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The Preparation of Some Tertiary ω,ω,ω-Triphenylalkylamines and Related Compounds

O. MÅRTENSSON* and E. NILSSON**

Research Division, AB Pharmacia, Uppsala, Sweden

Some tertiary ω,ω,ω-triphenylalkylamines and related compounds have been prepared by alkylation of tritylsodium with appropriate tertiary aminoalkyl halogenides as general procedure. Other routes have also been used for their synthesis. Quaternarization of the tertiary bases has been carried out by conventional method.

Many tertiary and quaternary nitrogen compounds of the ω,ω-diphenylalkylamine type have been prepared during the last decades during the search for pharmacologically active compounds, mainly spasmolytics and antihistaminics, but comparatively little interest seems to have been devoted to the corresponding ω,ω,ω-triphenyl compounds. As far as we can find, the tertiary and quaternary compounds containing a triphenylmethyl group as a hydrophobic end, which have been reported, belong to the group of basic esters of triphenylacetic acid [1,2] and to the group of basic ethers derived from triphenylcarbinol.[3–6] They are analogues of the trasentine (adiphenin) and benadryl series respectively in the diphenyl case.

Fairly few ω,ω,ω-triphenylalkylamines have been prepared or reported earlier. Triphenylethylamine (or its hydrochloride) has been synthetized *via* the N-bromotriphenylpropionamide by Hellerman [7,8] and by catalytic reduction of the corresponding nitrile by Décombe.[9]

Hellerman and Garner [10] have also prepared triphenylpropylamine by reduction of β,β,β-triphenylpropionitrile. Moreover, the branched α-methyl-γ,γ,γ-triphenylpropylamine hydrochloride has been prepared by these authors by reduction of methyl-2,2,2-triphenylethylketoxime. We have therefore found it to be of some interest from pharmacological and chemical points of view to prepare some tertiary and quaternary compounds of this type.

These tertiary amines have been synthetized by several routes, which have been chosen after the alkyl chain desired. Most of the compounds with a straight alkyl chain have been synthetized by a fairly simple, direct alkyla-

* Present address: Institute of Quantum Chemistry, University of Uppsala, Sweden.
** Present address: Chemical Institute, University of Uppsala, Sweden.

tion with tertiary aminoalkyl halogenides of the alkali metal compounds of triphenylmethane.

$$(C_6H_5)_3{\equiv}CM + RX \rightarrow (C_6H_5)_3{\equiv}CR + MX$$

The alkali metal compounds of triphenylmethane can be prepared in several ways. Triphenylmethane in an inert solvent can be converted to the sodium compound by means of phenylsodium. We have also applied the method of preparing tritylpotassium from the hydrocarbon and potassium in liquid ammonia, a procedure which can also be used for the preparation of tritylsodium. Since these methods are fairly laborious compared with the preparation of tritylsodium from trityl chloride, we have not made any attempts to refine them and do not discuss them here.

It is obvious that the best method of preparing tritylsodium is to add a solution of trityl chloride in a suitable solvent such as dry ether or dry toluene to a fine dispersion of sodium in toluene. Since ether has disadvantages (difficult to get dry, volatile and inflammable, *etc.*), we have replaced the main part of the ether by toluene. In this case the reaction is started by means of an initiating solution of trityl chloride in dry ether. The amount of this solution necessary for the start can be chosen very small compared with the charge (see under Experimental). This dispersion method is quite superior to the conventional method which includes the use of sodium amalgam.[13,14] However, both methods require a fairly pure trityl chloride. Moreover, the sodium dispersion must be prepared carefully. When the particle size is too large, the reaction does not start or proceeds too slowly to be used with success. The method is also to be preferred to that of phenylsodium as less laborious and as not connected with hazard.

As to the ability to form metal compounds the difference between triphenylmethane and the diphenylpyridylmethanes is very striking. As we have reported earlier [15] the sodium compounds of the diphenylpyridylmethanes (in particular the 2- and 4-pyridyl compounds) can be prepared by mere reflux of the hydrocarbon with sodamide in an inert solvent (toluene).

A trivial variation of the direct alkylation method described above is first to prepare the ω,ω,ω-triphenylalkyl halogenides (generally the chlorides). These are obtained in fairly good yields when tritylsodium is added to an excess of the appropriate 1,ω-alkylene dihalogenide (*e.g.* methylene chloride and butylene chloride). Ether bonds in the chain of the dihalogenide (*e.g.* bis-(2-chloroethyl) ether) do not seem to delimit the applicability. However, as pointed out below, 2,2,2-triphenylethyl chloride and the *p*-toluenesulphonate of 4,4,4-triphenylbutan-2-ol do not behave as desired.

As mentioned above, the primary 2,2,2-triphenylethylamine has earlier been prepared from triphenylacetonitrile and from triphenylpropionamide. However, tentative efforts indicate that the tertiary triphenylethylamines cannot be prepared by any simple route. The easiest route expected is *via* N,N-disubstituted amides of triphenylacetic acid followed by reduction of the amides with lithium aluminum hydride. However, these amides do not seem to react. More than half the amount of triphenylacetylpiperidine could be recovered in our attempts to reduce this amide, and no desired reaction product could be isolated from the small residue. The results were practically

the same whether ether or tetrahydrofurane was used as solvent. Nor did attempts to reduce the corresponding N-methylamide by the same procedure give the desired amine. The results are in agreement with that of Nystrom and Brown [16] who have reported that the method is not applicable in reduction of triphenylacetonitrile.

The route *via* 2,2,2-triphenylethyl halides obviously cannot be used. For example, 2,2,2-triphenylethyl chloride, which was prepared by us by a minor modification of the procedure given by Chalton *et al.*,[17] reacts very slowly with secondary amines. Thus, after heating for 10 h at 175—200° in an autoclave of a solution of 0.2 mole of piperidine and 0.1 mole of triphenylethyl chloride in 100 ml of toluene, 2.5 g of piperidine hydrochloride but no basic product could be isolated from the reaction mixture. The slow rate of substitution with this chloride has been pointed out by Dostrovsky, Hughes and Ingold [18] and is classified as a steric hindrance in bimolecular nucleophilic replacement.

