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HETEROCYCLIC ANALOGS OF PLEIADIENE.

51.* N-ACYLPERIMIDINES: RING OPENING INSTEAD OF DEACYLATION UNDER THE INFLUENCE OF NUCLEOPHILES

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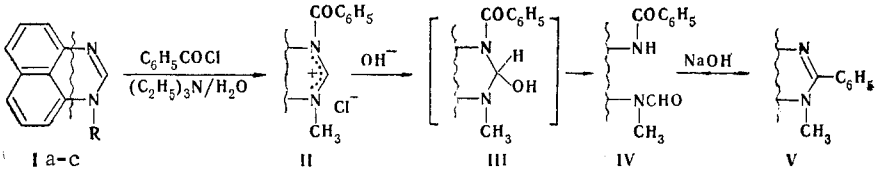
UDC 547.856.7

N-Acetyl- and N-benzoylperimidines, as well as quaternary salts based on them, were synthesized. It is shown that the heteroring is opened to give N-acyl derivatives of 1,8-naphthalenediamine by the action of nucleophiles on N-acylperimidines and N-benzoylperimidine salts.

We have previously observed recyclization in series of 1-substituted perimidines (Ia, for example), which consists in opening of their heteroring by the action of aromatic acid chlorides (the scheme for benzoyl chloride is presented below) in the presence of triethylamine to give 1,8-naphthalenediamine derivative (IV) [2-4]. The latter is readily converted to a 1,2-disubstituted perimidine (V) when it is heated with alkali, during which the radical of the acyl chloride used is incorporated in the 2 position. It was assumed that the first step in the process yields an N-acylperimidinium salt (II), which adds a hydroxide ion extremely readily to give pseudobase III, the open form of which is a compound of the IV type.



I a-c II III IV V

I a R = CH_3; b R = CH_3CO; c R = C_6H_5CO

A distinctive feature of the reaction is that it does not take place in a number of other diazole systems, particularly benzimidazoles and naphthimidazoles, the 1-substituted derivatives of which remain unchanged under the same conditions. It might have been assumed that the possibility of recyclization for Ia is due to two circumstances: the high positive charge in the 2 position of perimidines [5, 6] and the increased strength of the N–acyl bond in salts II. The combination of these factors should result in attack by the bases on the μ-carbon atom to give pseudobase III rather than attack on the carbonyl carbon atom of salts II (in this case the starting compound is regenerated, i.e., the reaction does not occur). In this connection, the aim of the present research was to obtain N-acylperimidines and their quaternary salts and to study their properties, particularly their behavior with respect to nucleophiles. It should be noted that the simplest N-acylperimidines have heretofore been unknown. The so-called perinones [7] should perhaps be regarded as a close model of them.

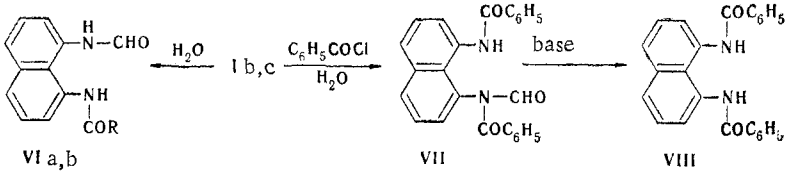
*See [1] for Communication 50.

Rostov State University, Rostov-on-Don 344006. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1398-1403, October, 1980. Original article submitted March 4, 1980.

 0009-3122/80/1610-1064$07.50

We synthesized the 1-acetyl- (Ib) and 1-benzoylperimidine (Ic) by the action of acetyl and benzoyl chloride on perimidine in absolute benzene; two equivalents of perimidine were used to tie up the resulting hydrogen chloride. Like all 1-substituted perimidines, Ib, c are bright-yellow crystalline substances that are crystallized from octane. The $\nu_{C=O}$ band in the IR spectra of chloroform solutions of Ib and Ic is found at 1715 and 1665 cm^{-1}, respectively; this is appreciably lower than in the case of N-acylazoles. Thus the $\nu_{C=O}$ band in the spectra of 1-acetylimidazole and 1-acetylbenzimidazole is found at 1747 and 1730 cm^{-1}, respectively [8, 9]. The decrease in the $\nu_{C=O}$ frequency for Ib, c indicates the great accessibility of the unshared electron pair of the pyrrole nitrogen atom in them with respect to conjugation with the carbonyl group. This is in complete agreement with the previously established decreased aromatic character of perimidines as compared with imidazole systems [10].

