Anal. Calcd. for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; Cl, 11.25; N, 8.90. Found: C, 64.45; H, 4.69; Cl, 11.20; N, 8.88.

3,7-Dichloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one (V).—One gram of III was finely powdered and treated with 1 ml. of thionyl chloride. An immediate reaction took place with the formation of a yellow solid. Anhydrous ether was added and the solid was collected and washed free of thionyl chloride. From analytical values the product, m.p. 151–153° dec., appeared to be a partial hydrochloride. It was suspended in 25 ml. of methylene chloride and 1 g. of Amberlite IRA-400 (OH) and 1 g. of barium oxide were added. The yellow color was discharged and the insoluble matter was immediately removed. The solution was treated with charcoal and slowly diluted with hexane to afford 0.5 g. of V, m.p. 179° dec.

Anal. Calcd. for $C_{15}H_{10}Cl_2N_2O$: C, 59.03; H, 3.30; Cl, 23.24; N, 9.18. Found: C, 59.57; H, 3.22; Cl, 22.05; N, 9.51.

The poor analysis was attributed to the extreme reactivity of V. Mere warming in alcohol afforded XV, identical with the compound obtained as a by-product in the preparation of IV.

Catalytic hydrogenation (1 mole) of V in dimethoxyethane over 5% palladium–charcoal gave 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-2-one, m.p. 214–216°, undepressed upon mixing with an authentic sample.[2]

Acknowledgment.—We are indebted to Dr. Gordon Ellis and his associates for the microanalyses and to Mr. Bruce Hofmann for helpful discussions of the spectra. Mr. Carl Gochman gave valuable technical assistance.

New Derivatives of 2,2,6,6-Tetramethylpiperidine

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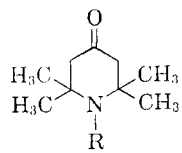
A number of new derivatives of 2,2,6,6-tetramethylpiperidine have been prepared for testing as ganglionic and neuromuscular blocking agents. Many of these are bisamines and are represented by both symmetrical and unsymmetrical types.

Interest in the chemistry and pharmacology of highly methylated derivatives of piperidine has been stimulated in recent years by the discovery[1–4] that 1,2,2,6,6-pentamethylpiperidine (Ia) is a potent ganglionic blocking agent. Further work has shown that such activity is not very specific



IIa. R = H
b. R = CH_3

but is associated with a certain optimum degree of shielding of the nitrogen atom of a secondary or tertiary amine by nearby substituents, particularly alkyl groups.[5] Ganglionic blocking agents of this type are characterized by excellent absorption from the gastrointestinal tract combined with moderately rapid excretion.[6] Ganglionic blockers of the quaternary type, on the other hand, are characterized by erratic gastrointestinal absorption. Usually the activity can be increased by incorporating two quaternary centers into a single molecule. The distance between the quaternary centers determines whether the compounds are predominantly ganglionic blocking or neuromuscular blocking.[7,8]

The present work was undertaken to ascertain whether bis-tertiary amines of the polymethylpiperidine type would show a structure-activity relationship similar to the quaternary amines while still retaining the favorable absorption properties of the tertiary amines. Thus we undertook the preparation of a series of compounds in which the separation of the amine nitrogens was six to ten methylene groups. These separations have been approximate maxima for ganglionic and neuromuscular blocking agents, respectively, in the bisquaternary series.

In Table I are listed the monobasic amines which were prepared. Most of these were studied for activity and were also used to prepare the bis structures shown in Table II. Miscellaneous compounds are listed in Table III.

The principal starting material for this work was triacetonamine (IIa) prepared by the method of Francis[9] from acetone, calcium chloride, and ammonia. The triacetonamine was usually isolated in the crude anhydrous form by fractional distillation of the reaction mixture rather than *via* the hydrate as described by Francis.

Contrary to the literature[10a] the *N*-methyl deriv-

(1) A. Spinks and E. H. P. Young, *Nature*, **181**, 1397 (1958).
(2) G. E. Lee, W. R. Wragg, S. J. Corne, N. D. Edge, and H. W. Reading, *ibid.*, **181**, 1717 (1958).
(3) S. J. Corne and N. D. Edge, *Brit. J. Pharmacol.*, **13**, 339 (1958).
(4) A. Spinks, E. H. P. Young, J. A. Farrington, and D. Dunlop, *ibid.*, **13**, 501 (1958).
(5) L. Bretherick, G. E. Lee, E. Lunt, W. R. Wragg, and N. D. Edge, *Nature*, **184**, 1707 (1959).
(6) M. Harington, P. Kincaid-Smith, and M. D. Milne, *Lancet*, **2**, 6 (1958).
(7) C. J. Cavillito, A. E. Soria, and J. O. Hoppe, *J. Am. Chem. Soc.*, **72**, 2661 (1950).
(8) L. E. Craig, *Chem. Revs.*, **42**, 285 (1948).
(9) F. Francis, *J. Chem. Soc.*, 2897 (1927).
(10) (a) J. Guareschi, *Ber.*, **28**, 160 Referate (1895); (b) E. Schering, German Patent 91,122 (February 19, 1897).

TABLE I

	Compound	M.P.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIa	Triacetonamine		$C_9H_{17}NO$						
IIb·HI	1,2,2,6,6-Pentamethyl-4-piperidone	198–199	$C_{10}H_{20}INO$	40.41	6.78	42.71[b]	40.64	6.85	43.03[b]
	2,2,6,6-Tetramethyl-4-piperidinol	128–131	$C_9H_{19}NO$	68.74	12.17		68.50	12.15	
XVII	2,2,6,6-Tetramethylpiperidine	151–154[a] $n^{20}D$ 1.4442	$C_9H_{19}N$						
	Triacetonamine oxime hydrochloride	284–285	$C_9H_{18}ClN_2O$						
	Triacetonamine hydrazone	61–64	$C_9H_{19}N_3$	63.86	11.34	24.83	63.66	11.24	24.53
	1,2,2,6,6-Pentamethyl-4-piperidone oxime	143–144	$C_{10}H_{20}N_2O$						
	—hydrochloride	227–228	$C_{10}H_{21}ClN_2O$	54.41	9.59	16.06[c]	54.59	9.64	16.25[c]
VIII	4-Hydroxy-1,1,2,2,6,6-hexamethylpiperidinium iodide	226–228 dec.	$C_{11}H_{24}INO$	42.18	7.72	40.52[b]	42.06	7.78	40.32[b]
Ib	1,2,2,6,6-Pentamethyl-4-piperidinol	73–74	$C_{10}H_{21}NO$			8.19			8.24
XXII	4-Amino-1,2,2,6,6-pentamethylpiperidine	97–99[a] (15 mm.)	$C_{10}H_{21}N_2$						
XVIII·HCl	2,2,6,6-Tetramethyl-1-(2-propynyl)piperidine hydrochloride	212–213 dec.	$C_{12}H_{22}ClN$	66.79	10.28	16.43[c]	66.85	10.18	16.48[c]
XIII	4-Ethynyl-2,2,6,6-tetramethyl-4-piperidinol	214–216	$C_{11}H_{19}NO$	72.88	10.56	7.73	72.76	10.51	7.80
IX·HBr	3-(1,2,2,6,6-Pentamethyl-4-piperidyloxy)propionitrile hydrobromide	176–178	$C_{13}H_{25}BrN_2O$	51.15	8.26	9.18	51.18	8.33	8.86

[a] B.p. [b] Iodine. [c] Chlorine.

