Deamination of Ethyl 1-Hydroxy-6-aminobenzo(f)quinoline-2-carboxylate.—A solution of 1.0 g. of V in 5 cc. of acetic acid was saturated with hydrogen chloride, cooled to 0°, stirred and 0.5 g. of isoamyl nitrite was added. After the mixture had been stirred for 10 minutes, it was poured into a stirred suspension of 5.0 g. of cuprous oxide in 25 cc. of ethanol. The mixture was heated at 70° for 15 minutes; during this time nitrogen was evolved. The hot mixture was filtered, the solvents were removed and the residue, ethyl 1-hydroxybenzo(f)quinoline-2-carboxylate, was recrystallized from ethanol; m.p. 271–272°, mixed m.p. with an authentic sample[9] 270–271°.

2-(1-Hydroxy)-propylamide of 1-Hydroxy-6-aminobenzo-(f)quinoline-2-carboxylic Acid Hydrochloride (VI).—The ethyl ester (V, 1.5 g.) and 15 cc. of 2-aminopropanol were heated in a flask, fitted with an air condenser, for 4 hours. The ethanol, which formed during the reaction, was allowed to escape through the condenser. The excess amino alcohol was removed by distillation under reduced pressure. The gummy residue was dissolved in absolute ethanol and the solution was treated with hydrogen chloride. After recrystallization from methanol, the hydrochloride melted at 220–222°, yield 1.0 g. (60%).

Anal. Calcd. for $C_{17}H_{18}O_3N_3Cl$: N, 12.08; Cl, 10.20. Found: N, 11.97; Cl, 10.24.

6-Nitro-1-naphthylamine.—This amine was obtained by partial reduction of 1,6-dinitronaphthalene[11,12] and also by the following process. 6-Nitro-1-naphthoic acid[14] (7.0 g.) was dissolved in 50 cc. of concd. sulfuric acid, 50 cc. of chloroform was added and the mixture was treated with 2.5 g. of sodium azide in the manner described above. The amine was recrystallized from ethanol; m.p. 168–170°,[19] yield 4.0 g. (66%).

6-Nitro-1-acetylaminonaphthalene.—A mixture of 4.0 g. of 6-nitro-1-naphthylamine, 40 cc. of acetic acid and 3.2 g. of acetic anhydride was heated for 15 minutes on a steam-bath. The acetyl derivative precipitated when the mixture was cooled in an ice-bath; m.p. 236–238°,[20] yield 4.0 g. (83%).

6-Amino-1-acetylaminonaphthalene (VII).—This compound was prepared in the same manner as 3-amino-1-acetylaminonaphthalene from 4.0 g. of 6-nitro-1-acetylaminonaphthalene, 19.2 g. of stannous chloride dihydrate, 40 cc. of acetic acid and hydrogen chloride. The amine melted at 146–147° after recrystallization from ethanol; yield 2.1 g. (62%).

Anal. Calcd. for $C_{12}H_{12}ON_2$: N, 14.00. Found: N, 13.85.

(19) Reference 13, m.p. 167°.
(20) Reference 13, m.p. 232–233°.

Diethyl 1-Acetylamino-6-naphthylaminomethylenemalonate (VIII).—Two grams of 6-amino-1-acetylaminonaphthalene was heated, in an open flask, to 130° in an oil-bath and 2.2 g. of diethyl ethoxymethylenemalonate[7] was added. The mixture solidified after it had been heated for 10 minutes. The product melted at 188–190° after it had been recrystallized from ethanol; yield 2.2 g. (60%).

Anal. Calcd. for $C_{20}H_{22}O_5N_2$: N, 7.57. Found: N, 7.66.

Ethyl 1-Hydroxy-7-acetylaminobenzo(f)quinoline-2-carboxylate (IX).—A mixture of 2.2 g. of *pure* diethyl 1-acetylamino-6-naphthylaminomethylenemalonate and 10 cc. of diphenyl ether was boiled for 15 minutes. The mixture was cooled and the precipitated product was boiled with acetone in order to purify it; m.p. 280–282°; yield 1.8 g. (93%). The ester was found to be insoluble in all of the common organic solvents.

Anal. Calcd. for $C_{18}H_{16}O_4N_2$: N, 8.64. Found: N, 8.47.

Ethyl 1-Hydroxy-7-aminobenzo(f)quinoline-2-carboxylate (X).—A mixture of 2.0 g. of IX and 15 cc. of concd. hydrochloric acid was stirred and heated at 50°. After all of the material had dissolved, the mixture was heated for 15 minutes longer, diluted with 30 cc. of water and the free amine was precipitated by the addition of solid sodium carbonate. In order to purify the amine, it was dissolved in 10% hydrochloric acid, the solution was filtered and the product was precipitated with sodium carbonate; m.p. 234–236°, yield 1.1 g. (64%).

Anal. Calcd. for $C_{16}H_{14}O_3N_2$: N, 9.93. Found: N, 9.68.

Deamination of Ethyl 1-Hydroxy-7-aminobenzo(f)quinoline-2-carboxylate.—This process was carried out in the manner already described with 1.0 g. of ethyl 1-hydroxy-7-aminobenzo(f)quinoline-2-carboxylate. There was obtained 0.2 g. (20%) of ethyl 1-hydroxybenzo(f)quinoline-2-carboxylate after the material had been recrystallized from ethanol; m.p. 271–272°, mixed m.p. with an authentic sample[9] 270–271°.

2-(1-Hydroxy)-propylamide of 1-Hydroxy-7-aminobenzo-(f)quinoline-2-carboxylic Acid Hydrochloride.—A mixture of 2.0 g. of the ethyl ester and 15 cc. of 2-aminopropanol was treated in the manner described above. Since the hydrochloride could not be recrystallized, it was extracted thoroughly with boiling ethanol; m.p. 225–227° dec., yield 1.4 g. (58%).

Anal. Calcd. for $C_{17}H_{18}O_3N_3Cl$: N, 12.08; Cl, 10.20. Found: N, 12.10; Cl, 10.37.

Ann Arbor, Michigan

Diuretics. α,α-Disubstituted 2-Piperidine-ethanols and 3,3-Disubstituted Octahydropyrid[1,2-c]oxazines

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Received December 5, 1953

A series of α,α-disubstituted 2-pyridine-ethanols were prepared and hydrogenated to yield the corresponding 2-piperidine-ethanols, which upon reaction with formaldehyde gave octahydropyrid[1,2-c]oxazines. The latter were reduced with aqueous formic acid to give α,α-disubstituted-1-alkyl-2-piperidine-ethanols. A number of the octahydropyridoxazines and piperidine-ethanols had diuretic and antifungal properties.

This investigation of α,α-disubstituted-2-piperidine-ethanols, their N-alkyl and oxazine derivatives was carried out with the purpose of developing new therapeutic agents. In most cases these products were prepared from α,α-disubstituted-2-pyridine-ethanols. Such pyridine-ethanols have been synthesized from α-picoline and ketones in the presence of phenyllithium[1-5] or sodamide.[6,7]

(1) V. Prelog, L. Frankiel and S. Szpilfogel, *Helv. Chim. Acta*, **29**, 484 (1946).

Various monosubstituted piperidine-ethanols,[8-10]

(2) A. J. Nunn and K. Schofield, *J. Chem. Soc.*, 589 (1952).
(3) J. F. Arens, D. A. van Dorp and G. M. van Dijk, *Rec. trav. chim.*, **69**, 287 (1950).
(4) D. W. Adamson, British Patent 689,234 (1953).
(5) D. A. van Dorp and J. F. Arens, U. S. Patent 2,475,729 (1949).
(6) A. E. Chichibabin, *Rec. trav. chim.*, **57**, 582 (1938).
(7) A. J. Nunn and K. Schofield, *J. Chem. Soc.*, 716 (1953).
(8) D. R. Howton and D. R. V. Golding, *J. Org. Chem.*, **15**, 1 (1950).
(9) K. Hess and A. Eichel, *Ber.*, **50**, 1407 (1917).
(10) G. Schuring and L. Winterhalder, U. S. Patent 1,980,038 (1934).

one disubstituted piperidine-ethanol[1] and two octahydropyrid[1,2-c]oxazines[9,11] have been previously reported.

The preferred method of synthesis is represented by the diagram
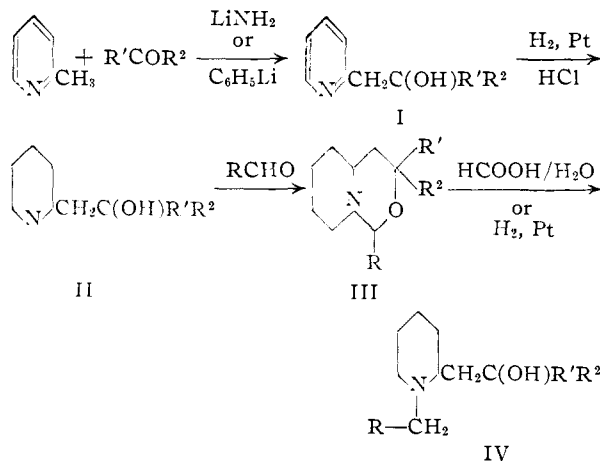
The quaternization of the pyridine-ethanols (I) with alkyl bromides followed by catalytic hydrogenation also was used to prepare certain type IV compounds, but this method was less successful when R' and R[2] were both aryl. In such cases the yield of quaternary salt often was low and purification difficult.

It also was possible to prepare type IV compounds (R = H) directly from type II by a modification of the Eschweiler-Clarke methylation procedure. This procedure, if carried out under the usual conditions, suffered from a tendency to give mixtures of types III and IV. This tendency is illustrated by initial experiments in which II (R' and R[2] = phenyl) gave a mixture of about equal amounts of the octahydropyridoxazine (III) and the 1-methylpiperidine-ethanol (IV). The identification and proof of structure of the two compounds isolated from the mixture is described in the Experimental part. However, if the methylation procedure was carried out in a formaldehyde-formic acid mixture containing more than five times the usual amount of water, type II compounds were converted directly to type IV (R = H) in good yields.[12] Compounds of type III (R = H) are not precluded as transitory products in this modified Eschweiler-Clarke procedure.

For the preparation of the pyridine-ethanols (I) from α-picoline and diaryl ketones, lithium amide was a good condensing agent; with fused ring ketones such as fluorenone, acenaphthenone and xanthone, and with aralkyl, arylcycloalkyl and dialkyl ketones phenyl lithium gave better yields. For the condensation of γ-picoline with benzophenone, lithium amide was used successfully; sodamide[7] was required for a similar condensation with β-picoline.

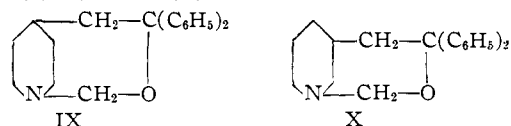(11) L. H. Goodson and H. Christopher, This Journal, 72, 358 (1950).

(12) In the standard procedure (H. T. Clarke, H. B. Gillespie and S. Z. Weisshaus, ibid., 55, 4571 (1933)), the molar equivalents of amine, formaldehyde, formic acid and water are 1.0, 2.2, 5.0 and 8.0, while in our modified procedure, the molar equivalents of reactants were 1.0, 1.6, 2.0 and 42.0.

