Anal. Calcd. for $C_{20}H_{24}ClNO_2$: C, 61.01; H, 6.14; N, 3.55. Found: C, 61.05; H, 6.49; N, 3.56.

Spatial relationships between the benzyl and 2-methyl derivatives remain uncertain.

N-Substitution of V.—Introduction of substituents into 1-position of V followed typical procedures described in the previous paper.[1] Products are presented in Table II (1–8).

Synthesis of VII.—VI was refluxed with 48% HBr for 20–30 min. and worked up in the usual way. The products are presented in Table II (9–16).

1-Acetyl-2,3-dimethyl-3-(3-methoxyphenyl)piperidine.—Acetyl chloride (0.59 g.) in acetone (3 ml.) was added to a mixture of V (R = CH_3) (1.1 g.), K_2CO_3 (1 g.), and acetone (20 ml.) at 2–4° over a period of 20 min. The mixture was stirred at 2–4° for 1 hr., at room temperature for 3 hr., then allowed to stand overnight at room temperature and filtered. Acetone was removed by distillation and the residue was dissolved in ether, washed with water, dried, and evaporated. Distillation of the residue gave a colorless oil (1 g.), b.p. 160–161° (0.35 mm.).

Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.65; H, 8.72; N, 5.36.

Acknowledgment.—The authors wish to thank Drs. Everette L. May and Nathan B. Eddy for the aid in arranging some of the compounds described here and previously for the monkey test of addiction liability at the University of Michigan.

Analgetics Based on the Pyrrolidine Ring. IV

J. F. CAVALLA, D. C. BISHOP, R. A. SELWAY, N. E. WEBB,

Parke, Davis and Company, Hounslow, Middlesex, England

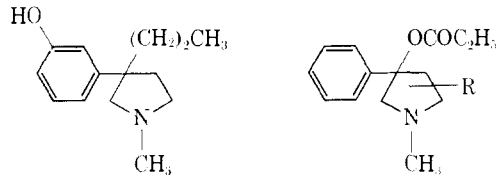
C. V. WINDER, AND M. WELFORD

Parke, Davis and Company, Ann Arbor, Michigan

Received September 19, 1964

Following the discovery of the meperidine level of analgetic activity in the pyrrolidinylphenol (I), over seventy additional compounds of this type have been synthesized. The chosen routes to these compounds provide, in some instances, novel aspects of synthetic pyrrolidine chemistry. Pharmacologically, few, if any, of the additional compounds prepared had activity as great as the original I; the activity of I itself was found to be distributed between its *d* and *l* optical isomers in a ratio of 1:2.

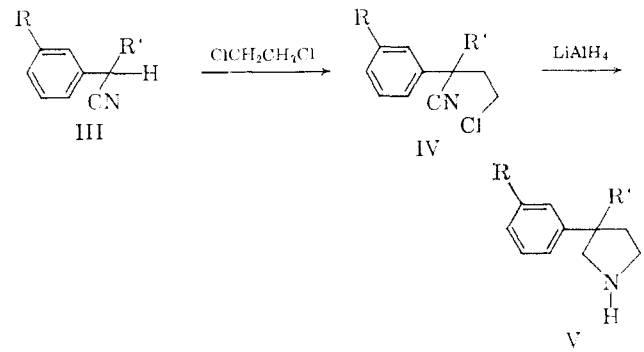
In earlier work on pyrrolidine analgetics[1] we showed that the inclusion of a further alkyl substituent in the pyrrolidine ring changed a compound of sub-codeine activity (II, R = H) into one having clear analgetic activity [II, R = 2- or 4-CH_3 or 2,5-$(CH_3)_2$]. When, therefore, we found a meperidine level of action in the pyrrolidinylphenol (I),[2] we decided to effect substitutions in the free positions of the ring; from this we were led to effect changes in other parts of the molecule.



I II

Chemistry.—While the 3,3-diarylpyrrolidines have been fairly extensively examined, the 3-alkyl-3-aryl and the 3,(2, 4, or 5)-dialkyl-3-arylpyrrolidines have received little attention.[3]

The major intermediate in our work was the chloronitrile IV, prepared by alkylating the appropriate benzyl cyanide with sodamide and an alkyl bromide, then treating the product III with more sodamide and 1,2-dichloroethane. Reduction of the chloronitrile IV with lithium aluminum hydride gave, in excellent yield, the 3,3-disubstituted pyrrolidine V. Other chemical reducing agents found to be inactive were potassium borohydride–aluminum chloride in ether, stannous chloride, sodium metabisulfite, and thiourea dioxide. Catalytic hydrogenation followed by cyclization was also unsuccessful. Probably the nitrile group is so hindered that reductive dehalogenation precedes reduction of the nitrile.



To prepare the 2-substituted pyrrolidines, the chloronitrile IV was allowed to react with a Grignard reagent in dibutyl ether when, on boiling, the Grignard complex VI cyclized spontaneously to the pyrroline VII.[4] It was found preferable to isolate the pyrroline at this stage, even if only in an impure state, then reduce with lithium aluminum hydride to the pyrrolidine VIII rather than add the crude reaction mixture directly to the hydride. Catalytic hydrogenation with a variety of catalysts (Raney nickel alone and with ammonia,

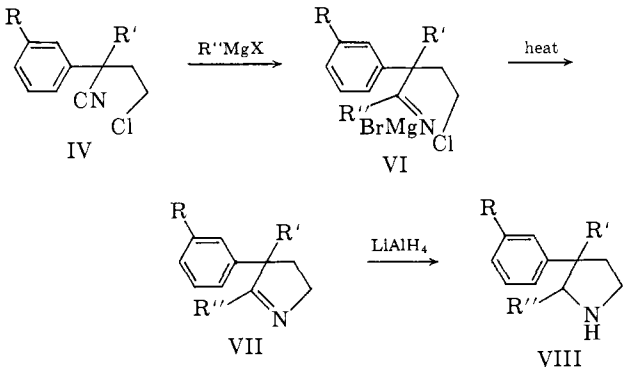
(1) J. F. Cavalla, J. Davoll, M. J. Dean, C. S. Franklin, D. M. Temple, J. Wax, and C. V. Winder, *J. Med. Pharm. Chem.*, **4**, 1 (1961); J. F. Cavalla, R. A. Selway, J. Wax, L. Scotti, and C. V. Winder, *ibid.*, **5**, 441 (1962).

(2) J. F. Cavalla, R. Jones, M. Welford, J. Wax, and C. V. Winder, *ibid.*, **7**, 412 (1964).

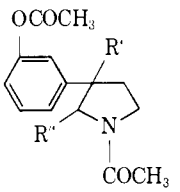
(3) P. J. A. Demoen and P. A. J. Janssen, *J. Am. Chem. Soc.*, **81**, 6281 (1959).

(4) L. C. Craig, H. Bulbrook, and R. M. Hixon, *ibid.*, **53**, 1821 (1931).

platinum in neutral and acid medium, and rhodium on alumina) was generally not satisfactory. In one case (VII, R = H; R′ = C_3H_7; R″ = CH_3) where catalytic hydrogenation of the pyrroline was successful, the resultant pyrrolidine appeared isomeric (*threo–erythro* isomerism?) with that obtained from chemical reduction.



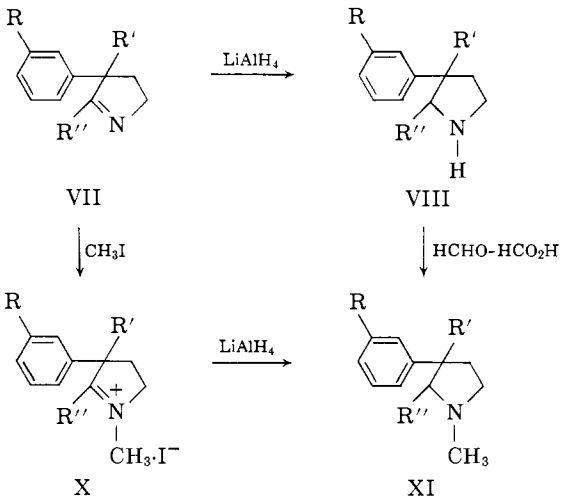
When a *m*-methoxy group was present (III–VIII, R = OCH_3), the above sequence of reactions did not proceed so straightforwardly. Thus in the Grignard step (IV → VI), both the yield and the nature of the products obtained were dependent upon the temperature at which the reaction was performed and on the nature of the Grignard. With methylmagnesium iodide, when the solvent was kept at 125°, the expected product (VII, R = OCH_3) was obtained but, if the dibutyl ether (b.p. 142°) were refluxed, partial demethylation occurred and a phenolic zwitterion (VII, R = OH) was isolated. From the analytical figures, the N-methyl structure could not be excluded, but our proposed structure was confirmed by reduction of the compound with lithium aluminum hydride to the pyrrolidine (VIII, R = OH) which on acetylation gave the N,O-diacetate (IX).



When ethylmagnesium iodide was used, both the normal product (VII, R = OCH_3; R′ = C_3H_7; R″ = C_2H_5) and the zwitterion (VII, R = OH; R′ = C_3H_7; R″ = C_2H_5) were formed, although the normal product was more stable than the analogous methyl compound and could be isolated from reactions where the dibutyl ether had been allowed to boil. With propylmagnesium iodide, no demethylation occurred even after 4 hr. of refluxing; only the methoxypyrroline (VII, R = OCH_3; R′ = R″ = C_3H_7) was isolated.

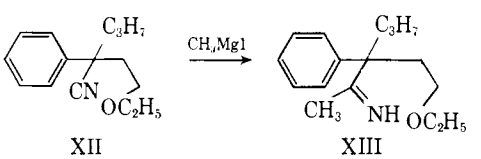
It is noteworthy that the infrared spectra of the three pyrrolidinyl phenols (XI, R = OH; R′ = C_3H_7; R″ = CH_3, C_2H_5, or C_3H_7) show a gradation in the zwitterionic character of the compound. Thus, in the 2500–3500-cm.$^{-1}$ region the NH^+ absorption of the 2-CH_3 compound is intense, that of the 2-C_2H_5 is moderate, while the 2-C_3H_7 shows hardly any NH^+ absorption, and only OH peaks can be seen.

