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CIRCULAR DICHROISM OF HETEROCYCLOHEXAN-4-ONIC SYSTEMS—II

THE SYNTHESIS OF THE 8-AZABICYCLO [3,2,1] OCTANIC SYSTEM

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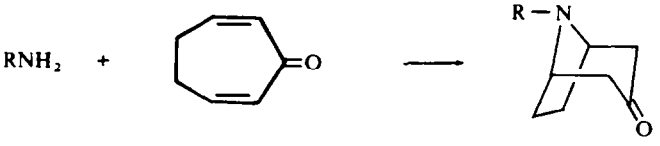
Abstract—The double Michael addition of amines to cyclohepta-2,6-dien-1-one was developed as a convenient and general method for the synthesis of new optically active N-substituted-nortropinones suitable for CD research (N-alkyl, N-aralkyl, N-cycloalkyl, N-carboalkoxyalkyl) as well as N-aryl-nortropinones; the structures proposed for the above compounds were confirmed by their NMR and mass spectra. The influence of the chiral N-substituent on the bicyclic skeleton protons, as seen in NMR, and its applications in conformational analysis are discussed. $Eu(dpm)_3$ complexation was used for a more accurate interpretation of the NMR spectrum.

WHILE CONDUCTING research on the stereochemistry of the tropanic and other piperidonic systems, a great number of new N-substituted nortropinones and norpseudopelletierines had to be prepared. Our main concern was in optically active compounds suitable for CD research; additionally, we were interested in the NMR study of the above and of the previously unknown N-aryl nortropinones.

Although the known Robinson-Schöpf synthesis[1] could be used, an alternative method was preferred, which proved itself suitable for a variety of N-substituted-nortropinones:

a. Optically active N-alkyl, N-aralkyl and N-cyclolkyl-nortropinones.
b. Optically active N-carboalkoxyalkyl-nortropinones (derived from esters of amino-acids).
c. N-Aryl-nortropinones.

The synthesis consists of a double Michael addition of the corresponding optically active amine or arylamine to cyclohepta-2,6-dien-1-one.[2]



This type of reaction was suggested by Horak[3] and used by us in the synthesis of N-(α-phenethyl)nortropinone, N-(α-phenethyl)norpseudo-pelletierine[4] and the 8-phosphabicyclo [3.2.1] octanic system.[5] While the Robinson-Schöpf synthesis is sensitive to reaction conditions, the synthesis *via* dienone proved itself simple, free of side-products and suitable for the preparation of a host of compounds, under almost the same experimental conditions.

TABLE 1. NMR SPECTRA OF ADDUCTS OF ALKYLAMINES, CYCLOALKYLAMINES AND ESTERS OF AMINO ACIDS

Compd.	N-substituent		1H, 5H	2H, 4H (*ax*)	2H, 4H (*eq*)	6H, 7H (*endo*)	6H, 7H (*exo*)	$\Delta\delta_{2\beta,4\beta}$
1	$-CH_3$	2·47s	3·43 m	2·67 (4·5 : 16)	2·15 (1 : 16)	2·0–2·25	1·44–1·72	—
2	CH_3 | CH_2 | $-CH$ | CH_3	0·94t (J = 7) 1·44q (J = 7) 2·66 m 1·15 d J = 6·5	3·75 m	2·62 (4 ; 15)	2·14 (1·5 : 15)	1·75–2·15	1·50–1·75	~0·01*
3	C_6H_{11} | $-CH$ | CH_3	1·10–2·05 2·68 m 1·03 d (J = 6·5)	3·70 m	2·61 (4 ; 15)	2·10 (1·5 : 15)	1·70–2·05	1·40–1·70	~0·01*
4	Ph | $-CH$ | CH_3	7·30 m 3·74 q (J = 6) 1·40 d (J = 6)	3·49 m 3·64 m	2·66 (4·5 ; 16) 2·63 (4·5 : 16)	2·10 (1·516) 2·10 (1·5 ; 16)	1·70–2·10	1·40–1·70	0·03
5	CO_2CH_3 | $-CH$ | CH_3	3·75 s 3·50 q (J = 6·6) 1·42 d (J = 6·6)	3·63 m	2·74 (4·5 : 16) 2·63 (4 : 16)	2·18 (2 ; 16) 2·20 (2 : 16)	1·80–2·16	1·50–1·80	0·11
6	CO_2Bu^t | $-CH$ | CH_3	1·48 s 3·33 q (J = 6·5) 1·36 d (J = 6·5)	3·66 m	2·72 (4 ; 16) 2·60 (4 ; 16)	2·18 (1·5 ; 16) 2·16 (1·5 : 16)	1·80–2·25	1·50–1·80	0·08
7	CO_2CH_3 | $-CH$ | CH_2 | Ph	3·53 s 3·68 m (ABX) 3·08 m (*ABX*) 7·20 m	3·68 m	2·72 (4 ; 15·5) 2·64 (4 ; 15·5)	2·20 (1·5 ; 15·5) 2·21 (1·5 ; 15·5)	1·80–2·20	1·50–1·80	0·08
8	CO_2CH_3 | $-CH$ | CH | $(CH_3)_2$	3·70 s 3·22 d (J = 7) 1·99 d ; 2·03 d (J = 7)	3·61 m	2·68 (4·5 ; 15·5) 2·58 (4·5 ; 15·5)	2·22 (1·5 ; 15·5) 2·22 (1·5 ; 15·5)	1·75–2·15	1·45–1·75	0·10