TABLE II

	Compound	M.P.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
VII	Bis(1,2,2,6,6-pentamethyl-4-piperidyl) succinate bishydrogen sulfate	252–256	$C_{24}H_{48}N_2O_{12}S_2$	46.43	7.79	4.51	46.46	7.87	4.63
	—bishydrogen oxalate	231–232	$C_{28}H_{48}N_2O_{12}$	55.61	8.01		55.39	8.27	
VIa	Triacetonamine azine	135–136	$C_{18}H_{34}N_4$	70.54	11.18	18.28	70.47	11.16	18.24
VIb	*N*-Methyltriacetonamine azine	98–99	$C_{20}H_{38}N_4$	71.80	11.45	16.75	71.84	11.52	16.56
	—bis(*p*-toluenesulfonate)	149–150	$C_{34}H_{54}N_4O_2S_6$	60.15	8.02	9.44[a]	60.06	8.04	9.20[a]
X·2HCl	4-(3-Aminopropoxy)-1,2,2,6,6-pentamethylpiperidine dihydrochloride	258–259	$C_{13}H_{30}Cl_2N_2O$	51.82	10.04	23.54	51.74	10.43	23.48
XI·2HCl	4-(3-Dimethylaminopropoxy)-1,2,2,6,6-pentamethylpiperidine dihydrochloride	252–253	$C_{15}H_{34}Cl_2N_2O$	54.70	10.41	21.53	54.67	10.44	21.57
XIIa	4,4′-Bis(2,2,6,6-tetramethyl-4-piperidinol)	176–178	$C_{18}H_{36}N_2O_2$	69.18	11.61	8.97	69.25	11.53	9.20
XIIb	4,4′-Bis(1,2,2,6,6-pentamethyl-4-piperidinol)	149–150	$C_{20}H_{40}N_2O_2$	70.54	11.84	8.23	70.44	11.80	8.21
XIV	1,4-Bis(2,2,6,6-tetramethyl-4-hydroxy-4-piperidyl)butadiyne	246–248	$C_{22}H_{36}N_2O_2$	73.29	10.07	7.77	73.17	10.33	7.75
XVa	1,4-Bis(2,2,6,6-tetramethyl-4-hydroxy-4-piperidyl)butane	128–129	$C_{22}H_{44}N_2O_2$	71.68	12.03	7.60	71.73	12.14	7.62
XVb	1,4-Bis(1,2,2,6,6-pentamethyl-4-hydroxy-4-piperidyl)butane	122–123	$C_{24}H_{48}N_2O_2$	72.67	12.20	7.06	72.59	12.22	7.01
XVI·2HCl	1,4-Bis(1,2,2,6,6-pentamethyl-4-piperidyl)butane dihydrochloride	289–290	$C_{24}H_{50}Cl_2N_2$	65.87	11.50	6.40	65.60	11.46	6.70
XIX	1,6-Bis(2,2,6,6-tetramethylpiperidino)-2,4-hexadiyne	120–121	$C_{24}H_{40}N_2$	80.84	11.31	7.86	80.65	11.23	7.63
XIX·2HCl	—dihydrochloride	228–229	$C_{24}H_{42}Cl_2N_2$	67.11	9.86	16.51[b]	66.90	9.94	16.65[b]
XX	1,6-Bis(2,2,6,6-tetramethylpiperidino)hexane	117–118	$C_{24}H_{48}N_2$						
XX·2HCl	—dihydrochloride	264–265	$C_{24}H_{50}Cl_2N_2$	65.87	11.50	16.21[b]	65.96	11.58	16.49[b]

[a] Sulfur. [b] Chlorine.

ative IIb was easily obtained by methylation of triacetonamine (IIa) with methyl iodide. When pure IIa was used, the hydriodide of IIb separated in excellent yield uncontaminated by impurities. When crude triacetonamine was used, one or more recrystallizations were necessary in order to obtain pure methylated product.

The patent literature[10b] indicates that treatment

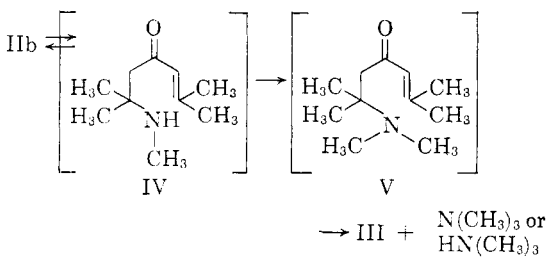
TABLE III

	Compound	M.P.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
XXI	4-Guanidino-1,2,2,6,6-pentamethylpiperidine dinitrate	225–226	$C_{11}H_{25}N_6O_6$	39.16	7.47	24.91	39.37	7.77	24.85
XXV·HCl	1-(*o*-Bromobenzyl)-2,2,6,6-tetramethylpiperidine hydrochloride	207–209	$C_{16}H_{25}BrClN$	55.42	7.27	10.26[a]	55.72	7.29	10.02[a]
XXIIIb	*N*-(1,2,2,6,6-Pentamethyl-4-piperidinyl)-1-tosyl-5-pyrrolidone-2-carboxamide	207.8–208.4	$C_{22}H_{33}N_3O_4S$	60.66	7.64	9.65	60.67	7.76	9.89
XXIV	1,2,2,6,6-Pentamethyl-4-(*N*-tosyl-L-α-glutamylamino)piperidine	200–215 dec.	$C_{22}H_{35}N_3O_5S$	58.25	7.78	9.26	58.22	7.82	9.10
XXV	1-(*o*-Bromobenzyl)-2,2,6,6-tetramethylpiperidine	72–77	$C_{16}H_{24}BrN$	61.93	7.80	25.76[b]	62.02	7.84	25.65[b]

[a] Chlorine. [b] Bromine.

of triacetonamine (IIa) with methyl iodide gives a crystalline hydriodide of IIa plus a liquid fraction consisting of the methylated free base IIb. We have never observed such a course for this reaction under our conditions.

Attempted methylation of triacetonamine with formaldehyde–formic acid gave mainly a volatile amine plus some yellow neutral material. The odor of the neutral material suggested phorone and the identity was established by comparison of the infrared absorption with that of an authentic sample. The expected *N*-methyltriacetonamine (IIb) was probably formed but then underwent a reverse Michael addition to give IV. Methylation of IV



followed by another reverse Michael lead through V to phorone (III) with evolution of di- or trimethylamine. Although some of the desired product could be detected by gas liquid chromatography, the reaction did not appear to be sufficiently clean-cut to warrant further investigation.

By contrast, the oxime of triacetonamine was smoothly methylated with formaldehyde–formic acid to give the oxime of IIb in good yield.

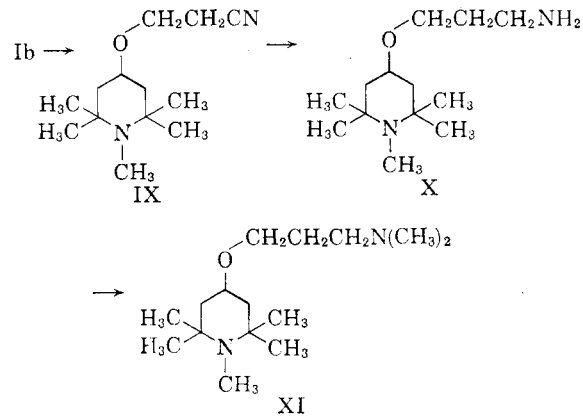
When warmed with one-half equivalent of hydrazine hydrate, IIa and IIb gave the corresponding azines VIa and VIb. Attempts to prepare VIb by methylation of VIa with methyl iodide or formaldehyde–formic acid were unsuccessful.

Although a hydrazone of IIa could be prepared, it tended to disproportionate into the corresponding azine and free hydrazine on standing at room temperature.