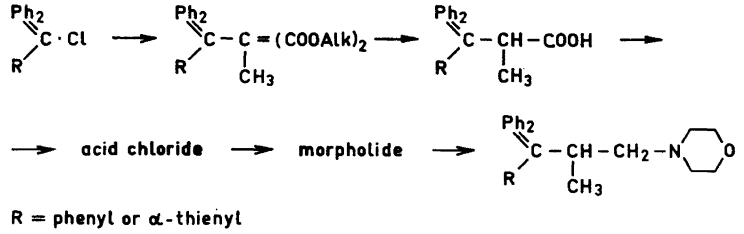
Propylene oxide reacts with tritylsodium under formation of 4,4,4-butan-2-ol in good yield. This alcohol gives well defined benzoate and *p*-nitrobenzoate. The *p*-toluenesulphonate, however, has a melting point which is definitely dependent on the rate of heating. It does not react with morpholine under formation of the expected 2-morpholino-4,4,4-triphenylbutane, but yields a compound which we, judging from its composition, presume to be 1,1,1-triphenyl-2-butene (m.p. 98.5—100.5°). In any case the hydrocarbon is not identical with 4,4,4-triphenyl-1-butene, which is ascribed the melting point 69.5—70.5°.[21] However, the isomeric 2-methyl-3,3,3-triphenylpropanol, obtained from ethyl 2-methyl-3,3,3-triphenylpropionate by reduction with lithium aluminum hydride, has a well defined *p*-toluenesulphonate.

This tosylate reacts with morpholine, yielding the same compound, 2-methyl-1-morpholino-3,3,3-triphenyl-propane, as was obtained by reduction of N-(2-methyl-3,3,3-triphenylpropionyl)-morpholine (compared as hydrochlorides).

Another suitable way of preparing at least some of these tertiary triphenylalkylamines is the route *via* the corresponding N,N-disubstituted carbonamides. For example, it is well known that triphenylpropionic acid can be easily made by merely heating a mixture of malonic acid and triphenylcarbinol.[7] Treatment of the acid with thionyl chloride gives in excellent yield the acid chloride which is converted to the appropriate N,N-disubstituted amide. Reduction with lithium aluminum hydride gives the desired tertiary amine in excellent yield.

This route has also been followed in the preparation of the branched 2-methyl-1-morpholino-3,3,3-triphenyl-propane and 2-methyl-1-morpholino-2,2-diphenyl-2-(α-thienyl)-propane. See the reaction scheme on p. 714. The position of the methyl group must be considered as established by this route, in contrast to when alkylation of tritylsodium with tertiary β-aminoisopropyl halogenides is carried out, in which case a mixture of two isomeric compounds must be expected to occur in the alkylation product.

The quaternary ammonium compounds have been prepared by conventional method, *i.e.* by treatment of the tertiary base with the appropriate halogenide, sulphate or toluenesulphonate in the presence of a suitable solvent or solvent



mixture from which the quaternary salt precipitates. The fourth group, introduced at the nitrogen by this procedure, has generally been selected from the group of lower alkyl groups. Of course, some of these salts can also be prepared *via* triphenylalkyl halogenides and appropriate tertiary amines. Since we have been interested also in the tertiary amines, we have found the route related above more convenient.

The tertiary bases have fairly low melting points and several have not been obtained in the crystalline state. Of the bases prepared, N-(3,3,3-triphenylpropyl)-morpholine has the highest melting point (165—167°). Their hydrochlorides are well defined with high melting points, often above 250°. The quaternary salts (generally the methylammonium bromides) are also well defined. Like several of the hydrochlorides, they are fairly difficult to get dry without drying at temperatures above 100°. At least one of the quaternary salts, N-methyl-N-(3,3,3-triphenylpropyl)-piperidinium chloride, crystallises with one mole of water.

The quaternary salts and still more the salts of the tertiary bases are sparingly soluble in water at room temperature (rarely above one per cent). The effect on the surface properties of the solutions of the tertiary compounds increases with the distance between the hydrophilic and hydrophobic groups. Several of the quaternary compounds show pronounced pharmacological activity as cholinergics and spasmolytics.

EXPERIMENTAL

Preparation of tritylsodium and general alkylation procedure. A 3-necked 0.5 l flask is equipped with a mechanical stirrer, thermometer, air condensor, and an inlet tube for nitrogen; a slow flux of nitrogen is maintained during the procedure. About 100 ml of an approximately 2 M suspension of sodium in toluene is transferred to the flask. (At suitable charge the suspension is advantageously made directly in the reaction vessel by means of the dispergator, in our case an Ultra-Turrax). A solution of 1 g of trityl chloride (m.p. 110—112°) in 5 ml of dry ether is added directly to the suspension. A yellowish red colour appears in the mixing zone, indicating that the suspension is sufficiently fine and that the trityl chloride is sufficiently pure for the purpose. The mechanical stirrer is started at the same time as, or some moments later, the addition of the remaining tritylchloride (26.9 g), dissolved in 75 ml of dry toluene, begins. This procedure takes about 20 min. Since the formation of tritylsodium is an exothermic, though not violent reaction, intermittent cooling with a bath (alcohol + dry ice is to be preferred for security) is necessary to keep the temperature below 50°. The tritylsodium formed gives the contents of the flask a beautiful blood-red colour. The stirring of the mixture is continued for about 30 min after the addition of the trityl chloride solution is completed while checking the temperature of the contents.

The procedure makes it possible to prepare tritylsodium without using ether except for initiating the reaction. The initiating ether solution described above is as to its amount sufficient to start the reaction in at least ten fold scale of that above. If for some reason it is more convenient to use ether as solvent, the ethereal trityl chloride solution should be added under gentle reflux from the reaction heat.

