CHEMISTRY OF NEOPENTYL DERIVATIVES—II[1]

RESTRICTED ROTATION IN 2,6-DISUBSTITUTED NEOPENTYLBENZENES

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Abstract—A series of neopentylbenzene derivatives with substituents in 2- and 6-positions has been synthesized. A number of compounds were investigated by dynamic NMR spectroscopy. Restricted rotation was observed in 3-methyl-2-neopentylbenzoic acid and its derivatives. Thermodynamic and Arrhenius parameters were obtained for the restricted rotation of the neopentyl group. An additional Me group in 3-position causes a COOMe group in 2-position to rotate out of the plane of the aromatic ring, and this change is effective in reducing the barrier to rotation of the neopentyl group by about 1 kcal mole^{-1}.

INTRODUCTION

In a previous publication[2] we reported on the restricted rotation about an sp^2-sp^3 carbon–carbon single bond[3] in 1.2-dialkyl-1,2-bis(2,6-dimethylphenyl)ethanes. It was found that, when the alkyl groups were t-butyl, rotation was completely inhibited, in both the ($\pm$)- and the *meso*-compound. We now wish to communicate the results of similar investigations on 2,6-disubstituted neopentylbenzene derivatives.

Restricted rotation of a neopentyl group with respect to an aromatic ring has been found by Newman *et al.*[4] in 1,2-dineopentyl-3,4,5,6-tetramethylbenzene, and by Carter *et al.*[5] in 2,4-dichloro- and 2,4-dibromo-1,3,5-trineopentylbenzene. In these compounds some of the possible combinations of rotation of the neopentyl groups are not allowed due to non-bonded repulsions. The majority of our compounds have only one neopentyl group and are therefore not subject to such effects.

The compounds investigated by dynamic NMR spectroscopy were chosen from a series of 2,6-disubstituted neopentylbenzenes on the criterion that in the conformations assumed to be preferred, the methylene protons of the neopentyl group are to be diastereotopic by internal comparison, and might therefore be anisochronous in favorable cases.[6]

The influence of additional substituents in 3- and 5-positions on the height of the rotational barrier was also investigated.

CHEMISTRY

The synthesis of neopentylbenzenes has been described in detail in the first part of this series.[1] Here we confine ourselves to a schematic presentation of the preparation of the hydrocarbons (Scheme 1).

