ASYMMETRICAL NITROGEN.

51.* SYNTHESIS AND OPTICAL ACTIVATION OF 1,6-DIAZABICYCLO-[3.1.0]HEXANE-5-CARBOXYLIC ACID AND ITS DERIVATIVES

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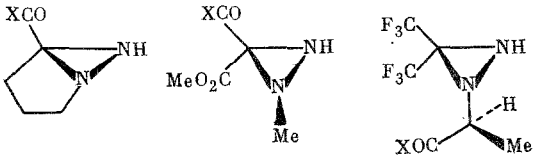
We have previously reported psychotropic activity in derivatives of 1,6-diazabicyclo-[3.2.0]hexane-5-carboxylic acid (Ia), namely its methyl ester (Ib) and N-methylamide (Ic) [2], obtained by epimination of the corresponding Δ^1-N-pyrroline-2-carboxylic acid [1]. In this connection, it was of interest to synthesize optically active derivatives of the acid (Ia).

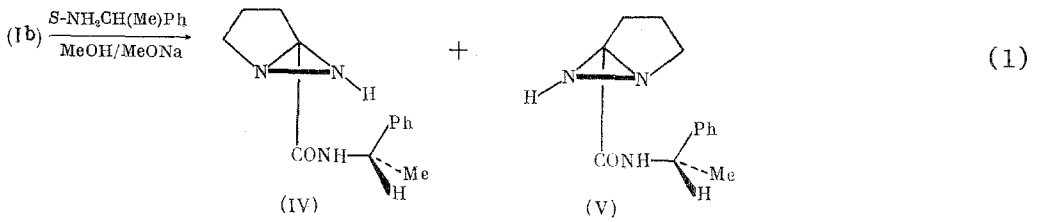


(Ia-d) (IIa-d) (IIIa,b)

X = OH (a), OMe (b), NHMe (c), O^-K^+ (d).

The monocyclic carboxylated diaziridines (II) and (III) were separated into their optical isomers as covalent diastereoisomers [3-5] and diastereoisomeric salts [6]. We therefore undertook the synthesis and separation of diastereoisomeric derivatives of the acid (Ia), namely the α-phenylethylamides (IV) and (V), and the total separation of the enantiomers (Ia-d) via their ℓ-ephedrine salts (VI) and (VII).

The presence of a single COOMe group in the diaziridine (Ib) rendered this group less reactive than in the previously studied diester (IIb) [3] toward amines. For instance, although the latter reacts with an equimolar amount of S-α-phenylethylamine in seven days at 20°C in methanol [3], the monoester (Ib) gives a mixture of diastereoisomeric amides (IV) and (V) only on boiling for 24 h in methanol with a twofold excess of S-α-phenylethylamine



(1)

The resulting mixture of amides (IV) and (V) (in a ratio of 1:1) was only enriched in diastereoisomer (V) to the extent of 5% after five recrystallizations from heptane.

The ester (Ib) remained unchanged on boiling in ether with CF_3COOH [35 h, molar ratio of (Ib)/CF_3COOH 5:1], thus giving confidence in the stability of the acid (Ia). In fact, (Ia) could be obtained under mild conditions by the alkaline hydrolysis of the ester (Ib) followed by treatment of the K salt (Id) with Dowex 50W × 12 sulfocation exchange resin (scheme 2). It was stable in the crystalline state for at least seven days at 20°C, and underwent conversion into the corresponding hydrazone (VIII) (70%) only on prolonged storage (~30 days) in chloroform at 20°C, apparently as a result of acidic autocatalysis (scheme 3).

*For communication 50, see [1].