On one occasion excess methyl iodide was used to make the methylmagnesium iodide prepared for reaction with the *m*-methoxyphenylchlorbutyronitrile (IV, R = OCH_3), when the solvent was not refluxed. The unreacted methyl iodide then stayed in the reaction mixture until the pyrroline VII was formed, when reaction between them occurred with the formation of the quaternary pyrrolinium iodide (X). This sequence was confirmed by treating the freshly prepared pyrroline with methyl iodide to obtain the same quaternary. Reduction of X with lithium aluminum hydride gave the N-methylpyrrolidine (XI). No such quaternaries could be obtained with the 2-ethyl- or 2-propylpyrrolines, even on treating the pure pyrroline with methyl iodide.

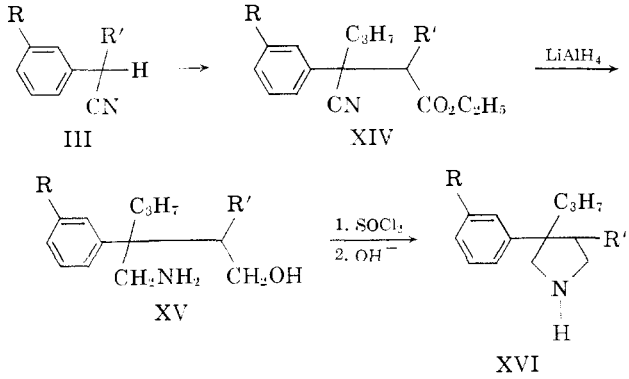


Apart from the reduction of pyrroline quaternaries, the pyrrolidines obtained by these routes were unsubstituted on the nitrogen atom. Methylation at this postion (VIII → XI) was readily effected by boiling with formic acid–formaldehyde mixtures. Demethylation of the *m*-methoxy group was accomplished by boiling with hydrobromic acid.[2]

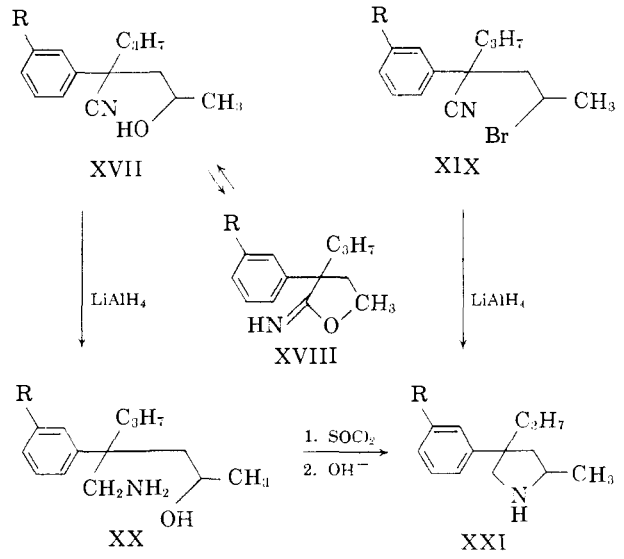
In an attempt to improve the yields obtained from the reaction of the chloronitriles IV with Grignard reagents, the 2-phenylvaleronitrile (III, R = H; R′ = C_3H_7) was alkylated with 2-ethoxyethyl bromide to give the ether XII which with methylmagnesium iodide gave the imine XIII, readily reduced with lithium aluminum hydride to the analogous amine. Difficulty, however, was experienced both in removing the protecting ethyl group and effecting cyclization of the resulting hydroxylamine; the route was not further examined.



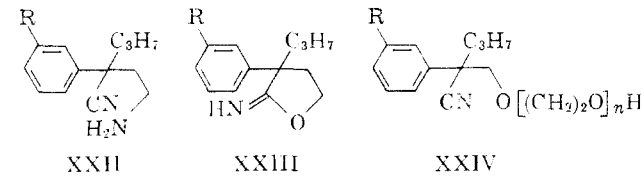
The 4-alkylated pyrrolidines (XVI, R′ = CH_3 or C_3H_7) were obtained by reaction of valeronitrile III with ethyl α-bromopropionate or ethyl α-bromovalerate to give the ester nitrile XIV. This with lithium aluminum hydride gave the hydroxylamine XV which, with thionyl chloride followed by elimination of the elements of hydrochloric acid, cyclized to the pyrrolidine XVI.



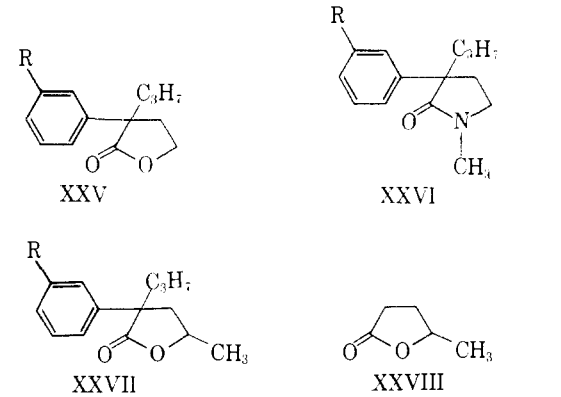
The only 5-alkyl compounds prepared were those having the 5-methyl substituent XXI. These were prepared by treating the valeronitrile III with propylene oxide to give the hydroxynitrile XVII. From the infrared spectrum of the product it was seen that it existed mainly as the imino ether XVIII. Probably for this reason, reaction of the compound with halogenating agents was unsatisfactory. Only in the case of the unsubstituted phenyl compound XVIII (R = H) was it found possible to proceed to the halogenonitrile XIX and from there to the pyrrolidine XXI by reduction and cylization. When the phenyl group was substituted (XVIII, R = OCH_3), the hydroxynitrile imino ether mixture was reduced to the unequivocal hydroxylamine XX which, using previous techniques, gave the pyrrolidine XXI without isolation of the halogenoamine.



Attempts to improve yields in the synthesis of I were were generally disappointing. Treatment of 1-chloro-1-*m*-methoxyphenylbutane with sodium cyanide resulted in considerable dehydrohalogenation. Substitution of 1-bromo-2-chloroethane or 1,2-dibromoethane for 1,2-dichloroethane in alkylation of III (R′ = C_3H_7) to IV resulted in little improvement. Ethylenimine failed to react with III (R′ = C_3H_7) to give the aminonitrile XXII. Substitution of ethylene oxide for propylene oxide to produce the imino ether XXIII[5] gave poor yields and the major product appeared to be the high-boiling polyether XXIV. The substitution of chlorohydrin for ethylene oxide[6] gave no better yields.



From the imino ether that was obtained from these routes, however, the corresponding lactone XXV was readily prepared and with methylamine, under pressure, gave the lactam XXVI. It is of interest that the corresponding 5-methyl lactone XXVII obtained by hydrolysis of the imino ether XVIII gave no lactam with methylamine under the most forcing conditions, unlike the simpler compound XXVIII which gave a lactam with ammonia.[7] The lactam XXVI gave the pyrrolidine with lithium aluminum hydride, but electrolytic reduction[7] was not effective.



Substitution, other than *m*-methoxy, on the 3-phenyl group was achieved by starting with the appropriately substituted butyrophenone following the synthesis given in our earlier work.[2]

Finally, variation of the nitrogen substituent was effected by treating a pyrrolidine possessing a free NH group (V) either with the requisite alkyl halide or, in one case, with a Mannich base quaternary following procedures described earlier.[1] The N-oxide was obtained by treating the N-methyl compound with monoperphthalic acid.

Attempts to resolve the most active compound I as its methyl ether with *d*- and *l*-tartaric acid were unsuccessful. Upon using *d*- and *l*-tolyltartaric acid, however, the two optical isomers were obtained which, with the customary chemical procedures, gave the two isomeric phenols and the two acetates.

Experimental[9]

The physical properties of the compounds prepared are collected in Tables I-IV. The experimental details given here directly relate to those tables.

Substituted Benzyl Cyanides (Table I). Method A.—This method is modeled on that of Murray and Cloke.[10] The benzyl cyanide (1 mole) was added to a suspension of sodamide (1 mole) in dry benzene (1 l.) while keeping the temperature below 5°, and stirred at this temperature for 1 hr. The alkyl halide

(5) F. Hoffmann-La Roche, British Patent 811,698 (April 8, 1959).

(6) F. E. King, K. G. Latham, and M. W. Partridge, *J. Chem. Soc.*, 4268 (1952).

(7) A. P. Dunlop and E. Sherman, U. S. Patent 2,681,349 (June 15, 1954).

(8) E. Späth and F. Breusch, *Monatsh.*, **50**, 349 (1928).

(9) Melting points are uncorrected, the work being completed before the requirements of American Chemical Society publications were known.

(10) J. V. Murray and J. B. Cloke, *J. Am. Chem. Soc.*, **68**, 126 (1946).

(1.1 moles) was then added slowly to the stirred mixture (temperature still below 5°). With continuous stirring, the whole was allowed to attain room temperature during 2 hr. The mixture was then refluxed for 3 hr., cooled, washed with water, dilute acid, and water until neutral and then concentrated and distilled *in vacuo*.

Method B.—The monosubstituted benzyl cyanide (1 mole) in dry benzene (600 ml.) was added to a stirred suspension of sodamide (1 mole) in dry benzene (1 l.) through which a stream of dry nitrogen was passing. No attempt was made to cool the reaction mixture; for convenience the addition was begun with the sodamide suspension at approximately 40°. Once addition was complete the mixture was refluxed and stirred for 3 hr. while continuing the passage of nitrogen. Heating was discontinued, the mixture was cooled to 5–10°, then treated slowly with the alkyl halide (1 mole). Generally, an exothermic reaction ensued, and efficient cooling was needed to maintain the temperature limits. After addition, the suspension was stirred, allowed to regain room temperature, refluxed for 3 hr., cooled, washed with water, and distilled *in vacuo*.

