The amine soon dissolved with evolution of some heat. The mixture was allowed to stand 10 minutes, excess concentrated hydrochloric acid was added and the solution was evaporated to dryness *in vacuo*. Concentrated hydrochloric acid was added to the residue and sodium chloride was separated by filtration, after which the filtrate again was evaporated to yield a yellow oil. Water was added and the solution was placed in a vacuum desiccator over potassium hydroxide. The resulting sticky, brown glass was transformed to a tan solid on warming with 95% ethanol. Recrystallization from the same solvent produced white microcrystals which had no definite melting point but which charred gradually over the range 240–300°. The yield of recrystallized solid was 214 mg. (54%).

Anal. Calcd. for $C_8H_9NSO_3$: C, 48.23; H, 4.55. Found: C, 47.94; H, 4.58.

Attempted Addition of Piperidine to V.—When 1.7 g. of piperidine was added to 1.17 g. of pyrindine, the color darkened. After a 4-hour reflux period, the piperidine was removed from the dark; tarry mixture under reduced pressure and the residue was distilled *in vacuo*. The recovery of unchanged starting material, b.p. 82–86° (16 mm.), $n^{24}D$ 1.5800, was 0.72 g. (62%). An appreciable, tarry residue remained. The distillate was converted to pyrindine picrate, m.p. 181–182.5° dec., both alone and on admixture with authentic material.

Absorption Spectra.—Ultraviolet spectra were measured with a Beckman model DU quartz spectrophotometer from cyclohexane solutions at 10^{-4} *M* concentration, except where otherwise specified. Infrared spectra were measured either with a Baird spectrophotometer or a Perkin–Elmer instrument by Dr. S. M. Nagy and associates at the Microchemical Laboratory, Massachusetts Institute of Technology, and by Dr. Louis A. Carpino, Department of Chemistry, University of Massachusetts.

AMHERST, MASS.

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Synthesis and Some Stereochemical Aspects of Carbon-methylated Piperazine Quaternary Salts and Related Compounds

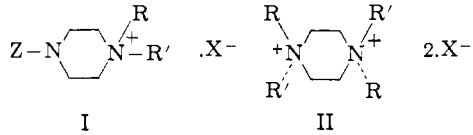
BY M. HARFENIST AND E. MAGNIEN

RECEIVED JUNE 6, 1958

A number of piperazine quaternary salts, most of which had methyl groups on the ring carbons, were made for anthelmintic testing. Procedures for the separation of the stereoisomeric forms of the monoquaternary salts III–V allowed the preparation of each of the stereoisomeric bis-quaternary salts VI, and the absolute identification of the racemic isomer VIb. The highest melting stereoisomer, VIa, had an excellent therapeutic index against *Syphacia obvelata* in the mouse.

The high activity against the mouse pinworm *Syphacia obvelata* of some of the piperazine monoquaternary salts previously reported[1] (I, Z = H, COOR, $CONR_2$, NO) led us to prepare a variety of related quaternaries. These include some monoquaternary salts like I, Z = $COOC_2H_5$ but with one or two ring carbons methylated, some like I but with Z = alkyl, and a number of piperazine bis-quaternaries, both with and without ring carbons methylated. Most of such compounds are tabulated below and require no further comment. However, it is necessary to consider certain facets of the stereochemistry of the bis-quaternary salts.

Only one isomer was isolated for each of the bis-quaternaries II; no attempt to obtain the other possible isomer was made. It can be assumed on the basis of earlier X-ray diffraction measurements[2] that, as would be anticipated, the isomers reported here are the (presumably less soluble) *trans* alkylated isomers shown.



I II

Because of the high therapeutic index (of the least soluble, highest melting isomer) of the 1,4-2,5-*trans*-tetramethyl-1,4-bis-dodecylpiperazinium salt VIa (see flow chart) against *S. obvelata* in the mouse, a more thorough study of its stereoisomers was made. It is apparent that VI exists as two *meso* forms VIa and VIc and one racemic pair (VIb and its enantiomer). It proved possible to isolate only the highest melting form directly in appreciable yield from the quaternization of N,N′-bis-dodecyl-2,5-*trans*-dimethylpiperazine with two moles of methyl iodide. A yield of about 40% of analytically pure material of constant melting point was obtained. This is shown below to be one of the *meso* forms.

