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PEORIA, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Piperidine Derivatives. XXX. 1,4-Dialkyl-4-arylpiperidines

BY S. M. MCELVAIN AND DAVID H. CLEMENS[1]

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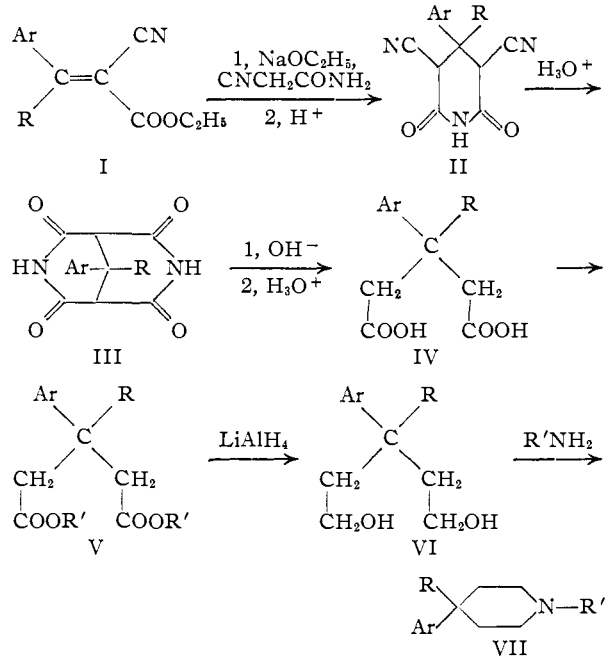
A series of trisubstituted piperidines mentioned in the title has been prepared and submitted for pharmacological screening for analgesic activity. These compounds were synthesized by a sequence of reactions that started with the ethyl 1-arylalkylidenecyanoacetates (I) and went through the β-alkyl-β-arylglutaric acids (IV) to the piperidines (VII). The 1-methyl-4-alkyl-4-phenylpiperidines showed low analgesic activity which appeared to increase as the 4-alkyl substituent was changed from methyl to *n*-propyl. Increase in the size of the 1-alkyl substituent produced no noticeable effect on the analgesic properties. The 1-methyl-4-alkyl-4-(*m*-hydroxyphenyl)-piperidines are potent analgesics, the 4-*n*-propyl compound being comparable to morphine in its analgesic activity. However, when the hydroxyl group is in the *o*- or *p*-position in the 4-phenyl substituent the analgesic activity disappears. Likewise, the replacement of the 4-alkyl substituent of these highly active compounds by hydrogen destroys their activity.

The synthesis of 4,4-disubstituted piperidines has been the subject of many researches, from which have resulted a number of compounds that possess marked analgesic activity.[2-4] Typical of these synthetic products are 1-methyl-4-phenyl-4-carbethoxypiperidine (Demerol) and the highly active 1-methyl-4-phenyl-4-propionoxypiperidine.[2,3]

In most of these synthetic analgesics as well as in the widely used, naturally occurring analgesic morphine, a polar oxygenated function shares the 4-position of the piperidine nucleus with the aryl substituent. It seemed of interest to determine whether such a polar substituent is essential for the analgesic activities of such compounds or whether a non-polar alkyl substituent would suffice. To this end a series of 1,4-dialkyl-4-arylpiperidines (VIIa-q, Tables I and VIII) has been prepared for pharmacological screening.

The synthesis of these compounds was accomplished by a sequence of reactions, which started with the ethyl 1-arylalkylidenecyanoacetate (I), readily prepared in good yield by Cope's procedure, and went through the β-alkyl-β-arylglutaric acids (IV) to the desired piperidines VII.

The first step in this sequence involved considerable study before the proper reaction conditions were determined. All attempts to add malonic ester or cyanoacetic ester to ethyl 1-phenylethylidenecyanoacetate (I, R is CH_3, Ar is C_6H_5) under various conditions for the Michael condensation were uniformly unsuccessful. Phalnikar and Nargund[5] have reported the preparation of the glutarimide (II, R = CH_3) in 2.7% yield by the Guareschi condensation[6] of acetophenone and ethyl cyanoacetate and ammonia. They hydrolyzed this imide to β-methyl-β-phenylglutaric acid (IV, R = CH_3), which is the only β-alkyl-β-phenylglutaric acid reported in the literature.



It seemed likely that the low yield of the glutarimide obtained by the Indian workers was due to the sluggish nature and reversibility of the initial Knoevenagel condensation[7] between acetophenone and ethyl cyanoacetate under the conditions of the Guareschi reaction. Indeed it was found that when the preformed ethylidene ester I (R is CH_3) was allowed to react with ethyl cyanoacetate in ethanol saturated with ammonia, the desired imide II was obtained in 31% yield. A neutral solid XV, m.p. 213–214°, the structure of which is discussed later, also was obtained from this reaction. However, when the homologous alkylidene ester Ib (R is C_2H_5) was allowed to react with ethyl cyano-

(1) Wisconsin Alumni Research Foundation Research Assistant 1954–1956; Procter and Gamble Co. Fellow 1956–1957; E. I. du Pont de Nemours and Co. Summer Research Assistant, 1954, 1955, 1956.

(2) J. Lee in C. M. Suter's "Medicinal Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1951, Vol. I, Chapter 6.

(3) C. M. Suter in F. F. Blicke and C. M. Suter's "Medicinal Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, Vol. II, Chapter 3.

(4) H. Krueger in R. H. F. Manske's "The Alkaloids," Academic Press, Inc., New York, N. Y., 1955, Vol. V, Chapter 38.

(5) N. L. Phalnikar and K. S. Nargund, *J. Univ. Bombay*, **6**, Pt. II, 102 (1937); *C. A.*, **32**, 3763 (1938).

(6) I. Guareschi, *Gazz. chim. ital.*, **49**, 124 (1919); A. I. Vogel, *J. Chem. Soc.*, 1758 (1934).

(7) J. Scheiber and F. Meisel, *Ber.*, **48**, 238 (1915), showed that this condensation proceeds to only 30% completion even when the reactants are heated for some time with an aniline–zinc chloride catalyst.

acetate under the same conditions only a trace of the glutarimide IIb was obtained and none of the corresponding neutral product appeared. Obviously, the conditions of the Guareschi reaction could not be used for the preparation of the glutarimides II containing an alkyl substituent larger than methyl.

Since cyanoacetamide appeared as a by-product in the preparation of II (R is CH_3) from I under the Guareschi conditions, it seemed that it might be the actual reacting species. It also seemed likely that the use of a stronger base than ammonia might facilitate both the Michael addition of the cyanoacetamide to I and form a more stable salt of the glutarimide II. This was found to be true, for when I (R is CH_3) was treated with one equivalent of the sodium salt of cyanoacetamide suspended in ethanol, the glutarimide (II, R is CH_3) was obtained in 92% yield. When these reaction conditions were applied to other alkylidene acceptors (Ib-g, Table II), the desired glutarimides (IIb-g, Table III) were obtained in 57–95% yields.

In these reactions the lower yields (57–64%) were obtained when the alkylidine acceptors were Ib, c and g (R is C_2H_5 and n-C_3H_7). In an attempt to discover the reason for these results, the neutral portion of the reaction mixture in the preparation of IIc was examined. It was found to contain about 30% of Ic. The presence of this unreacted starting material suggested two possible causes for the lower yield, (i) the salt of the imide IIc was in an unfavorable equilibrium with Ic or (ii) the cyanoacetamide was being consumed in a competing reaction before it could react with Ic. The first possibility (i) was eliminated when IIc was found to be quite stable in an alcoholic solution of sodium ethoxide. It appeared that the second alternative (ii) was involved as the yield of IIc was increased to 88% when two equivalents each of cyanoacetamide and sodium ethoxide were used in the reaction. Similarly, the yield of IIg was raised to 89% by this change in the ratio of reactants.

Hydrolysis of IIa (R is CH_3) in a mixture of sulfuric acid, acetic acid and water gave β-methyl-β-phenylglutaric acid IVa (Table V) in 91% yield. However, when the same conditions were applied to IIb (R is C_2H_5), an extremely insoluble acidic product crystallized from the hydrolysis mixture; this material did not dissolve even after prolonged heating. Analyses indicated this product to be the di-imide IIIb (Table IV). All attempts to hydrolyze IIb to the glutaric acid IVb with varying concentrations of sulfuric acid were unsuccessful. Any concentration of sulfuric acid sufficiently high to dissolve the intermediate IIIb rapidly converted it to an intractable tar. Each of the glutarimides IIa, b and c was readily transformed in good yields to the corresponding di-imides III in 60% sulfuric acid.

