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COTTON EFFECT OF DIMEDONE CONDENSATION COMPOUNDS WITH OPTICALLY ACTIVE AMINES

PIERRE CRABBÉ*, B. HALPERN[1] and E. SANTOS[2]

Facultad de Química, Universidad Nacional Autonoma de Mexico, Mexico 21, D.F., Mexico

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Abstract—The Cotton effect of dimedone condensation products of several optically active aliphatic, alicyclic, and aromatic amines was examined by rotatory dispersion and circular dichroism techniques. A correlation has been established between the sign of the Cotton effect and the absolute configuration of the asymmetric center under investigation. All dimedonyl derivatives of aliphatic and alycyclic amines investigated in this study having the (*R*) configuration exhibit a positive Cotton effect in the 280 mμ region. A negative Cotton effect is observed for compounds showing the (*S*) configuration. The hydrochlorides of some dimedonyl derivatives were prepared. The sign of the Cotton effect is the same as in the free base. Solvent-dependent equilibria were noted.

Résumé—On discute l'effet Cotton de nombreux produits de condensation d'amines optiquement actives avec la dimédone. Les dérivés de condensation d'amines aliphatiques et alicycliques de configuration (*R*) présentent un effet Cotton positif. Les amines de configuration (*S*) en revanche présentent un effet Cotton négatif. Dans le cas des produits de condensation d'amines aromatiques, on note un phénomène, d'homoconjugaison entre l'amide vinylogue et le cycle aromatique, ce qui peut affecter le signe et l'intensité de l'effet Cotton observé expérimentalement. Le chlorhydrate des produits de condensation présente un effet Cotton de même signe mais plus faible que celui de l'amide vinylogue libre. On note un effet de solvant qui est attribué à un changement de population des différents rotamères et à des mélanges variables en espèces solvatées.

I INTRODUCTION

PHYSICAL chemical methods have been widely used for the correlation of absolute configuration of organic compounds; for example, NMR,[3] X-ray analysis,[4] mass spectrometry,[5] gas–liquid chromatography[6] and ORD and CD have helped to resolve problems related to the spatial orientation of chiral molecules. In particular ORD[7–9] and CD[7,9,10] have been widely used for both configuration and conformation[11,12] studies. However, in the case of the aliphatic and alicyclic amines, which are devoid of chromophores absorbing between 220 to 700 mμ, the correct stereochemistry cannot be ascertained from their ORD and CD curves, since no Cotton effect,[7] appears in this wavelength range.[13] In these cases, one may use derivatives presenting favorable spectroscopic properties in the spectral region easily accessible by presently available ORD and CD instruments. Many derivatives have been examined and their optical properties have been thoroughly discussed. Among the most commonly used derivatives of the amino function are nitroso-amines,[14] nitroso-amides,[14] nitrosite,[15] alkyl-nitrites,[16] Schiff bases[17,18] (e.g. N-benzylidene,[19] N-isopropylidene,[23] N-salicylidene[24]), phthalimides,[20,21] maleyl,[21,22] phthaloyl,[22] and itaconyl,[22] derivatives, etc.

Unfortunately, many of these chromophoric compounds are hard to prepare and some are unsuitable because they sometimes exhibit undesirable optical properties,

* Author to whom inquiries may be addressed at Syntex S.A., Apartado Postal 2679, Mexico D.F., Mexico.

such as complex multiple Cotton effect curves, Cotton effect in the 300 mμ region, etc. Among the various compounds examined so far the salicylidene derivative, formed by the condensation of salicylaldehyde with amines, is one of the most commonly used chromophore for the assignment of relative and/or absolute stereochemistry to optically active amines and amino acids.[24] It has been found that most amines with the (*S*)[25]-configuration exhibit positive Cotton effect curves and (*R*)[25]-derivatives, negative curves. Unfortunately, the major optically active band of this chromophore lies in the 300 mμ region, i.e. in the wavelength range where the saturated carbonyl chromophore of ketones or aldehydes absorbs.[7]

In view of these drawbacks we have focused our attention to another potentially useful derivative of amines, namely the dimedonyl condensation compound. The reaction of dimedone with ammonia was first described back in 1909;[26] but it is only recently that a detailed study of the condensation reaction with amino acids esters[27] and amines[28] has been undertaken.