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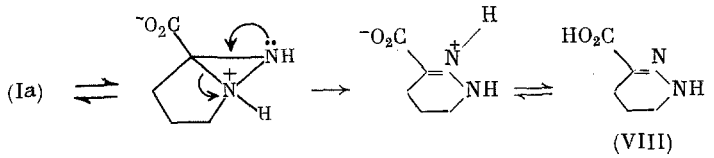
$$(Ib) \xrightarrow[MeOH,\ 20^\circ]{KOH} (Id) \xrightarrow[MeOH,,\ 20^\circ]{H^+} (Ia) \qquad (2)$$

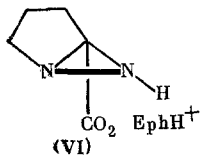


(VIII) (3)

The acid (Ia) is the second example (after (IIIa) [4, 5]) of a stable compound containing the diaziridine ring, which is sensitive to acid hydrolysis, and a free COOH group. Unlike (Ia) and (IIIa), the acid (IIa) decomposes violently on attempted isolation from its methanolic solution at 20°C following treatment of its potassium salt (IId) with cation exchange resin. This is apparently due to the higher acidity of (IIa) as a result of the presence of the COOMe group in the α position.

With ℓ-ephedrine, the acid (Ia) gives a mixture of diastereoisomeric salts (VI) and (VII), from which the major proportion of the dextrorotatory antipode (VII) is eluted by hot benzene. Nearly pure diastereoisomeric salt (VI) of the levorotatory antipode is obtained merely by a single recrystallization from acetonitrile. The ease of separation of (VI) and (VII), as is also the case with the ephedrine salts of the monoester of the diacid (IIa) [6], is evidently due to the strong association of the acid anion with the ephedrine cation as a result of hydrogen bonding and the interaction of polar groups.

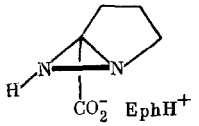
The resolving agent ℓ-ephedrine is readily removed from the diastereoisomeric salts (VI) and (VII) by treatment with KOH (scheme 4) or with a cation exchange resin (scheme 5). Esterification of the (+)- and (−)-acids (Ia) with diazomethane gives the enantiomeric esters (+)- and (−)-(Ib). On treatment with methylamine, the latter gives the optically active amide (−)-(Ic).



(VI)

$$\xrightarrow{KOH} (-)\text{-(Id)} \xrightarrow{H^+} (-)\text{-(Ia)} \xrightarrow{CH_2N_2} (-)\text{-(Ib)} \xrightarrow{MeNH_2} (-)\text{-(Ic)} \qquad (4)$$

(5)



(VII)

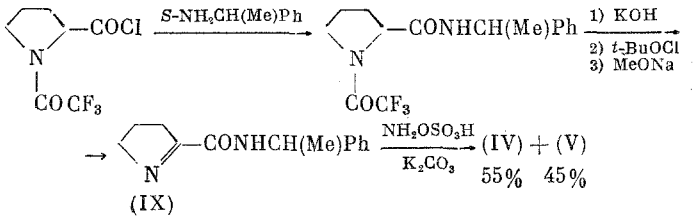
$$\xrightarrow{H^+} (+)\text{-(Ia)} \xrightarrow{CH_2N_2} (+)\text{-(Ib)}$$
$$\text{KOH} \downarrow$$
$$(+)\text{-(Id)}$$

The optical purity of the esters [(−)-(Ib) ≥ 98% and (+)-(Ib) ~ 94%] was determined by PMR in the presence of the chiral shift reagent europium tris-(3-trifluoroacetyl-d-camphorate), by integrating the signals for the MeO groups. Total separation of enantiomers of the substrate normally required both enantiomeric forms of the resolving agent [6, 7]. However, it will be seen that ℓ-ephedrine alone is adequate to provide nearly pure enantiomers of (Ia-d).

The 1S,5R,6S- absolute configuration of the anion of the diastereoisomerically pure salt (VI) was established by x-ray structural analysis* in coordinates of the chiral centers of the ℓ-ephedrinium cation of known configuration. It follows that enantiomers (−)-(Ia-d) have the 1S,5R,6S, and the anion of salt (VII) and enantiomers (+)−(Ia, b, d) the 1R,5S,6R-configurations.