These bicyclic imides, while quite stable in acid medium, were hydrolyzed readily in alkaline solution, after which the glutaric acids (IV) were produced by a brief period of reflux in acid solution. The methoxy-imides IId-g (Table III) did not yield crystalline products of the type IIIa-c, but instead gave oils which were converted to the corresponding glutaric acids by alkaline hydrolysis and decarboxylation.

The di-imide IIIb, obtained by the action of sulfuric acid on IIb, readily was converted to a neutral N,N′-dimethyl derivative. Attempts were made to hydrogenate IIIb to the bicyclic diamine over copper–chromium oxide catalyst, a procedure that has been employed successfully by Adkins and coworkers[8] for the conversion of monocyclic imides to the corresponding cyclic amines. However, under these conditions IIIb underwent more extensive hydrogenolysis to yield 4-ethyl-4-phenylpiperidine, which was characterized by N-methylation to VIIb.

Certain of the glutaric acids IV were isolated and purified as such before esterification; others were converted directly to the esters (*cf.* Tables V and VI). Reduction of the esters Va-c and Ve-g (Table VI) with lithium aluminum hydride gave the corresponding diols VI in good yields. Some interesting complications were involved in the preparation and reduction of the ester Vd (R is CH_3, Ar is *o*-methoxyphenyl); these are discussed below.

The 1,4-dialkyl-4-arylpiperidines VIIa-g and VIIn-q (Tables I and VIII) were prepared from the appropriate glycols and primary amines by the method developed by Adkins[8] for similar cyclizations. The 1,4-dialkyl-4-(hydroxyphenyl)-piperidines VIIh-m were obtained by the demethylation of the corresponding methoxyphenyl compounds VIId-g with hydrobromic acid.

When it was found that the 1-methyl-4-alkyl-4-(*m*-hydroxyphenyl)-piperidines (VIIj and m, Table I) possessed marked analgesic activity, it seemed of interest to prepare and test an analogous structure which did not have a 4-alkyl substituent. This compound (VIIr) was prepared from β-(*m*-methoxyphenyl)-glutaric acid by the reaction sequence IV → VII; from this ether the phenol VIIs readily was obtained by demethylation with hydrobromic acid.

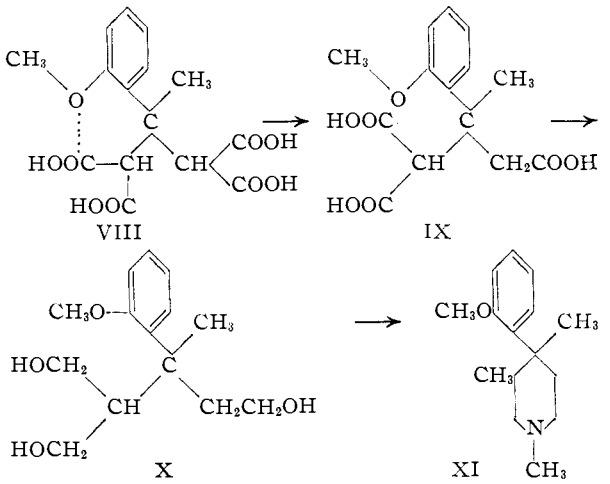
The methyl ester, presumed to be Vd, as obtained from the hydrolysis of the glutarimide IId, was reduced with lithium aluminum hydride and yielded a product, m.p. 87–92°. A sample of this solid was cyclized with methylamine and the resulting liquid amine converted to its hydrochloride. This salt proved to be a mixture, which was separated by fractional crystallization. The major constituent was the desired 1,4-dimethyl-4-(*o*-methoxyphenyl)-piperidine (VIId, Table VIII) hydrochloride. The second constituent of the mixture had an analysis for a compound containing one more methylene group than VIId. The infrared spectra of the free bases obtained from these separated salts were quite similar.

These results prompted an investigation of the diol from which these amines were prepared. This material also was found to be a mixture that could be separated by chromatography into the 3-methyl-3-(*o*-methoxyphenyl)-pentane-1,5-diol (VId) and a triol; VId gave the piperidine VIId in 86% yield when cyclized with methylamine. The triol yielded the minor constituent of the amine mixture when cyclized with methylamine.

The following sequence of reactions appears to

(8) J. H. Paden and H. Adkins, This Journal, **58**, 2487 (1936).

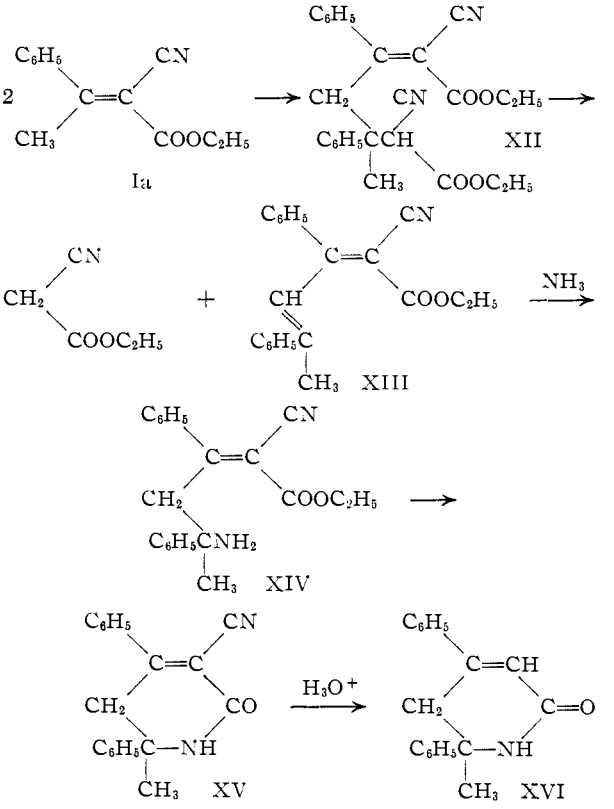
explain these unexpected products. The *o*-methoxy group of the tetraacid VIII resulting from basic hydrolysis of IId interacted with an adjacent carboxyl group to cause incomplete decarboxylation of this tetraacid. As a result the triacid IX was associated with the expected glutaric acid IVd. A mixture of esters thus was obtained on esterification and reduction of this mixture yielded the triol X and the diol VId. The formation of 1,3,4-trimethyl-4-(*o*-methoxyphenyl)-piperidine (XI) would be expected in the cyclization of the triol X with methylamine since hydrogenolysis of 1,3-diols under the conditions of this reaction is well precedented.[9]



The neutral solid, m.p. 213–214°, obtained as a by-product in the preparation of IIa from Ia under the conditions of the Guareschi reaction, was found to be a reaction product of Ia and ammonia. Analyses indicated the formula $C_{19}H_{16}N_2O$; the infrared spectrum exhibited bands at 3.19, 4.52 and 6.03 μ corresponding, respectively, to —NH, —C≡N, and amide carbonyl stretching; the ultraviolet spectrum had λ_{max} 288 mμ (log ϵ 4.02) and λ_{max} 228 mμ (log ϵ 3.88) and was quite similar to that of Ia (λ_{max} 282 mμ (log ϵ 3.96), λ_{max} 224 mμ (log ϵ 3.94)).

Prolonged hydrolysis of this compound in a sulfuric acid, acetic acid and water mixture yielded a second neutral solid, m.p. 194–195°. Analyses indicated this compound to have the formula $C_{18}H_{17}NO$; the infrared spectrum had bands at 6.02 and 3.19 μ but none in the 4.5 μ region. The ultraviolet spectrum had λ_{max} 277 mμ (log ϵ 4.13) and a shoulder at 223 mμ showing a marked similarity to the spectra of its precursor and to Ia.

The structures XV and XVI explain the chemical and physical data for these two compounds. Their formation from Ia is shown in the following sequence of reactions. Two moles of Ia underwent a Michael condensation to give the product XII which then lost cyanoacetic ester in a reverse Michael reaction to form cyanoacetic ester and XIII. A 1,6-addition of ammonia to the conjugated system of XIII followed by a rearrangement of the double bond from the β,γ- to the α,β-position yielded the amine ester XIV. This ester then cyclized to the lactam XV, the neutral product, m.p. 213–214°, that was isolated from the reaction. Hydrolysis of the cyano group of XV followed by decarboxylation produced the second neutral product XVI, m.p. 194–195°.