The alkylation is carried out by adding dropwise the alkylating agent (generally dissolved in or diluted with some inert solvent such as ether, benzene or toluene). The temperature is kept below 50°. Since the red colour disappears when the tritylsodium has been consumed, it is easy to follow the reaction. A few ml of ethanol is now added in order to destroy small amounts of sodium which may occur in excess in the preparation of tritylsodium. Water is added and the mixture is washed with water. In the case the reaction product is an amine, dilute (2 N) hydrochloric acid is added to the washed mixture while stirring until the reaction becomes acid. During this procedure the hydrochloride of the base precipitates. After some hours the precipitate is collected on a funnel and washed with a little water. It is dried at room temperature or, when necessary to remove crystal water, at higher temperature.

1-(N,N-Dimethylamino)-3,3,3-triphenylpropane

The synthesis was carried out according to the general procedure from 0.3 mole of trityl chloride. The yield of hydrochloride was 62.5 %. M.p. 255–260°. The base had m.p. 86.5–88° (two recrystallisations from petrol ether). (Found: C 87.75; H 8.16; N 4.28. Calc. for $C_{23}H_{25}N$ (315.44): C 87.57; H 7.99; N 4.44). 2.0 g of the base, dissolved in acetone, was *quaternized* with an excess of methyl bromide in benzene. The precipitate was collected and washed with ether. Yield 2.4 g. M.p. 274–277°. (Found: C 69.11; H 7.03; N 3.40; Br 19.39. Calc. for $C_{24}H_{28}BrN$ (410.39): C 70.24; H 6.88; N 3.41; Br 19.47).

N-(3,3,3-Triphenylpropyl)-pyrrolidine

3,3,3-Triphenylpropionylpyrrolidine was prepared from triphenylpropionyl chloride [7] (16.0 g, 0.05 mole) and 8.0 g of pyrrolidine in benzene. After recrystallisation of the crude product, 10.5 g of pyrrolidide was obtained. M.p. 190–191°. From the mother liquor another, less pure substance, was isolated.

N-(3,3,3-Triphenylpropyl)-pyrrolidine. A solution of 10.5 g (0.03 mole) of the pyrrolidide, dissolved in 150 ml of dry benzene, was added dropwise, while stirring, to a mixture of 2.0 g of $LiAlH_4$ in 100 ml of dry ether. During the course of the addition, the temperature raised to reflux and the reaction mixture was allowed to reflux gently. After the addition the mixture was refluxed for 6 h. After cooling to room temperature, 5 ml of water was added carefully. Anhydrous magnesium sulphate was added as drying agent. The hydroxides and the drying agent were filtered off and washed with ether, and the solvents evaporated. On scratching in petrol ether, the remainder solidified. Next day, the precipitate was filtered off, giving 9.2 g (91 %) of triphenylpropylpyrrolidine. M.p. 100–105°. Recrystallisation from ethanol + petrol ether yielded 8.2 g and m.p. 105–106.5°. (Found: C 88.29; H 7.93; N 4.12. Calc. for $C_{25}H_{27}N$ (341.48): C 87.93; H 7.97; N 4.10).

The *hydrochloride* was prepared in ether solution. M.p. of the salt 212–214° without recrystallisation. (Found: C 79.74; H 7.56; Cl 9.42. Calc. for $C_{25}H_{28}ClN$ (377.95): C 79.44; H 7.47; Cl 9.38).

The *methylpyrrolidinium bromide* was prepared by mixing a solution of 5.2 g (0.015 mole) of the free base with 10 ml of a solution of methyl bromide in acetone (0.36 mole/100 ml). Next day, 6.5 g (99.5 %) salt was filtered off and washed with ether. M.p. 260–265°. Recrystallisation from 20 ml of ethanol + 30 ml of acetone gave 3.2 g and m.p. 263–266°. From the mother liquor another yield of 2.5 g and m.p. 261–266° was obtained. (Found: C 71.39; H 7.02; N 3.17. Calc. for $C_{25}H_{30}BrN$ (436.43): C 71.55; H 6.93; N 3.21).

N-(3,3,3-Triphenylpropyl)-piperidine

1. *From trityl chloride.* Tritylsodium was treated with 2-piperidino-ethyl chloride, dissolved in toluene, according to the general procedure. The precipitated hydrochloride was dispersed in benzene and the base liberated by an excess of 2 N sodium hydroxide. The benzene solution was separated, dried with sodium sulphate and the solvent driven

off, giving a crude base in a yield of 70 %. M.p. 102–106°. Recrystallisation from ethanol with Norite gave a product with m.p. 107–109°, sufficiently pure to be used for quaternarisation. (Found: C 88.15; H 8.49; N 3.94. Calc. for $C_{26}H_{29}N$ (355.50): C 87.84; H 8.22; N 3.82). Further recrystallisations did not improve the m.p. above 109.5–111°.

The *hydrochloride* was precipitated from a benzene solution of the base by means of conc. hydrochloric acid. After recrystallisation from ethanol and drying at 110–115° for 6 h, the yield was 85 %. M.p. 265–268°. (Found: C 79.60; H 7.78; Cl 9.03. Calc. for $C_{24}H_{30}ClN$ (391.97): C 79.66; H 7.72; Cl 9.05).

2. *From triphenylmethane.* A solution of 12.2 g (0.05 mole) of triphenylmethane in 100 ml of dry toluene was added at room temperature to a suspension in toluene of 0.05 mole of phenylsodium under nitrogen. The mixture was warmed on a water bath while stirring for 2 h. After cooling to room temperature, a dried solution in toluene of 2-piperidinoethyl chloride (from 10.2 g of the hydrochloride) was added drop by drop while stirring. The reaction mixture was warmed on a water bath for 5 h cooled to room temperature and water added, the first drops carefully. The toluene layer was washed with water. Under vigorous stirring and cooling with ice water, 5 N hydrochloric acid was added to the toluene solution until the reaction became acid. The mixture was allowed to stand for some hours before the hydrochloride of triphenylpropylpiperidine was filtered off and washed with water and finally with ether. The yield of crude product was 66 %. M.p. 240–250°.