It was necessary to prepare the other isomers of VI by the more selective process illustrated in the flow chart.

The separation of the two possible isomers of compound III was accomplished by crystallization of the bulk of the higher melting IIIa, and chromatography of the remaining material. Mixtures of IIIa and IIIb were obtained with either dodecylation, followed by methylation with methyl iodide to III as shown in the flow sheet, or by methylation of 1-carbethoxy-2,5-*trans*-dimethylpiperazine by the Clarke–Eschweiler method, and then quaternization with dodecyl iodide. The latter procedure appeared to give somewhat more of the lower melting IIIb, but dehydrohalogenation of the dodecyl iodide made a quantitative study difficult. In view of the vast body of literature on quaternization in which only one of a possible pair of stereoisomers is obtained by one order of alkylation–quaternization, and the epimer alone by reversing the order of addition of the two alkyl groups,[3] further study of this reaction is contemplated.

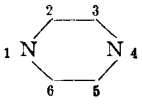
Decarbethoxylation of each isomer of III to the corresponding secondary amine IV with constant boiling aqueous hydrochloric acid was followed by dodecylation to the tertiary amines V. Treatment of the resulting isomers of V with methyl

(1) M. Harfenist, THIS JOURNAL, **79**, 2211 (1957).

(2) W. E. Hanby and H. N. Rydon, *J. Chem. Soc.*, 833 (1945).

(3) For a discussion of some factors influencing this specificity and many references, see G. Fodor, *Bull. soc. chim., France*, 1032 (1956); G. Fodor, *et al.*, *J. Chem. Soc.*, 1411 (1956), 3504 (1955); *cf.* also K. Zeile and W. Schulz, *Helv. Chim. Acta*, **88**, 1078 (1955).

