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MAGNETIC ANISOTROPY AND THE INTERPRETATION OF THE NMR SPECTRA OF LACTAMS—II

N-SUBSTITUTED PYRROLIDONES

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Abstract—The NMR spectra of a number of N-substituted pyrrolidones have been measured, and the cause of the magnetic non-equivalence of the methylene protons in the substituent side chain has been examined. In contrast to the previous lactams examined, this non-equivalence is not attenuated by the shielding effect of the side chain phenyl or the ring keto-group but is due purely to the asymmetric centre in the side chain. The chemical shifts of the lactam ring protons have been found to vary widely with substituent and this effect has also been investigated.

IN THE previous paper[1] several interesting features in the NMR spectra of lactams had been observed, and publications by other authors[2,3] had shown that there was a considerable amount of current interest in the question of non-equivalence associated with the amide grouping. The availability of some of the investigated compounds[4] prompted us to continue our studies, and examine other compounds which were required to clarify some of the features observed in the NMR spectra.

The NMR spectrum of 2-pyrrolidone itself[5] is completely uninterpretable using a simple treatment. The AA′BB′XX′ system is complicated by molecular motion, and only very approximate parameters can be obtained. Even the effect of N-methylation[6] does little to rectify this but when N-acetylation[7] is carried out the AA′BB′ part of the spectrum appears in a more recognisable form.

We have, therefore, examined several compounds of the type shown in Fig. 1 to see firstly if the magnetic non-equivalence of the methylene protons on C_6 could be observed, and secondly if the AA′BB′XX′ spectrum could be interpreted. The full list of compounds is set out in Table 1, together with the NMR constants obtained from the spectra.

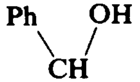
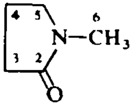
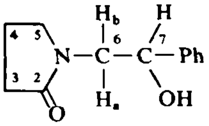
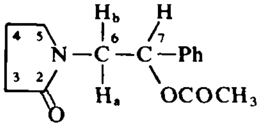
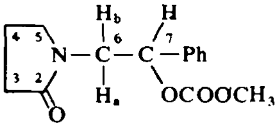
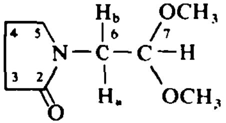
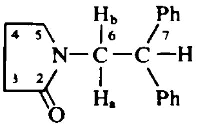
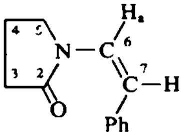
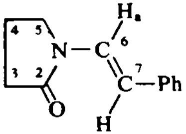
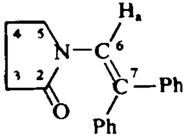
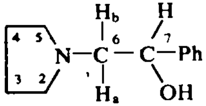
In the high resolution spectrum of N-methyl-pyrrolid-2-one with scale expansion, the "triplet" at 6·66 τ due to the protons on C_5 exhibited considerable fine structure, whilst the protons on C_3 and C_4 appeared with very similar chemical shifts, and it was not possible even roughly to analyse the spectrum using the "X" approximation. However, in II, the substitution of the  $\underset{\text{CH}}{\overset{\text{Ph}\quad\text{OH}}{\setminus\quad/}}$ group for one of the C_6 protons whilst introducing a methylene group attached to the nitrogen, resulted in a spectrum exhibiting several interesting features.

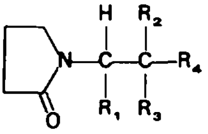
TABLE 1. NMR SPECTROSCOPIC DATA OF THE N-SUBSTITUTED PYRROLIDONES AND PYRROLIDINE

Compd	Formula	Chemical shift (τ) from TMS						Coupling constants in Hz			
		H_3	H_4	H_5	H_{6a}	H_{6b}	H_7	$J_{3/4}$*	$J_{4/5}$*	$J_{6a/7}$	$J_{6b/7}$
I				6·66	7·27						
II		7·70	8·11	6·75	6·53	6·53	5·13	7·0	8·5	6·0	6·0
III		7·70	8·06	6·66	6·29	6·48	4·02	6·7	8·2	8·5	4·5
IV		7·71	8·09	6·66	6·36	6·36	4·21	7·0	8·5	6·5	6·5
V		7·71	8·01	6·54	6·64	6·64	5·54	7·0	8·5	5·5	5·5

