[Contribution from the Research Laboratories of the Givaudan Corporation]

NITRO MUSKS. III.[1] ASYMMETRICAL MUSKS OF THE DINITRO-*tert*-BUTYL-*m*-XYLENE SERIES

M. S. CARPENTER and W. M. EASTER

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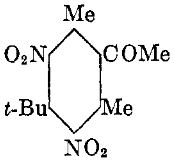
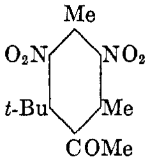
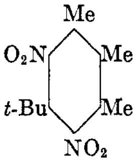
It has been established by Tchitchibabin (1) that Musk Ketone has the symmetrical structure I rather than the asymmetrical structure II which was originally assigned to it by Baur (2). Later, Fuson and co-workers (3) confirmed his conclusions and also established that Musk Tibetene has the symmetrical (III) rather than the asymmetrical structure IV, originally assigned to it by Carpenter (4).



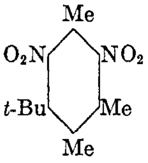
I



II



III



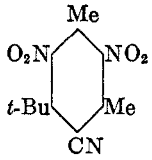
IV

Tchitchibabin stated that the liquid asymmetrical acetyl-*tert*-butyl-*m*-xylene had never been isolated and then, without offering any experimental details, stated that nitration of it (presumably in impure form) led to products having no musk odor and, in fact, a somewhat disagreeable odor. This seemed to be in harmony with the generalization which he advanced: that symmetrical structure is a favorable factor for odor.

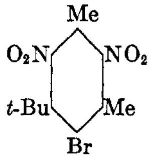
We deemed it desirable to prepare the asymmetrical compounds II and IV in order to determine whether, in this series, lack of symmetry would entail loss of musk odor.

In the case of II we were successful and we have established that it is, indeed, a musk of strength and quality comparable to its symmetrical isomer, Musk Ketone (I). We have not been able to prepare IV. In the light of the recent work of Brown and co-workers (5) on the inherent strains resident in similar structures, it is not surprising that the preparation of this substance should offer difficulties.

During the course of the work on the preparation of II, several new musks were prepared. The asymmetrical cyanide (V) and bromo (VI) musks are comparable in odor intensity and quality to their symmetrical isomers which have been prepared, respectively, by Baur (6) and Sack (7).



V



VI

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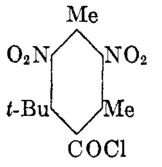
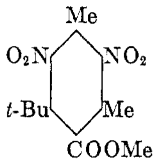
[1] Papers I and II, *J. Org. Chem.*, **16**, 586, 618 (1951).

Of greater interest were the asymmetrical acid chloride (VII) and methyl ester (VIII) musks:

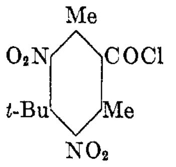


VII

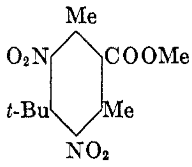


VIII

Never before, to our knowledge, has the musk odor been encountered in an acid chloride or its corresponding methyl ester. Baur (8) had prepared what he considered to be the asymmetrical compounds, but which the later work of Tchitchibabin and Fuson (1, 3) proved to have been the symmetrical isomers, IX and X:



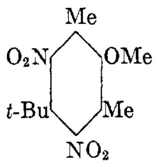
IX



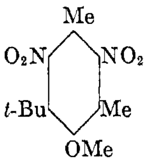
X

He made no mention of the odor of the acid chloride, but stated that the methyl ester was odorless. We have prepared these compounds and find that the acid chloride has a distinct musk odor comparable in intensity of that of VII, and the methyl ester a musk odor somewhat weaker than VIII. Our melting points were considerably higher than those reported by Baur (see experimental section).

We have found XI to be odorless, a fact which is in harmony with our *ortho* rule, according to which the alkoxy group must be *ortho* to the *tert*-alkyl group in order to have a musk odor (see Paper I of this series). We have been unable to prepare the asymmetrical isomer, XII, which should have a musk odor.