The neopentyl substituted aromatic carboxylic acids have been synthesized either

SCHEME 1
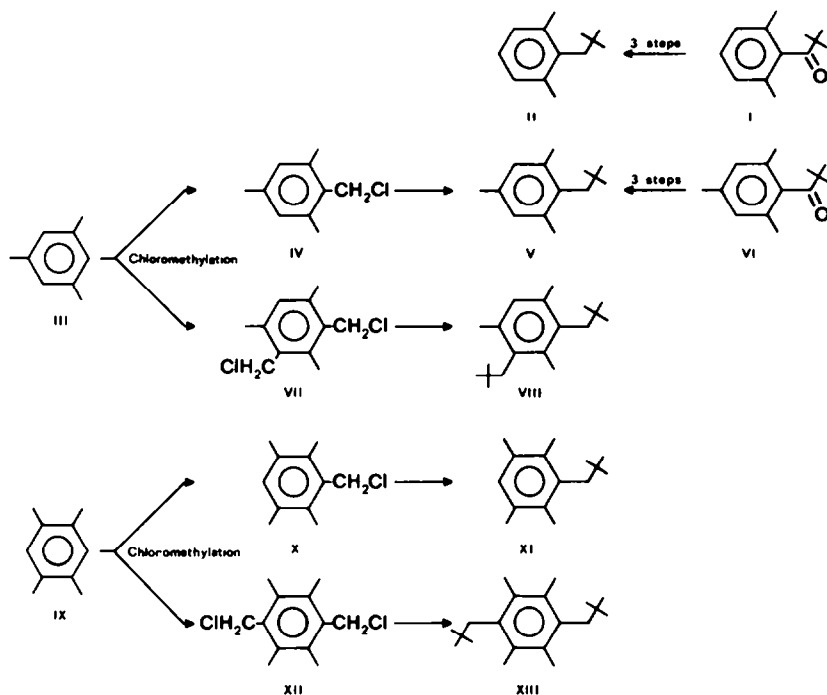
by oxidation of the hydrocarbons with alkaline potassium permanganate in aqueous pyridine,[7] or by treatment of the corresponding Grignard compound with solid CO_2. Scheme 2 illustrates the preparation of the acids and their derivatives.
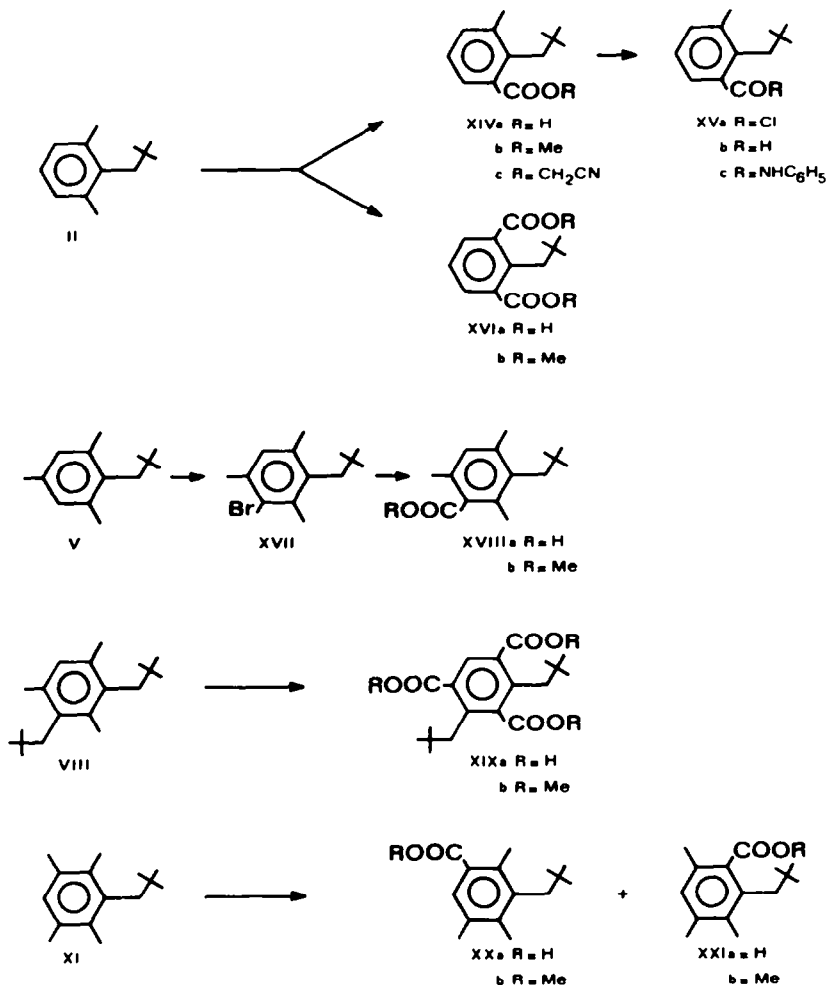
The following points are of interest: (i) The separation of the two acids XIVa and XVIa was based on the low solubility of the latter in boiling n-hexane. XVIa was purified by recrystallization of its diMe ester followed by alkaline hydrolysis. (ii) Treatment of XIVa with excess thionyl chloride gave the benzoyl chloride (XVa), which was reduced to the benzaldehyde (XVb) according to the method of Peters and Van Bekkum.[8] (iii) XVIIIa was prepared from XVII by the entrainment Grignard method as described for the synthesis of 2,4,6-trimethylbenzoic acid from bromo-mesitylene.[9] (iv) Oxidation of VIII surprisingly gave XIXa. Attempted oxidation of VIII to 2,4-dineopentyl-3,5-dimethylbenzoic acid has been unsuccessful so far. The use of other solvents, e.g. dry pyridine or acetone:water, resulted either in a much lower yield of XIXa or in the production of no acid at all. (v) XXa and XXIa were separated via preparative GLC of their methyl esters, followed by hydrolysis with concentrated sulfuric acid.[10]

METHODS AND RESULTS

NMR spectra

NMR spectra (60 MHz) were obtained from the compounds as 10% w/v solutes in CS_2. The relevant data are collected in Table 1. The methyl esters of the acids were