Pharmacological Data

The piperidines VIIa-VIId and VIIf-VIIq in the form of their hydrochlorides were screened for analgesic activity by Mr. E. B. Robbins of the Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, Ind. The results of these tests, which were made by subcutaneous injection in rats, are summarized in Table I.

Compounds VIIa-VIIc, which contain non-polar alkyl groups associated with a phenyl group in the 4-position and an N-methyl substituent, while possessing some analgesic activity, fail to produce any marked effect. Increasing the size of the 4-alkyl substituent from methyl to *n*-propyl results in a noticeable lowering in the dose required to produce a trace of analgesia, but there is no apparent effect on the degree of analgesia. These compounds are quite toxic at high dose levels.

Holding R constant as methyl and lengthening the N-alkyl substituent (R′) from the methyl to *n*-butyl (compounds VIIa and VIIn-VIIq) results in no significant change in analgesic properties. The N-methyl compound has slight activity, whereas the N-ethyl and N-propyl are inactive. Some activity returns when the N-substituent is isopropyl or *n*-butyl; however, none of these compounds produces any marked effect.

Introduction of a *m*-hydroxyl group into the aryl substituent of 1,4-dimethyl-4-phenylpiperidine (VIIa), however, markedly enhances the analgesic activity. Compound VIIj produces a moderate

(9) R. Connor and H. Adkins, THIS JOURNAL, **54**, 4678 (1932).

Table I

Pharmacological Properties of the 1,4-Dialkyl 4-Arylpiperidine (VII) Hydrochlorides, R′–N–CH_2–CH_2–CRAr–CH_2–CH_2·HCl, and Other Related Compounds

No.	R is	R′ is	Ar is	Analgesia Dose, mg./kg.	Analgesia Effect[a]	Toxicity Dose, mg./kg.	Toxicity Effect[b]
VIIa	CH_3	CH_3	C_6H_5	40–80	+	160	ccc
VIIb	C_2H_5	CH_3	C_6H_5	10–20	+	40	x
VIIc	n-C_3H_7	CH_3	C_6H_5	2–16	+	40	ccc
						80	x
VIId	CH_3	CH_3	$C_6H_4OCH_3$(o)	5–80	0	100	s
						200	ccc
VIIf	CH_3	CH_3	$C_6H_4OCH_3$(p)	1–20	0	25	ccc
						50	cccc
						75	xxx
VIIg	n-C_3H_7	CH_3	$C_6H_4OCH_3$(m)	4	++	16	c
				8	+++	80–100	xx
				16	++++		
VIIh	CH_3	CH_3	C_6H_4OH(o)	5–80	0	100	s
						200	cc
						400	cccc
VIIj	CH_3	CH_3	C_6H_4OH(m)	10	++	300	c
				20–80	+++ to ++++		
VIIk	CH_3	CH_3	C_6H_4OH(p)	10–80	+	100	s
						350	cccc
VIIm	n-C_3H_7	CH_3	C_6H_4OH(m)	0.5	+	2	c
				1	+++	25	p
				2	++++		
VIIn	CH_3	C_2H_5	C_6H_5	10–80	0		
VIIo	CH_3	n-C_3H_7	C_6H_5	5–40	0		
VIIp	CH_3	i-C_3H_7	C_6H_5	10–80	+		
VIIq	CH_3	n-C_4H_9	C_6H_5	10–80	+		
VIIr	H	CH_3	$C_6H_4OCH_3$(m)	10–80	0	250	c
VIIs	H	CH_3	C_6H_4OH(m)	5–80	+	80–240	z
Demerol				5	++		
				10–20	+++ to ++++		
Morphine				1	++		
				2–4	+++ to ++++		

[a] 0, no analgesia; +, trace; ++, moderate; +++, marked; ++++ profound. [b] c, some neutrotoxicity; cc, hypersensitivity and pilo erection; ccc, tremors; cccc, convulsions; x, occasional death; xx, death in 50% of cases; xxx, death in 75% of cases; s, sedation; p, prostration; z, marked salivation.

analgesia at one-fourth the dose at which VIIa shows only a trace of activity. As the doses of VIIj increase the analgesic effect becomes marked to profound. It is also interesting to note that quite low toxicities are observed with VIIj at thirty times the effective analgesic dose. The increase of activity on lengthening the 4-alkyl side chain in the series VIIa-VIIc is repeated when a m-hydroxyl group is present in the phenyl group. Compound VIIm, having a n-propyl group associated with a m-hydroxyphenyl substituent in the 4-position of the piperidine nucleus, produces profound analgesia at a dose level comparable to that of morphine. However, the toxicity of VIIm is also considerably higher than that of the 4-methyl homolog (VIIj).

Substitution of a m-methoxyl group for the m-hydroxyl group of VIIm gives an analgesic VIIg, which although somewhat less potent than VIIm, still retains considerable activity. The pharmacological relationship between the phenolic compound VIIm and its methyl ether VIIg in this pair of compounds parallels that found for morphine and its methyl ether codeine.

It is particularly interesting that the introduction of a hydroxyl or a methoxyl substituent in the o- or p-position of VIIa (compounds VIId, VIIf, VIIh and VIIk) results in an almost complete loss of analgesic activity. The only compound of this group to produce even a trace of analgesia is the p-hydroxyphenyl derivative VIIk; the remainder are completely inactive. Likewise, replacement of the 4-alkyl substituent of the active compounds VIIg, VIIj and VIIm by hydrogen gives the compounds VIIr and VIIs whose analgesic activities are insignificant.

Experimental

All melting points are uncorrected.

Alkyl Aryl Ketones.—Acetophenone, propiophenone, butyrophenone, p-methoxyacetophenone and o-hydroxyacetophenone were purchased from the Eastman Kodak Co., Rochester, New York. o-Methoxyacetophenone was prepared by methylation of o-hydroxyacetophenone. m-Methoxyacetophenone was prepared by the acylation of ketene dimethylacetal with m-methoxybenzoyl chloride and subsequent hydrolysis.[10] The preparation of m-methoxybutyrophenone followed a similar acylation of ethylketene dimethylacetal with m-methoxybenzoyl chloride. The preparations of this ketone and the requisite precursors are described below.

(10) S. M. McElvain and C. R. McKay, Jr., This Journal, 78, 6086 (1956).

Methyl iminobutyrate hydrochloride was prepared by treating butyronitrile with anhydrous hydrogen chloride in methanol.[11] The yield on a 2-mole run was 77.5% of material, which contained 29% ionic chlorine (calcd. 25.8%). This was found satisfactory for use in the next step.

Methyl orthobutyrate was prepared by methanolysis of methyl imino-*n*-butyrate using the procedure described by McElvain and Aldridge.[11] The yield on a 0.5-mole run was 72% of methyl orthobutyrate, b.p. 144–145° (reported[12] b.p. 145–147°), $n^{25}D$ 1.4017, d^{25}_4 0.9261.

The dealcoholization of 0.22 mole of methyl orthobutyrate with aluminum *t*-butoxide[13] gave 13.4 g. (53%) of **ethylketene dimethylacetal**, b.p. 119–121°, $n^{25}D$ 1.4160, d^{25}_4 0.8770.

Anal. Calcd. for $C_6H_{12}O_2$: C, 62.04; H, 10.41. Found: C, 61.80; H, 10.25.

A mixture of 19 g. of ethylketene dimethylacetal and 6.2 g. (0.04 mole) of *m*-methoxybenzoyl chloride was placed in a 250-ml. round-bottom flask fitted with a reflux condenser and warmed gently. Once started, the reaction proceeded vigorously with refluxing. When the initial reaction had subsided, the mixture was heated under reflux for 2 hours. Unused ethylketene dimethylacetal and volatile reaction products were distilled off under reduced pressure and redistilled to yield 4.0 g. of recovered ethylketene dimethylacetal, $n^{25}D$ 1.4153.

The *m*-methoxybenzoylethylketene dimethylacetal remaining in the reaction flask was hydrolyzed by the cautious addition of 10 ml. of water followed by 3 ml. of 5% hydrochloric acid. A solution (125 ml.), prepared by mixing 1 volume of water, 1 volume of concentrated hydrochloric acid and 3 volumes of glacial acetic acid, was added and the mixture heated under reflux overnight. Water (250 ml.) was added and the solution extracted with 700 ml. of ether in 5 portions. The combined ethereal extracts were washed with 10% potassium bicarbonate, dried and distilled to yield 5.9 g. (83%) of ***m*-methoxybutyrophenone**, b.p. 142–146° (11 mm.), $n^{25}D$ 1.5235, d^{25}_4 1.0397.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.11; H, 8.01.

m-Methoxybutyrophenone 2,4-dinitrophenylhydrazone, after recrystallization from ethyl acetate, melted at 172–173°.