The condensates are easily prepared in a crystalline state and the NMR spectra showed that the products had the vinylogous amide (—CO—CH=C—NH—) structure.[27,29]

The large specific rotations, the stability,[30] the ease of preparation and the absence of any racemization during their preparation made the condensation products ideal derivatives of the amino function. The compounds also exhibited interesting spectroscopic properties in the 280 mμ region (i.e. a region where few other chromophores absorb),[7] which made them potentially useful derivatives for configurational studies.

We now report on the preparation and on the physical and optical properties associated with the vinylogous amide chromophore of dimedone-amine condensates.[31]

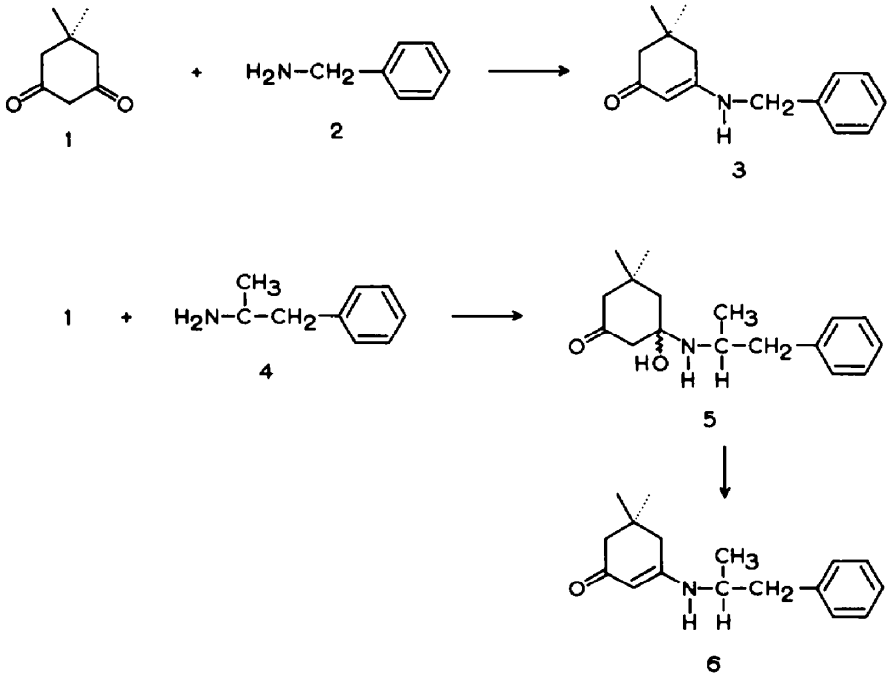
II DIMEDONE CONDENSATION COMPOUNDS OF AMINES

The dimedone condensates are easily formed in good yields, by reacting equimolar amounts of amine and dimedone in benzene, chloroform, or methanol solution, either under neutral conditions or in presence of a small amount of acid. For example the reaction of dimedone (**1**) with benzylamine (**2**) afforded N-(5,5-dimethyl-2-cyclohexen-1-on-3-yl)benzylamine (dimedonyl condensation compound **3**). This condensate **3** exhibited a rather high UV absorption (λ_{max} 278 mμ; log ε 4·33, in dioxan) which suggested that the vinylogous amide chromophore could be optically active if situated in an asymmetric surrounding.

Indeed, treatment of (*R*)-α-benzylethylamine (amphetamine; **4**) with dimedone (**1**) in benzene solution at reflux temperature in presence of *p*-toluenesulfonic acid, yielded compound **6**, which exhibited a negative Cotton effect in the 280 mμ region (*vide infra*). It is worth noting that in this case the reaction intermediate **5** could be isolated when the condensation was done in chloroform solution at room temperature. The elemental analysis of **5** indicated an empirical formula $C_{17}H_{25}O_2N$. Its structure was deduced from the NMR spectrum which was devoid of a vinylic proton signal and from the ORD curve which did not exhibit any substantial Cotton effect between 700 and 230 mμ. In addition, the intermediate **5** when heated in benzene solution, afforded the vinylogous amide **6** in excellent yield.