Method C.—The monosubstituted benzyl cyanide (1 mole) in dry ether (400 ml.) was added to a stirred suspension of sodamide (1 mole) in dry ether (700 ml.) through which a stream of nitrogen was passing. An exothermic reaction ensued, and the solvent boiled. After addition of the nitrile, the mixture was stirred and refluxed for 3 hr., (nitrogen atmosphere). The heat was then removed and the alkylene oxide (1.1 moles) was added in dry ether (200 ml.). After addition, the mixture was again refluxed for 2 hr., cooled, and washed with water. Concentration and distillation *in vacuo* gave the product as a mixture of hydroxynitrile and imino ether.

Method D.—The appropriate hydroxynitrile, imino ether, or nitrile ester (1 mole) in dry ether (400 ml.) was added to a suspension of lithium aluminum hydride (1–2 moles) in dry ether (600 ml.) with stirring. The mixture was then refluxed for 4 hr., 5 *N* caustic soda (50 ml.) was then added cautiously, and reflux and stirring were continued for another hour. The mixture was filtered, concentrated, and distilled to give the required hydroxyl- or alkoxyamine.

Method E.—The hydroxynitrile–imino ether mixture (1 mole) was added cautiously to phosphorus tribromide (2.5 moles). The mixture was refluxed for 30 min., cooled, and poured into ice–water. Extraction with benzene gave a light red oil which, on distillation *in vacuo*, gave the bromonitrile.

Method F.—Was essentially the method of Icke, *et al.*[11]

Method G.—The cyano ether (23.1 g.) in dry toluene (150 ml.) was added to a solution of methylmagnesium iodide [from 2.6 g. of Mg in dry ether (100 ml.)]. The ether was removed by distillation while replacing the lost volume with dry toluene. The toluene solution was refluxed gently overnight, cooled, shaken vigorously with NH_4Cl and ice–water, concentrated, and distilled *in vacuo* to give the imine.

Substituted Acrylic Esters (Table II).—These compounds were prepared following the method described in our previous work.[2]

Succinimides (Table III).—These compounds were prepared following the previously described method.[2]

Pyrrolines. Method H.—The chloronitrile (1 mole) in dibutyl ether (400 ml.) was added to a solution of the appropriate Grignard reagent (3 moles) in dibutyl ether (800 ml.), and the whole was refluxed and stirred for 6 hr. The mixture was cooled and shaken vigorously with NH_4Cl and ice–water (30%). The ether solution was concentrated and the crude pyrroline was either distilled or used as such.

Method I.—Using 3-cyano-3-(*m*-methoxyphenyl)hexyl chloride and methylmagnesium iodide in method H gave, after the addition of the cold aqueous NH_4Cl, an insoluble viscous gum which, on trituration with chloroform, furnished a crystalline solid. Further quantities of this solid were obtained from the dibutyl ether. In a potentiometric titration it had pK = 5.3 and 12.0, corresponding to the basic nitrogen and the phenolic hydroxyl. The structure for this compound was confirmed by conversion to 3-(*m*-acetoxyphenyl)-1-acetyl-2-methyl-3-propylpyrrolidine (Table IV).

Method J.—Method H was followed except that the dibutyl ether solution was kept at 125° for 4 hr. then hydrolyzed with 30% aqueous NH_4Cl at 60°.

Method K.—Following method H but refluxing for only 4 hr. gave an insoluble gum which, on trituration with chloroform, yielded the phenolic zwitterion, m.p. 144–148°. Concentration of the dibutyl ether layer gave the *m*-methoxyphenylpyrroline, b.p. 140–150° (1.0 mm.), which was not purified. As with the corresponding 2-methyl compound (method I) confirmation of the phenolic structure was obtained by preparation of the N,O-diacetate (Table IV).

Method L.—Using an excess of methyl iodide (1.8 moles) when making the Grignard reagent in dibutyl ether for use in method J gave a larger-than-usual quantity of insoluble gum. On trituration with ether this furnished the pyrrolinium quaternary, identical with that obtained by treating freshly distilled 3-(*m*-methoxyphenyl)-2-methyl-3-propylpyrrol-1-ine with methyl iodide in acetone.

Pyrrolidones and lactones (method M) were prepared from crude 3-cyano-3-(*m*-methoxyphenyl)-1-hexanol following the Hoffmann-LaRoche method.[5]

Method N.—3-Cyano-3-phenyl-1-hexanol[5] (24 g.) in aqueous methylamine (120 ml., 40%) was held at 190° (autoclave) overnight. Distillation *in vacuo* gave the pyrrolidone.

Substituted Pyrrolidines (Table IV). Method O.—The appropriate succinimide (Table III) was reduced with lithium aluminum hydride[12] to give the pyrrolidine.

Method P.—The appropriate halogenonitrile (Table I) (1 mole) in dry ether was added to a stirred suspension of lithium aluminum hydride (1 mole) in dry ether. The mixture was refluxed for 6 hr. then worked up following method D.

Method Q.—The appropriate pyrroline (Table III) (1 mole) was reduced with lithium aluminum hydride (1 mole) following method D.

Method R.—The pyrroline (5.2 g.) in absolute ethanol (100 ml.) containing concentrated HCl (2.5 ml.) was shaken at atmospheric pressure and 50° with palladized charcoal (0.5 g., 10%) and hydrogen; 470 ml. (theory, 580 ml.) was absorbed. Filtration, concentration, basification, and ether extraction followed by distillation *in vacuo* gave the pyrrolidine.

Method S.—The appropriate hydroxylamine (Table I) (1 mole) in chloroform (500 ml.) was saturated with HCl, cooled to 0°, and treated with thionyl chloride (2 moles). The mixture was stirred and allowed to regain room temperature, brought to reflux temperature during 1 hr., and held there for 2 hr. The solution was concentrated, poured into water, and strongly basified with K_2CO_3, and the stirred mixture was kept at 95° for 1 hr. Isolation and fractional distillation of the resulting water-insoluble oil gave the required pyrrolidine.

Method T.—The pyrroline methiodide (Table III) (5 g.), slurried in dibutyl ether (125 ml.), was added to a stirred suspension of lithium aluminum hydride (1 g.) in dibutyl ether (25 ml.). The whole was refluxed and stirred for 1 hr. Water (5 ml.) was added cautiously, and the mixture was stirred for 20 min. filtered, concentrated, and distilled.

Method U.—The appropriate methyl ether (Table IV) (0.1 mole) in hydrobromic acid (90 ml., 48%) was refluxed for 3 hr. and concentrated *in vacuo* to an oil. It was dissolved in water (100 ml.) and basified with K_2CO_3, and the precipitated oil was isolated by extraction with five 80-ml. portions of a benzene–ether mixture (2:1).

Method V.—The phenol (or, in one case, the secondary alcohol) (0.1 mole) in pyridine (40 ml.) with the appropriate acid anhydride (80 ml.) was held at 110° for 2 hr., and the mixture was concentrated and distilled *in vacuo*.

Method W.—The phenolic pyrroline (Table III) (1 mole) was reduced to the corresponding pyrrolidine in dry tetrahydrofuran using lithium aluminum hydride (1 mole) (method D). The crude product was then acetylated according to method V.

Method X.—The preparation of compounds somewhat similar to these is described in our earlier work.[1]

Method Y.—The racemic 3-(*m*-methoxyphenyl)-1-methyl-3-propylpyrrolidine (150 g.) in 2-propanol (1.5 l.) at 50° was treated with a solution of (−)-di-*p*-toluyl-L-tartaric acid (273 g.) in 2-propanol (1.2 l.) to give, on cooling and standing, the crude salt (253 g.), m.p. 121–123°, brought by three further crystallizations from 2-propanol to m.p. 138° (119 g.), $[\alpha]^{25}D$ −89.4° (*c* 0.8, ethanol).

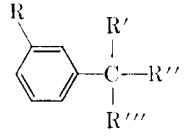
Anal. Calcd. for $C_{15}H_{23}NO \cdot C_{20}H_{18}O_8$: C, 67.8; H, 6.7; N, 2.3. Found: C, 67.7; H, 6.7; N, 2.2.

(11) R. N. Icke, B. B. Wisegarver, and G. A. Alles in "Organic Syntheses," Coll. Vol. III, E. C. Horning, Ed., John Wiley and Sons, Inc., New York, N. Y., 1955, p. 723.

(12) K. C. Schreiber and V. P. Fernandez, *J. Org. Chem.*, **26**, 1744 (1961).

