[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Structure and Synthesis of Muscopyridine

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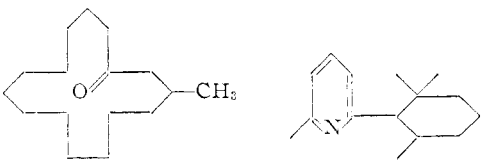
Biogenetic considerations led us to propose structure III f uscopyridine, a base isolated previously from the perfume gland of the musk deer. This structure has been verified by a total synthesis. Starting from cyclododecanone, the bicyclic hydrocarbon XIII was prepared *via* Stobbe condensation, cyclization, decarboxylation and Wolff–Kishner reduction. On treatment with hydrazoic acid followed by dehydrogenation a mixture of 2,3- and 2,6-decamethylenepyridines (XVI and XVII) was obtained. Rearrangement of the N-oxide XVIII followed by hydrolysis and Sarett oxidation gave the ketone XXII. The synthesis of racemic III was completed by direct methylation and Wolff–Kishner reduction of the monomethyl ketone XXIII. The product obtained was identical with natural muscopyridine (III) by infrared and ultraviolet absorption, index of refraction and density. Racemic III was resolved and characterized by a picrolonate which did not depress the melting point of muscopyridine picrolonate.

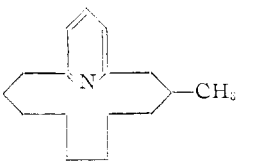
Since the pioneering researches of Ruzicka on the structures of civetone and muscone, I,[2] the number of naturally occurring substances found to contain large rings has increased steadily. Although the compounds first recognized to be macrocyclic contain carbon rings, the heterocyclic group is the most highly populated one today. In recent years a number of polypeptides (enniatin,[3] oxytocin,[4] gramicidin,[5] phalloidin[6]), alkaloids (tubocurarin[7]) and antibiotics (erythromycin, methymycin, carbomycin, magnamycin[8]) have been shown to belong to this class of natural products.

While these investigations on naturally occurring substances were in progress, theoretically minded organic chemists, particularly Cram, Huisgen, Prelog and Wiesner, became interested in the chemical and physical properties of compounds containing polymethylene chains joined to the *ortho*, *meta* or *para* positions of aromatic rings.[9] A good many of these substances have become available by synthesis and some of their properties have been studied. We have now found this interesting structural principle realized in a natural product.

In the course of their studies on the odoriferous constituents of natural musk from the musk deer (*Moschus moschiferus*), the Swiss group isolated an optically active base $C_{16}H_{25}N$, $[\alpha]^{23}D$ +17.4°, (λ_{max} 267 mμ, log ϵ 3.7) which was named muscopyridine.[10] Muscopyridine was rather resistant to potassium permanganate, but on prolonged oxidation pyridine-2,6-dicarboxylic acid was obtained. This observation proved the presence of a 2,6-disubstituted pyridine ring and furthermore suggested that the natural base did not contain any additional double bonds. After non-identity with an isomeric base II,[11] isolated from California petroleum, had been established, work on muscopyridine was discontinued, mainly because with the advent of the synthetic musks the natural material had become very rare.



I II



III

We made the reasonable assumption that the similarity in molecular composition between the two musk constituents muscone ($C_{16}H_{30}O$) and muscopyridine ($C_{16}H_{25}N$) is not fortuitous but due to a biogenetic relationship. Before discussing a possible biogenesis of muscopyridine we must briefly consider the origin of muscone. In the absence of experimental work on the biosynthesis of large ring ketones such considerations are bound to be of a highly speculative nature and additional uncertainty is introduced by the structural simplicity of the molecules to be discussed. Natural products containing only few functional groups, obviously, are more amenable to quick structure determination than highly substituted ones, but the reverse situation prevails in the field of biogenetic speculations.[12] The muscone molecule (I) provides only three clues (number of carbon atoms, carbonyl and methyl) which in the absence of tracer experiments are of any help in discerning its origin. Ruzicka[13] already suggested that the macrocyclic ketones might be formed *in vivo* from α,ω-dicarboxylic acids by a Claisen-type condensation which is followed by decarboxylation. This proposal re-

(1) Forris Jewett Moore predoctoral Fellow, 1954.

(2) For an authoritative discussion on musk and related substances see E. Lederer, in L. Zechmeister, "Progress in the Chemistry of Organic Natural Products," Vol. VI, Springer, Wien, 1950, p. 87.

(3) Pl. A. Plattner and U. Nager, *Helv. Chim. Acta*, **31**, 2192 (1948).

(4) H. Tuppy, *Biochim. Biophys. Acta*, **11**, 449 (1953); V. du Vigneaud, *et al.*, THIS JOURNAL, **75**, 4879 (1953).

(5) F. Sanger, *Biochem. J.*, **40**, 261 (1946); D. C. Hodgkin, *Cold Spring Harbor Symposia*, **14**, 65 (1949).

(6) Th. Wieland, *Ang. Chem.*, **69**, 44 (1957) and earlier papers.

(7) H. King, *J. Chem. Soc.*, 1381 (1935).

(8) R. B. Woodward, *Ang. Chem.*, **69**, 50 (1957). References to papers on the other antibiotics are given in this article.

(9) For a comprehensive review see V. Prelog in (Sir) A. R. Todd, "Perspectives in Organic Chemistry," Interscience Publishers, Inc., 1956, p. 96. See also V. Prelog and U. Geyer, *Helv. Chim. Acta*, **28**, 1677 (1945).

(10) H. Schinz, L. Ruzicka, U. Geyer and V. Prelog, *ibid.*, **29**, 1524 (1946).

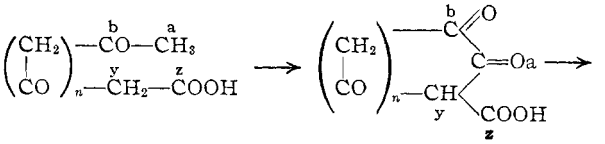
(11) B. Shive, S. M. Roberts, R. I. Mahan and J. R. Bailey, THIS JOURNAL, **64**, 909 (1942); V. Prelog and U. Geyer, *Helv. Chim. Acta*, **29**, 1587 (1946).

(12) This situation is exemplified perfectly by the case of griseofulvin. A. J. Birch, R. A. Massy-Westropp, R. W. Rickards and H. Smith, *J. Chem. Soc.*, Proceedings, 98 (1957).

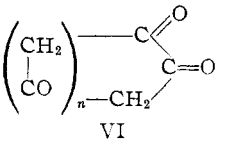
(13) L. Ruzicka, *Helv. Chim. Acta*, **9**, 230, 1008 (1926). See also R. A. Raphael in E. H. Rodd, "Chemistry of Carbon Compounds," Vol. IIA, Elsevier Publishing Co., Amsterdam, 1953, p. 283.

ceived support from the fact that all known naturally occurring macrocyclic ketones and alcohols, except muscone, contain an odd number of carbon atoms. To rationalize the presence of a methyl group in muscone, Stevens[14] suggested that this macrocyclic ketone is formed from hexadecane-2,15-dione by intramolecular aldol condensation. The diketone in turn was assumed to have originated from stearic acid.

