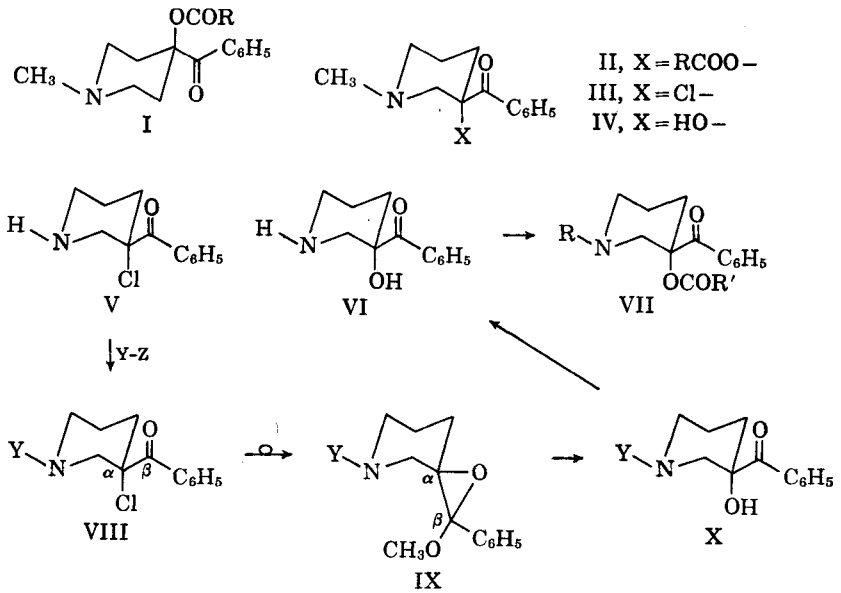
Chemistry of Some 3-Benzoylpiperidines

By T. B. ZALUCKY, L. MALSPEIS, H. PATEL, and G. HITE

Syntheses of 3-chloro-3-benzoylpiperidine and the corresponding diastereoisomeric (+)-10-camphorsulfonamides have been described. Although neither 3-chloro- nor 3-hydroxy-3-benzoylpiperidine could be resolved, von Braun demethylation of the corresponding easily resolvable *N*-methyl α-chloro and *N*-methyl α-acetoxy ketones was successful. Both α- and β-(+)-1-(10-camphorsulfonyl)-3-chloro-3-benzoylpiperidine represent models for the study of the scope of epoxy ether cleavage and formation from α-halo ketones. The von Braun demethylation of 1-methyl-3-benzoyl-3-acetoxypiperidine is the method of choice for the synthesis of racemic and optically active potential local anesthetic *N*-alkyl-3-benzoyl-3-acyloxypiperidines. The combined sequences afford a pathway for relating the configurations of (+)-1-methyl-3-benzoyl-3-hydroxypiperidine and (−)-1-methyl-3-benzoyl-3-chloropiperidine. The development of the synthetic scheme and of the design of the model sulfonamides and the implications of the configurational studies are discussed.

REPORTS OF the local anesthetic activity of 1-methyl-4-benzoyl-4-acyloxypiperidines (I) (1) and 1-methyl-3-benzoyl-3-acyloxypiperidines (II) (2), following detection of the local anesthetic activity of (−)-1-methyl-3-benzoyl-3-chloropiperidine (III) (3, 4), are in accord with previously recorded results (5) and prompted redirection of the evaluation of this pharmacophore to other 1-alkyl-3-benzoyl-3-acyloxypiperidines (II, VII), both optically active and racemic (Scheme I).

3-Benzoyl-3-chloropiperidine (V), a potential precursor to 3-benzoyl-3-hydroxypiperidine (VI) and 1-alkyl-3-benzoyl-3-acyloxypiperidines (VII),



(Y–Z = Amide-Forming Reagent)
Scheme I

presents a unique opportunity to establish the mechanism and stereochemical scope (6, 7) (*cf.* 8–10) of epoxy ether (*cf.* IX, XXVI) cleavage and formation from α-halo ketones. According to the mechanism proposed earlier (*cf.* 8, 9), nitrogen participation and consequent α-C-symmetrization during epoxy ether formation from α-halo ketones should be inhibited in a suitably constituted amide (VIII).

It is of interest to effect stereospecific conver-

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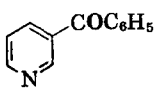
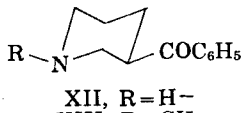
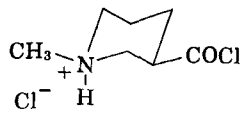


XI



XII, R = H−
XIII, R = CH_3−



XIV

sions of α-halo ketones of known absolute configuration (11, 12) to the corresponding α-oxygenated ketones (VIII → IX → X) in order to (*a*) relate the configurations of (−)-1-methyl-3-benzoyl-3-chloropiperidine (III) and (+)-1-methyl-3-benzoyl-3-hydroxypiperidine (IV) and thereby confirm the proposed mechanism (11) by which the latter arises from the former under *quasi*-Favorskii conditions, (*b*) facilitate studies on the relationship between optical rotatory dispersion and absolute configuration of α-oxygenated ketones (12, 13), and (*c*) permit examination of the absolute configurational requirements for activity and/or irritancy (14) of these local anesthetics prepared or simply related through this sequence.

The purpose of this report is to describe approaches to the synthesis of 3-benzoyl-3-chloropiperidine (V), 3-benzoyl-3-hydroxypiperidine (VI), and a suitable analog (VIII) of the latter with which to pursue these investigations.

DISCUSSION

The most obvious route to 3-benzoyl-3-chloropiperidine (V), *i.e.*, reduction of 3-benzoylpyridine (XI) hydrochloride followed by halogenation of 3-benzoylpiperidine (XII) (2), was abandoned in view of the low yield (about 5%) of the former reaction.[1] The high yield (89%) of 1-methyl-3-benzoylpiperidine (XIII) obtained earlier by Friedel-Crafts acylation of benzene with 1-methyl-3-benzoylpiperidine-3-carbonyl chloride hydrochloride (XIV) (18) and the recorded use of β-alanyl chloride in such acylations (19) prompted a parallel approach to XII.