The dimedone condensation compounds of amines, such as **6**, present two typical absorption bands in the IR, i.e. at ca. 3500 cm^{-1} corresponding to the N–H frequency

and a strong band at ca. 1590 cm^{-1}, attributed to the vinylogous amide function. The UV spectrum of such a chromophore exhibits one single absorption band between 220 and 700 mμ, namely in the 280 mμ region (in dioxan solution), with a high extinction coefficient (log ε 4·4). The position and intensity of this absorption maximum undergo bathochromic and hyperchromic shifts which are dependent on the polarity of the solvent (see below). This band is optically active and an intense Cotton effect is observed at ca. 280 mμ. The NMR spectrum of the vinylogous amide chromophore is characterized by two singlets between 0·78 and 1·07 ppm attributed to the *gem*-dimethyl of the dimedonyl ring (although in some cases they combine to form one single signal). Two singlets between 1·95 and 2·25 ppm are due to the methylene protons next to the dimethyl group and signals from the vinylic proton appear in the 4·88 to 5·2 ppm region.



A. *Aliphatic amines*

An examination of the ORD curves of dimedonyl derivatives of optically active aliphatic amines of known configuration such as (*S*)-2-amino-pentane (**7**), (*S*)-2-amino-3-methylbutane (**8**) and (*S*)-1,3-dimethylbutylamine (**9**) show multiple Cotton effects between 260 and 325 mμ. Since these compounds exhibit a single UV maximum at 279 mμ, the above data suggest that there must be other optically active transitions of weak intensity, which are not detected in the UV spectrum. The most important feature of these three ORD curves is that a *negative* Cotton effect is associated with the 279 mμ transition of the vinylogous amide chromophore of these (*S*)-amine derivatives (Table 1).

TABLE 1. ABSORPTION AND OPTICAL PROPERTIES OF DIMEDONYL DERIVATIVES OF ALIPHATIC AND ALICYCLIC AMINES*

Dimedonyl condensation compound Amine	UV absorption		Cotton effect in the 280 mμ region			Ref for configuration
	λ (mμ)	log ε	First extremum [Φ] (λ mμ)	Second extremum [Φ] (λ mμ)	Molecular amplitude[a]	
(*S*)-2-Amino-pentane (**7**)	279	4·36	−855° (300)	+1425° (276)	−23	*a*
(*S*)-2-Amino-3-methylbutane (**8**)	279	4·42	−878° (297)	−30° (273)	−8	*a*
(*S*)-1,3-Dimethylbutylamine (**9**)	279	4·38	−734° (303)	+1366° (272)	−21	*a*
(3*R*)-α-Amino-5α-pregnane (**10**)	280	4·43	+3527° (284)	−2697° (254)	+62	*b, c*
(3*S*)-β-Amino-5α-pregnane (**11a**)	280	4·44	−3842° (296)	+3174° (256)	−70	*b, c*
(3*S*)-β-Amino-17β-hydroxy-5α-androstane (**11b**)	281	4·42	−4513° (295)	+3924° (270)	−84	*d*
(3*S*)-β-Amino-20β-hydroxy-pregn-5-ene (**12a**)	280	4·43	−14,799° (288)	+3534° (260)	−183	*c, e*
(3*S*)-β-Amino-pregn-5-en-20-one (**12b**)	280	4·43	−15,350° (285)	+3840° (253)	−192	*c*
(3*R*)-Gitingensine (**13b**)	293 (MeOH)	4·52	+9344° (302)	−12,059° (274)	+214	*f*
(17*R*)-α-Amino-3β-hydroxy-5α-androstane (**14a**)	297 (MeOH)	4·50	+49,238° (302)	−46,424° (282)	+957	*g*
(17*S*)-β-Amino-3β-hydroxy-5α-androstane (**14b**)	298 (MeOH)	4·51	−30,837° (305)	+29,824° (286)	−607	*g*
(3*S*), (17*S*), 3β-17β-Diamino-androst-4-ene (**15**)	295 (MeOH)	4·81	−91,945° (294)	+33,366° (274)	−1253	*c*

* All UV and RD curves in dioxane, unless stated otherwise.