Methyl-3,3,3-triphenylpropyl-piperidinium chloride was prepared from 35.5 g of the base and 120 ml of an 1.6 M solution of methyl chloride in acetone in an autoclave. It was heated to about 60°, while shaking, until the base had dissolved, and was then kept at that temperature to the next day. After cooling to room temperature, the precipitated methylpiperidinium chloride was collected and washed with acetone. Yield 37.0 g (91 %), m.p. 220–225° (decomp.). Recrystallisation from 100 ml of 10 % methanol in acetone gave 25.0 g (62 %). M.p. 225–227° (decomp.). From the mother liquor 5.0 g (12 %) salt with m.p. 220–223° could be recovered by adding ether (about 20 ml) to it. The salt generally crystallises with one mole of water, which may be removed by drying to constant weight at 150°. (Found: C 79.04; H 7.84; N 3.46; Cl 8.75. Calc. for $C_{27}H_{32}ClN$ (406.00): C 79.87; H 7.95; N 3.45; Cl 8.73).

Methyl-3,3,3-triphenyl-propyl-piperidinium bromide was made from 14.5 g of the base, dissolved in 120 ml of acetone + 300 ml of ethanol, and 4 ml of methyl bromide. This solution was kept at room temperature for three days, when 16.2 g (88 %) of the quaternary compound could be collected. M.p. 232–236°. Recrystallisation from ethanol, combined with treatment with Norite, yielded 15.7 g colourless crystals. M.p. 234–238°. Recrystallisation again from 50 ml of ethanol gave 14.7 g (71 %) and m.p. 236–240°. (Found: C 70.89; H 7.33; Br 17.84. Calc. for $C_{27}H_{32}BrN$ (450.45): C 71.99; H 7.16; Br 17.74).

Ethyl-3,3,3-triphenylpropyl-piperidinium p-*toluene sulphonate* was prepared by refluxing a mixture of equal parts (6.0 g) of ethyl *p*-toluenesulphonate and of the base in benzene. 7.5 g of crude salt was obtained. M.p. about 185°. Recrystallisation from ethanol raised the m.p. to 190.5–192°. (Found: C 75.33; H 7.54; S 5.76. Calc. for $C_{15}H_{41}NO_3S$ (555.75): C 75.64; H 7.44; S 5.77).

Ethyl-3,3,3-triphenylpropyl-piperidinium ethyl sulphate was obtained when the base (7.1 g), diethyl sulphate (6.2 g), and 50 ml of benzene were refluxed for 1 h. After cooling, the precipitate was collected (5.9 g). M.p. about 205°. Recrystallisation from acetone + petrol ether improved the m.p. to 211–212.5°. (Found: C 70.83; H 7.69; S 6.49. Calc. for $C_{30}H_{39}NO_4S$ (509.69): C 70.70; H 7.71; S 6.29).

Amyl-3,3,3-triphenylpropyl-piperidinium bromide was obtained when 7.1 g of the base was dissolved in 20 g of amyl bromide, and the mixture refluxed for 5 h. After cooling the precipitate was collected and recrystallised from methanol + petrol ether. Yield 7.6 g. M.p. 244–245° (decomp.). (Found: C 72.78; H 8.09; Br 16.20. Calc. for $C_{31}H_{40}BrN$ (506.55): C 73.50; H 7.96; Br 15.78).

N-[3,3-Diphenyl-3-(*p*-tolyl)-propyl]-piperidine

The *hydrochloride* was prepared according to the general procedure but the trityl chloride was replaced by diphenyl-(*p*-tolyl)-methyl chloride [20] (0.1 mole). Yield 64.5 %. M.p. about 207°. Recrystallisation from ethanol raised the m.p. to 214–216°.

The *base*, prepared from 2.0 g of the hydrochloride, gave after recrystallisation from cyclohexane + petrol ether 1.8 g of m.p. 88–89°. (Found: C 87.80; H 8.54; N 3.80. Calc. for $C_{27}H_{31}N$ (369.53): C 87.75; H 8.46; N 3.79).

The *methylpiperidinium bromide* was prepared from 1.9 g of the base dissolved in in 25 ml of ether and 5 ml of a solution of methyl bromide in acetone (0.36 mole/100 ml). Next day the precipitate was collected and washed with ether. Yield 1.2 g. M.p. 258–261°. Another crop of 0.7 g with the same m.p. was collected next day. Total yield 80 %. (Found: C 72.84; H 7.51; Br 17.10. Calc. for $C_{28}H_{34}BrN$ (464.49): C 72.40; H 7.38; Br 17.21).

N-(3,3,3-Triphenylpropyl)-morpholine

Phenylsodium was used in the metalation of triphenylmethane as is described under N-(3,3,3-triphenylpropyl)-piperidine. Since the base has a fairly high melting point and crystallises easily, it may be isolated directly from the reaction mixture and not *via* the hydrochloride. The reaction mixture was therefore washed with water, the solution dried and the solvents driven off. When stirred in petrol ether, the remainder crystallised. The crude product was obtained in a yield of 74 % with m.p. 160–165°. Recrystallisation from benzene + ethanol raised the m.p. to 165–167°. Yield 70 %. (Found: C 84.13; H 7.66; N 3.84. Calc. for $C_{25}H_{27}NO$ (357.48): C 83.99; H 7.61; N 3.92).

The reaction product was also isolated as the *hydrochloride* in somewhat lower yield. After recrystallisation of the crude product from ethanol, the m.p. was 267–270°. (Found: C 75.85; H 7.15; Cl 9.17. Calc. for $C_{25}H_{28}ClNO$ (393.95): C 76.22; H 7.17; Cl 9.00).

The *methylmorpholinium bromide* (7.4 g) was obtained when a solution of 7.1 g of the base in 50 ml of benzene was mixed with 20 ml of a solution of methyl bromide in acetone (0.36 mole/100 ml). This mixture was kept at room temperature for two days. The precipitate was washed with benzene and petrol ether. M.p. 250–251.5°. (Found: Br 18.00. Calc. for $C_{26}H_{30}BrNO$ (452.43): Br 17.66).