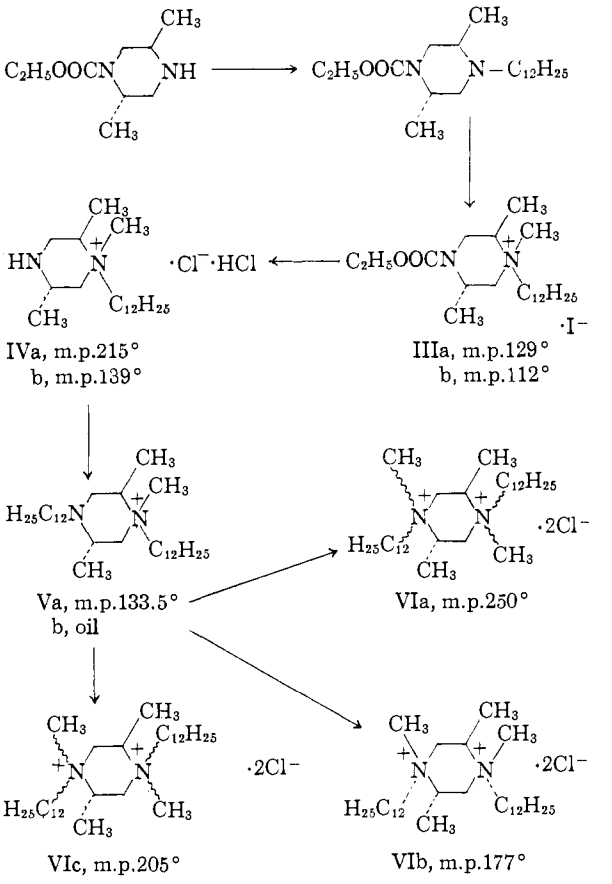
TABLE I. PROPERTIES OF PIPERAZINE QUATERNARIES



	1		4		X⁻	Recrystn. solvents[a]	M.p., °C.	Analyses, % Calculated C	Calculated H	Calculated Other	Found C	Found H	Found Other
				A. Derivatives of piperazine not alkylated on the piperazine ring carbons									
1	C_7H_{15}		CH_3	$C_{11}H_{23}$	$2Cl^{-b}$	M-E	215–220		Cl^-	16.83		Cl^-	16.97
2	$C_{11}H_{23}$		CH_3	$C_{11}H_{23}$	$2Cl^{-b}$	M-E	211–220	67.18	12.14		67.09	12.04	
3	$C_{14}H_{29}$		CH_3	$C_{11}H_{23}$	$2Cl^{-b}$	A	215–238	68.83	12.34		68.76	12.15	
4	CH_3	$C_{11}H_{23}$	CH_3	$C_{11}H_{23}$	$2I^-$	A-EA	224.5	49.56	8.91		49.25	9.10	
5	CH_3	$C_{12}H_{25}$	CH_3	$C_{12}H_{25}$	$2Cl^{-c}$	[d]	280–285		Cl^-	13.55		Cl^-	13.44
6	CH_3	$C_{16}H_{33}$	CH_3	$C_{16}H_{33}$	$2Cl^{-c}$	M	250–270		Cl^-	11.15		Cl^-	11.30
7	$CH_2C{\equiv}CH$	$CH_2C{\equiv}CH$	$CH_2C{\equiv}CH$	$CH_2C{\equiv}CH$	$2Br^-$	W-A-Ac	233–255		Br^-	39.97		Br^-	40.10
				B. Derivatives of 2-methylpiperazine									
8	CH_3	$C_{12}H_{25}$	CH_3	$C_{12}H_{25}$	$2I^-$	Ip	190–193		I^-	35.20		I^-	35.39
9	CH_3[e]	$C_{12}H_{25}$	CH_3	$C_{12}H_{25}$	$2Cl^-$	M-E	210–212		Cl^-	13.20		Cl^-	13.11
				C. Derivatives of 2,5-*trans*-dimethylpiperazine									
10	$COOC_2H_5$[e]		CH_3	$C_{10}H_{21}$	I^-	EA-E	131–132.5		I^-	27.10		I^-	27.25
11	$COOC_2H_5$[e]		CH_3	$C_{12}H_{25}$	I^-	EA	127.5–128.5		N	5.65		N	5.85[h]
12	$COOC_2H_5$[g]		CH_3	$C_{12}H_{25}$	I^-	EA	109.5–112		I^-	25.58		I^-	25.70
13	H[e]		CH_3	$C_{12}H_{25}$	$2Cl^-$	AcW	213.3–214.8[i]		Cl^-	18.31		Cl^-	18.30
14	H[g]		CH_3	$C_{12}H_{25}$	$2Cl^{-b}$	Ac	134–139		Cl^-	18.31		Cl^-	18.25
15	CH_3[e]		CH_3	$C_{10}H_{21}$	$2Cl^{-b}$	A-Ac	196.5–197	60.82	11.36		60.72	11.27	
16	CH_3[e]		CH_3	$C_{12}H_{25}$	$2Cl^{-b}$	A-Ac-E	195–196[f]		Cl^-	18.50		Cl^-	18.67
17	CH_3[e]		CH_3	$C_{12}H_{25}$	Cl^{-j}	EA	164–166.5[k]		N	8.05		N	8.05
18	$C_{12}H_{25}$[e]		CH_3	$C_{12}H_{25}$	$2Cl^{-b}$	A-E	87–89[l]		Cl^-	13.02		Cl^-	13.02[m,n]
19	CH_3	C_8H_{17}	CH_3	C_8H_{17}	$2I^-$	N	203–204		I^-	40.78		I^-	40.30
20	CH_3[e]	C_8H_{17}	CH_3	C_8H_{17}	$2Cl^-$	M-E	236–239		Cl^-	16.14		Cl^-	15.90
21	CH_3	$C_{10}H_{21}$	CH_3	$C_{10}H_{21}$	$2I^-$	N	198–199		I^-	37.40		I^-	37.40
22	CH_3[e]	$C_{10}H_{21}$	CH_3	$C_{10}H_{21}$	$2Cl^-$	M-Ac-E	232–237		Cl^-	14.31		Cl^-	14.24
23	CH_3	$C_{11}H_{23}$	CH_3	$C_{11}H_{23}$	$2I^-$	N	190–192		I^-	35.90		I^-	36.10
24	CH_3[e]	$C_{11}H_{23}$	CH_3	$C_{11}H_{23}$	$2Cl^-$	M-E	234–236		Cl^-	13.55		Cl^-	13.54
25	CH_3[e]	$C_{12}H_{25}$	CH_3	$C_{12}H_{25}$	$2I^-$	N	203–205		I^-	34.52		I^-	34.29
26	CH_3[c]	$C_{12}H_{25}$	CH_3	$C_{12}H_{25}$	$2Cl^-$	A-Ac	248–250		Cl^-	12.85		Cl^-	12.81
27	CH_3[c]	$C_{12}H_{25}$	CH_3	$C_{12}H_{25}$	$2Lac^-$	[o]	167–173		...	...		...	...
28	CH_3[f]	$C_{12}H_{25}$	CH_3	$C_{12}H_{25}$	$2Cl^-$	M-E-A	203–205		Cl^-	12.85		Cl^-	12.95
29	CH_3[p]	$C_{12}H_{25}$	CH_3	$C_{12}H_{25}$	$2Cl^-$	Ac-EA-E	176–177[q]		N	5.08		N	4.97
30	CH_3	$C_{13}H_{27}$	CH_3	$C_{13}H_{27}$	$2I^-$	N	179–184		I^-	33.30		I^-	33.80
31	CH_3	$C_{14}H_{29}$	CH_3	$C_{14}H_{29}$	$2I^-$	N	185–190		I^-	32.08		I^-	31.90
32	$CH_2CH{=}CH_2$	$C_{10}H_{21}$	$CH_2CH{=}CH_2$	$C_{10}H_{21}$	$2Br^-$	N	194–202		Br^-	25.10		Br^-	25.40
33	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	$2Br^-$	M	227–229		Br^-	36.62		Br^-	36.40
34	$CH_2C{\equiv}CH$[e]	$C_{12}H_{25}$	$CH_2C{\equiv}CH$	$C_{12}H_{25}$	$2Br^-$	A-Ac	233–233.5		Br^-	23.22		Br^-	23.58
35	$CH_2C{\equiv}CH$[g]	$C_{12}H_{25}$	$CH_2C{\equiv}CH$	$C_{12}H_{25}$	$2Br^-$	A-Ac-E	144–146.5		Br^-	23.22		Br^-	23.38
36	$C_{12}H_{25}$	O	$C_{12}H_{25}$	O	...	Ac	133–134[r]	68.30	11.93		67.94	11.64	