Anal. Calcd. for $C_{17}H_{18}N_4O_5$: C, 56.98; H, 5.06. Found: C, 56.85; H, 5.30.

Ethyl 1-Arylalkylidenecyanoacetates (I).—The ethyl 1-arylalkylidenecyanoacetates Ia-Ig were prepared by the condensation of the appropriate ketones with ethyl cyanoacetate using a procedure developed by Cope and coworkers.[14] The properties of these compounds are described in Table II. The following example illustrates the procedure.

Ethyl 1-(*m*-Methoxyphenyl)-ethylidenecyanoacetate (Ie).—A mixture of 22.0 g. (0.147 mole) of *m*-methoxyacetophenone, 16.6 g. (0.147 mole) of ethyl cyanoacetate, 7.2 g. of glacial acetic acid, 2.3 g. of ammonium acetate and 30 ml. of benzene was placed in a round-bottom flask fitted with a constant water separator and heated under reflux for 6 hours. A total of 6 ml. of lower layer was collected in the water separator. The reaction mixture was washed 3 times with water, dried over anhydrous magnesium sulfate, filtered and distilled. The main fraction, which amounted to 22.95 g. (64%), b.p. 150–166° (0.35 mm.), partially crystallized on scratching or seeding. However, only 38% of solid, m.p. 68–70°, could be isolated by crystallization from ether at −70°. Since it seemed likely that the solid was one of the two possible geometrical isomers of Ie and the oil the other, the oily reaction product was used in subsequent experiments without further purification.

In the preparation of ethyl 1-(*m*-methoxyphenyl)-butylidenecyanoacetate (Ig), an 86% yield was obtained as follows: two approximately equal portions of *m*-methoxybutyrophenone (58.1 g. total) were condensed with ethyl cyanoacetate as described above to yield 66.4 g. of Ig. The combined foreruns obtained in the distillation of these reactions were mixed with 1.2 g. of ammonium acetate, 4 g. of acetic acid and 100 ml. of benzene and heated under reflux as described above. Distillation yielded an additional 10.5 g. of Ig, making the total yield 76.9 g. (86%).

β-Alkyl-β-aryl-α,α′-dicyanoglutarimides (II).—The β-alkyl-β-aryl-α,α′-dicyanoglutarimides (II) were best prepared by the condensation of the appropriate ethyl 1-arylalkylidenecyanoacetates (I) with cyanoacetamide in the presence of sodium ethoxide. The properties of these compounds are described in Table III. The following example illustrates the procedure.

β-Methyl-β-phenyl-α,α′-dicyanoglutarimide (IIa).—A suspension of the sodium salt of cyanoacetamide in ethanol was prepared by the portionwise addition of 29.9 g. (0.356 mole) of cyanoacetamide to a magnetically stirred solution of sodium ethoxide in ethanol (prepared by reaction of 7.96 g. (0.356 mole) of sodium with 300 ml. of absolute ethanol contained in a 1000-ml. erlenmeyer flask protected by a drying tube and stirring for 20 minutes). To this suspension was added with continued stirring 76.5 g. (0.356 mole) of ethyl 1-phenylethylidenecyanoacetate (Ia). The reaction mixture became homogeneous after being stirred for 10 minutes, and was then allowed to stand overnight at room temperature. When 600 ml. of water was added and the reaction mixture strongly acidified with concentrated hydrochloric acid, 83.2 g. (92.5%) of β-methyl-β-phenyl-α,α′-dicyanoglutarimide (IIa), m.p. 285–287°, precipitated. Recrystallization from absolute ethanol gave glistening plates, m.p. 286–287°.

All of the β-alkyl-β-aryl-α,α′-dicyanoglutarimides were recrystallized from ethanol except IIb and IIc which were recrystallized from an acetic acid–water mixture.

In the preparation of β-ethyl-β-phenyl-α,α′-dicyanoglutarimide (IIb), β-*n*-propyl-β-phenyl-α,α′-dicyanoglutarimide (IIc) and β-*n*-propyl-β-(*m*-methoxyphenyl)-α,α′-dicyanoglutarimide (IIg) it was found best to extract the reaction mixture with ether after the addition of water in order to remove the neutral material. Yields of 64, 57 and 60%, respectively, were obtained by this method.

When the ethereal extract from the preparation of IIc was dried and distilled from a modified Claisen flask, about 30% recovered ethyl 1-phenylbutylidenecyanoacetate (Ic) was obtained.

If the general procedure was further modified by using 2 moles of sodium ethoxide and 2 moles of cyanoacetamide for each mole of ethyl 1-arylalkylidenecyanoacetate, the yields of IIc and IIg were raised to 88 and 89%, respectively.

It is of interest to note that β-*n*-propyl-β-phenyl-α,α′-dicyanoglutarimide (IIc) was found to exist in 2 crystalline forms: needles, m.p. 175–177°, and prisms, m.p. 194–196°. The lower melting form, being first crystallized from an acetic acid–water mixture, could be isolated by immediate filtration. On standing overnight in this solvent it changed to the higher melting form.

The stability of β-*n*-propyl-β-phenyl-α,α′-dicyanoglutarimide (IIc) in the presence of sodium ethoxide was demonstrated as follows. A mixture of 10.0 g. of IIc and a solution of sodium ethoxide in ethanol (prepared by treating 0.9 g. of sodium with 25 ml. of absolute ethanol) was allowed to stand at room temperature overnight. When 100 ml. of water was added and the solution acidified with concentrated hydrochloric acid 9.75 g. of IIc separated.

The Hydrolysis, Decarboxylation and Esterification of the Glutarimides II.—The imide IIa was converted to the glutaric acid IVa by the following procedure. A mixture of 20 g. (0.079 mole) of IIa, 100 g. of concentrated sulfuric acid, 100 ml. of water and 80 ml. of glacial acetic acid was placed in a round-bottom flask fitted with a reflux condenser and heated under reflux for 96 hours. The reaction mixture then was added to 650 ml. of water and placed in the refrigerator. On standing overnight 15.9 g. (91%) of β-methyl-β-phenylglutaric acid (IVa), m.p. 134–137°, crystallized. Recrystallization from water gave large stout needles, m.p. 142–143°. The analysis for this compound is given in Table V.

When treated in the same manner, IIb and IIc yielded the 9-alkyl-9-phenyl-3,7-diazobicyclo[3.3.1]nonane-2,4,6,8-tetraones, IIIb and IIIc. These compounds were obtained in better yield by the following procedure.

9-Ethyl-9-phenyl-3,7-diazobicyclo[3.3.1]nonane-2,4,6,8-tetraone (IIIb).—A mixture of 10 g. (0.037 mole) of finely powdered β-ethyl-β-phenyl-α,α′-dicyanoglutarimide (IIb), 60 ml. of concentrated sulfuric acid and 70 ml. of water was

(11) McElvain and Aldridge, THIS JOURNAL, **75**, 3987 (1953).
(12) L. G. S. Brooker and F. L. White, *ibid.*, **57**, 2480 (1935).
(13) S. M. McElvain and W. R. Davie, *ibid.*, **73**, 1400 (1951).
(14) A. C. Cope, *et al.*, *ibid.*, **63**, 3452 (1941).

Table II

Ethyl 1-Arylalkylidenecyanoacetates (I), RC(Ar)=C(CN)COOC$_2$H$_5$

No.	R is	Ar is	Formula	Yield, %	B.p., °C.	Mm.	$n^{25}D$	d^{25}_4	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Ia	CH_3	C_6H_5	$C_{13}H_{13}NO_2$	48	140–150	0.2	1.5468[a]					
Ib	C_2H_5	C_6H_5	$C_{14}H_{15}NO_2$	63	143–162	.3	1.5363[a]					
Ic	n-C_3H_7	C_6H_5	$C_{15}H_{17}NO_2$	67	142–150	.2	1.5315[a]					
Id	CH_3	$C_6H_4OCH_3(o)$	$C_{14}H_{15}NO_3$	79	150–161	.4	1.5443–1.5450	1.1150	68.55	6.16	68.95	6.17
Ie	CH_3	$C_6H_4OCH_3(m)$	$C_{14}H_{15}NO_3$	64	150–166	.35			68.55	6.16	69.02	6.07
If	CH_3	$C_6H_4OCH_3(p)$	$C_{14}H_{15}NO_3$	41	155–165	.1	1.5701–1.5705	1.1285	68.55	6.16	68.55	6.01
Ig	n-C_3H_7	$C_6H_4OCH_3(m)$	$C_{16}H_{19}NO_3$	86	150–160	.5	1.5353–1.5378	1.0778	70.31	7.01	70.43	6.87

[a] A. C. Cope, *et al.*, ref. 14, reported for Ia, b.p. 136–137° (2 mm.), $n^{25}D$ 1.5468; for Ib, b.p. 136–138° (2 mm.), $n^{25}D$ 1.5360 and for Ic, b.p. 135–136° (1 mm.), $n^{25}D$ 1.5318.