However, the conditions employed earlier (11, 18) failed. While acetyl chloride and phosphorus pentachloride (19) converted piperidine-3-carboxylic acid hydrochloride (XVI) to piperidine-3-carbonyl chloride hydrochloride (XVII), as indicated by a characteristic shift in the carbonyl absorption from 1715 cm.$^{-1}$ in the former to 1783 cm.$^{-1}$ in the latter, Friedel-Crafts conditions (11) again afforded only acid-insoluble tar. Accordingly, the use of amido acids (19) (*cf.* XXI*a*, *b*) was investigated.

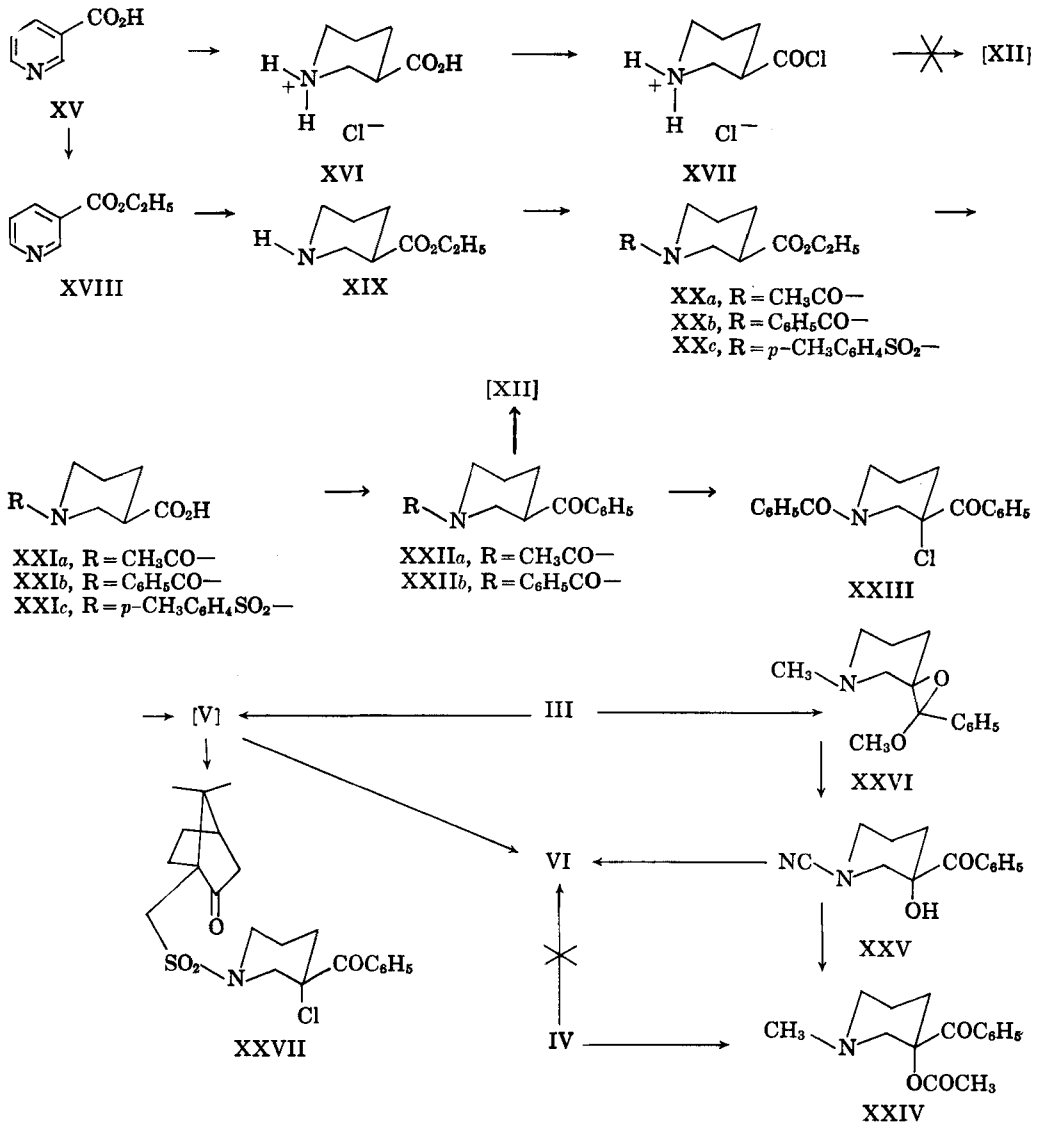
Reduction of ethyl nicotinate (XVIII) gave ethyl piperidine-3-carboxylate (XIX), which was treated with acetic anhydride to yield ethyl 1-acetylpiperidine-3-carboxylate (XX*a*). This amido ester (XX*a*) was hydrolyzed in dilute aqueous base to give 1-acetylpiperidine-3-carboxylic acid (XXI*a*), from which the corresponding ester (XX*a*) could be regenerated by treatment with thionyl chloride and subsequent alcoholysis of the intermediate acyl halide. The acyl halide, under Friedel-Crafts conditions, afforded 1-acetyl-3-benzoylpiperidine (XXII*a*) which could neither be crystallized nor purified by distillation. However, the infrared spectrum showed bands at 1630 and 1670 and a doublet at 1594–1578 cm.$^{-1}$, corresponding to amide, ketone, and phenyl moieties. Hydrolysis of crude XXII*a* afforded an oily amine (XII) which polymerized (*cf.* 20) upon distillation, afforded an amide with an infrared profile similar to XXII*a* upon acetylation, but failed to afford a crystalline derivative with the usual ketone, amine, and amide-forming reagents. To obviate decomposition of 3-benzoylpiperidine (XII) possibly initiated by a retrograde Mannich reaction and to facilitate purification of intermediates, it seemed advisable to employ a higher molecular weight *N*-acyl moiety and to effect hydrolysis of the amido ketone after halogenation.