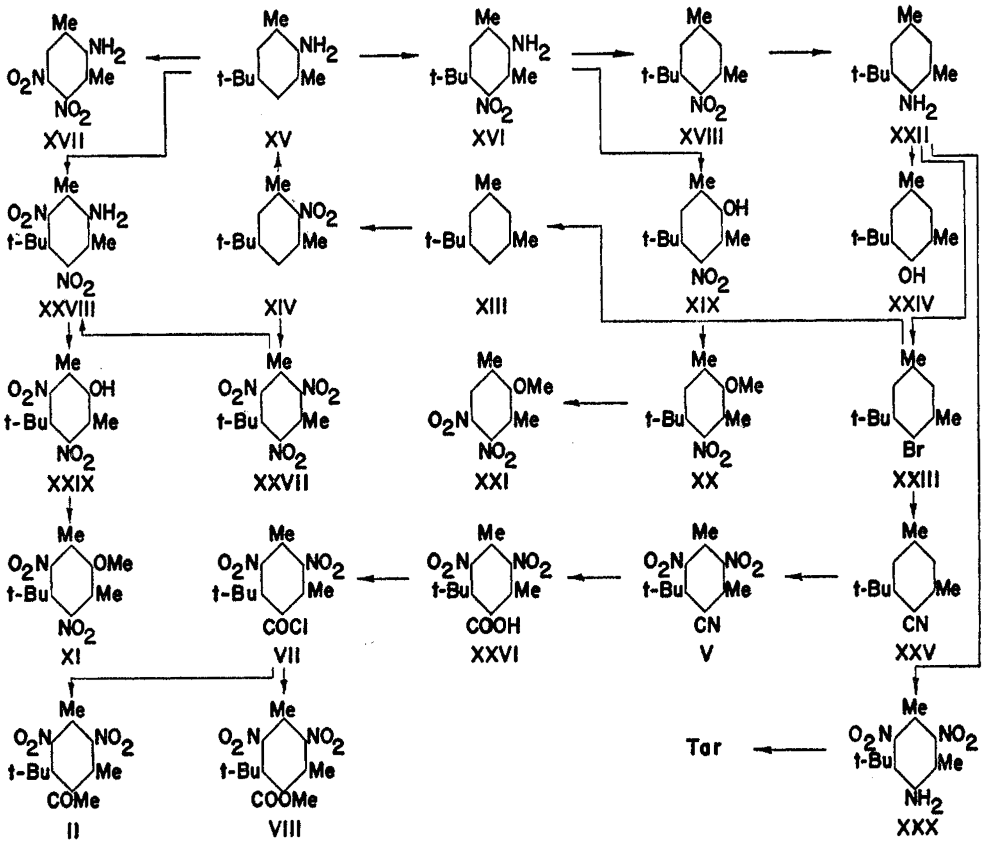
XI



XII

Nitration of *sym-tert*-butyl-*m*-xylene (XIII) (Flow Sheet A) led to the *sym*-mononitro derivative (XIV), which upon reduction gave the *sym*-amine (XV). Baur, who first prepared the amine (9), reported it to have m.p. 32°. Our preparation exhibited a double m.p.; depending upon the type of cooling, it had c.p. 10° and m.p. 10.5° or c.p. 28° and m.p. 29°. We have encountered polymorphism in several derivatives of *sym-tert*-butyl-*m*-xylene. Musk Xylene (XXVII) has been reported (10) to exist in three forms, having m.p.'s 84°, 107°, and 114°.

FLOW SHEET A



Nitration of the amine in sulfuric acid led to the nitroamine XVI and, as a minor by-product, 2,6-dimethyl-3,4-dinitroaniline (XVII). Diazotization and ethanol deamination of XVI led to the asymmetrical nitro derivative XVIII. This compound, hitherto reported as a liquid (2, 3), has been found to have c.p. 9.5° and m.p. 10°, or c.p. 18.5° and m.p. 19.5°, depending upon the degree of cooling. As a by-product of the diazotization there was produced the nitrophenol XIX, whose methyl ether XX had a mild, non musky odor. Further nitration of XX led, by replacement of the *tert*-butyl group, to 2,6-dimethyl-3,4-dinitroanisole (XXI). Iron reduction of XVIII led to the asymmetrical amine XXII, of c.p. −10° and m.p. −9°. The latter was converted by the Sandmeyer reaction to the corresponding bromo compound XXIII, of m.p. 34.5°. As a side product of the diazotization there was produced the phenol XXIV, of c.p. 21.5° and m.p. 23°. This product also gave evidence of polymorphism, but the lower m.p. was not well defined. Treatment of the bromo compound with lithium (magnesium failed to react), then with dimethyl sulfate, followed by hydrolysis, led to the starting material, *tert*-butylxylene (XIII), rather than to the expected 6-*tert*-butyl-pseudocumene. In similar fashion, treatment of the lithium compound of

XXIII with acetic anhydride at low temperature by an adaptation of the method of Newman and Smith (11) led only to the butylxylene (XIII), rather than to the expected asymmetrical acetyl-*tert*-butyl-*m*-xylene.