The ester (+)-(Ib), optical purity ~66.5%, reacts with an excess of S-α-phenylethylamine by scheme 1 to give a mixture of (IV) and (V), the diastereoisomer (V) predominating. On this basis, it is possible to assign absolute configurations to the diastereoisomers as 1S,5R,6S,α-S- (IV) and 1R,5S,6R-α-S- (V). These compounds are also obtained by an asymmetric reaction under the control of the chiral center of the α-phenylethylamide group in the pyrroline (IX) by scheme 6:

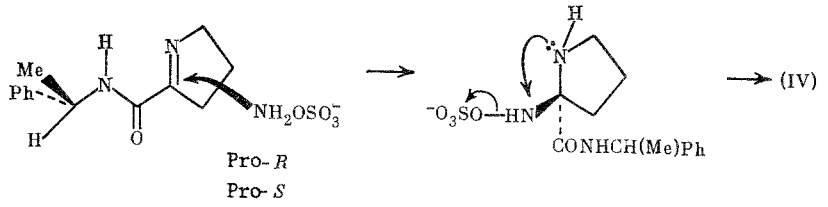
*A detailed report will be published.



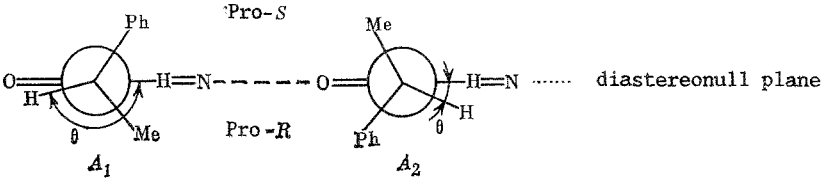
(6)

The mixture of (IV) and (V) formed by the epimination of pyrroline (IX) is enriched in diastereoisomer (IV).

It is reasonable to assume that diastereodifferentiation in this reaction takes place at the step of nucleophilic attack by $NH_2OSO_3^-$ on the azomethine carbon, since the configuration of the nitrogenous chiral centers formed in the subsequent step of cyclization of the gem-diamine is fully determined by the configuration of the nodal carbon atom (scheme 7). In accordance with the principle of steric control [8, 9], the relative rate of formation of the diastereoisomers in nucleophilic additions to π-bonds depends on the extent of steric screening of the diastereoface side of this bond. It follows from the fact that the 1S,5R, 6S,α-S- configuration is predominant in the diastereoisomer (IV), that the pro-R-side* is the most sterically accessible side of the C=N bond in the pyrroline (IX).



The orientation of the substituents on the asymmetrical α-carbon atom in (IX) with respect to the diastereonull plane may be determined from the dependence† of the $^3J_{HNCH}$ coupling constants on the dihedral angle (θ) [10]. According to this dependence, the $^3J_{HNCH}$ value of 8.3 Hz observed in the PMR spectrum of (IX) in C_6D_6 and $CDCl_3$ corresponds to the two conformations A_1 (θ ~ 160°) and A_2 (θ ~ 20°). The first of these may be assumed to be the stereochemical outcome of the reaction



This orientation of substituents on the asymmetric α-carbon atom is the closest to the model of Felkin [11], the correctness of which has been confirmed by nonempirical quantum-chemical calculations [12].

EXPERIMENTAL

Optical rotations were measured on a Polamat A polarimeter, IR spectra (in KBr disks) on a UR-20 spectrophotometer, and NMR spectra on Jeol JNM-C-60HL (^1H, 60 MHz, from HMDS), Bruker WP-80-SY (^1H, 80 MHz, from HMDS, ^{13}C, 20.15 MHz, from TMS), and Bruker WM-400 (^1H, 400 MHz, ^{13}C, 100.62 MHz, from TMS) instruments.

Potassium 1,6-Diazabicyclo[3.1.0]hexane-5-carboxylate (Id). To a solution of 2.81 g (50 mmole) of KOH in 75 ml of ethanol was added with stirring a solution of 7.39 g (52 mmole) of (Ib) [1] in 15 ml of ethanol. Stirring was continued for 1 h at 20°C, and the solvent was then removed under reduced pressure, and the residue washed with ether and dried in vacuo to give 8.06 g (97%) of (Id), decomp. ~247°C. Found, %: N 17.00. $C_5H_7KN_2O_2$. Calculated, %: N 16.85. IR spectrum (ν, cm^{-1}): 1610 (CO), 3240 (NH). ^{13}C NMR spectrum (in CD_3OD, 20.15 MHz, δ, ppm, J, Hz): 20.93 t, (C^3, $^1J_{CH}$ = 131.5), 27.38 t (C^4, 133.6), 54.39 t (C^2, 140.9), 68.32 s (C^5), 175.40 s (CO).