Although benzoylation or tosylation of ethyl piperidine-3-carboxylate (XIX) yielded viscous oils which could not be crystallized, hydrolysis of the intermediate amido esters (XX*b*, *c*) provided high yields of 1-benzoylpiperidine-3-carboxylic acid (XXI*b*) and 1-*p*-toluenesulfonylpiperidine-3-carboxylic acid (XXI*c*). Treatment of the former (XXI*b*) with thionyl chloride, followed by subjection of the intermediate acyl chloride to Friedel-Crafts conditions, gave 1,3-dibenzoylpiperidine (XXII*b*) which was chlorinated to afford 1,3-dibenzoyl-3-chloropiperidine (XXIII). Acid hydrolysis of XXIII yielded crude 3-benzoyl-3-chloropiperidine (V) which was also obtained by von Braun demethylation of 1-methyl-3-benzoyl-3-chloropiperidine (III). Dehydrohalogenation of V is rapid, as expected (21), in solvents other than chloroform at 0°. Attempts to resolve V failed.

The yield of 3-benzoyl-3-hydroxypiperidine (VI) obtained by treatment of crude 3-benzoyl-3-chloropiperidine (V) with base was unencouraging—about 10% over-all from 1,3-dibenzoyl-3-chloropiperidine (XXIII) or 1-methyl-3-benzoyl-3-chloropiperidine (III). While the demethylation sequence suggested alternate routes to 3-benzoyl-3-hydroxypiperidine (VI) *via* the Smissman (11) or Lyle (2) syntheses of 1-methyl-3-benzoyl-3-hydroxypiperidine (IV), the von Braun procedure fails to effect this conversion.[2] However, subjection of 1-methyl-3-benzoyl-3-acetoxypiperidine (XXIV) to the usual von Braun conditions afforded 3-benzoyl-3-hydroxypiperidine (VI), presumably through 1-cyano-3-benzoyl-3-hydroxypiperidine (XXV). The latter intermedi-

[1] While Bishop catalyst afforded 40% of 1-methyl-3-benzoylpiperidine (XIII) hydrobromide from 3-benzoylpyridine (XI) methobromide (15) (*cf.* 2), <5% of 3-benzoylpiperidine (XII) hydrochloride from 3-benzoylpyridine (XI) hydrochloride (15) (*cf.* 2), and good yields of the diastereoisomeric mixture of 2-piperidyl phenyl carbinol hydrochlorides from 2-benzoylpyridine hydrochloride (16), Englehard catalyst afforded 40% of 1-methyl-3-benzoylpiperidine (XIII) hydrobromide (15) (*cf.* 2) but failed here (17) (*cf.* 2) and in the reduction of 2-benzoylpyridine hydrochloride (16) although hydrogen was absorbed.

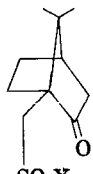
[2] It is noteworthy that Bently (22) refers to von Braun demethylation of both dihydro- and 14-hydroxycodeinone, while in fact the references cited (23) describe demethylation only of the corresponding 14-acetates prepared from the alcohols. These are conformationally similar to 1-methyl-3-benzoyl-3-hydroxypiperidine (VI) (11, 24, 25).



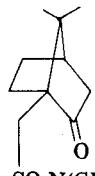
Scheme II

ate was prepared from 2-methoxy-2-phenyl-5-methyl-1-ox-5-azaspiro[2.5]octane (XXVI) by treatment with cyanogen bromide, followed by acidolysis of the crude cyanamide (IX, Y = NC—) with diluted hydrochloric acid in aqueous methanol. Hydrolysis of XXV in concentrated hydrochloric acid also afforded VI, which the authors have been unable to resolve. Although treatment of resolved 1-methyl-3-benzoyl-3-chloropiperidine (III) with cyanogen bromide, followed by stereospecific epoxy ether formation and cleavage (*cf.* VIII → IX → X, Y = NC—) (6–9), should afford optically active XXVI or VI, upon hydrolysis, the more efficient and facile resolution of 1-methyl-3-benzoyl-3-hydroxypiperidine (IV) makes the former approach (through XXIV) more suitable for the preparation of optically active 1-alkyl-3-benzoyl-3-acyloxypiperidines (III) (10). The syntheses and pharmacological activities of some racemic and optically active analogs of II and VII will be reported shortly.

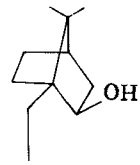
The choice of a suitable amide derivative (VIII) of 3-benzoyl-3-chloropiperidine (V) for studies on the mechanism and stereochemistry of epoxy ether formation was originally dictated by the following considerations. The apparently anomalous lack of over-all stereospecificity observed in the transformations, (−)-III → (+)- or (−)-XXVI → (±)-IV (6–9), made necessary an O^{18} tracer study to discriminate between or determine the relative importance of α-C-O and β-C-O cleavage of 2-methoxy-2-phenyl-5-methyl-5-azaspiro[2.5]-octane, XXVI, *cf.* IX (2, 7–9). In addition, it was of interest to append a blocking group which would preclude participation of the electron pair on nitrogen (8, 9) and so afford a reasonable model for normal epoxy ether formation from α-halo ketones. Thus, the blocking group should be incapable of O^{18} exchange. It should provide some functionality to facilitate separation of at least one of the four possible optical isomers (two enantiomorphic pairs) of the epoxy



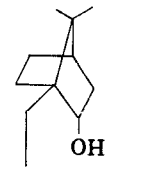
XXVIII*a*, X = HO−
XXVIII*b*, X = Cl−
XXVIII*c*, X = CH_3O−



XXIX



XXX



XXXI

ether (IX) and both of the optical isomers of VIII and X but should be neither acidic (8) nor basic. (Scheme II.)

The combination of a sterically hindered ketone and the expected steric strain in the incipient gem-diol (hydrated ketone) exchange intermediate from camphor prompted investigation of the O^{18} exchange of (+)-camphor-10-(*N,N*-dimethylsulfonamide) (XXIX) and (−)-borneol-10-(*N,N*-dimethylsulfonamide) (XXXI). The sulfonyl chloride (XXVIII*b*), formed by treatment of (+)-10-camphorsulfonic acid (XXVIII*a*) with thionyl chloride, was permitted to react with aqueous dimethylamine to afford (+)-camphor-10-(*N,N*-dimethylsulfonamide) (XXIX). Lithium aluminum hydride reduction gave two diastereoisomeric alcohols, (+)-isoborneol-10-(*N,N*-dimethylsulfonamide) (XXX) and (−)-borneol-10-(*N,N*-dimethylsulfonamide, (XXXI). Assignment of configuration of the hydroxyl group rests upon the fact that the reaction is carried out under thermodynamic control (26) and affords mainly (27) the levorotatory isomer, m.p. 83.5–84°, which therefore must have the borneol configuration. Isotopic analyses of analytically pure XXIX and XXXI, which had been treated with O^{18}-enriched water under conditions employed to tag III (9), show that the sulfonamide oxygens do not exchange, but that exchange into the carbonyl group, although slow, is significant.

