was added 2.3 g of ethyl formate and was stirred for 10 min. To the ice-cooled mixture was added a solution of 4.5 g of N-tosyl-4-keto-1,2,3,4-tetrahydroquinoline in 150 ml of C_6H_6 with stirring and allowed to stir for 18 hr at room temperature. The reaction mixture was hydrolyzed with cold H_2O. The organic layer was extracted (H_2O, dilute NaOH). Acidification of the combined aqueous portion with cold HCl gave 4.1 g (83.7%) of IV, mp 107–110° (from MeOH). *Anal.* ($C_{17}H_{15}NO_4S$) C, H, N.

A hot mixture of crude IV and MeOH, when treated with a small amount of HCl, gave **N-tosyl-3-methoxymethylene-4-keto-1,2,3,4-tetrahydroquinoline,** mp 178–178.5 (from MeOH). *Anal.* ($C_{18}H_{17}NO_4S$) C, H, N.

N-Tosyl-3-ethoxymethylene-4-keto-1,2,3,4-tetrahydroquinoline, mp 129–130.5° (from EtOH), was prepared similarly. *Anal.* ($C_{19}H_{19}NO_4S$) C, H, N.

N-Tosyl-1,2,3,4-tetrahydroquinolino[4,3-*d*]isoxazole (V).—A mixture of 3.3 g of IV, 1.6 g of powdered $HONH_2 \cdot HCl$, and 100 ml of AcOH was stirred for 8 hr at 80–85°. Most of the AcOH was removed under reduced pressure, and the residue was diluted with H_2O and extracted with C_6H_6–Et_2O. The organic layer was washed (saturated $NaHCO_3$ solution, H_2O), dried (Na_2SO_4), and concentrated to give 2.2 g (67.4%) of V, mp 175–179°. Recrystallization from EtOH gave a pure sample of mp 177–180.5°. *Anal.* ($C_{17}H_{14}N_2O_3S$) C, H, N.

N-Tosyl-3-cyano-4-keto-1,2,3,4-tetrahydroquinoline (VI).—A solution of 2.2 g of V in 30 ml of C_6H_6 was added to a cooled solution of 1 g of Na in 40 ml of MeOH. After stirring for 1.5 hr at room temperature, the mixture was treated with H_2O and extracted with 5% NaOH solution. Acidification of the combined aqueous solution with HCl gave 2.1 g (95.5%) of VI, mp 150.5–153° (from EtOH). *Anal.* ($C_{17}H_{14}N_2O_3S$) C, H, N.

N-Tosyl-3-cyano-3-methyl-4-keto-1,2,3,4-tetrahydroquinoline (VII). A. Directly from V.—To a solution of 1.0 g of K in 40 ml of *t*-BuOH was added 1.6 g of V and heated at 60–70° for 10 min. After cooling and adding 7 ml of MeI for 10 min, the reaction mixture was stirred at 60–70° for 3 hr, cooled, neutralized with AcOH, and concentrated *in vacuo*. The residue was treated with C_6H_6 and H_2O. The organic layer was washed (5% NaOH, H_2O) and dried (Na_2SO_4), and the solvent was removed. Recrystallizations from MeOH gave 1.0 g (60.0%) of VII, mp 128–129°. *Anal.* ($C_{18}H_{16}N_2O_3S$) C, H, N.

B. From VI.—To a solution of 1.0 g of K in 40 ml of *t*-BuOH was added 1.6 g of VI and heated for 10 min at 65°. After cooling, 7 ml of MeI was added during 10 min and refluxed for 3 hr, cooled, neutralized with AcOH, and evaporated nearly to dryness. The residue was treated with C_6H_6 and H_2O, washed (5% NaOH, H_2O), dried (Na_2SO_4), and concentrated to give 1.0 g (60.0%) of VII.

When the isomerization and methylation of V was carried out by using $NaOCH_3$, the yield of VII was poor.

Acknowledgment.—The authors wish to express their appreciation to Miss Teruko Nisida for advice and encouragement in this investigation.

Terpene Compounds as Drugs. IV. Terpenyl Derivatives of Local Anesthetics

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In connection with our interest in the field of terpene chemistry we have replaced the alkyl radicals of known local anesthetics, such as benzocaine, procaine, and lidocaine, with terpenyl groups, in order to seek possible changes in the pharmacological properties of the original drugs. The new substances, *i.e.*, farnesyl *p*-aminobenzoate (I), digeranylaminoethyl *p*-aminobenzoate (II), and 2-digeranylamino-2',6'-acetoxylidide (III), lacked local anesthetic activity.