	1	4	X⁻	Recrystn. solvents[a]	M.p., °C.	Calculated C	Calculated H	Analyses, % Other	Found C	Found H	Found Other
				D. Derivatives of 2,5-*cis*-dimethylpiperazine							
37	CH_3	$C_{12}H_{25}$	2I	MEK–EA	178–179		I⁻	34.52		I⁻	34.38
38	CH_3	$C_{12}H_{25}$	$2Cl^-$	M–E	190–194		Cl⁻	12.85		Cl⁻	12.90
				E. Derivatives of 2,6-(*trans* ?)-dimethylpiperazine							
39	CH_3	$C_{12}H_{25}$	CH_3	2I⁻	Ac–EA	175–180	I⁻	34.52		I⁻	34.45

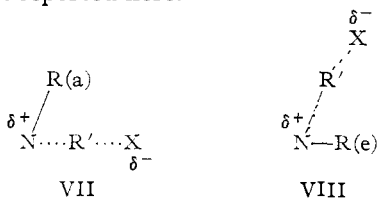
[a] Solvents for recrystallization: A = absolute ethanol; Ac = acetone; AcW = 2% water in acetone; B = benzene; E = absolute ether; EA = ethyl acetate; Ip = isopropyl alcohol; M = methanol; MEK = methyl ethyl ketone; N = nitromethane; W = water. [b] These salts were chloride hydrochlorides. [c] Di-iodide reported by D. R. Smith, J. W. Curry and R. L. Eifert, THIS JOURNAL, 72, 2969 (1950). [d] Not recrystallized; prepared from analytically pure iodide and silver chloride. [e] α-Isomer. [f] A low melting (β) stereoisomer, m.p. *ca.* 95–101°, was isolated but was not purified further. [g] β-Isomer. [h] Calcd. I⁻, 25.58. Found: I⁻, 25.80. [i] Monohydrate. [j] The quaternary chloride, free base was obtained by sodium carbonate treatment of the chloride hydrochloride. [k] The chloride hydrochloride had m.p. 204.5–206.5°. [l] This is m.p. of a hydrate. On drying at 80° and 0.1 mm. for analysis the compound became anhydrous. [m] By Mohr titration. [n] The quaternary chloride, free base was obtained by treatment of the chloride hydrochloride with aqueous sodium carbonate; melting point after recrystallization from absolute ether, 130.5–133.5°. Calcd.: N, 5.60. Found: N, 5.39. The chloride free base of the β-isomer could not be crystallized. [o] The dilactate was prepared from the dichloride and sodium lactate in absolute alcohol; no suitable solvent for recrystallization was found. [p] γ-Isomer. [q] Forms hydrate m.p. *ca.* 110°. [r] Dihydrate. The anhydrous dihydrochloride had m.p. 156.5–158.5°. Calcd.: Cl^-, 13.45. Found: Cl^-, 13.45. Only one isomer was found. [s] Cation stereochemically the same as that of the salt on the line above.