During concurrent studies directed toward relating the configurations of 1-methyl-3-benzoyl-3-chloropiperidine (III), 3-benzoyl-3-chloropiperidine, and a suitable amide derivative (VIII) of the latter (V), it was found that treatment of crude 3-benzoyl-3-chloropiperidine (V) with the sulfonylchloride derived from (+)-10-camphorsulfonic acid (XXVIII*a*) provided a facile route to optically pure α- and β-(+)-1-(10-camphorsulfonyl)-3-benzoyl-3-chloropiperidine, α- and β-(+)-XXVII (*cf.* VIII). Accordingly, to avoid the several cumbersome steps required to form a C=O^{18}-tagged borneol-10-sulfonamide, the investigation was carried out in two parts (9, 10). Submission of O^{18}-tagged III to the epoxy ether formation-cleavage sequence has shown that the epoxy ether cleavage proceeds exclusively by β-C-O scission (9) (*cf.* 7, 8).[3] An opticochemical analysis of the diastereoisomeric products (IX–X, Y = 10-camphorsulfonyl) obtained from α- and from β-(+)-XXVII has unequivocally established the validity of all the proposed mechanisms (6–9, 11) and will be published shortly (10).

EXPERIMENTAL

All melting points were obtained in a Hershberg-type (28) silicone (550-Dow) filled melting point apparatus equipped with Anschutz full-immersion thermometers and are uncorrected. The samples were placed in the circulating silicone bath 10° below the reported melting point and heated at a rate of 1–2° per minute.

Elemental analyses were performed by Weiler and Strauss, Oxford, England. Isotopic analyses were performed by Analytica Corp., New York, N. Y.

Specific rotations were determined with a Zeiss 0.01° polarimeter in a modified (29) 2-dm., 2-ml. syringe-filling polarimeter tube. Refractive indices were determined with a thermostated Abbe refractometer calibrated against water at 20°. Infrared spectra were taken with a Perkin-Elmer 421 double grating spectrophotometer. Spectra of solids and liquids were determined as mulls in mineral oil and liquid films, respectively, between salt plates. Assignment of absorption bands, believed accurate to ±5 $cm.^{-1}$, made on the basis of reported values (30).

The O^{18}-enriched water was obtained from Isomet Corp., Palisades Park, N. J.

Both 1-methyl-3-benzoyl-3-chloropiperidine (III) and 1-methyl-3-benzoyl-3-hydroxypiperidine (IV) were prepared from nicotinic acid (XV) *via* the Smissman (11) synthesis or from 3-benzoylpyridine[4] (XI), as described by Lyle (2). The epoxy ether, 2-methoxy-2-phenyl-5-methyl-1-ox-5-azaspiro[2.5]octane (XXVI) and 1-methyl-3-benzoyl-3-acetoxypiperidine (XXIV), were prepared from III and IV, respectively, as described by Zalucky *et al.* (8). The procedure of McElvaine (31) was used to reduce and to esterify nicotinic acid (XV) to give piperidine-3-carboxylic acid hydrochloride (XVI) and ethyl nicotinate (XVIII), respectively. The method of Zinner and Brossman (19) was used to prepare piperidine-3-carbonyl chloride hydrochloride (XVII) from XVI.

Ethyl Piperidine-3-carboxylate (XIX).—Reduction of 234 Gm. (1.25 moles) of ethyl nicotinate hydrochloride (XVIII) in 1000 ml. of methanol with 2.0 Gm. of platinum oxide at 1500 p.s.i. afforded, after removal of catalyst and solvent, ethyl piperidine-3-carboxylate hydrochloride, which was recrystallized from acetone, m.p. 110–111°. [Lit. (32) m.p. 110–111°.] The free base was isolated and distilled to give 137.5 Gm. (0.875 mole, 70%) of ethyl piperidine-3-carboxylate (XIX), b.p. 39–40° (0.23 mm.), n_D^{20} 1.4597. [Lit. (31) b.p. 102–104° (7 mm.), n_D^{19} 1.4592.]

Similarly, 454 Gm. (3.0 moles) of ethyl nicotinate (XVIII), when combined with 45 Gm. of dehydrated commercial[5] Raney nickel in 800 ml. of methylcyclohexane and hydrogenated at 4000 p.s.i. (start-

[3] As cited in *Reference 9*, this does not unequivocally preclude racemization during epoxy ether cleavage.

[4] Currently available from the Aldrich Chemical Co., Milwaukee, Wis.

[5] Davison Chemical Co., Division of W. R. Grace and Co., Cincinnati, Ohio, supplies a suspension (50% solids) in water.

ing pressure at 25°) at 150–160° until the theoretical amount (or less if the uptake slows to 50–100 p.s.i. per 30 min.) of hydrogen is absorbed (usually about 60 min.), afforded, after filtration and removal of the solvent under reduced pressure, 392.5 Gm. (2.5 moles, 83%) of ethyl piperidine-3-carboxylate (XIX) distilling at 39–40° (0.2 mm.), n_D^{20} 1.4590.

Ethyl 1-Acetylpiperidine-3-carboxylate (XXa).—To 157 Gm. (1 mole) of ethyl piperidine-3-carboxylate (XIX) were added 350 ml. of anhydrous benzene and 102 Gm. (1.0 mole) of acetic anhydride. The solution was refluxed overnight and poured into an aqueous sodium bicarbonate slurry. The benzene layer was combined with two chloroformic extracts of the aqueous phase. The organic phase was dried over sodium sulfate. The solvents were removed under reduced pressure, leaving a yellow oil. Distillation afforded 189 Gm. (0.95 mole, (95%) of ethyl 1-acetylpiperidine-3-carboxylate (XX*a*) b.p. 88–89° (0.1 mm.), 127–128° (1.0 mm.), n_D^{20} 1.4777. The infrared spectrum showed bands at 1726 and 1640 cm.$^{-1}$, corresponding to ester and amide carbonyls, respectively.