As an alternate route to II, the bromo compound XXIII was converted to the nitrile XXV, with the intention of hydrolyzing the latter to the acid, converting to the acid chloride, and treating with dimethylcadmium to form the ketone, nitration of which would have given II. Unfortunately, the nitrile resisted all attempts to hydrolyze it with either acid or alkali under drastic conditions. A precedent for this behavior was found in the experience of Küster and Stallberg (12) who found it impossible to hydrolyze cyanomesitylene; they found, however, that the mono- or dinitro-cyanomesitylenes could be hydrolyzed without difficulty. Accordingly, XXV was nitrated to the hitherto unknown asymmetric cyanide musk (V), the odor of which seems to be slightly more intense than that of its symmetrical isomer. The nitrile V was hydrolyzed readily by 75 % sulfuric acid to the corresponding acid (XXVI), which is odorless. The acid chloride (VII), readily obtained by treatment with thionyl chloride, has a definite, but weak, musk odor. Although Grignard-type reactions are not in general considered feasible with nitro compounds, it was found after a little experimentation that the acid chloride could be reacted with dimethylcadmium by the Gilman and Nelson method (13) to produce the desired ketone II. The crude ketone was difficult to free from resinous by-products by the conventional crystallization technique but it was found that sublimation in a high vacuum readily afforded a pure product. The pure ketone had m.p. 137–138° as compared with 136° for its symmetrical isomer, Musk Ketone (I). A mixture of I and II melted at 110–118°. The odor of II is quite similar in nuance to that of I, but somewhat weaker.

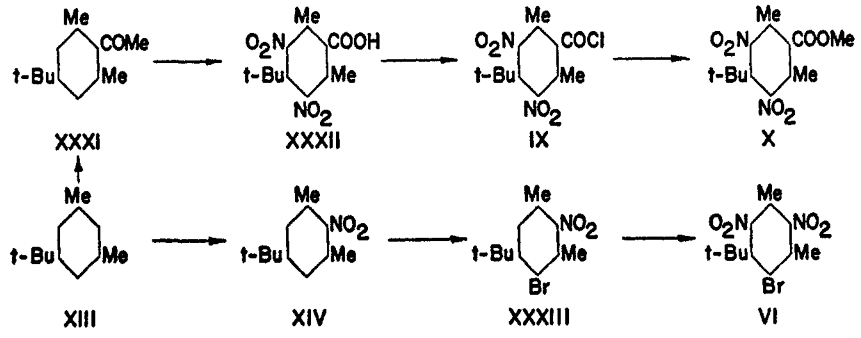
The acid chloride VII reacted readily with a solution of sodium in methanol to yield the corresponding methyl ester (VIII), having a distinct but somewhat weak musk odor, m.p. 93–94°.

Using the procedures of Tchitchibabin (1), Musk Xylene (XXVII), was converted to the *sym*-dinitrobutylxylidene (XXVIII) (it can also be prepared by nitration of XV), the corresponding phenol (XXIX), and the methyl ether (XI). According to that investigator both the phenol and its methyl ether had a faint musk odor. Our preparations were quite odorless. It is possible that his preparations were contaminated with a trace of the powerfully odorous Musk Xylene used as starting material.

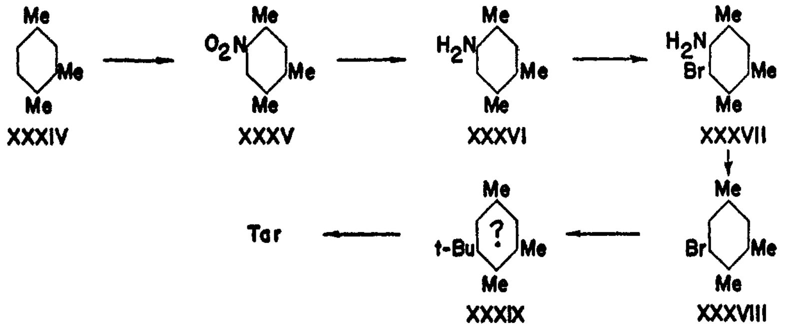
In an attempt to prepare the asymmetrical isomer (XII), the amine (XXII) was nitrated to *asymmetrical*-dinitrobutylxylidene (XXX). The latter, in spite of repeated attempts under varying conditions, gave upon diazotization nothing but tar. This is in sharp contrast to the ease with which the symmetrical isomer (XXVIII) diazotizes to the phenol (XXIX).