TABLE I

SUBSTITUTED BENZYL CYANIDES

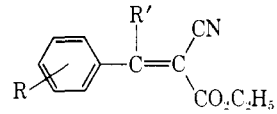


R	R′	R″	R‴	B.p., °C. (mm.)	$n^{20}D$	Method	Yield, %	Formula	Calcd., %			Found, %		
									C	H	N	C	H	N
H	n-C_3H_7	CH_2CH_2Br	CN	118 (0.4)	1.5329	E	60	$C_{13}H_{16}BrN$	58.6	6.1	5.3	59.6	6.3	5.0
H	n-C_3H_7	$CH_2CHBrCH_3$	CN	117–120 (0.3)	1.5296	E	67	$C_{14}H_{18}BrN$	60.0	6.5		60.2	6.4	
H	n-C_3H_7	$CH_2CH(OH)CH_3$	CN	125–130 (0.8)	1.5238	C	70	$C_{14}H_{19}NO$	77.4	8.8	6.5	77.6	9.3	6.3
H	n-C_3H_7	$CH_2CH_2OC_2H_5$	CN	114 (0.5)	1.4950	B	58	$C_{15}H_{21}NO$	77.9	9.2	6.1	77.9	9.2	6.1
H	n-C_3H_7	$CH_2CH_2NHCH_3$	CN	125–132 (0.4)	1.5410	B	20	$C_{14}H_{20}N_2$	77.7	9.3	13.0	77.2	9.4	13.2
H	n-C_3H_7	$CH(CO_2C_2H_5)CH_3$	CN	134–140 (0.7)	1.5000	B	42	$C_{16}H_{21}NO_2$	74.1	8.2	5.4	74.9	8.4	5.5
H	n-C_3H_7	$CH(CH_2OH)CH_3$	CH_2NH_2	148–152 (0.8)	1.5382	D	73	$C_{14}H_{22}NO$	76.0	10.5	6.3	76.2	10.5	6.4
H	n-C_3H_7	$CH_2CH_2OC_2H_5$	$C(NH)CH_3$	117 (0.4)	1.5090	G	35	$C_{16}H_{25}NO$	77.7	10.2		78.1	10.1	
H	n-C_3H_7	$CH_2CH_2OC_2H_5$	$CH(NH_2)CH_3$	119 (0.3)	1.5099	D	41	$C_{16}H_{27}NO$	77.1	10.9		77.2	11.0	
CH_3O	C_2H_5	H	CN	100–102 (0.4)	1.5142	A	90[a]	$C_{11}H_{13}NO$	75.4	7.5	8.0	76.2	7.7	7.7
CH_3O	n-C_3H_7	H	CN	112–115 (0.9)	1.5165	A	90	$C_{12}H_{15}NO$	76.2	8.0	7.4	76.1	8.4	7.5
CH_3O	n-C_4H_9	H	CN	118–120 (0.4)	1.5084	A	83	$C_{13}H_{17}NO$	76.8	8.4	6.9	77.4	8.2	6.4
CH_3O	C_2H_5	CH_2CH_2Cl	CN	127–134 (0.6)	1.5259	B	43	$C_{13}H_{15}ClNO$	65.6	6.8	14.9[b]	65.3	6.8	14.5[b]
CH_3O	n-C_3H_7	CH_2CH_2Cl	CN	131–136 (0.5)	1.5220	B	50	$C_{14}H_{18}ClNO$	66.9	7.2	14.1[b]	69.1	7.5	12.7[b]
CH_3O	n-C_3H_7	CH_2CH_2Br	CN	140–146 (0.7)	1.5310	B	43[d]	$C_{14}H_{18}BrNO$			27.0[c]			24.4[c]
CH_3O	n-C_4H_9	CH_2CH_2Cl	CN	145–146 (0.7)	1.5164	B	56[d]	$C_{15}H_{20}ClNO$	67.8	7.6	13.4[b]	70.4	8.4	10.0[b]
CH_3O	n-C_3H_7	CH_2CH_2OH	CN	140–150 (0.8)	1.5208	C	8	$C_{14}H_{19}NO_2$	72.1	8.2	6.0	71.5	8.0	5.6
CH_3O	n-C_3H_7	$CH_2CH(OH)CH_3$	CN	143–146 (0.7)	1.5270	C	72	$C_{15}H_{21}NO_2$	72.8	8.6	5.7	73.8	9.2	5.6
CH_3O	n-C_3H_7	$CH(CO_2C_2H_5)CH_3$	CN	145–150 (0.7)	1.5037	B	55	$C_{17}H_{23}NO_3$	70.6	8.0	4.8	70.1	8.0	4.3
CH_3O	n-C_3H_7	$CH(CO_2C_2H_5)C_3H_7$	CN	142–150 (0.8)	1.5062	B	23	$C_{19}H_{27}NO_3$	71.9	8.6	4.4	71.5	8.5	4.6
CH_3O	n-C_4H_7	$CH_2CH(OH)CH_3$	CH_2NH_2	153–155 (0.5)	1.5302	D	65	$C_{15}H_{25}NO_2$	71.7	10.0	5.6	72.0	10.1	5.5
CH_3O	n-C_3H_7	$CH(CH_2OH)CH_3$	CH_2NH_2	163–165 (0.7)	1.5400	D	85	$C_{15}H_{25}NO_2$	71.7	10.0	5.6	71.5	10.4	5.4
CH_3O	n-C_3H_7	$CH(CH_2OH)C_3H_7$	CH_2NH_2	180–190 (0.6)	[e]	D	56	$C_{17}H_{29}NO_2$	73.1	10.5	5.0	73.3	10.4	4.7
CH_3O	n-C_3H_7	$CH(CH_2OH)CH_3$	$CH_2N(CH_3)_2$	129–130[f]		F	40	$C_{17}H_{29}NO_2$	73.1	10.5	5.0	73.1	10.0	4.9
CH_3O	n-C_3H_7	$CH(CH_2OH)CH_3$	$CH_2N(CH_3)_2$	179–180[f]	[g]			$C_{17}H_{30}ClNO_2$	64.8	9.5	4.4	64.4	9.0	4.3

[a] K. Schmitt and E. Lindner [*Arch. Pharm.*, **295**, 744 (1962)] give b.p. 112–115° (0.2 mm.); H. Kugita and T. Oine [*Chem. Pharm. Bull.* (Tokyo), **11**, 253 (1963)] give b.p. 140–145° (5 mm.) [b] Chlorine analysis. [c] Bromine analysis. [d] Material used in this crude state. [e] Too viscous for measurement. [f] Melting point. [g] Hydrochloride.

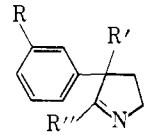
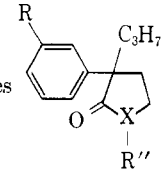
TABLE II

SUBSTITUTED ETHYL ACRYLATES



R	R′	B.p., °C. (mm.)	$n^{20}D$	Yield, %	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
p-CH_3O	*n*-C_3H_7	158–163 (0.6)	1.5505	70	$C_{16}H_{19}NO_3$	70.3	7.0	5.1	70.5	7.1	5.3
o-CH_3O	*n*-C_3H_7	163–166 (1.1)	1.5334	54	$C_{16}H_{19}NO_3$	70.3	7.0	5.1	70.6	7.3	5.4
m-CH_3	*n*-C_3H_7	155–157 (0.9)	1.5326	68	$C_{16}H_{19}NO_2$	74.7	7.4	5.4	75.0	7.6	5.3
m,p-$(CH_3O)_2$	*n*-C_3H_7	170–194 (0.8)	1.5546	42	$C_{17}H_{21}NO_4$	67.3	7.0	4.6	67.0	7.2	4.6
m-Cl	*n*-C_3H_7	138–142 (0.5)		73	$C_{15}H_{16}ClNO_2$	64.8	5.8	5.0	64.3	5.7	5.0

TABLE III

R	R′	R″ or X	B.p., °C. (mm.)	$n^{20}D$	Yield, %	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N	Method
Succinimides 													
m-OH	CH_3	CH_3	142[a]		54	$C_{12}H_{13}NO_3$	65.7	6.0	6.4	65.8	6.0	6.1	
o-CH_3O	*n*-C_3H_7	CH_3	Gum	*b*	69	$C_{15}H_{19}NO_3$	68.9	7.3	5.4	69.9	7.5	5.1	
p-CH_3O	*n*-C_3H_7	CH_3	180–184 (0.4)	*b*	52	$C_{15}H_{19}NO_3$	68.9	7.3	5.4	68.9	6.9	5.2	
m-CH_3	*n*-C_3H_7	CH_3	150–153 (0.9)		62	$C_{15}H_{19}NO_2$	73.4	7.8	5.7	73.3	7.7	5.6	
m-Cl	*n*-C_3H_7	CH_3	134–136 (0.2)	1.5498	70	$C_{14}H_{16}ClNO_2$	63.2	6.0	5.3	62.6	6.1	5.0	
m,p-$(CH_3O)_2$	*n*-C_3H_7	CH_3	94–96[a]		30	$C_{16}H_{21}NO_4$	66.0	7.3	4.8	65.6	7.3	5.1	
Pyrrolines 													
H	*n*-C_3H_7	CH_3	110–111 (1.0)	1.5250	41	$C_{14}H_{19}N$	83.5	9.5	7.0	83.5	9.7	6.5	H
OH	*n*-C_3H_7	CH_3	141–143[a]		28	$C_{14}H_{19}NO$	77.4	8.8	6.5	77.3	9.3	6.1	I
CH_3O	*n*-C_3H_7	CH_3	135–150 (0.4)	1.53[c]	35	$C_{15}H_{21}NO$	77.9	9.2	6.1	76.9	9.6	6.1	J
OH	*n*-C_3H_7	C_2H_5	144–148[a]		7	$C_{15}H_{21}NO$	77.9	9.2	6.1	77.9	9.0	6.2	K
CH_3O	*n*-C_3H_7	C_2H_5	140–150 (1.0)	1.535[c]	20								K
CH_3O	*n*-C_3H_7	CH_3	147–148[a]			$C_{16}H_{24}INO$[d]	51.5	6.5	3.8	51.2	6.7	4.0	L
Pyrrolidones and Lactones 													
CH_3O	...	O	158–165 (0.8)	1.5278	28	$C_{14}H_{18}O_3$	71.8	7.7		72.1	7.7		M
H	CH_3	N	130–140 (0.5)	1.5329	69	$C_{14}H_{19}NO$	77.4	8.8	6.5	77.8	9.0	6.1	N

[a] Melting point. [b] Too viscous for determination. [c] Could not be obtained pure. [d] Methyl iodide quaternary.

The bulked mother liquors from the above, on slight concentration, gave a further 29 g. of levo base salt.

The mother liquors were concentrated and treated with aqueous potassium carbonate, and the oily base was isolated and converted to its (+)-di-*p*-toluyl-D-tartaric acid salt, m.p. 129–131° (215 g.). Two further crystallizations from 2-propanol brought this to m.p. 138–139° (129 g.), $[\alpha]^{28}D$ +81.0° (*c* 0.9, ethanol).

Anal. Found: C, 68.1; H, 6.9; N, 2.2.

Treatment of these salts with base gave quantitative recovery of the two optical isomers listed in Table IV.