TABLE 1 *Contd.*

Compd.	N-substituent	1H, 5H	2H, 4H (*ax*)	2H, 4H (*eq*)	6H, 7H (*endo*)	6H, 7H (*exo*)	$\Delta\delta_{2\beta,2\beta}$
9	CO_2CH_3 3·67 s | —CH 4·34 s | Ph 7·34 (3H); 7·55 (2H)	3·44 m	2·76 (4·5; 15) 2·66 (4·5; 15)	2·18 (1·5; 15) 2·18 (1·5; 15)	1·80 2·15	1·45 1·76	0·10

* Estimated value.

Actually, the addition of the amines to cyclohepta-2,6-dien-1-one was performed in methanolic solution at room temperature (series a, b) or at reflux (series c) and monitored by GC or IR (experimental). Although the less basic arylamines required more drastic reaction conditions, yields remained quite good. After purification, the tropinones obtained were characterized by their NMR (Tables 1,2) mass spectra (Table 5) IR and elemental analysis.

In the stereochemical research of the tropanic and related systems, the NMR was one of the most important tools;[6-8] in this field the study of the new optically active compounds described in this paper represents a novel approach. Additionally, the interpretation of the NMR spectrum of tropinone itself, seems to us arguable in light of the contradictory literature data.[8,9] In an effort to assign more accurately the various signals, we studied the spectra of the above compounds and also the complexation of N-phenyl-nortropinone (**10**) with tris(dipivalomethano) europium(III) ($Eu(dpm)_3$).

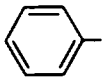
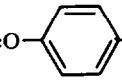
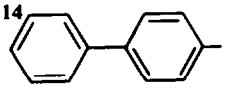
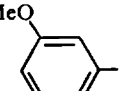
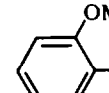
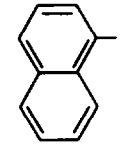
The NMR spectra of N-aryl-nortropinones **10–16** show at high field, five distinct signals for the various skeleton proton groups (Table 2), the pattern being similar to that observed for tropinone itself.[8] Whereas the identification of the $C_1(C_5)$, $C_2(C_4)$ and $C_6(C_7)$ *endo* and *exo** proton groups is quite easy, being based on their chemical shifts, the distinction between $C_2(C_4)$ axial and equatorial ones is not straightforward.

The $C_2(C_4)$ axial and equatorial protons together with the $C_1(C_5)$ proton give rise to an ABX system; Ohashi *et al.*[8] attributed the upfield part of the AB group to the axial rather than to the equatorial $C_2(C_4)$ protons. We arrived at the opposite conclusion, based on the different coupling constants observed in the two halves of the AB pattern. The latter observation points to different dihedral angles[10] between C_1–H/$C_{2\alpha}$–H and C_1–H/$C_{2\beta}$–H, *i.e.* ring deformation towards a more planar form as already suggested.[8,9,11] Inspection of the Dreiding model, deformed as above, and use of Karplus equations allows the assignment of the greater coupling constant (4·0–4·5 Hz) to $C_{2\beta}$–H($C_{4\beta}$–H) and the smaller one (1–2 Hz) to $C_{2\alpha}$–H($C_{4\alpha}$–H), therefore the signal appearing upfield in the AB part of the spectrum belongs to $C_{2\alpha}$–H ($C_{4\alpha}$–H).† A similar assignment for the $C_2(C_4)$ protons in the case of the pseudopelletierine was made by Le Fêvre *et al.*[9]

* The endo C_6, C_7 protons appear at higher field than the exo C_6, C_7 protons, due to the shielding effect of the neighbouring carbonyl.

