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CIRCULAR DICHROISM OF HETEROCYCLOHEXAN-4-ONIC SYSTEMS

PART I—OPTICALLY ACTIVE N-(α-PHENETHYL)-DERIVATIVES OF 4-PIPERIDONE, NORTROPINONE AND NORPSEUDOPELLETIERINE

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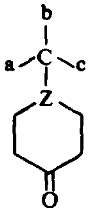
Abstract—New optically active 4-piperidonic compounds possessing an asymmetric group lying in the symmetry plane of the ring were prepared and characterized. Although the carbonyl chromophore is situated 4 σ-bonds away from the asymmetric group, it was nonetheless strongly enough perturbed to exhibit a $n \rightarrow \pi^*$ Cotton effect. N-Epimeric methiodides (4 and 5) of the tropanic system were prepared and found to undergo easy equilibration in aqueous solution. The possible mechanisms of asymmetric perturbation are discussed and their relative importance assessed by comparing the CD data obtained for the bases 1–3 and the methiodides 4 and 5. The conformer populations, their Cotton effect signs and amplitudes, as predicted by Octant Rule and theoretical considerations, were confirmed by CD, assisted by a suitable NMR technique. In the quaternary compounds the epimer having the asymmetric group in the axial position, gave rise as predicted to the strongest Cotton effect, an observation which, if proved general, will allow the assignment of N-stereochemistry by CD.

THE conformational and configurational problems which have arisen in the tropanic and other piperidonic systems have been investigated by various methods of which the most important are: NMR,[1] X-ray crystallography,[2] dipole-moment,[3] kinetic measurements,[1c] IR spectroscopy[4] and chemical methods.[1]

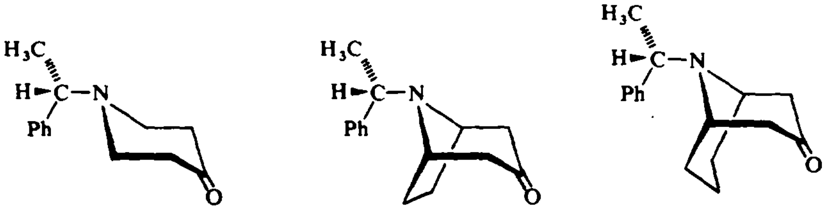
We wish to present a new approach to the above problems based on a study of the CD spectra of 4-piperidonic and related heterocyclic systems and, more generally, of systems of the general formula (i).



(i) Z = N,C,P,$S^{\oplus}$

Such compounds should yield valuable information about the conformation of Z (when Z = tertiary N) or its configuration (when Z = C, P, $S^{\oplus}$ or $N^{\oplus}$) if, as it turned out, the asymmetric group bound to Z were to perturb the symmetrical C=O chromophore strongly enough to produce an observable Cotton effect. Compounds of the general formula (I) seemed very attractive for the proposed study because the asymmetric centre lies in the symmetry plane of the ring, and interesting comparisons could be made by changing the bulk and the electronic properties of the groups a, b, c.

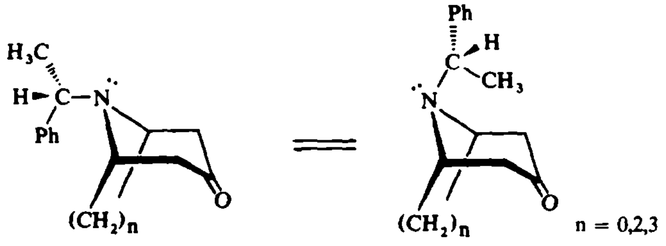
Of the many compounds prepared and tested, the (S)-N-(α-phenethyl) substituted systems (1–3) are reported in this first paper.



1 2 3

SCHEME 1

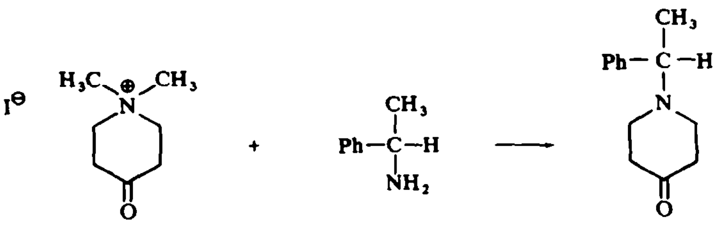
Three stereochemical models were chosen, all containing a 4-piperidonic ring, but differing greatly in ring mobility, strain and sterical requirements in the two "nitrogen conformers", (ax) and (eq).