Method Z.—Oxidation of the pyrrolidine (15 g.) in ether (350 ml.) with monoperphthalic acid (33 g.) at room temperature for 3 days gave an insoluble oily solid. The supernatant liquid was removed and the solid was dissolved in aqueous 2 *N* Na_2CO_3 and isolated with seven 100-ml. portions of chloroform. The crude buff solid was purified by crystallization from chloroform–ether mixtures.

1-*m*-Methoxyphenyl-1-butanol.—*m*-Methoxybenzaldehyde (1.8 kg.) in dry ether (3 l.) was added to a stirred solution of propylmagnesium bromide (from 440 g. of magnesium and 2.3 kg. of propyl bromide) in dry ether (5 l.). The mixture was refluxed for 7 hr., cooled, and poured onto a stirred mixture of NH_4Cl (2 kg.), water (4 l.), and crushed ice (3 kg.). Isolation in the normal way gave the almost pure secondary alcohol (2385 g.), a portion of which distilled at b.p. 106° (0.8 mm.), $n^{20}D$ 1.5236.

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.3; H, 9.0. Found: C, 73.3; H, 8.9.

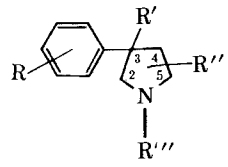
1-Chloro-1-*m*-methoxyphenylbutane.—1-*m*-Methoxyphenyl-1-butanol (90 g.) in pyridine (55 ml.) was treated below 30° with thionyl chloride (66 g.) during 1 hr. The stirred mixture was warmed to 80°; an exothermic reaction set in and the temperature rose to 110°. The mixture was allowed to cool to 40°, poured into ice–water, and acidified with 2 *N* H_2SO_4. Isolation with ether and distillation gave the slightly impure secondary chloride (77 g.), b.p. 89–93° (0.8 mm.), $n^{20}D$ 1.5264, which was analyzed as follows.

Anal. Calcd. for $C_{11}H_{15}ClO$: C, 66.5; H, 7.6; Cl, 17.8. Found: C, 68.3; H, 8.1; Cl, 15.7.

Reaction of 1-Chloro-1-*m*-methoxyphenylbutane with Sodium Cyanide.—The secondary chloride (49 g.) was added dropwise to

TABLE IV

SUBSTITUTED PYRROLIDINES



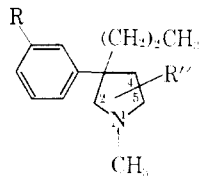
	R	R'	R''	R'''	B.p., °C. (mm.)	Method	Yield, %	$n^{22}D$	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N	[α]D	c in EtOH
1	H	*n*-C_3H_7	H	H	94–95 (0.5)	P	80	1.5316	$C_{13}H_{19}N$	82.5	10.1	7.4	82.8	10.2	7.3		
2	H	*n*-C_3H_7	2-CH_3	H	100–102 (0.3)	R	48	1.5282	$C_{14}H_{21}N$	82.7	10.4	6.9	82.6	10.2	7.0		
3	H	*n*-C_3H_7	2-CH_3	H	183–185[a]	R		*b*	$C_{14}H_{22}ClN$	70.1	9.3	5.8	70.2	9.0	5.7		
4	H	*n*-C_3H_7	2-CH_3	H	110–125 (1.0)	Q	30	1.5237	$C_{14}H_{21}N$	82.7	10.4	6.9	82.4	10.0	7.5		
5	H	*n*-C_3H_7	2-CH_3	H	231–235[a]	Q		*b*	$C_{14}H_{22}ClN$	70.1	9.3	14.8[c]	70.4	9.4	14.9[c]		
6	H	*n*-C_3H_7	4-CH_3	H	120 (1.2)	S	72	1.5305	$C_{14}H_{21}N$	82.7	10.4	6.9	82.2	10.7	6.7		
7	H	*n*-C_3H_7	5-CH_3	H	94–95 (0.6)	P	80	1.5214	$C_{14}H_{21}N$	82.7	10.4	6.9	82.8	10.4	6.7		
8	H	*n*-C_3H_7	2-CH_3	CH_3	123–125 (2.5)	F	33	1.5185	$C_{15}H_{23}N$	82.9	10.7	6.5	82.5	10.8	6.2		
9	H	*n*-C_3H_7	4-CH_3	CH_3	172–174[a]	F	76	*b*	$C_{15}H_{24}ClN$	71.0	9.5	5.5	70.7	9.9	5.6		
10	H	*n*-C_3H_7	5-CH_3	CH_3	88–89 (0.5)	F	80	1.5110	$C_{15}H_{23}N$	82.9	10.7	6.5	83.5	10.7	6.3		
11	*o*-CH_3O	*n*-C_3H_7	H	CH_3	101 (0.5)	O	69	1.5233	$C_{15}H_{23}NO$	77.2	9.9	6.0	76.9	10.1	5.9		
12	*o*-OH	*n*-C_3H_7	H	CH_3	163–165[a]	U	72	*d*	$C_{13}H_{20}BrNO$	56.0	7.3	4.7	55.9	7.4	4.3		
13	*o*-CH_3CO_2	*n*-C_3H_7	H	CH_3	128 (0.9)	V	70	1.5164	$C_{16}H_{23}NO_2$	73.5	8.9	5.4	73.8	8.9	5.3		
14	*m*-Cl	*n*-C_3H_7	H	CH_3	116–118 (1.1)	O	63	1.5308	$C_{13}H_{20}ClN$	70.8	8.4	5.9	70.8	8.6	6.0		
15	*m*-CH_3	*n*-C_3H_7	H	CH_3	141–142[a]	O	70	*b*	$C_{15}H_{24}ClN$	71.0	9.5	5.5	71.2	9.4	5.5		
16	*p*-CH_3O	*n*-C_3H_7	H	CH_3	118–126 (0.5)	O	12	1.5270	$C_{15}H_{23}NO$	77.2	9.9	6.0	76.9	9.9	5.9		
17	*p*-OH	*n*-C_3H_7	H	CH_3	144–149 (0.2)	U	64	*e*	$C_{14}H_{21}NO$	76.7	9.7	6.4	76.4	9.9	6.5		
18	*p*-CH_3CO_2	*n*-C_3H_7	H	CH_3	122 (0.2)	V	70		$C_{16}H_{23}NO_2$	73.5	8.9	5.4	73.9	9.1	5.4		
19	*m,p*-$(CH_3O)_2$	*n*-C_3H_7	H	CH_3	158–159[a]	O	83	*b*	$C_{16}H_{26}ClNO_2$	64.1	8.5	11.8[c]	64.3	8.5	12.0[c]		
20	*m,p*-$(OH)_2$	*n*-C_3H_7	H	CH_3	192–195 (0.9)	U	40	*e*	$C_{14}H_{21}NO_2$	71.5	9.0	6.0	71.9	8.7	5.7		
21	*m*-CH_3O	C_2H_5	H	H	117–119 (0.5)	P	67	1.5390	$C_{13}H_{19}NO$	76.1	9.3	6.8	76.5	9.4	6.5		
22	*m*-CH_3O	C_2H_5	H	CH_3	108–109 (0.4)	F	89	1.5278	$C_{14}H_{21}NO$	76.7	9.7	6.4	77.0	9.7	6.3		
23	*m*-CH_3O	*n*-C_4H_9	H	H	130–132 (0.5)	P	45[f]	1.5284	$C_{15}H_{23}NO$	77.2	9.9	6.0	76.8	10.0	5.9		
24	*m*-CH_3O	*n*-C_4H_9	H	CH_3	123–124 (0.4)	F	82	1.5199	$C_{16}H_{25}NO$	77.7	10.2	5.7	78.0	10.2	5.3		
25	*m*-CH_3O	*n*-C_3H_7	2-CH_3	H	126–127 (0.4)	Q	89	1.5321	$C_{15}H_{23}NO$	77.2	9.9	6.0	77.2	10.1	5.7		
26	*m*-CH_3O	*n*-C_3H_7	2-CH_3	CH_3	120–121 (0.4)	T	85	1.5224	$C_{16}H_{25}NO$	77.7	10.2	5.7	78.0	10.1	5.5		
27	*m*-CH_3O	*n*-C_3H_7	4-CH_3	H	121 (0.7)	S	63	1.5342	$C_{15}H_{23}NO$	77.2	9.9	6.0	76.6	9.9	5.9		
28	*m*-CH_3O	*n*-C_3H_7	4-CH_3	CH_3	114 (0.8)	F	91	1.5213	$C_{16}H_{25}NO$	77.7	10.2	5.7	77.2	10.3	5.6		
29	*m*-CH_3O	*n*-C_3H_7	5-CH_3	H	124 (0.3)	S	69	1.5292	$C_{15}H_{23}NO$	77.2	9.9	6.0	77.0	10.1	5.7		
30	*m*-CH_3O	*n*-C_3H_7	5-CH_3	CH_3	112–116 (0.5)	F	60	1.5184	$C_{16}H_{25}NO$	77.7	10.2	5.7	78.1	10.5	5.8		
31	*m*-CH_3O	*n*-C_3H_7	2-C_2H_5	H	131–133 (0.6)	Q	42	1.5300	$C_{16}H_{25}NO$	77.7	10.2	5.7	77.2	10.6	5.4		
32	*m*-CH_3O	*n*-C_3H_7	2-C_2H_5	CH_3	124–125 (0.6)	F	80	1.5240	$C_{17}H_{27}NO$	78.1	10.4	5.4	78.2	10.6	5.1		
33	*m*-CH_3O	*n*-C_3H_7	2-*n*-C_3H_7	H	150–152 (0.7)	Q	24	1.5297	$C_{17}H_{27}NO$	78.1	10.4	5.4	78.0	10.5	5.0		
34	*m*-CH_3O	*n*-C_3H_7	2-*n*-C_3H_7	CH_3	130–136 (0.8)	F	31	1.5235	$C_{18}H_{29}NO$	78.5	10.6	5.1	78.6	10.7	5.3		
35	*m*-CH_3O	*n*-C_3H_7	4-*n*-C_3H_7	H	146–148 (1.0)	S	49	1.5299	$C_{17}H_{27}NO$	78.1	10.4	5.4	78.0	10.1	5.0		
36	*m*-CH_3O	*n*-C_3H_7	4-*n*-C_3H_7	CH_3	129–136 (0.5)	F	80	1.5203	$C_{18}H_{29}NO$	78.5	10.6	5.1	78.6	10.8	4.9		
37	*m*-CH_3O	*n*-C_3H_7	H	CH_3, O[e]	170–171[a]	Z	25		$C_{15}H_{23}NO_2$	72.3	9.3	5.6	72.3	8.9	5.8		
38	*m*-CH_3O	*n*-C_3H_7	H	C_2H_5	149–150[a]	X	67	*b*	$C_{16}H_{26}ClNO$	67.7	9.2	4.9	67.7	9.0	4.9		
39	*m*-CH_3O	*n*-C_3H_7	H	*n*-C_4H_9	160–162 (0.5)	X	40	1.5065	$C_{20}H_{35}NO$	79.4	11.1	4.1	79.1	11.2	4.6		