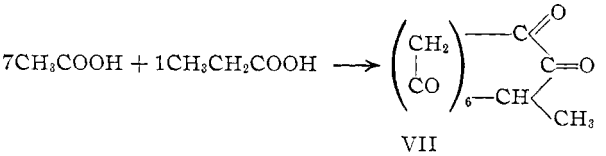
There is good experimental evidence available today which demonstrates that straight chain *aliphatic* acids are synthesized from acetate *via* polyketocarboxylic acids.[15,16] The investigations of Birch[12,15] and Woodward[8] on the other hand have clarified the role of these polyketocarboxylic acids in the biogenesis of *cyclic* compounds such as phenols, pyrones and lactones. It seems attractive to invoke these versatile intermediates, rather than the saturated dicarboxylic acids, in the biosynthesis of macrocyclic ketones. The simplest cyclizations between a and z in IV leading to straight chain cyclic ketones with an even number of carbon atoms and between b and y, after decarboxylation, leading to β-alkylated ketones with an even number of carbon atoms in the ring seem unimportant in this class of compounds as evidenced by their absence in natural products.



IV V



VI



VII

It then becomes necessary to assume that the change from the polyketocarboxylic acids to the macrocyclic ketones is initiated by ω-oxidation at a and continued by cyclization between a and y (*cf.* IV → V). The process is terminated by decarboxylation (V → VI) and reduction. We favor the idea that muscone (I) also is formed by a similar process and, if this assumption is granted, we have to rationalize the presence and location of the extraneous methyl group.

In our opinion the sequence proposed by Stevens[14] is unlikely because (a) muscone would have to be formed by a sequence differing drastically from the one operative in the biosynthesis of the other known macrocyclic ketones and (b) the required 2,15-hexadecanedione is available from acetate only by a very circuitous route. We would like to suggest that muscone (I) is formed *in vivo* from seven molecules of acetic and one of propionic acid.[17] The C_{17}-polyketocarboxylic acid could then undergo ω-oxidation and cyclization as discussed, giving VII. It is however also conceivable that the extra methyl group is actually introduced at a later stage, possibly by alkylation of VI. In support of this notion we may cite biochemical work on the origin of the extra methyl groups in ergosterol[18] and eburicoic acid.[19]

It appeared that a methylated cyclic polyketone (*e.g.*, VII) might not only serve as a precursor of I but also of muscopyridine. One can easily visualize a change involving (a) reaction between VII and ammonia or its "biological equivalent" and (b) reduction accompanied by aromatization to give III. There is no evidence in favor of a conversion of muscone to muscopyridine because the required β-oxidations have been observed with carboxylic acids only and are usually followed by loss of carbon atoms.[20] The three experimental findings on muscopyridine already discussed are not in contradiction with structure III and we decided to prepare this compound for comparison with the natural product.

We concentrated our efforts first on the preparation of the unsubstituted C_{15}-compound XVII. The bicyclic system under consideration could be constructed by any one of three approaches. (1) Cyclization of a suitable 2,6-disubstituted pyridine; (2) direct introduction of nitrogen into a macrocyclic intermediate already containing the finished carbon skeleton and (3) elaboration of the pyridine ring from a monocyclic precursor. The first approach was never considered seriously because we anticipated complications from the reactive pyridine ring in the acyloin condensation. Our early synthetic efforts followed the second scheme and it was planned to add ammonia to the cross conjugated dienone XXV. This scheme had to be abandoned at an early stage because we were unable to prepare XXV. Our attention was then directed to the third approach which in a sequence of ten steps led to muscopyridine (III).

Stobbe condensation[21] of cyclododecanone[22] (VIII) with diethyl succinate gave a carboxylic acid which had λ_{max} 223 mμ, log ϵ 3.94, and therefore must be the α,β-unsaturated isomer IX. Cyclization of IX either with zinc chloride[23] in acetic acid or preferably with polyphosphoric acid[24] led to the bicyclic vinylogous β-keto ester (X), which on

(14) P. G. Stevens, THIS JOURNAL, **67**, 907 (1945).

(15) Reviewed by A. J. Birch in (Sir) A. R. Todd, "Perspectives in Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1956, p. 134.

(16) (Sir) R. Robinson, "The Structural Relations of Natural Products," Clarendon Press, Oxford, 1955.

(17) Examples of condensations leading to branched carbon chains are given in ref. 16, p. 4, and in ref. 8.

(18) H. Danielsson and K. Bloch, THIS JOURNAL, **79**, 500 (1957).

(19) W. G. Dauben, G. J. Fonken and G. A. Boswell, *ibid.*, **79**, 1000 (1957).

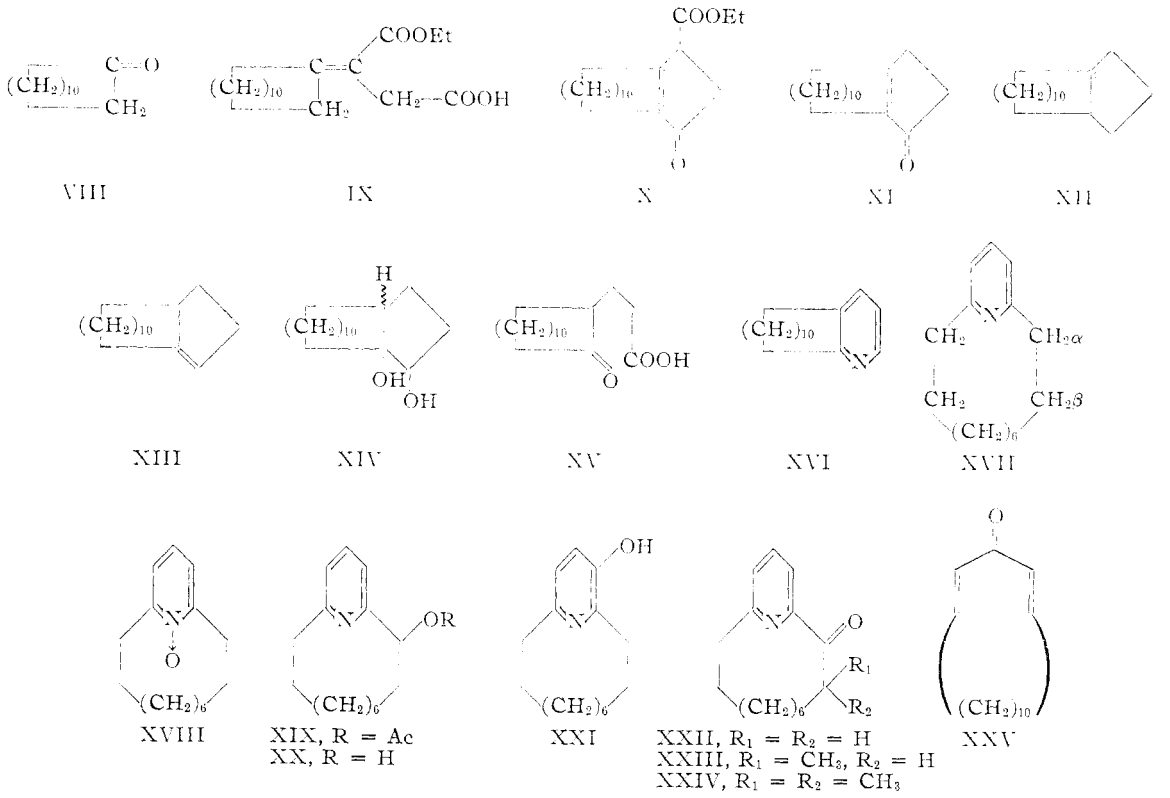
(20) A. L. Lehninger in V. A. Najjar, "Fat Metabolism," Johns Hopkins Press, Baltimore, Md., 1954, p. 117.