In the manufacture of Musk Ketone (I) by the nitration of *sym*-acetyl-*tert*-butyl xylene (XXXI) (Flow Sheet B), there is produced as a minor by-product the corresponding acid (XXXII). This was converted to the acid chloride (IX) of m.p. 108–109° (Baur reported 99°) which had a musk odor almost as powerful as Musk Ketone. Treatment with a solution of sodium in methanol yielded the

FLOW SHEET B



FLOW SHEET C



methyl ester (X) of m.p. 122–123° (Baur reported 96°) which had a musk odor somewhat weaker than its asymmetrical isomer (VIII).

An attempt to prepare the asymmetrical bromo musk (VI) by direct nitration of XXIII (Flow Sheet A) was not successful, but the synthesis was effected by bromination of *sym*-nitro-*tert*-butylxylene (XIV) (Flow Sheet B) to XXXIII and nitration of the latter to VI. It has a powerful musk odor. An attempt to prepare the asymmetrical methyl ether (XII) by refluxing VI with sodium methoxide in methanol or xylene was unsuccessful.

In our work with the musks we have noted frequent instances of the extreme adversion of the *tert*-butyl group to entry in a position *ortho* to a methyl group in the benzene nucleus: the butylation of *m*-xylene leads exclusively to the symmetrical isomer; the *tert*-butyl group enters *p*-cymene almost exclusively *ortho* to isopropyl rather than to methyl; butylation of toluene gives predominately *para*, together with some *meta* (14); the *tert*-butyl group enters *m*-cresol methyl ether in position *para* to methyl; butylation of pseudocumene by the Friedel-Crafts reaction results in the migration of methyl group from a position *ortho* to *tert*-butyl with production of *sym*-*tert*-butylhemimellitene; the *tert*-butylation of mesitylene has not yet been accomplished. The failure of the above-mentioned attempt to prepare *tert*-butylpseudocumene by reacting the lithium compound of XXIII with dimethyl sulfate suggests that the same adversion obtains regardless of the order of entry of the two groups. The above facts are in harmony with the strain considerations discussed recently by Brown (5).

Regardless of these adverse circumstances an attempt was made, as outlined in Flow Sheet C, to prepare the desired 6-*tert*-butylpseudocumene. Nitration of pseudocumene (XXXIV) led to 5-nitropseudocumene (XXXV) (15), which was reduced to 5-aminopseudocumene (XXXVI). Bromination of the latter by the method of Huender (16) gave 5-amino-6-bromopseudocumene (XXXVII) which, after diazotization, gave 6-bromopseudocumene (XXXVIII). Treatment of the Grignard compound of the latter with an excess of *tert*-butyl chloride gave a product which was probably an impure XXXIX. Upon nitration with mixed acid nothing was obtained but tar which had no suggestion of musk odor.

EXPERIMENTAL

FLOW SHEET A

A solution of 680 g. of 98% nitric acid in 430 g. of acetic acid and 430 g. of acetic anhydride was added with agitation to a solution of 1,166 g. of *tert*-butyl-*m*-xylene (XIII) in 1,300 g. of acetic anhydride during 1 hour at 20°. After quenching in ice and water the crude product was taken up in benzene, washed with dilute sodium hydroxide, finally with water to neutrality, and the solvent was evaporated. The 1,490 g. of crude material was chilled in brine, filtered, and the 906 g. of crystals recrystallized from 210 g. of ethanol to yield 791 g. of XIV, m.p. 85°. Reworking of the mother liquor yielded 76 g. more, to a total of 867 g. The mother liquor consists principally of the asymmetrical isomer, XVIII.

A mixture of 867 g. of XIV, 810 g. of 40-mesh iron powder, 1,670 g. of water, 81 g. of 31% hydrochloric acid, and 100 ml. of ethanol was refluxed with vigorous agitation for 40 hours and neutralized by addition of soda ash. After cooling, 500 ml. of benzene was stirred in and the mixture was filtered through a bed of Filter-Cel. Distillation yielded 713 g. of XV as a colorless oil of b.p. 100°/3 mm. Upon moderate cooling a c.p. of 10° and m.p. 10.5° were observed, but with stronger cooling another crystal form was obtained of c.p. 28° and m.p. 29°.