Table III

β-Alkyl-β-aryl-α,α′-dicyanoglutarimides (II), HNCOCH(CN)C(R)(Ar)CH(CN)CO

No.	R is	Ar is	Formula	Yield, %	M.p., °C.	Analyses, % Calcd. C	Calcd. H	Found C	Found H
IIa	CH_3	C_6H_5	$C_{14}H_{11}N_3O_2$	92.5	286–287[a]	66.35	4.38	66.74	4.48[b]
IIb	C_2H_5	C_6H_5	$C_{15}H_{13}N_3O_2$	64	209–213	67.40	4.90	67.56	4.83
IIc	n-C_3H_7	C_6H_5	$C_{16}H_{15}N_3O_2$	88	194–196 (175–177)[c]	68.31	5.38	68.33	5.24
IId	CH_3	$C_6H_4OCH_3(o)$	$C_{15}H_{13}N_3O_3$	95	283–287	63.59	4.63	63.29	4.67
IIe	CH_3	$C_6H_4OCH_3(m)$	$C_{15}H_{13}N_3O_3$	86.5	214–217	63.59	4.63	63.41	4.56
IIf	CH_3	$C_6H_4OCH_3(p)$	$C_{15}H_{13}N_3O_3$	89	275–281 d.	63.59	4.63	63.95	4.62
IIg	$C_3H_7(n)$	$C_6H_4OCH_3(m)$	$C_{17}H_{17}N_3O_3$	89	166.5–168.5	65.59	5.51	65.76	5.51

[a] N. L. Phalnikar and K. S. Nargund, ref. 5, reported m.p. 270° for this compound. [b] Calcd.: N, 16.59. Found: N, 16.6. [c] Polymorphic forms.

Table IV

9-Alkyl-9-phenyl-3,7-diazabicyclo[3.3.1]nonane-2,4,6,8-tetraones (III)

No.	Alkyl	Formula	Yield, %	M.p., °C.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIIa	CH_3	$C_{14}H_{12}N_2O_4$	37	288–289	61.76	4.44		62.19	4.21	
IIIb	C_2H_5	$C_{15}H_{14}N_2O_4$	82	310–312	62.93	4.93	9.79	62.79	4.87	10.00
IIIc	C_3H_7	$C_{16}H_{16}N_2O_4$	84	310–314 d.	63.99	5.37	9.35	64.20	5.30	9.5

placed in a 500-ml. round-bottom flask fitted with a reflux condenser and heated under reflux for 1.5 hours with frequent shaking. After cooling to 25° (cooling to 0° results in an impure product), the crude solid was filtered off through a sintered glass funnel, dissolved in 5% aqueous sodium hydroxide, and this solution filtered. When concentrated hydrochloric acid was added, 8.7 g. (82%) of IIIb, m.p. 310–312°, precipitated.

The homolog IIIa was prepared from IIa by the above method. The properties of IIIa-c are listed in Table IV.

Only these compounds were obtained in crystalline form. Similar hydrolyses of IIe and IIg gave oily products which were converted as such to the glutaric esters Ve and Vg. The following example illustrates the procedure.

Dimethyl β-Methyl-β-(*m*-methoxyphenyl)-glutarate (Ve).—A mixture of 12 g. of β-methyl-β-(*m*-methoxyphenyl)-α,α′-dicyanoglutarimide (IIe), 105 ml. of water and 90 ml. of concentrated sulfuric acid was placed in a round-bottom flask fitted with a reflux condenser and heated under reflux for 0.5 hour with frequent shaking. Water (400 ml.) was added, and after cooling the mixture was extracted 5 times with ether. The combined ethereal extracts were dried over anhydrous magnesium sulfate, filtered, and the ether distilled off on the steam-bath. The residual red oil and 112 ml. of 20% aqueous sodium hydroxide were heated under reflux for 48 hours. A solution of 68 g. of concentrated sulfuric acid in 200 ml. of water was then added and reflux continued for 2 hours. The mixture was extracted 5 times with ether and the ethereal extracts dried over anhydrous magnesium sulfate and filtered. An excess of an ethereal solution of diazomethane was added, and after standing a few minutes the excess diazomethane destroyed with a few drops of glacial acetic acid. The ethereal solution was washed first with 10% aqueous potassium bicarbonate and then with water, dried over anhydrous magnesium sulfate, filtered, and the ether distilled off on the steam-bath. The residual oil was distilled twice from a modified Claisen flask to give 7.1 g. (60%) of Ve.

This method gave quite low yields when applied to IIf and IId. Yields of 63 and 80%, respectively, were obtained in these cases by using the following procedure. A mixture of 10 g. (0.035 mole) of β-methyl-β-(*p*-methoxyphenyl)-α,α′-dicyanoglutarimide (IIf) and 100 ml. of a solution, prepared by mixing 1 volume of water, 1 volume of concentrated hydrochloric acid and 3 volumes of glacial acetic acid, was heated under reflux until all solid was in solution (20–30 hours). The hydrolyzing solution was distilled off on the steam-bath under reduced pressure and a solution of 60 g. of sodium hydroxide in 180 ml. of water added. This solution was heated under reflux for 3 days and treated in the same manner as described above in the preparation of Ve.

When the ester Vd was prepared by this procedure it was contaminated with trimethyl β-methyl-β-(*o*-methoxyphenyl)-α-carboxyglutarate. For this reason the properties and analyses of Vd are not reported with the other glutaric esters in Table VI. Products derived from this triester are described below.

The bicyclic diimides IIIb and IIIc were converted to the glutaric esters Vb and Vc by the following procedure. A solution of 20 g. (0.07 mole) of 9-ethyl-9-phenyl-3,7-diazabicyclo[3.3.1]nonane-2,4,6,8-tetraone (IIIb) in 200 ml. of 20% aqueous potassium hydroxide was placed in an alkali resistant flask fitted with a reflux condenser and heated under reflux for 48 hours. After cooling, a solution of 71 g. of concentrated sulfuric acid in 200 ml. of water was added and reflux continued for 4 hours. On cooling overnight 16.15 g. (98%) of crude β-ethyl-β-phenylglutaric acid (IVb), m.p. 80–110°, crystallized. A 5.4-g. (0.023 mole) sample of the crude acid was dissolved in ether and treated with excess diazomethane in ether solution. The excess diazomethane was destroyed with a few drops of glacial acetic acid,

TABLE V

β-ALKYL-β-ARYLGLUTARIC ACIDS (IV), $HOOCCH_2CRArCH_2COOH$

No.	R is	Ar is	Formula	M.p., °C.	Analyses, % Calcd. C	Calcd. H	Calcd. Neut. equiv.	Found C	Found H	Found Neut. equiv.
IVa	CH_3	C_6H_5	$C_{12}H_{14}O_4$	142–143[a]	64.85	6.35	111.1	65.02	6.42	111.4
IVb	C_2H_5	C_6H_5	$C_{13}H_{16}O_4$	114–115	66.08	6.83	118.1	66.24	6.85	118.3
IVc	n-C_3H_7	C_6H_5	$C_{14}H_{18}O_4$	128–131	67.18	7.25	125.0	68.01	7.52	123.2
IVe	CH_3	$C_6H_4OCH_3(m)$	$C_{13}H_{16}O_5$	126–127	61.89	6.39	126.1	62.35	6.55	125.9
IVr	H	$C_6H_4OCH_3(m)$	$C_{12}H_{14}O_5$	127–129	60.50	5.92	119.1	60.48	5.99	118.2

[a] N. L. Phalnikar and K. S. Nargund, ref. 5, reported m.p. 132–133° for this compound.