Anal.—Calcd. for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60. Found: C, 60.48; H, 8.59.

1-Acetylpiperidine-3-carboxylic Acid (XXIa).—After dissolving 159 Gm. (0.8 mole) of ethyl 1-acetylpiperidine-3-carboxylate (XX*a*) in 1500 ml. of water, a solution of 4 *N* sodium hydroxide was added dropwise to maintain the pH at about 10. Phenolphthalein was used as an internal indicator. When base was no longer consumed, the solution was neutralized with acid, concentrated under reduced pressure to 400 ml., placed in a heavier-than-water liquid-liquid extractor with 220 ml. of 4 *N* hydrochloric acid, and extracted with chloroform for 36 hr. After drying the extracts over sodium sulfate and removing the solvent under reduced pressure, the resulting oil was crystallized from acetone, yielding 116 Gm. (0.68 mole, 85%) of 1-acetylpiperidine-3-carboxylic acid (XXI*a*), m.p. 130.5–131.5°. The infrared spectrum showed bands at 1590 and 1700 cm.$^{-1}$, corresponding to amide and unionized carboxyl groups, respectively.

Anal.—Calcd. for $C_8H_{13}NO_3$: C, 56.12; H, 7.65; N, 8.18. Found: C, 56.05; H, 7.56; N, 8.20.

Treatment of 85.5 Gm. (0.5 mole) of 1-acetylpiperidine-3-carboxylic acid (XXI*a*) with 50 ml. of thionyl chloride at room temperature for 30 min., followed by removal of the thionyl chloride under reduced pressure, afforded an orange oil which was mixed with 150 ml. of absolute ethanol. The reaction mixture was stirred for 1 hr., poured into 1500 ml. of water, and extracted with chloroform. The organic layer was dried over sodium sulfate, filtered, and evaporated under reduced pressure, leaving an oily residue which, on distillation, afforded 90 Gm. (0.45 mole, 90%) of ethyl 1-acetylpiperidine-3-carboxylate (XX*a*), b.p. 125–126° (1.0 mm.), n_D^{20} 1.4777.

1-Benzoyl- and 1-(p-Toluenesulfonyl)-piperidine-3-carboxylic Acid (XXIb and XXIc).—Treatment of ethyl piperidine-3-carboxylate (XIX) with either benzoyl chloride or *p*-toluenesulfonyl chloride in the presence of aqueous sodium bicarbonate afforded viscous neutral oils (XX*b*, *c*) which could not be crystallized. However, upon hydrolysis with potassium hydroxide in aqueous ethanol, followed by removal of the alcohol under reduced pressure and acidification with hydrochloric acid, these oils afforded solids which were washed with water and ether and recrystallized to give 1-benzoylpiperidine-3-carboxylic acid (XXI*b*) from acetone, m.p. 188.5–189.5° dec., and 1-*p*-toluenesulfonylpiperidine-3-carboxylic acid (XXI*c*) from water, m.p. 166.5–167.5° dec. [Lit. (33) m.p. 167°.]

Anal.—Calcd. for $C_{13}H_{15}NO_3$: C, 66.92; H, 6.48; N, 6.03. Found: C, 66.93; H, 6.48; N, 5.93.

Similarly, 71 Gm. (0.45 mole) of ethyl piperidine-3-carboxylate (XIX) and 112 Gm. (0.5 mole) of benzoic anhydride were heated to 80° in an oil bath for 2 hr. To this was added 1 L. of crushed ice and 1100 ml. of 1 *N* sodium hydroxide. After stirring for 3 hr., the solution was acidified and cooled to 0°. The precipitate was filtered, washed with ice water, and finally with ether. The 1-benzoylpiperidine-3-carboxylic acid (XXI*b*), m.p. 188–189° dec., weighed 100 Gm. (0.43 mole, 95%) and exhibited bands at 1565 and 1710 cm.$^{-1}$, indicative of amide and unionized carboxyl carbonyls, respectively. Conventional Schotten-Baumann conditions also affords XXI*b* but in lower yield (74%).

1,3-Dibenzoylpiperidine (XXIIb).—When 537 Gm. (2.3 moles) of 1-benzoylpiperidine-3-carboxylic acid (XXI*b*) was treated with thionyl chloride and the corresponding acyl halide subsequently was subjected to Friedel-Crafts conditions (19), an amber mass was obtained after the usual work-up. The infrared spectrum showed bands at 1625 and 1672 and a doublet at 1575–1597 cm.$^{-1}$, corresponding to the expected profile for amide and ketone carbonyls and a phenyl group, respectively. Dissolution in methanol, followed by seeding and reworking of the liquors, afforded 470 Gm. (1.60 moles, 70%) of 1,3-dibenzoylpiperidine (XXII*b*), m.p. 95–96°. [Lit. (2) m.p. 92–94°.] A 1.0-Gm. sample of XXII*b*, upon hydrolysis in 3.0 *N* hydrochloric acid, afforded 0.2 Gm. of an oily amino ketone (XII), exhibiting a band at 1672 cm.$^{-1}$ and a doublet at 1579–1595 cm.$^{-1}$, corresponding to ketone and phenyl groups, respectively, expected of 3-benzoylpiperidine (XII). Rebenzoylation regenerated XXII*b* (0.02 Gm.) which afforded crystals from petroleum ether, b.p. 20–60°.

Anal.—Calcd. for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.78. Found: C, 77.58; H, 6.50; N, 4.82.

1,3-Dibenzoyl-3-chloropiperidine (XXIII).—A solution of 29.3 Gm. (0.1 mole) of 1,3-dibenzoyl piperidine (XXII*b*) in 600 ml. of chloroform was saturated with chlorine gas and refluxed. Additional amounts of chlorine were introduced periodically over the next 5 hr. After removal of the solvent under reduced pressure, the resulting syrup was dissolved in ether. Crystallization was exceedingly slow (5–7 days). Approximately 25 Gm. of crude solid was obtained and recrystallized from *n*-hexane to give 19.7 Gm. (0.06 mole, 60%) of 1,3-dibenzoyl-3-chloropiperidine (XXIII), m.p. 106.5–107.5°.