(21) W. S. Johnson and G. H. Daub, *Org. Reactions*, **6**, 1 (1951).

(22) M. Stoll, *et al.*, *Helv. Chim. Acta*, **30**, 1815, 1822, 1837 (1947); V. Prelog, L. Frenkiel, M. Kobelt and P. Barman, *ibid.*, **30**, 1741 (1947).

(23) W. S. Johnson, H. C. E. Johnson and J. W. Petersen, THIS JOURNAL, **67**, 1360 (1945); Pl. A. Plattner and G. Büchi, *Helv. Chim. Acta*, **29**, 1068 (1946).

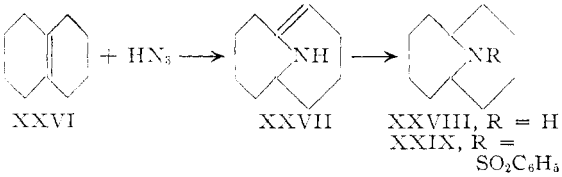
(24) S. Dev, *Chemistry & Industry*, 1071 (1954).



acid hydrolysis was converted smoothly to the bicyclic ketone XI, m.p. 27°, λ_{max} 237 mμ, log ε 4.17. Wolff–Kishner reduction of XI resulted in the formation of a mixture of bicyclic olefins (XII and XIII). The isomer distribution in this mixture was determined by osmylation followed by cleavage of the glycols (mainly XIV) with lead tetraacetate which gave 70% of a ketocarboxylic acid which we formulate as XV. The olefin mixture therefore contains at least 70% of the trisubstituted isomer XIII and Wolff–Kishner reduction of XI evidently caused migration of the original double bond.[25]

It now became necessary to introduce a nitrogen atom between C_1 and C_{12} in XIII and the Schmidt reaction appeared to be the most expedient method to achieve the desired change. The synthesis of unsaturated amines from olefins and hydrazoic acid in the presence of a mineral acid catalyst was first discussed in the patent literature[26] and subsequently studied in some detail by McEwen and co-workers.[27] The same products are formed when secondary alcohols[28] rather than olefins are used and it has been suggested that the corresponding azides[29] are the common intermediates. The product composition in these reactions seems to be governed by both the migratory aptitudes of the substituents in the azide and the stability of the Schiff base formed. Alicyclic alcohols[26,28] have been reported to yield mainly cyclic Schiff bases, whereas the more easily hydrolyzable Schiff bases derived from aliphatic alcohols and olefins are subsequently converted to the corresponding amines and ketones.

We were thus fairly confident that the Schmidt reaction applied to XIII would lead, at least partly, to the desired amine XXXI. Nevertheless, we decided to test the utility of the reaction for the synthesis of azabicyclo compounds with a simple model. Thus, the reaction of 9,10-octalin (XXVI) with hydrazoic acid led to XXVII[30] in 25% yield. On reduction over a platinum catalyst XXVII was converted to the saturated base XXVIII which on acylation with benzenesulfonyl chloride yielded XXIX, identical with an authentic sample.[30] The unsaturated base XXVII might well have been accompanied by an isomeric substance but no attempt was made to ascertain this point.



After the satisfactory outcome of this model study, XIII was allowed to react with hydrazoic acid in chloroform solution under closely defined conditions. A sensitive basic material was forthcoming which was not characterized further but transformed directly into its more stable aromatic form by dehydrogenation over a palladium cata-

(25) The reduction of α,β-unsaturated carbonyl compounds has been studied by R. Fischer, G. Lardelli and O. Jeger, *Helv. Chim. Acta*, **33**, 1335 (1950) and earlier papers cited.

(26) K. F. Schmidt and W. Klavehn, German Patent 583,565 (1933); *Frdl.*, **20**, 947 (1935).

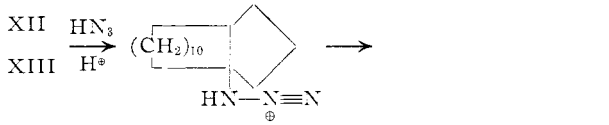
(27) D. R. Nielsen and W. E. McEwen, THIS JOURNAL, **76**, 4042 (1954), and earlier papers.

(28) J. H. Boyer and F. C. Canter, *ibid.*, **77**, 3287 (1955).

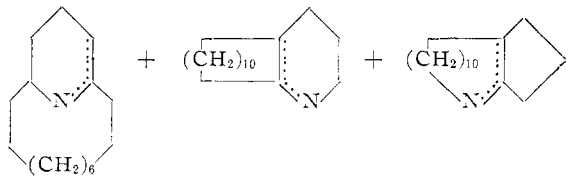
(29) In a few cases azides actually have been isolated: S. N. Ege and K. W. Sherk, *ibid.*, **75**, 354 (1953).

(30) A. C. Cope, R. J. Cotter and G. R. Roller, *ibid.*, **77**, 3590 (1955). We are indebted to Prof. A. C. Cope for a sample of the benzenesulfonamide XXIX.

lyst in 1-methylnaphthalene solution.[31] The desired 2,6-decamethylenepyridine (XVII), m.p. 15°, $\lambda\lambda_{max}$ 213, 267 mμ; log ε 3.82, 3.62, was accompanied by an equal amount of unwanted 2,3-decamethylenepyridine (XVI), m.p. 23°, $\lambda\lambda_{max}$ 268, 274 mμ; log ε 3.66, 3.55,[32] but quantitative separation could be achieved simply by chromatography over alumina. The assignment of structure to these two isomeric bases rests on (a) comparison of the resonance bands due to the aromatic hydrogens in the nuclear magnetic resonance spectra of XVI and XVII with those of 2,3-dimethylpyridine[33] and 2,6-dimethylpyridine[33] and (b) oxidation of XVII to 2,6-pyridinedicarboxylic acid. The formation of the two products isolated can be rationalized with the commonly accepted mechanism of the Schmidt reaction. The indiscriminate migration of alkyl groups in the decomposition of the azide[34] should actually lead to three products. It should be noted though that in contrast to XXXI and XXXII the third product XXXIII cannot aromatize and could well have polymerized during the treatment with palladium and thus escaped detection.