XV (713 g.) was added to 8,380 g. of 80% sulfuric acid with agitation and the solution was cooled to 0°. To the slurry of amine salt was added 293 g. of 98% nitric acid during ½ hour at 0° and the temperature then was allowed to rise to 25° during ½ hour. The clear solution was quenched in ice-water and the thick suspension of yellow crystals was filtered and washed with water. To the crystals were added 2 liters of benzene and 2 liters of water, and then, with agitation, 40% sodium hydroxide until the aqueous layer remained alkaline. The resulting emulsion was filtered and the benzene-insoluble crystals were washed with benzene and crystallized from acetone, yielding 15 g. of lemon-yellow needles of m.p. 229–231°.

Anal. Calc'd for $C_8H_9N_3O_4$(XVII): C, 45.49; H, 4.29; N, 19.89.

Found: C, 45.56; H, 4.32; N, 19.76.

The benzene solution was washed to neutrality, the solvent was removed, and the crude crystals (770 g.) were taken up in an equal weight of hot naphtha, filtered to remove 2 g. of insoluble crystals (XVII), chilled, and filtered to yield 733 g. of XVI, as yellow-orange crystals of m.p. 88–89°. Reworking of the mother liquor yielded 23 g. more, to a total of 756 g.

A solution of 375 g. of XVI in 2 liters of ethanol and 845 g. of 40% sulfuric acid was heated to reflux and a solution of 234 g. of sodium nitrite in an equal weight of water was added during 2 hours. After cooling, the solution was diluted with an equal volume of water, the oil layer was removed, and the aqueous phase twice was extracted with benzene. The oil and the extracts were combined and washed with 5% sodium hydroxide to remove phenol, then to neutrality with water, and distilled to yield 215 g. of XVIII as a colorless oil of b.p. 101°/2.5 mm.; d_{25}^{25} 1.0345; n_D^{20} 1.5140. Upon moderate cooling a c.p. of 9.5° and m.p. of 10° were observed, but upon stronger cooling another crystal form was obtained of c.p. 18.5° and m.p. 19.5°.

Acidification of the alkaline washes, followed by crystallization from benzene-naphtha yielded 24 g. of XIX as yellow prisms of m.p. 80–81°. Methylation of XIX with dimethyl sulfate gave the corresponding methyl ether (XX) as a pale yellow oil of mild odor, b.p. 122°/3 mm.; c.p. 26.5°; m.p. 27°.

A solution of 34 g. of XX in 13 g. of acetic anhydride was added with agitation to a solution of 23 g. of 98% nitric acid in 37 g. of acetic anhydride during 45 min. at −12°. The crystalline slurry was quenched in ice-water, and the crystals were filtered, taken up in benzene, washed with dilute sodium hydroxide and water, and the solvent was removed. Crystallization from ethanol yielded 23 g. of XXI as pale yellow needles of m.p. 111–112.5°, having a faint, musty odor.

Anal. Calc'd for $C_9H_{10}N_2O_5$: C, 47.78; H, 4.41; N, 12.38.
Found: C, 47.73; H, 4.42; N, 12.81.

A mixture of 430 g. of XVIII, 411 g. of 40-mesh iron powder, 800 g. of water, and 39 g. of 31% hydrochloric acid was refluxed with agitation for 48 hrs., neutralized with soda ash, cooled, filtered, and the crude amine was converted to the hydrochloride; the latter was washed with naphtha and the amine was liberated and distilled to yield 329 g. of XXII, b.p. 97°/3.5 mm.; c.p. −10°; m.p. −9°.

By means of the Sandmeyer reaction, 214 g. of XXII was converted to the bromo compound XXIII in a yield of 96 g.; b.p. 92–93°/3.5 mm.; c.p. 33.2°, m.p. 34.5°. As a by-product, obtained by extracting the crude reaction product with Claisen's solution, there was isolated 54 g. of XXIV, b.p. 93°/3.5 mm.; c.p. 21.5°; m.p. 23°.