Reduction of triacetonamine with sodium borohydride followed by methylation with formaldehyde–formic acid gave 1,2,2,6,6-pentamethyl-4-piperidinol (Ib).[11] This was used to prepare a symmetrical bis ester. When Ib was heated with succinic anhydride in benzene, a half-ester was produced which on further treatment with Ib and an acid catalyst gave the bis ester VII. This product was characterized both as the bis hydrogen sulfate and as the bis hydrogen oxalate.

The quaternary 4 - hydroxy - 1,1,2,2,6,6 - hexamethylpiperidinium iodide (VIII) was also desired for pharmacological studies and was prepared from Ib and methyl iodide by heating the components in a sealed tube.

The unsymmetrical bisamine XI was prepared from Ib by the sequence shown.



Cyanoethylation of Ib with acrylonitrile in the presence of sodium *t*-butoxide gave IX in 52–83% yield. Reduction of IX to X was attempted with diborane[12] but the reaction apparently did not proceed to completion. Lithium aluminum hydride in ether,[13] however, gave excellent yields of X. The methylation of X was accomplished by the Eschweiler-Clark procedure. Compound XI was isolated as the dihydrochloride in 58% yield.

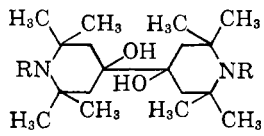
Considerable effort was directed toward the preparation of the pinacol reduction product XIIa of triacetonamine. When amalgamated aluminum in ethanol–benzene[14] was used, the only substance

(11) L. Orthner, *Ann.*, **456**, 251 (1927).

(12) H. C. Brown and B. C. Subba Rao, *J. Org. Chem.*, **22**, 1135 (1957).

(13) The use of tetrahydrofuran was avoided because compounds of the type R—OCH_2CH_2CN are frequently cleaved by lithium aluminum hydride in this solvent. T. Soffer and E. Parrotta, *J. Am. Chem. Soc.*, **76**, 3580 (1954).

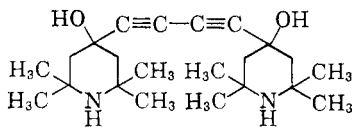
(14) M. S. Newman, *J. Am. Chem. Soc.*, **62**, 1685 (1940).



XIIa. R = H
b. R = CH_3

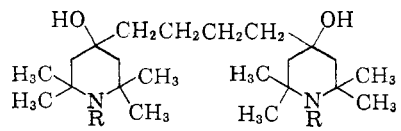
which could be isolated was the monocyclic reduction product, 2,2,6,6-tetramethyl-4-piperidinol. A number of other systems were tried with similar lack of success. Yellow viscous oils and/or the monocyclic reduction product were the only materials isolated. In one experiment using amalgamated aluminum in benzene[15] a 22% yield of the desired product was obtained. Several attempts to repeat this experiment afforded some product, but the yields were under 10%. In some experiments the aluminum was amalgamated *in situ*. In others, it was pre-amalgamated in alcoholic mercuric chloride. These variations had no desirable effect on the yield. The small amount of available XIIa was smoothly methylated with formaldehyde–formic acid to give XIIb in excellent yield.

Oxidative coupling of terminal acetylenes was used to prepare two other series of bisamines. Ethynylation of triacetonamine with sodium acetylide in liquid ammonia gave 4-ethynyl-2,2,6,6-tetramethyl-4-piperidinol (XIII) in 32–69% yield. Oxidative coupling of XIII using cuprous chloride

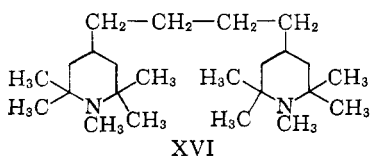


XIV

and ammonium chloride in aqueous solution[16] in the presence of oxygen gave XIV in yields of 80–90%. An attempted methylation of XIV by formaldehyde–formic acid gave only brown resinous material. On the other hand, the octahydro compound XVa, obtained by the catalytic hydrogenation of XIV, was methylated to XVb in 79–95% yield.



XVa. R = H
b. R = CH_3

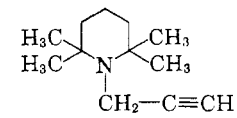


XVI

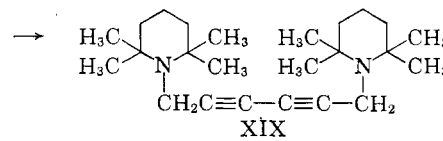
The hydrogenation of XIV was carried out in aqueous acetic acid using a mixture of platinum- and palladium-on-charcoal in the hope that the propargylic hydroxyl groups would be removed,[17] but no hydrogenolysis products could be detected in the reaction mixtures.

The dehydration of XVb to a diene was accomplished with boiling 20% sulfuric acid. Unlike the starting material, the product showed no OH absorption at 3300 cm.$^{-1}$ but showed instead a rather weak band at 1680–1700 cm.$^{-1}$, probably indicating unsaturation. Since this product was presumed to be a mixture of isomers, it was not fully characterized but was hydrogenated directly to XVI. High pressure hydrogenation at 100° was required for the reduction to the completely saturated material, which was characterized as the dihydrochloride.

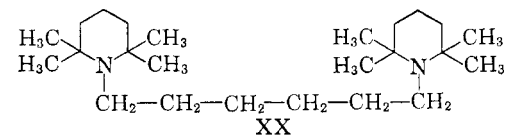
The bisamine XX was also prepared by a series of reactions in which the oxidative coupling of an acetylene was the key step



XVIII



XIX



XX

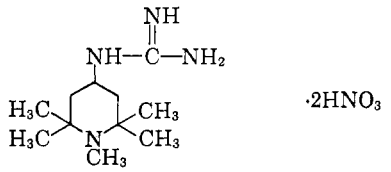
Wolff-Kishner reduction of triacetonamine IIa by the procedure of Leonard[18] gave 2,2,6,6-tetramethylpiperidine (XVII). With propargyl bromide the latter gave XVIII in 24–50% yield. Oxidation with cupric acetate in methanol–pyridine[19] gave the diyne XIX. The usual cuprous chloride–ammonium chloride–water–oxygen system was much less effective in carrying out this coupling.

Unexpected difficulty was encountered in the catalytic hydrogenation of XIX to the saturated compound XX. Aqueous acetic acid and petroleum ether were used as solvents. A variety of catalysts were tried including platinum-on-charcoal, Raney nickel, Adam's catalyst, rhodium-on-charcoal, and a mixture of platinum-on-charcoal and palladium-on-charcoal. Much 2,2,6,6-tetramethylpiperidine was isolated from the reaction mixtures accompanied by a higher boiling fraction which we believe to be 1-hexyl-2,2,6,6-tetramethyl-

(15) M. Quadrat-i-Khuda and A. Kumar Ray, *J. Ind. Chem. Soc.*, **16**, 525 (1939).
(16) J. B. Armitage, C. L. Cook, N. Entwhistle, E. R. H. Jones, and M. C. Whiting, *J. Chem. Soc.*, 1998 (1952).
(17) K. Zeile and H. Meyer, *Ber.*, **75**, 356 (1942).
(18) N. J. Leonard and E. Nommensen, *J. Am. Chem. Soc.*, **71**, 2810 (1949).
(19) G. Eglinton and A. R. Galbraith, *J. Chem. Soc.*, 889 (1959).

piperidine. These products evidently arose *via* cleavage of the propargylic C—N linkage. Similar observations have been made in other laboratories.[20] The best catalyst-solvent combination found was rhodium-on-charcoal in petroleum ether, which gave about 60% of XX. The saturated bisamine was characterized as the dihydrochloride.