Some of the 1-methyl-2-piperidine-ethanols (Table I, compounds 3C-6C and 18C-20C) of type IV were prepared by the reaction of 1-methyl-2-phenacylpiperidine[8] (V) with Grignard reagents or organolithium compounds. One piperidine-ethanol (Table I, compound 25C) was prepared by the reaction of p-chlorophenylmagnesium bromide with methyl 1-methyl-2-piperidineacetate (VI).

It is interesting that cyclohexylmagnesium bromide in excess failed to react with V, and with VI gave cyclohexyl 1-methyl-2-piperidylmethyl ketone (VII) instead of the expected α,α-dicyclohexyl-1-methyl-2-piperidine-ethanol. The structure of VII was proven by independent synthesis; cyclohexyl 2-pyridylmethyl ketone, obtained from the condensation of α-picoline with ethyl cyclohexanecarboxylate, was converted to the methobromide, which was hydrogenated to give the ketone VII. Similarly, phenylmagnesium bromide failed to react with VII. The α-phenyl-α-cyclohexyl- and α,α-dicyclohexyl-1-methyl-2-piperidine-ethanols sought by these reactions were finally prepared by hydrogenation of the analogous pyridine-ethanol methobromides.

An attempt to prepare α,β-diphenyl-1-methyl-2-piperidine-ethanol (VIII) by hydrogenation of α-phenyl-2-phenacylpyridine methobromide was unsuccessful. Hydrogenolysis occurred giving 1-methylpiperidine and desoxybenzoin. The desired ethanol VIII was obtained finally by the hydrogenation of α-phenyl-2-phenacylpyridine to the piperidine-ethanol followed by N-methylation.

Attempts to prepare 3-(1-phenylcyclohexyl) and 3,3-di-t-butyloctahydropyrid[1,2-c]oxazines from the piperidine-ethanols were unsuccessful. Steric factors may be responsible for this failure. The interesting γ-piperidine derivative IX was easily prepared, but the β-isomer X was not obtained from the appropriate 3-piperidine-ethanol. Fisher-Tay-

lor-Hirschfelder models were successfully made for all four of these compounds.

Pharmacological and Microbiological Activity.— These compounds are generally characterized by diuretic and antifungal activity. Some of the members have appreciable activity of both types. Diuresis following oral administration was determined in rats. The most potent diuretics are the 1-alkyl-2-piperidine-ethanols and the octahydropyridoxazines containing two substituents of the aryl or cycloalkyl type, α,α-Diphenyl-1-methyl-2-piperidine-ethanol and 3-phenyl-3-cyclohexyl-octahydropyrid[1,2-c]oxazine are typical. At a 15-20 mg./kg. dose level these compounds appear to be as effective as formoguanamine.[13]

Antifungal activity was determined using an agar plate technique with paper discs impregnated with the test substance. Inhibition zones indicated the antifungal activity against C, albicans, C. neoformans, N, asteroides, M. audouini, T.

(13) W. L. Lipschitz and Z. Hadidian, J. Pharmacol. Exptl. Therap., 81, 84 (1944).

Table I

Substituted Piperidine-ethanols and Octahydropyridoxazines

A. (piperidine)—CH₂—CR′R²—OH   B. (octahydropyridoxazine with R′, R², O)   C. (N-CH₃ piperidine)—CH₂—CR′R²—OH

No.	R′	R²	Method	M.p., °C. cor.ᵃ	Yield,ᵇ %	Formula of base	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1A	Phenyl	Phenyl		190–192		C₁₉H₂₃ON^d	81.10	81.27	8.24	8.22
1A	Phenyl	Phenyl	F	202–203	85	C₁₉H₂₃ON	71.80	71.73	7.61	7.63
1B	Phenyl	Phenyl		77–79		C₂₀H₂₃ON^d	81.87	81.99	7.90	7.97
1B	Phenyl	Phenyl	H	224–226	75	C₂₀H₂₃ON	72.82	73.13	7.33	7.48
1C	Phenyl	Phenyl		121–123		C₂₀H₂₅ON^d	81.31	81.25	8.53	8.81
1C	Phenyl	Phenyl	Iᵉ	239–240	50	C₂₀H₂₅ON	72.40	72.25	7.90	7.85
2A	Phenyl	p-Tolyl		165–166ᶠ		C₂₀H₂₅ON^d	81.31	81.41	8.53	8.29
2A	Phenyl	p-Tolyl	F	213–215ᶠ	80	C₂₀H₂₅ON	72.40	72.09	7.90	8.10
2B	Phenyl	p-Tolyl	H	140–141	61	C₂₁H₂₅ON	73.35	73.58	7.62	8.10
2C	Phenyl	p-Tolyl		96–97		C₂₁H₂₇ON^d	81.50	81.83	8.80	8.86
2C	Phenyl	p-Tolyl	P	205–207	55	C₂₁H₂₇ON	72.95	73.00	8.16	8.47
3A	Phenyl	p-Phenetyl	F	133–135ᵍ	30	C₂₁H₂₇O₂N	69.71	69.37	7.80	7.68
3B	Phenyl	p-Phenetyl	H	210–212	55	C₂₂H₂₇O₂N	70.67	70.82	7.55	7.65
3C	Phenyl	p-Phenetyl	I	173–174	20	C₂₂H₂₉O₂N	70.30	70.41	8.05	8.24
4A	Phenyl	p-Chlorophenyl	F	235–236	48	C₁₉H₂₂ONCl	64.79	64.78	6.58	6.68
4B	Phenyl	p-Chlorophenyl	H	232–234	39	C₂₀H₂₂ONCl	65.93	66.17	6.36	6.32
4C	Phenyl	p-Chlorophenyl	I	163–165	28	C₂₀H₂₄ONCl	65.57	65.49	6.88	6.93
5C	Phenyl	m-Chlorophenyl	I	185–188	22	C₂₀H₂₄ONCl	65.57	65.77	6.88	7.30
6C	Phenyl	Benzyl	I	230–231	47	C₂₁H₂₇ON	72.95	72.58	8.16	8.17
7A	Phenyl	Bicyclo-	h	241–242	58	C₂₀H₂₉ON	71.51	71.49	9.00	9.17
7B	Phenyl	[2·2·1]-	H	210–212	71	C₂₁H₂₉ON	72.51	72.90	8.69	8.52
7C	Phenyl	2-heptyl	P	237–239	62	C₂₁H₃₁ON	72.10	71.91	9.22	9.18
8A	Phenyl	Cycloheptyl		84–86		C₂₀H₃₁ON^d	79.68	79.61	10.38	10.35
8A	Phenyl	Cycloheptyl	F	190–193	90	C₂₀H₃₁ON	71.08	71.47	9.54	9.47
8B	Phenyl	Cycloheptyl	H	270–272	75	C₂₁H₃₁ON	72.10	72.53	9.22	9.39
9A	Phenyl	4-Methyl-	F	208–210	42	C₂₀H₃₁ON	71.08	70.70	9.54	9.45
9B	Phenyl	cyclo-	H	273–275	53	C₂₁H₃₁ON	72.10	72.12	9.22	9.27
9C	Phenyl	hexyl	P	166–168	60	C₂₁H₃₃ON	71.69	71.73	9.74	9.67
10A	Phenyl	Cyclohexyl		130–132		C₁₉H₂₉ON^d	79.40	79.57	10.17	10.12
10A	Phenyl	Cyclohexyl	F	206–208	96	C₁₉H₂₉ON	70.46	70.33	9.34	9.30
10B	Phenyl	Cyclohexyl	H	268–269	93	C₂₀H₂₉ON	71.51	71.68	9.00	9.27
10C	Phenyl	Cyclohexyl	P	191–193	77	C₂₀H₃₁ON	71.08	71.16	9.54	9.16
10C	Phenyl	Cyclohexyl	M	150–155	60	C₂₀H₃₁ON^i	62.82	62.83	8.44	8.44
11A	Phenyl	1-Methyl-3-	F	241–243ᶠ	86	C₂₂H₃₅ON	72.21	72.19	9.91	9.69
11B	Phenyl	isopropyl-	H	191–193ᶠ	98	C₂₃H₃₅ON	73.11	73.03	9.61	9.66
11C	Phenyl	cyclopentyl	N	188–190ᶠ	52	C₂₃H₃₇ON	72.73	72.28	10.09	9.90
12A	Phenyl	Cyclopentyl	F	183–185	77	C₁₈H₂₇ON	69.78	70.06	9.11	9.03
12B	Phenyl	Cyclopentyl	H	238–240	67	C₁₉H₂₇ON	70.91	70.65	8.77	9.03
12C	Phenyl	Cyclopentyl	P	142–144	65	C₁₉H₂₉ON	70.46	70.28	9.34	9.51
13A	Phenyl	Undecyl	F	134–136	89	C₂₄H₄₁ON	72.80	72.08	10.69	10.80
13B	Phenyl	Undecyl	H	212–213	79	C₂₅H₄₁ON	73.58	73.19	10.38	10.33
13C	Phenyl	Undecyl	P	82–84ⁱ	73	C₂₅H₄₃ON	73.23	73.00	10.82	10.97
14A	Phenyl	Octyl	F	151–153	68	C₂₁H₃₅ON	71.25	71.19	10.25	10.36
14B	Phenyl	Octyl	H	226–228	92	C₂₂H₃₅ON	72.21	71.96	9.91	9.86
14C	Phenyl	Octyl	P	91–93	59	C₂₂H₃₇ON	71.81	71.81	10.41	10.50
15A	Phenyl	Hexyl	F	167–168	74	C₁₉H₃₁ON	70.02	70.02	9.90	10.16
15B	Phenyl	Hexyl	H	235–236	94	C₂₀H₃₁ON	71.08	70.96	9.54	9.37
15C	Phenyl	Hexyl	P	110–112	82	C₂₀H₃₃ON	70.65	70.51	10.08	10.04
16A	Phenyl	Pentyl	F	164–166	72	C₁₈H₂₉ON	69.31	69.21	9.70	9.81
16B	Phenyl	Pentyl	H	244–246	66	C₁₉H₂₉ON	70.46	70.73	9.34	9.40
16C	Phenyl	Pentyl	P	145–147	50	C₁₉H₃₁ON	70.02	69.92	9.90	9.96
17A	Phenyl	i-Propyl	F	215–216	53	C₁₆H₂₃ON	67.70	67.85	9.23	9.16
17B	Phenyl	i-Propyl	H	273–274	97	C₁₇H₂₅ON	69.01	68.93	8.86	8.81
17C	Phenyl	i-Propyl	P	181–183	48	C₁₇H₂₇ON	68.54	68.00	9.47	9.39
18A	Phenyl	2-Thienyl	k	163–165	25	C₁₇H₂₁ONS^{b,d}	71.02	71.35	7.37	7.51
18C	Phenyl	2-Thienyl	J	100–101		C₁₈H₂₃ONS^{m,d}	71.72	71.88	7.69	7.80

TABLE I (Continued)