A characteristic feature of Ib, c is their high lability under the influence of even traces of moisture; this hinders their isolation and purification substantially and explains the low yield (18%); the reaction of Ib, c with water is not accompanied by deacylation as in the case of N-acylimidazoles [11] but rather by the formation of colorless crystalline compounds identified as N-formyl-N'-acyl-1,8-naphthalenediamines (VI). The preparation of the latter from Ib, c is carried out particularly conveniently in alcohol: VI are formed in almost quantitative yields even in the case of brief heating of a solution of Ib, c in non-anhydrous ethanol. Thus our assumption regarding the increased stability of the nitrogen–acyl bond in N-acylperimidines with respect to nucleophiles was confirmed.

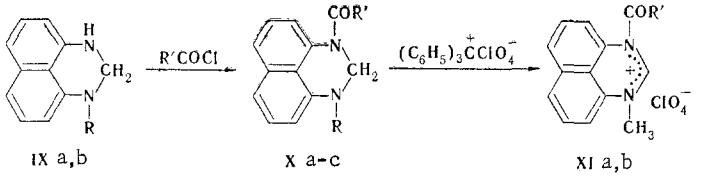


VI a,b VII VIII

VI a R = CH_3; b R = C_6H_5

N,N'-Dibenzoyl-N'-formyl-1,8-naphthalenediamine (VII) is formed in 58% yield by the action of excess benzoyl chloride on Ic or on perimidine itself in aqueous benzene. The initially formed 1,3-dibenzoylperimidinium salt evidently is attacked by a molecule of water in the 2 position and undergoes conversion to pseudobase VII. When VII is treated with alkali and even triethylamine, it is readily deformylated to give VIII. The impossibility of cyclization of VII to 2-phenylperimidine in this case is explained by pronounced passivation of the anion formed during its deformylation by the N-benzoyl group. We also observed similar passivation of the anion for other pseudobases IV with electron-acceptor substituents attached to the nitrogen atom (C_6H_5 and CH_3OCH_2) [4].

It seemed of interest to obtain a 1-methyl-3-acylperimidinium salt. The action of benzoyl chloride in absolute benzene on Ia gives 1-methyl-3-benzoylperimidinium chloride (II), which is distinguished by its high instability with respect to moisture. In view of this, we obtained the more stable 1-methyl-3-acylperimidinium salts XI via the scheme presented below. The extremely accessible 2,3-dihydroperimidines IX served as the starting compounds; they were acylated to X, after which they were dehydrogenated with triphenylmethylcarbonium perchlorate in methylene chloride. Since the aromatization of 2,3-dihydroperimidines has



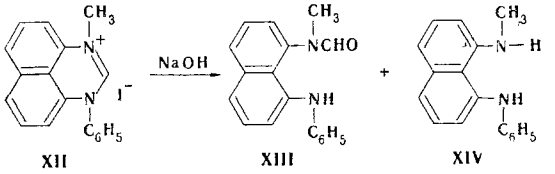
IX a,b X a-c XI a,b

IX a R = H, b R = CH_3; X a R = R' = CH_3, b R = CH_3, R' = C_6H_5, c R = C_6H_5CO, R' = C_6H_5; XI a R' = CH_3, b R' = C_6H_5

not been carried out by means of this reagent, we checked this method in two cases. We found that 1,3-dimethyl-2,3-dihydroperimidine is also converted to 1,3-dimethylperimidinium perchlorate very readily by the action of trityl perchlorate. On the other hand, 1,3-dibenzoyl-2,3-dihydroperimidine (Xc) is not dehydrogenated by this reaction, undoubtedly as a consequence of the reduced hydride lability under the influence of two benzoyl groups.