Anal.—Calcd. for $C_{19}H_{18}ClNO_2$: C, 69.61; H, 5.54; Cl, 10.81; N, 4.27. Found: C, 69.52; H, 5.55; Cl, 11.08; N, 4.44.

3-Benzoyl-3-chloropiperidine (V); Hydrolysis of 1,3-Dibenzoyl-3-chloropiperidine (XXIII).—To 82 Gm. (9.25 moles) of XXIII were added 500 ml. of ethanol and 500 ml. of 6 *N* hydrochloric acid. The solution was allowed to reflux for 48 hr. The ethanol was removed under reduced pressure, and the acid aqueous phase was extracted with chloroform.

Only 22 Gm. of crude amino ketone (V) could be isolated from the dried chloroformic extract of the aqueous phase which had been neutralized with sodium bicarbonate. Thus, the chloroform extractive of the acid aqueous phase was recycled using concentrated hydrochloric acid alone. An additional 31 Gm. of crude oil (V) was obtained, corresponding to about 95% hydrolysis.

The oil (V) could not be crystallized. Rebenzoylation with benzoic anhydride afforded 1,3-dibenzoyl-3-chloropiperidine (XXIII), m.p. and mixed m.p. 105–106°.

The amino ketone (V) decomposed rapidly in polar solvents, as evidenced by rapid development of water-soluble halogen. Solutions of the amine could be kept for extended periods at 0° in chloform.

Treatment of the oil (V) with (+)-10-camphorsulfonic acid in ethanol afforded a salt which was repeatedly recrystallized from ethanol, m.p. 194.5–195°, $[\alpha]_D^{27}$ (absolute methanol) +18.9° (c = 8.95). The free amine regenerated from this salt showed no rotation, $\alpha_{obs.} = 0.02°$, (c = about 20) in ethanol or in chloroform.

Anal.—Calcd. for $C_{22}H_{30}ClNO_5S$: C, 57.94; H, 6.63; Cl, 7.78; N, 3.07; S, 7.03. Found: C, 57.84; H, 6.86; Cl, 8.01; N, 3.27; S, 7.04.

After treatment of 1.5 Gm. of (+)-10-camphorsulfonic acid (XXVIII*a*) with 10 ml. of thionyl chloride for 1 hr. and removal of the excess thionyl chloride under reduced pressure, 8 ml. of methanol was added to the residual oily sulfonylchloride (XXVIII*b*) to form the corresponding methyl ester (XXVIII*c*). The mixture was poured into ice water, neutralized with sodium bicarbonate, and extracted with chloroform. The dried organic extract was combined with 1.5 Gm. of crude 3-benzoyl-3-chloropiperidine (V). The chloroform was removed under reduced pressure, and the residue was recrystallized from ethanol–ethyl acetate to give 0.1 Gm. of the dextrorotatory salt of (+)-10-camphorsulfonic acid with (−)-1-methyl-3-benzoyl-3-chloropiperidine, m.p. and mixed m.p. 181–182°. [Lit. (11) m.p. 182–183°.]

von Braun Degradation of 1-Methyl-3-benzoyl-3-chloropiperidine (III).—To a stirred solution of 2.2 Gm. (0.2 mole) of cyanogen bromide in 100 ml. of dry benzene was added, over a period of 1 hr., a solution of 31.7 Gm. (0.133 mole) of 1-methyl-3-benzoyl-3-chloropiperidine (III) in 150 ml. of dry benzene. The temperature was maintained at 45° during the addition, then raised to 55–60° for 1 hr. After filtering off 5 Gm. (0.015 mole, 11%) of the methobromide, the benzene solution was washed with diluted hydrochloric acid and water. The residue, after removing the excess cyanogen bromide and benzene under reduced pressure (0.01 mm.), showed bands in the infrared at 2218 and 1660 and a doublet at 1580–1600 cm.$^{-1}$, corresponding to cyanamide, ketone, and phenyl groups, respectively. The cyanamide was refluxed with 100 ml. of concentrated hydrochloric acid for 48 hr. The aqueous solution was extracted with benzene, made basic with saturated sodium bicarbonate solution, and extracted with chloroform. The organic phase was dried over sodium sulfate, filtered, and concentrated to a syrup under reduced pressure (0.01 mm.) at 0° to give 20.5 Gm. (0.093 mole, 70%) of crude 3-benzoyl-3-chloropiperidine (V).

α-(+)- and β-(+)-1-(10-Camphorsulfonyl)-3-benzoyl-3-chloropiperidine [α-(+)-XXVII and β-(+)-XXVII].—A solution of 11.2 Gm. (0.05 mole) of crude 3-benzoyl-3-chloropiperidine (V) in 50 ml. of chloroform was added slowly to 50 ml. of a benzene solution of the camphorsulfonyl chloride (XXVIII*b*), prepared from 15.5 Gm. (0.067 mole) of (+)-10-camphorsulfonic acid (XXVIII*a*), as described in the previous experiment. The solution was heated to 50° and stirred for 2 hr. A slurry of 7 Gm. of sodium bicarbonate in 50 ml. of water was added. After cooling and stirring the mixture for 1 hr., the organic layer was separated, and the aqueous solution was extracted with benzene. The organic extract was washed with 5% hydrochloric acid and dried over sodium sulfate. The gummy residue remaining after removal of the solvent under reduced pressure was recrystallized to constant rotation from methanol and afforded 2.2 Gm. (5.0 mmoles, 10%) of α-(+)-1-(10-camphorsulfonyl)-3-benzoyl-3-chloropiperidine, α-(+)-XXVII, m.p. 131–132°, $[\alpha]_D^{27}$ (benzene) +60.4° (c = 5.08).

Anal.—Calcd. for $C_{22}H_{28}ClNO_4S$: C, 60.33; H, 6.44; Cl, 8.10; N, 3.20; S, 7.32. Found: C, 60.57; H, 6.63; Cl, 8.53; N, 3.30; S, 7.31.

