), $[\theta]_{220}=-20800$. *Anal.* Found: C, 63.84, H, 7.44; N, 8.51. Calcd. for $C_{17}H_{24}O_4N_2$: C, 63.73; H, 7.55; N, 8.74%.

6-Nitroanthranilic Acid (IX)——60 mg of VIb was treated with 2.0 ml of 5%-KOH in MeOH under reflux for 2.5 hr. The reaction mixture was diluted with 2.0 ml of H_2O and concentrated under reduced pressure to about a half of the volume. The concentrated aqueous solution was washed with ether, acidified with 4N HCl to pH 0.5—2.0, there formed slight turbidity and it grew crystalline on leaving a few hours at room temp. The crystals were filtered off and washed with a small volume of water and dried *in vacuo* affording 11 mg of the product. The filtrate and washings were combined and extracted with ether. Evaporation of the dried ether–layer over Na_2SO_4 afforded 17 mg of the residue, which crystallized on leaving. Total yield 28 mg corresponds to 81%. Orange yellow crystals. mp 178—181° (decomp.). TLC $Rf=0.66$ (BuOH: AcOH: $H_2O=4:1:5$ upper layer), $Rf=0.20$ (EtOAc). UV λ_{max}^{MeOH} nm (ε): 356 (2800); 238 (11200), 212 (12900). IR ν_{max}^{KBr} cm^{-1}: 3480, 3360 (NH_2), 3080—2300 (carboxyl-OH), 1670 (carboxyl), 1620, 1580 (arom. C=C), 1540, 1380 (nitro). PMR (MeOH-d_4) δ ppm: 6.78—7.00 (2H, complex multiplet); 7.11—7.38 (1H, quartet, 7 Hz, 8 Hz). The crystals had sweet taste. This substance was also obtained by similar hydrolysis of Vb (lit,[6]) mp 184°).

Methyl N-_t_-Butoxycarbonyl-6-nitroanthranilate (Va)——It was prepared by similar procedure as for VIa starting from 110 mg of Ia. The yield was 88 mg (61%). Faint yellow prisms. mp 82—85° (Kofler). TLC $Rf=0.06$ ($CHCl_3$). UV λ_{max}^{MeOH} nm (ε): 322 (2240), 234 (17800), 213 (16600). IR ν_{max}^{KBr} cm^{-1}: 3380, 3400 (amide NH), 1735 (ester CO), 1720 (urethane CO). PMR (CCl_4) δ ppm: 1.56 (9H, singlet); 3.96 (3H, singlet); 7.50 (1H, d-d, 8 Hz, 2 Hz); 7.65 (1H, triplet, 8 Hz); 8.75 (1H, double doublet, 8 Hz, 2 Hz); 8.82 (1H, broad-singlet). The proton magnetic resonance (PMR) spectrum was measured with JNM PS-100 NMR Spectrophotometer. *Anal.* Found: C, 52.55; H, 5.75; N, 9.17. Calcd. for $C_{13}H_{16}O_6N_2$: C, 52.70; H, 5.44; N, 9.46%. 14 mg of Vb was also obtained (Yield: 7%).

Methyl 6-Nitroanthranilate (Vb)——It was prepared by similar procedure as for VIb starting from 51 mg of Va. The yield was 33 mg (98%). Orange yellow crystals, mp 108—110° (Kofler). TLC $Rf=0.3$ ($CHCl_3$). UV λ_{max}^{MeOH} nm (ε): 363 (3160), 237 (13200), 216 (16600). IR ${}_{max}^{KBr}$ cm^{-1}: 3510, 3380 (NH_2), 1720 (ester), 1520, 1350 (NO_2). PMR (CCl_4) δ ppm: 3.74 (3H, singlet), 5.27 (2H, broad singlet), 6.57—6.88 (2H, multiplet) 1.12 (1H, triplet, 8 Hz). *Anal.* Found: C, 49.52; H, 4.27; N, 13.84. Calcd. for $C_8H_8O_4N_2$: C, 48.98; H, 4.11; N, 14.28%.

Methyl N-_t_-Butoxycarbonyl-3-nitroanthranilate (VIIa)——It was prepared by similar procedure as for VIa starting from 114 mg of II. Pale yellow crystals. The yield was 103 mg (69%). mp 80—84° (Kofler).

TLC $Rf=0.60$ ($CHCl_3$). UV λ_{max}^{MeOH} nm (ε): 326.5 (1990), 271 (sh, 3800), 240 (14100). IR ν_{max}^{KBr} cm^{-1}: 3360 (NH), 1745 (ester CO), 1700 (urethane CO), 1540, 1355 (NO_2). PMR (CCl_4) δ ppm: 1.49 (9H, singlet), 3.91 (3H, singlet), 7.12 (1H, triplet, 8 Hz), 8.06 (2H, multiplet), 9.48 (1H, broad singlet). *Anal.* Found: C, 53.23; H, 5.56; N, 9.25. Calcd. for $C_{13}H_{16}O_6H_2$: C, 52.70; H, 5.44; N, 9.25%. 23 mg of VIIb was also obtained (Yield: 23%).