No.	R'	R	Method	M.p. °C. cor.[a]	Yield,[b] %	Formula of base	Hydrochloride[c] Analyses, %			
							Carbon Calcd.	Found	Hydrogen Calcd.	Found
18C	Phenyl	2-Thienyl	J	160–162	32	$C_{18}H_{23}ONS$	63.97	63.88	7.16	7.37
19C	Phenyl	2-Furyl	I	238–240	10	$C_{18}H_{23}O_2N$	67.18	67.82	7.51	7.69
20A	Phenyl	2-Pyridyl	k	181–183	45	$C_{18}H_{22}ON_2{}^d$	76.56	76.43	7.86	7.74
20B	Phenyl	2-Pyridyl	H	149–150	61	$C_{19}H_{22}ON_2{}^d$	77.51	77.63	7.54	7.79
20C	Phenyl	2-Pyridyl	J	104–106	50	$C_{19}H_{24}ON_2{}^d$	77.05	77.11	8.17	8.05
21C	Phenyl	2-Piperidyl	n	191–193	70	$C_{19}H_{30}ON_2$	67.33	67.49	9.22	9.24
22A	p-Tolyl	p-Tolyl	F	209–210	87	$C_{21}H_{27}ON$	72.95	73.21	8.16	8.29
22B	p-Tolyl	p-Tolyl	H	236–238	87	$C_{22}H_{27}ON$	73.82	73.89	7.88	8.07
22C	p-Tolyl	p-Tolyl	P	214–216	91	$C_{22}H_{29}ON$	73.41	73.14	8.40	8.48
23A	p-Anisyl	p-Anisyl	F	177–179°	75	$C_{21}H_{27}O_3N$	66.74	66.28	7.52	7.86
23B	p-Anisyl	p-Anisyl	H	218–220	63	$C_{22}H_{27}O_3N$	67.77	67.20	7.24	7.38
23C	p-Anisyl	p-Anisyl	M	202–204	50	$C_{22}H_{29}O_3N^i$	60.53	60.47	6.93	7.06
24A	p-Anisyl	m-Bromophenyl	F	134–137	38	$C_{20}H_{24}O_2NBr$	56.29[p]	58.04	5.91	6.06
24B	p-Anisyl	m-Bromophenyl	H	135–138	60	$C_{21}H_{24}O_2NBr$	57.48	57.27	5.74	5.76
25C	p-Chlorophenyl	p-Chlorophenyl	L	190–193	19	$C_{20}H_{23}ONCl_2$	59.93	59.97	6.04	6.24
26A	Cyclohexyl	Cyclohexyl	F	260–262	70	$C_{19}H_{35}ON$	69.17	69.59	11.00	11.13
26B	Cyclohexyl	Cyclohexyl	H	272–273	95	$C_{20}H_{35}ON$	70.25	70.33	10.61	10.64
26C	Cyclohexyl	Cyclohexyl	M	180–183	63	$C_{20}H_{37}ON^i$	61.84	62.01	9.86	10.10
27A	Cyclohexyl	Hexyl	F	132–134[f]	91	$C_{19}H_{37}ON$	68.75	68.79	11.54	11.37
27B	Cyclohexyl	Hexyl	H	250–251	49	$C_{20}H_{37}ON$	69.82	69.68	11.14	11.01
27C	Cyclohexyl	Hexyl	P	121–124	33	$C_{20}H_{39}ON$	69.45	70.04	11.65	11.53
28A	Cyclohexyl	H	F	218–219	44	$C_{13}H_{25}ON$	63.01	62.70	10.58	10.50
28B	Cyclohexyl	H	H	173–175	65	$C_{14}H_{25}ON$	64.72	64.12	10.09	10.44
28C	Cyclohexyl	H	P	147–149	73	$C_{14}H_{27}ON$	64.23	64.23	10.77	11.05
29A	Octyl	Ethyl	F	159–160	10	$C_{17}H_{35}ON$	66.74	66.70	11.86	12.02
29B	Octyl	Ethyl	H	190–192	80	$C_{18}H_{35}ON$	68.00	67.87	11.42	11.63
29C	Octyl	Ethyl	P	117–119	67	$C_{18}H_{37}ON$	67.57	67.26	11.99	11.69
30A	Heptyl	Heptyl	F	57–58	54	$C_{21}H_{43}ON$	69.68	70.00	12.25	12.06
30B	Heptyl	Heptyl	H	206–207	81	$C_{22}H_{43}ON$	70.65	70.24	11.86	11.81
30C	Heptyl	Heptyl	P	59–60[q]	58	$C_{22}H_{45}ON$	70.27	69.67	12.33	12.19
31A	Hexyl	Hexyl	F	76–77	43	$C_{19}H_{39}ON$	68.33	68.48	12.07	11.91
31B	Hexyl	Hexyl	H	229–230	76	$C_{20}H_{39}ON$	69.43	69.71	11.65	11.88
31C	Hexyl	Hexyl	O	83–85[i]	72	$C_{20}H_{41}ON$	69.02	68.44	12.17	12.15
32A	i-Butyl	i-Butyl	F	156–158	91	$C_{15}H_{31}ON$	64.81	64.83	11.61	11.73
32B	i-Butyl	i-Butyl	H	244–245	96	$C_{16}H_{31}ON$	66.29	66.22	11.12	11.14
32C	i-Butyl	i-Butyl	P	103–105	43	$C_{16}H_{33}ON$	65.85	65.75	11.74	11.74
33A	t-Butyl	t-Butyl	F	247–249[r]	98	$C_{15}H_{31}ON$	64.81	64.59	11.61	11.52
33C	t-Butyl	t-Butyl	O	245–246[r]	50	$C_{16}H_{33}ON$	65.85	65.09	11.74	11.44

R'R²C<

No.	R'	R	Method	M.p. °C. cor.[a]	Yield,[b] %	Formula of base	Carbon Calcd.	Found	Hydrogen Calcd.	Found
34A	1-Indanylidene		F	224–225	48	$C_{15}H_{21}ON$	67.26	67.27	8.28	8.49
34B	1-Indanylidene		H	290–292	86	$C_{16}H_{21}ON$	68.68	68.60	7.93	8.06
35A	9-Fluorenylidene		F	250–252	73	$C_{19}H_{21}ON$	72.26	72.03	7.02	6.95
35B	9-Fluorenylidene		H	242–244	98	$C_{20}H_{21}ON$	73.29	73.28	6.77	6.91
35C	9-Fluorenylidene		P	115–116		$C_{20}H_{23}ON^d$	81.87	81.52	7.90	7.94
35C	9-Fluorenylidene		P	213–214	50	$C_{20}H_{23}ON$	72.81	72.45	7.33	7.41
36A	1-Acenaphthenylidene		F	197–198	74	$C_{18}H_{21}ON$	71.16	70.81	7.30	7.56
36B	1-Acenaphthenylidene		H	230–232	83	$C_{19}H_{21}ON$	72.26	71.95	7.02	7.16
37A	9-Xanthylidene[p]		F	193–195	60	$C_{19}H_{21}O_2N$	68.78	69.32	6.69	7.07
38A	2-Cyclohexyl-		F	249–250	57	$C_{18}H_{33}ON$	68.43	68.74	10.84	10.87
38B	cyclohexyl-		H	281–282	80	$C_{19}H_{33}ON$	69.59	69.71	10.45	10.62
38C	idene		P	248–250	77	$C_{19}H_{35}ON^s$	65.57	65.21	11.00	11.03
39A	2-p-Anisyl-		F	223–224	77	$C_{19}H_{29}O_2N$	67.12	67.19	8.89	8.83
39B	cyclohexyl-		H	235–236	24	$C_{20}H_{29}O_2N$	68.25	68.15	8.59	8.47
39C	idene		P	215–216	50	$C_{20}H_{31}O_2N$	67.88	67.57	9.12	8.95
40A	d-Bornylidene		F	302–303	85	$C_{16}H_{29}ON$	66.76	66.54	10.50	10.55
40B	d-Bornylidene		H	246–248	85	$C_{17}H_{29}ON$	68.08	68.09	10.09	10.33
40C	d-Bornylidene		P	212–214	75	$C_{17}H_{31}ON$	67.64	67.82	10.68	10.53
41A	dl-Fenchylidene		F	86–87		$C_{16}H_{29}ON^d$	76.43	76.47	11.63	11.63
41A	dl-Fenchylidene		F	269–270	52	$C_{16}H_{29}ON$	66.76	66.79	10.50	10.39
41B	dl-Fenchylidene		H	288–290	70	$C_{17}H_{29}ON$	68.08	68.04	10.09	10.25
41C	dl-Fenchylidene		P	258–250	50	$C_{17}H_{31}ON$	67.64	67.66	10.68	10.50

TABLE I   (*Continued*)

A. [structure with CHR^2—CR'—C_6H_5 and R^3, N, H, OH]   B. [structure with R_2, R', C_6H_5, O, R^3 R^4, N]   C. [structure with CHR^2—CR'—C_6H_5, R_3, N, R^4, OH]

No.	R'	R²	R³	R⁴	Pt	Method	M.p. °C cor.a	Yield,b %	Formula of base	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
42A	C₆H₅	H	CH₃	..	2	F	235–237	30	$C_{20}H_{25}ON$	72.41	72.69	7.90	7.92
42B	C₆H₅	H	CH₃	H	2	H	266–267	48	$C_{21}H_{25}ON$	73.36	73.83	7.62	8.42
42C	C₆H₅	H	CH₃	H	2	M	198–199	60	$C_{21}H_{27}ON^i$	64.61	64.99	7.23	7.28
43A	H	CH₃	H	..	2	G	268–270	50	$C_{14}H_{21}ON$	65.73	66.13	8.67	8.62
43B	H	CH₃	H	H	2	H	188–190	16	$C_{15}H_{21}ON$	67.26	67.21	8.28	8.39
44A	H	C₆H₅	H	..	2	G	255–258f	64	$C_{19}H_{23}ON$	71.80	71.65	7.61	7.44
44B	H	C₆H₅	H	H	2	H	192–195	94	$C_{20}H_{23}ON$	72.82	72.80	7.33	7.55
44C	H	C₆H₅	H	H	2		137–139		$C_{20}H_{25}ON^d$	81.35	81.57	8.53	8.61
44C	H	C₆H₅	H	H	2	P	99–100j	66	$C_{20}H_{25}ON$	72.40	72.35	7.90	8.03
45C	C₆H₅	CH₃	H	H	2	K	134–138	48	$C_{21}H_{27}ON^d$	81.47	80.86	8.79	8.86
46A	C₆H₅	H	H	..	3	F	107–109		$C_{19}H_{23}ON^d$	81.10	80.81	8.24	8.42
46A	C₆H₅	H	H	..	3	F	198–201	95	$C_{19}H_{23}ON$	71.80	71.51	7.61	7.64
46C	C₆H₅	H	H	H	3	M	166–168	70	$C_{20}H_{25}ON^i$	63.84	63.54	6.97	7.21
47A	C₆H₅	H	H	..	4	F	266–267	85	$C_{19}H_{23}ON$	71.80	71.48	7.61	7.94
47B	C₆H₅	H	H	H	4u	H	277–278	71	$C_{20}H_{23}ON$	72.82	73.12	7.33	7.54
47C	C₆H₅	H	H	H	4	M	213–214	60	$C_{20}H_{25}ON^i$	63.84	63.64	6.97	7.07
48B	C₆H₅	H	H	CH₃	2	H	139–141	53	$C_{21}H_{25}ON$	73.36	73.24	7.62	7.91
48C	C₆H₅	H	H	C₂H₅	2	N	193–195	24	$C_{21}H_{27}ON$	72.93	73.00	8.16	8.21
49B	C₆H₅	H	H	C₂H₅	2	H	91–92		$C_{22}H_{27}ON^d$	82.21	82.12	8.47	8.57
49B	C₆H₅	H	II	C₂H₅	2	H	162–164	63	$C_{22}H_{27}ON$	73.81	74.35	7.88	7.91
49C	C₆H₅	H	H	C₃H₇	2	N	229–230	48	$C_{22}H_{29}ON$	73.41	73.30	8.40	8.67