Compd	Formula	Chemical shift (τ) from TMS						Coupling constants in Hz			
		H_3	H_4	H_5	H_{6a}	H_{6b}	H_7	$J_{3/4}$*	$J_{4/5}$*	$J_{6a/7}$	$J_{6b/7}$
VI		7·85	8·32	7·00	6·10	6·10	5·64	6·7	8·1	8·2	8·2
VII		7·45	7·87	6·84	3·20	—	4·03	7·0	8·3	9·0	—
VIII		7·49	7·89	6·40	2·38	—	4·15	6·7	8·3	15·0	—
IX		7·67	8·22	7·09	2·85	—	—	7·0	8·2	—	—
X		8·15–8·35		7·3–7·5	7·29	7·44	5·31	—	—	9·5	4.1

* Time averaged values.

The protons on C_5 appeared as a fairly broad triplet whilst the protons on C_3 and C_4 at 7·70 τ and 8·11 τ respectively, seemed to exhibit the A_2B_2 part of an $A_2B_2X_2$ spectrum. Spin decoupling experiments were carried out by irradiating the protons on C_5 and this resulted in a simplification of the region between 7·5 τ and 8·5 τ (Fig. 2). However, the fact that this decoupled spectrum was similar to an A_2B_2 spectrum does not necessarily mean that it may be solved on this basis.



Compd	R_1	R_2	R_3	R_4
II	H	H	OH	Phenyl
III	H	H	$OCOCH_3$	Phenyl
IV	H	H	$OCOOCH_3$	Phenyl
V	H	H	OCH_3	OCH_3
VI	H	H	Phenyl	Phenyl
VII	—	H	—	Phenyl
VIII	—	—	H	Phenyl
IX	—	—	Phenyl	Phenyl

FIG. 1. General formula and table of substituents of the investigated pyrrolidones.

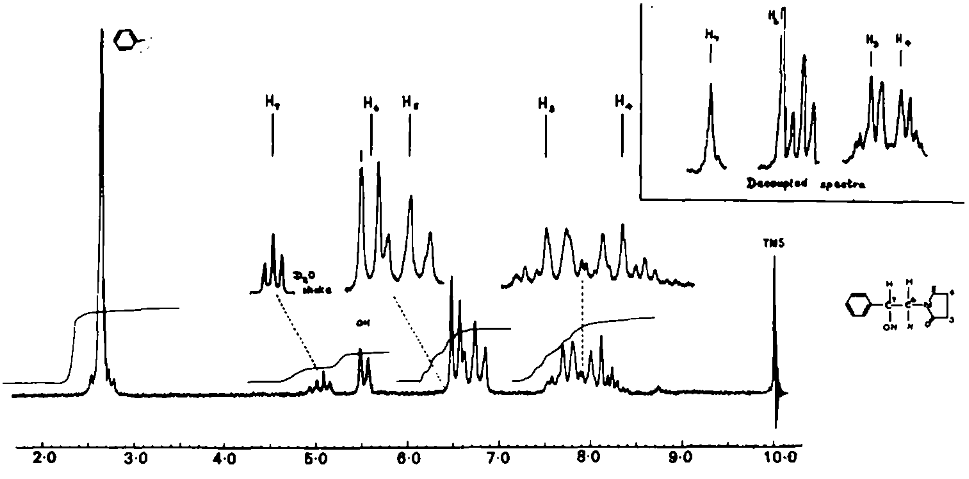


FIG. 2. The NMR spectrum of N- (2′-phenyl-2′-hydroxyethyl)-pyrrolid-2-one (II).

In such a ring system one would expect an AA'BB'XX' system to be present, and although ring puckering motion will result in some averaging of the coupling constants, it is still possible that the time average value of J_{cis} will not equal the time averaged value of J_{trans} (Fig. 3).