1-3 (eq) 1-3 (ax)

SCHEME 2

(S)-N-(α-phenethyl)-4-piperidone (1) was prepared from N-methyl-4-piperidone methiodide, by a method essentially described in the literature.[5]



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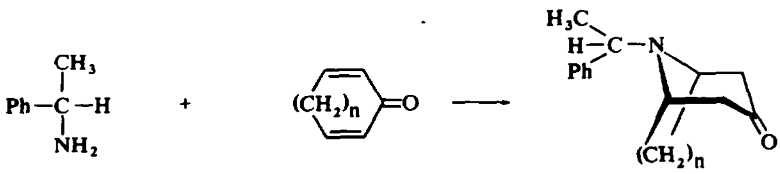
The reaction which probably proceeds through the corresponding enone intermediates afforded compound **1**, which is unstable in acid medium, and was characterized by its NMR, IR and mass spectrum which showed the expected pattern (Experimental).

The new bicyclic compounds: (S)-8-(α-phenethyl)-8-azabicyclo[3.2.1]octan-3-one (**2**) and (S)-9-(α-phenethyl)-9-azabicyclo[3.3.1]nonan-3-one (**3**) were prepared by the Robinson–Schöpf synthesis of the tropinone and pseudopelletierine systems,[6] using optically active (S)-(−)α-phenethylamine.[7]

Alternatively, these and other related compounds were also prepared by a new method, similar to that described[8] for the 8-phosphabicyclo[3.2.1]octanic system.



n = 2 or 3

2 n = 2
3 n = 3

This method will be described in more detail in a subsequent report. The NMR, mass spectra, IR and UV unequivocally confirm the proposed structures of **2** and **3** (Experimental). Owing to the asymmetry, the C_1 and C_5 protons as well as the C_2 and C_4 protons show distinct signals, this observation and its possible use in the conformational analysis is being further investigated.

Although, *a priori*, it was not certain that compounds such as **1**–**3** would exhibit measurable Cotton effects for the carbonyl chromophore, their CD and ORD spectra did actually show Cotton effects in the 290 nm region (Table 1 and Fig 1). These

TABLE 1. THE n → π* CARBONYL ABSORPTION OF 4-PIPERIDONIC COMPOUNDS: CD, ORD AND UV

Compound	CD, θ(λ)			ORD, α(λ)	UV, ε(λ)
	H_2O	CH_3OH	isooct.	CH_3OH	H_2O
1	1270 (285)	—	1320 (297)	—	—
2	2200 (288)	2100 (292)	1290 (299)	31 (275, trough) (311, peak)	23 (282)
3	1350 (285)	—		—	34 (280)
4	3150 (291)	2930 (295)	Insol.	36 (270, trough) (317, peak)	*a*
5	1800 (291)	—	—	—	*a*

[a] Submerged by a strong absorption at lower wavelength.

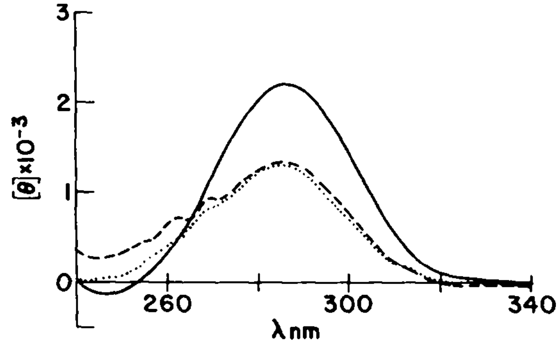


FIG 1. CD of 1 · · · · · ·, 2 ——— and 3 - - - - - in water at r.t.

bands were assigned to the carbonyl n → π* transition, the assignation being based on the following facts:

(a) The maxima in the CD and UV spectra of 1–3 (285–299 nm) as well as the ORD midpoint (293 nm) appear at the wavelength expected for the n → π* transition, and are red-shifted in solvents less polar than water. The transition energies (E_T) plotted against the appropriate Kosower Z values[9] afforded a straight line whose equation is:

$$E_T = 0{\cdot}11\,Z + 88{\cdot}6 \qquad (1)$$

CD measurements recorded in aqueous, methanolic and isooctanic solutions, showed the expected order of amplitudes (see Table 1 and Fig 2).