XXX



XXXI XXXII XXXIII

With the synthesis of XVII the first objective had been reached but to complete the synthesis of III the β-methyl group remained to be placed. Because we were unaware of a method which would permit the direct introduction of this substituent it became necessary to introduce an activating function in the α-position which in turn would provide the desired β-activation. It was hoped that the required α-substituent could be generated by the elegant pyridine N-oxide rearrangement which can lead to monosubstitution products only.[35] In fact the N-oxide XVIII, m.p. 78–80°, formed by oxidation of XVII with hydrogen peroxide, on heating with acetic anhydride gave the acetate XIX which was hydrolyzed without further purification to XX, m.p. 88°. An isomeric product $C_{15}H_{23}ON$, m.p. 201–202°, was formed concomitantly in 5% yield in the N-oxide rearrangement. We were aware of the possibility that a transannular reaction involving hydrogen transfer across the 13-membered ring might have led to an isomeric alcohol but both the high melting point and the insolubility of this by-product were in disagreement with this proposal. The most plausible alternate is substitution on either the 3- or 4-position of the pyridine ring. The positive ferric test, the ultraviolet absorption spectrum in ethanol solution (neutral: $\lambda\lambda_{max}$ 289, 226 mμ, log ε 3.71, 3.86; *N*/10 HCl: $\lambda\lambda_{max}$ 305, 236 mμ, log ε 3.96, 3.86; *N*/5 NaOEt: $\lambda\lambda_{max}$ 313, 249 mμ, log ε 3.74, 4.05) and the absence of pyridone bands in the 1650 cm.$^{-1}$ region in the infrared spectrum are in favor of structure XXI.[36]

The synthesis of III was continued by oxidation of XX with chromium trioxide to the bicyclic ketone XXII, m.p. 47°. Considerable experimentation was necessary to develop conditions for the preferential monoalkylation of XXII. The most straightforward method, involving direct alkylation of XXII with methyl iodide in the presence of potassium *t*-butoxide, was found to be most satisfactory. The three homologous ketones (XXII, XXIII and XXIV) were separated by adsorption chromatography and the composition of the individual fractions was determined by infrared absorption measurements in the region between 1500 and 1300 cm.$^{-1}$. Under more vigorous conditions the dimethyl ketone XXIV was formed exclusively. Reduction of XXIII by the Wolff–Kishner method gave an oily substance characterized by a picrolonate, m.p. 163–166° dec. This melting point was not lowered on admixture of the picrolonate of natural (+) muscopyridine, m.p. 163–166° dec., and the two salts are therefore isomorphic. The infrared and ultraviolet spectra of the synthetic base III regenerated from its picrolonate were superimposable on the spectra of natural muscopyridine (III) and identity was demonstrated further by comparison of densities and indices of refraction. Finally, the racemic base was resolved by means of di-*p*-toluoyl-L-tartaric acid. With the material available a complete resolution was not possible, but after five crystallizations of the salt the regenerated base had $[\alpha]^{25}D$ +13.3° (indicating a mixture of 88% of the (+)-isomer and 12% of the (−)-isomer) and gave a picrolonate, m.p. 163–166° dec. The melting point of the synthetic picrolonate was not depressed on admixture of the derivative prepared from natural muscopyridine.

Acknowledgments.—The authors wish to express their appreciation to Firmenich and Co., Geneva, for generous financial support, to Drs. M. Stoll and H. Schinz for the remaining 17 mg. of muscopyridine picrolonate, and to Prof. R. B. Woodward for the di-*p*-toluoyltartaric acids.

(31) Dehydrogenation in *p*-cymene (H. Rapoport and H. D. Baldridge, THIS JOURNAL, **74**, 5365 (1952)) was too slow and led to extensive polymerization.

(32) Cycloheptено- and cyclopentadeceno-2,3-pyridine have λ_{max} 267, log ε 3.65: V. Prelog and S. Szpilfogel, *Helv. Chim. Acta*, **28**, 1684 (1945).

(33) H. J. Bernstein, J. A. Pople and W. G. Schneider, *Can. J. Chem.*, **35**, 65 (1957).

(34) Fortunately both XII and XIII lead to the same azide XXX.

(35) G. Kobayashi and S. Furukawa, *Pharm. Bull.*, **1**, 347 (1953); V. Boekelheide and W. J. Linn, THIS JOURNAL, **76**, 1286 (1954); O. H. Bullitt and J. T. Maynard, *ibid.*, **76**, 1370 (1954).

(36) The formation of a 3-hydroxypyridine in the N-oxide rearrangement has been observed previously by G. Kobayashi, S. Furukawa and Y. Kawada, *J. Pharm. Soc. Japan*, **74**, 790 (1954), and J. A. Berson and T. Cohen, THIS JOURNAL, **77**, 1281 (1955). For the rearrangement of isoquinoline-N-oxide see N. M. Robison and B. L. Robison, *J. Org. Chem.*, **21**, 1337 (1956).

These authors, and V. Boekelheide and D. L. Harrington, *Chemistry & Industry*, 1423 (1955), have discussed possible mechanisms for the rearrangement.

Experimental[37]

Stobbe Condensation with Cyclododecanone (VIII).—To a potassium *t*-butoxide solution prepared from 24.2 g. (0.62 g. atom) of potassium and 1 l. of boiling *t*-butyl alcohol, which had been dried by distillation from calcium hydride, was added in two portions a warm mixture of 103 g. (0.565 mole) of cyclododecanone[22,38] and 148 g. (0.85 mole) of diethyl succinate. The yellow solution was boiled under reflux in an atmosphere of dry nitrogen for 22 hours.[21] The brown reaction mixture was cooled and acidified with 120 ml. of 6 *N* hydrochloric acid. Most of the butanol was distilled under reduced pressure, 300 ml. of water was added to the remaining product, and it was extracted twice with ether. The ethereal solution was washed with water and extracted with a total of 800 ml. of 1.7 *N* ammonia. This was acidified with hydrochloric acid and the oil which separated was taken up in ether. After drying and evaporation of the solvent there was obtained 148.4 g. (84.5%) of crude β-carbethoxy-β-cyclododecylidenepropionic acid (IX) as a yellow oil.