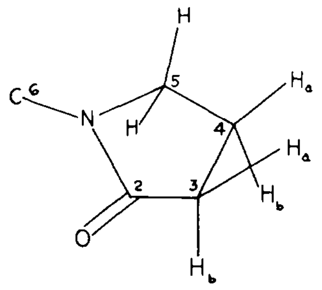


FIG. 3. One of the conformers of the pyrrolid-2-one ring.

The decoupled spectrum approximates very closely to an A_2B_2 spectrum ($J/\delta \approx 0{\cdot}32$) but this is most likely to be a deceptively simple AA'BB' spectrum, molecular motion having contributed to the apparent simplicity. The "coupling constant" $J_{3/4}$ is thus an average of the two time average values of J_{cis} and J_{trans}.

This compound II had been initially examined because it combined in one molecule many of the features which cause magnetic non-equivalence. These are an asymmetric centre, an amide group, a Ph group, in which the shielding and deshielding influence of the π electrons could attenuate any possible difference in the chemical shift of the C_6 protons, and an OH group. This OH could possibly form a hydrogen bond to either the ring nitrogen or to the keto-group resulting in a stabilization of one particular conformer as was previously observed in the piperidones.[1] IR dilution studies however, showed that there was only a very weak intramolecular hydrogen bond, and a considerable percentage of the free OH was present. Hence this latter feature would contribute very little to magnetic non-equivalence. In spite of such a combination of effects, the protons on C_6 and C_7 appeared as a simple A_2B system (Fig. 2) and a detailed analysis gave the constants as set out in Table 1. The OH proton exchanged more slowly than normal, possibly due to the weak hydrogen bonding, and so a coupling was observed between this and the C_7 proton which was removed on shaking with D_2O, giving the pure B part of a A_2B spectrum. As no magnetic inequivalence was observed it must be concluded that conformers are present in which, coincidently, the magnetic environment of the H_{6a} is the same as that of H_{6b} and hence both appeared at the same field, i.e. some of the contributing causes have cancelled out.

Acetylation of compound II to give compound III, removed the weak hydrogen bonding whilst retaining the other three influences. The protons on C_6 however, appeared at different fields; the C_6 and C_7 protons exhibited a typical ABX pattern (Fig. 4), and a detailed analysis of the three spin system gave the constants $H_{6a} = 6{\cdot}29\ \tau$, $H_{6b} = 6{\cdot}48\ \tau$, $H_7 = 4{\cdot}02\ \tau$, $J_{6a/7} = 8{\cdot}5$ Hz, $J_{6b/7} = 4{\cdot}5$ Hz, $J_{6a/6b} = 14{\cdot}0$ Hz. Although the peak due to the protons on C_5 overlapped with the peaks due to H_{6b}, the "triplet" was quite clear and showed no fine splitting with only slight line broadening. This peak could be analysed using the "X" approximation, as decoupling experiments had shown that for the time averaged $A_2B_2X_2$ system in the pyrrolidone ring, there was negligible coupling between the C_3 and C_5 protons. The C_3 and C_4 protons then exhibited a perfect A_2B_2 system due to time averaging effects. Such an analysis

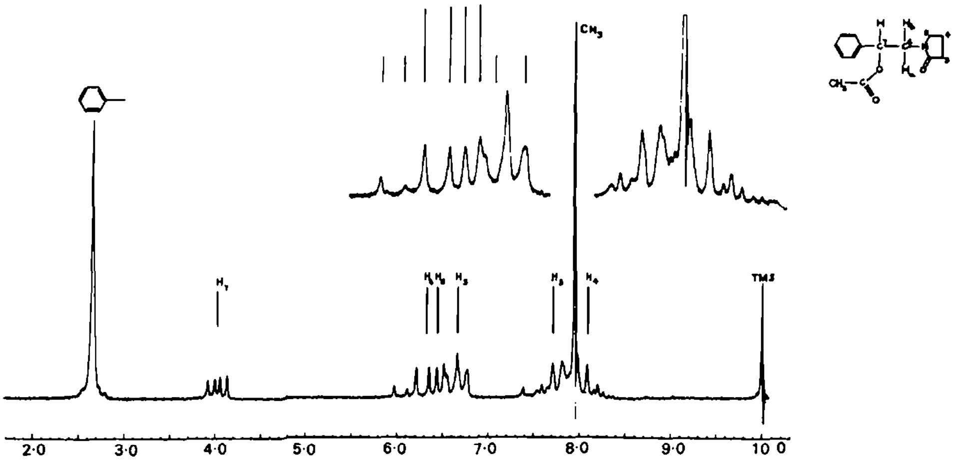


FIG. 4. The NMR spectrum of N-(2′-phenyl-2′-acetoxyethyl)pyrrolid-2-one (III).