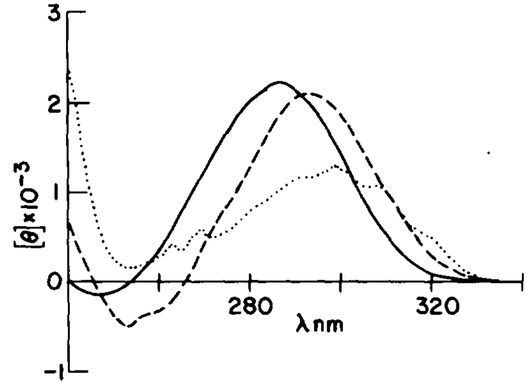


FIG 2. CD of 2 in water ———, methanol - - - - - and isoctane · · · · · · at r.t.

(b) The reduction of the ketone in compound 2 results in the total disappearance of the 288 nm band, thus proving its asymmetrically perturbed carbonyl origin.

The fine structure pattern in the CD spectrum (Fig 1), appearing as shoulders on the broad n → π* absorption of 1–3 at $\lambda = 255, 261, 267$ nm was assigned to the ^1L_b transition of the phenyl chromophore. These shoulders, barely noticeable in neutral aqueous solution, are intensified in isooctane or on acidification. In the UV spectra of compounds 2 and 3, the same shoulders were observed, submerged in a much stronger

$\pi \rightarrow \pi^*$ absorption appearing at lower wavelength. On acidification, four distinct bands, free from background absorption appeared at $\lambda = 252, 258, 263, 268$ nm ($\varepsilon = 192, 247, 232, 164$) in the aqueous solution of compound **2**. The origin of other bands appearing at lower wavelengths in the CD spectra of **1–3** is being presently investigated.

The inherently symmetrical carbonyl chromophore in **1–3** can possibly be perturbed by the asymmetric group in one or more of the following ways: through bonds, through space[18] and/or by coupling with the asymmetrically perturbed nitrogen lone-pair. A direct transannular interaction between the ketone and the nitrogen, as observed in larger ring amino-ketones,[10a] may be disregarded in our case, as implied by infrared and dipole-moment studies.[10b]

In a recent communication by Hudec[11] dealing with α- and β-amino-ketones, it was postulated that the coupling between the nitrogen lone-pair and the carbonyl is responsible for the enhancement of the $n \rightarrow \pi^*$ absorption in UV and CD, and the appearance of a new band at 220–240 nm (which is probably a split $\pi \rightarrow \pi^*$ transition). Moreover, the effect of this coupling is dependent on the geometry of the molecule. In our 4-piperidonic systems in which, in contrast to the above mentioned compounds, the chiral substituent on N is the only one responsible for the $C{=}O$ perturbation, enhancement should take place only in the axial N-conformer, whereas in the equatorial isomer, anti-octant behaviour is predicted. The coupling between the carbonyl and the asymmetrically perturbed nitrogen lone-pair should thus be regarded as a possible mechanism of perturbation, whose contribution remains to be established.

The systems **1–3** possess ring mobility to various extents, and are expected to exist as an equilibrium mixture of the different ring conformers. According to present knowledge of tropane stereochemistry[12] and from thermodynamical expectations of N-substituted 4-piperidonic systems,[13] the chair conformers should form the vast majority of the equilibrium mixture. For compound **3** this assumption is on less secure ground but even in this case recent findings[14] show that the chair–chair (Scheme 1) conformation prevails. In addition, the N-substituent may occupy the equatorial or the axial position to the 4-piperidonic ring (Scheme 1). Compound **1** is expected to exist almost exclusively as the equatorial conformer,[13] whereas in **2** and **3** the population of the axial conformer cannot be neglected.

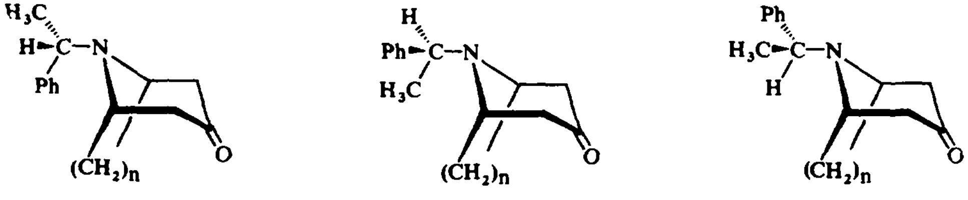
If one assumes in first approximation, that the two N-conformers of the chair form are mainly responsible for the intensity of the Cotton effect, it follows that the amplitude of the total observed effect may be derived from Eq (2).

$$\theta_T = \theta_{ax} \cdot X_{ax} + \theta_{eq} \cdot X_{eq} \qquad (2)$$

For conformers possessing effects of identical signs the above equation is easily relatable to the experimental curve. When the signs are opposite, however, the matter is somewhat complicated.[15a,b] Wellman *et al.*,[15a] showed, that "when two oppositely signed CD curves of similar amplitude are overlapping strongly, the resulting apparent rotational strengths are only a fraction of those of the contributing curves. Double-humped CD curves are observed in such cases, the form depending on the wavelength separation of the maxima and on the amplitudes of the original individual CD curves".