TABLE VI

DIALKYL β-ALKYL-β-ARYLGLUTARATES (V), $R'OOCCH_2CRArCH_2COOR'$

No.	R is	R′ is	Ar is	Formula	Yield, %	B.p. °C.	B.p. Mm.	$n^{25}D$	d^{25}_4	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Va	CH_3	C_2H_5	C_6H_5	$C_{16}H_{22}O_4$	90	149–152	0.3	1.4928	1.0664	69.04	7.97	68.97	7.80
Vb	C_2H_5	CH_3	C_6H_5	$C_{15}H_{20}O_4$	82	127	.8	1.5044	1.1002	68.16	7.63	68.00	7.62
Vc	n-C_3H_7	CH_3	C_6H_5	$C_{16}H_{22}O_4$	83	120–123	.3	1.5011	1.0764	69.04	7.97	69.49	8.01
Ve	CH_3	CH_3	$C_6H_4OCH_3(m)$	$C_{15}H_{20}O_5$	60	151–155	.15	1.5112–1.5108	1.1706	64.27	7.19	63.70	7.00
Vf	CH_3	CH_3	$C_6H_4OCH_3(p)$	$C_{15}H_{20}O_5$	63	153–170	.1	1.5049–1.5124	1.1806	64.27	7.19	63.85	6.99
Vg	n-C_3H_7	CH_3	$C_6H_4OCH_3(m)$	$C_{17}H_{24}O_5$	60	150–151	.07	1.5056–1.5098	1.1089	66.21	7.85	66.09	7.84
Vr	H	CH_3	$C_6H_4OCH_3(m)$	$C_{14}H_{18}O_5$		162–166[a]	.35			63.14	6.81	63.18	7.03

[a] M.p. 56–58°.

TABLE VII

3-ALKYL-3-ARYLPENTANE-1,5-DIOLS (VI), $HOCH_2CH_2CArRCH_2CH_2OH$

No.	R is	Ar is	Formula	Yield, %	M.p., °C.	Analyses, % Calcd. C	Calcd. H	Found C	Found H
VIa	CH_3	C_6H_5	$C_{12}H_{18}O_2$	96	75–77	74.19	9.34	74.24	9.22
VIb	C_2H_5	C_6H_5	$C_{13}H_{20}O_2$	80	88–90	74.86	9.68	75.08	9.45
VIc	n-C_3H_7	C_6H_5	$C_{14}H_{22}O_2$	80	92–94	75.63	9.97	75.71	10.02
VId	CH_3	$C_6H_4OCH_3(o)$	$C_{13}H_{20}O_3$	..	114–116[a]	69.61	8.99	69.86	9.28

[a] This glycol, after purification by chromatography, reacted with 2.1 moles of acetic anhydride (*cf.* ref. 19).

and the solution extracted once with 5% aqueous sodium hydroxide and once with water. The ethereal solution was dried over anhydrous magnesium sulfate, the ether distilled off on the steam-bath, and the residual oil distilled from a modified Claisen flask to yield 5.1 g. (84%) of dimethyl β-ethyl-β-phenylglutarate (Vb).

The ethyl ester of IVa was prepared by heating a mixture of 18.9 g. of IVa, 0.2 ml. of concentrated sulfuric acid, 20 ml. of 95% ethanol and 30 ml. of benzene in a 100 ml. round-bottom flask fitted with a constant water separator and a reflux condenser under reflux for 7 hours. A total of 12 ml. of lower layer was collected in the water separator. Anhydrous sodium carbonate (3 g.) was added, and the reaction mixture allowed to stand for 4 hours with occasional swirling, then filtered and distilled from a modified Claisen flask. The main fraction, 21.5 g. (90%), was diethyl β-methyl-β-phenylglutarate (Va).

β-(*m*-Methoxyphenyl)-glutaric acid (IVr) was prepared by the saponification and decarboxylation of diethyl α,α′-dicarbethoxy-β-(*m*-methoxyphenyl)-glutarate, prepared in 62% yield by the condensation[15] of sodiomalonic ester with ethyl *m*-methoxybenzalmalonic ester, which was obtained from the condensation of *m*-methoxybenzaldehyde with malonic ester.[16]

The properties and analyses of the dialkyl β-alkyl-β-arylglutarates Va-c, Ve-g and Vr are listed in Table VI.

The glutaric acids IVb, IVc and IVe were prepared by saponification of the corresponding dimethyl esters with 10% sodium hydroxide. The properties of these compounds are listed in Table V.

3-Alkyl-3-arylpentane-1,5-diols (VI).—These diols were prepared by reduction of the corresponding dialkyl β-alkyl-β-arylglutarates Va-g with lithium aluminum hydride. The diols VIe–g, which were obtained as oils and not purified, were found satisfactory for use in the next step. Complications, discussed below, arose in the preparation of VId. The properties of these diols which were obtained crystalline (VIa–d) are listed in Table VII. The following example illustrates the procedure.

A 13.9-g. (0.05 mole) sample of diethyl β-methyl-β-phenylglutarate (Va) was added dropwise to a suspension of 2.2 g. of finely powdered lithium aluminum hydride in 100 ml. of dry ether, and the mixture heated on the steam-bath with stirring for 1 hour. Excess lithium aluminum hydride was destroyed by the cautious addition of 5 ml. of water, and the resulting suspension rinsed into a beaker with 30 ml. of 10% aqueous sulfuric acid. The ether was decanted and the sludge extracted 5 times with ether. The combined ethereal extracts were dried over anhydrous magnesium sulfate, filtered and the ether removed by distillation. There remained 9.3 g. (96%) of 3-methyl-3-phenylpentane-1,5-diol (VIa), m.p. 68–73°. Recrystallization from benzene gave prisms.

1,4-Dialkyl-4-arylpiperidines (VII) and Their Hydrochlorides.—The 1,4-dialkyl-4-arylpiperidines VIIa–g and VIIn–r were prepared by the condensation of the corresponding 3-alkyl-3-arylpentane-1,5-diols (VI) with the appropriate amine in the presence of copper chromium oxide. The properties of these compounds are listed in Table VIII. The following example illustrates the procedure.

A mixture of 7.76 g. (0.04 mole) of 3-phenyl-3-methylpentane-1,5-diol (VIa), 1.8 ml. of methylamine, 2.4 g. of copper–chromium oxide[17] and 25 ml. of purified dioxane[18] was

(15) A. Kotz and G. Stalmann, *J. prakt. Chem.*, [2] **68**, 162 (1903).

(16) *Cf.* "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 377.

(17) H. Adkins, *et al.*, THIS JOURNAL, **54**, 1138 (1932).

(18) L. F. Fieser, "Experiments in Organic Chemistry," second edition, D. C. Heath and Co., New York, N. Y., 1941, p. 368.