[a] P. Karrer and P. Dinkel, *Helv. Chim. Acta* **36**, 122 (1953); see also Ref. 23.

[b] M. M. Janot, W. Khuong-Huu, X. Lusinchi and R. Goutarel, *Bull. Soc. Chim. Fr.* 1669 (1960).

[c] See Ref. 25*b*.

[d] M. M. Janot, Q. Khuong-Huu and R. Goutarel, *Bull. Soc. Chim. Fr.* 1640 (1960).

[e] M. M. Janot, A. Cavé and R. Goutarel, *Ibid.* 896 (1959).

[f] See Ref. 32.

[g] M. Davis, E. W. Parnell and D. Warburton, *J. Chem. Soc.* (C), 1688, 1698 (1966).

B. *Alicyclic series*

In order to reduce the conformational mobility existing in the aliphatic series (*vide supra*), compounds containing the steroid nucleus which have a more rigid conformation were used. The condensates of various steroidal amines were prepared and submitted to ORD (and CD) examination. The Cotton effect curves of such compounds are rather simple. This is shown in Fig. 1 which reproduces the UV and ORD curves of the dimedonyl derivatives of (3*R*)-α-amino-5α-pregnane (**10**) and its (3*S*)-isomer (**11a**). Although both specific rotations are positive,[32] it is quite apparent that a positive Cotton effect is associated with the (3*R*)-configuration (**10**), whereas the (3*S*)-derivative (**11a**) exhibits a negative ORD curve, showing a fine structure in the region of the trough.