In this context, it was of utmost importance to establish whether the two N-conformers exhibit Cotton effects of identical or opposite signs.

The application of the Octant Rule to the tertiary bases **1**–**3** was complicated by the existence of rotation about the C-N bond. However, conformational analysis and inspection of the Drieding models revealed that the rotamers having the hydrogen on the asymmetric carbon situated in the ring symmetry plane (Scheme 3c) should be greatly preferred. This preference is somewhat less for compound **1**, where the absence of the methylene bridge reduces the energy differences between the rotamers.



n = 0,2,3 **a** **b** **c**

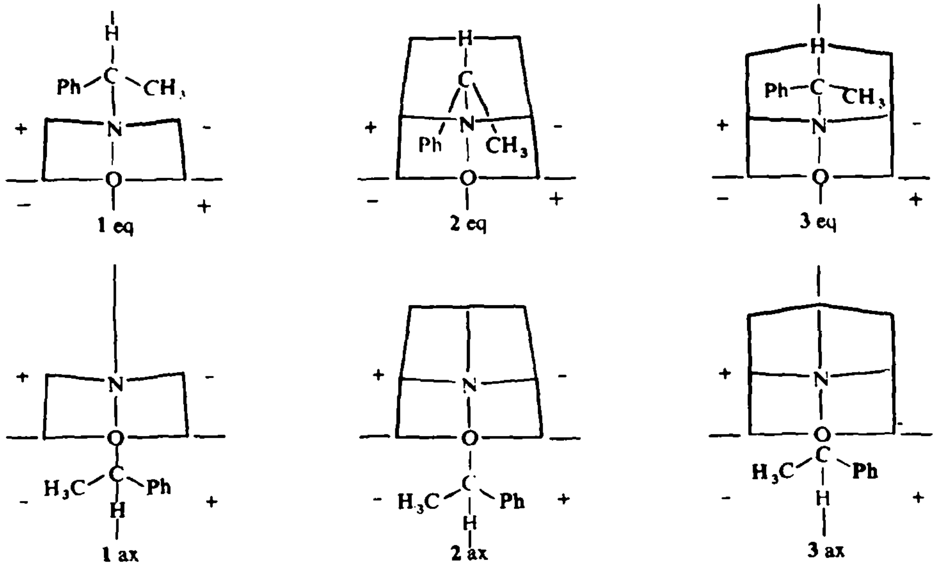
SCHEME 3. C-N rotamers of **1**–**3**

Supposing that the contribution of rotamers **a** and **b** is negligible, both the axial and the equatorial N-conformers should exhibit positive Cotton effects, in accordance with the Octant Rule. It is implied, of course, that the phenyl group prevails over the Me in deciding the sign (Chart 1).

It must be emphasized that, whereas the conclusions from the Octant Rule are obtained on models of individual N-conformers, the actual measurements are effected on an equilibrium mixture whose total Cotton effect is probably given by Eq (2). In the event, the measured $n \rightarrow \pi^*$ Cotton effects of compounds **1**–**3** (Table 1) in several solvents, were found to be positive.