*Existing by virtue of the R configuration of C^5 in the final product (IV).

†$^3J_{HNCH} = 9.4\cos^2\theta - 0.5\cos\theta + 0.9\sin^2\theta$.

1,6-Diazabicyclo[3.1.0]hexane-5-carboxylic Acid (Ia). A solution of 7.81 g (47 mmole) of (Id) in 70 ml of methanol was stirred for 1 h with 20 g of Dowex 50W × 12 cation exchange resin in the H^+ form. Following filtration to remove the resin, the solvent was removed under reduced pressure and the residue recrystallized from acetonitrile to give 4.16 g (69%) of (Ia), mp 107-109°C. Found, %: C 46.78, H 6.47, N 21.96. $C_5H_8N_2O_2$. Calculated, %: C 46.87, H 6.29, N 21.86. IR spectrum (ν, cm^{-1}): 1700 (CO), 3270 (NH, OH). ^{13}C NMR spectrum (in $CDCl_3$, 100.62 MHz, δ, ppm, J, Hz): 20.93 t (C^3, $^1J_{CH}$ = 130.6), 25.85 t (C^4, 133.1), 52.98 t (C^2, 137.9), 66.30 s (C^5), 174.7 s (CO).

ℓ-Ephedrine Salts of 1.6-Diazabicyclo[3.1.0]hexane-5-carboxylic Acid (VI) and (VII). To a solution of 3.77 g (29.4 mmole) of (Ia) in 15 ml of methanol was added a solution of 4.96 g (30 mmole) of ℓ-ephedrine in 20 ml of methanol, and following removal of the solvent under reduced pressure the residue (8.72 g, mp 112-130°C, $[\alpha]_D^{20}$ −29.7°, $[\alpha]_{546}^{20}$ −35.0° (C 2.2, methanol)) was washed with hot benzene (100 ml) and recrystallized from 200 ml of acetonitrile to give 2.90 g (67%) of the salt (VI), mp 168-169°C, $[\alpha]_D^{20}$ −61.3°, $[\alpha]_{546}^{20}$ −74.8° (C 1.2, MeOH). Found, %: C 61.52, H 7.98, N 14.25. $C_{16}H_{23}N_3O_3$. Calculated, %: C 61.41, H 7.90, N 14.32. IR spectrum (ν, cm^{-1}): 1605, 1630 (CO), 3150, 3230 (NH, OH). PMR spectrum (in C_5D_5N, 400 MHz, δ, ppm, J, Hz): 1.05 d (Me, ^3J = 6.6), 1.62 m (3-H_a, 3-H_e), 2.14 m (4-H_e, $^2J_{4e,4a}$ = −13.9, $^3J_{4e3a}$ = 7.3, $^3J_{4e3e}$ = 1.5), 2.28 m (4-H_a, $^3J_{4a3a}$ = 11.0, $^3J_{4a3e}$ = 8.5), 2.81 m (2-H_a, $^2J_{2a2e}$ = −12.5, $^3J_{2a2a}$ = 10.5, $^3J_{2a3e}$ = 7.8), 3.00 m (2-H_e, $^3J_{2a3a}$ = 7.8, $^3J_{2e3e}$ = 2.0), 3.41 d.q (HCN, ^3J = 6.6 and 2.9), 4.90 br.s (NH, OH), 5.11 d (HCO), 7.00-7.20 m (Ph).

The benzene solution was evaporated in vacuo, and salt (VII) extracted from the residue with acetonitrile. Removal of the acetonitrile gave 4.72 g of a colorless, viscous residue consisting mainly of (VII) and having a PMR spectrum in C_5D_5N identical with that of (VI), $[\alpha]_D^{20}$ −7.0°, $[\alpha]_{546}^{20}$ −7.7° (C 4.3, MeOH).