† Were the different coupling constants connected in some way to a chair-boat equilibrium the above assignment should still hold true.

TABLE 2. NMR SPECTRA OF N-ARYL-NORTROPINONES

Compd.	N-substituent	1H, 5H	2H, 4H (*ax*)	2H, 4H (*eq*)	6H, 7H (*endo*)	6H, 7H (*exo*)	Aromatic protons	
10 (**11**)		4·46 m $J_{1,7}=4$* $J_{1,7'}=2·5$	2·65 (4; 15)	2·30 (1; 15)	1·95–2·40	1·60–1·95	6·86(3H) 7·30(2H)	
12 (**13**)	MeO 	4·42 m $J_{1,7}=4$* $J_{1,7'}=2·5$	2·68 (4·5; 15)	2·28 (1; 15)	2·00–2·30	1·65–1·90	6·84 s $\Delta W_{\frac{1}{2}}=3$	OMe 3·77 s
14		4·50 m	2·68 (4·5; 15)	2·33 (1; 15)	1·95–2·30	1·62–1·95	6·92(2H) 7·65(7H)	
15	MeO  MeO	4·40 m	2·73 (4; 15)	2·29 (1; 15)	1·94–2·30	1·60–1·94	6·03(3H)	OMe 3·77 s
16	OMe  MeO	4·58 m	2·75 (4·5; 16)	2·29 (1·5; 16)	1·90–2·50	1·58–1·90	6·14–6·84(3H)	OMe 3·74 3·80
17		4·22 m	2·98 (4; 16)	2·46 (1·5; 16)	1·90–2·30	1·60–1·90	6·90(1H) 7·26(1H) 7·44(3H) 7·82(1H)	8·26(1H)

* The *J*-values were measured in the 2,2,4,4-tetradeuterated compound.

The complexation of N-phenylnortropinone (**10**) with Eu $(dpm)_3$ improved its NMR spectrum in such a way that each class of protons gave rise to a separate signal:

	1H, 5H	2H, 4H (ax)	2H, 4H (eq)	6H, 7H (endo)	6H, 7H (exo)	Aromatic protons		
$\delta_{0·75}$† (*J*)	6·70 m	9·07 dd (~4; 16)	9·92 dd (~1; 16)	5·42 m	3·94 m	8·18d (8) (*ortho*)	7·65t (8) (*meta*)	7·00t (8) (*para*)
$\Delta\delta_{0·75}$†	2·24	6·42	7·62	3·20	~2·20	1·32	0·35	0·14

It must be emphasized that two sites (C=O and $\rangle$N:) are available for complexation,[12] perhaps to different extents, and the fact that the $C_2(C_4)$ protons (α to C=O)

† Eu $(dpm_2)_3$/substrate ratio.

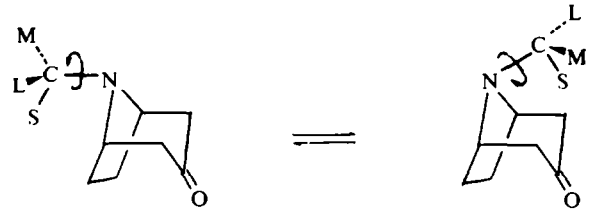
are more shifted than the $C_1(C_5)$ protons (α to N)· is by itself, insufficient to assign the stereochemistry of the complexated forms; blocking of the N moiety will allow to clear this point, by comparison. The assignment of the C_6, C_7 *endo* protons (which are the more shifted) was confirmed.

TABLE 3. NMR SPECTRA OF N-SUBSTITUTED-NORTROPINONE HYDROCHLORIDES (IN D_2O).