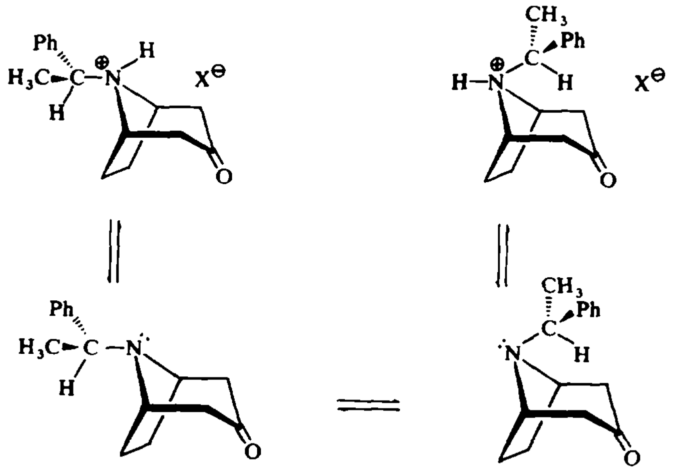
CHART 1

Application of octant rule to systems **1**–**3**



The positive sign of the Cotton effect for **1** (almost exclusively equatorial) supports the expectation that the **1-3** (eq) N-conformers, should all exhibit positive effects, as predicted by the Octant Rule (Chart 1). The relatively small influence of solvents of very different polarities on the shape of the n → π* Cotton effects (Fig 2) points to a mixture of conformers of identical signs.* Furthermore, the fact that the axial methiodide **4** exhibits a positive Cotton effect is a strong evidence that the effects of the axial N-conformers of **1-3** should also be positive. In conclusion, both N-conformers exhibit positive Cotton effects, in agreement with the Octant Rule prediction. As to the intensities of the effects, one would expect the axial conformers to give rise to a stronger Cotton effect than the equatorial ones, owing to the closeness of the chiral substituent to the carbonyl chromophore, and perhaps also to better coupling with the nitrogen lone-pair.[11] Consequently, **2**, in which (contrary to **1**) the population of the axial conformer cannot be neglected, should exhibit a stronger effect than **1**. This was indeed the case, confirming the assumptions about the relative intensity and sign of the conformers (Table 1). According to the same rationale the similarity of the results for **1** and **3** may indicate that the latter exists mainly in the equatorial form.

The conformer populations in **2** and **3** were independently assessed by an NMR technique developed by Closs.[16] The method is based on the observation that, on strong acidification, the exchange-rate between the protonated conformers is greatly reduced, and separate signals are obtained for the equatorial and the axial conformers.



In D_2O solution acidified with DCl to pH ≃ 1, 2 showed two doublets for the methyl (deuterated reagents were used in order to avoid further peak multiplication by the acidic proton). Whereas this method was previously applied to N-Me compounds, we found that the Me group situated one bond further showed a similar behaviour, obviously with a smaller Δδ value. According to Closs,[16] conformer populations in acidified solution should not differ greatly from those in the free bases, as the steric requirements of the lone pair and of the proton are similar.

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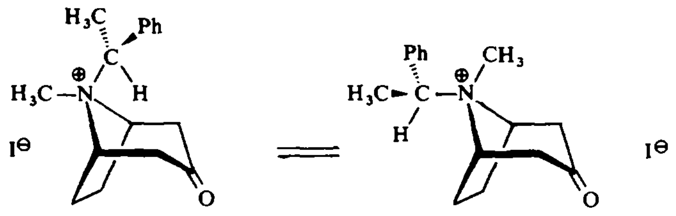
* It is known that, some conformer mixtures where the signs of the individual conformers are opposite, show dramatic changes in the shape of their Cotton effects, on changing the solvent (see also ref. 15a).

Based on this assumption, the following populations for **2** were obtained from the integration ratio: $X_{eq} \simeq 0{\cdot}66$ and $X_{ax} \simeq 0{\cdot}33$. The values obtained for **3** were $X_{eq} \simeq 0{\cdot}85$ and $X_{ax} \simeq 0{\cdot}15$, which is in agreement with the conclusion drawn from CD data (see above).

Using the above approximate values, and supposing that the Cotton effect amplitude of **2** (eq) is well enough approximated by that of **1**, Eq (2) affords a value of $\theta_{ax} \simeq 4000$ for the axial conformer **2** (ax). This value, approximate as it is, is in agreement with our earlier assumption that the axial N-conformer exhibits a stronger Cotton effect than the equatorial one.

Additional support was obtained by studying the CD spectra of the methiodides **4** and **5**.



4 **5**

The importance of these methiodides stems from the following:

(a) The α-phenethyl group is situated in a fixed configuration.

(b) Owing to the quaternization, the coupling between the nitrogen lone-pair and the carbonyl, present in the free base, is no longer existent, thus, allowing for the assessment of its contribution.

The reaction of **2** with methyl iodide in acetone yielded mainly one methiodide, to which structure **4** was tentatively assigned, based on the consensus[1a] that in tropane quaternization the last group entering, preferentially occupies the equatorial position. A small amount of the other methiodide **5**, was detected by NMR in the reaction mixture. On recrystallizing the methiodide **4** from water, it was found that it underwent equilibration to a mixture of **4** and **5**. This discovery was quite surprising as Fodor[1a] reported that a strong base as aluminium t-butoxide is needed for such a process. The equilibration was followed by NMR at room temperature and was found to be almost complete after 48 hr, yielding a mixture of **4** and **5** in 40% and 60% respectively. By fractional recrystallization from ethanol, the more soluble methiodide **5** could be obtained in more than 95% purity.* The relative chemical shifts of $CH_3C\underline{H}Ph$, N—$C\underline{H}_3$ and $C\underline{H}_3$ CHPh (ref 1*a* and Experimental) as well as the CD data (*vide infra*) support the structural assignments (Table 1). The equilibrium populations are similar to those obtained for the hydrochlorides by the method of Closs,[16] although the species involved are somewhat different. Qualitatively, both results point to the equatorial isomer as the thermodynamically preferred.