Potassium Salt of (−)-(Id). To a solution of 2.35 g (8 mmole) of the salt (VI) in 40 ml of ethanol was added with stirring a solution of 0.45 g (8 mmole) of KOH in 10 ml of ethanol. The mixture was concentrated under reduced pressure to a volume of 20 ml, ether (40 ml) added, and the solid filtered off and dried in vacuo to give 1.31 g (98%) of the salt (−)-(Id), decomp. ~245°C, $[\alpha]_D^{20}$ −72.7°, $[\alpha]_{546}^{20}$ −86.1° (C 1.1, MeOH).

Acid (−)-(Ia). Obtained from 1.16 g (7 mmole) of the salt (−)-(Id) in 74% yield as for the racemic acid (Ia) (see above), mp 105-108°C (from acetonitrile), $[\alpha]_D^{20}$ −76.0°, $[\alpha]_{546}^{20}$ −90.0° (C 1.1, MeOH).

Methyl Ester (−)-(Ib). To a solution of 0.64 g (6 mmole) of (−)-(Ia) in 5 ml of dry methanol was added dropwise with stirring and cooling (−30°C) an ethereal solution of diazomethane until a persistent yellow color was obtained. Removal of the solvent under reduced pressure and distillation of the residue gave 0.63 g (89%) of the ester (−)-(Ib), bp 50-52°C (1 mm) (cf. [1]), $[\alpha]_D^{20}$ −59.6°, $[\alpha]_{546}^{20}$ −72.0° (C 1.6, MeOH).

N-Methylamide (−)-(Ic). A solution of 0.57 g (4 mmole of (−)-(Ib) and 1.24 g (40 mmole) of methylamine in 20 ml of dry methanol was kept for seven days at 20°C. Removal of the solvent under reduced pressure and recrystallization of the residue from a mixture of benzene and ether gave 0.54 g (95%) of the amide (−)-(Ic), mp 83-85°C (cf. [1]), $[\alpha]_D^{20}$ −69.2°, $[\alpha]_{546}^{20}$ −82.9° (C 1.6, MeOH).

Acid (+)-(Ia). A solution of 2.93 g (10 mmole) of a mixture of (VI) and (VII) consisting principally of diastereoisomer (VII) in 20 ml of methanol was stirred for 1 h with 7.5 g of cation exchange resin in the H^+ form. Following removal of the resin by filtration, the solvent was removed under reduced pressure, and the residue recrystallized five times from acetonitrile to give 0.58 g (45%) of (+)-(Ia), mp 106-109°C, $[\alpha]_D^{20}$ +72.6°, $[\alpha]_{546}^{20}$ +88.0° (C 1.1, MeOH).

Methyl Ester (+)-(Ib) was obtained in 82% yield as for the enantiomer (−)-(Ib), $[\alpha]_D^{20}$ +58.4°, $[\alpha]_{546}^{20}$ +70.6° (C 1.2, MeOH).

Potassium Salt (+)-(Id). To a solution of 0.38 g (3 mmole) of (+)-(Ia) in 10 ml of ethanol was added with stirring a solution of 0.17 g (3 mmole) of KOH in 10 ml of ethanol. The mixture was diluted with 30 ml of ether, and the solid filtered off and dried in vacuo to give 0.47 g (95%) of the salt (+)-(Id), decomp. ~250°C, $[\alpha]_D^{20}$ +70.5°, $[\alpha]_{546}^{20}$ +82.1° (C 1.1, MeOH).