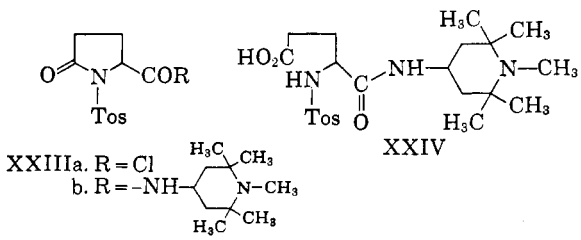
The hypotensive activity of guanethidine[21] suggested the preparation of XXI. The requisite



XXI

starting material, 4-amino-1,2,2,6,6-pentamethylpiperidine (XXII), was prepared by reduction of *N*-methyltriacetonamine oxime either catalytically or with lithium aluminum hydride. This material had the properties described by Orthner[11] for material prepared by reduction of the oxime with sodium and isoamyl alcohol. The desired product XXI was obtained from XXII by guanylation of the latter with 1-guanyl-3,5-dimethylpyrazole nitrate.[22,23]

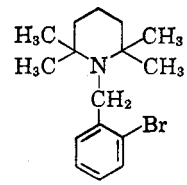
Compound XXII was also used to prepare two amino acid derivatives. Thus, condensation of L-*N*-tosyl-5-pyrrolidone-2-carbonyl chloride[24,25] XXIIIa with XXII in chloroform or methylene chloride afforded 5-oxo-*N*-(1,2,2,6,6-pentamethyl-4-piperidinyl)-1-(*p*-toluenesulfonyl)-L-2-pyrrolidinecarboxamide (XXIIIb) in 60% yield. Opening the pyrrolidone ring of XXIIIb with barium hydroxide in aqueous methanol gave



XXIV

1,2,2,6,6-pentamethyl-4-(*N*-tosyl-L-α-glutamyl amino)-piperidine (XXIV). Although XXIV was obtained analytically pure, the wide melting range observed (200–215°) suggested the presence of impurities or racemate. The presence of methanol in the hydrolytic medium could also lead to the formation of a certain amount of methyl ester. However, the infrared spectrum of the product showed no evidence of ester absorption nor is the combustion analysis in accord with such a possibility. Since two different preparations gave rather different rotations, partial racemization is probably the best explanation of the observed melting point behavior. In other respects—*i.e.*, melting point behavior and infrared spectrum—the products from the two runs were the same.

Compound XXV, which has some structural similarities to bretylium compounds, was prepared by heating 2,2,6,6-tetramethylpiperidine with *o*-bromobenzyl chloride in a sealed tube.



XXV

Experimental[26–28]

Triacetonamine (IIa).—In a 5-l. round-bottom three-necked flask equipped with heavy duty stirrer, condenser, and oil heating bath were placed 800 g. of calcium chloride and 3160 ml. of commercial acetone. Ammonia was bubbled intermittently through the stirred mixture for 2 days. After refluxing the mixture for 2 hr., distillation was begun and continued until the vapor temperature reached *ca.* 75°. The remaining liquid was decanted from the cake of inorganic salts and distilled at 15 mm. The fraction boiling at 88–92° was collected and weighed 179 g. (8%). On cooling it crystallized in long yellow needles sufficiently pure for most purposes.

Hall[29] describes conditions for obtaining yields of about 20% from this reaction although a considerably longer reaction time and more complicated work-up are required.

2,2,6,6-Tetramethyl-4-piperidinol.—Crude anhydrous triacetonamine (7.75 g., 0.05 mole), sodium borohydride (0.95 g., 0.025 mole), and 26 ml. of 95% ethanol were magnetically stirred in a round-bottom flask for 4 hr. The flask was occasionally immersed in a cold water bath to prevent boiling. The solvent was then removed on a rotary evaporator and the residue triturated with 20 ml. of water. After standing for 2 days, the water was removed on the rotary evaporator, and the remaining powder extracted with ligroin, (b.p. 90–97°) in a Soxhlet extractor for 2 hr. The extract was concentrated to *ca.* 65 ml. and cooled. The crystals which separated were collected, washed with petroleum ether (b.p. 30–60°), and dried. The crop of slightly yellow crystals, m.p. 128–131°,[30] weighed 7.87 g. (96.5%).

1,2,2,6,6-Pentamethyl-4-piperidinol (Ib).—A mixture of 35.5 g. of 2,2,6,6-pentamethyl-4-piperidinol, 35.5 g. (33 ml.) of 37% formalin, and 7.6 ml. of formic acid was heated under a reflux condenser on the steam bath for 7 hr. The reaction mixture was made basic with 10 *M* potassium hydroxide and the product extracted with 370 ml. of ether in five portions. The combined extract was dried over potassium carbonate

(20) J. Guermont, *Bull. Soc. Chim.*, **20**, 386 (1953); R. F. Kleinschmidt and C. W. Kruse, Abstracts of Papers, 138th Meeting, American Chemical Society, New York, September 11–16 (1960).

(21) R. A. Maxwell, R. P. Mull, and A. J. Plummer, *Experientia*, **15**, 267 (1959).

(22) R. A. B. Bannard, A. A. Casselman, W. F. Cockburn, and G. M. Brown, *Can. J. Chem.*, **36**, 1541 (1958).

(23) A. F. S. A. Habeeb, *Biochem. et Biophys. Acta*, **34**, 294 (1959).

(24) J. Rudinger, *Collection Czechoslov. Chem. Communs.*, **19**, 365 (1954).

(25) J. Stedman, *J. Am. Chem. Soc.*, **79**, 4691 (1957).

(26) Melting points were taken in capillaries using Anschutz-type thermometers in a Hershberg apparatus.

(27) Analyses were performed by Mrs. Lucy Ermanis, Mrs. Unni Zeek, and Mr. Tom Wildeman.

(28) Unless otherwise specified, sublimations were carried out at 0.05 mm. just below the melting point of the compound.

(29) H. K. Hall, *J. Am. Chem. Soc.*, **79**, 5444 (1957).

(30) W. Heintz, *Ann.*, **183**, 303 (1876), records m.p. 128.5°.

and the ether distilled through a short helices-packed column. The residue was then sublimed at 0.05 mm., bath temperature 88°. The white sublimate weighed 37.6 g. (97%) and melted at 72.8–74.0°. The literature[31] records m.p. 74°. Exposure to humid air yielded a hydrate, m.p. 57–59°. The literature[11] records m.p. 60° for the hydrate.

4-Hydroxy-1,1,2,2,6,6-hexamethylpiperidinium Iodide (VIII).—A mixture of 0.85 g. (5 mmoles) of 1,2,2,6,6-pentamethyl-4-piperidinol and 1.90 ml., 2.84 g. (20 mmoles), of methyl iodide was maintained at 70–75° in a sealed tube for 23 hr. The resulting solid was collected and washed with ether to give 1.48 g. (95%) of white crystals, m.p. 216–220° dec. Recrystallization from 3:2 methanol and then methanol afforded analytically pure material, m.p. 226–228°.

Triacetonamine Hydrazone.—A solution of 7 g. (0.04 mole) of triacetonamine and 7.3 ml. (0.15 mole) of hydrazine hydrate in 10 ml. of methanol was kept at room temperature for 2 days. Evaporation of the mixture without heating afforded 6.8 g. (99%) of an oil which crystallized on cooling in an ice bath. An analytical sample, m.p. 61–64°, was prepared by two recrystallizations from 90–97° ligroin and sublimation of the product. On standing triacetonamine hydrazone gradually disproportionated into the azine and hydrazine. When *two* equivalents of triacetonamine were treated with slightly less than one equivalent of hydrazine hydrate in methanol *without application of heat* the hydrazone was again obtained in good yield. Heating the reaction mixture gave the azine.