A solution of 50.2 g. of XXIII in 50 g. of ether was added during 2 hrs. to a suspension of 5.6 g. of lithium pellets (100% excess) in 225 g. of ether and the mixture was refluxed overnight. In the morning the excess lithium was removed and 80 g. of dimethyl sulfate in 80 g. of ether was added to the solution and the whole was refluxed overnight. The solution was quenched in iced dilute hydrochloric acid, the ether was removed, the oil was stirred with hot dilute sodium hydroxide to destroy dimethyl sulfate, and finally was washed and distilled to yield 24 g. of XIII, b.p. 59°/3.5 mm.; c.p. −17° (unchanged upon admixture with an authentic specimen). In similar fashion the lithium compound prepared from 100 g. of XXIII was cooled to −70° and a solution of 89 g. of acetic anhydride in 89 g. of ether was added during 2 hrs. at −70°. After 2 hrs. further at that temperature the solution was allowed to warm to −10°, quenched in ice-water, and the ether layer was washed neutral and distilled, yielding 50 g. of XIII.

XXV was prepared by a simplification of the procedure described in *Organic Syntheses* for α-naphthonitrile (17). A mixture of 245 g. of XXIII, 112 g. of cuprous cyanide, and 10 ml. of pyridine was heated with agitation to 220°, at which point the temperature rose rapidly to 255°. Slight cooling was applied for 2–3 minutes until the heat of reaction had subsided, after which the mixture was heated for 15 minutes at 245–250°. It was cooled to 150° and was poured slowly into one liter of 15% ammonia. The mixture was warmed and stirred until no lumps remained, benzene was added and the whole was filtered through a fritted glass funnel. The benzene solution was washed with dilute ammonia, water, dilute hydrochloric acid, water to neutrality, and was distilled to yield 177 g. of XXV, b.p. 103–104°/3 mm.; m.p. 57–58°.

To a mixture of 155 g. of 98% nitric acid and 465 g. of 93% sulfuric acid was added 115 g. of XXV with agitation at 25–30°. The crystalline slurry was warmed to 50° for a few minutes, cooled, quenched on ice, and the crystals were taken up in benzene, washed with dilute sodium hydroxide, then with water, and the solvent was removed. The 170 g. of crude yielded after crystallization from ethanol 155 g. of V as pale yellow plates of m.p. 115–116°, having a strong musk odor.

Anal. Calc'd for $C_{13}H_{15}N_3O_4$: C, 56.30; H, 5.45; N, 15.15.
Found: C, 56.24; H, 5.61; N, 15.2.

A mixture of 50 g. of V and 150 g. of 75% sulfuric acid was agitated during 3 hrs. at 180–190°, cooled, and diluted with water. The crystals were filtered off, taken up in dilute sodium hydroxide, and the solution was filtered from scum, washed with benzene, and the crude acid liberated. It was taken up in hot benzene, and the solution was filtered to remove carbonaceous material and diluted with naphtha to precipitate the acid, XXVI, as colorless odorless needles (40 g.) of m.p. 200–201°.

Anal. Calc'd for $C_{13}H_{16}N_2O_6$: Mol. Wt. 296. Found (by titration): Mol. Wt. 297.

A mixture of 39 g. of XXVI, 30 ml. of benzene, and 25 g. of thionyl chloride was warmed to refluxing during 1 hr., refluxed 1 hr. further and the solvent and excess thionyl chloride were removed *in vacuo*. The crude, 42 g., was taken up in 100 ml. of hot naphtha, treated with Tonsil (infusorial earth); and the practically colorless filtered solution was evaporated to 70 g., chilled in an ice-salt mixture, and filtered to yield 40 g. of VII as pale yellow, compact prisms of m.p. 97–98°, having a weak, but definite musk odor.

To a Grignard solution prepared from 4.6 g. of magnesium, 30 g. of methyl iodide, and 150 ml. of ether was added, with cooling, 19.2 g. of cadmium chloride. After refluxing ½ hr. a solution of 15.5 g. of VII in 50 ml. of ether was added as rapidly as refluxing would permit. The mixture was quenched on iced, dilute sulfuric acid and the ether solution was washed repeatedly with 5% sulfuric acid until the washings no longer produced a precipitate upon being made alkaline. The solution was then washed with dilute sodium hydroxide, finally with water to neutrality, and the solvent was removed, leaving 11 g. of tacky, reddish-amber crystals. After several alternate crystallizations from methanol and naphtha, which removed some resin and a small amount of a high-melting, insoluble powder, there remained 4 g. of crystals of m.p. 128–134°. These were sublimed in a high vacuum onto a cold finger, after which they melted at 131–136°. A final crystallization from methanol gave 2.5 g. of II as nearly colorless plates of m.p. 137–138°, having an odor similar to that of Musk Ketone (I), but weaker. A mixture of I and II melted at 110–118°.