Compd.	N-substituent	1H. 5H	2H. 4H (*ax*)	2H. 4H (*eq*)	6H. 7H (*endo*)	6H. 7H (*exo*)	—CHCH$_3$ Solution Acidified to pH ≃ 1 (DCl)	
2	CH_3 1·22t (7·5) CH_2 —CH 3·65 m CH_3 1·64d (6·5)	4·68m	3·28 (4;18)	2·84 (~1;18)	1·90–2·60	1·90–2·60	1·70d (6·5) 1·74d (6·5)	~40% ~60%
3	C_6H_{11} —CH 3·98m CH_3 1·56d (6·5)	4·66m	3·30* (4;18)	2·80* (~1;18)	1·30–2·60	1·30–2·60	1·72d (6·5) 1·74d) (6·5)	50% 50%
5	CO_2CH_3 4·07s —CH 4·56q(7) CH_3 1·91d(7)	4·63m	3·32* (4;18)	2·89* (1·5;18)	2·43–2·74	2·13–2·43	1·97d (7) 2·02d (7)	~75% ~25%
6	CO_2Bu^t 1·75s —CH 4·43q(7) CH_3 1·88d(7)	4·60m	3·32* (4;18)	2·91* (1·5;18)	2·00–2·74	2·00–2·74	1·94d (7) 1·98d (7)	~75% ~25%
7	CO_2CH_3 3·88s —CH 4·72dd (4·5; 9) CH_2 3·40–3·80 Ph 7·60m	4·58m	3·30* (4;18)	2·87 (1;18)	2·42–2·74	2·14 2·42		
9	CO_2CH_3 4·01s —CH 5·49s Ph (7·83)	4·67m 4·08m	3·12 (4·18) 3·46 (4;18)	2·82	2·50–2·90	2·15–2·50	One Isomer	

* Broad signal.

N-substituted-nortropinones may exhibit conformational mobility due to N-inversion as well as rotation around the C—N bond.



In the a and b series, the chiral group gives rise to magnetic non-equivalence of the protons situated on both sides of the skeleton symmetry plane, chiefly observable in the signals of $C_{2\beta}$–H and $C_{4\beta}$–H, and the fact that these signals are mainly affected, is in agreement with the above assignment of the $C_2(C_4)$ proton signals. The proton non-equivalence in the chiral compounds also helps in obtaining information on the conformational mobility.

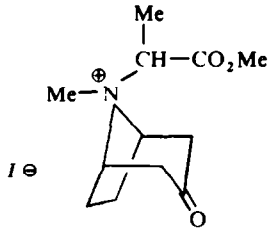
Conformational analysis and inspection of the Dreiding models showed that the rotamers having the smallest group *S* (*e.g.* hydrogen) in the skeleton symmetry plane should be greatly preferred.[4] It follows that the N-inversion is interconnected with the C–N rotation in such a way that the two other groups (M and L) interchange positions during the inversion. This behaviour may explain the coalescence of the C_1–H and C_5–H signals in most compounds of the a, b series; while the $C_{2\beta}$–H and $C_{4\beta}$–H, affected by the assymetric group only when in the axial position (the less preferred conformer in most cases) appear distinct (Table 1).

On removing the conformational mobility by quaternization (compounds **18–22**) the C_1–H and C_5–H signals appear separately (Table 4), which seems to confirm the above assumption. The $\Delta\delta = \delta_{1H} - \delta_{5H}$ as well as $\Delta\delta = \delta_{2H} - \delta_{4H}$ values depend, as expected, on the difference between the two groups M and L.

In order to estimate, at least qualitatively, the population of the two N-conformers, the Closs method[6] was used (Table 3) affording the approximate ratios between the N-conformers. Assignment of the signals to the individual conformers could not always be made on the basis of NMR alone, and a CD study of these compounds is being undertaken in this purpose.

The reaction of the N-substituted-nortropinones with MeI afforded mainly one epimeric methiodide, the NMR spectra of the mixtures showing, in most cases, that the quarternization was stereospecific, and in some cases highly stereoselective. Compound **5** for example, reacts with MeI to give mainly one epimeric methiodide (δ_{N-Me} 3·24) while the other epimer was also found in the mixture in small amount (δ_{N-Me} 3·30). Comparing the above data to those of similar compounds* prepared by Fodor[7] by a different method, and supposing that the additional methyl α-to nitrogen would not much alter the magnetic anisotropy, it follows that the major epimer (**20**) is obtained by equatorial attack.