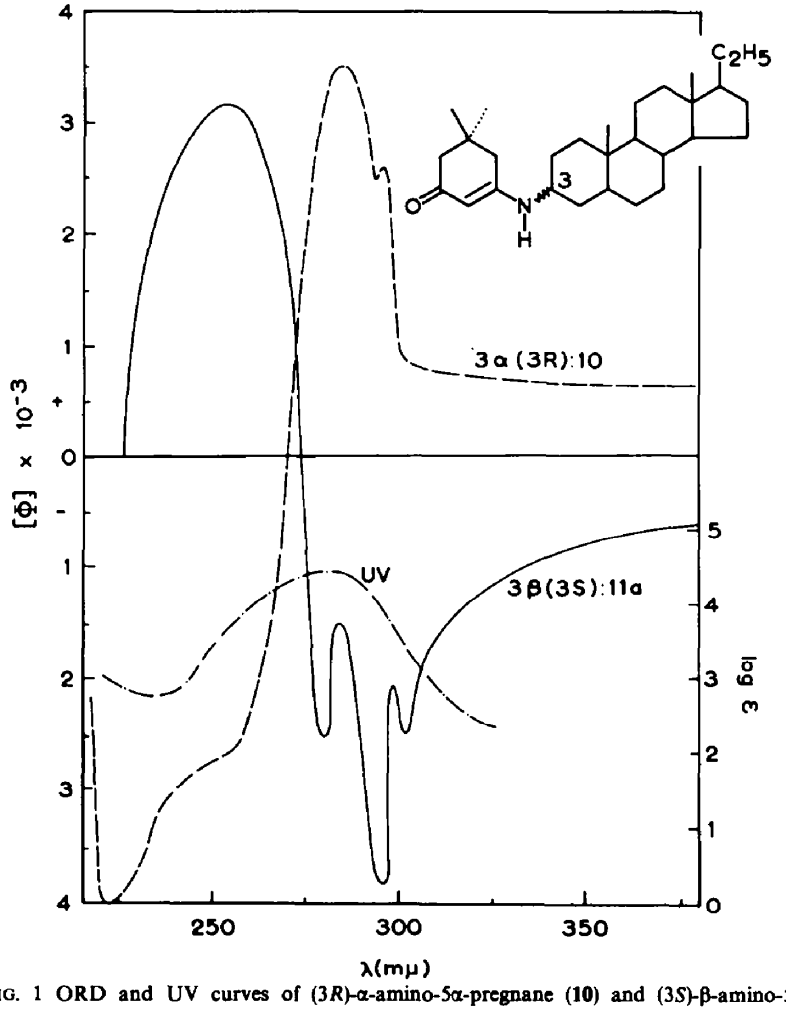


FIG. 1 ORD and UV curves of (3*R*)-α-amino-5α-pregnane (**10**) and (3*S*)-β-amino-5α-pregnane (**11a**) in dioxan solution.

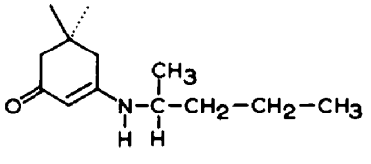
The Cotton effects associated with various steroidal dimedonyl derivatives are listed in Table 1. Comparison of the optical properties of **11a** and **12a** indicates that the presence of a double bond at C-5 in 3-amino derivatives does not affect the sign

of the Cotton effect, but only its intensity. The enhancement of the Cotton effect observed in **12a** is attributed to an orbital overlap between the vinylogous amide at C-3 and the double-bond electrons at C-5. These observations were applied recently to establish the configuration at C-3 in the steroidal alkaloid gitingensine (**13a**).[3,2] Since the dimedonyl derivative **13b** presents a positive Cotton effect in the 280 mμ region, the (*R*) configuration was assigned to the amino grouping at C-3.

The ORD curve of the keto-steroid (**12b**) (Experimental) shows a satisfactory separation between the negative Cotton effect associated with the vinylogous amide at C-3 and the positive Cotton effect of the 17β-acetyl side chain.[7] This separation will permit assignment of configuration to dimedonyl derivatives of amino compounds containing a saturated carbonyl chromophore in their molecule.

Noteworthy is the very intense Cotton effect exhibited by the condensates **14a**, **14b** and **15** (Table 1). This enhancement of the molecular amplitudes is attributed to restricted rotation around the C_{17}–N bond, due to steric hindrance induced by the 18-Me group. The absence of conformational mobility is also reflected in the shape of these ORD curves (Experimental) which do not show the multiple Cotton effect observed in the aliphatic series for example. Since the negative molecular amplitude characterizing the 17β-chromophore in **14b** is $a = -607$, one can conclude that a strongly negative Cotton effect ($a = -646$) is associated with the Δ^4-3β-condensate in the bis-adduct **15**. This very intense Cotton effect shown by the 3-dimedonyl derivative in **15** is presumably due to homoconjugation existing between the chromophore at C-3 and the π electrons of the double bond at C-4.

The main conclusion deduced from the above observations is that all dimedonyl derivatives of optically active alkylamines with the (*R*) configuration exhibit a positive Cotton effect at ca. 280 mμ, whilst a negative Cotton effect is associated with the derivatives presenting the (*S*) absolute configuration.



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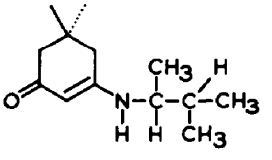

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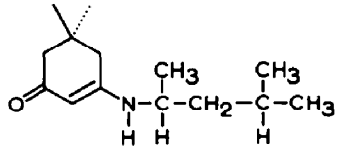

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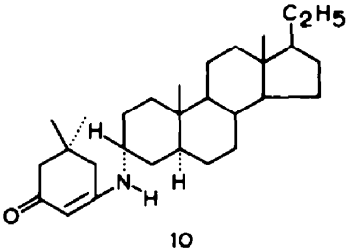