1,6-Diazabicyclo[3.1.0]hexane-5-carboxylic Acid S-α-Phenylethylamides (IV) and (V). A solution of 1.42 g (10 mmole) of the ester (Ib) and 1.42 g (20 mmole) of S-α-phenylethylamine ($[\alpha]_D^{20}$ −40.6°, pure) in 10 ml of dry methanol containing a trace of MeONa was boiled for 24 h. The solvent was removed under reduced pressure, and the product extracted from the residue with dry ether. Following removal of the ether, the residue was washed with pentane and recrystallized five times from heptane to give 1.43 g (62%) of a mixture of (IV) and (V) in a ratio of 56:44, mp 94-97°C, $[\alpha]_D^{20}$ −73.2°, $[\alpha]_{546}^{20}$ −89.3° (C 2.4, MeOH). Found, %: C 67.41, H 7.32, N 18.25. $C_{13}H_{17}N_3O$. Calculated, %: C 67.51, H 7.41, N 18.17. IR spectrum (ν, cm^{-1}): 1640 (CO), 3265 (NH). PMR spectrum (in $CDCl_3$, 80 MHz, δ, ppm, J, Hz): 1.38 d (Me, ^3J = 7.0 (IV)), 1.39 d (Me, ^3J = 7.0 (V)), 1.41-2.57 m (CH_2N_2), 2.83 m (CH_2N), 4.89 quint. (CH), 6.41 br.d (HNCO), 7.04 m (Ph).

1,2-Diazabicyclohex-2-ene-5-carboxylic Acid (VIII). A solution of 0.26 g (2 mmole) of (Ia) in 3 ml of $CDCl_3$ was kept for one month at 20°C, and following removal of the solvent under reduced pressure the residue was chromatographed on L 400/100 silica gel (column length 15 cm, diameter 1 cm, eluant ethanol) to give 0.16 g (62%) of (VIII), decomp. ~250°C. Found, %: N 22.09. $C_5H_8O_2N_2$. Calculated, %: N 21.86. PMR spectrum (in $CDCl_3$, δ, ppm, J, Hz): ^1H (60 MHz) 2.18 m (CCH_2C), 2.75 t (CH_2C=, ^3J = 7.5), 3.61 t (CH_2N, ^3J = 7.1), 8.84 br.s (NH, OH); ^{13}C (100, 62 MHz), 20.73 t (C^5, $^1J_{CH}$ = 135.5), 30.12 t (C^4, $^1J_{CH}$ = 135.5), 46.84 t (C^6, $^1J_{CH}$ = 145.3), 171.22 s (C^3), 174.77 s (CO).

N-Trifluoroacetyl-dℓ-proline S-α-Phenylethylamide. To a mixture of a solution of 3.03 g (25 mmole) of S-α-phenylethylamine in 15 ml of methylene chloride and a solution of 4.14 g (30 mmole) of K_2CO_3 in 20 ml of water was added with stirring and cooling (5°C) a solution of 5.74 g (25 mmole) of N-trifluoroacetyl-d,ℓ-proline chloride [13] in 25 ml of methylene chloride. Stirring was continued for 0.5 h at 20°C, and the organic layer separated and dried over $MgSO_4$. Following removal of the solvent under reduced pressure, the residue was recrystallized from a mixture of benzene, ether, and hexane to give 7.7 g (98%) of product, mp 103-111°C, $[\alpha]_D^{20}$ −115.9°, $[\alpha]_{546}^{20}$ −139.7° (C 1.8, MeOH). Found, %: C 57.24, H 5.65, N 8.75. $C_{15}H_{17}F_3N_2O_2$. Calculated, %: C 57.32, H 5.45, N 8.91. PMR spectrum (in $CDCl_3$, 60 MHz, δ, ppm, J, Hz): 1.40 d (Me, ^3J = 6.9), 2.05 m (CH_2CH_2), 3.65 m (CH_2N), 4.46 m (HCN), 4.98 quint (HCNH), 6.69 br.s (HNCO), 7.20 m (Ph).