SCHEME 2

II

XIVa R = H
b R = Me
c R = CH$_2$CN

XVa R = Cl
b R = H
c R = NHC$_6$H$_5$

XVIa R = H
b R = Me

V → XVII → XVIIIa R = H
b R = Me

VIII → XIXa R = H
b R = Me

XI → XXa R = H
b R = Me + XXIa = H
b = Me

chosen in the experiments at low temperatures because the acids themselves were insufficiently soluble under these conditions. Compounds VIII, XIVb, XIVc, XVa, XVb, XVc, XVII, XVIIIb, XIXb, XXb and XXIb were selected for a study by variable temperature NMR. Of these, VIII, XVII and XVIIIb did not show a significant change of their NMR spectrum on cooling to −100°. XXb showed a broadening of the signal attributed to the methylene protons of the neopentyl group, but the "no-exchange" limit could not be reached.* The corresponding signals of the compounds XIVb, XIVc, XVa, XVb, XVc, XIXb and XXIb changed gradually from a singlet to an AB-pattern as the temperature was lowered. In XIVc the signal of the methylene protons of the cyanomethyl group remained a singlet at all temperatures. In Table 2 the relevant data for the seven compounds are summarized.

* −100° was the lowest temperature attainable with the instrumental facilities

TABLE 1. CHEMICAL SHIFTS OF 2,6-DISUBSTITUTED NEOPENTYLBENZENES IN CS_2 AT 39°
(δ-values, ppm, from TMS)

Compound	arom. $\underline{H}$	—CH_2—	—CH_3	—C_4H_9	—OCH_3
II	6·77	2·62	2·26	0·94	—
V	6·70	2·56	2·22 (6H); 2·16 (3H)	0·90	—
VIII	6·70	2·63	2·21	0·90	—
XI	6·69	2·70	2·12	0·89	—
XIII	—	2·74	2·15	0·86	—
XIVa	7·8–6·9	3·2	2·37	0·87	· —
XIVb	7·6–6·9	3·1	2·35	0·82	3·73
XIVc[a]	7·9–7·1	3·2	2·42	0·83	—
XVa	7·9–6·9	3·0	2·36	0·87	—
XVb[b]	7·6–6·9	3·03	2·35	0·87	—
XVc[c]	7·5–6·7	2·85	2·28	0·77	—
XVIa[d]	8·2–7·5	3·55	—	0·79	—
XVIb	7·9–7·1	3·49	—	0·71	3·78
XVII	6·81	2·67	2·35– 2·28 ; 2·22	0·90	—
XVIIIa	6·81	2·66	2·31	0·93	—
XVIIIb	6·77	2·63	2·28 ; 2·16 ; 2·13	0·92	3·75
XIXa[d]	8·29	3·4	—	0·83	—
XIXb	8·10	3·1	—	0·73	3·78
XXa	7·62	2·82	2·53 (3H); 2·28 (6H)	0·91	—
XXb	7·37	2·77	2·41 (3H); 2·22 (6H)	0·90	3·73
XXIa	6·83	2·90	2·33 ; 2·24 ; 2·18	0·89	—
XXIb	6·78	2·73	2·23 (3H); 2·16 (6H)	0·82	3·73

[a] —OCH_2CN δ = 4·88 ppm
[b] —CH=O δ = 9·82 ppm
[c] —NH— δ = 8·0 ppm
[d] measured in DMSO-d_6

TABLE 2. NMR DATA OF THE METHYLENE PROTONS AT 39° AND −60°, AND COALESCENCE TEMPERATURES

Compound	δ-values (ppm)			J (Hz)	T_c (K)
	39°	$W_{\frac{1}{2}}$ (Hz)	−60°		
XIVb	3·1	7	3·57 2·49	13·0	290
XIVc	3·2	14	3·54 2·55	13·5	285
XVa	3·0	7	3·31 2·55	13·5	284
XVb	3·03	2	3·56 2·38	14·0	263
XVc	2·85	2	3·29 2·35	14·0	268
XIXb	3·1	12	3·76 2·54	14·0	290
XXIb	2·73	1	2·79 2·61	14·0	265

Computer calculations[5]

The computer program† for the calculation of the theoretical lineshapes was based on the density matrix lineshape equations[11] for the coupled AB system.[12] The AB patterns were completely symmetrical and no long-range coupling with the aromatic

† Programs were kindly put at our disposal by Dr R. E. Carter of the University of Göteborg. Sweden and by Prof J. D. Roberts and Dr B. Hawkins of the California Institute of Technology. USA. We thank Mr J. H. Kelderman for adapting both programs for the IBM 360/65 computer of this University.

protons was observed for any of the compounds investigated. Values for the transverse relaxation time (T_2) were obtained under conditions of "no-exchange" from the width of a line of the AB-quartets; $1/T_2^0$ was assumed to be negligible. The coupling constant, J_{AB}, was assumed to be invariant throughout the entire temperature range.

