Mechanism and Stereochemistry of a Novel Reaction of Cyanogen Bromide with (+)-1-Methyl-3-benzoyl-3-hydroxypiperidine

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Abstract ☐ The reaction of cyanogen bromide and (+)-1-methyl-3-benzoyl-3-hydroxypiperidine affords two unusual products, (−)-1-methyl-3-bromo-3-benzoylpiperidine hydrobromide [(−)-VII-HBr] and (+)-1-cyano-3-bromo-3-benzoylpiperidine [(+)-VIII], which are formed stereospecifically with retention of configuration. The mechanism involves initial formation of 1-methyl-3-cyanato-3-benzoylpiperidine (IX), followed by displacement of cyanate by bromide *via* a closed ion-pair.

Keyphrases ☐ Cyanogen bromide—mechanism and stereochemistry of reaction with (+)-1-methyl-3-benzoyl-3-hydroxypiperidine ☐ (+)-1-Methyl-3-benzoyl-3-hydroxypiperidine—mechanism and stereochemistry of reaction with cyanogen bromide

In contrast to the behavior of Compounds I–IV under the conditions of the von Braun demethylation of tertiary amines with cyanogen bromide (1), Compound V behaves anomalously to give VI after acid hydrolysis of the acid-insoluble, benzene-soluble fraction (2). Analysis of the reaction mixture obtained from V indicated the presence of VII and VIII (2). It was inferred that IX, an alkyl cyanate, was the precursor of VII. The unusual stereomechanistic aspects of reactions involving anchimeric assistance of amine nitrogen have long been of interest in these laboratories (3–8). Recent studies on the chemistry of alkyl cyanates revealed a "superhalogenoid" propensity for participation in ionically mediated substitutions, eliminations, and rearrangements (9–14). The novelty of this transformation prompted this reinvestigation using an optically active substrate to determine the mechanism and stereochemistry of this reaction, first noted during attempts to prepare some local anesthetic esters of X where R_1 represents various alkyl substituents.

EXPERIMENTAL[1]

Reaction of (*R*)-(+)-1-Methyl-3-benzoyl-3-hydroxypiperidine [*R*-(+)-V] with Cyanogen Bromide—A solution of 6 g (27.4 mmoles) of *R*-(+)-V in 50 ml of dry (sodium) benzene was added over 4 hr to a stirred solution of 7.2 g (68 mmoles) of freshly distilled cyanogen bromide. Nitrogen was passed through the reaction vessel, which was maintained at 50–55° during the addition. The cooled (25°) reaction mixture was stirred overnight and filtered to remove the precipitated, water-soluble salt, which was washed with three 10-ml portions of benzene. The dried solid was recrystallized from ethanol–ether to give 3.0 g (8.22 mmoles, 30%) of (*R*)-(−)-1-methyl-3-bromo-3-benzoylpiperidine hydrobromide [*R*-(−)-VII-HBr], mp 159.5–161°; NMR (D_2O): δ 8.37–7.20 (m, 5H, C_6H_5), 4.37–1.17 (m, 8H, $CH_2NCH_2CH_2CH_2$), and 3.03 (s, 3H, NCH_3) ppm; IR (mull): 1680 (C=O, ketone) cm^{-1}; $[\alpha]_D^{25}$ (ethanol) −27.6 ± 0.5° (c 0.203).

Anal.—Calc. for $C_{13}H_{17}Br_2NO$: C, 42.99; H, 4.72; Br, 44.02; N, 3.86. Found: C, 42.9; H, 4.62; Br, 44.3; N, 3.81.

The benzene-soluble filtrate was evaporated and the residue was dissolved in 30 ml of ether. This solution was extracted with two 15-ml portions of 1.2 *N* HCl. The ether was dried, filtered, and concentrated to about 10 ml. On standing (5°), this gave 1.3 g (4.38 mmoles, 16%) of (*R*)-(+)-1-cyano-3-bromo-3-benzoylpiperidine [*R*-(+)-VIII], mp 76–77°; NMR ($CDCl_3$): δ 8.20–7.25 (m, 5H, C_6H_5), 3.75 (s, 2H, NCH_2CBr), 3.55–3.03 (m, 2H, NCH_2), and 2.57–1.35 (m, 4H, $NCCH_2CH_2$) ppm; IR (mull): 1660 (C=O, ketone) and 2220 (C≡N) cm^{-1}; $[\alpha]_D^{25}$ (ethanol) +24.5 ± 0.5° (c 0.266).