Anal. Calc'd for $C_{14}H_{18}N_2O_5$: C, 57.13; H, 6.16; N, 9.51.
Found: C, 57.36; H, 6.26; N, 9.28.

To a suspension of 9 g. of VII in 50 g. of methanol was added 66 g. of a 1% solution of sodium in methanol; then the mixture was warmed and a little excess sodium methoxide solution was added until alkalinity to litmus persisted. The suspension was diluted with water and extracted with benzene. Washing of the benzene solution with dilute sodium carbonate removed 2 g. of acid, m.p. 197–199°. Upon removal of the solvent there remained 7 g. of m.p. 89–170°; this was triturated with 150 g. of methanol at 50°, and the suspension was cooled to 15° and filtered, thus removing a small amount of acid anhydride of m.p. >240°. Evaporation of the solvent left 6 g. of yellow crystals of m.p. 89–92°. Two crystallizations from methanol gave 4.5 g. of VIII as pale yellow, transparent, hexagonal plates of m.p. 93–94°, having a distinct, but somewhat weak, musk odor.

Anal. Calc'd for $C_{14}H_{18}N_2O_6$: C, 54.18; H, 5.84; N, 9.02.
Found: C, 54.31; H, 5.78; N, 9.25.

Musk Xylene (XXVII) was converted, by the procedures of Tchitchibabin (1), successively to XXVIII, XXIX, and XI. All were odorless.

XXII (66 g.) was dissolved in 800 g. of 100% sulfuric acid and to the solution was added 70 g. of 98% nitric acid at 25–30°, followed by 200 g. of 20% oleum. The mixture was warmed to 60° and after 15 min. was cooled and quenched on ice. The gummy yellow crystals were taken up in benzene and were washed repeatedly with dilute sodium hydroxide until the washes were light colored, finally to neutrality with water, and the solvent was removed. The 42 g. of tacky, reddish crystals yielded, after repeated crystallization from 90% methanol, 23 g. of XXX as bright yellow plates of m.p. 120–121°.

Anal. Calc'd for $C_{12}H_{17}N_3O_4$: C, 53.91; H, 6.41; N, 15.72.
Found: C, 53.94; H, 6.29; N, 15.64.

Attempts to diazotize XXX to the corresponding phenol by the procedure used for the symmetrical isomer XXIX led only to tar formation, as did several other attempts by various modified diazotization techniques.

FLOW SHEET B

The acid XXXII, pale yellow needles of m.p. 237°, obtained as a minor by-product in the manufacture of Musk Ketone, was converted to the acid chloride IX by the same procedure used for the asymmetrical isomer VII (Flow Sheet A). It was obtained as pale yellow plates of m.p. 108–109°, having a strong musk odor [Baur (8) gave m.p. 99°].

To a suspension of 30 g. of IX in 150 g. of methanol was added 73.5 g. of a 3% solution of sodium in methanol and the whole was heated to boiling. A little more of the sodium methoxide solution was added until alkalinity persisted. The cooled mixture was diluted with water, and the crystals were taken up in benzene and washed with dilute sodium carbonate. Removal of the solvent left 29 g. of m.p. 120–123°. Crystallization from methanol gave 28 g. of X as pale yellow, cube-like prisms of m.p. 122–123° [Baur (8) gave m.p. 96°], having a musk odor somewhat weaker than that of the asymmetrical isomer VIII. The difference in solubility of the two isomers in hot methanol is quite marked: X requires 6.5× its weight, while VII is soluble in less than an equal weight.

Anal. Calc'd for $C_{14}H_{18}N_2O_6$: C, 54.18; H, 5.84; N, 9.02.
Found: C, 54.13; H, 5.83; N, 9.16.

Bromination of 204 g. of XIV in carbon tetrachloride solution in the presence of iron powder yielded, after crystallization from ethanol, 260 g. of XXXIII as pale yellow crystals of m.p. 75–76°, having a mild odor similar to that of butylxylene. To a solution of 11 g. of 98% nitric acid in 29 g. of 93% sulfuric acid was added 20 g. of XXXIII, followed by 8 g. of 20% oleum. The mixture was held at 50° for 15 minutes, cooled, quenched on ice, and the crude product was taken up in benzene, washed with dilute sodium hydroxide, and the solvent was removed. The remaining oil was taken up in 250 g. of naphtha and filtered to remove a little insoluble, high-melting powder. Removal of the solvent left crystals which, after three crystallizations from methanol, yielded 12 g. of VI as pale yellow hair-like crystals of m.p. 67–68°, having a strong musk odor.