Salts XI are yellow crystalline substances that are extremely stable in solid form in the course of several days. The absorption band of the C=O group in the IR spectra of solid samples of XIa, b appears at 1770 and 1765 cm^{-1}, respectively; this is also typical for the N-acyl salts of other heterocycles [12]. Salts XI have considerably lower stability in solution. Thus their PMR spectrum in d_6-DMSO is identical to the spectrum of 1-methylperimidine hydroperchlorate, which indicates splitting out of an N-acyl group in this solvent. Similarly, the electrical conductivity of the salts in DMSO also changes rapidly with time and soon becomes close to the electrical conductivity of 1-methylperimidine hydroperchlorate or 1,3-dimethylperimidinium perchlorate (λ = 36.5 Ω-cm^2/g-eq when c = 0.052 g-eq/liter).

Whereas chloride IIa is instantaneously hydrolyzed by water to 1-methylperimidinium chloride, salt XI is decomposed rapidly by water only with heating. The reaction product in the case of salt XIa is 1-methylperimidinium hydroperchlorate, whereas opening of the heteroring and the formation of pseudobase IV in 26% yield is observed for salt XIb in addition to detachment of an N-benzoyl group (73%) under these conditions. This pseudobase is formed in high yield (57 and 90%, respectively) when salts XIb and II are heated with triethylamine in benzene; this thus confirms the correctness of the previously adopted [2-4] point of view relative to the nature of the first step in the recyclization reaction. As regards salt XIa, it also splits out an N-acetyl group under the influence of triethylamine and undergoes conversion to 1-methylperimidine. This is in agreement with the fact, which we established, that 1-R-perimidines do not undergo recyclization under the influence of aliphatic acid chlorides. It is apparent that the positive charge on the C_2 atom is lower in salts of the XIa type than on the C atom of the carbonyl group, which is also primarily attacked by the nucleophile. Thus pseudobases of the III type, which are formed from 1-alkyl-3-aroylperimidinium salts, in contrast to carbonyl psuedobases from 1,3-dialkylperimidinium salts [13], do not undergo disproportionation to give a 1,3-disubstituted perimidone and 2,3-dihydroperimidine. This can be explained by a decrease in the hydride lability in III, which is yet another factor that promotes recyclization. On the basis of this, one might have assumed that in the case of perimidinium salts that contain other electron-acceptor groups attached to the nitrogen atoms the reaction involving ring opening under the influence of alkalis would also predominate over the disproportionation reaction. We confirmed this in the case of 1-methyl-3-phenylperimidinium iodide, which on heating with alkali was converted to a mixture of pseudobase XIII and N-methyl-N'-phenyl-1,8-naphthalenediamine (XIV). It is known that the N-phenyl group in XII has extremely significant electron-acceptor character [14].



XII XIII XIV

EXPERIMENTAL

The IR spectra of solutions of the compounds in $CHCl_3$ and mineral oil suspensions were recorded with a UR-20 spectrometer. The PMR spectra of the compounds were recorded with Tesla BS-487 (80 MHz) and Tesla BS-467 (60 MHz) spectrometers; the chemical shifts are presented on the δ scale with respect to hexamethyldisiloxane.

1-Acetylperimidine (Ib). A suspension of 5.0 g (0.03 mole) of perimidine and 1 ml (0.015 mole) of freshly distilled acetyl chloride in 250 ml of dry benzene was stirred at 20°C for 20 h, after which the precipitated perimidine hydrochloride (3.5 g) was removed by filtration. The benzene was removed from the filtrate by distillation at 40-45°C under the vacuum created by a water aspirator (a capillary with a calcium chloride tube was used), and the residue was dissolved in 20 ml of chloroform. The N-acetyl-N'-formyl-1,8-naphthalenediamine (VIa) was removed by filtration, and the chloroform solution was chromatographed with a column (with L 40/100μ silica gel and dry ethyl acetate). The yellow first fraction was collected and worked up to give 0.6 g (18%) of yellow crystals with mp 176-178°C (from benzene). IR spectrum: 1715 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 2.50 (s, 3H, CH_3), 7.10 (m, 4-H—8-H), 7.88 (s, 1H, 2-H), and 8.12 ppm (q, 1H, 9-H). Found: C 74.2; H 4.9; N 13.6%. $C_{13}H_{10}N_2O$. Calculated: C 74.3; H 4.8; N 13.3%.

The second zone of the column was cut out and extracted with DMF. The extract was diluted with water, and the resulting precipitate was removed by filtration to give 1.8 g (52%) of VIa.