40	*m*-CH_3O	*n*-C_3H_7	H	$(CH_2)_2O(CH_2)_2OH$	182–184 (0.6)	X	25	1.5270	$C_{18}H_{29}NO_3$	70.3	9.5	4.6	71.1	9.2	4.9		
41	*m*-CH_3O	*n*-C_3H_7	H	$(CH_2)_2O(CH_2)_2OH$	106–107[a]			*b*	$C_{18}H_{30}ClNO_3$	62.9	8.8	4.1	63.6	8.8	4.3		
42	*m*-CH_3O	*n*-C_3H_7	H	$(CH_2)_2C_6H_4$-*p*-NO_2	102–104[a]	X	30	*b*	$C_{22}H_{29}ClN_2O_3$	65.3	7.2	6.9	65.4	7.6	6.7		
43	*m*-CH_3O	*n*-C_3H_7	H	$(CH_2)_2C_6H_4$-*p*-NH_2	254–255[a]	X	50	*h*	$C_{22}H_{32}Cl_2N_2O^i$	63.5	7.9	6.7	63.4	7.7	6.8		
44	*m*-CH_3O	*n*-C_3H_7	H	$(CH_2)_2N$⟨⟩O	216–218[a]	X	30	*h*	$C_{22}H_{34}Cl_2N_2O_2$	59.3	8.4	6.9	59.6	8.3	6.7		
45	*m*-CH_3O	*n*-C_3H_7	H	$(CH_2)_2COC_6H_5$	67–68[a]	X	75		$C_{23}H_{29}NO_2$	78.6	8.3	4.0	78.0	8.3	4.0		
46	*m*-CH_3O	*n*-C_3H_7	H	$(CH_2)_2COC_6H_5$	120–121[a]			*b*	$C_{23}H_{30}ClNO_2$	71.2	7.8	3.6	71.4	7.8	3.7		
47	*m*-CH_3O	*n*-C_3H_7	H	$(CH_2)_2CHOHC_6H_5$	84–85[a]	X	51		$C_{21}H_{31}NO_2$	78.1	8.8	4.0	78.4	8.9	4.0		
48	*m*-CH_3O	*n*-C_3H_7	H	$(CH_2)_2CHOHC_6H_5$	169–170[a]			*b*	$C_{21}H_{32}ClNO_2$	70.9	8.3	3.6	70.8	8.4	3.7		
49	*m*-CH_3O	*n*-C_3H_7	H	$(CH_2)_2CH(OCOC_2H_5)C_6H_5$	220–224 (1.0)	X	30	1.5369	$C_{27}H_{35}NO_3$	76.2	8.6	3.4	76.4	8.8	3.7		
50	*m*-CH_3O	*n*-C_3H_7	H	$(CH_2)_2CH(OCOC_2H_5)C_6H_5$	157–158[a]			*b*	$C_{26}H_{36}ClNO_3$	70.1	8.1	3.1	69.7	8.0	3.3		
51	*m*-OH	CH_3	H	CH_3	142–143 (0.4)	O	26	*e*	$C_{12}H_{17}NO$	75.4	9.0	7.3	75.4	9.2	7.6		
52	*m*-OH	C_2H_5	H	CH_3	153–156 (0.6)	U	78	*e*	$C_{13}H_{19}NO$	76.1	9.3	7.8	75.9	9.4	6.7		
53	*m*-OH	C_2H_5	H	CH_3	163–165[a]			*b*	$C_{13}H_{20}ClNO$	64.6	8.3	5.8	64.7	8.2	6.0		
54	*m*-OH	*n*-C_4H_9	H	CH_3	160–164 (0.4)	U	84	*e*	$C_{15}H_{23}NO$	77.2	9.9	6.0	77.7	10.0	5.9		
55	*m*-OH	*n*-C_3H_7	2-CH_3	H	175–180 (0.6)	U	41	*e*	$C_{14}H_{21}NO$	76.7	9.7	6.4	77.1	9.3	6.3		
56	*m*-OH	*n*-C_3H_7	2-CH_3	CH_3	167–169 (1.5)	U	50	*e*	$C_{15}H_{23}NO$	77.2	9.9	7.0	78.0	10.2	5.6		
57	*m*-OH	*n*-C_3H_7	4-CH_3	H	175 (0.6)	U	45	*e*	$C_{14}H_{21}NO$	76.7	9.7	6.4	76.4	9.5	6.7		
58	*m*-OH	*n*-C_3H_7	4-CH_3	CH_3	150 (0.8)	U	70	*e*	$C_{15}H_{23}NO$	77.2	9.9	6.0	77.1	9.9	6.4		
59	*m*-OH	*n*-C_3H_7	5-CH_3	H	174–180 (0.6)	U	55	*e*	$C_{14}H_{21}NO$	76.7	9.7	6.4	76.7	10.0	6.7		
60	*m*-OH	*n*-C_3H_7	5-CH_3	CH_3	147–149 (0.4)	U	74	*e*	$C_{15}H_{23}NO$	77.2	9.9	6.0	77.1	9.9	5.8		
61	*m*-OH	*n*-C_3H_7	2-C_2H_5	CH_3	160–162 (0.9)	U	41	*e*	$C_{16}H_{25}NO$	77.7	10.2	5.7	78.0	10.1	5.7		
62	*m*-OH	*n*-C_3H_7	2-*n*-C_3H_7	CH_3	154–160 (0.7)	U	72	*e*	$C_{17}H_{27}NO$	78.1	10.4	5.4	77.4	10.1	5.3		
63	*m*-OH	*n*-C_3H_7	4-*n*-C_3H_7	CH_3	161–165 (0.5)	U	60	*e*	$C_{17}H_{27}NO$	78.1	10.4	5.4	78.3	10.5	5.7		
64	*m*-CH_3CO_2	CH_3	H	CH_3	114–115 (0.3)	V	52	1.5164	$C_{14}H_{19}NO$	72.1	8.2	6.0	71.7	8.2	6.2		
65	*m*-CH_3CO_2	CH_3	H	CH_3	146–147[a]			*b*	$C_{14}H_{20}ClNO^j$	60.3	7.6	5.0	60.1	7.7	5.3		
66	*m*-CH_3CO_2	C_2H_5	H	CH_3	127 (0.4)	V	78	1.5170	$C_{15}H_{21}NO_2$	72.8	8.6	5.7	72.6	8.7	5.6		
67	*m*-CH_3CO_2	*n*-C_4H_9	H	CH_3	138–140 (0.4)	V	59	1.5120	$C_{17}H_{25}NO_2$	74.1	9.2	5.1	74.5	9.5	5.2		
68	*m*-CH_3CO_2	*n*-C_3H_7	2-CH_3	CH_3	140–141 (0.8)	V	40	1.5171	$C_{17}H_{25}NO_2$	74.1	9.2	5.1	73.2	9.1	4.9		
69	*m*-CH_3CO_2	*n*-C_3H_7	2-CH_3	CH_3CO	192–195 (0.6)	W	60	*e*	$C_{18}H_{25}NO_3$	71.3	8.3	4.6	71.5	8.4	4.4		
70	*m*-CH_3CO_2	*n*-C_2H_7	4-CH_3	CH_3	126 (0.6)	V	89	1.5133	$C_{17}H_{25}NO_2$	74.1	9.2	5.1	74.0	9.3	5.4		
71	*m*-CH_3CO_2	*n*-C_3H_7	5-CH_3	CH_3	131–133 (0.8)	V	80	1.5100	$C_{17}H_{25}NO_2$	74.1	9.2	5.1	74.5	9.1	5.2		
72	*m*-CH_3CO_2	*n*-C_3H_7	2-C_2H_5	CH_3	142–144 (0.5)	V	90	1.5195	$C_{18}H_{27}NO_2$	74.7	9.4	4.8	74.7	9.7	4.8		
73	*m*-CH_3CO_2	*n*-C_3H_7	2-C_2H_5	CH_3CO	166–170 (0.5)	W	40	*e*	$C_{19}H_{27}NO_3$	71.9	8.6	4.4	71.7	9.1	3.9		
74	*m*-CH_3CO_2	*n*-C_3H_7	2-*n*-C_3H_7	CH_3	138–140 (0.7)	V	63	1.5145	$C_{19}H_{29}NO_2$	75.2	9.6	4.6	74.4	9.5	4.3		
75	*m*-$C_2H_5CO_2$	*n*-C_3H_7	H	CH_3	142–146 (0.8)	V	60	1.5086	$C_{17}H_{25}NO_2$	74.1	9.2	5.1	74.5	9.3	5.4		
76	*m*-*n*-$C_3H_7CO_2$	*n*-C_3H_7	H	CH_3	146–150 (1.0)	V	45	1.5054	$C_{18}H_{27}NO_2$	74.7	9.4	4.8	75.0	9.8	5.0		
77	*m*-*i*-$C_3H_7CO_2$	*n*-C_3H_7	H	CH_3	146–148 (1.0)	V	40	1.5060	$C_{18}H_{27}NO_2$	74.7	9.4	4.8	74.9	9.3	5.6		
78	*m*-CH_3O	*n*-C_3H_7	H	CH_3	115 (0.8)	Y	61	1.5239	$C_{15}H_{23}NO$	77.2	9.9	6.0	77.1	9.9	5.9	+18.3	1.0
79	*m*-OH	*n*-C_3H_7	H	CH_3	160 (0.8)	U	88	*e*	$C_{14}H_{21}NO$	76.7	9.7	6.4	76.4	9.7	6.6	+17.2	1.2
80	*m*-OH	*n*-C_3H_7	H	CH_3	142–145[a]			*b*	$C_{14}H_{22}ClNO$	65.7	8.7	5.5	65.9	8.9	5.8	+14.8	0.9
81	*m*-CH_3CO_2	*n*-C_3H_7	H	CH_3	138–139 (1.1)	V	84	1.5144	$C_{16}H_{23}NO_2$	73.5	8.9	5.4	5.4	8.8	5.3	+18.4	1.0
82	*m*-CH_3O	*n*-C_3H_7	H	CH_3	111 (0.6)	Y	57	1.5244	$C_{15}H_{23}NO$	77.2	9.9	6.0	77.3	9.9	6.0	−20.3	1.1
83	*m*-OH	*n*-C_3H_7	H	CH_3	153–154 (0.5)	U	92	*e*	$C_{14}H_{21}NO$	76.7	9.7	6.4	76.2	9.7	6.7	−19.4	1.0
84	*m*-OH	*n*-C_3H_7	H	CH_3	145–147[a]			*b*	$C_{14}H_{22}ClNO$	65.7	8.7	5.5	65.6	8.7	5.4	−11.3	0.85
85	*m*-CH_3CO_2	*n*-C_3H_7	H	CH_3	129 (0.6)	V	88	1.5139	$C_{16}H_{23}NO_2$	73.5	8.9	5.4	73.3	8.8	5.3	−19.2	1.0