Thermodynamic and kinetic parameters

The values of τ, the mean lifetime, obtained by visually matching the theoretical with the experimental spectra, were used to calculate the value of $\Delta G^{\ddagger}$ at a given temperature by means of the Eyring equation,[13]

$$\Delta G^{\ddagger} = 2 \cdot 3026 RT \log \frac{2\kappa\tau kT}{h}$$

in which κ was assumed to be unity. $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were calculated from $\Delta G^{\ddagger}$ and the temperature T, according to the equation

$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$$

using the method of least-squares.[14]

The Arrhenius parameters, E_a and log A, were obtained from the equation

$$\log \kappa = \log(1/2\tau) = \log A - E_a/2 \cdot 3026 RT$$

Here, as with the thermodynamic parameters, the mechanistic rate constant, k, is used instead of the kinetic. As there are two possible pathways for rotation, the mechanistic rate constant corresponds to $1/2\tau$ if the two substituents in 2- and 6-position are equivalent, and $k = 1/2\tau = (k_1 + k_2)/2$ when they are different, but both pathways for rotation of the neopentyl group are allowed. The parameters are collected in Table 3.

TABLE 3. ACTIVATION PARAMETERS FOR INTERNAL ROTATION AT ROOM TEMPERATURE (298 K)[a]

Compound	$\Delta G^{\ddagger}$ kcal mole^{-1}	$\Delta H^{\ddagger}$ kcal mole^{-1}	$\Delta S^{\ddagger}$ e.u.	E_a kcal mole^{-1}	log A
XIVb	14·6 ± 0·1	13·1 ± 0·1	−5·2 ± 1·0	13·6 ± 0·1	12·1 ± 0·1
XIVc	14·5 ± 0·1	12·7 ± 0·1	−6·1 ± 1·1	13·2 ± 0·1	11·8 ± 0·1
XVa	14·6 ± 0·1	12·6 ± 0·1	−6·8 ± 1·1	13·4 ± 0·1	11·9 ± 0·1
XVb	13·2 ± 0·1	11·9 ± 0·1	−5·1 ± 1·3	12·4 ± 0·1	12·0 ± 0·1
XVc	13·6 ± 0·1	11·7 ± 0·1	−7·0 ± 1·0	12·3 ± 0·1	11·7 ± 0·1
XIXb	14·5 ± 0·1	13·3 ± 0·1	−4·2 ± 1·0	13·8 ± 0·1	12·3 ± 0·1
XXIb	13·8 ± 0·1	11·7 ± 0·1	−7·2 ± 1·0	12·3 ± 0·1	11·7 ± 0·1

[a] The error limits are calculated assuming random errors only. and are almost certainly too low. More realistic error limits are ±0·5 kcal mole^{-1} in $\Delta G^{\ddagger}$. $\Delta H^{\ddagger}$. E_a. and log A. and ±2 e.u. in $\Delta S^{\ddagger}$

DISCUSSION

We assume that the preferential conformations of 2,6-disubstituted neopentylbenzene derivatives are chiefly determined by the non-bonded repulsions between the t-Bu group and the substituents. Non-bonded repulsions between the methylene protons and the substituents can be estimated to be of the order of 2 kcal mole^{-1},

as in *o*-xylene,[15] while other factors such as those playing an important role in toluene[16] are negligible. The preferential conformations are represented by **a** and **b** (Fig 1) and are energetically equivalent. Conformations **c** and **d** correspond to maxima in the energy curve. These maxima need not be equal when $R_1 \neq R_2$. A conformational change (**a → b**) can occur *via* **c** or *via* **d**, two pathways with in principle different probabilities, and therefore to be associated with different rate constants, k_1 and k_2.
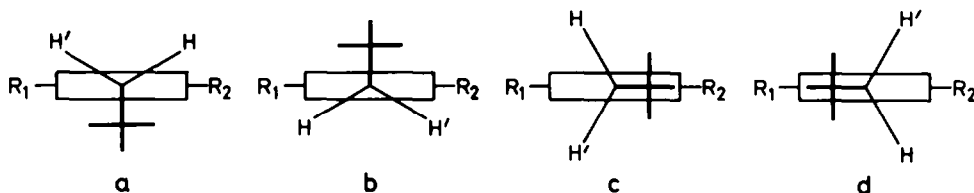

FIG 1.