Experimental Section[1]

Farnesyl *p*-Aminobenzoate (I).—A mixture of methyl *p*-aminobenzoate (9 g, 0.06 mole), farnesol (13.3 g, 0.06 mole), and NaOMe (0.5 g) was gradually heated over 8 hr to 145° under N_2. The reaction mixture was cooled to room temperature and then taken up in ether, and the ethereal extract was washed (dilute HCl, dilute NaOH, H_2O) until neutral. After drying, the ethereal solution was evaporated and the residue was distilled, giving 6.6 g of an oil, bp 206–211° (0.2 mm). The product was purified by chromatography on silica gel, using C_6H_6–Me_2CO (8:2) as eluent. I (5.4 , 26%) was obtained as a colorless oil, $n^{25}D$ 1.5512, R_f (tlc) 0.64.

Anal. Calcd for $C_{22}H_{31}NO_2$: C, 77.37; H, 9.15; N, 4.10. Found: C, 77.42; H, 9.13; N, 4.05.

Digeranylamine occurred as a by-product from the preparation of geranylamine[2] in a 10–12% yield, viscous colorless oil, bp 135–137° (0.03 mm).

Anal. Calcd for $C_{20}H_{35}N$: C, 82.97; H, 12.19; N, 4.84. Found: C, 83.04; H, 12.11; N, 4.85.

2-(Digeranylamino)ethanol.—A solution of geranyl bromide (86.8 g, 0.4 mole) in anhydrous ether (200 ml) was dropped into a solution of 2-aminoethanol (12.2 g, 0.2 mole) and triethylamine (40.5 g, 0.4 mole) in anhydrous ether (300 ml). The suspension was refluxed for 45 hr, cooled, and washed (H_2O), and the ethereal layer was dried (Na_2SO_4) and evaporated. The residue was distilled to yield a viscous colorless oil (34.6 g, 52%), bp 161–163° (0.025 mm).

Anal. Calcd for $C_{22}H_{39}NO$: C, 79.21; H, 11.78; N, 4.20. Found: C, 79.30; H, 11.75; N, 4.19.

The same product was obtained, but in lower yields, by warming at 110° for 7 hr digeranylamine, ethylene chlorohydrin, and anhydrous pyridine in equimolecular amounts.

Digeranylaminoethyl *p*-Aminobenzoate (II).—Methyl *p*-aminobenzoate (6.0 g, 0.04 mole), 2-(digeranylamino)ethanol (13.3 g, 0.04 mole), and NaOMe (0.5 g) were made to react as described in the preparation of I. The crude product obtained was purified by chromatography on silica gel using C_6H_6–Me_2CO (9:1) as eluent to give II (4.3 g, 24%) as a colorless oil, $n^{25}D$ 1.5455, R_f (tlc) 0.42.

Anal. Calcd for $C_{29}H_{44}N_2O_2$: C, 76.94; H, 9.80; N, 6.19. Found: C, 77.03; H, 9.88; N, 6.16.

2-Digeranylamino-2',6'-acetoxylidide (III).—A mixture of 2,6-(α-chloroacetoxy)xylidine (9.9 g, 0.05 mole), digeranylamine (14.5 g, 0.05 mole), and anhydrous pyridine (4 g, 0.05 mole) was warmed at 150–160° for 6 hr. After cooling, the reaction product was taken up with H_2O and ether, and the ethereal layer was washed (dilute HCl, H_2O) until neutral. After drying and evaporating, the residue was chromatographed on silica gel, using $CHCl_3$–Me_2CO (9:1) as eluent. II (6.8 g, 30%) was obtained as a colorless oil, $n^{25}D$ 1.5255, R_f (tlc) 0.70.

Anal. Calcd for $C_{30}H_{46}N_2O$: C, 79.95; H, 10.29; N, 6.22. Found: C, 80.01; H, 10.28; N, 6.23.

(1) Boiling points are uncorrected. The R_f values were determined on glass chromatostrips coated with silica gel G (Merck); the thin layer chromatograms (tlc) were developed with 85:15 C_6H_6–Me_2CO and the spots were developed with $KMnO_4$.

(2) M. S. Kharasch, W. Nudemberg, and E. K. Fields, *J. Am. Chem. Soc.*, **66**, 1276 (1944).

Mannich Bases of 4-(Methylthio)phenol and 3-Methyl-4-(methylthio)phenol

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Certain phenolic Mannich bases possess quinidine-,[1] ergonetrine-,[2] as well as oxytocin-like[3] effects. In this report, we describe the synthesis of several Mannich bases of 4-(methylthio)-phenol (I) and 3-methyl-4-(methylthio)phenol (II), the first

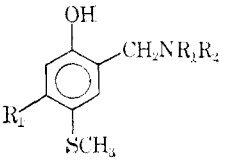
(1) Hoffmann-LaRoche and Co., Belgian Patent 549279 (1956).

(2) A. Cohen, R. A. Hall, B. Heath-Brown, W. M. Parkes, and A. H. Rees, *J. Pharmacol. Chemotherapy*, **12**, 194 (1957).

(3) W. M. Duffin, British Patent 788,196, 788,082, 788,122 (1955); *Chem. Abstr.*, **52**, 11941, 11942 (1958).