Table VIII

1,4-Dialkyl-4-arylpiperidines (VII) and Their Hydrochlorides

$$R'NCH_2CH_2CR(Ar)CH_2CH_2$$

No.	R is	R′ is	Ar is	Formula	Yield, %	B.p. °C.	Mm.	$n^{25}D$	d^{25}_4	Calcd. C	Calcd. H	Found C	Found H	Hydrochlorides of VII M.p., °C.	Formula	Analyses, % C	Calcd. H	Cl	Found C	Found H	Cl
VIIa	CH_3	CH_3	C_6H_5	$C_{12}H_{19}N$	73	70–74	0.13	1.5284	0.9635	82.48	10.12	82.97	10.26	212–215	$C_{13}H_{20}ClN$	69.16	8.93	15.7	68.99	8.79	15.9
VIIb	C_2H_5	CH_3	C_6H_5	$C_{13}H_{21}N$	54	92–94	.6	1.5288		82.70	10.41	82.89	10.19	222–223[a]	$C_{14}H_{22}ClN$	70.12	9.25	14.8	70.44	9.10	15.1
VIIc	n-C_3H_7	CH_3	C_6H_5	$C_{14}H_{23}N$	67	82–95	.3	1.5198	0.9499	82.89	10.67	82.50	10.80	204–206	$C_{15}H_{24}ClN$			14.0			14.0
VIId	CH_3	CH_3	$C_6H_4OCH_3(o)$	$C_{14}H_{21}NO$	86	[b]		1.5357	[b]	76.66	9.65	76.12	9.31	190–191.5	$C_{14}H_{22}ClNO$	65.73	8.67	13.9	65.83	8.43	13.7
VIIe	CH_3	CH_3	$C_6H_4OCH_3(m)$	$C_{14}H_{21}NO$	46	102–106	.15	1.5317	1.0089	76.66	9.65	76.51	9.78								
VIIf	CH_3	CH_3	$C_6H_4OCH_3(p)$	$C_{14}H_{21}NO$	55	112–118	.4	1.5329	1.0107	76.66	9.65	76.55	9.47	$C_{14}H_{22}ClNO$	238–245 d.	65.73	8.67		65.91	8.66	
VIIg	n-C_3H_7	CH_3	$C_6H_4OCH_3(m)$	$C_{16}H_{25}NO$	80	121–123	.5	1.5278	0.9925	77.68	10.19	78.43	10.29	$C_{16}H_{26}ClNO$	186–188	67.70	9.23		67.54	9.05	
VIIh	CH_3	CH_3	$C_6H_4OH(o)$	$C_{13}H_{19}NO$	80	177–179[c]				76.05	9.33	76.05	9.18	$C_{13}H_{20}ClNO$	266–270 d.	64.58	8.34		64.15	8.49	
VIIi	CH_3	CH_3	$C_6H_4OH(m)$	$C_{13}H_{19}NO$	68	146–149[c]				76.05	9.33	76.07	9.33	$C_{13}H_{20}ClNO$	214–215	61.58	8.34		64.95	8.13	
VIIk	CH_3	CH_3	$C_6H_4OH(p)$	$C_{13}H_{19}NO$	76	169–172[c]				76.05	9.33	76.28	9.27	$C_{13}H_{20}ClNO$	262–270 d.	61.58	8.34		61.19	8.27	
VIIm	n-C_3H_7	CH_3	$C_6H_4OH(m)$	$C_{15}H_{23}NO$	83	162–164[c]				77.20	9.94	77.41	9.77	$C_{15}H_{24}ClNO$	187–190	66.77	8.97		66.54	8.81	
VIIn	CH_3	C_2H_5	C_6H_5	$C_{14}H_{21}N$	60	78–87	.25	1.5257	0.9594	82.70	10.41	82.85	10.40	$C_{14}H_{22}ClN$	258–261			14.8			14.6
VIIo	CH_3	n-C_3H_7	C_6H_5	$C_{15}H_{23}N$	63	82–90	.15	1.5210	.9516	82.89	10.67	82.74	10.71	$C_{15}H_{24}ClN$	229–232			14.0			13.9
VIIp	CH_3	i-C_3H_7	C_6H_5	$C_{16}H_{25}N$	59	80–85	.3	1.5216	.9615	82.89	10.67	82.93	10.68	$C_{16}H_{26}ClN$	285–288			14.0			14.1
VIIq	CH_3	n-C_4H_9	C_6H_5	$C_{15}H_{25}N$	71	103–110	.3	1.5164	.9398	83.04	10.89	83.34	10.90	$C_{16}H_{26}ClN$	244–245			13.3			13.2
VIIr	H	CH_3	$C_6H_4OCH_3(m)$	$C_{13}H_{19}NO$	52	90–95	.5	1.5326		76.05	9.33	76.18	9.02	$C_{13}H_{20}ClNO$	112–115			14.7			14.6
VIIs	H	CH_3	$C_6H_4OH(m)$	$C_{12}H_{17}NO$	65	162–163[c]				75.35	8.96	75.79	8.76	$C_{12}H_{18}ClNO$	208–210			15.6			15.9

[a] This compound was recently reported by T. D. Perrine, *J. Org. Chem.*, **22**, 1484 (1957). [b] This material is a mixture; VIId was obtained pure only as the hydrochloride. [c] These values are melting points.

placed in a steel hydrogenation bomb. Hydrogen was admitted and the bomb heated with shaking at 250° and 4400 p.s.i. pressure of hydrogen for 1 hour. After cooling, the reaction mixture was filtered and the filtrate distilled from a modified Claisen flask. The main fraction, which amounted to 5.55 g. (73%), boiled at 70–74° (0.15 mm.).

An analytically pure sample of 1,4-dimethyl-4-phenylpiperidine (VIIa) was prepared as follows: A 0.3-g. sample of pure 1,4-dimethyl-4-phenylpiperidine hydrochloride, prepared as described below, was treated with 10% aqueous potassium bicarbonate and the aqueous solution extracted with several portions of ether. The combined ethereal extracts were dried over anhydrous magnesium sulfate, filtered and the ether distilled from a steam-bath. The residual oil was evaporatively distilled 3 times at 60° (0.1 mm.) to yield pure 1,4-dimethyl-4-phenylpiperidine (VIIa).

1,4-Dimethyl-4-phenylpiperidine hydrochloride was prepared by treating a dry ethereal solution of the amine as obtained from the hydrogenation with an excess of an ethereal solution of anhydrous hydrogen chloride. The precipitated salt then was recrystallized from an isopropyl alcohol–ethyl acetate mixture. The hydrochlorides of VIIb–g and VIIn–r were recrystallized from this solvent pair or from isopropyl alcohol.

The hydroxyphenylpiperidines VIIh–m and VIIs were prepared by demethylation of the corresponding methoxyphenylpiperidines with hydrobromic acid. The properties of these compounds are listed in Table VIII. The following example illustrates the procedure. A mixture of 2.5 g. of 1-methyl-4-*n*-propyl-4-(*m*-methoxyphenyl)-piperidine (VIIg) hydrochloride and 10 ml. of constant boiling hydrobromic acid was heated under reflux for 1 hour. When 5 ml. of water was added, the hydrobromide of VIIm crystallized from the reaction mixture. This was separated by filtration and decomposed with 10% potassium bicarbonate solution to yield 1.1 g. of 1-methyl-4-*n*-propyl-4-(*m*-hydroxyphenyl)-piperidine (VIIm), m.p. 158–163°. The filtrate was then neutralized with 10% potassium bicarbonate solution and evaporated to dryness on the steam-bath under a stream of nitrogen. The resulting white solid was extracted with several portions of boiling ethanol. The extracts were combined, evaporated to dryness on the steam-bath under a stream of nitrogen, and the resulting solid recrystallized from an ethanol–water mixture to yield an additional 0.6 g. of VIIm.

The other 1,4-dialkyl-4-(hydroxyaryl)-piperidines VIIh–k and VIIs were purified by recrystallization from this solvent pair or by sublimation.

A sample of VIIm was dissolved in a minimum amount of isopropyl alcohol and 10 volumes of dry ether added. An excess of an ethereal solution of anhydrous hydrogen chloride then was added. After standing overnight in the refrigerator, the hydrochloride of VIIm was isolated by filtration and recrystallized from isopropyl alcohol. The hydrochlorides of VIIh–k and VIIs were recrystallized from this solvent or from an isopropyl alcohol–ethyl acetate mixture.

β-Methyl-β-phenyl-α,α′-dicyanoglutarimide (IIa) and 6-Methyl-4,6-diphenyl-3-cyano-5,6-dihydro-2-pyridone (XV).—A mixture of 32.25 g. (0.15 mole) of ethyl 1-phenylethylidenecyanoacetate (Ia) and 16.9 g. (0.15 mole) of ethyl cyanoacetate was added to 60 ml. of absolute ethanol which previously had been saturated with anhydrous ammonia at 0°. The flask containing this mixture was stoppered and placed in the refrigerator for 4 days. The precipitated solid was isolated by filtration and boiled with 150 cc. of water. The resulting aqueous suspension was filtered to yield 5.0 g. (23%) of 6-methyl-4,6-diphenyl-3-cyano-5,6-dihydro-2-pyridone (XV), m.p. 211–214°. Recrystallization from a chloroform–petroleum ether (b.p. 60–68°) mixture gave prisms, m.p. 213–214°; $\lambda_{max}^{C_2H_5OH}$ 288 mμ (log ε 4.02), 288 mμ (log ε 3.88).

Anal. Calcd. for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.72. Found: C, 79.10; H, 5.39; N, 9.60.

Acidification of the filtrate precipitated 8.2 g. of β-methyl-β-phenyl-α,α′-dicyanoglutarimide (IIa). When ether was added to the remainder of the reaction mixture, more solid precipitated. When this was isolated by filtration, dissolved in water and strongly acidified, an additional 3.8 g. of IIa was obtained. The total yield was 12.0 g. (31%).

Compound XV was also prepared directly from Ia. A mixture of 10.75 g. (0.05 mole) of Ia and 30 ml. of absolute ethanol which previously had been saturated with ammonia

at 0° was allowed to stand in the refrigerator for 10 days. During this time 1.65 g. (23%) of XV, m.p. 208–213°, crystallized.