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C. *Aralkylamines*

The dimedone derivatives of (*R*)-α-phenylethylamine (*R*-**16**) and its enantiomer (*S*-**16**), in which the aromatic ring is adjacent to the asymmetric C atom, exhibit intense Cotton effect curves. Fig. 2, which reproduces the ORD and CD curves of (*R*)-**16** and (*S*)-**16**, indicates clearly that a positive Cotton effect is associated with the 279 mμ UV absorption band of the (*R*)-isomer, and a negative Cotton effect with the

(*S*)-configuration.[33] The molecular amplitude of these ORD curves, as well as the molecular ellipticity of the corresponding CD curves (Table 2) are reminiscent of the Cotton effects exhibited by inherently dissymmetric chromophores.[7] This suggests that the chromophore under investigation is an homoconjugated system formed by the vinylogous amide and the aromatic ring.[34] However, it should be noted that whilst the intensity of the Cotton effect is enhanced in these aralkylamines, the extinction coefficient of their UV absorption band is not affected. This observation has also been made in the case of the salicylidene derivative of amines.[24]

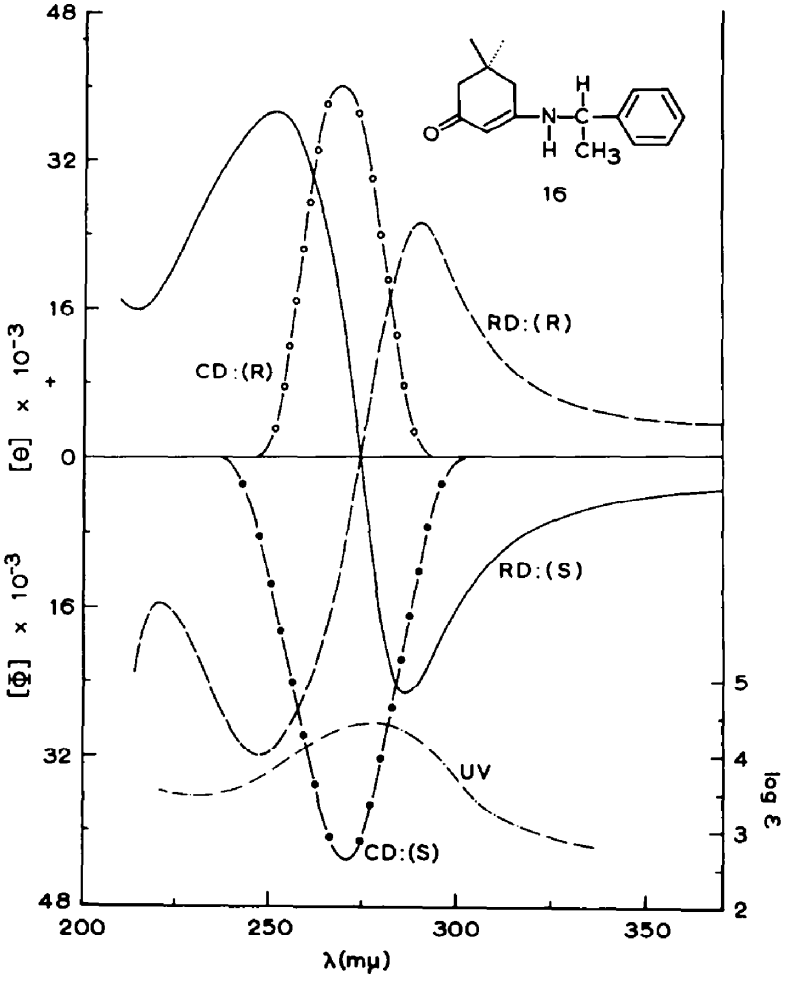
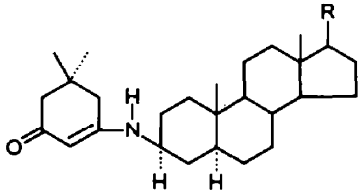


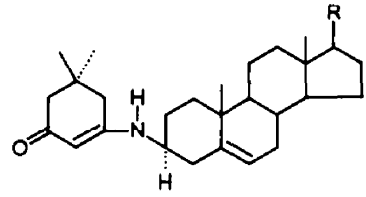
FIG. 2 ORD, CD and UV curves of (*R*)-α-phenylethylamine (*R*-16) and (*S*)-α-phenylethylamine (*S*-16) in dioxan solution.