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* The aqueous solution of **5** yielded, after 48 hrs the same equilibrium mixture as **4**, as shown by NMR and CD. The latter measurement excludes the possibility of racemization as the cause for amplitude decrease on equilibration.

Both methiodides **4** and **5** have positive Cotton effects as was presupposed for the conformers **2** (ax) and **2** (eq) and, most important, the axial epimer (**4**) shows a greater effect than the equatorial one (**5**). This result is, most probably, due to a greater contribution of the through-space perturbation mechanism in the former. The above observations could, if proved general, be used as a new method for the assignment of nitrogen stereochemistry in the quaternization of the 4-piperidonic and similar systems.

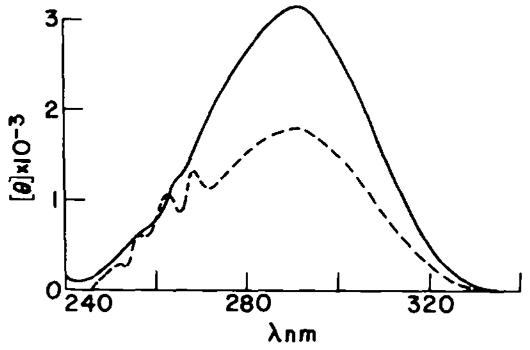

FIG 3. CD of **4** ——— and **5** ----- in water at r.t.

The Cotton effect amplitude of **1** (mostly equatorial) is lower than that of **5**, while the approximated value for **2** (ax) ($\theta_{ax} \simeq 4000$) is higher than that of **4**. This relationship seems to agree with the predictions of J. Hudec about anti-octant behaviour (amplitude reduction) or enhancement of the $n \rightarrow \pi^*$ transition as a function of the geometry of the molecule (the influence of the quaternization of the nitrogen on the $n \rightarrow \pi^*$ effect amplitude, if any, has to be established). More compounds of type **1**–**3** are presently being studied in order to obtain a more general conclusion.

The scope of the present research will be broadened by measurements of compounds containing different a, b, c groups as in formula (i) which will allow comparisons to be made as to group contribution to the Cotton effect as a function of bulk and electronic properties.

EXPERIMENTAL

M.ps were taken on a Unimelt Thomas and Hoover's capillary m.p. apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer Infracord model 337 spectrophotometer, UV spectra were recorded on a Cary 14 UV spectrophotometer. NMR spectra were taken on a Varian HA-100 spectrometer on 5–10% solutions in $CDCl_3$ (unless otherwise indicated), containing TMS as an internal standard and chemical shifts are quoted in units of δ. Mass spectra were taken with a Hitachi Perkin–Elmer RMU 6 instrument. CD and ORD spectra were taken on a Cary 60 Recording Spectropolarimeter with the Model 6000 CD attachment.

(S)-N-(α-*Phenethyl*)-4-*piperidone* (**1**)

N-methyl-4-piperidone methiodide (2·55 g) was reacted with (−)-1-phenylethylamine (1·2 g) ($[\alpha]_D^{20} = -39 \pm 1°$, Fluka AG) by a method similar to that described[5] to give 2 g crude product. Following repeated chromatography on neutral Al_2O_3, compound **1** was obtained as an oil: ν_{max}^{neat} 2950, 1710, 1450, 1350, 1180, 700 cm^{-1}: NMR 1·36 (d, J = 6·5 Hz, $C\underline{H}_3CHPh$), 2·52 (m, ring protons (8H)), 3·55 (q, J = 6·5 Hz, $CH_3C\underline{H}Ph$), and 7·20 (m, Ph). Mass spectrum *m/e* 203 ($M^{\oplus\cdot}$ 7%); 188 ($M^{\oplus\cdot}$ —CH_3, 100%, m* 174) and 105 ($Ph\overset{\oplus}{C}HCH_3$, 70%).