resulted in the constants shown in Table 1, the coupling constants for the ring protons again not being the true but time average values.

The spectrum of the carbonate (IV) was not as easy to interpret as that of the acetate, as the peak due to the Me protons moved downfield from 7·92 τ to 6·29 τ and almost coincided with the C_6 protons. Despite this, the three spin system of protons on C_6 and C_7 had reverted to an A_2B system and a detailed analysis gave the constants set out in Table 1. In view of the fact that the asymmetric centre, the amide grouping and the Ph group are still present, one can only assume that, once again, it is purely fortuitous that the two protons on C_6 have the same chemical shift. As observed in II and III, the ring protons on C_3, C_4 and C_5 still exhibited the same typical time averaged $A_2B_2X_2$ system, the constants for this compound are also included in Table 1.

Because magnetic non-equivalence of the protons on C_6 was only sometimes exhibited, it was of interest to examine a series of compounds in which the possible causes of this non-equivalence had each been eliminated in turn.

In compound V, the asymmetric centre had been eliminated, thus if non-equivalence occurred, this would be due to slow rotation about the C_6—N bond. Unfortunately, the chemical shifts of the ether methyl groups at 6·67 τ were almost identical to those of the protons on C_6. Although these two protons appeared to have the same chemical shift, this was not an unambiguous assignment, due to the presence of the Me group signal; and the close proximity of the signal due to the C_5 protons at 6·54 τ. Examination of the X part of the spectrum at 5·54 τ did not resolve this matter completely, for although the signal was a perfect triplet, this could have been due either to an A_2X system or to the special case of an ABX system in which the A and B protons have different chemical shifts but identical coupling constants with the X proton, or this may be a so-called "deceptively simple spectrum". The rest of the spectrum showed the $A_2B_2X_2$ type of pattern previously observed in the compounds so far examined and analysis yielded the following time averaged constants H_3 = 7·71 τ, H_4 = 8·01 τ, H_5 = 6·54 τ, $J_{3/4}$ = 7 Hz, $J_{4/5}$ = 8·5 Hz.

In view of the fact that it still had not been possible to decide definitely whether the magnetic anisotropy of the C_6 protons was due solely to the asymmetric centre on C_7, the diphenyl compound (VI) was synthesized. This compound has no asymmetric centre but the amide moiety was still attached to the methylene group (at C_6). The two Ph groups should not only attenuate any non-equivalence present, but also give signals well clear of the region of prime interest. The spectrum (Fig. 5) resolved the problem as the methylene protons at C_6 appeared at 6·10 τ as the A_2 part of an A_2B system, whilst the proton on C_7, at 5·64 τ, showed the four-line pattern characteristic of the B part of such a system. A detailed analysis gave the constants as set out in Table 1. It appeared therefore that the presence of the neighbouring asymmetric centre on C_7 was the cause of the magnetic non-equivalence of the protons on C_6.