Triacetonamine Azine (VIa).—A mixture of 12 g. (0.077 mole) of triacetonamine and 1.9 g. (0.038 mole) of hydrazine hydrate was heated on the steam for 3 hr. during which time a mass of crystals separated. The reaction product was recrystallized from 75 ml. of petroleum ether (b.p. 65–70°) and gave 9.75 g. (84%) of white crystals melting at 135–136°.

An analytical sample was prepared by recrystallizing crude material twice from petroleum ether (b.p. 65–70°) and subliming the product.

***N*-Methyltriacetonamine Azine (VIb).**—*N*-Methyltriacetonamine (8.45 g., 0.05 mole), hydrazine hydrate (1.25 g., 0.025 mole), and 1 ml. of ethanol were heated at 85–88° for 4 hr. The product, which crystallized on cooling, was slurried in 3 ml. of acetonitrile, collected on a Büchner funnel, and washed with the same solvent to give 4.45 g. (53%) of crystals, m.p. 97–99°. An analytical sample m.p. 98–99° was prepared by recrystallization of the crude material from acetonitrile and sublimation of the product.

The bis-*p*-toluenesulfonate was prepared and melted at 149–150° after recrystallization from 2-propanol–ethyl acetate–ether.

1,2,2,6,6-Pentamethyl-4-piperidone (IIb).—Crude anhydrous triacetonamine (98 g.), methyl iodide (90 ml.), and 2-propanol (60 ml.) were placed in a 500-ml. Erlenmeyer flask and stoppered. The reaction was mildly exothermic necessitating application of a cold water bath to avoid volatilization of methyl iodide. Twenty-milliliter portions of 2-propanol were added after 1- and 2-hr. periods in order to keep the crystals covered which had pushed through the surface of the liquid. After 2 days the product was ground in a large mortar with 2-propanol and filtered. The filter cake, well washed with 2-propanol and ether, weighed 155 g. (83%) when dry and melted 189–194°.

This was dissolved in 750 ml. of boiling methanol, filtered, and diluted with 250 ml. of hot 2-propanol. The crystals which separated on cooling were washed with 2-propanol and ligroin. The dry slightly tan product weighed 115 g. (62%) and melted at 198–199°.

When the same reaction was carried out with a sample of pure triacetonamine hydrate, the product separated in 94% yield as white crystals, m.p. 198–200°. Recrystallized for analysis from methanol, it melted at 198–199°. Although the literature m.p. is 172°,[32] our material had the correct percentage composition and reacted chemically as would be expected for a salt of *N*-methyltriacetonamine.

The free base was obtained in 65% yield by treating an aqueous solution of the hydriodide with aqueous alkali and extracting the product into ether. After drying the ether layer over potassium carbonate, the solvent was stripped on the steam bath and the residue distilled at 15 mm. pressure. The desired product was in the fraction boiling at 100–102° and solidified on cooling. The literature[11] records b.p. 122° (23 mm.).

1,2,2,6,6-Pentamethyl-4-piperidone Oxime. Method A.—Triacetonamine oxime hydrochloride[33] (12.4 g., 0.06 mole), sodium formate (8.4 g., 0.122 mole), 37% aqueous formaldehyde (18 ml., *ca.* 0.22 mole), and 1 ml. of formic acid were mixed together and heated on the steam bath for 2 hr. One-milliliter portions of formic acid were added as required to keep the mixture approximately neutral. The initially vigorous evolution of carbon dioxide had become imperceptible at the end of 2 hr. The product was precipitated by the addition of concd. ammonium hydroxide to the cooled reaction mixture. The solid was filtered, washed with ice water, and dried over phosphorus pentoxide to give 9.0 g. (81%) of product melting at 135–142°. Recrystallization from acetonitrile raised the melting point to 142–144°. The literature[11] records m.p. 143°.

The hydrochloride was prepared by dissolving the solid in warm 2-propanol and adding a solution of hydrogen chloride in 2-propanol. The precipitated salt, 8.6 g., m.p. 227–228° dec., was analytically pure.

Method B.—1,2,2,6,6-Pentamethyl-4-piperidone (18.3 g., 0.108 mole) and a solution of 10 g. (0.15 mole) of hydroxylamine hydrochloride in 20 ml. of water were mixed with vigorous swirling. After the initial exothermic reaction had subsided, the mixture was heated for a few minutes on the steam bath. The mixture was allowed to cool slowly to room temperature after which it was made basic by adding sodium hydroxide pellets and vigorously swirling the flask. After standing overnight the precipitated product was slurried with water and filtered. The filter cake was dried, dissolved in ether, and some insoluble material removed by filtration. Evaporation of the ether left 14.9 g. (75%) of a crystalline residue of the desired product, m.p. 143–144°.

Bis(1,2,2,6,6-pentamethyl-4-piperidyl) Succinate (VII).—In a 250-ml. round-bottom flask were placed 12.0 g. (70 mmoles) of 1,2,2,6,6-pentamethyl-4-piperidinol, 3.5 g. (35 mmoles) of powdered succinic anhydride and 60 ml. of benzene. The mixture was maintained at reflux under a 2 × 24-cm. column packed with glass helices for 1 hr. The solids dissolved initially but were rapidly replaced by a new crystalline material, probably the half-ester. The reaction mixture was cooled and a solution of 18.1 g. (105 mmoles) of *p*-toluenesulfonic acid in 60 ml. of benzene[34] added. Benzene–water azeotrope was slowly distilled through the column during a period of 21 hr. The light tan reaction mixture was cooled and stirred with a solution of 27 g. of potassium carbonate in 75 ml. of water. The mixture was transferred to a separatory funnel with the aid of 40 ml. of ether and 55 ml. of water. The lower layer was separated and extracted with 60 ml. of ether in three portions. The combined extract was filtered through a bed of potassium carbonate, then further dried by distilling the benzene–ether through a column. Residual solvent was removed at the water pump leaving a yellow oil. This was diluted with 30 ml. of ether and treated with a solution of 2.7 ml. of concd. sulfuric acid in 15 ml. of cold 2-propanol. Ethyl acetate (25 ml.) was added and the supernate decanted from the gummy product. The gum was

(31) E. Fischer, *Ber.*, **16**, 1605 (1883).

(32) P. Petrenko-Kritschenko, E. Putjata, and A. Gandelmann; *Chem. Zentr.*, **I**, 1590 (1923).

(33) S. C. Dickerman and H. G. Lindwall, *J. Org. Chem.*, **14**, 530 (1949).

(34) Prepared by dissolving 20.0 g. of the monohydrate in 150 ml. of benzene and distilling 90 ml. of the solvent.

warmed with 25 ml. of 1-propanol. Crystallization followed rapidly. The decantate also deposited crystals on standing. The two products were collected on a Büchner funnel and washed successively with 2-propanol, ethyl acetate, and ether. The dry product weighed 8.20 g. The filtrate from this material treated with 1.5 ml. of concd. sulfuric acid gave an additional 9.1 g. of material. The combined crops were recrystallized from methanol–2-propanol to give 16.6 g. (76.5%) of small crystals, m.p. 250–253°, softening at 249°. The analytical sample was prepared by recrystallization from methanol–ethanol and drying the product at 110° for 18 hr. at 0.05 mm. over phosphorus pentoxide. It melted at 252–256° with softening above 250° (bath preheated to 245°). The infrared spectrum showed ester carbonyl absorption at 1710–1720 cm.$^{-1}$.