[a] Melting point. [b] Hydrochloride. [c] Chlorine analysis. [d] Hydrobromide. [e] Too viscous for measurement. [f] Prepared by the reduction of the crude chloronitrile followed by fractional distillation. [g] N-oxide. [h] Dihydrochloride. [i] Quarter molecule of water. [j] Hemihydrate.

TABLE V

RING SUBSTITUTIONS

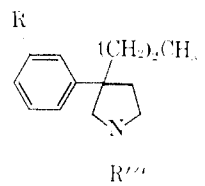


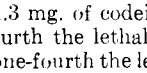
No.	R″	Estd. i.p. potency[a]	Estd. av. i.p. lethal dose (mg. of base/kg.)[b]	Potency × lethal dose[c] (0.8 × 133)
R = OH				
d	H	2.5	83	1.9
60	5-CH_3	2.0	77	1.4
56	2-CH_3	1.2	97	1.1
61	2-C_2H_5	0.8	86	0.7
62	2-*n*-C_3H_7	(0.5)[e]	77	(0.4)
58	4-CH_3	(0.2)[e]	115	(0.2)
63	4-*n*-C_3H_7	(0.3)[e]	84	(0.2)
R = CH_3CO_2				
d	H	1.7	97	1.5
71	5-CH_3	1.7	75	1.2
68	2-CH_3	1.7	91	1.4
72	2-C_2H_5	0.3[f]	163[f]	0.5
74	2-*n*-C_3H_7	(0.3)[e]	103	(0.3)
70	4-CH_3	(0.2)[g]	109	(0.2)
R = CH_3O				
d	H	1.3	67	0.8
30	5-CH_3	1.2	63	0.7
26	2-CH_3	0.8	77	0.6
32	2-C_2H_5	1.1	73	0.8
34	2-*n*-C_3H_7	0.7	77	0.5
28	4-CH_3	None[d]	65	...
36	4-*n*-C_3H_7	(0.3)	77	(0.3)

[a] Relative to codeine (base/base), 30 min. after treatment. [b] From small numbers of young, male, Sprague–Dawley rats of differing lots. [c] 1,2-Dimethyl-3-phenyl-3-propionoxypyrrolidine of the earlier ester series is equal to 1. [d] See ref. 2. [e] Figures in parentheses were obtained by extrapolation. The effect, equivalent to 11.3 mg. of codeine base/kg., was not actually attained at one-fourth the lethal dose. [f] Base dissolved in vegetable oil. [g] At one-fourth the lethal dose.

TABLE VI

SUBSTITUTIONS ON THE NITROGEN



No.	R‴	Estd. i.p. potency[a]	Estd. av. i.p. lethal dose (mg. of base/kg.)[b]	Potency × lethal dose[c] (0.8 × 133)
R = OH				
d	CH_3	2.5	83	1.9
d	H	(0.1)[e]	119	(0.11)
d	*n*-C_3H_7	None[f]	130	...
R = CH_3CO_2				
d	CH_3	1.7	97	1.5
d	*n*-C_3H_7	None[f]	59	...
R = CH_3O				
d	CH_3	1.3	67	0.8
38	C_2H_5	(0.4)[e]	64	(0.2)
d	*n*-C_3H_7	(0.3)[e]	84	(0.2)
d	$CH{\equiv}CCH_2$	(0.2)[e]	168	(0.3)
39	*n*-C_7H_{15}	None[g]	387[g]	...
41	$HO(CH_2)_2$-$O(CH_2)_2$	(0.2)[e]	137	(0.2)
d	$C_6H_5CH_2$	(0.1)[e,h]	189[h]	(0.2)
42	*p*-$NO_2C_6H_4$-$(CH_2)_2$	0.4[h]	167[h]	0.6
43	*p*-$NH_2C_6H_4$-$(CH_2)_2$	0.9	56	0.5
44		(0.1)[e]	112	(0.11)
46	$C_6H_5CO(CH_2)_2$	(0.6)[e,h]	59[h]	(0.31)
48	$C_6H_5CH(OH)$-$(CH_2)_2$	(0.5)[e]	59	(0.3)
50	$C_6H_5CH(OC$-$OC_2H_5)(CH_2)_2$	0.2[h,i]	317[h]	0.5

[a] Footnote *a*, Table V. [b] Footnote *b*, Table V. [c] Footnote *c*, Table V. [d] See ref. 2. [e] Footnote *e*, Table V. [f] Footnote *g*, Table V. [g] Footnote *f*, Table I. [h] Partly dissolved, balance suspended. [i] Just about codeine grade at one-fourth the lethal dose; probably biased upward by relatively poorer solubility at lethal dose levels.

a stirred solution of sodium cyanide (14.2 g.) in dimethyl sulfoxide (80 ml.) at 110°; an exothermic reaction occurred and the temperature rose to 140°. The mixture was held at 110° for 3 hr., cooled, and poured into ice–water, and the oil was isolated with ether and fractionally distilled to give two components, b.p. 73–80° (0.8 mm.), 15 g., and b.p. 108–112° (0.8 mm.), 28 g. The first of these was ***m*-methoxy-β-ethylstyrene**: λ_{max} 216, 254, and 295 mμ (ε 31,300, 14,200, and 3230).

Anal. Calcd. for $C_{11}H_{14}O$: C, 81.4; H, 8.7. Found: C, 80.9; H, 8.9.

The second fraction was **α-*m*-methoxyphenylvaleronitrile** (Table I).

Pharmacology

Acute lethal toxicities and antinociceptive (analgetic) activities were determined in young male rats by the intraperitoneal route as described earlier by Cavalla, *et al.*[1] When possible, soluble addition salts, or bases with equivalents of HCl, were dissolved in 0.9% NaCl. Exceptions forced by poor solubilities are noted in Tables V and VI.

It was shown earlier[2] that substitution on the phenyl nucleus is necessary for activity in this series. The specific nature of the required substitution is now examined in more detail in Table VII. It is inferred that substitution of an oxygen function (HO, $AlkCO_2$, or CH_3O) in the *meta* position converts an inactive compound into a clearly active one,[2] that such substitution at no other position does this, that further substitution of CH_3O or OH in the *para* position substantially annuls the activity, and that CH_3 or Cl cannot serve in place of the *meta*-oxygen function.

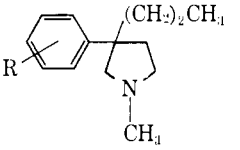
The nearly uniform activities of the various esters of the *meta* phenol (Table VII) suggest that these activities may result from *in vivo* hydrolysis to the more active phenol. Methyl etherification gives somewhat lower activity and greater toxicity,[2] either with the optimal 3-*n*-propyl configuration (Table VII) or with a non-optimal 3-configuration (Table VIII).

Of 3-*n*-alkyl substitutions on the pyrrolidine ring, the *n*-propyl, earlier[2] found good, is seen in Table VIII to be probably optimal, although fairly good activity can also be obtained with *n*-butyl or ethyl. Going to methyl results in failure.

The good activity found[2] earlier when substitution in the pyrrolidine ring occurred only at positions 1 and 3 could not be improved with additional substitution (Table V). Methylation at 5 apparently resulted in a

TABLE VII

SUBSTITUTION ON PHENYL

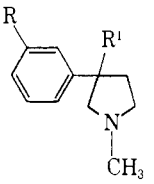


No.	R	Estd. i.p. potency[a]	Estd. av. i.p. lethal dose (mg. of base/kg.)[b]	Potency × lethal dose[c] / (0.8 × 133)
	meta			
d	OH	2.5	83	1.9
d	CH_3CO_2	1.7	97	1.5
75	$C_2H_5CO_2$	1.8	91	1.6
76	n-$C_3H_7CO_2$	1.7	137	2.2
77	i-$C_3H_7CO_2$	1.7	103	1.6
d	CH_3O	1.3	67	0.8
15	CH_3	(0.4)[e]	62	(0.2)
14	Cl	None[f]	61	...
d	H	None[f]	65	...
	para			
17	HO	(0.2)[e]	122	(0.3)
18	CH_3CO_2	(0.1)[e]	154	(0.2)
16	CH_3O	(0.3)[e]	92	(0.2)
	meta, para			
20	$(OH)_2$	(0.1)[e]	223	(0.2)
19	$(CH_3O)_2$	None[f]	68	...
	ortho			
12	HO	None[f]	17	...
11	CH_3O	None[f]	31	...