Anal. Calc'd for $C_{12}H_{15}BrN_2O_4$: C, 43.50; H, 4.56; N, 8.45.
Found: C, 43.66; H, 4.76; N, 8.21.

Upon refluxing VI with an equivalent of sodium methoxide in methanol no halogen replacement occurred. In boiling xylene nothing but tar was formed.

FLOW SHEET C

The nitration of pseudocumene (XXXIV) was carried out by the procedure of Schultz (15), but in our hands the yield was considerably lower than that claimed by him: 240 g. of the hydrocarbon (c.p. −52°; m.p. −49°) gave only 93 g. of XXXV, m.p. 70–71°. Iron reduction led to the amine (XXXVI), colorless crystals of m.p. 63–64°.

XXXVII was prepared by a modification of the method of Huender (16). A solution of 50 g. of XXXVI in 50 g. of acetic acid was added with agitation to 1,250 g. of 31% hydrochloric acid. A solution of 61 g. of bromine in 60 g. of acetic acid was added to the slurry of amine salt during 3 hrs. The mixture was diluted with 1 liter of water, filtered, and the crystals were washed with benzene and air-dried to yield 82 g. of the hydrochloride of XXXVII.

A solution of 250 g. of the hydrochloride of XXXVII in 1,000 g. of ethanol and 320 g. of 40% sulfuric acid was heated to refluxing and a solution of 138 g. of sodium nitrite in 200 g. of water was added with agitation at a rate sufficient to maintain refluxing without application of heat. The solution was steam-distilled, the oil layer was washed with dilute sodium hydroxide, and finally with water to neutrality and then distilled *in vacuo* to yield 95 g. of XXXVIII, b.p. 71°/3 mm.

To the Grignard reagent prepared from 130 g. of XXXVIII, 16.5 g. of magnesium, and 265 g. of ether was added, during 6 hrs., a solution of 120 g. (100% excess) of *tert*-butyl chloride in 60 g. of ether. The mixture was refluxed overnight and then quenched in iced dilute hydrochloric acid. The ether layer was washed and distilled to yield 43 g. of pseudocumene and 21 g. of a fraction of b.p. 71°/3 mm., d_{25}^{25} 0.9004, n_D^{20} 1.5084, which was probably not quite pure XXXIX.

Anal. Calc'd for $C_{13}H_{20}$: C, 88.55; H, 11.45.
Found: C, 85.5; H, 11.1.

The hydrocarbon contained bromine and was probably contaminated with a little XXXVIII, which has the same boiling point.

XXXIX (18 g.) was added during 1 hr. to a mixture of 14 g. of 98% nitric acid and 58 g. of 93% sulfuric acid with agitation at 20°. Considerable heat developed and the mixture turned black. When the addition was complete 35 g. of 93% sulfuric acid was added and the mixture was warmed to 60° for 15 min., cooled, and quenched on ice. The black tar was taken up in benzene and the solution was washed repeatedly with dilute sodium hydroxide. Acidification of the washes liberated tar. The solution was washed to neutrality and the solvent was removed, leaving 9 g. of totally odorless black tar.

All analyses were performed by Mr. D. Johnston and the staff of the Analytical Laboratory.

SUMMARY

1. The asymmetrical isomer of Musk Ketone has been synthesized and found to possess a musk odor of somewhat lower intensity than the latter.

2. Attempts to prepare the asymmetrical isomer of Musk Tibetene have been unsuccessful.

3. Four new asymmetrical musks in the dinitro-*tert*-butyl-*m*-xylene series have been synthesized: the nitrile, the acid chloride, the carboxymethyl ester, and the bromo analogs.

4. Two new symmetrical musks in the same series have been synthesized: the acid chloride and the carboxymethyl ether.

5. Attempts to prepare the asymmetrical phenol methyl ether of the same series have been unsuccessful.

6. The symmetrical phenol of the same series, and its methyl ether, which have been stated to have weak musk odors, have been found to be odorless when pure.

DELAWANNA, NEW JERSEY

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