A bis acid oxalate was prepared by treating the crude base with oxalic acid in ethanol. An analytical sample, m.p. 231–232°, was prepared by recrystallization of the material from 1-propanol.

3-(1,2,2,6,6-Pentamethyl-4-piperidinyloxy)propionitrile Hydrobromide (IX).—To 10.3 g. (0.06 mole) of molten 1,2,2,6,6-pentamethyl-4-piperidinol was added a solution of 4 mg. of sodium in about 0.5 ml. of *t*-butyl alcohol. The mixture was then swirled briefly followed by the addition of 13 ml. (10.5 g., 0.19 mole) of acrylonitrile. The solution was allowed to stand for 2 days at room temperature then heated for 2 hr. at steam bath temperature. After diluting with ether, some polymeric material separated and was filtered off with the aid of Super-cel. Treatment of the filtrate with hydrogen bromide yielded the crystalline hydrobromide, 16 g. (90%), m.p. 175–178°.

Two recrystallizations from 2-propanol and sublimation of the product gave material melting at 176–178° and having the characteristic nitrile absorption at 2280 cm.$^{-1}$ in the infrared.

4-(3-Aminopropoxy)-1,2,2,6,6-pentamethylpiperidine Dihydrochloride (X).—To a stirred solution of 3 g. of lithium aluminum hydride in 85 ml. of ether was added an ethereal solution of 3-(1,2,2,6,6-pentamethyl-4-piperidinyloxy)propionitrile prepared by dissolving 12 g. (0.035 mole) of the hydrobromide in water, treating with base, extracting the resulting oil with ether, and drying the ether solution over potassium carbonate. After keeping the mixture at reflux for 2 hr. it was cooled, treated cautiously with 10 *M* potassium hydroxide, and the product extracted with several portions of ether. Treatment of the dried ether solution with hydrogen chloride gave a gummy salt which was recrystallized from ethanol–ethyl acetate to give 10.3 g. of material, m.p. 253–255°. An analytical sample, m.p. 258–259° was obtained by further recrystallization from methanol–ethyl acetate.

4-(3-Dimethylaminopropoxy)-1,2,2,6,6-pentamethylpiperidine Dihydrochloride (XI).—4-(3-Aminopropoxy)-1,2,2,6,6-pentamethylpiperidine dihydrochloride (10.3 g., 0.0395 mole), sodium formate (4.7 g., 0.079 mole), 37% aqueous formaldehyde (27 ml., *ca.* 0.395 mole), and 47.5 g. (1.03 mole) of formic acid were maintained at steam bath temperature for 1 week. The cooled solution was diluted with water, extracted several times with ether, and the extract discarded. The solution was then made strongly basic with potassium hydroxide and extracted four times with ether. The combined extract was dried over potassium carbonate, filtered, and the filtrate treated with gaseous hydrogen chloride giving 10.0 g. (77%) of white crystalline dihydrochloride, m.p. 248–251°. Three crystallizations from 2-propanol gave analytically pure material, m.p. 252–253°.

4,4′-Bis(2,2,6,6-tetramethyl-4-piperidinol) (XIIa).—In a 250-ml. round-bottomed flask fitted with a 2 × 24-cm. column packed with glass helices and mechanical stirrer were placed 27.6 g. (0.178 mole) of crude anhydrous triacetonamine and 100 ml. of benzene. About 70 ml. of benzene was distilled in order to dry the reaction mixture. Mercuric chloride (1.5 g.) was then added followed by 3.3 g. of freshly scratched aluminum foil (Alcoa Wrap). After 1 hr. of stirring at reflux temperature, no apparent reaction had taken place. Some strips of aluminum foil pre-amalgamated in alcoholic mercuric chloride were then added followed by some small crystals of iodine. After several minutes the mixture appeared to thicken and after 3 hr. had become greenish gray, most of the aluminum appearing to have reacted. On adding 50 ml. of 10 *M* potassium hydroxide, two liquid layers were formed. The upper layer contained some white crystalline material. The lower layer was discarded and the upper layer filtered. The solid thus obtained melted at 169–174° and, unlike 2,2,6,6-tetramethyl-4-piperidinol, was insoluble in ethyl acetate. It was dissolved in dilute acetic acid, filtered, and precipitated with aqueous potassium hydroxide. The product, collected and washed with cold aqueous ammonia, weighed 5.57 g., m.p. 176–180°.

Recrystallization from toluene gave 3.58 g. of small crystals, m.p. 176–179°. Working up the filtrates gave additional material which after recrystallization from petroleum ether (b.p. 90–97°) melted at 177–179° and weighed 2.7 g. The yield was thus 6.28 g. or 22.7%.

The analytical sample was prepared by recrystallization from petroleum ether and melted at 176–178°.

Attempts to repeat this preparation gave yields which varied from zero to 8%.

When benzene–ethanol was used as the reaction solvent, the only product which could be isolated was 2,2,6,6-tetramethyl-4-piperidinol. With amalgamated magnesium in benzene, no product could be isolated. With calcium in liquid ammonia the only product which could be isolated was 2,2,6,6-tetramethyl-4-piperidinol in 20% yield.

4,4′-Bis(1,2,2,6,6-pentamethyl-4-hydroxypiperidine) (XIIb).—The above pinacol (1.0 g., 0.0032 mole), 2 ml. of 37% formalin, and just enough formic acid (a few drops) to make the mixture slightly acid were heated together in a test tube for about 9 hr. on the steam bath. Formic acid was added periodically to keep the mixture nearly neutral. The reaction mixture was then made strongly basic with 10 *M* potassium hydroxide the product separating as white crystals. The semisolid mass was dispersed in about 80 ml. of water, filtered, and washed with water. When dry it weighed 0.8 g. (74%), m.p. 140–149°. This was dissolved in 10 ml. of methanol, filtered, and the filtrate diluted with about 15 ml. of water. The crystals which separated weighed 0.7 g. (64.5%), m.p. 146–148°.

Some of this material was sublimed for analysis at 0.05 mm., bath temperature 110–150°. The product melted at 149–150°.

4-Ethynyl-2,2,6,6-tetramethyl-4-piperidinol (XIII).—In a 2-l. three-necked round-bottomed flask fitted with Hershberg stirrer, Dry Ice condenser protected by a tube filled with sodium hydroxide, and a gas inlet tube was condensed *ca.* 800 ml. of liquid ammonia distilled from sodium. Sodium metal (13.8 g., 0.06 g.-atom) was then added in small pieces and a current of acetylene passed in until the blue color was discharged and for an additional hour thereafter. Crude anhydrous triacetonamine (35.5 g., 0.225 mole) was then added and the stream of acetylene continued for an additional 5.5 hr. The ammonia was then permitted to evaporate, a warm water bath being used near the end. A current of dry nitrogen was then passed through the vessel. The walls of the flask were rinsed with ethanol followed by the addition of 100 ml. of water. The suspended solid was then filtered and washed. The crude wet solid was dissolved in dilute acetic acid, treated with decolorizing charcoal (Darco), and precipitated with dilute potassium hydroxide. The solid was washed and dried affording 21.6 g. (54%) of white powder m.p. 213–214°.

An analytical sample, m.p. 214–216°, was obtained by sublimation at 0.15 mm.

1,4-Bis(2,2,6,6-tetramethyl-4-hydroxy-4-piperidyl)butadiyne (XIV).—In a 500-ml. three-necked flask fitted with a mechanical stirrer were placed 20.15 g. (0.112 mole) of 4-ethynyl-2,2,6,6-tetramethyl-4-piperidinol, 45 g. of ammonium chloride, 28 g. of cuprous chloride, 22.5 ml. of 6 *N*

hydrochloric acid, 112 ml. of water, and sufficient ammonium hydroxide to bring the pH to *ca.* 5.5. Oxygen was bubbled through the stirred suspension of solids by means of a sintered glass tube for 1.5 hr. The mixture was made strongly basic with ammonium hydroxide and the product filtered. The crude material weighed 18.3 g. (92%), m.p. 226–230°.