1-Benzoylperimidine (Ic). This compound was obtained in 18% yield by a method similar to that used to obtain 1-acetylperimidine Ib. Recrystallization from octane gave yellow crystals with mp 106-107°C. IR spectrum: 1665 cm^{-1}. PMR spectrum ($CDCl_3$): 7.86 (m, aromatic protons), 8.07 (s, 1H, 2-H), and 9.08 ppm (q, 1H, 9-H). N-Benzoyl-N'-formyl-1,8-naphthalenediamine was obtained in 49% yield.

N-acetyl-N'-formyl-1,8-naphthalenediamine (VIa). A solution of 0.05 g (0.03 mmole) of 1-acetylperimidine in 5 ml of ethanol was refluxed for 10 min, after which it was cooled, and the resulting precipitate was removed by filtration to give 0.051 g (94%) of white crystals with mp 178-179°C (from alcohol). IR spectrum: 3250 (NH) and 1665 cm^{-1} (C=O). Found: C 68.1; H 5.2; N 12.3%. $C_{13}H_{12}N_2O$. Calculated: C 68.4; H 5.3; N 12.3%.

N-Benzoyl-N'-formyl-1,8-naphthalenediamine (VIb). This compound was similarly obtained from 1-benzoylperimidine in 90% yield. Recrystallization from DMF gave white crystals with mp 190-191°C. IR spectrum: 3290 (NH) and 1645 cm^{-1} (C=O). Found: C 74.4; H 5.0; N 9.1%. $C_{18}H_{14}N_2O_2$. Calculated: C 74.5; H 4.8; N 9.7%.

N,N'-Dibenzoyl-N-formyl-1,8-naphthalenediamine (VIII). A 0.05-ml (2 mmole) sample of benzoyl chloride was added to a solution of 0.17 g (0.62 mmole) of 1-benzoylperimidine in 10 ml of absolute benzene, and the mixture was stirred for 5 min. Five drops of water were added, and the mixture was refluxed for 1.5 h. It was then cooled, and the resulting precipitate was removed by filtration to give 0.14 g (58%) of white crystals that darkened at 172°C and did not melt above 300°C (from acetic acid). IR spectrum: 3400 (NH) and 1680 cm^{-1} (C=O). Found: C 76.4; H 4.6; N 7.0%. $C_{25}H_{18}N_2O_3$. Calculated: C 76.2; H 4.6; N 7.1%.

N,N'-Dibenzoyl-1,8-naphthalenediamine (X). A) A 0.35-ml (3.2 mmole) sample of benzoyl chloride and 0.36 ml (3.2 mmole) of triethylamine were added to a solution of 0.81 g (3 mmole) of Ic in 30 ml of benzene, and the mixture was refluxed with stirring for 3 h. The benzene was evaporated, and the residue was washed with water and dried to give 0.6 g (60%) of white crystals with mp 310-311°C (from DMF) (mp 311-312°C [15]). IR spectrum: 3340 (NH) and 1650 cm^{-1} (C=O).

B) A suspension of 0.1 g (2.6 mmole) of VII in 3 ml of a 10% solution of KOH was refluxed for 1 h, after which it was cooled, and the precipitate was removed by filtration and washed with water to give the product in quantitative yield. The melting point and IR spectrum were in agreement with the melting point and IR spectrum of the compound obtained by method A.

C) A solution of 0.4 g (0.01 mole) of sodium hydroxide in 1 ml of water was added to a solution of 1.58 g (0.01 mole) of 1,8-naphthalenediamine in 5 ml of dioxane, and the mixture was stirred for 10 min. Water (30 ml) was added, and the resulting precipitate was removed by filtration. 2-Phenylperimidine (0.95g) was separated from N,N'-dibenzoyl-1,8-naphthalenediamine with hot ethanol. The yield of VIII was 0.35 g (10%). The melting point and IR spectrum of the product were in agreement with the melting point and IR spectrum of the compound obtained by method A.

1-Methyl-3-acetyl-2,3-dihydroperimidine (Xa). A 0.77-ml (10.8 mmole) sample of freshly distilled acetyl chloride was added to a suspension of 2 g (10.8 mmole) of IXb [16] and 1.5 g (10.8 mmole) of ground potassium carbonate in 50 ml of absolute benzene, and the mixture was stirred at 20°C for 30 min. Water (50 ml) was added, and the benzene layer was separated and evaporated. The residue was triturated with diethyl ether to give 2.2 g (91%) of white crystals with mp 115-116αC (from methanol). IR spectrum: 1670 cm^{-1} (C=O). Found: C 74.5; H 6.4; N 12.7%. $C_{14}H_{14}N_2O$. Calculated: C 74.4; H 6.2; N 12.4%.