Upon concentration of the methanolic mother liquors, two crops of crystals were obtained. The first crop, m.p. 87–89°, was chlorine free and was discarded. The second crop, 0.88 Gm. (2.0 mmoles, 4%), m.p. 123–124°, the β-(+)-diastereoisomer, was recrystallized to constant rotation, $[\alpha]_D^{27}$ (benzene) +24.0° (c = 2.90).

Anal.—Calcd. for $C_{22}H_{28}ClNO_4S$: C, 60.33; H, 6.44; Cl, 8.10; N, 3.20; S, 7.32. Found: C, 60.52; H, 6.59; Cl, 8.56; N, 2.98; S, 7.77.

(+) - Camphor - 10 - (N,N - dimethylsulfonamide) (XXIX).—The camphorsulfonyl chloride (XXVIII*b*) was prepared from 23.2 Gm. (0.1 mole) of (+)-10-camphorsulfonic acid (XXVIII*a*), as described in the previous experiment. After adding 50 ml. of 25% aqueous dimethyl amine, heating on the steam bath for 1 hr., and cooling, (+)-camphor-10-(*N,N*-dimethylsulfonamide) (XXIX) was obtained and recrystallized from methanol–water, m.p. 64.5–65.5°, $[\alpha]_D^{27}$ (absolute ethanol) +35.5° (c = 2.00), 16.2 Gm. (0.062 mole, 62%).

Anal.—Calcd. for $C_{12}H_{21}NO_3S$: C, 55.54; H, 8.16; N, 5.40; S, 12.36. Found: C, 56.04; H, 8.32; N, 5.18; S, 12.28.

(+) - Isoborneol - 10 - (N,N - dimethylsulfonamide) and (—)-Borneol-10-(N,N-dimethylsulfonamide) (XXX and XXXI).—After dissolving 2.67 Gm. (20.0 mmoles) of anhydrous aluminum chloride in 50 ml. of cold (0°) anhydrous ether, the solution was added to 0.209 Gm. (5.5 mmoles) of lithium aluminum hydride in 25 ml. of cold (0°) anhydrous ether. A solution of 5.19 Gm. (20.0 mmoles) of (+) - camphor - 10 - (*N,N* - dimethylsulfonamide) (XXIX) in anhydrous ether was added slowly. After 3 hr., 2 drops of acetone was added, followed 5 min. later by 50 ml. of water and 50 ml. of 5% sulfuric acid. The ether layer was separated, dried, and the solvent was removed under reduced pressure. Crystallization to constant rotation from petroleum ether afforded 4.17 Gm. (16.0 mmoles, 80%) of the more soluble alcohol (3500 cm.$^{-1}$), $[\alpha]_D^{27}$ (absolute ethanol) −23.0° (c = 2.00), m.p. 83.5–84°, (−)-borneol-10-(*N,N*-dimethylsulfonamide) (XXXI).

Anal.—Calcd. for $C_{12}H_{23}NO_3S$: C, 55.14; H,

8.87; N, 5.38; S, 12.27. Found: C, 55.34; H, 8.65; N, 5.37; S, 12.53.

The less soluble, optically pure, isomeric, dextrorotatory alcohol (3540 cm.$^{-1}$), 0.10 Gm. (0.4 mmole, 2%) $[\alpha]_D^{27}$ (absolute ethanol) +26.8° (c = 2.00), m.p. 134–135° (XXX), was also isolated in the same way from the mother liquors.

Anal.—Calcd. for $C_{12}H_{23}NO_3S$: C, 55.14; H, 8.87; N, 5.38; S, 12.27. Found: C, 55.06; H, 8.50; N, 5.83; S, 12.08.

Isotopic (O^{18}) Exchange Studies.—To 30 mg. each of (+)-camphor-10-(*N,N*-dimethylsulfonamide) (XXIX) and (−)-borneol-10-(*N,N*-dimethylsulfonamide) (XXXI) were added 2 ml. of O^{18}-enriched (5.85 atoms per cent excess) water, 5 ml. of methanol, and 0.01 ml. of 1 *N* hydrochloric acid. The solutions were heated at 40–50° for 96 hr. in sealed flasks. The methanol was removed from the flask containing (−)-borneol-10-(*N,N*-dimethylsulfonamide) (XXXI) which was then extracted with petroleum ether and recrystallized, m.p. 83.5–84°. (+)-Camphor-10-(*N,N*-dimethylsulfonamide) (XXIX) crystallized after removing some of the methanol under reduced pressure, m.p. 134–135°. Dried (0.001 mm., 27°) samples of these (XXIX, XXXI) and a sample of untreated ketone (XXIX), when analyzed for O^{18}, showed 0.031, 0.004, and 0.003 atoms per cent excess of O^{18}, respectively. Elemental analyses of the three dried samples conformed (±0.5%) to accepted standards.

1 - Cyano - 3 - benzoyl - 3 - hydroxypiperidine (XXV).—Treatment of 20.9 Gm. (90.0 mmoles) of 2 - methoxy - 2 - phenyl - 5 - methyl - 1 - ox - 5 - azaspiro[2.5]octane (XXVI) with cyanogen bromide, as described under the preparation of V, afforded 3.0 Gm. (9 mmoles, 10%) of methobromide and a crude semisolid benzene soluble cyanamide (2220 cm.$^{-1}$) which was dissolved in methanol and treated with 0.2 *N* aqueous hydrochloric acid. After standing for 24 hr., the resulting solid was recrystallized from methanol, m.p. 131.5–132.5°, to give 13.9 Gm. (60 mmoles, 67%) of 1-cyano-3-benzoyl-3-hydroxypiperidine (XXV), which exhibited bands at 3289, 2222, and 1684 cm.$^{-1}$, corresponding to hydroxyl, cyano, and ketone functions, respectively.

Anal.—Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.13. Found: C, 67.86; H, 6.06; N, 12.31.

3-Benzoyl-3-hydroxypiperidine (VI); von Braun Demethylation of 1-Methyl-3-benzoyl-3-acetoxypiperidine (XXIV).—Subjection of 24.7 Gm. (0.1 mole) of XXIV to the demethylation sequence described for 1-methyl-3-benzoyl-3-chloropiperidine afforded 17.0 Gm. (0.045 mole, 45%) of 3-benzoyl-3-hydroxypiperidine (VI) *p*-toluenesulfonate, m.p. 192–193°, from absolute ethanol.