[a] Footnote *a*, Table V. [b] Footnote *b*, Table V. [c] Footnote *c*, Table V. [d] See ref. 2. [e] Footnote *e*, Table V. [f] Footnote *g*, Table V.

TABLE VIII

3-ALKYLATIONS



No.	R^1	Estd. i.p. potency[a]	Estd. av. i.p. lethal dose (mg. of base/kg.)[b]	Potency × lethal dose[c] / (0.8 × 133)
R = HO				
d	n-C_3H_7	2.5	83	1.9
54	n-C_4H_9	1.7	81	1.3
53	C_2H_5	1.0	65	0.6
51	CH_3	(0.2)[e]	122	(0.2)
R = CH_3CO_2				
d	n-C_3H_7	1.7	97	1.5
67	n-C_4H_9	1.3	86	1.0
66	C_2H_5	1.2	103	1.2
65	CH_3	(0.2)[e]	135	(0.3)
R = CH_3O				
d	n-C_3H_7	1.3	67	0.8
24	n-C_4H_9	0.9	61	0.5
22	C_2H_5	(0.7)[e]	51	(0.3)

[a] Footnote *a*, Table V. [b] Footnote *b*, Table V. [c] Footnote *c*, Table V. [d] See ref. 2. [e] Footnote *e*, Table V.

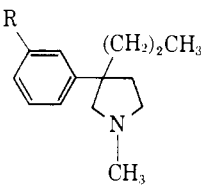
slight decrease in activity and/or an increase in toxicity. Alkylation at 4 destroyed clear activity. 2-Alkylation had intermediate effects, leading to the disappearance of clear activity with propyl except where the phenolic function was etherified; in this circumstance fairly good activity remained. The steep, downward gradation of activity of the phenol (and hydrolyzable ester?) with heaviness of 2-alkylation is reminiscent of the parallel gradation in zwitterionic character toward steep diminution in NH^+ absorption in the 2500–3500-cm.$^{-1}$ region (*vide supra*). *meta* Etherification seemingly nuzzles this graded intramolecular interaction with its presumed influence on biological activity.

The good activity originally[2] found with tertiary N-methylation could not be improved (Table VI). Indeed, with two exceptions, any other N-substitution tried, or the secondary amine, failed to yield a clear grade of activity. The two clear exceptions were phenethylamine, with p-NO_2 or -NH_2.

A dozen compounds of Table IV in addition to those listed, in Tables V–IX were studied pharmacologically. All were secondary amines and/or lacked the *meta*-oxygen function; none attained a clear grade of antinociceptive activity.

TABLE IX

OPTICAL ISOMERS



No.	Optical form	Estd. i.p. potency[a]	Estd. av. i.p. lethal dose (mg. of base/kg.)[b]	Potency × lethal dose[c] / (0.8 × 133)
R = HO				
d	*dl*	2.5	83	1.9
80	*d*	2.0	93	1.7
84	*l*	3.0	55	1.5
R = CH_3CO_2				
d	*dl*	1.7	97	1.5
81	*d*	1.2	115	1.3
85	*l*	2.2	68	1.4
R = CH_3O				
d	*dl*	1.3	67	0.8
78	*d*	0.8	76	0.5
82	*l*	1.9	66	1.2

[a] Footnote *a*, Table V. [b] Footnote *b*, Table V. [c] Footnote *c*, Table V. [d] See ref. 2.

In the three structures resolved (*m*-OH, *m*-CH_3CO_2, *m*-CH_3O), the levo isomers were, in general, twice as potent as the dextro (Table IX), with racemates intermediate. Oral comparisons of the phenols have yielded a ratio much closer to 2:1 than the estimates in Table IX suggest for this structure.

The present series of 3-alkylpyrrolidines differs in several respects in structure–activity relationships from the older 3-acyloxypyrrolidines.[1] The optimal structure is three or four times as active in the present series, presumably reflecting a more nearly specific receptor complimentariness. Thus, approaching nearer to the more potent central analgetics in receptor fit, alterations of structure have sharper effects on activity and, coincidentally, the levo enantiomer rather than the dextro becomes the more potent.

Lacking the 3-oxygen function of the older series, the present series apparently requires a *meta*-oxygen function on the phenyl nucleus; any alteration from simple

phenyl tried in the 3-oxy series had been deleterious. Whereas the 3-oxy series had required 2- or 4-substitution on the pyrrolidine ring, the *meta*-oxy series suffers slight to complete loss of activity on ring substitution additional to 1,3-, in the order 5-, 2-, 4-. There are interesting relationships in the *meta*-oxygen series between heaviness of 2-alkylation, gradation in zwitterionic character, and loss of activity. *meta* Etherification seemingly muzzles considerably these interactions of 2-alkylation.

Finally, effects of alterations in N-substitution are much sharper in the *meta*-oxygen series than in the older series. Replacing methyl is, in most instances, clearly deleterious.

Acknowledgment.—The authors thank Dr. R. E. Bowman and Dr. H. M. Crooks, Jr., for helpful advice and consultation, Mr. F. H. Oliver for the microanalyses, Miss E. M. Tanner for the physical measurements, Mr. K. E. Richards for help in the resolution of the parent compound, and Miss L. Scotti, Miss J. Wax, and Mrs. S. Stanat for important participation in the pharmacological work.

Bicyclic Homologs of Piperazine. VII.[1] Synthesis and Analgesic Activity of 3-Aralkenyl-8-propionyl-3,8-diazabicyclo[3.2.1]octanes

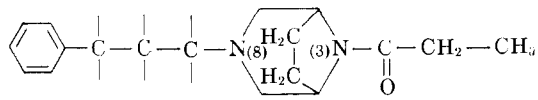
GIORGIO CIGNARELLA, EMILIO OCCELLI, AND EMILIO TESTA

Laboratories of Lepetit S.p.A., Milan, Italy

Received December 28, 1964

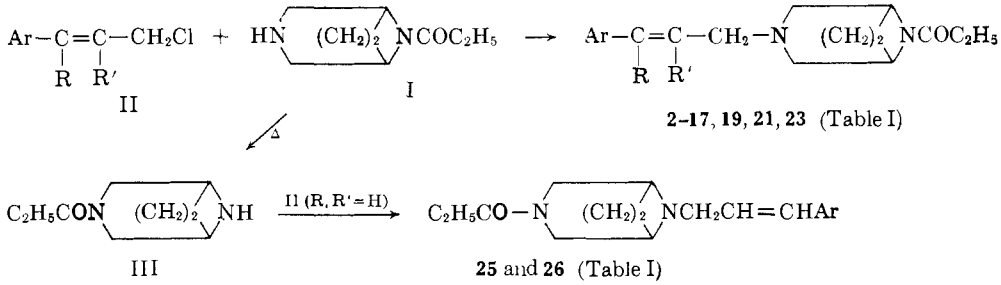
With the aim of enhancing the analgesic activity of 3-cinnamyl-8-propionyl-3,8-diazabicyclo[3.2.1]octane (1), 25 derivatives were synthesized in which the 3-aralkenyl group was variously modified. Some of these compounds exhibited an analgesic potency comparable with that of 1.

In the preceeding paper of this series,[1] the synthesis of analgesic 3-substituted 8-propionyl-3,8-diazabicyclo-[3.2.1]octanes was reported and the effect of the 3- and 8-substituent on the activity was discussed. It was observed that the greatest analgesic action is associated with the presence in the 8-position of a propionyl group and in position 3 of an aralkyl group whose aliphatic chain consisted of three carbon atoms.



Unsaturation of this chain markedly enhanced the analgesic potency, the 3-cinnamyl-8-propionyl-3,8-diazabicyclo[3.2.1]octane (**1**, Table I) being the most active compound of the series, approximately 10 times more potent that morphine hydrochloride. It seemed, therefore, of interest to study the effects on the analgesic activity of the introduction of substituents in the cinnamyl group. We describe in this paper the syntheses and the properties of a number of 8-propionyl-3,8-diazabicyclo[3.2.1]octanes, in which the cinnamyl group of the model compound **1** was modified by substitutions on the aromatic ring (**2–12**) and on the ethylenic bond (**13–17**), replacement of the phenyl with α-naphthyl group (**18**) and with hydrogen (**21**), change in the unsaturation (**22**) and/or in the length of the aliphatic chain (**19**, **20**, and **23**), and replacement of the methylene group of the aliphatic chain with a carbonyl (**24**). In addition, two other derivatives (**25** and **26**) were synthesized in which the position of the propionyl and of the aralkenyl groups was reversed.

Chemistry.—Preparation of compounds listed in Table I was effected by condensing 8-propionyl-3,8-diazabicyclo[3.2.1]octane[1] (I) with aralkenyl chlorides II (**2–18**, **20**, and **23**), allyl bromide (**21**), phenylpropargyl bromide (**22**), and cinnamoyl chloride (**24**). Condensation of I with phenylacetaldehyde according to the method of Mannich[2] led to **19**. Compounds **25** and **26** were prepared by condensing 3-propionyl-3,8-diazabicyclo[3.2.1]octane[3] (III) with cinnamyl- and *p*-ethoxycinnamyl chloride, respectively. It is to be noted that **26** was first isolated during attempts to condense I with *p*-ethoxycinnamyl chloride; in this case the reaction conditions (refluxing in benzene for 15 hr.) clearly favored an $N_8 \rightarrow N_3$ acyl migration[3] of I to the



(1) Paper VI: G. Cignarella, E. Occelli, G. F. Cristiani, L. Paduano, and E. Testa, *J. Med. Chem.*, **6**, 764 (1963).

(2) C. Mannich and H. Davidsen, *Ber.*, **69B**, 2106 (1936).

(3) G. Cignarella, E. Testa, and C. R. Pasqualucci, *Tetrahedron*, **19**, 143 (1963).