In each of the preferential conformations the methylene protons are diastereotopic when $R_1 \neq R_2$, as in compounds XIVb, XIVc, XVa, XVb, XVc, and XXIb, or, if $R_1 = R_2$, when groups in 3- and 5-positions are different, as in compounds VIII, XVII, XVIIIb, XIXb, and XXb. A conformational change will result in an interchange of protons H and H' with respect to the substituents. The system is suitable for dynamic NMR investigation if the resonance frequencies for the protons in their environments are sufficiently different, and the life-times of the conformations are favorable. The observed temperature-dependence of the 60 MHz spectra of compounds XIVb, XIVc, XVa, XVb, XVc, XIXb, XXb and XXIb shows that in these cases all conditions are fulfilled.

For compounds XIVb, XIVc, XVa, XVb and XVc we assigned the highest chemical shift value (3·57–3·29 ppm, at −60°; *cf.* Table 2) to the methylene proton neighboring the oxygen containing group, *i.e.* proton H in Fig 1a, when R_1 = Me and R_2 = COR', using the chemical shift values of the methylene protons from Table 1 (*cf.* II, $R_1 = R_2$ = Me. δ = 2·62 ppm; XVIb, $R_1 = R_2$ = COOMe, δ = 3·49 ppm). One would expect about the same values for the low-temperature chemical shifts of the methylene protons in compound XXIb, but actually the values 2·61 and 2·79 ppm are found. We take this to mean that the COOMe group is rotated out of the plane of the aromatic ring by the *ortho* Me group. Additional evidence for this interpretation was obtained from the UV spectra of the acid (see Experimental). The lower energy of activation for rotation of the neopentyl group in compound XXIb as compared with compound XIVb (Table 3) may be a reflection of this change in conformation of the COOMe group.

In compound XIXb the chemical shift value of 2·54 ppm is assigned to a methylene proton near the COOMe group between the two neopentyl groups. The other value, 3·76 ppm, was considered to be normal for a methylene proton in the neighborhood of an "undisturbed" COOMe group. Here again, the central COOMe group must be rotated out of the plane of the aromatic ring.

For the compounds which failed to show a temperature dependence in their NMR spectra the condition that in the preferential conformation the difference in resonance

frequencies must be sufficient was not fulfilled. This is easily verified by inspection of the chemical shift values of the methylene protons under fast-exchange conditions (Table 1). Compound XXb is a borderline case in which the frequency condition is not favorable.

The activation parameters (Table 3) do not allow the evaluation of the contributions of the two possible pathways for rotation. However, the differences in activation energies and enthalpies for compounds XIVb, XIVc, XVa, XVb and XVc do suggest that rotation proceeds at least partially *via* conformation c. On the other hand, the observations for compound XXb make it highly unlikely that rotation *via* conformation **d** is completely inhibited. We feel safe to conclude that the steric effect of the Me group does not differ greatly from that of the COOMe group or other oxygen containing groups.

EXPERIMENTAL

With the technical assistance of Messrs J. Klomp and A. van Vliet. The elemental analyses were performed by Mr M. van Leeuwen of this Laboratory. All m.ps and b.ps are uncorrected. UV spectra were obtained on a Cary 15 spectrophotometer.

NMR spectra were obtained on a Varian A-60 spectrometer equipped with a V-6031B variable-temperature probe and a V-6040 variable-temperature controller. Temperatures were measured by means of a Varian MeOH sample (No. 943346–06) and shift-temperature correlation charts; their absolute values are correct to within $\pm 2^\circ$.