An analytical sample was prepared by dissolving the crude product in aqueous acetic acid, decolorizing with charcoal, and precipitating with ammonia. It melted at 246–248° and exhibited OH absorption in the infrared at 3550 cm.$^{-1}$ but, as expected, no acetylenic absorption. On standing the melting point changed to 231–232°.

1,4-Bis(2,2,6,6-tetramethyl-4-hydroxy-4-piperidyl)butane (XVa).—1,4-Bis(2,2,6,6-tetramethyl-4-hydroxy-4-piperidyl)butadiyne (1.84 g., 0.005 mole) was dissolved in 50 ml. of 4:1 acetic acid–water and shaken in a Parr apparatus with hydrogen in the presence of a mixture of 10% palladium-on-charcoal and 5% platinum-on-charcoal. Initial pressure was 40 p.s.i. and uptake ceased when about four moles of hydrogen had been absorbed. The catalysts were then filtered, the filtrate made basic, and the product extracted with ethyl acetate. Evaporation of the solvent gave crude material which was recrystallized from petroleum ether (b.p. 90–97°) to give 1.8 g. (97%) of white needles m.p. 128–130°.

An additional recrystallization from petroleum ether followed by sublimation of the product gave analytically pure material, m.p. 128–129°.

1,4-Bis(1,2,2,6,6-pentamethyl-4-hydroxy-4-piperidyl)-butane (XVb).—A mixture of 7.37 g. (0.02 mole) of 1,4-bis-(2,2-6,6-tetramethyl-4-hydroxy-4-piperidyl)butane, 32 ml. of 37% aqueous formaldehyde, and 15 ml. of formic acid were heated at steam bath temperature for 2 days. Treatment with 10 *M* potassium hydroxide gave a gummy solid which was triturated with boiling petroleum ether (b.p. 90–97°). This extract on cooling deposited 7.56 g. (95%) of white crystals, m.p. 120–122°.

An analytical sample, m.p. 122–123°, was obtained by recrystallizing similar material twice from ligroin and subliming the product.

1,4-Bis(1,2,2,6,6-pentamethyl-4-piperidyl)butane Dihydrochloride (XVI·HCl).—XVb (9.2 g.) was maintained at reflux for 6.5 hr. with 300 ml. of 20% sulfuric acid. Hydrogenation of the crude diene was then attempted in a Parr apparatus without isolation of the product. An initial pressure of 40 p.s.i. and a mixture of platinum-on-charcoal and palladium-on-charcoal was used. After 2 days at room temperature only 75% of the theoretical uptake of hydrogen was observed. The solution was then made basic with 10 *M* potassium hydroxide and the precipitated product collected along with a large amount of potassium sulfate. The filter cake was treated with a little dilute hydrochloric acid and the inorganic material removed by filtration. The filtrate was made basic and the product extracted into ether. Evaporation of the dried ether solution afforded 8.3 g. of a crude product m.p. 115–116°. It reacted rather rapidly with potassium permanganate in acetone indicating incomplete hydrogenation. Recrystallization from methanol raised the m.p. to 116–117°. However, a potassium permanganate test for unsaturation was positive. An additional recrystallization raised the m.p. to 118.6–119.4°. Infrared analysis indicated the absence of hydroxyl groups hence the probable impurity was assumed to be olefinic material rather than undehydrated substances.

The remaining material was then subjected to high pressure hydrogenation in 25% acetic acid at 1800–1900 p.s.i. over a mixture of platinum-on-charcoal and palladium-on-charcoal. On treatment of the filtered solution with base the product crystallized. After recrystallization from methanol, it melted at 120–121°. Treated with gaseous hydrogen chloride in ether it gave a dihydrochloride, m.p. 276–277°. After one recrystallization from ethanol–ethyl acetate and four recrystallizations from 2-propanol, 2.5 g. (25%) of product, m.p. 289–290° dec., was obtained.

1-Propargyl-2,2,6,6-tetramethylpiperidine (XVIII).—A mixture of 42.3 g. (0.3 mole) of 2,2,6,6-tetramethylpiperidine, 71.4 g. of freshly distilled propargyl bromide,[35] 12.0 g. (0.3 moles) of magnesium oxide, 60 ml. of ethanol, and 30 ml. of water was heated in a nitrogen atmosphere on the steam bath with vigorous stirring for 94 hr. The mixture was then acidified with hydrochloric acid and steam distilled until propargyl bromide could no longer be detected in the distillate. The receiver was then changed, the mixture made strongly basic with 10 *M* potassium hydroxide, and steam distillation resumed. The approximately 4.5 l. of distillate which was collected was extracted four times with ether, the total extract amounting to about 2.5 l. This was washed with saturated sodium sulfate and the ether stripped by distillation through a 2 × 25-cm. column packed with glass helices. The oily residue was fractionated at 15 mm. to give 15 g. of material boiling at 44–90° and consisting mostly of tetramethylpiperidine. A second fraction consisting of the desired product boiled at 93–95° and weighed 28.6 g. (54%) or 82.5% based on unrecovered starting material. The product crystallized on cooling and melted at 30–34°.

A sample of crude product from an earlier run was purified for analysis by regeneration from the silver salt.

Three grams of crude material was dissolved in a mixture of 15 ml. of water, 1 ml. of acetic acid, and 3 ml. of 6 *N* nitric acid. Silver nitrate (3.0 g.) was then added and the flask swirled rapidly. A thick white precipitate suddenly separated, probably a nitrate of the silver salt. Concentrated ammonium hydroxide was then added and the precipitate filtered. It weighed about 2.0 g. when dry and a small sample exploded weakly when dropped on a hot plate. The silver salt was then treated with a solution of 6 g. of potassium cyanide in 15 ml. of water. The product was extracted into ether, the extract dried over potassium carbonate, and the filtered solution treated with hydrogen chloride. A white precipitate, m.p. 207.6–208.4°, weighing 1.9 g., was obtained. Two recrystallizations from 2-propanol–acetone followed by sublimation at 85–100° (0.02 mm.) afforded an analytical sample, m.p. 212–213°. Very strong peaks characteristic of the acetylenic function were observed at 2150 cm.$^{-1}$ and 3185 cm.$^{-1}$ in the infrared.

1,6-Bis(2,2,6,6-tetramethylpiperidino)-2,4-hexadiyne (XIX).—1-Propargyl-2,2,6,6-tetramethylpiperidine (26.2 g., 0.146 mole) was dissolved in 120 ml. of a solution obtained by stirring together 15 g. of cupric acetate monohydrate, 70 ml. of dry pyridine, and 70 ml. of methanol and decanting the supernate. After standing for 3 days at room temperature, concd. ammonium hydroxide (30 ml.) and water (60 ml.) were added and the crystals collected and washed with 5:5:1 methanol–water–ammonium hydroxide. The crude product weighed 23 g. (89%), and melted at 119–120°. Analytically pure material, m.p. 120–121°, was obtained by further recrystallization of the crude product from ethanol. If the crystals were permitted to remain in contact with the solvent for an extended period of time, a polymorphic form, m.p. 115–116°, was often obtained. Treatment of an ether solution of the base with hydrogen chloride gave the dihydrochloride. Recrystallization from a mixture of 1-propanol and ethyl acetate gave analytically pure material, m.p. 228–229°.