Anal.—Calcd. for $C_{19}H_{23}NO_5S$: C, 60.50; H, 6.16; N, 3.72; S, 8.49. Found: C, 60.62; H, 5.96; N, 3.84; S, 8.19.

Hydrolysis of 1-Cyano-3-benzoyl-3-hydroxypiperidine (XXV).—Hydrolysis of 6.9 Gm. (0.03 mole) of the cyanamid (XXV), as described under the preparation of 3-benzoyl-3-chloropiperidine (V), afforded 7.9 Gm. (0.021 mole, 70%) of 3-benzoyl-3-hydroxypiperidine (VI) *p*-toluenesulfonate, m.p. 191–193°, after crystallization from absolute ethanol.

Hydrolysis of 3-Benzoyl-3-chloropiperidine (V).—Following acid hydrolysis of 12.0 Gm. (0.0365 mole) of 1,3-dibenzoyl-3-chloropiperidine (XXIII) or demethylation of 10.0 Gm. (0.0365 mole) of 1-methyl-3-benzoyl-3-chloropiperidine (III), the acid aqueous fractions containing crude V were treated with 4 *N* aqueous sodium hydroxide. The base was added slowly together with acetone to hold the amines in solution at a pH of about 12. After standing overnight, the acetone was removed under reduced pressure. The chloroformic extracts of the aqueous phases were dried over sodium sulfate, filtered, and evaporated to give crude 3-benzoyl-3-hydroxypiperidine (VI) which could be recrystallized from petroleum ether or acetone, m.p. 151–152°, but which yellowed upon standing.

Anal.—Calcd. for $C_{12}H_{15}NO_2$: C, 70.21; H, 7.37; N, 6.83. Found: C, 69.59; H, 7.35; N, 6.38.

The crude amine fractions afforded 1.4 Gm. (3.8 mmoles, 10%) and 1.1 Gm. (2.8 mmoles, 8%) of 3-benzoyl-3-hydroxypiperidine (VI) *p*-toluenesulfonate, m.p. 192–193°, from 1-methyl-3-benzoyl-3-chloropiperidine (III) and 1,3-dibenzoylpiperidine (XXIII), respectively.

REFERENCES

(1) Lyle, R. E., Troscianiec, H. J., and Warner, G. H., *J. Org. Chem.*, **24**, 338(1959).
(2) Lyle, R. E., and Warner, G. H., *J. Med. Chem.*, **3**, 596(1961).
(3) Hite, G., personal communications to Long, L., Parke-Davis, Detroit, Mich., and Smissman, E. E., 1958.
(4) Hite, G., Ph.D. thesis, University of Wisconsin, Madison, 1959.
(5) Hite, G., and Zalucky, T. B., unpublished data.
(6) Stevens, C. L., and Weinheimer, H. J., *J. Am. Chem. Soc.*, **80**, 4072(1959).
(7) Stevens, C. L., and Dykstra, S. J., *ibid.*, **75**, 5975 (1953).
(8) Zalucky, T. B., Malspeis, L., and Hite, G., *J. Org. Chem.*, **29**, 3143(1964).
(9) Zalucky, T. B., *et al.*, *ibid.*, to be published.
(10) Patel, H., and Hite, G., unpublished data.
(11) Smissman, E. E., and Hite, G., *J. Am. Chem. Soc.*, **82**, 3375(1960).
(12) Djerassi, C., "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, pp. 115–131.
(13) *Ibid.*, pp. 111–114; Klyne, W., *Tetrahedron*, **13**, 32 (1961).
(14) Ariens, E. J., Simonis, A. M., and Van Rossum, J. M., "Molecular Pharmacology," Ariens, E. J., ed., Academic Press Inc., New York, N. Y., 1964, p. 352 and references cited therein.
(15) Patel, H., personal communication.
(16) Malspeis, L., and Turner, J., personal communication.
(17) Tanna, P., personal communication.
(18) Smissman, E. E., and Hite, G., *J. Am. Chem. Soc.*, **81**, 1201(1959).
(19) Zinner, H., and Brossman, G., *J. Prakt. Chem.*, (No. 4) **5**, 91(1957).
(20) Mosher, H. S., in "Heterocyclic Compounds," vol. 1, Elderfield, R. C., ed., John Wiley & Sons, Inc., New York, N. Y., 1950, pp. 629–631.
(21) Fuson, R. C., and Zirkle, C. L., *J. Am. Chem. Soc.*, **70**, 2760(1948); Grob, C. A., and Jenny, F. A., *Tetrahedron Letters*, (No. 23) 25(1960); *cf. Bull. Soc. Chim. France*, **1960**, 1360; and Bottini, A. T., Grob, C. A., and Schumacher, E., *Chem. Ind.*, **1958**, 757.
(22) Bently, K. W., "The Chemistry of the Morphine Alkaloids," Oxford University Press, London, 1954, p. 258.
(23) Speyer, E., and Sarre, K., *Ber.*, **57**, 1427(1924); and Freund, M., and Speyer, E., *J. Prakt. Chem.*, **94**, 135(1916).
(24) Zalucky, T., and Hite, G., *J. Med. Chem.*, **3**, 615(1961).
(25) Hite, G., West, R., and Smissman, E. E., *J. Am. Chem. Soc.*, **82**, 1207(1960).
(26) Eliel, E. L., and Rerick, M. N., *ibid.*, **82**, 1367(1960).
(27) Takeshita, T., and Kitajima, M., *Nippon Kagaku Zasshi*, **79**, 1472(1958); through *Chem. Abstr.*, **54**, 5729(1960).
(28) Hershberg, E. B., *Ind. Eng. Chem., Anal. Ed.*, **8**, 312 (1936).
(29) Hite, G., and Lyons, J., *Chemist-Analyst*, **53**, 84 (1964).
(30) Bellamy, L. J., "The Infrared Spectra of Complex Molecules," John Wiley & Sons, Inc., New York, N. Y., 1960.
(31) McElvaine, S. M., and Adams, R., *J. Am. Chem. Soc.* **45**, 2738(1923).
(32) Charonnat, R., *et al.*, *Bull. Soc. Chim. France*, **1948**, 1014.
(33) Freudenberg, K., *Ber.*, **51**, 1668(1918).