a All of the hydrohalides melt with some decomposition. The m.p. given is that of an analytical sample. b This is the yield after one recrystallization. c Except where stated the hydrochloride was isolated and analyzed. d Data in this row refer to the base. e Methods P and N gave, respectively, 75 and 50% yields; crystallization from butanone–methanol gave a polymorph, m.p. 219–221°; mixtures of the two melt at 240°. f Racemates were encountered in several cases. They were characterized as such by the depression of m.p. when mixed with the other racemate, and by analysis. Racemates of 2A were a more soluble hydrochloride, m.p. 211–212° dec. and a base more soluble in methanol, m.p. 181–183°. Found: C, 81.40; H, 8.57. A racemate of 11A hydrochloride, m.p. 227–228°, was converted in 61% yield to a racemate hydrate of 11B hydrochloride, m.p. 122–124°. This in turn gave in 53% yield a racemate of 11C hydrochloride, m.p. 245–247° dec. *Anal.* Found (11A): C, 72.30; H, 9.94. Calcd. for $C_{23}H_{35}ON\cdot HCl\cdot H_2O$ (11B): C, 69.76; H, 9.67. Found: C, 70.63; H, 9.67. Found (11C): C, 72.27; H, 9.90. A racemate of 27A hydrochloride was isolated from a second experiment in 81% yield, m.p. 179–181°. Found: C, 68.52; H, 11.48. A more soluble racemate obtained along with 44A melted at 248–250° dec. Found: C, 71.81; H, 7.71. g After keeping in a closed vial for six months at room temperature the m.p. was 166–168°. Analytical composition was unchanged. h Compound 5, Table III was completely hydrogenated to obtain this substance. i Data in this row refer to the hydrobromide. j Hygroscopic. k Special preparation in Experimental section. l Calcd.: S, 11.16. Found: S, 10.83. m Calcd.: S, 10.64; N, 4.65. Found: S, 10.63; N, 4.51. n Obtained by hydrogenation of 20C in the presence of one added mole equivalent of alcoholic hydrogen chloride. o A polymorph, m.p. 138–140°, resulted when this was crystallized from methanol–ether. The analysis was unchanged. p Unstable. Though 24A was converted to an oxazine, the conversion failed with 37A. q This hygroscopic substance liquefied when dried over P_2O_5 preparatory to analysis. r A mixture of 33A and 33C melted at 230–240°. s A monohydrate. t This column shows the point of attachment of the CHR² group to the piperidine ring. u This is a position isomer of I B; *i.e.*, 4,4-diphenyl-1-aza-5-oxabicyclo-[4.2.2]decane hydrochloride.

rubrum, *T. mentagrophytes*, *T. tonsurans*, *H. capsulatum* and *B. dermatidis* test organisms. The most potent compounds were found in the α-alkyl-α-phenyl-2-piperidine-ethanol series, with peak activity in compounds having about eight carbon atoms in the alkyl group. Generally, the pyridoxazines were less potent than the piperidine-ethanols.

Acknowledgment.—We wish to acknowledge the special assistance of Dr. Geraldine Krueger, Mr. Paul Tiernan, Mr. William F. Boyd, Dr. E. D. Carkhuff and Mr. Martin Gordon in many phases of this work. The authors are indeed very much indebted to Dr. Edwin R. Andrews for his contribution, which included the identification and structure proof of 3,3-diphenyloctahydropyrid-[1,2-c]oxazine and the elucidation of the optimum

conditions for the preparation of 1-methyl-α,α-diphenyl-2-piperidine-ethanol using formic acid as the reducing medium. Diuretic and antifungal evaluations were carried out in these laboratories under the direction of Drs. H. W. Werner and F. J. Murray and will be reported in detail elsewhere.

Experimental

Ketones.—Most of the ketones were obtained from commercial sources. 2-(*p*-Anisyl)-cyclohexanone was prepared by the method of Bachmann, *et al.*[14] Others were prepared by addition of a nitrile to a Grignard reagent or a Grignard reagent to an acid chloride as given in the following examples.

(a) **Cycloheptyl Phenyl Ketone.**—To a stirred mixture of 6.5 g. (0.27 mole) of magnesium turnings in 300 ml. of anhydrous ether was added 34 g. (0.19 mole) of cycloheptyl

(14) W. E. Bachmann, G. I. Fujimoto and L. B. Wick, THIS JOURNAL, 72, 1995 (1950).

bromide over a period of two hours.[15] The ether solution was decanted, and to this stirred solution was added 26 g. (0.25 mole) of benzonitrile. The reaction mixture was refluxed for 30 minutes, then decomposed with ammonium chloride solution. About 100 ml. of petroleum ether (40–60°) was added, and the organic layer was fractionally distilled. Ketones no. 1–5 and 7–11 (Table II) were prepared in this manner. In the preparation of no. 8 from cyclohexylmagnesium bromide and enanthonitrile, a 60% yield of an enanthonitrile trimer was obtained as an insoluble hydrochloride when the reaction mixture was decomposed with ammonium chloride solution. This trimer is believed to be a new compound, 2,6-dihexyl-5-pentyl-4-aminopyrimidine hydrochloride,[16] m.p. 130–132°. An analytical sample melted at 132–134°.

Anal. Calcd. for $C_{21}H_{39}N_3 \cdot HCl \cdot H_2O$: C, 65.10; H, 10.85; N, 10.80; Cl, 9.15. Found: C, 65.37; H, 10.21; N, 10.81; Cl, 9.30.

TABLE II
INTERMEDIATE KETONES: R'-CO-R²

No.	R'	R²	B.p. °C.	Mm.	Yield, %
1	Phenyl	Bicyclo[2.2.1]5-heptene-2-yl[a]	107–110	0.5	51
2	Phenyl	Cycloheptyl[b]	115–117	0.2	31
3	Phenyl	4-Methylcyclohexyl[c]	159–162	14	81
4	Phenyl	Cyclohexyl[d]	164–165	18	71
5	Phenyl	Cyclohexen-3-yl[e]	165–170	18	64
6	Phenyl	1-methyl-3-(2-propyl)-cyclopentyl[f]	118–120	0.12	72
7	Phenyl	Cyclopentyl[g]	142–144	12	70
8	Phenyl	Hexyl[h]	148–151	14	90
9	Cyclohexyl	Hexyl[i]	138–142	12	48
10	Hexyl	Hexyl[j]	130–133	11	45
11	Octyl	Ethyl[k]	125–127	12	48

[a] $n^{25}D$ 1.5650; reported: b.p. 122–124° (3 mm.), $n^2 D$ 1.5648; C. F. H. Allen, A. C. Bell, A. Bell and J. van Allan, THIS JOURNAL, **62**, 656 (1940). Starting 3-cyano-1,4-*endo*methylenecyclohexene-5, H. A. Bruson, *ibid.*, **64**, 2457 (1942). [b] $n^{25}D$ 1.5405. 2,4-Dinitrophenylhydrazone, m.p. 170–171°. *Anal.* Calcd. for $C_{20}H_{22}O_4N_4$: C, 62.81; H, 5.80. Found: C, 62.79; H, 5.90. [c] M.p. 47–48°. *Anal.* Calcd. for $C_{14}H_{18}O$: C, 83.11; H, 8.97. Found: C, 83.26; H, 9.06. 2,4-Dinitrophenylhydrazone, m.p. 181–183°. *Anal.* Calcd. for $C_{20}H_{22}O_4N_4$: N, 14.65. Found: N, 14.40. [d] M.p. 57–60° (reported: m.p. 59–60°; b.p. 60–61 (8 mm.); S. L. Friess and N. Farnham, THIS JOURNAL, **72**, 5518 (1950)). [e] $n^{25}D$ 1.5572. 2,4-Dinitrophenylhydrazone, m.p. 170–171°. *Anal.* Calcd. for $C_{12}H_{18}O_4N_4$: N, 15.30. Found: N, 15.65. [f] $n^{25}D$ 1.5220. 2,4-Dinitrophenylhydrazone, m.p. 142–144° (reported: m.p. 138–139°; P. L. Pickard and E. F. Engles, *ibid.*, **74**, 4607 (1952)). [g] Reported: b.p. 138–140° (16 mm.). D. H. Hey and O. C. Musgrave, *J. Chem. Soc.*, 3156 (1949). [h] Reported: b.p. 138–139° (14 mm.); M. Sulzbacher and E. Bergmann, *J. Org. Chem.*, **13**, 303 (1948). [i] Reported: b.p. 73–80° (0.05 mm.); M. S. Kharasch, W. H. Urry and B. M. Kuderna, *ibid.*, **14**, 248 (1949). [j] M.p. 29–31° (reported: m.p. 30–31°; R. R. Briese and S. M. McElvain, THIS JOURNAL, **55**, 1697 (1933)). [k] Semicarbazone, m.p. 87° (reported: m.p. 89–90°; M. Hinder, H. Schinz and C. F. Seidel, *Helv. Chim. Acta*, **30**, 1495 (1947)).

The base was obtained from the hydrochloride as an oil.

Anal. Calcd. for $C_{21}H_{39}N_3$: C, 75.65; H, 11.80. Found: C, 75.10; H, 11.65.

This identical trimer was obtained in about 30% yield from the reaction of enanthonitrile with hexylmagnesium bromide.

(b) **Cyclohexyl Hexyl Ketone.**—Cyclohexylmagnesium bromide, from 122 g. (0.75 mole) of cyclohexyl bromide, 20 g. (0.85 mole) of magnesium turnings and 350 ml. of ether, was added to 100 g. (0.67 mole) of heptoyl chloride in 250 ml. of ether during 2 hours at −15 to −20°. The reaction mixture was worked up as described above. The yield of

the desired ketone, b.p. 130–136° (11 mm.), was 71 g. (52%). Compound no. 6 in Table II also was prepared by this method.

Substituted Pyridine-ethanols[17] (Table III). (a) α,α-Diphenyl-2-pyridine-ethanol (**Method A**).—A mixture of 55 g. (0.6 mole) of dry α-picoline, 55 g. (0.3 mole) of benzophenone and 9.2 g. (0.4 mole) of lithium amide was refluxed with stirring for 16–20 hours. The reaction mixture was poured cautiously into 400 ml. of water, filtered and the precipitate washed with two 200-ml. portions of water. The crude product, when dry, amounted to 81 g. (96%), m.p. 138–140°. Recrystallization from methanol or benzene gave pure product melting at 152–153° (reported[6] m.p. 142°).