When the coupling of XVIII was carried out with the usual cuprous chloride system, the yield of XIX was only 25%.

1,6-Bis(2,2,6,6-tetramethylpiperidino)hexane Dihydrochloride (XX·2HCl).—The diyne (1.0 g.) and 5% rhodium-on-charcoal in 50 ml. of petroleum ether were shaken for 18 hr. with hydrogen in a Parr apparatus at an initial pressure of 40 p.s.i. Uptake of hydrogen was theoretical.

The catalyst was removed by filtration and the solvent was evaporated from the filtrate leaving a white crystalline product which was slurried in methanol and filtered. The dry product weighed 0.61 g. (60%) and melted at 117–118°.

(35) Gift of Antara Chemicals Div. of General Aniline and Film Corp.

When treated with hydrogen chloride in ether, a dihydrochloride was obtained. After several recrystallizations from 1-propanol–ethyl acetate and 2-propanol–acetonitrile the product melted at 264–265°. Other catalyst-solvent combinations were inferior to the above.

1,2,2,6,6-Pentamethyl-4-aminopiperidine (XXII).—1,2,2,6,6-Pentamethyl-4-piperidone oxime (17 g., 0.092 mole) in 100 ml. of dry tetrahydrofuran was added dropwise during 20 min. to a stirred solution of 8.4 g. (0.22 mole) of lithium aluminum hydride in 150 ml. of tetrahydrofuran. After maintaining the solution at reflux for 1 hr., it was left at room temperature for 2 days. Most of the solvent was then removed by distillation and ether added to the residue. Potassium hydroxide (10 *N*, 100 ml.) was then cautiously added followed by continuous ether extraction for 24 hr. The ether was removed by distillation through a 2 × 25 cm. column packed with glass helices and the product distilled at 15 mm. The fraction boiling at 97–99° was collected and weighed 11.7 g. (75%) $n^{20}D$ = 1.4813.

4-Guanido-1,2,2,6,6-pentamethylpiperidine Dinitrate (XXI).—1-Guanyl-3,5-dimethyl-pyrazole nitrate (9.3 g., 0.046 and 4-mole) amino-1,2,2,6,6-pentamethylpiperidine (3.9 g., 0.023 mole) were fused together at a bath temperature of 110° for 3 hr. Treatment of the cooled melt with 25 ml. of boiling 2-propanol gave 3.95 g. of white crystals m.p. 211–213°. Recrystallization of this material from 75 ml. of acetonitrile gave 2.49 g. (32%) of product, m.p. 212–215° dec. In a capillary evacuated to *ca.* 0.1 mm. and sealed, the m.p. was 227–229° without apparent decomposition.

The analytical sample was prepared by recrystallizing material from an earlier run twice from ethanol. In a sealed evacuated capillary it melted at 225–226°.

1-(*o*-Bromobenzyl)-2,2,6,6-tetramethylpiperidine (XXV). *o*-Bromobenzyl chloride[36] (2.0 g., 0.01 mole) and 2,2,6,6-tetramethylpiperidine (2.82 g., 0.02 mole) were heated in a sealed tube for 42 hr. at 145°, 12 hr. at 100°, 10 hr. at 160°, 185–200° for 10 hr., and at 230° for 3 days. The crude reaction mixture was dissolved in ether and basic substances extracted into 6 *N* hydrochloric acid. The aqueous extract was then made basic with 10 *M* potassium hydroxide and the product extracted with four portions of ether. The combined extract was dried over potassium carbonate and the ether distilled. Unchanged tetramethylpiperidine was removed by distillation at 40–60° at 15 mm. The residue which remained was dissolved in ether, filtered, and treated with hydrogen chloride to give 0.8 g. (23%) of white leaflets melting at 207–210°. An analytical sample, 207–209° was prepared by an additional recrystallization from acetone–ether. Some impure hydrochloride from a different run was converted to the free base with aqueous potassium hydroxide. The resulting oily-looking crystals, m.p. 64–70°, were extremely soluble in most organic solvents. Sublimation at 0.1 mm. led to no significant purification. Loose crystals which gave a fairly satisfactory analysis were obtained by washing the crude material with methanol at −8°. The product melted at 72–77°.

***N*-(1,2,2,6,6-Pentamethyl-4-piperidinyl)-1-tosyl-5-pyrrolidone-2-carboxamide (XXIIIb).**—*N*-Tosyl-L-pyrrolid-5-one-2-carbonyl chloride[25] (3.0 g., 0.01 mole) in 10 ml. of chloroform was cooled in an ice bath and treated dropwise with 1,2,2,6,6-pentamethyl-4-aminopiperidine (1.70 g., 0.01 mole). After 40 min. at room temperature, 10 ml. of ethyl acetate was added and the mixture poured into 50 ml. of ether. The precipitated hydrochloride was collected and washed with ether and ligroin. When dry it weighed 4.6 g., m.p. 198–215°. The filtrate deposited an additional 500 mg., m.p. 201–214° dec. As no suitable solvent for purifying this salt could be found, it was dissolved in 50 ml. of water, made basic with 5% sodium bicarbonate and the product extracted into 150 ml. of ether. The solvent was then removed on the steam bath and the residue crystallized from 25 ml. of benzene. The product weighed 3.15 g. (73%) and melted at 198–203°. Two additional recrystallizations from benzene gave analytically pure material, m.p. 208,° $[\alpha]^{26.5}D$ −75.7° (*c* 1, in 1% acetic acid).

1,2,2,6,6-Pentamethyl-4-(*N*-tosyl-L-α-glutamylamino)-piperidine (XXIV).—The preceeding compound (14.6 g.) was dissolved in 50 ml. of methanol and stirred vigorously while a solution of 11.1 g. (0.065 mole) of barium hydroxide in the minimum amount of water was quickly added. A thick white precipitate separated immediately. After 10 min. at room temperature the solid was dissolved by the addition of 350 ml. of water. After an additional 15 min., carbon dioxide was bubbled through the solution until the precipitation of barium carbonate appeared to be complete. The *p*H was then adjusted to 8 with ammonium hydroxide and the barium carbonate filtered. Evaporation of the solvent on a rotating evaporator at 15 mm. gave a glassy residue which was dissolved in 220 ml. of acetone. The crystals which separated on standing overnight weighed 13.4 g. (90.5%). After recrystallization from methanol–acetone the melting point was 200–215° dec., $[\alpha]^{26.5}D$ +20.6° (*c* 1, in water). The product from a second run had the same melting point and infrared spectrum but the specific rotation was +27.0°.

NOTE ADDED IN PROOF. Triacetonamine azine (VIa) has been reported previously by R. M. Haines and W. A. Waters, *J. Chem. Soc.*, 3221 (1958).

(36) M. S. Newman, *J. Am. Chem. Soc.*, **62**, 2298 (1940).

2-Sulfobenzoic Acid Esters. I. 2-Sulfamyl Derivatives

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Improved syntheses of 2-sulfamylbenzoic acid esters and a number of substituted derivatives are described. Isomeric sulfamylbenzoates and carbamyl and sulfonyl analogs have also been prepared.

This paper describes some new general methods of synthesis of sulfamylbenzoates, and the preparation of a number of derivatives and related compounds. Our work was prompted by the discovery in these laboratories that certain compounds of this type possessed marked anticonvulsant activity.[1]

The known methyl and ethyl esters of 2-sulf-

(1) Unpublished results. We are indebted to Dr. A. Kandel and coworkers for carrying out the pharmacological examination of these compounds. The study of these compounds was prompted by the biological activity displayed by a related series of compounds (Part II of this series) kindly supplied to us by Dr. Glenn H. Hamor of the University of Southern California.