1-Methyl-3-benzoyl-2,3-dihydroperimidine (Xb). This compound was obtained in 82% yield by a method similar to that used to prepare Xa. Recrystallization from methanol gave white crystals with mp 106-107°C. IR spectrum: 1650 cm^{-1} (C=O). PMR spectrum (in d_6-DMSO): 2.82 (s, 3H, CH_3), 4.75 (s, 2H, CH_2), 6.55 (q, 1H, 4-H), and 7.15 (m, 11H). Found: C 78.8; H 5.6; N 9.3%. $C_{19}H_{16}N_2O$. Calculated: C 79.2; H 5.6; N 9.7%.

1,3-Dibenzoyl-2,3-dihydroperimidine (Xc). This compound was obtained in 67% yield from 1 mole of IXa [17], 2 mole of benzoyl chloride, and 2 moles of potassium carbonate by a method similar to that used to prepare Xa. Recrystallization from alcohol gave white crystals with

mp 210-211°C (from alcohol). IR spectrum: 1665 cm^{-1} (C=O). Found: C 79.3; H 4.8; N 7.9%. $C_{25}H_{18}N_2O_2$. Calculated: C 79.4; H 4.8; N 7.4%.

1-Methyl-3-acetylperimidinium Perchlorate (XIa). A solution of 1.5 g (4.4 mmole) of trityl perchlorate in 1 ml of methylene chloride was added to a solution of 1 g (4.4 mmole) of Xa in 3 ml of dry methylene chloride, and the resulting precipitate was removed by filtration and washed with dry diethyl ether to give 1.1 g (78%) of yellow crystals that darkened at 124°C and had mp 142-143°C (decomp.). IR spectrum: 1770 (C=O) and 1100 cm^{-1} (ClO_4^-). PMR spectrum (in d_6-DMSO): 1.85 (s, 3H, CH_3CO), 3.40 (s, 3H, N—CH_3), 6.77 (q, 2H, 4-H, 9-H), 7.45 (m, 4H, 5-H—8-H), and 8.55 ppm (broad s, 1H, 2-H). The spectrum is very similar to the spectrum of 1-methylperimidine hydroperchlorate (see below).

1-Methyl-3-benzoylperimidinium Perchlorate (XIb). This compound was obtained in 73% yield by a method similar to that used to prepare XIa. The yellow crystals darkened at 136°C and had mp 149-151°C (decomp.). IR spectrum: 1755 (C=O) and 1100 cm^{-1} (ClO_4^-). The PMR spectrum (in d_6-DMSO) corresponded closely to the spectra of salt XIa and 1-methylperimidine hydroperchlorate.

1-Methyl-3-benzoylperimidinium Chloride (II). A solution of 1.41 g (10 mmole) of freshly distilled benzoyl chloride in 5 ml of absolute benzene was added to a refluxing solution of 1.82 g (10 mmole) of 1-methylperimidine in 60 ml of absolute benzene, and the mixture was refluxed for 1 h. It was then cooled, and the precipitate was removed by filtration and transferred to a desiccator containing phosphorus pentoxide. The yield was 2.5 g (83%). The yellow crystals had mp 230°C (in a sealed capillary). Because of its instability, this salt was not analyzed.

Hydrolysis of 1-Methyl-3-benzoylperimidinium Perchlorate. A suspension of 0.5 g (1.3 mmole) of XIb in 30 ml of water was refluxed with stirring for 30 min, after which it was cooled, and the precipitate was removed by filtration to give 0.2 g (26%) of product. The thin-layer chromatogram, melting point, and IR spectrum were the same as those obtained for the compound prepared by the method in [2]. Evaporation of the aqueous filtrate gave 0.25 g (73%) of 1-methylperimidine hydroperchlorate. The yellow crystals had mp 219-221°C (from aqueous alcohol). PMR spectrum (in d_6-DMSO): 3.40 (s, 3H, CH_3), 6.76 (q, 2H, 4-H, 9-H), 7.40 (m, 3H, 5-H—8-H), and 8.57 (s, 1H, 2-H).