iodide, then silver chloride gave the bis-quaternary salts as shown in the chart. It was possible to separate the low melting, relatively soluble VIb from the very high melting, insoluble VIa comparatively readily. It was also possible to separate a moderate amount of VIb from the higher melting VIc and to isolate VIc in good purity, since it was contaminated only by the much more soluble VIb. None of the readily-isolable VIa was obtained by this quaternization of Vb. This indicates that no significant amount of isomer Va was present in Vb. In addition to allowing the isolation of pure VIb and VIc, this procedure allows the unequivocal identification of the lowest melting bis-quaternary as the racemic pair of isomers VIb. This follows from the production of only this isomer from each of the monoquaternary salt series IIIa–Va and IIIb–Vb. It is obvious that only this isomer, which has one methyl on nitrogen *cis* to its adjacent C-methyl group but the other methyl on nitrogen *trans* to the other C-methyl groups could be formed from each of the two monoquaternaries III, which have opposite relationships of the quaternizing groups to the adjacent methyls.

It would be desirable to determine the configuration of the two bis-quaternaries VIa and VIc, each of which has its dodecyl groups in a *trans* relationship. Attempts to do this by considerations of first principles, unfortunately, are complicated by a lack of knowledge of the geometry of the transition state for these quaternizations. For example, even if it is assumed that the precursor of III exists

in a chair form[4] and that the 2- and 5- methyls are fixed in the equatorial position, it is necessary to decide whether the existing alkyl group (see VIII) or the attacking alkyl halide (see VII) assumes the equatorial position in the transition state. In the case of certain of the atropine alkaloids, an axial position for the quaternizing alkyl group has been found,[3] but this is a somewhat different situation from that reported here.



It was thought to be desirable to assess the influence of "classical" steric hindrance (free of the undetermined factors peculiar to the 6-membered ring) on the direction of approach of the quaternizing group. This was attempted by determining the products of alternative orders of alkylation of prolinol by methyl iodide and methyl α-chloroacetate. A similar study has been started independently by Fodor and his associates.[5] Unfortunately, a great deal of difficulty has been encountered in crystallizing some of the reaction products. An alternative approach to the configurational problem would be an X-ray determination of the structure of the compounds III which, together with the proof of configuration of VIb, would allow identification of VIa and VIc.

Biological Activity.—The detailed results of the testing of these compounds (and of some others not reported here because of priority of synthesis by others) will be submitted for publication elsewhere. In summary, it can be said that the bis-quaternary salts made from 2,5-*trans*-dimethylpiperazine have a higher therapeutic index against *S. obvelata* in the mouse than do the corresponding compounds made from 2,5-*cis*-dimethyl-, 2-methyl-, 2,6-dimethyl-, or non-C-methylated piperazines. The therapeutic index of the bis-quaternary salt VIa (table, line 26) is comparable to that of piperazine, which is at present the standard anthelmintic for human pinworm and *Ascaris* infection. The quaternary salt VIa also appears[6] to cause irreversible paralysis of *Ascaris lumbricoides* var. *suum in vitro*, as compared to the reversible paralysis to this worm due to piperazine.