The *ethylmorpholinium tosylate* was prepared by gentle heating of a mixture of the base (7.1 g) and ethyl *p*-toluenesulfonate (5.0 g). After cooling to room temperature, the reaction product was recrystallised from 25 ml of benzene, yielding 6.0 g of quaternary compound. M.p. 240–242.5° (decomp.). (Found: C 72.73; H 7.00; S 5.75. Calc. for $C_{34}H_{39}NO_4S$ (557.53): C 73.21; H 7.05; S 5.75).

N-(4,4,4-Triphenylbutyl)-piperidine

The general procedure gave 77 % (33.5 g) of crude hydrochloride. The *base* was liberated by shaking the salt with a 2 N sodium hydroxide solution and benzene. The benzene layer was dried and the main part of the solvent evaporated. The remaining oil solidified when stirred with petrol ether, giving 26.5 g of crude base. After two recrystallisations from ethanol, 16.1 g base with m.p. 79.5–81° was obtained. (Found: C 87.90; H 8.33; N 3.74. Calc. for $C_{27}H_{31}N$ (369.53): C 87.75; H 8.46; N 3.79).

The *hydrochloride*, prepared from the crude base and recrystallised from acetone had m.p. 219–222°. (Found: C 79.94; H 7.89; Cl 8.83. Calc. for $C_{27}H_{32}ClN$ (406.00): C 79.87; H 7.95; Cl 8.73).

To 7.4 g (0.02 mole) of the base, dissolved in 25 ml of dry ether, was added 25 ml of a solution of methyl bromide in acetone (0.36 mole/100 ml). Next day 8.5 g of *methylpiperidinium bromide* was collected. M.p. 219–221°. Recrystallisation from about 30 ml of ethanol to which some ml of petrol ether was added, gave 8.0 g. M.p. 223–224.5°. (Found: Br 16.96. Calc. for $C_{28}H_{24}BrN$ (464.48): Br 17.21).

N-(2-Methyl-3,3,3-triphenylpropyl)-morpholine

Diethyl methyl-trityl-malonate. A suspension of sodium ethylate was prepared from 6.9 g (0.3 mole) of sodium and ethanol in 200 ml of dry toluene. The diethyl methylmalonate (52.3 g, 0.3 mole), was added at about 50° and the ethanol distilled off through a short column. A solution of 83.7 g (0.3 mole) of trityl chloride in 150 ml of dry toluene

was added dropwise to the refluxing mixture. During this procedure the sodium compound disappeared, the contents became dark for some moments and finally yellowish and gelatinous of precipitated sodium chloride. The reflux was continued for 3 h. After cooling, the toluene mixture was washed with water and dried with anhydrous sodium sulphate. The toluene and some unreacted diethyl methylmalonate were distilled off *in vacuo* (about 10 mm). After a fore-run at 160°/0.3–0.5 mm, the main part of the remainder was driven over at 220–230°/0.3–0.5 mm. The yield of the ester, a reddish viscous oil, was 76 g (61 %). It was used directly for the next step. Redistillation of a part of the crude oil gave the b.p. interval 215–217°/0.2 mm, without notable losses. We have not been able to get the ester in the crystalline state.

Methyl-trityl-malonic acid. 41.7 g (0.1 mole) of the ester from the preceding step and 100 ml of 5 N sodium hydroxide were refluxed for 3 h. The almost clear solution was washed with ether after cooling. The solution was carefully acidified to pH 3 at about 0°. In spite of cooling, some carbon dioxide was evolved. The precipitated oil was taken up in ether, the ether solution dried with sodium sulphate and the ether evaporated. The remaining acid (31 g, 86 %) crystallised on scratching in petrol ether. It decomposed at 143–147°, and was used directly in the next step. (Found: C 76.37; H 5.72. Calc. for $C_{23}H_{20}O_4$ (360.39): C 76.65; H 5.59).

2-Tritylpropionic acid. 10.0 g of the malonic acid from the preceding step was refluxed in 50 ml of mesitylene for 2 h. After cooling, 8.8 g (theor. yield) of 2-tritylpropionic acid was collected as a precipitate. M.p. 155–156°.

N-(2-Tritylpropionyl)-morpholine. A mixture of the acid (10.0 g, 0.031 mole), and thionyl chloride (20 ml) was refluxed for 4 h. The excess of thionyl chloride was driven off *in vacuo* and the remaining oil dissolved in 50 ml of dry benzene. To this mixture was added, while cooling and stirring, a solution of 8 g of morpholine in 50 ml of dry benzene. The precipitated morpholine hydrochloride was filtered off and the benzene solution washed with water, dried with magnesium sulphate, and the benzene evaporated. The remaining oil crystallised on standing, giving 12.1 g of crude morpholide with m.p. about 95°. Recrystallisation from 50 ml of cyclohexane gave 10.2 g (85 %) with m.p. 99–101°, which was used in the next step.

2-Methyl-1-morpholino-3,3,3-triphenylpropane hydrochloride. To a stirred mixture of 1.6 g of $LiAlH_4$ and 50 ml of dry ether, a solution of 10.2 g of the morpholide in a mixture of 20 ml of dry benzene and 50 ml of dry ether was added dropwise. The temperature of the reaction mixture was allowed to raise to gentle reflux. After the addition, the reflux was continued for 4 h. After cooling to room temperature, 5 ml of water was added carefully, followed by magnesium sulphate in order to get the solution free from excess of water. The hydroxides and the drying agent mixture was filtered off and washed with ether. The ethereal solution was acidified with alcoholic hydrogen chloride and the precipitated hydrochloride (10.2 g, 95 %), collected. M.p. 225–232°. Recrystallisation from 50 ml of ethanol gave 9.2 g with m.p. 230–232.5°. (The liberated base, a viscous oil, did not crystallise). (Found: C 76.49; H 7.47; N 8.44. Calc. for $C_{26}H_{30}ClNO$ (407.98): C 76.54; H 7.41; N 8.69). This hydrochloride has also been prepared *via* the tosylate of 2-methyl-3,3,3-triphenyl-propanol (See under this alcohol).

The *methylmorpholinium bromide*, recrystallised from ethanol and dried at 115°, has m.p. 235–237°. (Found: C 69.01; H 6.88; Br 17.39. Calc. for $C_{27}H_{32}BrNO$ (466.46): C 69.52; H 6.92; Br 17.13).