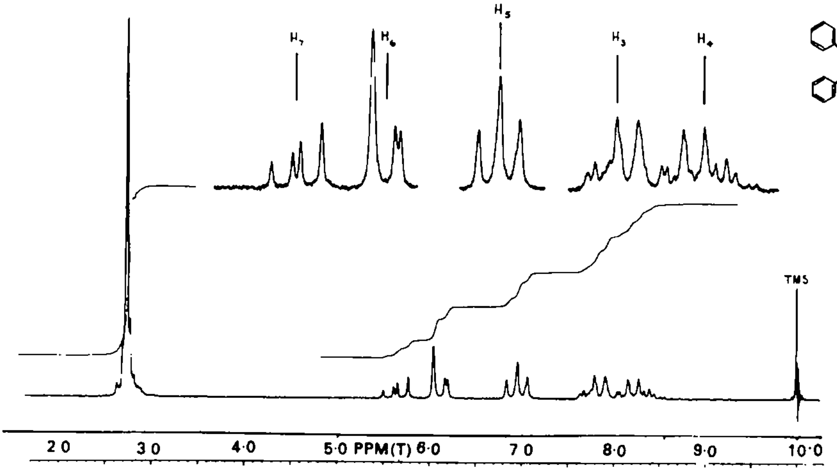


FIG. 5. The NMR spectrum of N-(2′,2′-diphenylethyl)pyrrolid-2-one (VI).

This was confirmed by examination of compound X which has an asymmetric centre, but in which the amide group is absent. In this compound hydrogen bonding played a very much larger role in fixing the conformation, as IR dilution studies confirmed the presence of a very strong intra-molecular hydrogen bond. A considerable difference in the chemical shifts of the C_6 protons was observed in this compound (Fig. 6) and these protons appeared at about the same field as the C_2 and C_5 protons. However, a detailed analysis of the region 7·1–7·7 τ in association with the region at 5·3 τ gave the following constants, H_{6a} = 7·29 τ, H_{6b} = 7·44 τ, H_7 = 5·31 τ, $J_{6a/6b}$ = 12·1 Hz, $J_{6a/7}$ = 9·5 Hz, $J_{6b/7}$ = 4·1 Hz. The protons on the pyrrolidine ring appeared at 7·3 τ–7·6 τ (H_2 and H_5) and 8·15 τ–8·35 τ (H_3 and H_4) respectively. but only an approximate assignment of the chemical shift was possible here. The OH proton at 5·96 τ showed no coupling with the C_7 proton, and rapidly exchanged on D_2O shake, a fact which was a little surprising in view of the infra-red studies.

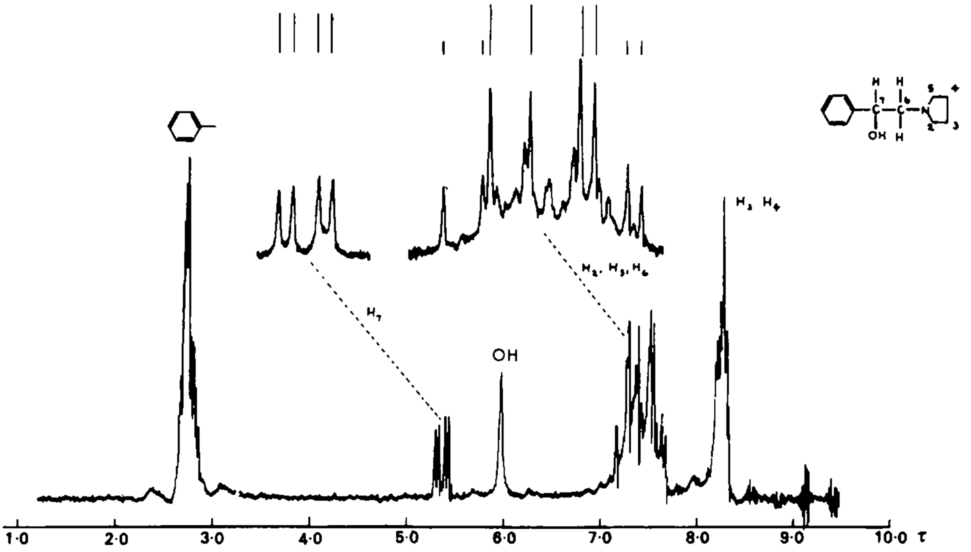


FIG. 6. The NMR spectrum of N-(2′-phenyl-2′-hydroxyethyl)pyrrolidine (X).