Anal.—Calc. for $C_{13}H_{13}BrN_2O$: C, 53.26; H, 4.47; Br, 27.26; N, 9.54. Found: C, 53.3; H, 4.64; Br, 27.1; N, 9.44.

(*R*)-(+)-3-Benzoyl-3-hydroxypiperidine *p*-Toluenesulfonate [*R*-(+)-X-*p*-Toluenesulfonate]—A solution of 600 mg (2.3 mmoles) of *R*-(+)-III[2] was allowed to react with cyanogen bromide in a manner identical to that described for *R*-(+)-V. The same work-up afforded a benzene-soluble oil containing 1-cyano-3-acetoxy-3-benzoylpiperidine (XI); IR (film): 2220 (C≡N) and 1730 (C=O, acetate) cm^{-1}. This was dissolved in 10 ml of 50% water–ethanol. To the stirred solution was added a drop of phenolphthalein indicator. Over 12 hr, a 5% solution of sodium hydroxide was added dropwise until the pink color persisted. The solution was evaporated and the residue was mixed with 10 ml of ether. This mixture was extracted twice with 10-ml portions of water and was dried, filtered, and concentrated to 4–5 ml. On standing (0°), 100 mg (0.44 mmole, 19%) of (*R*)-(+)-1-cyano-3-benzoyl-3-hydroxypiperidine [*R*-(+)-XII] crystallized, mp 130–132°; $[\alpha]_D^{25}$ (methanol) +69.0 ± 0.5° (c 0.232); IR (mull): 3350 (OH), 2220 (C≡N), and 1670 (C=O, ketone) cm^{-1}. The ether filtrate yielded an oil as well. This was assigned the structure 1-carboxamido-3-hydroxy-3-benzoylpiperidine (XIII); NMR ($CDCl_3$): δ 8.32–6.97 (m, 5H, C_6H_5), 5.25 (s, 1H, OH, D_2O exchangeable), and 4.17–0.63 (m, 10H, $CH_2NCH_2CH_2CH_2$ and $CONH_2$, D_2O exchangeable) ppm; IR (film): 3400 (OH) and 1660 (C=O, urea) cm^{-1}. This was mixed with 10 ml of 12 *N* HCl. The mixture was allowed to reflux for 24 hr. The reaction mixture was extracted with ether and the extracts were discarded. The aqueous solution was evaporated and the residue was dissolved in 5 ml of water.

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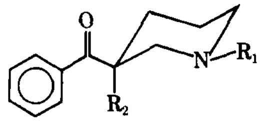
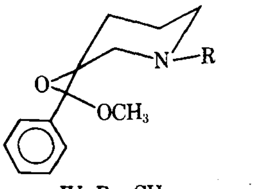
[1] Melting points were determined in a Thomas-Hoover Unimelt apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer model 141 photoelectric polarimeter in a 1.000-dm cell. IR spectra were determined with a Perkin-Elmer model 421 spectrophotometer using sodium chloride plates or cells. Mulls were prepared from mineral oil (Nujol). Assignments of absorption bands, believed accurate to within ±5 cm^{-1}, were made by analogy with reported values (15). Proton nuclear magnetic resonance spectra were determined with a Varian A-60D spectrometer. Assignments of absorption bands, believed accurate to within ±1 Hz, were made by analogy with reported values (16). When designation of exchangeable protons was of interest, samples were treated with D_2O. Tetramethylsilane was used as the internal reference. Drying, clarifying, and decolorizing of solutions were carried out simultaneously with anhydrous sodium sulfate and activated charcoal (Norit), followed by suction filtration through diatomaceous earth (Celite) pads in sintered-glass funnels. All solvents were evaporated in a rotary evaporator under reduced pressure. Oils and solids were dried (0.1 mm Hg, 27°, 4–12 hr) prior to spectral analysis. Petroleum ether refers to the fraction boiling from 30 to 60°. Elemental analyses were performed by Dr. F. B. Strauss, Oxford, England. (+)-1-Methyl-3-benzoyl-3-hydroxypiperidine [(+)-V], mp 72.5–73°, $[\alpha]_D^{28}$ (ethanol) +10.9 ± 0.5° (c 5.25), and (+)-1-methyl-3-benzoyl-3-acetoxypiperidine [(+)-III], mp 66–67°, $[\alpha]_D^{25}$ (ethanol) +34.7 ± 0.2° (c 10.56), were prepared as described previously (7, 17, 18). Both compounds have the *R*-configuration (19, 20).