(b) α-**Cyclohexyl-α-phenyl-2-pyridine-ethanol** (**Method B**).—An ether solution of picolyllithium[18] was prepared from 11 g. (1.6 moles) of lithium wire, 126 g. (0.8 mole) of bromobenzene, 80 ml. (0.8 mole) of α-picoline and 340 ml. of anhydrous ether. To this stirred mixture was rapidly added 124 g. (0.66 mole) of cyclohexyl phenyl ketone in 250 ml. of anhydrous ether at about −20°.[19] The reaction mixture was then decomposed with dilute ammonium chloride solution and filtered.[20] The white precipitate was washed with petroleum ether and dried; yield 110 g. (60%), m.p. 107–109°. The ether layer from the filtrate was evaporated to a volume of about 100 ml., then diluted with 400 ml. of hot petroleum ether (90–100°). The solution was cooled and filtered, yielding an additional 38 g. (20%) of the desired product, m.p. 106–108°.

(c) **9-(2-Pyridylmethyl)-9-fluorenol** (**Method C**).—Method B was followed with fluorenone (119 g., 0.66 mole) in 200 ml. of dry toluene substituted for cyclohexyl phenyl ketone. The reaction mixture was heated with stirring for about eight hours at 115–120° at which temperature ether evaporated through the condenser. The reaction mixture was decomposed with aqueous ammonium chloride, and the toluene layer evaporated under reduced pressure. The residue was crystallized from a mixture of ether and petroleum ether yielding 70 g. (37%) of white product melting at 84–86°. The melting point of pure fluorenone (83–84°) was lowered by 10° when mixed with an equal portion of this product.

Substituted 2-Pyridine-ethanol Hydrochlorides (Method D).—When crystalline free bases could not be obtained as described above, hydrochlorides were prepared in the following manner. The ether or toluene extract of the decomposed reaction mixture was evaporated under reduced pressure to remove both solvent and unchanged α-picoline. The residue was dissolved in 500 ml. of anhydrous ether and treated with less than the equivalent amount of alcoholic hydrogen chloride solution. Excess acid was avoided to minimize possible dehydration of the pyridine-ethanols. The crystalline or gummy hydrochlorides were isolated by filtration or decantation, and most of these were recrystallized from ethyl acetate–methanol mixtures. Generally the more soluble α-alkyl substituted 2-pyridine-ethanol hydrochlorides were recrystallized from ethyl acetate–ether mixtures. In some cases, as with α,α-dialkyl-2-pyridine-ethanol hydrochlorides, ether alone was a suitable recrystallization solvent.

Substituted 2-Pyridine-ethanol Methobromides (Method E).—The methobromides of Table IV were prepared as follows: 0.2 mole of the substituted pyridine-ethanol in 250 ml. of methanol and an excess of methyl bromide were heated in a pressure bottle at 60–75° for three to five days. The reaction mixture was evaporated on the steam-bath and the residue recrystallized from ethyl acetate–methanol. α,α-Diphenyl-2-pyridine-ethanol methobromide could not be obtained pure although the conditions for the reaction

(15) L. Ruzicka, P. Barman and V. Prelog, *Helv. Chim. Acta*, **34**, 401 (1951).

(16) Similarly, 2,6-diethyl-5-methyl-4-aminopyrimidine has been obtained from propionitrile, cf. R. Frankland and H. Kolbe, *Ann.*, **65**, 269 (1848).

(17) Pyridine-ethanols were not obtained from 2-benzoylpyridine and desoxybenzoin by method A, anthrone by methods A, B and C, or from thioxanthone and 2,4-dichlorobenzophenone by method C. By method A the dichlorobenzophenone was converted to an unidentified hydrochloride, m.p. 177–179°. *Anal.* Found: C, 54.22; H, 3.93; N, 8.23.

(18) R. B. Woodward and E. C. Kornfeld, *Org. Syntheses*, **29**, 44 (1949).

(19) The temperature of the reaction could be maintained at the reflux temperature of ether without appreciable decrease in yields, but the ketone addition then required 1–2 hours.

(20) In most cases, the pyridine-ethanols were completely soluble in the ether, and this filtration was omitted.

were varied over a wide range. α-Phenyl-α-cyclohexyl- and α,α-dicyclohexyl-2-pyridine-ethanol methobromides were prepared in good yields.

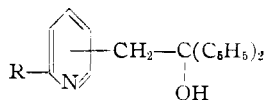**Substituted Piperidine-ethanols (Table I. Type A). (a) Hydrogenation of Pyridine-ethanols (Method F).**—A mixture of 0.2 mole of the substituted pyridine-ethanol hydro-

TABLE III
SUBSTITUTED PYRIDINE-ETHANOLS

$$\text{—CH}_2\text{—CR'R}^2\text{—OH}$$

No.	R'	R²	Method	M.p., °C. cor.[a]	Yield, %	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
1	Phenyl	Phenyl	A	152–153[b]	85	$C_{19}H_7ON$	82.88	82.67	6.23	6.30
	Phenyl	Phenyl		221–222		$C_{19}H_{17}ON \cdot HCl$	73.16	73.08	5.82	5.78
2	Phenyl	p-Tolyl	A	117–119	73	$C_{20}H_{19}ON$	83.00	83.27	6.62	6.69
	Phenyl	p-Tolyl		206–207		$C_{20}H_{19}ON \cdot HCl$	73.72	73.82	6.19	6.38
3	Phenyl	p-Phenetyl	A	122–124	68	$C_{21}H_{21}O_2N$	78.96	78.97	6.63	6.62
	Phenyl	p-Phenetyl		169–170		$C_{21}H_{21}O_2N \cdot HBr$	63.01	63.21	5.54	5.51
4	Phenyl	p-Chlorophenyl	A	111–112	70	$C_{19}H_{16}ONCl$	73.62	73.74	5.21	5.50
	Phenyl	p-Chlorophenyl		213–215		$C_{19}H_{16}ONCl \cdot HCl$	65.89	66.24	4.95	5.39
5	Phenyl	Bicyclo[2.2.1]-5-hepten-2-yl	B	111–113	85	$C_{20}H_{21}ON$	82.44	82.30	7.27	7.35
	Phenyl			183–184		$C_{20}H_{21}ON \cdot HCl$	73.29	73.35	6.77	6.90
6	Phenyl	Cycloheptyl	B	78–79	68	$C_{20}H_{23}ON$	81.31	81.51	8.54	8.55
	Phenyl	Cycloheptyl		184–186		$C_{20}H_{25}ON \cdot HCl$	72.38	72.40	7.90	8.00
7	Phenyl	4-Methylcyclohexyl	B	120–121	82	$C_{20}H_{25}ON$	81.31	81.52	8.54	8.72
	Phenyl	4-Methylcyclohexyl		165–167		$C_{20}H_{25}ON \cdot HCl$	72.38	71.96	7.90	7.87
8	Phenyl	Cyclohexyl	B	107–109	80	$C_{19}H_{23}ON$	81.10	81.23	8.24	8.36
	Phenyl	Cyclohexyl		179–181		$C_{19}H_{23}ON \cdot HCl$	71.74	71.60	7.61	7.50
9	Phenyl	1-Methyl-3-i-propyl-cyclopentyl	B	205–207	44	$C_{22}H_{29}ON \cdot HCl$	73.40	73.62	8.40	8.16
10	Phenyl	Cyclopentyl	B	87–89	67	$C_{18}H_{21}ON$	80.81	81.21	7.92	8.09
	Phenyl	Cyclopentyl		193–194		$C_{18}H_{21}ON \cdot HCl$	71.16	71.14	7.30	7.40
11	Phenyl	Undecyl	B	66–68	77	$C_{24}H_{35}ON$	81.53	81.22	9.97	9.88
	Phenyl	Undecyl		142–144		$C_{24}H_{35}ON \cdot HCl$	73.92	74.02	9.31	9.40
12	Phenyl	Octyl	B	57–59	84	$C_{21}H_{29}ON$	80.98	80.80	9.38	9.34
	Phenyl	Octyl		142–144		$C_{21}H_{29}ON \cdot HCl$	72.51	71.93	8.69	8.71
13	Phenyl	Hexyl	B	74–75	73	$C_{19}H_{25}ON$	80.51	81.05	8.89	9.05
	Phenyl	Hexyl		149–150		$C_{19}H_{25}ON \cdot HCl$	71.34	71.44	8.19	8.41
14	Phenyl	Pentyl	B	75–77	84	$C_{18}H_{23}ON$	80.21	80.08	8.60	8.54
	Phenyl	Pentyl		122–124		$C_{18}H_{23}ON \cdot HCl$	70.70	70.70	7.91	7.97
15	Phenyl	i-Propyl	B	209–211	46	$C_{16}H_{19}ON \cdot HCl$	69.15	69.44	7.26	7.37
16	p-Tolyl	p-Tolyl	A	137–139	25	$C_{21}H_{21}ON$	83.13	83.75	6.98	7.07
	p-Tolyl	p-Tolyl		197–198		$C_{21}H_{21}ON \cdot HCl$	74.23	74.52	6.53	6.55
17	p-Anisyl	p-Anisyl	A	111–112	80	$C_{21}H_{21}O_3N$	75.22	75.07	6.32	6.38
	p-Anisyl	p-Anisyl		207–208		$C_{21}H_{21}O_3N \cdot HCl^c$	9.56[d]	9.70		
18	p-Anisyl	m-Bromophenyl	A	106–107	34	$C_{20}H_{18}O_2NBr$	62.51	62.35	4.72	4.60
	p-Anisyl	m-Bromophenyl		139–143		$C_{20}H_{18}O_2NBr \cdot HCl$	8.40[d]	8.43		
19	p-Dimethylamino-phenyl	p-Dimethylamino-phenyl	A	190–192	34	$C_{23}H_{27}ON_3$	76.41	76.14	7.52	7.60
				160–163[e]		$C_{23}H_{27}ON_3 \cdot 3HCl$	22.58[d]	22.20		
20	Cyclohexyl	Cyclohexyl	B	66–67	60	$C_{19}H_{29}ON$	79.39	79.41	10.17	10.26
	Cyclohexyl	Cyclohexyl		195–197		$C_{19}H_{29}ON \cdot HCl$	70.45	69.69	9.35	9.42
21	Cyclohexyl	Hexyl	B	148–150	57	$C_{19}H_{31}ON \cdot HCl$	70.01	70.22	9.90	9.78
22	3-Cyclohexenyl	Hydrogen	B[f]	71–74[g]	72	$C_{13}H_{17}ON \cdot HBr$	54.98	54.61	6.38	6.33
23	Octyl	Ethyl	B	90–93	44	$C_{17}H_{29}ON \cdot HCl$	68.08	67.75	10.09	10.08
24	Heptyl	Heptyl	B	95–97	81	$C_{21}H_{37}ON \cdot HCl$	70.86	70.55	10.76	10.72
25	Hexyl	Hexyl	B	95–96	55	$C_{19}H_{33}ON \cdot HCl$	66.00[g]	66.42	10.49	10.48
26	i-Butyl	i-Butyl	B	156–157	33	$C_{15}H_{25}ON \cdot HCl$	66.26	66.36	9.64	9.85
27	t-Butyl	t-Butyl	B	63–65	73	$C_{15}H_{25}ON$	76.51	76.60	10.70	10.87
	t-Butyl	t-Butyl		214–216		$C_{15}H_{25}ON \cdot HCl$	66.26	66.00	9.64	9.63
		–CR'R²–								
28	1-Indanylidene		B	143–144	20	$C_{15}H_{15}ON \cdot HCl$	68.84	68.85	6.16	6.08
29	9-Fluorenylidene		C	84–86	37	$C_{19}H_{15}ON$	83.49	83.60	5.53	5.57
	9-Fluorenylidene			167–169		$C_{19}H_{15}ON \cdot HCl$	73.66	73.49	5.20	5.48
30	1-Acenaphthenylidene		C	166–167	40	$C_{18}H_{15}ON \cdot HCl$	72.58	72.09	5.42	5.50
31	9-Xanthylidene		C	108–110	66	$C_{19}H_{15}O_2N$	78.87	78.81	5.23	5.38
32	2-Cyclohexylcyclohexylidene		B	92–93	39	$C_{18}H_{27}ON$	79.07	79.22	9.96	10.01
	2-Cyclohexylcyclohexylidene			210–212		$C_{18}H_{27}ON \cdot HCl$	69.75	69.82	9.11	9.12