Bicyclo[10.3.0]-1(12)-pentadecen-13-one (XI).—To 500 ml. of hot polyphosphoric acid was added during 45 min. with stirring 46.7 g. of β-carbethoxy-β-cyclododecylidenepropionic acid (IX). The mixture was stirred at 95–98° for a total of 3 hr., cooled and poured into 1 l. of ice and water under vigorous stirring. The product was extracted with ether. Concentration of the dried solution under reduced pressure yielded crude ethyl bicyclo[10.3.0]-1(12)-pentadecen-13-one-15-carboxylate (X), a sample of which was distilled at 1.1 mm. in a similar run; $n^{25}D$ 1.5102. The 2,4-dinitrophenylhydrazone melted, after recrystallization from ethyl acetate–ethanol, at 147–148.2°.

Anal. Calcd. for $C_{24}H_{32}N_4O_6$: C, 61.00; H, 6.83; N, 11.86. Found: C, 61.11; H, 7.07; N, 12.16.

The undistilled keto ester X was heated under reflux for 19 hr. with a mixture of 50 ml. of glacial acetic acid, 50 ml. of water and 5 ml. of concentrated hydrochloric acid. After cooling the product was poured into 1 l. of water and extracted four times with ether. The combined ethereal solutions were washed with water, three times with 5% sodium carbonate and with sodium chloride solution. The ether solution was dried, concentrated under reduced pressure and the remaining oil distilled at 3.5 mm. The main fraction (b.p. 161.5–163°) consisted of 15.45 g. (47%) of bicyclo[10.3.0]-1(12)-pentadecen-13-one (XI), m.p. 27–28.5°, $n^{25}D$ 1.5238. Ultraviolet absorption: λ_{max} 237 mμ (log ε 4.17). Principal infrared bands: 2920, 2860, 1695, 1637, 1470, 1445, 1362 and 1160 cm.$^{-1}$ (in carbon tetrachloride).

The 2,4-dinitrophenylhydrazone of XI, recrystallized from ethyl acetate, melted at 192–193°.

Anal. Calcd. for $C_{21}H_{28}N_4O_4$: C, 62.98; H, 7.05; N, 13.99. Found: C, 62.74; H, 7.28; N, 13.66.

The semicarbazone of XI, recrystallized from methanol–water, melted at 215–217° dec.

Anal. Calcd. for $C_{16}H_{27}N_3O$: C, 69.27; H, 9.81. Found: C, 68.90; H, 10.00.

Bicyclo[10.3.0]-12-pentadecene (XIII).—To a solution of 12.46 g. of sodium in 200 ml. of freshly distilled diethylene glycol was added 19.93 g. of the bicyclic ketone XI and 20 ml. of hydrazine (95+%). The mixture was heated to reflux in a metal-bath for 3 hr. The flask was then connected with a take-off condenser and the excess hydrazine and the water formed distilled during one hour. The content of the flask was then heated to 227° for three additional hours. The distillate (*ca.* 20 ml.) was combined with the reaction mixture, diluted with 800 ml. of water and extracted three times with petroleum ether. The organic layer was washed with water twice, dried over sodium sulfate and concentrated under reduced pressure. The brown oil obtained (17.73 g.) was chromatographed on 250 g. of alumina (act. I, neutral). Petroleum ether eluted 13.14 g. of a colorless oil, which was distilled through an 18 in. spinning band column at 1.7 mm. Bicyclo[10.3.0]-12-pentadecene (XIII), 10.35 g. (55.2%), was collected at 112–115°, $n^{25}D$ 1.5021–1.5055. Principal infrared bands: 3050, 2920, 2860, 1645, 1470, 1447, 1345, and 790 cm.$^{-1}$ (pure liquid). A sample was redistilled for analysis.

Anal. Calcd. for $C_{15}H_{26}$: C, 87.30; H, 12.70. Found: C, 87.46; H, 12.42.

Bicyclo[10.3.0]pentadecane-12,13-diol (XIV).—To 25 ml. of pyridine and 2.00 g. (0.00786 mole) of osmium tetroxide was added 1.62 g. (0.00786 mole) of XIII. After 17 days in the dark, with daily shaking, the solution was filtered and the filtrate concentrated under reduced pressure. To the residue was added 50 ml. of benzene–ethanol (1:1) and a mixture of 10.3 g. of mannitol, 10.3 g. of potassium hydroxide, 25 ml. of water and 50 ml. of ethanol. The solution was heated under reflux for 7 hr. and concentrated under reduced pressure to 30 ml. The residue was extracted with ether and the crude, crystalline diol (1.65 g.) obtained was chromatographed on 100 g. of alumina (act. III, neutral) in benzene. The first fractions contained 250 mg. of starting material XIII, whereas a total of 1.40 g. (88%) of crystalline material was eluted with ether plus 1% of methanol. After recrystallization from benzene–petroleum ether the m.p. was 120–120.8°. Principal infrared bands: 3400, 2900, 2850, 1470, 1450, 1100, 1045 and 1015 cm.$^{-1}$ (in potassium bromide).

Anal. Calcd. for $C_{15}H_{28}O_2$: C, 74.95; H, 11.75. Found: C, 74.91; H, 11.79.

β-(2-Ketocyclododecane)-propionic Acid (XV).—The mixture of diols, 1.2 g. (0.005 mole) and lead tetraacetate, 2.44 g. (0.0055 mole), were dissolved in 20 ml. of glacial acetic acid and left at room temperature for 11 hours. The mixture was concentrated to a paste under reduced pressure, the residue extracted with 4 portions of ether and boiled with 2 more portions of ether. Concentration of the filtered ether solutions under reduced pressure was followed by the addition of 10 ml. of water, 2.58 g. (0.015 mole) of silver nitrate, 21.4 ml. of 1.4 *N* sodium hydroxide (0.0303 mole) and 30 ml. of ethanol. The black suspension was shaken vigorously for 15 minutes and allowed to stand at room temperature for 4 hours. The solids were filtered and the precipitate washed with a large volume of water and ether. The ether layer was separated and the aqueous phase extracted with 5 portions of ether. The combined ether solutions were washed with water, filtered and dried. Concentration of this solution under reduced pressure yielded 229 mg. of an oil. The aqueous phase remaining after the above extraction was acidified with hydrochloric acid and extracted with 4 portions of ether. The combined ether solutions were washed with water, filtered and dried. Concentration of the ether solution under reduced pressure yielded 900 mg. (71%) of the crystalline β-(2-ketocyclododecane)-propionic acid, m.p. 104.4–105.8° after recrystallization from acetone–water. Principal infrared bands: 2900 (broad), 1659, 1470, 1439, 1410, 1280, 1242, 1220, 1117, 1064, 1026, 935 and 735 cm.$^{-1}$ (in potassium bromide).

Anal. Calcd. for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.98; H, 10.40.