* N_b-Methoxycarbonylmethyl-3-oxo-tropanium bromide (δ_{N-Me} 3·59) and N_a-Methoxycarbonylmethyl-3-oxo-tropanium bromide (δ_{N-Me} 3·36) from ref. 7. The stereochemistry of these compounds was unequivocally proven by the lactonization method.[7]



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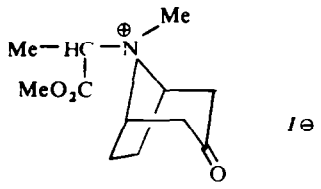

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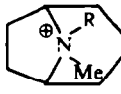
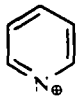
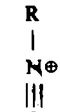
The fragmentation pattern in the mass spectra of the new tropinones of series a–c depends upon the N-substituent. Whenever the N-substituent is a stable group, (alkyl or aryl) the most abundant peaks in the mass spectrum are those corresponding

TABLE 4. NMR SPECTRA OF METHIODIDES

Compd.		1H. 5H	2H. 4H (*ax*)	2H. 4H (*eq*)	6H. 7H (*endo*)	6H. 7H (*exo*)	N–Me
18	CH_3 1·24 t (7) CH_2 2·04 m CH 4·15 m CH_3 1·71 d (6·5)	4·56 m	3·42 m	2·90 m	2·50–2·80	2·00–2·50	3·21 s
19	C_6H_{11} 1·20–2·80 CH 4·08 q (6·5) CH_3 1·62 d (6·5)	4·48 m 4·80 m	3·48 m	2·88 m	1·20–2·80	1·20–2·80	3·26 s
20	CO_2CH_3 4·08 s CH 4·04 s (minor) CH_2 2·02 d	5·00 m 4·64 m	3·42 m	2·92 m	2·60–2·95	2·20–2·60	3·24 s (major) 3·30 s minor)
21	CO_2Bu^t 1·72 s CH 5·14 q CH_3 1·97 d	4·61m 4·83 m	3·47 m	2·92 m	2·28–2·90	2·28–2·90	3·41 s
22	CO_2CH_3 3·92 s CH 5·14 m CH_2 3·80 m Ph 7·59 m	4·65 m 4·76 m	3·45 m	2·70–3·20	2·70–3·20	2·20–2·55	3·65 s

to the bicyclic skeleton fragmentation, as in the case of tropinone (Table 5).[13] Conversely, when the N-substituent itself is easily cleaved (adducts of amino acid esters and aralkylamines)[4] its fragments turned out to be the most abundant, as seen in the following: Adduct of l-alanine methyl ester (**5**): 211 (1%, M^+); 180 (0·5%, [M–OMe]); 152 (100%[M–CO_2Me]) and 110 (26%, [152–CH_2=C=O], m* 79·8). Adduct of l-phenylalanine methyl ester (**7**): 287 (1·5%, $M^{\oplus}$); 228 (36%, [M–CO_2Me]); 196 (100%, [M–PhCH_2]); and 154 (9%, [196–CH_2=C=O], m* 121); in both cases no other skeleton fragments were observable.

TABLE 5. MASS SPECTRA OF N-SUBSTITUTED NORTROPINONES

Compound	N-substituent	M^+	M—C_2H_4	M—(C_2H_4 + H)	M—CH_2=C=O	M—(C_2H_2O + H)	M—(C_2H_4 + CO) or R + 67 − H		 (R + 67)		Other peaks
1	Met†	139 (15)	111 (4)	110 (8)	97 (13)	96 (36)	81 (43)	94 (4)	82 (100)	42 (96)	
10	Ph	201 (53)	173 (3)	172 (8)	159 (8)	158 (29)	143 (66)	156 (3)	144 (100) m*103	104 (53)	77; 51 (79); (34)
11	Ph 2.2.4.4-$-d_4$	205 (52)	177 (1)	175 (6)	161 (6)	160 (20)	143 (75)	156 (1)	144 (100) m*99	104 (38)	77; 51 (60); (22)
12	C_6H_4OMe	231 (55)	203 (2)	202 (6)	189 (6)	188 (17)	173 (41)	186 (2)	174 (100)	134 (41)	216; 107 (3); (11)
13	C_6H_4OMe 2.2.4.4-$-d_4$	235 (100)	207 (2)	205 (6)	191 (7)	190 (21)	173 (57)	—	174 (99)	134 (39)	220; 107 (3); (10)

† See reference 13.

CD measurements on the methiodides **18–22** and their N-epimers obtained by an equilibration technique[4] are presently being undertaken in order to confirm their structure. The chiral substituent on the nitrogen in the compounds studied produced a perturbation of the carbonyl chromophore, the extent of which depends on the difference between the various groups on the asymmetric carbon.