Acknowledgments.—We thank Mr. Samuel W. Blackman for carbon–hydrogen elemental analyses reported here and Veronica Purdy for the nitrogen analyses, which were done by the Kjeldahl method.

Experimental[7]

Procedures used in making the compounds in the table are analogous to those previously reported.[8] Quaternary salts almost invariably were prepared in acetone solution, since enough solvolysis occurred in methanol to complicate work up especially when bis-quaternary salts were being prepared.

Isomers of 1-Carbethoxy-4-2,5-*trans*-trimethyl-4-dodecylpiperazinium Iodide.—A solution of 71 g. (0.2 mole) of 1-carbethoxy-2,5-dimethyl-4-*n*-dodecylpiperazine and 40 g. (0.28 mole) of methyl iodide in 100 ml. of acetone was kept in a citrate of magnesia pressure bottle at about 40° for 25 days. It was then warmed on the steam-bath and treated with a nearly equal volume of ether to incipient turbidity, filtered and cooled. A first crop of 40.5 g. had m.p. *ca.* 125°. This was recrystallized from ethyl acetate four times to give 34.4 g. of platelets or needles of α-isomer, m.p. 127.5–128.5°, not raised on further recrystallization from acetone–ethyl acetate.[9]

From the original crop I mother liquors by further additions of ether, 53.8 g. of crop II was obtained, m.p. 96–105° (turbid), and 4.1 g. of rather sticky crop III, m.p. 90.5–94°. These last two crops were combined and recrystallized from ethyl acetate, giving 8.3 g. of α-isomer as platelets, m.p. 128–131°. The mother liquors were distilled to dryness *in vacuo* at the water-pump. The residual 50 g. was dissolved in dry distilled benzene and chromatographed, using a column 40 cm. high containing 2.6 lb. of Merck Alumina for Chromatography. The column was washed with 2 l. of benzene, then developed with 2 l. of benzene containing 3% of ethyl acetate. It was next eluted with 2% of ethanol in benzene, following the appearance of iodide ion by means of the sodium nitrite–acetic acid test, and evaporation of the fractions giving a positive test. The first positive fractions on recrystallization from ethyl acetate gave 4.8 g. of α-quaternary, m.p. 125–129°, followed by an intermediate fraction of 14.4 g., m.p. 96.5–100°, and 27 g. of fractions mostly melting 107–112°. A final elution with pure ethanol after 15 l. of 2% ethanol in benzene gave only 2.1 g. more of product, m.p. 108–111°.

Rechromatography of the intermediate fractions gave 6 g. of the lower melting (β) isomer and 9 g. of higher melting (α) isomer. An additional gram of α-isomer was obtained by repeated crystallization of poorer β-isomer fractions.

After further recrystallizations and working up of the mother liquors, a total of 51 g. of pure α-isomer, m.p. *ca.* 128.5°, and 22.5 g. of β-isomer, m.p. 107.5–110°,[10] was obtained.

1,4-2,5-*trans*-Tetramethyl-1,4-bis-dodecylpiperazinium Chloride, α- and γ-Isomers.—A solution of 16.7 g. of the α-isomer of 1-2,5-*trans*-trimethyl-1,4-bis-dodecylpiperazinium chloride (m.p. 132°) and 30 g. of methyl iodide in 100 ml. of acetone was kept in a pressure bottle at *ca.* 40° for 10 days. The resulting crystal brei was transferred to a flask with methanol and evaporated to dryness on the steam-bath *in vacuo*. The product was converted to chloride by HCl in methanol,[11] and crystallized from ethanol–ethyl acetate–ether. The crystalline solid (two crops) was 8.01 g., m.p. 237–239° (the fate of the filtrate A is given below). Two recrystallizations from ethanol–acetone gave 7.76 g. of the α-isomer of the bis-quaternary, m.p. 247.5°.

The initial mother liquor (filtrate A) on evaporation *in vacuo*, solution in acetone and addition of ether in excess gave crystals and an oil. The latter could be dissolved in acetone leaving 4.53 g. of a crystalline solid, m.p. 168–174°.

(4) 1,4-Dichloropiperazine in the solid state has been shown to be in the chair form by X-ray diffraction; P. Andersen and O. Hassel, *Acta Chem. Scand.*, **3**, 1180 (1949).