2,3- and 2,6-Decamethylenepyridines (XVI) and (XVII).—In a 500-ml. 3-neck flask, fitted with thermometer, dropping funnel and reflux condenser, which was connected with a gas-measuring device, a mixture of 325 ml. of chloroform (Mallinckrodt, A.R.), 11 ml. of absolute ethanol and 16 ml. of concd. sulfuric acid was heated to 50°. The content of the flask was stirred magnetically during the entire reaction. A solution of 9.57 g. (0.047 mole) of the bicyclic hydrocarbon XIII in 54 ml. (0.094 mole) of 1.74 *N* hydrazoic acid in chloroform[39] was added during 50 min. (390 ml. of nitrogen evolved). A total of 13 ml. of concd. sulfuric acid was added in three portions during the following two hours; an additional 875 ml. of nitrogen was evolved by that time. The mixture was cooled to 10°, poured into 200 ml. of ice-

(37) Melting points and boiling points are uncorrected. Infrared spectra were determined with a Perkin–Elmer (model 21C) or Baird (model B) recording spectrophotometer. Ultraviolet spectra were determined in 95% ethanol with a Cary ultraviolet recording spectrophotometer, model 11MS. We are indebted to Dr. S. M. Nagy and his associates for the analyses.

(38) 11-Bromoundecanoic acid was prepared by the method of R. G. Jones, THIS JOURNAL, **69**, 2350 (1947), and converted to 1,12-dodecanedioic acid by the procedure of J. Walker and J. S. Lumsden, *J. Chem. Soc.*, **79**, 1197 (1901). Esterification was accomplished with methanol in the presence of sulfuric acid giving dimethyl 1,12-dodecanedioate (69% yield from 10-undecenoic acid), b.p. 133–135° (1.1 mm.), m.p. ~30°, $n^{25}D$ 1.4408. The acyloin was reduced as described for sebacoin by A. C. Cope, J. Barthel and R. D. Smith, *Org. Syntheses*, **36**, 14 (1956).

(39) H. Wolff, *Org. Reactions*, **3**, 307 (1946).

cold sodium chloride solution and 50 g. of ice and made slightly alkaline with cold concd. sodium hydroxide. The mixture was stirred and kept between 10 and 20° while adding the base. The chloroform phase was separated, the aqueous layer extracted twice with chloroform, the combined chloroform solutions washed with sodium chloride solution, dried and concentrated under reduced pressure at *ca.* 30°. The remaining brown oil was distilled quickly at 0.5 mm. pressure and a bath temp. of 150–180°. The residue formed a dark resin. The distillate, 6.04 g. of slightly yellow oil, was dissolved in 17 ml. of 1-methylnaphthalene and heated under reflux in a metal-bath with 1 g. of palladium on charcoal (10% Pd). A stream of carbon dioxide was passed through the apparatus[40] and the rate of evolution of hydrogen was followed by absorbing the carrier gas in potassium hydroxide solution. After 3.5 hr. no more hydrogen was evolved. The cooled reaction mixture was diluted with petroleum ether, filtered from the catalyst and extracted three times with 20% sulfuric acid. The aqueous phase was washed with pet. ether, alkalized and extracted again with pet. ether. Evaporation of the solvent gave 3.95 g. of a brownish oil which was chromatographed on 300 g. of alumina (act. II, neutral). Petroleum ether eluted 1.76 g. (17.6%) of 2,6-decamethylenepyridine (XVII), present in fractions 4–11 (175 ml. each), whereas fractions 17–19, eluted with pet. ether–ether (10:1), contained 1.60 g. (16%) of 2,3-decamethylenepyridine (XVI). All these fractions solidified after cooling to 0°.

2,6-Isomer XVII.—A sample was distilled at 3.7 mm. (152–158° bath temp.); $n^{26}D$ 1.5241, m.p. 15.5–16.6°. Ultraviolet absorption: $\lambda\lambda_{max}$ 213, 267 mμ (log ε 3.82, 3.62). Principal infrared bands: 3075, 2920, 2860, 1590, 1516, 1456, 990 (in carbon tetrachloride), 781, 746 and 699 cm.$^{-1}$ (in carbon disulfide).

Anal. Calcd. for $C_{15}H_{23}N$: C, 82.89; H, 10.67. Found: C, 82.66; H, 10.62.

Picrate of XVII: m.p. 165–166°, after recrystallization from ethanol.

Anal. Calcd. for $C_{21}H_{26}N_4O_7$: C, 56.49; H, 5.87. Found: C, 56.78; H, 6.11.

Picrolonate of XVII: m.p. 183–185° (dec.) after recrystallization from ethanol.

Anal. Calcd. for $C_{25}H_{31}N_5O_5$: C, 62.35; H, 6.49. Found: C, 62.27; H, 6.60.

2,3-Isomer XVI.—A sample was distilled at 3.7 mm. (165–175° bath temp.); $n^{26}D$ 1.5370, m.p. 21.8–23.4°. Ultraviolet absorption: $\lambda\lambda_{max}$ 267.7, 274.5 mμ (log ε 3.66, 3.55), λ_{min} 273 mμ (log ε 3.53). Principal infrared bands: 3050, 2920, 2860, 1585, 1572, 1472, 1443, 1345 (in carbon tetrachloride), 819, 787, and 725 cm.$^{-1}$ (in carbon disulfide).

Anal. Calcd. for $C_{15}H_{23}N$: C, 82.89; H, 10.67. Found: C, 82.85; H, 10.89.

Picrate of XVI: m.p. 154–155° (from ethanol).

Anal. Calcd. for $C_{21}H_{26}N_4O_7$: C, 56.49; H, 5.87. Found: C, 56.45; H, 6.20.

Oxidation of 2,6-Decamethylenepyridine (XVII) with Permanganate.—The base XVII (0.4 g.) was heated to reflux with 20 ml. of water and 0.5 g. of potassium permanganate for 9.5 hr. Additional 1.1 g. of oxidant was added in two portions and consumed during this time. The reaction mixture was extracted with ether for 1 hr. in a Soxhlet extractor. From the ether phase the unreacted starting material was recovered as its picrate (250 mg., recrystallized from ethanol). The aqueous phase was filtered, concentrated to 11 ml. and concd. hydrochloric acid added to make it 1.5 *N* in acid. When kept in the refrigerator overnight, long needles separated, which were collected and recrystallized from water. The dipicolinic acid obtained (13.7 mg.) melted at 235–236° dec., undepressed after admixture of an authentic sample of m.p. 239° dec.[41] Both samples exhibited the same infrared spectrum. Principal bands: 3500–2500, 1750–1650, 1581, 1470, 1418, 1330, 1300, 1270, 1081, 998, 920, 852, 755 and 698 cm.$^{-1}$ (in potassium bromide).