The conversion of some of the tropinones described herewith to the corresponding N-substituted-noratropines as well as their pharmacological properties will be described in a forthcoming paper.

EXPERIMENTAL

M.ps were taken on a Büchi-Tottoli capillary m.p. apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer Infracord Model 337 spectrophotometer. NMR spectra were taken on a Varian HA-100 spectrometer on 5–10% solutions in $CDCl_3$ (unless otherwise indicated) containing TMS

as internal standard, and chemical shifts are quoted in units of δ. Mass spectra were taken with a Hitachi-Perkin-Elmer RMU 6 instrument. Gas chromatography was performed on a Packard Gas Chromatograph with all-glass $\frac{1}{4}$"/6 ft column packed with 2% SE-30 on GCQ 80–100 mesh. Purification by column chromatography was done on grade II neutral Al_2O_3 (Woelm) eluted with pet. ether–$CHCl_3$ mixtures. TLC was performed on 20 × 20 cm chromatoplates coated with Silicagel G (Merck) and eluted with a 80% benzene–20% EtOAc mixture.

Cyclohepta-2,6-dien-1-one was prepared following a procedure described by Garbisch,[2] this compound should be handled with care as its contact may cause burns.

Amino-acid ester hydrochlorides. 1-Alanine methyl ester hydrocyloride and 1-alanine t-butyl ester hydrochloride, were commercial products (Fluka AG). The remaining amino-acid ester hydrochlorides were prepared from the corresponding optically active amino-acids (commercially available) by a method described by Brenner.[14]

(S)-2-*Butylamine* was prepared from racemic 2-butylamine as described in the literature.[15] Hydrochloride: m.p. 151–3° (EtOAc) $[\alpha]_{4359}^{25°} = -1{\cdot}7°$ (*c*, 5·0, 1N HCl) (lit.[16] $[\alpha]_{4359}^{15°} = -1{\cdot}60°$).

(S)-α-*Cyclohexylethylamine* was prepared from (−)-α-phenethylamine (Fluka AG, $[\alpha]_D = -39° \pm 1°$) by reduction with 5% Ru/C, essentially as described by Freifelder.[17] Hydrochloride, m.p. 236° (lit.[17] 239–40°). $[\alpha]_D^{27°} = -0{\cdot}67$*.

Compounds **1–17** were prepared by one or more of the following methods:

Method A—To a solution of cyclohepta-2,6-dien-1-one (1·08 g, 10 mM) in MeOH (2 ml) was added slowly while swirling a primary amine (10 mM) and the mixture was allowed to stand at room temp until no more dienone could be detected by GC, TLC or IR. The mixture was evaporated to dryness and the residue chromatographed to yield the N-substituted-nortropinone, identified by its NMR, mass spectrum (Tables 1–5) IR and elemental analysis. In most cases (arylamines excepted) the hydrochloride could be prepared by treatment with isopropanolic HCl and crystallization from 95% EtOH.

Method B. As in Method A, with the exception that the mixture was refluxed until the reaction was complete.

Method C. To a solution of amine hydrochloride (10 mM) in MeOH (10 ml) was added anhyd. Na_2CO_3 (1·06 g, 10 mM), then cyclohepta-2,6-dien-1-one (1·08 g, 10 mM) while magnetically stirring at room temp. When the reaction was complete, the mixture was filtered, evaporated to dryness and chromatographed.

Method D. The corresponding primary amine was reacted with 2,5-dimethoxy-tetrahydrofuran and acetone dicarboxylic acid as described in the literature.[1] (Robinson-Schöpf method).

Tropinone (**1**).—Method A (60% yield), identical with an authentic sample (Aldrich Chem. Co. Inc.) in respect of the IR, NMR and mass spectrum.

(S)-N-(2-*Butyl*)*nortropinone* (**2**). —Method C (70%); hydrochloride, m.p. 198–9° dec. (iPrOH); ν_{max}^{KBr} 2960, 2410, 1720, 1470, 1420, 1390, 1340, 1115, 1062, 1010 cm^{-1}. (Found: C, 60·55; H, 9·33; N, 6·60; Cl, 16·21, $C_{11}H_{20}NOCl$ requires: C, 60·80; H, 9·20; N, 6·45; Cl, 16·35%). Methiodide, see **18**.