As compounds II to V had shown, the presence of substituents on the side chain, even two C atoms removed from the ring, was sufficient to affect the chemical shift of the ring protons, and in VI, the spectrum almost verged on the $A_2M_2X_2$ type. No complete and detailed analysis was possible as the spectrum was the result of time averaging, but some of the constants could be calculated: the chemical shifts were $H_3 = 7·85$ τ, $H_4 = 8·32$ τ and $H_5 = 7·0$ τ the time averaged coupling constants were $J_{3/4} = 6·7$ Hz, and $J_{4/5} = 8·1$ Hz.

As the chemical shifts were affected, it was of interest to investigate further the effects of side chain substituents on the ring protons, and the availability of several olefines from pyrolysis experiments made this possible.[4]

Compound VII, N-(*cis*-2′-phenyl-ethylene)-pyrrolid-2-one, although only obtained mixed with the corresponding *trans*-olefine (VIII), showed a typical AB disubstituted ethylene pattern at 3·20 τ and 4·03 τ, $J_{6/7} = 9$ Hz, and apart from the Ph resonance at 2·74 τ, the rest of the spectrum exhibited the now typical $A_2B_2X_2$ pattern with the C_5 proton at 6·84 τ, and the C_3 and C_4 protons at 7·45 τ and 7·87 τ respectively. The respective coupling constants are set out in Table 1. The *trans*-olefine (VIII) contaminated with some *cis*-olefine (VII) had shown a spectrum very similar to the *cis*-olefine, and the respective constants are set out in Table 1, the spectrum itself being as in Fig. 7. In the diphenyl substituted olefine (IX) however, the chemical shifts of the ring protons were moved up field with respect to the monophenyl olefines, (VII and VIII) and the same analysis as previously applied gave the constants $H_3 = 7·67$ τ, $H_4 = 8·22$ τ and $H_5 = 7·09$ τ, whilst the time averaged coupling constants were $J_{3/4} = 7·0$ Hz and $H_{4/5} = 8·2$ Hz.

An attempt to correlate the chemical shift of the protons on C_3, C_4 and C_5 was not particularly successful, and it would be of doubtful value to try to relate the chemical shifts directly to the electronegativity, as this would ignore the shielding or deshielding effect of the π electrons on the phenyl group. This latter undoubtedly plays a part in the variations in chemical shift observed, for a comparison of compounds II and V will show that although the C_6 protons are at higher field in II than in V, the reverse is true of the C_3, C_4 and C_5 protons. This may be due to the orientation of the phenyl group being fixed in II whilst in V this is not the case. This explanation however, cannot be used to relate IV and V, as in IV, similar chemical shift values to those found in II are obtained, although it is difficult to imagine any stabilization of a conformer.

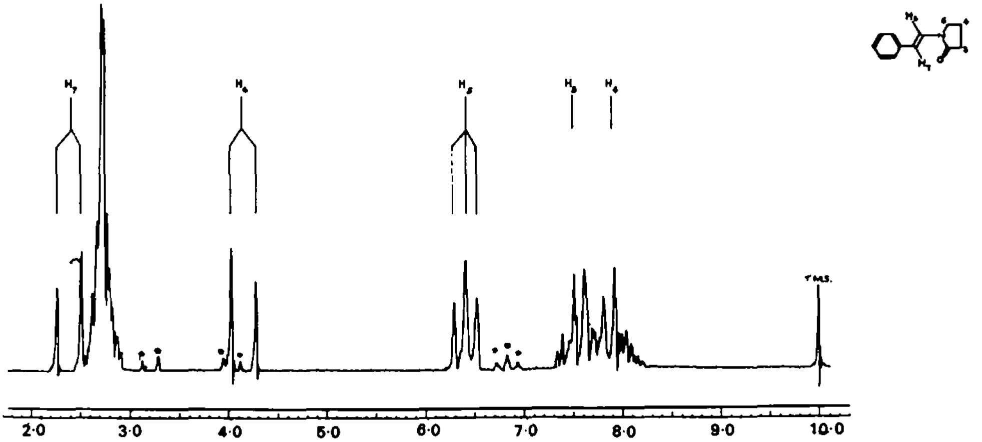


FIG. 7. The NMR spectrum of N-(*trans*-2′-phenylethylene)pyrrolid-2-one (VIII). This spectrum shows some of the peaks (*) due to about 7–8% of the corresponding *cis* olefine (VIII) as contaminent.