Another characteristic feature of the curves (Fig. 2) is that the fine structure (or multiple Cotton effect), observed in the aliphatic and alicyclic series, has completely disappeared in the case of the aralkylamines discussed here. This is in contrast to the rather complex ORD and CD curves recently reported[35] for (*S*)-α-phenylethylamine which incidently exhibits multiple positive Cotton effect curves.

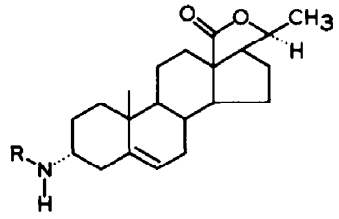
The UV and ORD curves of (*R*)-α-(1-naphthyl)-ethylamine (*R*)-**17** and its isomer (*S*)-**17** show mirror-image ORD curves. As illustrated in Fig. 3, the derivative (*R*)-**17** has a positive Cotton effect whereas its stereoisomer (*S*)-**17** presents a negative molecular amplitude. The dramatic Cotton effect characterizing these derivatives (Table 2)* supports the above mentioned hypothesis that in these compounds the system under investigation is an homoconjugated chromophore, involving the naphthalene ring and the vinylogous amide grouping. Here again fine structure was absent in the ORD curves.



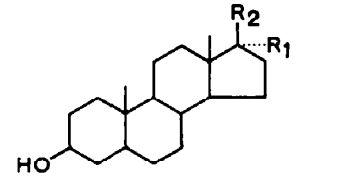
11 a, R = C_2H_5
b, R = OH



12 a; R = CHOH–CH_3
b, R = CO–CH_3



13 a, R = H
b, R = dimedonyl



14 a, R_1 = NH-dimedonyl; R_2 = H
b, R_1 = H; R_2 = NH-dimedonyl

In (*R*)-α-benzylethylamine (*R*)-**6** and its (*S*)-isomer (*S*)-**6**, where the aromatic ring is separated from the asymmetric center by one methylene group, the sign of the Cotton effect is now positive for the (*S*) and negative for the (*R*)-isomer as indicated in Table 2, and the intensity of the Cotton effect is considerably reduced. Moreover, the ORD curves of these compounds exhibit an inflexion in the 310 mμ region (Experimental).

The hydrochlorides of the dimedone condensates of several amines were also prepared. The formation of such derivatives indicates that the N atom of the dimedonyl compounds still has some basic properties. As indicated in Table 2 and Experimental, the absorption and optical properties of the hydrochlorides are different from these of the free bases. The 290 mμ Cotton effects of the salts are generally less intense than in the free bases and in addition the curves seem to be concentration and solvent-dependent.

In a number of cases unexpected shifts of the observed Cotton effects were also noticed with the free bases. These occurred on changing concentration and solvent. Such shifts are reflections of what is observed in the UV, as in the case of compounds **11b**, **13b**,**14a**, **b** and **15**, which show their absorption maximum at higher wavelength

* In the course of our work, it was observed that often the (*R*)-isomer of amines are not 100% optically pure. This accounts for the quantitative differences sometimes noted between the Cotton effects of (*R*) and (*S*) enantiomers.