TABLE III (*Continued*)

No.	-CR'R²-	Method	M.p., °C. cor.[a]	Yield, %	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
33	2-*p*-Anisylcyclohexylidene	B	85–87	77	$C_{19}H_{23}O_2N$	76.72	76.97	7.80	7.81
34	*d*-Bornylidene	B	67–68	91	$C_{16}H_{23}ON$	78.31	78.70	9.45	9.48
	d-Bornylidene		196–199		$C_{16}H_{23}ON \cdot HCl$	68.20	68.19	8.58	8.65
35	*dl*-Fenchylidene	B	110–111	35	$C_{16}H_{23}ON$	78.31	78.46	9.45	9.45

$$R-\overset{}{\underset{N}{\bigcirc}}-CH_2-\underset{\underset{OH}{|}}{C}(C_6H_5)_2$$

No.	R	Position[h]	Method	M.p., °C. cor.[a]	Yield, %	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
36	Methyl	2	A	122–124	72	$C_{20}H_{19}ON$	83.00	82.60	6.62	6.90
	Methyl	2		220–222		$C_{20}H_{19}ON \cdot HCl$	73.71	73.48	6.19	6.55
37	Hydrogen	3	i	256–257	7[j]	$C_{19}H_{17}ON \cdot HCl$	73.16	73.04	5.82	5.84
38	Hydrogen	4	A	122–124	70	$C_{19}H_{17}ON$	82.88	82.91	6.23	6.02
	Hydrogen	4		265–266		$C_{19}H_{17}ON \cdot HCl$	73.16	73.42	5.82	6.02

[a] The hydrohalides melt with some decomposition. [b] Reference 6, m.p. 142°. [c] Unstable in water, hydrolyzing in minutes to dianisyl ketone. [d] Chlorine, %. [e] Hygroscopic. [f] 1,2,5,6-Tetrahydrobenzaldehyde was used in place of a ketone. [g] Calcd. for a monohydrate. [h] This indicates the point of attachment of the diphenylethanol side chain on the pyridine ring. [i] The procedure of reference 7 was used. [j] The yield of crude base was 24%.

TABLE IV

METHOBROMIDES OF SUBSTITUTED PYRIDINE-ETHANOLS

$$R^3-\overset{R'}{\underset{\underset{CH_3 \quad Br}{\overset{|}{N}}}{\bigcirc}}-CH_2-\underset{\underset{OH}{|}}{\overset{\overset{R'}{|}}{C}}-R^2$$
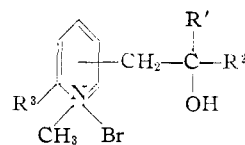
No.	R'	R²	R³	P[a]	M.p., °C. cor.[b]	Yield, %	Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Bromine Calcd.	Bromine Found
1	Phenyl	Phenyl	CH_3	2	214–216	45	$C_{21}H_{22}ONBr$	65.64	65.79	5.76	5.89	20.80	20.50
2	Phenyl	*p*-Chlorophenyl	H	2	202–204	38	$C_{20}H_{19}ONClBr$	59.33	59.38	4.73	4.90	19.74	19.74
3	Phenyl	Cyclohexyl	H	2	222–223	60	$C_{20}H_{26}ONBr^c$	63.84	63.56	6.97	7.30	21.25	21.20
4	*p*-Anisyl	*p*-Anisyl	H	2	205–208	40	$C_{22}H_{24}O_3NBr^d$	61.40	60.82	5.62	5.39	18.57	18.55
5	*p*-Anisyl	*m*-Bromophenyl	H	2	209–210	12	$C_{21}H_{21}O_2NBr_2^e$	52.64	52.66	4.42	4.58		
6	Cyclohexyl	Cyclohexyl	H	2	210–212	79	$C_{20}H_{32}ONBr$	62.80	62.84	8.44	8.46	20.90	20.85
7	Phenyl	Phenyl	H	3	250–251	2	$C_{20}H_{20}ONBr^f$	64.88	64.43	5.45	5.85	21.60	21.60
8	Phenyl	Phenyl	H	4	213–215	86	$C_{20}H_{20}ONBr$	64.88	64.24	5.45	5.61	21.60	21.70

[a] Position of ethanol residue on pyridine ring. [b] All compounds melted with decomposition. [c] Calcd.: N, 3.72. Found: N, 3.97. [d] Calcd.: N, 3.25. Found: N, 3.12. [e] Obtained as second crop; first crop had unsatisfactory analysis and m.p. 281–283°. [f] Calcd.: N, 3.78. Found: N, 3.44.

chloride, 200 ml. of methanol and 0.6–0.8 g. of platinum oxide catalyst was shaken with hydrogen at 3 to 4 atmospheres pressure in a Parr hydrogenation apparatus until the theoretical amount (0.6 mole) of hydrogen had been absorbed. The catalyst was removed by filtration, and the filtrate concentrated to approximately one-fourth volume. Approximately 200 ml. of hot ethyl acetate was added, and the solution was cooled to −12°, then filtered to remove the piperidine-ethanol hydrochloride.

(b) **Hydrogenation of Picolyl Ketones (Method G).**—Method F was followed with the appropriate picolyl ketone hydrochloride (Table V, type A) substituted for the pyridine-ethanol hydrochloride; four instead of three molar equivalents of hydrogen were absorbed. Compounds no. 43A and 44A of Table I were prepared by this method.

Substituted **Octahydropyrid[1,2-c]oxazines (Table I, Type B) (Method H).**—A mixture of 0.3 mole of the appropriate piperidine-ethanol hydrochloride (Table I, type A), 500 ml. of methanol and 40 ml. (0.48 mole) of formalin was refluxed 7 to 16 hours. About 300 ml. of methanol was distilled from the reaction mixture and three to five volumes of ethyl acetate then added. The mixture was cooled, and the desired octahydropyridoxazine hydrochloride was filtered. Second and third crops were isolated by reworking filtrates. The combined crops were recrystallized from ethyl acetate with 2-propanol.

Piperidine-ethanol free bases also can be used in this procedure. In these cases, the crude octahydropyridoxazine free bases were isolated by dilution of the hot reaction mixture with distilled water to the point of cloudiness followed by cooling and filtering.

This method failed with compound 18A of Table I.

The octahydropyridoxazines were usually stable compounds. However, 1-alkyl substitution appears to decrease stability. For example, 3 - cyclohexyl - 3 - phenyloctahydropyrid[1,2-c]oxazine hydrochloride was recovered in 92% yield after stirring 24 hours in 10% hydrochloric acid or in 40% yield after five hours in concentrated hydrochloric acid. The hydrochloride of the corresponding 1-methyl derivative, m.p. 150–151° dec., decomposed into acetaldehyde and α-cyclohexyl-α-phenyl-2-piperidine-ethanol hydrochloride upon standing at room temperature for a few days. This instability may account for the failure of formic acid to reduce 1-methyl- and 1-ethyl-3,3-diphenyloctahydropyrid[1,2-c]oxazines to the corresponding N-ethyl- and N-propyl-2-piperidine-ethanols (method P). In these two cases, α,α-diphenyl-2-piperidine-ethanol was regenerated.

Attempted Preparation of 1,3-Diphenyloctahydropyrid[1,2-c]oxazine.—A mixture of 24 g. (0.1 mole) of α-phenyl-2-piperidine-ethanol hydrochloride,[8] 13 g. (0.12 mole) of benzaldehyde and 100 ml. of methanol was refluxed for 24 hours. The reaction mixture was worked up as described in method H. The sole product isolated was 8 g. of the starting ethanol.

Attempted Preparation of Spiro-cyclohexane-1'-(3',3'-diphenyl)-octahydropyrid[1,2-c]oxazine and 1-*p*-Anisyl-3,3-diphenyloctahydropyrid[1,2-c]oxazine.—In the procedure of Goodson and Christopher[11] α,α-diphenyl-2-piperidine-ethanol did not react during a 24-hour reflux period with an equimolar amount of *p*-anisaldehyde or with a 100% excess of cyclohexanone. No water collected in the water trap, and the original ethanol was recovered.

TABLE V

2-PYRIDYLMETHYL AND 2-PIPERIDYLMETHYL KETONES AND ESTERS

A. [structure: pyridine ring, R² O, —CH—C—R']   B. [structure: pyridinium ring, R² O, —CH—C—R', CH₃ Br]   C. [structure: piperidine ring, R² O, —CH—C—R', CH₃]

No.	R'	R²	M.p., °C. cor.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1A	Phenyl	CH₃	66–68		C₁₄H₁₃ON	79.59	79.67	6.20	6.11
1A	Phenyl	CH₃	200–202	35	C₁₄H₁₃ON·HCl	67.89	68.04	5.70	5.94
1B	Phenyl	CH₃	163–165ᵃ	50	C₁₅H₁₆ONBr	58.83	58.59	5.27	5.30
1C	Phenyl	CH₃	138–140	45	C₁₅H₂₁ON·HBr	57.68	57.54	7.10	7.21
2A	Phenyl	Phenyl	173–176	54	C₁₉H₁₅ON·HCl	73.65	73.15	5.22	5.32
2B	Phenyl	Phenyl	216–218ᵃ	74	C₂₀H₁₈ONBr	65.24	65.04	4.93	4.94
3A	Cyclohexyl	H	133–135	31	C₁₃H₁₇ON·HClᵇ	65.12	65.05	7.57	7.62
3B	Cyclohexyl	H	196–198ᵃ	77	C₁₄H₂₀ONBr	56.38	56.40	6.76	6.83
3C	Cyclohexyl	H	175–177	94	C₁₄H₂₅ON·HBrᶜ	55.26	55.84	8.61	8.81
3C	Cyclohexyl	H	171–173		C₁₄H₂₅ON·HCl	64.71	64.61	10.09	10.12
4A	2-Pyridyl	H	87–88	38	C₁₂H₁₀ON₂ᵈ	72.71	72.82	5.09	5.10
4B	2-Pyridyl	H	192–193ᵃ	7	C₁₄H₁₆ON₂Br₂ᵉ				
5A	1-Phenylcyclohexylᶠ	H	197–198	50	C₁₉H₂₁ON·HCl	72.26	72.09	7.02	7.08
6A	OCH₃	H	115–117ᵍ (12 mm.)	39	C₈H₉O₂N				
6B	OCH₃	H	127–128ᵃ	86	C₉H₁₂O₂NBr	43.92	43.96	4.92	5.03
6C	OCH₃	H	133–135	88	C₉H₁₇O₂N·HBr	42.87	43.16	7.19	7.17