Δ^1-Pyrroline-2-carboxylic Acid S-α-Phenylethylamide (IX). To a solution of 6.29 g (20 mmole) of N-trifluoroacetyl-d,ℓ-proline S-α-phenylethylamide in 20 ml of methanol was added dropwise with stirring to a solution of 1.12 g (20 mmole) of KOH in 10 ml of dry methanol, and kept for 24 h at 20°C. Following removal of the solvent under reduced pressure, the product was extracted from the residue with 3 × 20 ml of ether. To the ether solution was added dropwise with stirring and cooling (5-10°C) a solution of 1.89 g (17.4 mmole) of tert-butyl hypochlorite in 10 ml of ether, followed by a solution of 0.40 g (17.4 mmole) of sodium in 20 ml of dry methanol. Stirring was continued for 2 h at 20°C, and the solvent then removed under reduced pressure. The residue was dissolved in 50 ml of methylene chloride, washed with water, dried over K_2CO_3, the solvent removed, and the residue recrystallized from a mixture of ether and hexane to give 3.45 g (80%) of (IX), mp 92-93°C, $[\alpha]_D^{20}$ −43.2°, $[\alpha]_{546}^{20}$ −53.2° (C 1.3, MeOH). Found, %: C 72.30, H 7.51, N 12.91. $C_{13}H_{16}N_2O$. Calculated, %: C 72.19, H 7.45, N 12.95. PMR spectrum (in $CDCl_3$, 80 MHz, δ, ppm, J, Hz): 1.48 d (Me, ^3J = 6.9), 1.88 quint (CCH_2C, ^3J = 7.2), 2.79 m (CH_2C=), 3.94 m (CH_2N), 5.12 d.q (HC, $^3J_{NHCH}$ = 8.3), 7.27 m (Ph, NHCO).

Epimination of Pyrroline (IX). To a solution of 2.16 g (10 mmole) of the pyrroline (IX) in 20 ml of benzene was added 2.76 g (20 mmole) of K_2CO_3, 2.26 g (20 mmole) of H_2NOSO_3H, and 0.02 g of $Et_3N^+CH_2PhCl^-$, followed with vigorous stirring and cooling (10-15°C) by 2 ml of water. Stirring was continued for 10 h at 20°C, the benzene solution separated from the solid, and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave 1.59 g of a mixture of (IV) and (V) in a ratio of 55:45 (from the PMR spectrum in $CDCl_3$).

CONCLUSIONS

1. Total separation of the (−)-1S,5R,6S- and (+)-1R,5S,6R-enantiomers of the stable 1,6-diazabicyclo[3.1.0]hexane-5-carboxylic acid is effected via the diastereoisomeric salts with ℓ-ephedrine.

2. The diastereoisomeric α-phenylethylamides of 1,6-diazabicyclo[3.1.0]hexane-5-carboxylic acid have been obtained in relatively low optical purity (10-12%) by amidating the methyl esters followed by recrystallization and the asymmetric epimination of Δ^1-pyrroline-2-carboxylic acid S-α-phenylethylamide.

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ASYMMETRICAL NITROGEN.

52.* NUCLEOPHILIC SUBSTITUTION AT NITROGEN IN N-CHLORO-N-ALKOXYAMINES

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The mechanism of nucleophilic substitution at tervalent nitrogen has received limited attention. For example, it has been shown by kinetic methods that substitution in the system H_2NX when X = Cl [2], $HOSO_3$ [3], and 2,4-$(O_2N)_2C_6H_3O$ [4] occurs by the S_N2 mechanism. We have previously observed that N-chloro-N-alkoxy-N-tert-alkylamines [5] readily undergo nucleophilic substitution of chlorine [5, 6]. In this case, it was suggested that, by analogy with α-chloroalkyl esters [7], nitrenium-oxonium ions are formed as intermediates. In order to check the validity of this suggestion, we have attempted to elucidate the mechanism of nucleophilic substitution in some reactions of N-chloro-N-alkoxyamines using kinetic and stereochemical data.

It has previously been shown that the alkoxyamination of pyridine takes place cleanly and irreversibly [6]:

$$\underset{(I)}{MeO_2CCMe_2N(OMe)Cl} + NC_5H_5 \rightarrow \underset{(II)}{MeO_2CCMe_2\overset{+}{N}(OMe)\overset{+}{N}C_5H_5Cl^-}$$

We have examined by PMR (80 MHz, CD_3CN) the kinetic features of this reaction at constant concentrations of (I) (~0.11 mole/liter) and pyridine concentrations of 1.37-2.43 mole/liter at 20°C, and using an equimolar ratio of reactants (concentration ~0.16 mole/liter) at temperatures of 15, 20, 25, and 35°C. The current concentrations of (I), a − x, and (II), x, were found by integrating the signals for the MeO groups. All the points on the kinetic plots

*For communication 51, see [1].

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