Methyl 3-Nitroanthranilate (VIIb)——It was prepared by similar procedure as for VIb starting from 50 mg of VIIa. Orange yellow needles. The yield was 26 mg (79%). mp 95—97° (Kofler). TLC $Rf=0.73$ ($CHCl_3$). UV ν_{max}^{MeOH} nm (ε): 409 (11500), 260 (8710), 235 (24500). IR ν_{max}^{KBr} cm^{-1}: 3460, 3310 (NH_2), 1700 (ester CO), 1520, 1360 (nitro). PMR (CCl_4) δ ppm: 3.89 (3H, singlet), 6.55 (1H, triplet, 8 Hz), 8.15 (1H, double doublet, 8 Hz, 2 Hz), 8.32 (1H, double doublet, 8 Hz, 2 Hz), 8.4 (broad singlet). *Anal.* Found: C, 49.52; H, 4.27; N, 13.84. Calcd. for $C_8H_8O_4N_2$: C, 48.98; H, 4.11; N, 14.28%.

3-Nitroanthranilic Acid (X)——It was prepared by similar procedure as for IX starting from 30 mg of VIIb. The yield was 19 mg (69%). mp 191—195°. Orange crystals. UV λ_{max}^{MeOH} nm (ε): 417 (5900), 263 (4790), 233 (12900). IR ν_{max}^{KBr} cm^{-1}: 6300, 3480, 3350 (NH_2), 1675 (carboxyl CO). PMR (MeOH-d_4) δ ppm: 6.58 (1H, triplet, 8 Hz), 8.24 (2H, doublet, 8 Hz) (lit,[6] mp 202—203°).

Dimethyl N-*t*-Butoxycarbonyl-3-amino-6-nitrophthalate (VIIIa)——It was prepared by similar procedure as for VIa starting from 90 mg of III. The yield was 8.8 mg (74%). Colorless crystals. mp 133—138° (Kofler). UV λ_{max}^{MeOH} nm (ε): 313 (12600), 243 (infl., 10700), 211 (20900). IR ν_{max}^{KBr} cm^{-1}: 3330 (NH), 1740 (ester CO), 1720 (urethane CO), 1520, 1360 (NO_2). PMR ($CDCl_3$) δ ppm: 1.50 (9H, singlet), 3.88 (9H, singlet), 3.90 (3H, singlet), 8.17 (1H, d, 9 Hz), 8.62 (1H, doublet, 9 Hz), 9.78 (1H, broad singlet).

Dimethyl 3-Amino-6-nitrophthalate (VIIIb)——(a) It was prepared by similar procedure as for VIb starting from 69 mg of VIIIa. The yield was 39 mg (79%). Yellow crystals. mp 149—151° (Kofler). UV λ_{max}^{MeOH} nm (ε): 349 (10700), 247 (infl. 4900), 233 (infl. 7590), 218 (13800). IR ν_{max}^{KBr} cm^{-1}: 3480, 3360 (NH_2), 1745, 1710 (ester CO), 1510, 1380 (NO_2). PMR ($CDCl_3$) δ ppm: 3.84 (3H, singlet), 3.92 (3H, singlet), 6.40 (2H, broad singlet), 6.68 (1H, doublet, 8 Hz), 8.30 (1H, doublet, 9 Hz). *Anal.* Found: C, 47.78; H, 4.15; N, 10.93. Calcd. for $C_{10}H_{10}O_6N_2$: C, 47.25; H, 3.97; N, 11.02%. (b) 53 mg (0.18 mmoles) of XI was dissolved in 0.3 ml of AcOH. 127 mg (0.56 mmoles) of $SnCl_2 \cdot 2H_2O$ was dissolved in 0.1 ml of conc. HCl. The two solutions were mixed and stirred 3 hrs. A few drops of NEt_3 was added to neutralize HCl and to make free the amine formed. The reaction mixture was then rotoevaporated to very viscous slurry. The residue was treated with ether and H_2O. After separation of the two layers, the aqueous layer containing slurry ppt. was centrifiuged and the ppt. was washed with small amount of H_2O. The combined aqueous solutions were extracted with ether many times. The ether-layers were all combined and dried over Na_2SO_4. On removal of Na_2SO_4 and ether, 29 mg of the residue was obtained and purified by preparative layer chromatography. From the fastest moving yellow band 3.5 mg of yellow crystals were obtained. Their mp was 151—154° and showed no depression on admixture with the sample prepared by the above route (a), mixed mp 151—154°, (lit,[7] mp 146°). Their IR-spectra were superimposable. The low yield seems due to easier reduction of VIIIb to diamino derivative (XII) than XI.

Dimethyl 3,6-Dinitrophthalate (XI)——85 mg of the corresponding acid prepared by the known procedure[8] was treated with diazomethane in ether. On evaporation of ether 75 mg (85%) of the residue was obtained. mp 175—177°. TLC $Rf=0.4$ ($CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3460, 3370 (NH_2), 1700 (ester CO). PMR ($CDCl_3$) δ ppm: 3.79 (6H, singlet), 4.35 (4H, broad singlet), 6.65 (2H, singlet).

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