2-Methyl-3,3,3-triphenyl-propanol

10.0 g of methyltritylmalonic acid was decarboxylated by boiling in mesitylene for 2 h. After cooling, 8.0 g of *2-tritylpropionic acid* was collected as a precipitate. M.p. 153–155°.

The acid was refluxed for 3 h with 50 ml of thionyl chloride. The excess of thionyl chloride was distilled off *in vacuo* and the remainder treated with 30 ml of absolute ethanol. The excess of alcohol was driven off and the remaining oil distilled. The main fraction (6.0 g) was distilled at 190–195°/0.4 mm. The *ethyl 2-tritylpropionate* did not crystallise.

The ester was dissolved in 50 ml of dry ether and this solution added dropwise to 1.5 g of $LiAlH_4$ in 50 ml of dry ether. When the exothermic reaction had subsided, the mixture was refluxed for 4 h. 10 ml of water was added carefully and the ether solution

filtered and dried with potassium carbonate. When the ether was evaporated, a viscous, almost semisolid alcohol was obtained.

The p-*nitrobenzoate* had m.p. 95.5–98° (from cyclohexane + petrol ether). (Found: C 77.40; H 5.80; N 3.01. Calc. for $C_{29}H_{35}NO_4$ (451.50): C 77.14; H 5.58; N 3.10).

The crude p-*toluenesulphonate* (1.2 g) was prepared by conventional method from 1.0 g of the alcohol in pyridine. M.p. 82–86°. Reflux for 10 h of 1.0 g of the tosylate with morpholine in benzene, washing of the reaction mixture with water and adding dilute hydrochloric acid gave 0.4 g of a substance with m.p. 228–232.5°. No change in m.p. was observed when this hydrochloride was mixed with 2-methyl-1-morpholino-3,3,3-triphenyl-propane prepared by reduction of the corresponding morpholide.

1-Methyl-3,3,3-triphenyl-propanol

This compound was prepared by adding dropwise 20 g (0.34 mole) of freshly distilled propylene oxide to tritylsodium prepared from 83.7 g (0.3 mole) of trityl chloride according to the general procedure described above. After the addition of the propylene oxide (*i.e.* after about 30 min) the mixture was stirred for additional 1.5 h at room temperature. The reaction mixture was washed with water and dilute hydrochloric acid. After drying with magnesium sulphate, the solvents were evaporated *in vacuo*. On scratching in petrol ether, the remaining oil solidified and 80 g of crude product with m.p. 80–87° was collected. Recrystallisation including treatment with Norite from a mixture of 100 ml of ethanol and 200 ml of petrol ether followed by another from cyclohexane gave 41 g (45 %) of the desired alcohol with m.p. 87–90°. Repeated recrystallisations did not improve the m.p. interval above 89–91.5°. (Found: C 87.29; H 7.33. Calc. for $C_{22}H_{22}O$ (302.40): C 87.37; H 7.33).

The p-*nitrobenzoate:* M.p. 209–210.5°. (Found: C 77.42; H 5.73; N 3.25. Calc. for $C_{29}H_{25}NO_4$ (451.50): C 77.14; H 5.58; N 3.10).

The p-*toluenesulphonate* is not well defined as to its decomposition point which depends on the rate of heating; m.p. interval about 115–125°.

A solution of 2.2 g of the tosylate and 1.5 g of morpholine in 15 ml of toluene was refluxed for 20 h. After cooling, the mixture was shaken with water. The toluene layer was extracted with dilute hydrochloric acid. The combined acid solutions gave only an opalescence when made alkaline with dilute sodium hydroxide. The toluene layer was dried with sodium sulphate and the toluene distilled off. The remainder was dissolved in hexane and the solution filtered in order to remove impurities. After evaporation of the solvent, 1.2 g of a solid substance was obtained. One recrystallisation from methanol + water yielded a product of m.p. 98.5–100.5°, presumed to be *4,4,4-triphenyl-2-butene*. (Found: C 93.04; H 7.11. Calc. for $C_{22}H_{20}$ (284.38): C 92.91; H 7.09).

N-[3,3-Diphenyl-2-methyl-3-(α-thienyl)]-morpholine

Diethyl [diphenyl-(α-thienyl)-methyl]-methyl-malonate was prepared analogously to diethyl methyl-tritylmalonate. However, the solution of the diphenyl-(α-thienyl)-methyl chloride [22] was added at a temperature of 50–60° of the sodium diethyl methylmalonate mixture. The fraction 220–230°/0.5 mm, a reddish oil, was collected and used in the next step. Yield 64 %.

3,3-Diphenyl-2-methyl-3-(α-thienyl)-propionic acid. The oil (27 g) from the preceding step, was boiled for 30 min with 50 ml of 5 N sodium hydroxide. The clear, reddish solution, was washed with ether. While cooling, the solution was acidified carefully with conc. hydrochloric acid. The precipitated viscous oil was taken up in benzene. The benzene was distilled off and the remainder decarboxylated *in vacuo*. The semisolid remainder was recrystallised from a mixture of cyclohexane and petrol ether, giving 13 g of crude acid with m.p. 110–115°. Recrystallisation from cyclohexane raised the m.p. to 114–116°. (Found: C 74.75; H 5.72; S 10.01. Calc. for $C_{20}H_{28}O_2S$ (322.41): C 74.50; H 5.63; S 9.94).

N-[3,3-Diphenyl-2-methyl-3-(α-thienyl)-propionyl]-morpholine was prepared analogously to the corresponding triphenyl compound from 7.0 g of the crude propionic acid. It was obtained as a brownish oil, which was used directly in the next step.

N-[3,3-Diphenyl-2-methyl-3-(α-thienyl)-propyl]-morpholine. The viscous oil from the preceding step, dissolved in 50 ml of dry ether, was added dropwise to a stirred mixture of 1.2 g of $LiAlH_4$ and 50 ml of dry ether as is described under the corresponding triphenyl analogue. The yield of crude *hydrochloride* was 8.2 g (91 %). Recrystallisation from 100 ml of acetone gave white crystals. M.p. 187—188°. (Found: C 69.50; H 6.89; Cl 8.53. Calc. for $C_{24}H_{28}ClNOS$ (413.99): C 69.62; H 6.82; Cl 8.57).