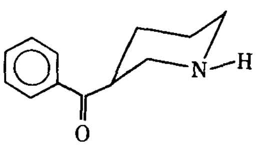
[2] NMR ($CDCl_3$): δ 8.13–7.13 (m, 5H, C_6H_5), 3.62–1.50 (m, 8H, $CH_2NCH_2CH_2CH_2$), 2.28 (s, 3H, NCH_3), and 1.98 (s, 3H, CH_3CO) ppm; IR (chloroform): 1735 (C=O, ester) and 1670 (C=O, ketone) cm^{-1}.



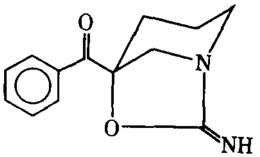
I: $R_1 = CH_3, R_2 = Cl$
II: $R_1 = CH_3, R_2 = OCH_3$
III: $R_1 = CH_3, R_2 = O_2CCH_3$
V: $R_1 = CH_3, R_2 = OH$
VII: $R_1 = CH_3, R_2 = Br$
VIII: $R_1 = CN, R_2 = Br$
IX: $R_1 = CH_3, R_2 = OCN$
X: $R_1 = H, R_2 = OH$
XI: $R_1 = CN, R_2 = O_2CCH_3$
XII: $R_1 = CN, R_2 = OH$
XIII: $R_1 = CONH_2, R_2 = OH$
XV: $R_1 = \underset{\displaystyle OCH_3}{\underset{|}{C}}{=}NH, R_2 = OH$
XVII: $R_1 = CN, R_2 = OCN$



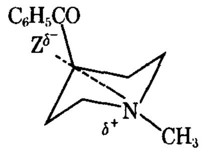
IV: $R = CH_3$
XIV: $R = \underset{\displaystyle OCH_3}{\underset{|}{C}}{=}NH$



VI



XVI



XVIII: Z = Br or OCN

Pathways used to define the steric relationships between (+)-V, (−)-VII-HBr, and (+)-VIII:

(+)-V → (+)-III → XI → (+)-XII + XIII → (−)-X
↓
(+)-X-*p*-toluenesulfonate

(−)-VII-HBr
↓
(+)-VIII → XIV → XV → (+)-X →
(−)-X-*p*-toluenesulfonate

Scheme I

The solution was alkalized with 10% aqueous sodium carbonate solution and was extracted with two 10-ml portions of ether. The extract was dried, filtered, and concentrated to 3–4 ml. On standing (25°), 30 mg (0.15 mmole, 6.5%) of (*R*)-(−)-3-benzoyl-3-hydroxypiperidine [*R*-(−)-X] crystallized, mp 158–160.5°; NMR ($CDCl_3$): δ 8.28–7.11 (m, 5H, C_6H_5), 3.59–2.18 (m, 6H, CH_2NCH_2 and OH, NH, D_2O exchangeable), and 2.18–1.13 (m, 4H, $NCCH_2CH_2$) ppm; $[\alpha]_D^{25}$ (chloroform) −10.8 ± 1° (*c* 0.315). This was converted to the *p*-toluenesulfonate salt [*R*-(+)-X-*p*-toluenesulfonate], mp 121–122° [lit. (5) mp 124–125°]; $[\alpha]_D^{25}$ (methanol) +7.9 ± 1° (c 0.260) [lit. (5) $[\alpha]_D^{25}$ (methanol) +11.4 ± 0.3° (c 2.73)]; NMR (D_2O): δ 8.28–7.03 (m, 9H, C_6H_5 and C_6H_4), 3.90–1.32 (m, 8H, $CH_2NCH_2CH_2CH_2$), and 2.38 (s, 3H, CH_3) ppm.