ᵃ Melted with decomposition.   ᵇ 2,4-Dinitrophenylhydrazone·HCl, m.p. 188–189°.   *Anal.* Calcd. for C₁₉H₂₁O₄N₅·HCl: N, 16.69. Found: N, 16.01.   ᶜ Calcd.: N, 4.60; Br, 26.3. Found: N, 4.61; Br, 26.4. The picrate melted at 133–134.5° (ref. 8, m.p. 131.4–131.8°).   ᵈ Reported m.p. 88–89°; J. P. Wibaut and J. I. de Jong, *Rec. trav. chim.*, 68, 485 (1949). ᵉ Dimethobromide. *Anal.* Calcd.: Br, 41.2. Found: Br, 41.5.   ᶠ Starting material was ethyl 1-phenylcyclohexane-carboxylate: C. H. Tilford, M. G. Van Campen, Jr., and R. S. Shelton, THIS JOURNAL, 69, 2902 (1947).   ᵍ Ref. 18, b.p. 122–125° (21 mm.).

α,α-Disubstituted 1-Alkyl-2-piperidine-ethanols (Table I, Type C). (a) From 1-Methyl-2-phenacylpiperidine and Grignard Reagents (Method I).—To the appropriate Grignard reagent (0.2 mole) in refluxing ether was added 22 g. (0.1 mole) of 1-methyl-2-phenacylpiperidine⁸ over a period of about an hour. The reaction mixture was refluxed for 30 minutes, then treated with dilute ammonium chloride solution. An equal volume of petroleum ether (70–90°) was added, and the organic layer was evaporated to a volume of about 150 ml. on a steam-bath. The solution was cooled overnight at −12° and filtered. The base was usually a white crystalline solid.

Where the free base was not a solid, the petroleum ether solution was diluted with three volumes of anhydrous ether and treated at −10° with 0.07–0.09 mole of alcoholic hydrogen chloride avoiding an excess of acid. This white hydrochloride was recrystallized from ethyl acetate with 2-propanol.

When cyclohexylmagnesium bromide was used as the Grignard reagent, this procedure was unsuccessful whether carried out in boiling ether or boiling toluene. Only the starting ketone (50% yield) was isolated. A similar attempt to prepare α-cyclohexyl-α-phenyl-1-methyl-2-piperidine-ethanol (Table I, compound 10C) from cyclohexyl-1-methyl-2-piperidylmethyl ketone (VII) and phenylmagnesium bromide was also unsuccessful.

(b) From 1-Methyl-2-phenacylpiperidine and Organolithium Agents (Method J).—The appropriate organolithium compound was substituted for the Grignard reagent of method I.

(c) From 1-α-Dimethyl-2-phenacylpiperidine and Phenyllithium (Method K).—1,α-Dimethyl-2-phenacylpiperidine (compound 1C, Table V) was substituted for the 1-methyl-2-phenacylpiperidine of method I.

(d) From Methyl 1-Methyl-2-piperidineacetate and Grignard Reagents (Method L).—This procedure corresponds to method I except that methyl 1-methyl-2-piperidineacetate (compound 6C, Table V) was added to three molar equivalents of the appropriate Grignard reagent.

The reaction of cyclohexylmagnesium bromide with methyl 1-methyl-2-piperidineacetate for 24 hours in boiling toluene gave an 85% yield of cyclohexyl 1-methyl-2-piperidylmethyl ketone (VII) hydrochloride, m.p. 171–173°, rather than the expected α,α-dicyclohexyl-1-methyl-2-piperidine-ethanol (compound 26C, Table I). The identity

of VII was proven by an unequivocal synthesis (compound 3C, Table V).

(e) Hydrogenation of Substituted Pyridine-ethanol Methobromides (Method M).—The appropriate methobromide of Table IV (prepared by method E) was substituted for the pyridine-ethanol hydrochloride of method F, hydrogenation conditions being the same. The 1-methyl-2-piperidine-ethanol hydrobromides were obtained as white crystalline solids.

(f) Reductive Alkylation of α,α-Disubstituted-2-piperidine-ethanols. (1) Catalytic (Method N).—As an example, a mixture of 7 g. (0.025 mole) of α,α-diphenyl-2-piperidine-ethanol, 3.1 g. (0.07 mole) of acetaldehyde and 75 ml. of methanol was refluxed for 20 minutes. The resulting solution was then heated on the steam-bath to remove most of the volatile products. A mixture of 0.5 g. of platinum oxide and 75 ml. of methanol was added and the mixture hydrogenated until the theoretical amount of hydrogen was absorbed. The mixture was filtered and heated on the steam-bath to evaporate most of the methanol. The residue was dissolved in ether, and slightly less than an equivalent amount of alcoholic hydrogen chloride was added at 0°. The precipitate was recrystallized from ethyl acetate–methanol or ethyl acetate–ether. The product was compound 48C, Table I.

(2) Formic Acid (Method O).—A mixture of 0.06 mole of the disubstituted piperidine-ethanol, 8 g. (0.1 mole) of formalin, 6 g. (0.12 mole) of 98–100% formic acid and 40 ml. of water was refluxed for 24 hours. The reaction mixture was diluted with 200 ml. of water, made alkaline with 10% sodium hydroxide solution, and extracted with 200 ml. of a 1:1 mixture of ether and petroleum ether. The extract was treated with alcoholic hydrogen chloride (0.05 mole) at 0°, then filtered. The white, crystalline product was recrystallized from ethyl acetate–methanol or ethyl acetate–ether.

When it was more convenient to use the piperidine-ethanol hydrochloride as a reactant, 7 g. (0.1 mole) of sodium formate was added to the reaction mixture.

(g) Reduction of Octahydropyrid[1,2-c]oxazines with Formic Acid (Method P).—The appropriate octahydropyridoxazine (Table I, type B) was substituted in method O for the piperidine-ethanol, and formalin was omitted. This method failed with compounds 34B and 36B of Table I.

2-Pyridylmethyl and 2-Piperidylmethyl Ketones and Esters (Table V).—The procedure used for the preparation of these

compounds was similar to that reported[8] for the preparation of 2-phenacylpyridine, its methobromide and 1-methyl-2-phenacylpiperidine, with the exception that one equivalent of phenyllithium was used in place of potassium amide in the formation of the 2-pyridylmethyl ketones.[21]

2-Phenacylpiperidine.—2-Phenacylpyridine hydrochloride was hydrogenated by the procedure reported[8] for the corresponding methobromide; the product obtained as the hydrochloride melted at 167–169° after one recrystallization from ethyl acetate with 2-propanol.

Anal. Calcd. for $C_{13}H_{17}ON \cdot HCl$: C, 65.15; H, 7.57; N, 5.84. Found: C, 65.30; H, 7.84; N, 6.10.

The semicarbazone hydrochloride melted at 217–218° dec.

Anal. Calcd. for $C_{14}H_{20}ON_4 \cdot HCl$: N, 18.88. Found: N, 18.95.

2-Phenacylpiperidine was obtained by neutralization of the hydrochloride with saturated sodium carbonate solution and extracting with petroleum ether (40–60°). The extract was concentrated under reduced pressure on the steambath. The residual oil was sufficiently pure for use in subsequent reactions.

α-(2-Pyridyl)-α-phenyl-2-piperidine-ethanol.—This compound was prepared from 2-phenacylpiperidine and approximately four equivalents of 2-pyridyllithium[22] according to method J. The properties of the product are given in Table I (20A).

α-(2-Thienyl)-α-phenyl-2-piperidine-ethanol.—The immediately preceding method was used with 2-thienyllithium[23] substituted for 2-pyridyllithium.

Hydrogenation of α-Phenyl-2-phenacylpyridine Methobromide.—This methobromide (compound 2B, Table V) (24 g., 0.065 mole) was hydrogenated in 100 ml. of methanol using 0.5 g. of platinum oxide (method M). The absorption of hydrogen (0.22 mole) was somewhat greater than three molar equivalents (0.195 mole) but less than four (0.26 mole). The mixture was filtered and most of the methanol evaporated on a steam-bath. The residue was dissolved in 250 ml. of ethyl acetate, cooled and filtered. The white, hygroscopic precipitate gave analytical values close to those of N-methylpiperidine hydrobromide.

Anal. Calcd. for $C_6H_{13}N \cdot HBr$: Br, 44.38. Found: Br, 43.5.

The filtrate was evaporated on the steam-bath, and the residue was recrystallized from 85% methanol yielding 5 g. of product melting at 53–55°. The melting point of a mixture of this product with an authentic sample of desoxybenzoin (m.p. 55–56°) was not depressed, but the melting point of a mixture with an authentic sample of 1,2-diphenylethanol (m.p. 66–67°) was depressed 30°.

1-Phenylcyclohexyl 2-Piperidylmethyl Ketone.—A mixture of 32 g. (0.1 mole) of 1-phenylcyclohexyl 2-pyridylmethyl ketone hydrochloride (compound 5A, Table V), 130 ml. of methanol and 0.6 g. of platinum oxide was hydrogenated until hydrogen uptake ceased. The uptake of hydrogen (0.34 mole) was intermediate between the amount required for hydrogenation of the pyridine ring and of both the pyridine ring and ketone component. The mixture was heated to 75°, filtered and cooled to yield a white solid (6 g.), m.p. 317–318° dec., which proved to be α-(1-phenylcyclohexyl)-2-piperidine-ethanol hydrochloride.

Anal. Calcd. for $C_{19}H_{29}ON \cdot HCl$: C, 70.45; H, 9.34. Found: C, 70.82; H, 9.50.

The mother liquor was evaporated on a steam-bath. The residue was dissolved in 200 ml. of hot ethyl acetate and cooled to yield 25 g. (77%) of the desired ketone hydrochloride as white crystals melting at 187–189°. An analytical sample melted at 188–190°.

Anal. Calcd. for $C_{19}H_{27}ON \cdot HCl$: C, 70.88; H, 8.77. Found: C, 70.72; H, 9.01.

Infrared spectra of this product exhibited a strong ketone band at 1720 cm.$^{-1}$, a band which was not present in the spectra of the product melting at 317–318° dec.

α-(1-Phenylcyclohexyl)-2-piperidine-ethanol.—The 1-phenylcyclohexyl 2-piperidylmethyl ketone hydrochloride

obtained above was reduced catalytically with platinum oxide (1 g.), one molar equivalent of hydrogen having been absorbed in 24 hours. A 75% yield of α-(1-phenylcyclohexyl)-2-piperidine-ethanol hydrochloride, m.p. 319–320° dec., was obtained. This product was identical with the first crop obtained in the hydrogenation of 1-phenylcyclohexyl 2-pyridylmethyl ketone hydrochloride.