The liberated *base*, a viscous oil which did not solidify, was dissolved in acetone and *quaternized* with methyl bromide in benzene. The precipitate was collected next day and washed with ether. M.p. 229—231.5° (decomp.). (Found: C 63.58; H 6.41; Br 16.93; S 6.97. Calc. for $C_{25}H_{30}BrNOS$ (472.48): C 63.55; H 6.40; Br 16.91; S 6.79).

N-(4,4,4-Triphenyl-2-methyl-butyl)-morpholine

The *hydrochloride* was prepared according to the general procedure from tritylsodium (from 0.1 mole of trityl chloride) and N-(3-chloro-2-methylpropyl)-morpholine (0.105 mole). The yield after one recrystallisation from acetone was 22.0 g (52 %). M.p. 185—189°. A second recrystallisation gave 14.0 g with m.p. 188.5—190°.

The *base* was precipitated from 5.0 g of the hydrochloride dissolved in 50 ml of warm water. It was then taken up in ether, the solvent evaporated, and the remainder recrystallised from alcohol. Yield 4.0 g. M.p. 97—99.5°. (Found: C 84.13; H 8.18; N 3.61. Calc. for $C_{27}H_{31}NO$ (385.53): C 84.11; H 8.11; N 3.63).

The *methylmorpholinium bromide* precipitated very slowly from a solution of the base in acetone to which had been added an excess of methyl bromide in benzene. M.p. 230—231.5°. (Found: C 70.02; H 7.19; Br 16.98. Calc. for $C_{28}H_{34}BrNO$ (480.49): C 69.99; H 7.13; Br 16.63).

N-Methyl-N-(2-morpholinoethyl)-5,5,5,-triphenylpentylamine

5,5,5-Triphenylpentyl chloride was prepared by adding slowly tritylsodium (from 0.5 mole of trityl chloride) to 200 g of butylene chloride. The reaction was carried out under nitrogen while stirring. The temperature was allowed to rise to about 50°. After the addition of the tritylsodium, the now yellowish brown reaction mixture was stirred for 1 h. Some ml of ethanol was added to destroy the small excess of sodium. The reaction mixture was washed with water, dried with sodium sulphate, and the solvents including the excess of butylene chloride were distilled off *in vacuo*. The remaining oil, which could not be obtained in the solid state, was used directly in the next step.

N-Methyl-N-(2'-hydroxyethyl)-5,5,5-triphenylpentylamine. The oil from the preceding step was diluted with 250 ml of toluene, 100 g of 2-(N-methylamino)-ethanol was added, and the mixture refluxed for 7 h. After cooling to room temperature, water was added to the mixture which was washed several times. 100 ml of 5 N hydrochloric acid was added while stirring. Most of the mother liquor was filtered off from the precipitated, gelatinous hydrochloride. The hydrochloride was dispersed in benzene and the base liberated by excess of 5 N sodium hydroxide solution. The benzene layer was separated, dried with sodium sulphate, and treated with Norite. The main part of the benzene was evaporated and the remaining concentrated solution stirred with petrol ether until the oily precipitate had solidified. 107 g with a m.p. of about 70° was collected. Recrystallisation from cyclohexane + petrol ether gave 102 g (55 %) and m.p. 70—73°. In spite of considerable losses, two recrystallisations did not improve the m.p. appreciably. (71 g and m.p. 72—74.5°). (Found: C 83.89; H 8.46; N 3.90. Calc. for $C_{26}H_{31}NO$ (373.52): C 83.60; H 8.37; N 3.75).

The *hydrochloride* was prepared from 3.7 g of the base, dissolved in 50 ml of ether, by adding a slight excess of methanolic hydrogen chloride. 4.0 g crude product was obtained. Two recrystallisations from methanol gave no definite m.p. A third recrystallisation from acetone, after which the salt was dried at 100° for 3 h gave a m.p. of 142—146° (slight decomp.). (Found: Cl 8.72. Calc. for $C_{26}H_{31}ClNO$ (409.99): Cl 8.65).

3.7 g of the base, dissolved in 50 ml of dry ether, was quaternized by adding 10 ml of a solution of methyl bromide in acetone (0.36 mole/100 ml). The crude yield of 4.0 g

gave, after two recrystallisations from methanol + acetone, 2.3 g of *dimethyl-(2'-hydroxyethyl)-5,5,5-triphenylpentyl-ammonium bromide*. M.p. 195—196.5°. (Found: C 69.24; H 7.42; Br 16.82. Calc. for $C_{27}H_{34}BrNO$ (468.47): C 69.22; H 7.32; Br 17.06).

N-(2'-Chloroethyl)-N-methyl-5,5,5-triphenylpentylamine. 60 ml of thionyl chloride was added, while cooling, to 37.4 g (0.1 mole) of 2'-hydroxyethyl-methyl-5,5,5-triphenylpentylamine. When all the thionyl chloride had been added a solution was obtained. This was refluxed for 5 h. The excess of thionyl chloride was distilled off *in vacuo* and the remaining solid taken on a filter and washed with dry ether. Yield 42.5 g (99.5 %). M.p. 176—180°. Recrystallisation from 150 ml of acetone + 20 ml of methanol and treatment with Norite gave 28.0 g (66 %), m.p. 180—182°, of the hydrochloride.