(*S*)-(−)-3-Benzoyl-3-hydroxypiperidine *p*-Toluenesulfonate [*S*-(−)-X-*p*-Toluenesulfonate] from *R*-(+)-VIII—A solution of 200 mg of *R*-(+)-VIII in 5 ml of anhydrous methanol was added to a solution of 20 mg of sodium in 5 ml of anhydrous methanol. The solution was stirred for 45 min and the solvent was evaporated. The residue was mixed with 10 ml of ether. This mixture was extracted twice with 10 ml of water and was dried, filtered, and evaporated to yield a halogen-free oil assigned the structure 2-methoxy-2-phenyl-5-carbiminomethoxy-1-oxo-5-azaspiro[2.5]octane (XIV); NMR ($CDCl_3$): δ 7.68–7.18 (m, 5H, C_6H_5), 4.83 (broad s, 1H, C=NH, D_2O exchangeable), 3.88–2.90 (m, 4H, CH_2NCH_2), 3.65 (s, 3H, $N{=}COCH_3$), 3.20 (s, 3H, $CH_3OCC_6H_5$), and 2.48–0.72 (m, 4H, $NCCH_2CH_2$) ppm; IR (film): 3380 (=NH) and 1620 (C=N, iminocarbamate) cm^{-1}; no absorption in the region of 3500 (OH) or 1680 (C=O, ketone) cm^{-1}. A solution of XIV in 10 ml of methanol was acidified with 10 ml of 1% HCl, and the solution was stirred for 5 min. The methanol was evaporated. The remaining, aqueous solution was mixed with 10 ml of ether and treated with solid sodium carbonate to alkalize the aqueous layer. Three subsequent 10-ml ether extracts of the aqueous fraction were combined, dried, filtered, and evaporated to yield a basic oil assigned the structure 1-carbiminomethoxy-3-benzoyl-3-hydroxypiperidine (XV); NMR (carbon tetrachloride): δ 8.25–7.00 (m, 5H, C_6H_5), 5.08 (broad s, 2H, C=NH and OH, D_2O exchangeable), 4.08–3.00 (m, 4H, CH_2NCH_2), 3.53 (s, 3H, OCH_3), and 2.17–1.10 (m, 4H, $NCCH_2CH_2$) ppm. This oil was allowed to reflux with 10 ml of 12 *N* HCl for 24 hr. The solution was extracted with ether and the extract was discarded. The aqueous solution was evaporated, and the residue was dissolved in 5 ml of water. The solution was alkalized with 10% sodium carbonate solution and extracted with two 10-ml portions of ether. The extract was dried, filtered, and concentrated to 1–2 ml. On standing, crystals of *S*-(+)-X were obtained. The NMR and IR spectra were superimposable upon those of *R*-(−)-X. The IR and NMR spectra of the *p*-toluenesulfonate salt [*S*-(−)-X-*p*-toluenesulfonate], $[\alpha]_D^{25}$ (water) −10.0 ± 1° (c 0.250), were superimposable upon those of *R*-(+)-X-*p*-toluenesulfonate.

(*R*)-(+)-1-Cyano-3-bromo-3-benzoylpiperidine [*R*-(+)-VIII] from *R*-(−)-VII-HBr—A solution of 600 mg of *R*-(−)-VII-HBr in 15 ml of water was mixed with 10 ml of chloroform and alkalized with 5% sodium carbonate solution. The chloroform fraction and two subsequent 10-ml chloroform extracts were combined, dried, filtered, and evaporated under a stream of nitrogen at 5°. The free base was dissolved in 40 ml of benzene. This was allowed to react with cyanogen bromide as described for *R*-(+)-V. Work-up of the reaction mixture, as described for *R*-(+)-V, gave *R*-(+)-VIII, mp 76–77°, $[\alpha]_D^{25}$ (ethanol) +24.1 ± 0.5° (c 0.100), from the benzene-soluble fraction. The IR and NMR spectra of *R*-(+)-VIII obtained in this way were superimposable on those of *R*-(+)-VIII obtained from *R*-(+)-V.

RESULTS AND DISCUSSION

Treatment of *R*-(+)-V with cyanogen bromide afforded a benzene-insoluble precipitate. The presence of a center of asymmetry was confirmed by its optical activity. Lack of absorption in the 3500-cm^{-1} region demonstrated that the hydroxyl group was either functionalized or absent. That the benzoyl moiety was intact was shown by carbonyl absorption at 1680 cm^{-1} and by aromatic proton absorption at 8.37–7.20 ppm. This water-soluble material gave an instantaneously positive test (silver nitrate) for halogen and was convertable to a free amine which also contained organically bound halogen. Together with the elemental analyses, this information led to the assignment of structure (−)-VII-HBr to this product in which the 3-bromo substituent has stereospecifically or stereoselectively replaced the hydroxyl group.