6-Methyl-4,6-diphenyl-5,6-dihydro-2-pyridone (XVI).—A suspension of 1.5 g. of 6-methyl-4,6-diphenyl-3-cyano-5,6-dihydro-2-pyridone (XV) in a mixture of 6.25 g. of concentrated sulfuric acid, 6.25 ml. of water and 5 ml. of glacial acetic acid was heated under reflux for 72 hours. During the first 48 hours the solid gradually disappeared. Addition of water precipitated 1.0 g. (73%) of XVI, m.p. 150–180°. Recrystallization from benzene gave prisms, m.p. 194–195°; $\lambda_{max}^{C_2H_5OH}$ 277 mμ (log ε 4.13), shoulder at 223 mμ.

Anal. Calcd. for $C_{18}H_{17}NO$: C, 82.10; H, 6.51. Found: C, 82.36; H, 6.47.

9-Ethyl-9-phenyl-3,7-dimethyl-3,7-diazabicyclo[3.3.1]-nonane-2,4,6,8-tetraone.—To a solution of sodium methoxide in methanol, prepared by treating 2.52 g. (0.105 mole) of sodium hydride with 100 ml. of anhydrous methanol contained in a 10-inch evaporating dish, was added 15 g. (0.0525 mole) of 9-ethyl-9-phenyl-3,7-diazabicyclo[3.3.1]-nonane-2,4,6,8-tetraone (IIIb). A stream of air was directed at the surface of the solution and the methanol boiled off on the steam-bath with continuous stirring. The remaining solid was dried under vacuum to give 16.7 g. of the disodium salt of IIIb.

A suspension of 9.9 g. (0.03 mole) of this disodium salt in 60 ml. of dimethylformamide was placed in a round-bottom flask fitted with a Hershberg stirrer and a reflux condenser, and 11.4 g. of methyl iodide added. The solution became quite warm, and most of the suspended solid went into solution. An additional 10 g. of methyl iodide was added and the solution stirred for 1 hour. When 400 ml. of water was added, 9.3 g. (99%) of 9-ethyl-9-phenyl-3,7-dimethyl-3,7-diazabicyclo[3.3.1]nonane-2,4,6,8-tetraone, m.p. 272–274°, crystallized. Recrystallization from chloroform gave fine white needles, m.p. 274–276°.

Anal. Calcd. for $C_{17}H_{18}N_2O_4$: C, 64.95; H, 5.77. Found: C, 65.09; H, 5.65.

4-Ethyl-4-phenylpiperidine Hydrochloride.—A mixture of 5.2 g. (0.018 mole) of IIIb, 4 g. of copper–chromium oxide[17] and 25 ml. of purified dioxane[18] was placed in a steel hydrogenation bomb. Hydrogen was admitted and the mixture heated with shaking at 250° for 25 hours at an initial pressure of 3510 p.s.i. of hydrogen. After cooling, the reaction mixture was filtered, the dioxane distilled off under reduced pressure, and the residual oil distilled from a modified Claisen flask to yield 2.35 g. of 4-ethyl-4-phenylpiperidine, b.p. 80–86° (0.2 mm.). A portion of this amine was converted to its hydrochloride, which, after several recrystallizations from an isopropyl alcohol–ethyl acetate mixture melted at 208–213°; reported (*cf.* footnote *a*, Table VIII) m.p. 210–211°.

Anal. Calcd. for $C_{13}H_{20}NCl$: C, 69.16; H, 8.93. Found: C, 68.77; H, 8.73.

A 0.75-g. sample of 4-ethyl-4-phenylpiperidine ($n^{25}D$ 1.5310), 1 ml. of 37% formaldehyde solution and 1 ml. of formic acid were placed in a 25-ml. erlenmeyer flask fitted with a reflux condenser and the mixture heated on the steam-bath overnight. An excess of 10% aqueous sodium hydroxide was added and the solution extracted with ether. The ethereal extracts were dried over anhydrous magnesium sulfate, filtered and the ether distilled off on the steam-bath. The residual oil was distilled from a modified Claisen flask to give 0.7 g. of a colorless oil, which was dissolved in anhydrous ether and treated with an excess of an ethereal solution of anhydrous hydrogen chloride in ether. Filtration gave 0.7 g. (74.9%) of 1-methyl-4-ethyl-4-phenylpiperidine (VIIb) hydrochloride, m.p. 216–220°. Recrystallization from an isopropyl alcohol–ethyl acetate mixture gave material melting at 218–220.5°, which gave no depression on admixture and melting with an authentic sample which had been prepared from the diol VIb.

3-Methyl-3-(*o*-methoxyphenyl)-pentane-1,5-diol (VId) and 2-Hydroxymethyl-3-methyl-3-(*o*-methoxyphenyl)-pentane-1,5-diol (X).—A 28-g. sample of the presumed dimethyl β-methyl-β-(*o*-methoxyphenyl)-glutarate (Vd) obtained *via* the hydrolysis of β-methyl-β-(*o*-methoxyphenyl)-α,α′-dicyanoglutarimide (IId) was reduced with lithium aluminum hydride as described above for the preparation of 3-alkyl-3-arylpentane-1,5-diols. The product was obtained as an oil, which on crystallization from benzene yielded 12.3 g. of solid, m.p. 87–92°.

A sample of this solid was chromatographed in the following manner: A column of silicic acid 4 cm. in diameter and 14.5 cm. in height was prepared by suspending 90 g. of silicic acid (prepared for use by washing with distilled acetone, drying at 95° overnight and screening through a 30-gauge screen) in 300 ml. of chloroform and allowing the slurry to settle in a 4-cm. diameter column having a sintered glass disk sealed in the bottom. The column was run almost dry and a solution of 4.9 g. of the solid, m.p. 87–92°, in a minimum of chloroform was poured onto it. The column was eluted with a total of 2 liters of solvent, varying from a 2.75% ethanol in chloroform mixture at the start to a 10.75% ethanol in chloroform mixture at the end of the chromatogram.

Separation of the mixture into 2 distinct opaque bands was observed. The solvent containing each band was collected and evaporated to dryness on the steam-bath under a stream of nitrogen.

The first band (2.6 g.) was 3-methyl-3-(*o*-methoxyphenyl)-pentane-1,5-diol (VId). Recrystallization from water gave long glistening needles, m.p. 114–116°, analyses of which appear in Table VII.

The second band (2.1 g.) was **3-methyl-3-(*o*-methoxyphenyl)-2-hydroxymethylpentane-1,5-diol (X)**, which on recrystallization from benzene gave fine needles melting at 132–133°. This compound consumed 3.1 moles of acetic anhydride on quantitative acetylation.[19]

Anal. Calcd. for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 66.84; H, 8.53.

This triol yielded a tri-*p*-nitrobenzoate, m.p. 116–120°.

Anal. Calcd. for $C_{35}H_{31}N_3O_{13}$: C, 59.91; H, 4.45. Found: C, 59.61; H, 4.45.

1,3,4-Trimethyl-4-(*o*-methoxyphenyl)-piperidine (XI) Hydrochloride and 1,4-Dimethyl-4-(*o*-methoxyphenyl)-piperidine (VIId) Hydrochloride.—An 11.9-g. sample of the mixture of 3-methyl-3-(*o*-methoxyphenyl)-pentane-1,5-diol (VId) and 3-methyl-3-(*o*-methoxyphenyl)-2-hydroxymethylpentane-1,5-diol (X) melting at 87–92° was cyclized with methylamine as described above for the preparation of 1,4-dialkyl-4-arylpiperidines. An amine mixture (8.3 g.), b.p. 98–102° (0.02 mm.), $n^{25}D$ 1.5353–1.5361, was obtained. These amines were converted to hydrochlorides, which were separated by fractional crystallization from isopropyl alcohol–ethyl acetate mixtures. The less soluble component (1.7 g.) was 1,3,4-trimethyl-4-(*o*-methoxyphenyl)-piperidine (XI) hydrochloride, m.p. 271–275° dec.

Anal. Calcd. for $C_{15}H_{24}ClNO$: C, 66.77; H, 8.97; Cl, 13.1. Found: C, 66.83; H, 8.69; Cl, 13.1.

A small sample of the hydrochloride of XI was converted to the free base, $n^{25}D$ 1.5333, using the procedure described for the preparation of pure 1,4-dialkyl-4-arylpiperidines.

Anal. Calcd. for $C_{15}H_{23}NO$: C, 77.20; H, 9.94. Found: C, 77.62; H, 9.62.

The more soluble component (5.3 g.) was 1,4-dimethyl-4-(*o*-methoxyphenyl)-piperidine (VIId) hydrochloride, m.p. 190–191°. This latter compound was prepared in high yield (86%) when diol VId that had been purified by chromatography was used in the cyclization with methylamine. In a similar manner the hydrochloride of XI was prepared from the purified triol X in 34% yield.

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