(S)-8-(α-*Phenethyl*)-8-*azabicyclo*[3.2.1]*octan*-3-*one* (2)

(a) 2,5-Dimethoxyfuran (5 g) was reacted with (−)-1-phenethylamine (10 g) and acetone dicarboxylic acid (11·1 g) according to the Robinson–Schöpf method.[6a] The crude product was chromatographed through neutral Al_2O_3 to yield a solid, m.p. 65–67° (light petroleum): ν_{max}^{neat} 2950, 1720, 1600, 1490, 1450, 1350, 1190, 1130, 1000, 700: NMR 1·40 (d, $J = 6$ Hz), 1·55 (m, C_6,C_7 protons (2H)), 1·98 (m, C_6,C_7 protons (2H)), 2·17 (m, 2 α-H and 4 α-H), 2·64 (m, 2 β-H and 4 β-H), 3·49 (m, 1-H), 3·64 (m, 1-H), 3·64 (m, 5-H), 3·74 (q, $J = 6$ Hz, $Ph\overset{\oplus}{C}\underline{H}CH_3$) and 7·30 (m, Ph). Mass spectrum *m/e* 229 ($M^{\oplus}$, 73%), 214 ($M^{\oplus}$—CH_3, 35%) and 105 (Ph $CHCH_3$, 100%). (Found: C, 78·43; H, 8·15; N, 6·28. $C_{15}H_{18}NO$ requires: C, 78·56; H, 8·35; N, 6·11%). Hydrochloride, m.p. 205–6° (dec) (i-PrOH), ν_{max}^{KBr} 2940, 2500, 1720, 1490, 1380, 765 and 705 cm^{-1}: NMR (D_2O) 2·00 (d, $J = 6·5$ Hz, CH_3): NMR (in D_2O + DCl to pH ~ 1) 2·03 (d, $J = 6·5$ Hz, CH_3 (ax)) 2·06 (d, $J = 6·5$ Hz, CH_3 (eq)), 4·56 (q, $J = 6·5$ Hz, $PhC\underline{H}CH_3$ (eq)), 5·18 (q, $J = 6·5$ Hz, $PhC\underline{H}CH_3$ (ax)); (δ's are pH-dependent).

(b) A mixture of cyclohepta-2,6-dienone[17] (2 g) and (−)-1-phenethylamine (2·2 g) in methanol (25 ml) was left at r.t. overnight. When the reaction was over, according to G.C. and the IR spectrum of the mixture (i.e. disappearance of the band at 1650 cm^{-1} and appearance of the CO band at 1700 cm^{-1}) the soln was evaporated and the residue worked up as in method (a) to give **2** (70% yield).

(S)-9-(α-*Phenethyl*)-9-*azabicyclo*[3.3.1]*nonan*-3-*one* (3)

(a) Compound **3** was prepared from a 50% aqueous soln of glutaraldehyde following the procedure described for **2**: m.p. 70° (hexane) ν_{max}^{neat} 1710 cm^{-1}: NMR 1·34 (d, $J = 6·5$ Hz, $C\underline{H}_3CHPh$), 1·40–2·00 (m, C_6, C_7 and C_8 protons (6H)), 2·00–2·82 (m, C_2 and C_4 protons (4H)), 3·32 and 3·56 (m, C_1 and C_5 protons (2H)), 3·98 (q, $J = 6·5$ Hz, $CH_3C\underline{H}Ph$), 7·30 (m, Ph). NMR (in D_2O acidified with DCl to pH ≃ 1), 2·035 (d, $J = 6·5$ Hz, CH_3 (ax)), 2·05 (d, $J = 6·5$ Hz, CH_3 (eq)). (Found: C, 78·80: H, 8·95; N, 5·85, $C_{16}H_{21}NO$ requires: C, 78·97; H, 8·70; N, 5·76%): hydrochloride, m.p. 242–244° dec (EtOH); ν_{max}^{KBr} 2900, 2500, 1720, 1170, 765, 710 cm^{-1}.

(b) A mixture of cycloocta-2,7-dienone[17] (2 g) and (−)-1-phenethylamine (2 g) in MeOH (25 ml) was left at r.t. overnight; following work up as described for **2**, compound **3** was obtained.

N_a(α-*Phenethyl*)-3-*oxotropanium iodide* (4)

A soln of **2** (1 g) in acetone (10 ml) eas refluxed for 48 hr with an excess of MeI. The solid separated, (0·7 g) was filtered off and recrystallized, m.p. 185–6° dec; (95% EtOH); ν_{max}^{KBr} 2940, 1725, 1480, 1445, 1210, 1110, 1090, 1060, 870, 775 and 715 cm^{-1}: NMR 2·10 (d, $J = 6·5$ Hz, $C\underline{H}_3CHPh$), 3·20 (s, $C\underline{H}$—N), 3·88 and 4·08 (m, 1-H and 5-H), 5·70 (q, $J = 6·5$ Hz, $CH_3C\underline{H}Ph$), 7·79 (m, Ph). (Found: C, 51·61: H, 6·08: N, 4·04: I, 34·43, $C_{16}H_{22}INO$ requires: C, 51·76: H, 5·97; N, 3·77 and I 34·18%).