(5) G. Fodor, private communication.

(6) R. Burrows, personal communication.

(7) Melting points are not corrected. Analyses given in the table are not repeated for those compounds whose preparations are given in detail in this section.

(8) See ref. 1 for quaternary salt procedures; M. Harfenist, THIS JOURNAL, **76**, 4991 (1954), and R. Baltzly, *ibid.*, **76**, 1164 (1954), and references cited in these, for alkylations and removal of the carbethoxy group.

(9) Melting points of up to 132° were obtained by variations in the rate of heating, and by careful drying *in vacuo*. Identity of m.p. of a sample retained from the previous recrystallization and the subsequent one, when both were run simultaneously, was the criterion used in this work. This non-reproducibility of melting points was found with most of the compounds prepared several different times.

(10) Either this was still not pure or it equilibrated with the α-isomer to some extent during hydrolysis of the carbethoxy group in the next reaction (two days under reflux with constant boiling aqueous hydrochloric acid) since 4.1 g. of the α-isomer of 4-2,5-*trans*-trimethyl-1-dodecylpiperazinium chloride hydrochloride (IV) was obtained in hydrolysis of this 22.5-g. fraction. Only 6.9 g. of the β-isomer of IV was simultaneously isolated. However, it is felt that the isolated α-isomer probably represents essentially all that was present in the sample of IV so prepared. The proportion of β-IV is undoubtedly higher than is indicated by the amount isolated, because of the higher solubility and lower crystallizing ability of the β-isomer.

(11) A. P. Phillips and R. Baltzly, THIS JOURNAL, **74**, 5231 (1952).

The oil was dissolved in 50% aqueous methanol and titrated with standard sodium hydroxide solution to *p*H 9.3 to convert small amounts of the hydrochloride of the starting monoquaternary chloride to monoquaternary chloride base, treated with carbon dioxide, evaporated down on the steam-bath *in vacuo* and recrystallized alternately from acetone–ethyl acetate and acetone–ether (twice from each), adding a small amount of water since the hydrate crystallized much more readily than the anhydrous bis-quaternary salt. Samples of the hydrate melted unreproducibly about 96–102°, so the progress to constant melting point was followed by drying samples at 80° (0.1 mm.). The anhydrous bis-quaternary so produced had a m.p. 176–177°. A total of 7.5 g. of γ-isomer of this m.p. was isolated. Analyses of both isomers will be found in the table.

1,4-2,5-*trans*-Tetramethyl-1,4-bis-dodecylpiperazinium Chloride, β- and γ-Isomers.—The 27.5 g. of the non-crystalline 1,4-2,5-*trans*-trimethyl-1,4-bis-dodecylpiperazinium chloride prepared by dodecylating the β-isomer of compound IV was treated with 25 g. of methyl iodide in 120 ml. of acetone. The solution was stored at 40° for 9 days. The solid (A) formed by this procedure (9.58 g.) was filtered, and the mother liquor (B) maintained at 40° an additional week. The solid A was converted to chloride by use of silver chloride in methanol, and recrystallized to give 5.43 g., m.p. 200.5–203°. This was combined with more solid melting in the same range which had been isolated by the chromatography procedure outlined below to give 7.56 g. of β-isomer of the bis-quaternary. This was recrystallized from nitromethane–ethyl acetate yielding 6.23 g., m.p. 202.5–205°.

The mother liquor B was evaporated down, leaving 28.1 g. of dark glass, which was converted to chloride with silver chloride in methanol to give 21 g. of oil. This was dissolved in boiling ethyl acetate after titrating with standard aqueous sodium hydroxide to *p*H 7 (it contained over 14 g. of monoquaternary starting material) and treated with acetone–ether to crystallize 660 mg. more of solid m.p. >200°. The residue of evaporation of the mother liquor was dissolved in benzene and chromatographed on an alumina column 77 cm. high and 6 cm. in diameter. Elution by means of 16 l. of benzene containing first 1.5% then 2.5% and finally 7.5% of ethanol gave small amounts of material, m.p. *ca.* 198–199°, then much uncrystallizable oil which was soluble in ether (presumably the starting bis-dodecyl monoquaternary). Most of this came out after elution with the first 1.5 l. of 7.5% ethanol in benzene. The next 500 ml. of this mixture gave an oil which, on extraction with ether, deposited crystals insoluble in the solvent. Elution of the column with absolute ethanol then gave 3.4 g. of residue insoluble in ether. Several recrystallizations from ethyl acetate gave 860 mg. of the bis-quaternary γ-isomer as hydrate, m.p. 97.5–101°. It contained no base or base hydrochloride detectable by the shape of its titration curve and, when dried, had m.p. 174–178.5°.