2.6-Dimethylneopentylbenzene (II). The synthesis of this compound starting from I has been described elsewhere.[2]

2.4.6-Trimethylneopentylbenzene (V). 32·0 g VI[17] was reduced with LAH in dry ether to give *2.2-dimethyl-1-(2.4.6-trimethylphenyl)propanol-1*. This compound was treated with $SOCl_2$ in dry C_6H_6 to yield the corresponding chloride. which was reduced with Li in liq. NH_3.[2] V was obtained in 60% yield. b.p. 122–124°/17 mm. n_D^{25} 1·5080. The physical data were in excellent agreement with the data of V prepared by the Grignard method.[1]

1.3-Dineopentyl-2.4.6-trimethylbenzene (VIII). 163·0 g VII[18] in 500 ml dry C_6H_6 was added to a soln of 233·0 g t-BuMgCl[19] in 500 ml dry ether. The mixture was refluxed for 24 hr and worked up in the usual way. Distillation *in vacuo* yielded 26·0 g of a mixture b.p. 110–140°/0·7 mm, n_D^{25} 1·5125. which contained 80% VIII. This product was subjected to preparative GLC. The fraction containing VIII was recrystallized twice from acetone to yield 13·7 g (7%) VIII. m.p. 37–39°. (Found: C. 87·7; H. 12·3. Calc. for $C_{19}H_{32}$: C. 87·62; H. 12·38%).

2.3.5.6-Tetramethylneopentylbenzene (XI). A soln of 91·0 g t-BuMgCl in 350 ml dry ether was added to a soln of 95·0 g X^{20} in 250 ml ether. The mixture was refluxed for 24 hr. hydrolyzed with 2N HCl. separated. and H_2O layer was extracted twice with ether. The combined ether layers were washed with a 5% $NaHCO_3$ soln and H_2O. The organic layer was filtered from *2.2'.3.3'.5.5'.6.6'-octamethylbibenzyl.* 30·0 g (39%). m.p. 232–233 . The filtrate was dried and ether evaporated. The residue was distilled *in vacuo*. The fraction boiling 138–148°/5 mm collected and recrystallized twice from EtOH. 12·0 g (11%) XI. m.p. 31·5–33°. (Found: C. 88·3; H. 11·8. Calc. for $C_{15}H_{24}$: C. 88·16; H. 11·84%).

1.4-Dineopentyl-2.3.5.6-tetramethylbenzene (XIII). As described for VIII was obtained from 53·0 g VII[21] 8·0 g (13%) XIII. m.p. 111–111·5° (from acetone). (Lit.[22] m.p. 110·2–111·6°).

3-Methyl-2-neopentylbenzoic acid (XIVa). 70·0 g II was oxidized with $KMnO_4$ in aq. pyridine.[7] The crude mixture of acids was separated by extraction with boiling n-hexane. Extracts were evaporated to dryness and crude XIVa recrystallized from MeOH. 52·0 g (63%) XIVa. m.p. 119–120°. (Found: C. 75·7; H. 8·7. Calc. for $C_{13}H_{18}O_2$: C. 75·69; H. 8·63%). UV: ε^{234} 5170. ε^{284} 1170 (0·85 N HCl in 55% EtOH).

A sample was treated with CH_2N_2 to yield the *Me ester* (XIVb). m.p. 38–39°. (Found: C. 76·7; H. 9·3. Calc. for $C_{14}H_{20}O_2$: C. 76·32; H. 9·15%).

1·0 g XIVa was mixed with 0·75 g Et_3N and 5·0 g chloroacetonitrile. heated to 70° then kept at 60°. Excess chloroacetonitrile was removed *in vacuo* and 50 ml dry EtOAc was added. The ppt of $Et_3N.HCl$ was filtered and crude EtOAc soln washed with 2N HCl. 5% $NaHCO_3$ soln. and H_2O. After drying the solvent was removed and the residue distilled to yield 1·0 g (84%) *cyanomethyl ester* (XIVc). b.p. 70°/0·1 mm. n_D^{25} 1·5148. (Found: C. 73·3; H. 7·7. Calc. for $C_{15}H_{19}NO_2$: C. 73·44; H. 7·81%).

3-Methyl-2-neopentylbenzaldehyde (XVb). 1·0 g XIVa was treated with an excess of purified $SOCl_2$ to give the *benzoyl chloride* (XVa). 0·5 g XVa was reduced over 10% Pd/C in acetone using $Et(iPr)_2N$ as HCl acceptor to give XVb (94%). b.p. 130°/10 mm. it solidified upon standing.*

3-Methyl-2-neopentylbenzanilide (XVc). The remainder of XVa was heated with 0·5 g aniline to give XVc. m.p. 140–141° (after several crystallizations from aq. EtOH).