TABLE I

MANNICH BASE HYDROCHLORIDES OF 4-(METHYLTHIO)PHENOL AND 3-METHYL-4-(METHYLTHIO)PHENOL



No.	R_1	NR_1R_2	Mp, °C	Yield, %	Formula[a]	Pmr[a] aromatic protons (singlets)
1	H	Piperidino	160–161	30	$C_{13}H_{19}NOS \cdot HCl$	
2	H	Diethylamino	123–124	37	$C_{12}H_{19}NOS \cdot HCl$	
3	H	Morpholino	192–194	61	$C_{12}H_{17}NO_2S \cdot HCl$	
4	H	2-Methylpiperidino	177–178	52	$C_{14}H_{21}NOS \cdot HCl$	
5	CH_3	Diethylamino	202–203	59	$C_{13}H_{21}NOS \cdot HCl$	6.95, 7.28
6	CH_3	Pyrrolidino	178–180	42	$C_{13}H_{19}NOS \cdot HCl$	6.93, 7.29
7	CH_3	Piperidino	175–176.5	50	$C_{14}H_{21}NOS \cdot HCl$	6.92, 7.28
8	CH_3	N-Methylbenzylamino	216.5–218	53	$C_{16}H_{21}NOS \cdot HCl$	6.95, 7.35–7.85[b,c]
9	CH_3	2-Methylpiperidino	177–178	54	$C_{15}H_{23}NOS \cdot HCl$	6.97, 7.60[c]
10	CH_3	Morpholino	162–163.5	*d*	$C_{13}H_{19}NO_2S \cdot HCl$	6.95, 7.32

[a] Values are expressed in δ units. Obtained for D_2O solutions using Tier's salt as internal reference unless otherwise stated. [b] Multiplet. [c] Obtained for dimethyl sulfoxide-d_6 solutions with TMS as internal reference. [d] The free base, mp 106–107.5°, was obtained in 65% yield. *Anal.* ($C_{13}H_{19}NO_2S$) C, H, N. [e] All compounds were analyzed for C, H, N.

examples of phenolic Mannich bases incorporating the methylthio substituent. These compounds were prepared from I or II, formaldehyde, and various secondary amines. Aminomethylation of II gave the 1,2,4,5-substituted benzene derivatives as evidenced by the nmr spectra of the products which showed the aromatic proton resonances as two unsplit peaks.

Experimental Section[4]

2-Piperidinomethyl-4-(methylthio)phenol Hydrochloride.—The procedure described for the preparation of this compound is typical. For physical and analytical data see Table I. To a solution of 14.0 g (0.10 mole) of 4-(methylthio)phenol and 8.51 g (0.10 mole) of piperidine in 25 ml of 95% EtOH was added 8.11 ml of 37% aqueous formaldehyde in one portion. Some heat was evolved during the mixing. The reaction mixture was stored at room temperature for 1 week. The solvents were removed under reduced pressure on a water bath. Absolute EtOH (50 ml) was added to the residue and distilled under reduced pressure. This process was repeated two more times. The residue was dissolved in 20 ml of absolute EtOH and acidified with ethanolic HCl. Solvent and excess HCl were removed under reduced pressure, 50 ml of absolute EtOH was added and also removed under reduced pressure. The addition of alcohol and its removal under reduced pressure was repeated two more times. The residue was dissolved in 15 ml of absolute EtOH and allowed to stand until crystallization occurred. The white salt was filtered and recrystallized from absolute EtOH, yield 8.12 g (30%), mp 160–161°.

(4) Melting points were determined using a Fisher-Johns melting point apparatus and are uncorrected. Elemental analyses were performed by Dr. Kurt Eder, Geneva, Switzerland. Nmr spectra were determined with a Varian Model A-60A nmr spectrometer. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

Book Reviews

Les Concepts de Claude Bernard sur le Milieu Intérieur. Masson and Cie., Éditeurs, Libraires de L'Académie de Médecine, Paris VI^e^. 1967. 423 pp. 17 × 25 cm. 65 Francs.

Philosophie et Méthodologie Scientifiques de Claude Bernard. Masson and Cie., Éditeurs, Libraries de L'Académie de Médecine, Paris VI^e^. 1967. 170 pp. 17 × 25 cm. 30 Francs.

These two volumes contain the papers given at an International Symposium organized to celebrate the one-hundredth anniversary of the publication of the "Introduction to the Study of Experimental Medicine" by Claude Bernard. The first volume contains papers by numerous authors in the fields of osmoregulation, regulation of the blood pressure, and temperature regulation. These are three subjects discussed by Claude Bernard in his formulation of the maintenance of the internal environment. The papers illustrate that the work of Claude Bernard is continued in present physiological experimentation. The second book contains numerous papers by various authors. These papers are concerned with the actual work of Claude Bernard and its influence. The two volumes are valuable for illustrating the development and present use of the doctrine of the stability of the internal environment.

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