An optically active benzene-soluble, acid-insoluble product was also isolated. Its acid insolubility, C≡N absorption at 2220 cm^{-1}, and lack of N—CH_3 absorption in the NMR spectrum prove that this is a cyanamide. Spectral evidence established that the hydroxyl group was functionalized or absent and that the benzoyl moiety was intact. The presence of bromine was demonstrated. This information and elemental analyses are consistent with structure (+)-VIII in which a bromo substituent has stereospecifically or stereoselectively replaced the 3-hydroxyl function.

The characterization of these products corroborates an earlier inference of a unique conversion of the 3-hydroxyl to the 3-bromo analog. The stereochemistry of the transformations was established through the sequence of reactions shown in Scheme I. Under von Braun conditions, (+)-III afforded XI. Mild basic hydrolysis gave XIII and a small amount of (+)-XII. Vigorous acidic hydrolysis of XIII yielded (−)-X from which (+)-X-*p*-toluenesulfonate was prepared. Treatment of (+)-VIII with sodium methoxide in methanol gave XIV which was converted to XV in diluted hydrochloric acid. Hydrolysis of XV in 12 *N* HCl provided (+)-X from which (−)-X-*p*-toluenesulfonate was prepared. Finally, (−)-VII-HBr was converted to (+)-VIII under von Braun conditions. This establishes the configurations of all compounds in Scheme I and thus the stereochemistry of the transformations of (+)-V to (−)-VII-HBr and (+)-VIII under von Braun conditions.

It is known that the conversion of (+)-VIII to XIV proceeds stereospecifically with retention of configuration and that the rest of the reactions of Scheme I do not affect the original center of asymmetry (3–7). Accordingly, the fact that (+)-V and (+)-VIII afford antipodal X-p-toluenesulfonates proves that they have the same configuration. The conversion of (−)-VII-HBr to (+)-VIII establishes that it, too, has the same configuration as (+)-V and (+)-VIII. This proves that the conversion of (+)-V to (−)-VII-HBr and (+)-VIII proceeds with retention of configuration. Within the limits of experimental error, the rotations of the p-toluenesulfonates indicate that the reaction is stereospecific (90 ± 10%).

If cyanogen bromide attacks at nitrogen to give XII, the only *direct* route to a 3-bromo analog must involve XVI, which would result in inversion of configuration. The less direct route through XVII and XII is also untenable on stereochemical grounds. Thus, the mechanism of the reaction must involve initial attack of cyanogen bromide on the hydroxyl to give IX (*cf.*, 2). Displacement of cyanate by bromide is consistent with both the chemistry of alkyl cyanates (9–14) and the formation of (+)-V from (−)-I *via* a closed ion-pair (XVII) with 15% retention of configuration under *quasi*-Favorskii conditions (4, 5, 8). Accordingly, VII is the precursor of VIII.

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COMMUNICATIONS

General Influence of Physicochemical Properties on Drug–Receptor Combination

Keyphrases ☐ Drug–receptor combinations—influence of physicochemical properties ☐ Structure–activity relationships—influence of physicochemical properties on drug-receptor combinations ☐ Receptor sites—influence of physicochemical properties on interaction with drugs

Sir:

Previous publications (1–10) showed how the physicochemical properties of chemically and structurally related compounds, particularly homologs, can be the principal determinant of the structure–biological activity "parabolic" profile for a congeneric family by reason of the influence of the physicochemical properties on relative rates of transport. There are, of course, circumstances that preclude involvement of transport in the determination of activity profiles. Even in the absence of a significant or identifiable transport component, so-called "parabolic" dependencies are generally still observed for compounds chemically similar in polar functionality but widely dissimilar in hydrophobic property (11). Again, models founded on fundamental physicochemical relationships have been proposed to explain some of these data (12, 13), the most sophisticated treatment being that of Higuchi and Davis (13) in which the relative degree of receptor site occupation is computed using a quasiequilibrium distributional model. Among other things, the Higuchi and Davis model assumes the net receptor interaction or "occu-