Finally it appears that these compounds illustrate the difficulty of projecting shielding parameters obtained from measurements on simple alkanes and alkenes onto complex molecules where orientation considerations are probably more important.

EXPERIMENTAL

The NMR spectra were determined in an approximate 10% solution in $CDCl_3$ using 1% of TMS as internal standard for determining the chemical shifts. Compounds I, II, III, IV, VII and VIII were measured at 60 Mc/s on a Varian A 60A whilst compounds V, VI, IX and X were measured at 100 Mc/s on a Varian HA-100. All compounds were measured at the normal operating temperature.

The preparations of some of these compounds have already been described.[4]

N-(2′2′-*Dimethoxyethyl*)*pyrrolid-2-one* (V). DMSO (purified by chromatography over basic aluminium oxide (Woelm, activation stage 1) (20 ml) was placed in a 3-necked round bottomed flask fitted with stirrer, condenser and dropping funnel, together with an oily suspension (55%) of NaH (5·3 g): Pyrrolid-2-one (10·3 g) was carefully added with vigorous stirring, and after warming, bromacetaldehydedimethyl acetal (20 g) was added to the luke-warm mixture, which was then heated to 80° for 3 hr. After cooling the products were carefully decomposed with water, and the alkaline soln extracted with CH_2Cl_2. After working up, a yellow oil was obtained which was distilled under vacuum; after a small first fraction (b.p. 65°/2 mm), the desired product was obtained as a colourless constant b.p. oil (b.p. 110°/2 mm), which was shown to be pure by TLC. The product was redistilled for analysis. (Found: C, 55·37; H, 8·69; N, 8·23; $C_8H_{15}NO_3$ requires: C, 55·47; H, 8·73; N, 8·09%).

Attempts to prepare this product from the sodium salt of pyrrolid-2-one by reaction with bromacetaldehyde dimethyl acetal in toluene in a Carius tube gave only a mixture of products. From these it was not found possible to isolate V in the pure state. Hydrolysis of this compound with HCl gave the aldehydro derivative from which the dianilinoethane derivative was prepared by adapting the method of Wanzlick and Lochel.[7] Sublimation under vacuum (160°/2 mm) gave a product m.p. 173–174°. (Found: C, 74·60; H, 6·98; N, 13·19. $C_{20}H_{23}N_3O$ requires: C, 74·74; H, 7·21; N, 13·07%).

N-(2'2'-*Diphenyl-ethyl*)*pyrrolid-2-one* (VI). N-(2'2'-Diphenylethylene)-pyrrolid-2-one (5 g) was dissolved in AcOH (50 ml) and hydrogenated at room temp and normal press over PtO_2 (0·2 g). After take-up of the calculated amount of H_2 the experiment was interrupted, the catalyst filtered off, and the AcOH removed in vacuum. The residue was recrystallized from CH_2Cl_2–ether, m.p. 107°–108° (droplets formed after 105°). (Found: C, 81·53; H, 7·27; N, 5·20: $C_{18}H_{19}NO$ requires: C, 81·47; H, 7·22; N, 5·28%).

N-(2'2'-*Diphenylethylene*)*pyrrolid-2-one* (IX). The method of Eiden and Nagar[8] was adapted. Diphenylacetaldehyde (5·9 g) and pyrrolid-2-one (2·6 g) in a round bottom flask fitted with a Dean–Stark apparatus, were heated in benzene (50 ml) with the addition of *p*-toluene sulphonic acid (50 mg) until the calculated amount of water had been eliminated. The benzene was evaporated under reduced press and the residue recrystallized from EtOH (6·7 g, 84·7%), m.p. 134·5° (droplets appearing above 130°). (Found: C, 81·99; H, 6·42; N, 5·28. $C_{18}H_{17}NO$ requires: C, 82·10; H, 6·51; N, 5·32%); IR: 1630 cm^{-1} (C=C), 1697 cm^{-1} (N C=O).

1 *Phenyl-2-piperidino-ethanol* (X). The method of Roth and Brandau[9] was used.

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