2,6-Decamethylenepyridine-N-oxide (XVIII).—Two and one-half grams of 2,6-decamethylenepyridine was dissolved in 25 ml. of glacial acetic acid, 1.30 ml. of 30% hydrogen peroxide was added and the mixture heated to 80° for 45 hr. Additional 1.30 ml. of peroxide was added in three portions during this time. The mixture was then concentrated under reduced pressure, the residue dissolved in ether and extracted three times with bicarbonate solution. The ether layer was washed with water, dried and evaporated giving 2.44 g. of a yellow oil, which crystallized partially on scratching. It was chromatographed on 100 g. of alumina (act. III, neutral). Petroleum ether eluted 0.708 g. (28%) of starting material, followed by 1.61 g. (61%) of the N-oxide XVIII, m.p. 78–80°, using pet. ether–ether (1:1). A sample was recrystallized twice from petroleum ether; m.p. 79–80.5°.

Anal. Calcd. for $C_{15}H_{23}ON$: C, 77.20; H, 9.94. Found: C, 77.10; H, 10.05.

Principal infrared bands: 2920, 2860, 1520, 1490, 1465, 1437, 1400, 1240 (in carbon tetrachloride) and 762 cm.$^{-1}$ (in carbon disulfide). Ultraviolet absorption: $\lambda\lambda_{max}$ 226, 270 mμ (log ε 4.38, 3.95).

α-Hydroxy-2,6-decamethylenepyridine (XX).—The N-oxide (1.59 g.) was heated for 12 hr. to 100° in 7 ml. of acetic anhydride. The excess anhydride was removed under reduced pressure and the residue refluxed for 3.5 hr. with a mixture of 30 ml. of methanol and 12 ml. of 20% aqueous potassium hydroxide solution. After cooling, most of the methanol was distilled, 50 ml. of water was added and the product extracted with ether. The crystalline residue from evaporation of the ether was extracted with petroleum ether and filtered from 82 mg. (5.2%) of insoluble material. The filtrate was concentrated, cooled and the precipitated material filtered: 1.26 g. (80%) of the carbinol XX, m.p. 86–89°. A sample was recrystallized once more for analysis; m.p. 88–89°.

Principal infrared bands: 3450, 2920, 2860, 1592, 1574, 1457, 1035, 990, 797, 740 cm.$^{-1}$ (in potassium bromide). Ultraviolet absorption: $\lambda\lambda_{max}$ 212, 266 mμ (log ε 3.77, 3.54).

Anal. Calcd. for $C_{15}H_{23}ON$: C, 77.20; H, 9.94. Found: C, 76.85; H, 9.90.

The product insoluble in petroleum ether, XXI, m.p. 198–200°, was further purified by sublimation at 0.1 mm. and 125–130° and melted then at 201–202°. Principal infrared bands at 3400 (broad), 2920, 2860, 2500 (broad), 1576, 1492, 1450, 1275, 1168, 1110 and 1023 cm.$^{-1}$ (in potassium bromide). Ultraviolet absorption: in ethanol: $\lambda\lambda_{max}$ 226, 289 mμ (log ε 3.86, 3.71); in *N*/10 ethanolic HCl: $\lambda\lambda_{max}$ 236, 305 mμ (log ε 3.86, 3.96); in *N*/5 sodium ethoxide: $\lambda\lambda_{max}$ 249, 313 mμ (log ε 4.05, 3.74).

Anal. Calcd. for $C_{15}H_{23}ON$: C, 77.20; H, 9.94. Found: C, 77.32; H, 10.07.

α-Keto-2,6-decamethylenepyridine (XXII).—Chromium trioxide (1.65 g.) was added in small portions to 20 ml. of pyridine at 0–5°. A solution of the carbinol XX (1.26 g.) in 15 ml. of pyridine was added and the mixture kept at room temperature for 14 hr. It was then poured into 135 ml. of water and extracted with petroleum ether (3 times 75 ml.), which was washed with water and dried. After evaporation of the solvent and chromatography of the residue on 40 g. of alumina (act. III, neutral), 1.166 g. (93%) of the ketone, m.p. 47–48°, was obtained. Principal infrared bands: 2920, 2860, 1691, 1588, 1456, 1345, 1245, 993 cm.$^{-1}$ (in carbon tetrachloride). Ultraviolet absorption: $\lambda\lambda_{max}$ 236, 278 mμ (log ε 3.81, 3.66).

Anal. Calcd. for $C_{15}H_{21}ON$: C, 77.88; H, 9.15. Found: C, 77.89; H, 9.31.

2,4-Dinitrophenylhydrazone, m.p. 191–192°.

Methylation of the Ketone XXII.—A solution of 1.256 g. of the ketone in 4 ml. of dry benzene was added to 23 ml. of *t*-butoxide (equiv. to 303 mg. of potassium) and refluxed for 5 minutes. After cooling, 0.65 ml. of methyl iodide was added and the mixture heated to reflux again for five minutes. A white precipitate appeared immediately. The reaction was stopped by adding 10 ml. of water and cooling. More water was added and the mixture was extracted with ether twice. After drying, the organic solvents were removed under reduced pressure. A slightly yellow oil was obtained (1.207 g.) which crystallized partially on cooling and seeding with starting material. It was chromatographed on 112 g. of alumina (act. II, neutral) and eluted with petroleum ether. Fractions of 50 ml. each were collected. Fraction 16–18: 49 mg. of a mixture of di- and mono-methylated

(40) L. F. Fieser in "Experiments in Organic Chemistry," Second Edition, D. C. Heath and Company, New York, N. Y., 1941, p. 461.

(41) G. Black, E. Depp and B. B. Corson, *J. Org. Chem.*, **14**, 14 (1949).

ketones (XXIV and XXIII), fr. 19–30: 317 mg. pure methylated ketone (XXIII), fr. 31–42: 250 mg. of a mixture of methylated ketone and starting material XXII, fr. 43–53: 535 mg. of starting material, m.p. 45–47.5° (the last three fractions eluted with 15% ether). The composition of the individual fractions was followed by their infrared absorption in the region between 1500 and 1300 cm.$^{-1}$ (in carbon tetrachloride). Beginning with fr. 33 the eluted oil showed an increasing tendency to crystallize on seeding with starting material.

A sample of the combined fractions 19–30 was converted to the picrolonate, which melted at 113–115° dec. after recrystallization from ethanol.

Anal. Calcd. for $C_{26}H_{31}O_6N_5$: C, 61.28; H, 6.13. Found: C, 61.09; H, 6.26.

Principal infrared bands of the ketone XXIII: 2920, 2860, 1691, 1585, 1460, 1362, 1215, 990 cm.$^{-1}$ (in carbon tetrachloride).