Hydrolysis of perchlorate XIa under similar conditions gave 1-methylperimidine hydroperchlorate in 92% yield, while hydrolysis of chloride II gave 1-methylperimidine hydrochloride in 97% yield. The yellow needles had mp 260-261°C (from alcohol with ether) (mp 260-261°C [18]).

Action of Triethylamine on Salts XIa, b. A) A suspension of 0.8 g (2.5 mmole) of perchlorate XIa in 40 ml of benzene and 0.5 ml (5 mmole) of triethylamine was refluxed for 30 min, after which the benzene solution was decanted from the resinous residue and evaporated to give 0.2 g (50%) of Ia. The thin-layer chromatogram and melting point were in agreement with the data in [18].

B) A suspension of 1 g (2.5 mmole) of perchlorate XIb in 50 ml of benzene and 0.5 ml (5 mmole) of triethylamine was refluxed for 30 min, after which the benzene solution was decanted from the resinous residue and evaporated. The residue was passed through a column (with Al_2O_3 and chloroform) to give 0.43 g (57%) of product. The thin-layer chromatogram, melting point, and IR spectrum corresponded to the compound obtained by the method in [2].

Action of Alkali on 1-Phenylperimidinium Methiodide (XII). A suspension of 1.1 g (2.8 mmole) of XII [14] in 40 ml of water was treated with 20 ml of a 10% solution of NaOH, and the mixture was heated on a boiling water bath for 1 h. It was then cooled, and the precipitate was removed by filtration, washed with water, dried, and dissolved in chloroform. The chloroform solution was passed through a column (Al_2O_3, $CHCl_3$), and the first fraction was collected and worked up to give 0.1 g (14%) of white crystals of XIII with mp 112-114°C. IR spectrum: 3380 cm^{-1} (NH). Found: C 82.1; H 6.6; N 11.3%. $C_{17}H_{16}N_2$. Calculated: C 82.3; H 6.5; N 11.3%. The second fraction was worked up to give white crystals of XIV with mp 104-106°C. IR spectrum: 1690 (C=O) and 3340 cm^{-1} (NH). Found: C 78.0; H 5.8; N 10.0%. $C_{18}H_{16}N_2O$. Calculated: C 78.3; H 5.8; N 10.1%.

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DIAZABICYCLOALKANES WITH NITROGEN ATOMS IN THE NODAL POSITIONS. 5.* SYNTHESIS AND SOME REACTIONS OF 2-HYDROXYMETHYL-1,4-DIAZABICYCLO[2.2.2]OCTANE

G. V. Shishkin and V. I. Vysochin

UDC 547.895.07

2-Hydroxymethyl-1,4-diazabicyclo[2.2.2]octane was synthesized by reduction of 1,4-diazabicyclo[2.2.2]octane-2-carboxylic acid or its methyl ester with lithium aluminum hydride in tetrahydrofuran and by hydrolysis or hydrogenation of 2-benzyloxymethyl-1,4-diazabicyclo[2.2.2]octane. Depending on the conditions, 2-hydroxymethyl-1,4-diazabicyclo[2.2.2]octane reacts with methyl iodide to give primarily either a bisquaternary or a monoquaternary derivative. The latter is the only product in its alkylation with methyl esters of benzoic and caproic acids.

We have previously described [2, 3] 1,4-diazabicyclo[2.2.2]octane-2-carboxylic acid (I) and 2-benzyloxymethyl-1,4-diazabicyclo[2.2.2]octane (II). Continuing our search for methods for the synthesis of functional derivatives of 1,4-diazabicyclo[2.2.2]octane and our study of the properties of I and II, we used them for the preparation of 2-hydroxymethyl-1,4-diazabicyclo[2.2.2]octane (III) and investigated some of its reactions. 2-Hydroxymethyl-1,4-diazabicyclo[2.2.2]octane bis(methobromide) (IV) has been reported [4]; however, information regarding the synthesis and reactions of base III was not revealed.

The same compound, viz., III, which was characterized in the form of the dihydrobromide (VI), was obtained in the reduction of both acid I and its methyl ester (V) with lithium

*See [1] for Communication 4.

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