N_b-(α-*Phenethyl*)-3-*oxotropanium iodide* (5)

Compound **4** (0·5 g) was dissolved in water (20 ml) and allowed to stand at room temp for 48 hr (when equilibration was complete), evaporated to dryness and fractionally crystallized from 95% EtOH. The first two crops consisted mainly of **4**; the third crop was almost pure **5** (≥95% by NMR), m.p. 155°–156° dec.; ν_{max}^{KBr} 2930, 2870, 1720, 1460, 1205, 1085, 1055, 990, 805, 770, 710 cm^{-1}; NMR (2·05 (d, $J = 6·5$ Hz, $C\underline{H}_3CHPh$), 3·39 (s, $C\underline{H}_3$—N), 4·31 and 4·75 (m, 1-H and 5-H), 5·16 (q, $J = 6·5$ Hz, $CH_3C\underline{H}Ph$), 7·75 (m, Ph). (Found: C, 51·74; H, 6·02; $C_{16}H_{22}INO$ requires: C, 51·76; H, 5·97%).

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REFERENCES

[1] [a] G. Fodor, R. V. Chastain, Jr., D. Frehel, M. J. Cooper, N. Mandava and E. L. Gooden, *J. Am. Chem. Soc.* **93**, 403 (1971);

[b] J. McKenna, *Topics in Stereochemistry* (Edited by E. L. Eliel and N. L. Allinger) Vol 5, 1970 pp. 275–308, Interscience, N.Y. (1970);

[c] R. A. Y. Jones, A. R. Katritzky and P. G. Mente, *J. Chem. Soc.* (B), 1210 (1970)

[2] P. Benci, C. H. Stam and C. H. MacGillavry, *Tetrahedron Letters* No. 3, 243 (1970)

[3] J. M. Eckert and R. J. W. LeFêvre, *J. Chem. Soc.* 3991 (1962)

[4] J. McKenna, J. M. McKenna, A. Tulley and J. White, *J. Chem. Soc.*, 1711 (1965)

[5] E. A. Mistryukov, N. J. Aronova and V. F. Kucherov, Isvest. *Akad. Nauk SSSR Otdel Khim. Nauk.* **5**, 932 (1961)

[6] N. Elming, *Advances in Organic Chemistry* Vol. II, p. 67. Interscience, N.Y. (1960); [b] K. Ziegler and H. Wilms, *Liebigs Ann.* **567**, 1 (1950); [c] C. F. Boehringer and Soehne Gmb-H, Netherland Appl. 284, 570; *Chem. Abstr.* **63**, 4354 (1965)

[7] H. E. Smith, S. L. Cook and M. E. Warren, Jr., *J. Org. Chem.* **29**, 2265 (1969)

[8] Y. Kashman and O. Awerbouch, *Tetrahedron* **26**, 4213 (1970)

[9] E. M. Kosower, *J. Am. Chem. Soc.* **80**, 3253 (1958)

[10] [a] N. J. Leonard, J. A. Adamcik, C. Djerassi and O. Halpern, *Ibid.* **80**, 4858 (1958); [b] N. J. Leonard, D. F. Morrow and M. T. Rogers, *Ibid.* **79**, 5476 (1957)

[11] J. Hudec, *Chem. Comm.* 829 (1970)

[12] G. Fodor, *The Tropane Alkaloids*, in *Alkaloids* (Edited by R. H. F. Manske), Vol. IX, pp. 263–303, Academic Press, N.Y. (1967)

[13] R. A. Y. Jones, A. R. Katritzky, A. C. Richards and R. J. Wyatt, *J. Chem. Soc.* 122, (1970)

[14] C. Y. Chen and R. J. W. LeFêvre, *J. Chem. Soc.* (B), 539 (1966)

[15] [a] K. M. Wellman, P. H. A. Laur, W. S. Briggs, A. Moscowitz and C. Djerassi, *J. Am. Chem. Soc.* **87**, 66 (1965); [b] See also W. Kuhn, *Ber. Dtsch. Chim. Ges.* **63B**, 190 (1930)

[16] G. L. Closs, *J. Am. Chem. Soc.* **81**, 5456 (1959)

[17] E. W. Garbisch, *J. Org. Chem.* **30**, 2109 (1965)

[18] R. Hoffmann, *Accounts Chem. Res.* **4**, 1 (1971)