(S)-N-(α)-*Cyclohexylethyl*)*nortropinone* (**3**). – Method A (65%); hydrochloride, m.p. 197–8° (iPrOH); ν_{max}^{KBr} 2910, 2415, 1720, 1340, 1140, 1070, 1010 cm^{-1}. (Found: N, 4·90, $C_{15}H_{26}NOCl$ requires: N, 5·15%). Methiodide, see **19**.

(S)-N-(α-*Phenethyl*)*nortropinone* (**4**). Method A (70%); see ref. 4 .

(S)-N-(1-*Carbomethoxyethyl*)*nortropinone* (**5**). (adduct of l-alanine methyl ester). Method C (75%); method D (50%); hydrochloride, m.p. 182–3° dec. (iPrOH); ν_{max}^{KBr} 2950, 2370, 1770, 1730, 1460, 1390, 1215, 1005 cm^{-1}. (Found: C, 53·14, H, 7·26; N, 5·81; Cl, 14·23, $C_{11}H_{18}NO_3Cl$ requires: C, 53·4; H, 7·29; N, 5·66; Cl, 14·35%). Methiodide, see **20**.

(S)-N-(1-*Carbo-t-butoxyethyl*)*nortropinone* (**6**). (adduct of l-alanine t-butyl ester). Method C (80%); hydrochloride, m.p. 180–1° dec. (iPrOH); ν_{max}^{KBr} 2980, 2820, 1755, 1745, 1490, 1470, 1380, 1225, 1165, 1005 cm^{-1}. Mass spectrum *m/e* 253 ($M^{\oplus}$) ($C_{14}H_{23}NO_3$ requires: $M^{\oplus}$ 253) methiodide, see **21**.

(S)-N-(1-*Carbomethoxy-2-phenyl-ethyl*)*nortropinone* (**7**) (adduct of l-phenylalanine methyl ester). Method A (60%), Method C (75%); hydrochloride, m.p. 148–9° dec. (iPrOH); ν_{max}^{KBr} 3560, 3370, 1750, 1730, 1650, 1470, 1230, 770, 710 cm^{-1} (Found: N, 4·11, $C_{17}H_{22}NO_3Cl$ requires: N, 4·33%).

(S)-N-(1-*Carbomethoxyisobutyl*) *nortropinone* (**8**) (adduct of l-valine methyl ester). Method C (65%); oil; NMR, Table 1. Mass spectrum *m/e* 239 ($M^{\oplus}$) ($C_{13}H_{21}NO_3$ requires: $M^{\oplus}$ 239).

(R)-N-(*Carbomethoxybenzyl*)*nortropinone* (**9**) (adduct of D-phenylglycine methyl ester). Method C

* Partial racemization is suspected to have occurred during the reduction. However, even this slight optical activity was sufficient for the CD study.

(70%); hydrochloride, m.p. 170–1° dec. (iPrOH); ν_{max}^{KBr} 2940, 2350, 1760, 1740, 1450, 1380, 1340, 1310, 1275, 1005, 750, 715 cm^{-1}). (Found: N, 4·49, $C_{16}H_{20}NO_3Cl$ requires: N, 4·53%).

N-*Phenyl-nortropinone* (**10**). Method B (75%), Method D (40%), m.p. 107–8° (MeOH–H_2O); ν_{max}^{KBr} 2960, 1720, 1610, 1510, 1370, 1340, 1270, 1200, 1170, 1005, 765, 755, 700 cm^{-1}. (Found: C, 77·41; H, 7·25; N, 6·92. $C_{13}H_{15}NO$ requires: C, 77·58; H, 7·51; N. 6·96%). Picrate: m.p. 120–1°.

N-*Phenyl*-2,2,4,4-*tetradeuterio-nortropinone* (**11**). N-phenyl-nortropinone (**10**) was deuterated by a method described by Blossey *et al.*[13] M.p. 106–7°, ν_{max}^{KBr} 2950, 2290, 1710, 1610, 1510, 1370, 1310, 1190, 755, 690 cm^{-1}. See NMR and mass spectra in Tables 2 and 5 respectively.

N-(p-*Methoxyphenyl*)*nortropinone* (**12**). Method B (70%) m.p. 132–3° (MeOH); ν_{max}^{KBr} 2940, 1720, 1520, 1360, 1310, 1260, 1240, 1030, 820 cm^{-1}. (Found: C, 72·74; H, 7·30; N, 6·23. $C_{14}H_{17}NO_2$ requires: C, 72·70; H, 7·41 N, 6·06%).