***rac*-Muscopyridine (III).**—To a solution of 700 mg. of sodium in 10 ml. of freshly distilled diethylene glycol was added 534 mg. of the methylated ketone XXIII and 0.75 ml. of hydrazine (95+%). The reaction mixture was heated to reflux for 2 hr. under nitrogen and an additional portion of 0.2 ml. of hydrazine was added during this period. The bath temperature was raised to 255° during 1/2 hr. and kept there for three additional hours. The excess hydrazine, water and some of the product accumulated in the distillate. After cooling the reaction mixture was combined with the distillate, diluted with 70 ml. of water and extracted three times with petroleum ether. The organic phase was dried, evaporated and the remaining oil (512 mg.) chromatographed on 28 g. of alumina (act. II, neutral). Petroleum ether eluted 356 mg. (71%) of a colorless oil. This was converted to the picrolonate: 701 mg. (91.5%), yellow needles. A sample was recrystallized twice from ethanol; m.p. 163–166° dec. The picrolonate of natural (+) muscopyridine and a mixture of both samples showed the same behavior on melting.[42]

Anal. Calcd. for $C_{25}H_{33}N_5O_5$: C, 63.01; H, 6.71. Found: C, 62.83; H, 6.88.

The picrolonate was decomposed by passing a benzene solution through a column of alumina (act. III, neutral). The eluted free base was distilled at 2.2 mm. (138–143° bath temp.). The distillate showed $n^{25}D$ 1.5206 (lit.[10] 1.5202), d^{24}_4 0.9669 (lit.[10] d^{25}_4 0.9642); ultraviolet absorption: $\lambda\lambda_{max}$ 213, 267 mμ (log ε 3.79, 3.61); principal infrared bands: 3060, 2920, 2860, 1590, 1576, 1458, 1376, 1347, 992 and 702 cm.$^{-1}$ (in carbon tetrachloride).

Resolution of *rac*-III.—The racemic base (282 mg.) was mixed with 0.2 ml. of acetone and a solution of 450 mg. of di-*p*-toluoyl-D-tartaric acid in 1.8 ml. of acetone was added. After standing overnight at −15° crystals had separated. This precipitate was collected, washed with acetone and dried: 357 mg. The mother liquor was concentrated and the base isolated by adding alkali followed by extraction with petroleum ether. The oil obtained was distilled at 2.5 mm. and the distillate (156 mg.) exhibited $[\alpha]^{25}D$ +1.38° (α + 0.106°, *c* 7.65 in chloroform, 1 dm. tube). 152 mg. of this product was combined with 250 mg. of di-*p*-toluoyl-L-tartaric acid in 1.4 ml. of acetone. The material obtained was recrystallized three more times from acetone. The last precipitate (39.5 mg.) melted at 103–105° dec. The free base was regenerated by addition of alkali and extraction with petroleum ether. After distillation at 2.5 mm. there was obtained 11.9 mg. of a colorless oil which exhibited $[\alpha]^{25}D$ +13.31° (±0.22°) (α + 0.120°, *c* 0.902 in chloroform, 1 dm. tube). The picrolonate melted at 163–166° dec., unchanged on mixing with the natural (+) muscopyridine picrolonate.[42]

α-Keto-β,β-dimethyl-2,6-decamethylenepyridine (XXIV).—A solution of 46 mg. of the ketone XXII in 1 ml. of *t*-butyl alcohol was added to 10 ml. of *t*-butoxide (from 0.36 g. of potassium) and refluxed for 10 min. After cooling 1.3 g. of methyl iodide was added over a period of three minutes and the mixture was heated under reflux for 9 hr. and worked up as described for the monoalkylation. The crude product was purified by distillation at 0.36 mm. (150–160° bath temp.) rather than by chromatography. The colorless oil obtained (38 mg.) exhibited ultraviolet absorption at $\lambda\lambda_{max}$ 235, 275 mμ (log ε 3.69, 3.58). Principal infrared bands: 3060, 2920, 2860, 1682, 1585, 1455, 1385, 1360, 1155 and 990 cm.$^{-1}$ (in carbon tetrachloride).

β,β-Dimethyl-2,6-decamethylenepyridine.—The dimethyl ketone XXIV, 24 mg., was reduced according to the procedure used for the monomethyl ketone XXIII, using 1.5 ml. of diethylene glycol, 100 mg. of sodium and 0.5 ml. of hydrazine. Chromatography of the crude product on 2 g. of alumina (act. III, neutral) gave 9 mg. (40%) of a colorless oil. Principal infrared bands: 3060, 2920, 2860, 1590, 1577, 1457, 1385, 1365 and 990 cm.$^{-1}$ (in carbon tetrachloride).

The base was converted to the picrolonate, yellow needles of m.p. 170–172° dec.[42]

Anal. Calcd. for $C_{27}H_{35}N_5O_5$: C, 63.63; H, 6.92. Found: C, 63.73; H, 6.99.

11-Azabicyclo[4.4.1]-1-undecene (XXVII).—A mixture of 120 ml. of chloroform (Mallinckrodt A.R.) and 5 ml. of concentrated sulfuric acid was heated to 46°. To this was added during 1.5 hr. with magnetic stirring a solution of 9,10-octalin (XXVI), 1.50 g. (0.011 mole), and hydrazoic acid[39] (3.3 equivalents) in 38.1 ml. of chloroform; 300 ml. of nitrogen was evolved. After cooling the reaction vessel in an ice-bath, 70 ml. of water was added and the two phases separated; the water layer was extracted with several portions of chloroform. The combined chloroform solutions were extracted with sodium bicarbonate solution, filtered and dried. Upon removal of the solvent, 270 mg. of hydrocarbon was recovered. Neutralization of the water phase with potassium hydroxide was followed by extraction with four 50-ml. portions of ether. The combined ether solutions were dried and the solvent removed under reduced pressure; distillation of the residue from a Claisen flask gave 420 mg. (25%) of 11-azabicyclo[4.4.1]-1-undecene (XXVII), b.p. 74–75° (0.5 mm.) (bath temperature 100–180°), $n^{25}D$ 1.5200 (reported[30] b.p. 79–81° (3 mm.), $n^{25}D$ 1.5139). The undistillable residue amounted to 700 mg.

The 11-Benzenesulfonyl-11-azabicyclo[4.4.1]undecane (XXIX).—A sample of the amine XXVII was hydrogenated in methanol using 10% palladium on charcoal as the catalyst. After filtration of the catalyst, the solution was concentrated under reduced pressure to a small volume, diluted with benzene and again concentrated. The saturated amine on treatment with benzenesulfonyl chloride and potassium hydroxide produced the crystalline 11-benzenesulfonyl-11-azabicyclo[4.4.1]undecane (XXIX), which after recrystallization from ethanol melted at 171.4–173.0° when heated at 3° per minute. An authentic sample[30] under the same conditions melted at 171.0–172.7°; melting point of mixture 171.0–172.7°.

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(42) The melting points were determined on a Kofler micro apparatus.