2-Neopentylisophthalic acid (XVIa). The acid insoluble in n-hexane (see XIVa) was esterified and the ester recrystallized twice from MeOH. Elemental analysis and NMR proved it the *dimethyl ester* of *2-neopentylisophthalic acid* (XVIb). m.p. 73–73·5°. (Found: C. 68·1; H. 7·6. Calc. for $C_{15}H_{20}O_4$: C. 68·16; H. 7·63%).

Alkaline hydrolysis of XVIb yielded 5·2 g (6%, based on converted II) XVIa. m.p. 233–236°. (Found: C. 66·1; H. 6·9. Calc. for $C_{13}H_{16}O_4$: C. 66·08; H. 6·83%).

3-Bromo-2.4.6-trimethylneopentylbenzene (XVII). 36·0 g Br_2 in 23 ml CCl_4 was added dropwise to a soln of 35·0 g V in 16 ml CCl_4 below 10°. After addition the mixture was stirred for 1 hr at room temp. poured in water and the organic layer separated. This layer was washed with a 5% $NaHSO_3$ aq and H_2O. Solvent was evaporated and the residue distilled *in vacuo* to give 40·6 g (80%) XVII. b.p. 132–134°/2·5 mm. n_D^{25} 1·5438. (Found: C. 62·2; H. 7·7; Br. 30·0. Calc. for $C_{14}H_{21}Br$: C. 62·45; H. 7·86; Br. 29·69%).

3-*Neopentyl-2.4.6-trimethylbenzoic acid* (XVIIIa). 40·0 g XVII was converted as described for bromomesitylene[9] to yield 25·5 g (73%) XVIIIa. m.p. 164–165·5. (Found: C. 77·0; H. 9·4. Calc. for $C_{15}H_{22}O_2$: C. 76·88; H. 46%).

Dineopentyltrimesic acid (XIXa). 12·0 g VIII was oxidized[7] to yield 5·0 g (29%) of the monohydrate of XIXa. m.p. >300°. (Found: C. 61·8; H. 7·7. Calc. for $C_{19}H_{26}O_6 . H_2O$: C. 61·94; H. 7·66%).

3-Neopentyl-2.4.5-trimethylbenzoic acid (XXa) and *2-neopentyl-3.4.6-trimethylbenzoic acid* (XXIa). A mixture of 9·5 g XI. 100 ml pyridine. 20 ml H_2O. and 16·0 g $KMnO_4$ was heated under reflux for 6 hr. The mixture was cooled to room temp and enough $NaHSO_3$ added to dissolve the ppd MnO_2. The mixture was acidified with conc. HCl and acids taken up in ether. The ether extracts were washed with H_2O and extracted with 2N KOH. The alkaline extracts were acidified and the acids were taken up in ether. The ether extracts were washed with H_2O and dried. Treatment with an excess of CH_2N_2 yielded a mixture of the Me esters. separated by preparative GLC. Two fractions were obtained. The first was taken up in MeOH. cooled to −30°. and crystals filtered. recrystallized from pet. ether (b.p. 40–60°) to give 0·9 g (8%) XXIb. m.p. 44·5–45·5°. (Found: C. 77·6; H. 9·6. Calc. for $C_{16}H_{24}O_2$: C. 77·37; H. 9·74%).

The ester was hydrolyzed[10] to yield 0·8 g (94%) XXIa. m.p. 126·5–130·5° (from pet. ether). Further recrystallizations did not change this m.p. (Found: C. 77·0; H. 9·4. Calc. for $C_{15}H_{22}O_2$: C. 76·88; H. 9·46%). UV: ε^{242} 940 (weak inflection). ε^{283} 670 (0·85 N HCl in 55% EtOH).

The second fraction would not crystallize. although GC and NMR showed it homogeneous. It was hydrolyzed[10] to give 0·75 g (7%) XXa. m.p. 137–138·5° (from aq. EtOH). (Found: C. 77·0; H. 9·4. Calc. for $C_{15}H_{22}O_2$: C. 76·88; H. 9·46%).

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