N-(2'-Morpholinoethyl)-N-methyl-5,5,5-triphenylpentylamine. 17.3 g (0.04 mole) of 2'-chloroethyl-methyl-5,5,5-triphenylpentylamine hydrochloride was dispersed in 100 ml of water, 50 ml of xylene was added, and the base liberated by addition of 33 % sodium hydroxide in excess. The xylene layer was separated and the water phase washed two times with 50 ml of xylene. The combined xylene solutions were dried with potassium carbonate. To the dried solution was added 14 g of morpholine and the mixture was refluxed for 5 h. After cooling to room temperature, water was added and the xylene layer washed with water and dried with sodium sulphate. The xylene was distilled off. Since the remaining oil did not crystallise, it was dissolved in ether and the hydrochloride precipitated by means of alcoholic hydrogen chloride. The precipitate was collected, giving 19.0 g (92.5 %) of crude *dihydrochloride*. M.p. about 240°. Recrystallisation from 50 ml of ethanol + 100 ml of acetone yielded 14.2 g and m.p. 240—244°. Two further recrystallisations gave 10.5 g and m.p. 245—247°. From the mother liquor 3.5 g of salt with m.p. 245—248° could be obtained. Total yield 68.5 %.

5.2 g of the dihydrochloride was dissolved in 100 ml of water. The *base* was liberated with 2 N sodium hydroxide and the oil taken up in ether (3 × 25 ml). The joined ethereal solutions were dried with potassium carbonate, and the solvent evaporated. The remainder formed an oil at room temperature.

2'-Morpholinoethyl-methyl-5,5,5-triphenylpentylamine bismethobromide. The oil of the diamine, prepared straight forwardly from 8.0 g of 2'-hydroxyethyl-methyl-5,5,5-triphenylpentylamine, was dissolved in 100 ml of ethanol, and this solution was mixed in an autoclave with 25 ml of a solution of methyl bromide (0.09 mole) in acetone. The mixture was kept at 55° for 60 h. The solution was evaporated to about 50 ml, and the bisquaternary salt was precipitated by adding ether. Yield 13.0 g. M.p. about 212°. Recrystallisation from 10 ml of ethanol + 50 ml of acetone yielded 6.6 g (49 %), with m.p. 219—222°. Further recrystallisation of a small sample raised the m.p. to 224.5—226°. This sample was dried for 4 h before analyses. (Found: C 60.92; H 7.12; Br 24.97; N 4.50. Calc. for $C_{32}H_{44}Br_2N_2O$ (632.52): C 60.76; H 7.01; Br 25.27; N 4.43).

N,N-Diethyl-N-(6,6,6-triphenyl-3-oxa-hexyl)-amine, (3,3,3-triphenylpropyl-2'-(N,N-diethylamino)-ethyl ether)

The *hydrochloride* of this ether was prepared quite analogously to the morpholino analogue (see next compound). Yield 31 %. The m.p. 151.5—153.5° could not be improved by recrystallisation from ethanol. From the toluene solution unreacted triphenylpropyl-chloroethyl ether could be recovered. (Found: C 76.32; H 8.09; Cl 8.37. Calc. for $C_{27}H_{34}ClNO$ (424.02): C 76.48; H 8.09; Cl 8.36).

The base (from 3.0 g of the hydrochloride) was taken up in ether, the solution dried with magnesium sulphate, and 10 ml of a solution of methyl bromide in acetone (0.36 mole/100 ml) was added. Next day 2.5 g of the *methylammonium bromide* could be collected. M.p. 149—150°. (Found: C 68.59; H 7.87; Br 16.57. Calc. for $C_{28}H_{36}BrNO$ (482.50): C 69.70; H 7.52; Br 16.56).

N-(6,6,6-Triphenyl-3-oxa-hexyl)-morpholine, (3,3,3-triphenylpropyl-2'-morpholinoethyl ether).

3,3,3-Triphenylpropyl-2'-chloroethyl ether. Tritylsodium was prepared from 0.2 mole of trityl chloride. This mixture was added during the course of half an hour to an excess

of bis-(2-chloroethyl) ether (0.8 mole). The reaction was carried out under nitrogen while stirring vigorously. The reaction is somewhat exothermic and the temperature rose from 20° to about 50°. After the addition the reaction mixture was stirred for half an hour. The excess of sodium was destroyed by adding about 5 ml of ethanol, and the mixture was then carefully washed with water. The solution was dried with sodium sulphate and the solvents and the excess of bis-(2-chloroethyl) ether were distilled off *in vacuo* (about 10 mm Hg). The semisolid remainder was recrystallised two times from cyclohexane. Yield 28.5 %. M.p. 102–103.5°. (Found: C 78.65; H 6.61; Cl 10.00. Calc. for $C_{23}H_{23}ClO$ (350.88): C 78.72; H 6.61; Cl 10.11).

N-(6,6,6-Triphenyl-3-oxa-hexyl)-morpholine. A mixture of 29.0 g (0.08 mole) of 3,3,3-triphenylpropyl-2′-chloroethyl ether, 26.1 g (0.3 mole) of morpholine and 100 ml of toluene was refluxed for about 24 h. After cooling 7.5 g of morpholine hydrochloride was filtered off. The toluene solution was washed with water. The hydrochloride of the desired triphenyl-3-oxa-hexylmorpholine was precipitated by adding 25 ml of 5 N hydrochloric acid to the stirred toluene solution. The precipitate was filtered off and washed with water and ether. A dried sample showed m.p. 194.5–196.5°.

The hydrochloride was dispersed in water, and the base was liberated by dilute sodium hydroxide solution and taken up in ether. The ether was driven off from the dried solution. The remaining oil which did not solidify, was dissolved in 150 ml of dry ether, and the *hydrochloride* precipitated again with hydrogen chloride dissolved in ethanol. The precipitate was collected and washed with ether. Yield 22.0 g (61 %). M.p. 194–197°. Recrystallisation from 100 ml of acetone + 10 ml of ethanol gave 15.5 g and m.p. 195–197.5°. (Found: C 74.46; H 7.42; Cl 8.05. Calc. for $C_{27}H_{32}ClNO_2$(438.00): C 74.03; H 7.37; Cl 8.10).

The *methylmorpholinium compound* was prepared from a dried ethereal solution of the base and excess of methyl bromide in benzene. Repeated recrystallisations from acetone gave a salt which after drying over night at 100°, showed the m.p. 182–184°. (Found: C 67.64; H 7.03; N 2.87. Calc. for $C_{28}H_{34}BrNO_2$ (496.48): C 67.63; H 6.90; N 2.82).

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