N-(p-*Methoxyphenyl*)-2,2,4,4-*tetradeuterio-nortropinone* (**13**) was prepared from **12** as described above for **11**; ν_{max}^{KBr} 2950, 2270, 1710, 1520, 1460, 1360, 1300, 1235, 1030, 815 cm^{-1}. See NMR and mass spectra in Tables 2 and 5 respectively.

N-(p-*Biphenyl*)*nortropinone* (**14**). Method B (60%); m.p. 162° (acetone); ν_{max}^{KBr} 2940, 1710, 1620, 1490, 1370, 1330, 1270, 1190, 1005, 820, 760 cm^{-1}. (Found: C, 82·40; H, 7·00; N, 5·15. $C_{19}H_{20}NO$ requires: C, 82·28; H, 6·91; N, 5·05%).

N-(3,5-*Dimethoxy-phenyl*)*nortropinone* (**15**). Method B (70%), m.p. 96–97° (iPrOH); (Found: C, 68·85; H, 7·23; N, 5·56, $C_{15}H_{19}NO_3$ requires: C, 68·94; H, 7·33; N, 5·36%).

N-(2,5-*Dimethoxy-phenyl*)*nortropinone* (**16**). Method B (50%), oil, see NMR in Table 2, Mass spectrum *m/e* 261 ($M^{\oplus}$), ($C_{15}H_{19}NO_3$ requires: $M^{\oplus}$261).

N-(α-*Naphtyl*)*nortropinone* (**17**). Method B (50%); oil, see NMR Table 2, Mass spectrum *m/e* 251 ($M^{\oplus}$), ($C_{17}H_{17}NO$ requires: $M^{\oplus}$251).

Methiodides **18–22**. To a N-substituted-nortropinone (5 mM) in acetone (2 ml) was added an excess of MeI (2 ml), the mixture was refluxed for 24–48 hr, and the solid separated was filtered. Both the solid and the mother liquors were checked by NMR. After crystallization, the solid was in all cases a pure epimer.*

N-(2-*Butyl*)-N-*methyl*-3-*oxo-nortropanium iodide* (**18**). M.p. 195–198°; ν_{max}^{KBr} 3400, 2950, 1730, 1455, 1440, 1320, 1200, 1110, 990, 905 cm^{-1}. See NMR, Table 4.

N-(α-*Cyclohexylethyl*)-*N-methyl*-3-*oxo-nortropanium iodide* (**19**). M.p. 202°–203° dec. (95% EtOH); ν_{max}^{KBr} 3400, 2900, 1730, 1450, 1195, 1105, 1050, 990, 880 cm^{-1}. (Found: C, 50·68; H, 7·34. $C_{16}H_{28}NOI$ requires: C, 50·90; H, 7·42%).

N-(1-*Carbomethoxyethyl*)-N-*methyl*-3-*oxo-nortropanium iodide* (**20**). M.p. 162–163° dec. (95% EtOH); ν_{max}^{KBr} 3400, 2950, 2920, 1750, 1730, 1455, 1430, 1260, 1230, 1090, 940 cm^{-1}. (Found: C, 40·96; H, 5·60, $C_{12}H_{20}NO_3I$ requires: C, 40·80; H, 5·70%).

N-(1-*Carbo*-t-*butoxyethyl*)-N-*methyl*-3-*oxo-nortropanium iodide* (**21**). M.p. 168–171° dec. (iPrOH); ν_{max}^{KBr} 3400, 2990, 2950, 2900, 1750, 1740, 1725, 1350, 1260, 1160, 1130, 840 cm^{-1}. (Found: C, 45·11; H, 6·37; N, 3·26. $C_{15}H_{26}NO_3I$ requires: C, 45·4; H, 6·58; N, 3·54%).

N-(1-*Carbomethoxy*-2-*phenylethyl*)-N-*methyl*-3-*oxo-nortropanium iodide* (**22**). M.p. 160° dec. (95% EtOH); ν_{max}^{KBr} 3400, 2950, 1740, 1725, 1440, 1325, 1275, 1260, 1180, 900, 750, 700 cm^{-1}. (Found: C, 50·67; H, 5·65; N, 3·37, $C_{18}H_{24}NO_3I$ requires: C, 50·36; H, 5·64; N, 3·26%).

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