Anal. Calcd. for $C_{32}H_{68}N_2Cl_2$: N, 5.08. Found: N, 5.03.

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

The Preparation and Stereochemistry of Some Cinnamonitriles, Some Cinnamamidines and Related Compounds

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Mixtures of the *cis* and *trans* isomers of several substituted cinnamonitriles have been prepared by reaction of the benzaldehydes or aryl ketones with cyanoacetic acid followed by decarboxylation. Use of pyridine–piperidine as reaction medium led to the direct formation of a mixture containing about 75% of *trans*-nitrile in the case of *o*-chlorobenzaldehyde. A two-step procedure, comprising formation of apparently stereochemically homogeneous *o*-chlorobenzylidenecyanoacetic acid and its subsequent copper-catalyzed decarboxylation, gave a considerably greater proportion of *cis*-nitrile. The separation of these isomers of *o*-chlorocinnamonitrile and aspects of the infrared absorption curves of these and some related compounds are discussed. On treatment with various halomagnesium dialkylamides both *cis*- and *trans*-cinnamonitriles gave good yields of only the *trans*-cinnamamidines. N,N-Dibutyl-β-cyclocitrylidenoacetamidine (III) was made by a series of reactions in which the β-*trans* configuration of β-ionone was retained, as shown by comparison of the pertinent infrared and ultraviolet spectra with those of other substances of known configuration.

Several amidines have been reported to have local anesthetic activity.[1] Certain of these amidines, and in particular the cinnamamidines appear to possess antifibrillatory activity in the dog.[2] It therefore seemed to be worthwhile to prepare additional variants of the cinnamamidines. This paper reports work along these lines, as well as the preparation of an analogous amidine in which an alicyclic group replaced the phenyl group, and some incidental studies of the stereochemistry of the preparative methods for the cinnamonitriles.

In order to prepare the amidines of interest it was desirable to have a good general synthesis of the cinnamonitriles required as starting materials. We have used two methods of synthesis of the nitriles, both involving the condensation of aromatic aldehydes with cyanoacetic acid: (1) A modification of the Doebner synthesis[3] of cinnamic acids which involves heating the reactants in pyridine with piperidine as a catalyst. In this process, condensation is followed immediately by decarboxylation and the cinnamonitrile is isolated directly from the reaction mixture. (2) A two-step process consisting of: (a) base-catalyzed condensation of the reactants to give the benzylidenecyanoacetic acid, which is isolated; (b) decarboxylation, catalyzed by copper powder to give the cinnamonitrile. The former "Doebner-like" method generally was preferred, since it appeared to be quicker and more convenient.

Preparation of *p*-methylcinnamonitrile by this method gave a liquid cinnamonitrile, which was assumed to be a mixture of the *cis* and *trans* isomers. Since what is presumably the *trans p*-methylcinnamonitrile has been reported to melt at 79–80°,[4] attempts were made to separate this isomer by several redistillations, followed by crystallization, but this procedure was not successful. It would seem likely by comparison with the results reported with cinnamonitrile[5] and with our results (below) with *o*-chlorocinnamonitrile that this mixture would be more than half *trans*. However, in view of the

(1) E. Lorz and R. Baltzly, THIS JOURNAL, **70**, 1904 (1948); **73**, 483 (1951).

(2) Private communication from Dr. C. H. Ellis of these laboratories.

(3) J. R. Johnson, "Organic Reactions," Vol. I, R. Adams, Editor, John Wiley and Sons, Inc., New York, N. Y., 1942, pp. 222, 235 *et seq.*

(4) E. Fiquet, *Ann. chim. phys.*, [6] **29**, 479 (1893).

(5) E. J. Corey and G. Fraenkel, THIS JOURNAL, **75**, 1168 (1953).