A sample of the base recrystallized from methanol melted at 80–81°.

Anal. Calcd. for $C_{19}H_{29}ON$: C, 79.40; H, 10.17. Found: C, 79.64; H, 10.23.

A small second crop of the base, possibly a second racemate, was isolated: m.p. 97–98°. A mixture with an equal portion of the first crop melted over the range 70–80°.

Anal. Found: C, 79.20; H, 10.28.

An attempt to convert α-(1-phenylcyclohexyl)-2-piperidine-ethanol hydrochloride to the corresponding octahydropyrid[1,2-c]oxazine by method H was unsuccessful; unchanged starting material was recovered.

α-(1-Phenylcyclohexyl)-1-methyl-2-piperidine-ethanol.—Reductive alkylation of α-(1-phenylcyclohexyl)-2-piperidine-ethanol hydrochloride by method O gave 66% of the desired 1-methyl derivative, a hygroscopic substance melting at about 100°.

Anal. Calcd. for $C_{20}H_{31}ON \cdot HCl$: C, 71.09; H, 9.55. Found: C, 71.17; H, 9.67.

The base melted at 75–76°.

Anal. Calcd. for $C_{20}H_{31}ON$: C, 79.68; H, 10.37. Found: C, 79.82; H, 10.31.

3,3-Diphenyloctahydropyrid[1,2-c]oxazine Methobromide (Method Q).—A solution of 4.5 g. (0.015 mole) of compound 1B of Table I, 7 ml. of methanolic methyl bromide (77%) and 15 ml. of methanol was heated at 50° for two days in a pressure bottle. The solution was evaporated to half the original volume on the steam-bath, diluted with three volumes of ethyl acetate, cooled and filtered; yield 4 g. (67%) of white crystals, m.p. 263–265° dec. When recrystallized from ethyl acetate with 2-propanol, the product melted at 272–273°.

Anal. Calcd. for $C_{21}H_{26}ONBr$: C, 64.98; H, 6.75. Found: C, 65.45; H, 6.87.

3-Cyclohexyl-3-phenyloctahydropyrid[1,2-c]oxazine Methobromide.—Compound no. 10B of Table I was converted to the methobromide by method Q. The desired product was isolated in an 80% yield as a white crystalline hemihydrate melting at 272–274° dec.

Anal. Calcd. for $C_{21}H_{32}ONBr \cdot 1/2H_2O$: C, 62.53; H, 8.24. Found: C, 62.42; H, 8.18.

Attempts to remove the water of crystallization by heating *in vacuo* led to decomposition.

α,α-Diphenyl-1-methyl-2-piperidine-ethanol Methobromide.—Compound 1C of Table I was converted to the methobromide by method Q. The white crystalline product obtained in a 75% yield melted at 181–182°. A second crop, evidently a polymorph, melted at 229–230° dec.; a mixture with an equal portion of the first crop melted at 229–230°.

Anal. Calcd. for $C_{21}H_{28}ONBr$: C, 64.61; H, 7.23. Found: C, 64.30; H, 7.27.

Proof of Structure of α,α-Diphenyl-1-methyl-2-piperidine-ethanol and 3,3-Diphenyloctahydropyrid[1,2-c]oxazine.—The necessity for differentiating between these two compounds (1C and 1B, Table I) appeared early in this investigation as the following experiments will indicate.

A solution of 215 g. (0.77 mole) of α,α-diphenyl-2-piperidine-ethanol (1A, Table I) in 250 g. (4.9 moles) of 90% formic acid and 150 g. (1.85 moles) of formalin was refluxed for 30 hours according to the procedure of Clarke and co-workers.[12] The mixture was evaporated under reduced pressure on a steam-bath, made alkaline with sodium hydroxide solution and extracted with benzene. Evaporation of the benzene left an oily base, which in ether solution was acidified with a slight excess of alcoholic hydrogen chloride. The white hydrochloride weighed 124 g. (47%), m.p. 195–205°.

Anal. Calcd. for $C_{20}H_{25}ON \cdot HCl$: Cl, 10.68. Found: Cl, 10.60.

This material was recrystallized from mixtures of 2-propanol and ethyl acetate to give two main fractions: (A) 40 g., m.p. 228–230° dec. and (B) 30 g., m.p. 224–226° dec.

(21) N. Goldberg, L. Barkley and R. Levine, THIS JOURNAL, **73**, 4301 (1951); N. Goldberg and R. Levine, *ibid.*, **74**, 5217 (1952).

(22) J. P. Wibaut, A. P. de Jonge, H. G. P. van der Voort and P. Ph. H. L. Otto, *Rec. trav. chim.*, **70**, 1054 (1951).

(23) W. E. Truce and E. Wellisch, THIS JOURNAL, **74**, 5177 (1952).

Equal mixtures of the two fractions melted at 202–203°. The base obtained from A melted at 116–118°; that from B melted at 75–77°.

(a) **Fraction A.**—α,α-Diphenyl-1-methyl-2-piperidine-ethanol was synthesized unequivocally from 1-methyl-2-phenacylpiperidine and phenylmagnesium bromide (method I). The base, m.p. 118–120° (from 95% ethanol), was identical with the base obtained from A. The hydrochloride (1C, Table I), m.p. 236–238° dec., was identical with A.[24] Subsequently, this compound was prepared in good yields (75–80%) by the methylation of α,α-diphenyl-2-piperidine-ethanol with formaldehyde and formic acid in dilute aqueous solution.[12] This method has been developed as a good procedure for preparing certain disubstituted 1-methyl-2-piperidine-ethanols (see method O).[25]

(b) **Fraction B.**—A solution of α,α-diphenyl-2-piperidine-ethanol (0.1 mole) and formalin (0.2 mole) in methanol or ethanol was refluxed for several hours, followed by evaporation of the solvent and recrystallization of the residue from aqueous acetone. The product was a white, crystalline solid, m.p. 77–79°. This was identical with the base obtained from fraction B. The hydrochloride, m.p. 224–226° dec., was identical with B.

(24) The decomposition point of the pure salt usually occurred in the range 230–240°, depending on the rate of heating.

(25) R. B. Burtner and J. M. Brown, This Journal, **69**, 630 (1947), described a similar procedure carried out under pressure.

A solution of the base, m.p. 77–79°, in 5% hydrochloric acid was slowly distilled. Formaldehyde evolved, was collected in the aqueous distillate and was identified as its 2,4-dinitrophenylhydrazone, m.p. 163.5–165°.[26] A mixture with authentic formaldehyde 2,4-dinitrophenylhydrazone melted at 164–166°.

Based on the method of synthesis, the analytical data (compound 1B, Table I) and the fact that the compound upon degradation evolved formaldehyde, the structure 3,3-diphenyloctahydropyrid[1,2-c]oxazine (III, R = H; R′ = R² = phenyl) was assigned to this new compound. In addition, the infrared spectra of type II and type IV 2-piperidine-ethanols exhibited a characteristic absorption band at 3300 cm.$^{-1}$, which was attributed to the tertiary hydroxyl group present. This absorption was absent in type III oxazines.

Finally, it was found that 3,3-diphenyloctahydropyrid-[1,2-c]oxazine, when refluxed with excess 25% formic acid, was reduced to α,α-diphenyl-1-methyl-2-piperidine-ethanol. This reaction has been developed as a general method (method P) for the preparation of type IV compounds (R = H).

(26) A similar procedure was used by W. J. Burke, ibid., **71**, 609 (1949). See also W. J. Burke, R. P. Smith and C. Weatherbee, ibid., **74**, 602 (1952).

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Mannich Reactions of Pyrimidines. II. 2-Methylmercapto-4-methyl-6-hydroxypyrimidine and 2-Thio-6-methyluracil[1,2]

By H. R. Snyder, Harold M. Foster[3] and Gustav A. Nussberger

2-Methylmercapto-4-methyl-6-hydroxypyrimidine and 2-thio-6-methyluracil react with piperidine and formaldehyde to yield monopiperidylmethyl derivatives. That condensation in both cases had occurred at the same position of the pyrimidine was shown by desulfurization of both Mannich bases to the same piperidylmethyl derivative of 4-methyl-6-hydroxypyrimidine. Catalytic hydrogenation of the desulfurized Mannich base yielded 2-methylbutyramide, proving the presence of the piperidylmethyl group at the 5-position of the pyrimidine nucleus. A preliminary study of the reactivity of the 5-piperidylmethyl derivative of 4-methyl-6-hydroxypyrimidine as an alkylating agent is reported.
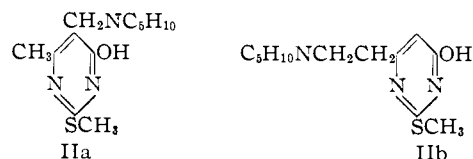
In the first paper in this series[1] the reactivity in the Mannich process of the 2-methyl group of 2,6-dimethyl-4-hydroxypyrimidine, a methylpyrimidine which has but a single ring-activating substituent, was reported. 2-Methylmercapto-4-methyl-6-hydroxypyrimidine (I) contains but a single, strongly ring-activating substituent, the hydroxyl group. The methylmercapto group would be expected to activate the nucleus to some extent. However, since the methylmercapto group cannot tautomerize its effect should be much less pronounced than that of a hydroxyl, thio or amino group.[4] It was felt that it would be of interest to study the reactivity of I in the Mannich reaction and to elucidate the structure of any Mannich bases which might be isolated. It was hoped that this study would help to evaluate the effect of the methylmercapto group as a ring-activating substituent.

An attempt to condense I with dimethylamine hydrochloride and formaldehyde met with failure. However, 2-methylmercapto-4-methyl-6-hydroxy-

pyrimidine (I) was successfully condensed with piperidine and formaldehyde in ethanol solution to yield a Mannich base having the composition calculated for $C_{12}H_{19}N_3OS$ (II). This composition corresponds to a monopiperidylmethyl derivative of I. The Mannich base II could conceivably
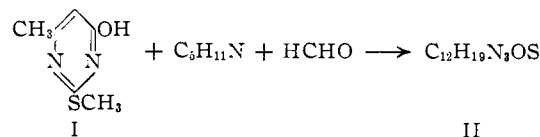
have one of two structures IIa or IIb. Structure IIa, 2-methylmercapto-4-methyl-5-(1-piperidyl-

methyl)-6-hydroxypyrimidine, is given support by the report of Poetsch and Behrend[5] of a nuclear hydroxymethylation of I.

It appeared that the best approach for deciding between structures IIa and IIb would be cleavage

(1) For Paper I in this series, see H. R. Snyder and H. M. Foster, This Journal, **76**, 118 (1954).

(2) Grateful acknowledgment is made of the partial support of this research by a grant (G135) from the National Science Foundation 1954.

(3) National Science Foundation Fellow, September, 1952, to July, 1953.

(4) B. Lythgoe, Quart. Revs., **3**, 181 (1949).

(5) G. Poetsch and R. Behrend, Ann., **448**, 89 (1926).