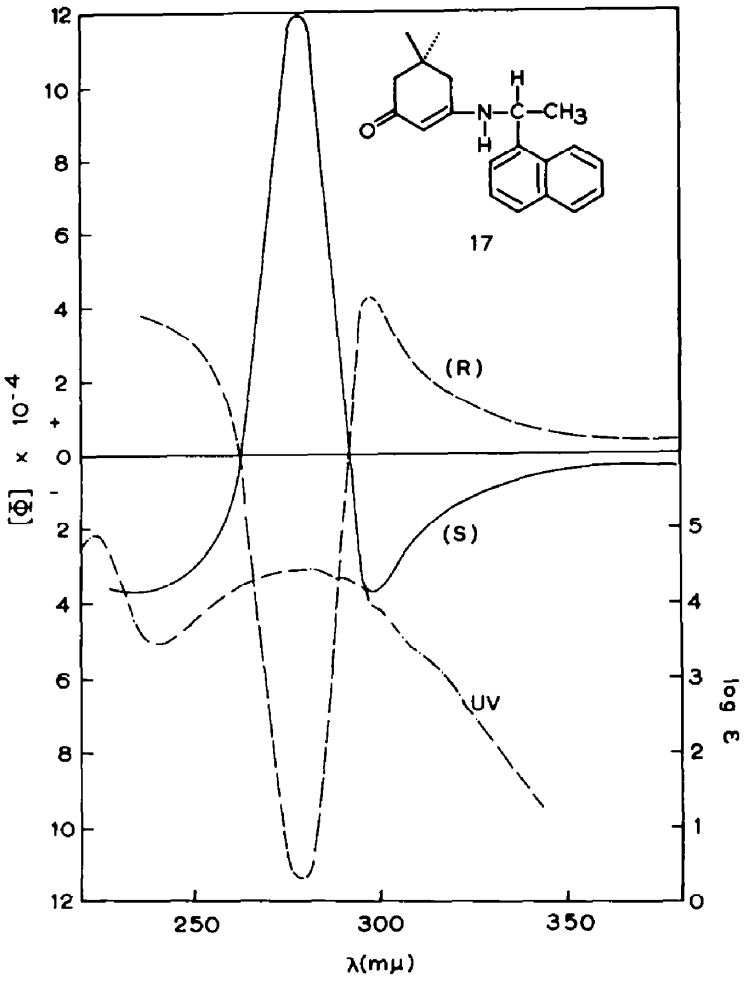


FIG. 3 ORD and UV curves of (*R*)-α-(1-naphthyl)-ethylamine (*R*)-**17** and (*S*)-α-(1-naphthyl)-ethylamine (*S*)-**17** in dioxan solution.

in methanol than in dioxane solution (Experimental). Although the shifts are less marked with the free bases than with the quarternary ammonium salts, the experimental results seem to indicate the existence of differently solvated species in solution. These anomalies are presumably due to solvent-influenced changes in rotamer composition and may indicate the existence of solvent-dependent equilibria involving differently solvated species. Such solvent effects have been observed previously with amino acid derivatives.[36]

The UV absorption maximum of the condensation compounds of dimedone with secondary amines, such as (*R*)-deoxyephedrine (*R*)-**18** and its antipode (*S*)-**18** appears at ca. 291–292 mμ (in dioxan solution). It should be noted that there is a UV bathochromic shift of about 10 mμ in going from primary to secondary amine condensates. This displacement is reflected in the ORD curves, but the sign of the Cotton effects is not affected (Table 2). One may take advantage of this bathochromic shift to establish

TABLE 2. ABSORPTION AND OPTICAL PROPERTIES OF DIMEDONYL DERIVATIVES OF ARALKYLAMINES AND HYDROCHLORIDES*

Dimedone condensation compound Amine	UV absorption		ORD in the 280 mμ region			Ref. for configurati
	λ (mμ)	log ε	First extremum [Φ] (λ mμ)	Second extremum [Φ] (λ mμ)	Molecular amplitude a	
(*R*)-α-Phenylethylamine, (*R*)-**16**	279	4·39	+25,071° (290)	−32,062° (248)	+572	*a*
(*S*)-α-Phenylethylamine, (*S*)-**16**	279	4·40	−25,134° (286)	+36,991° (252)	−620	*a*
(*R*)-α-(1-Naphthyl)-ethylamine, (*R*):**17**	282	4·40	+42,681° (297)	−114,201° (279)	+1569	*b*
(*S*)-α-(1-Naphthyl)-ethylamine, (*S*)-**17**	283	4·44 +	−37,059° (298)	+120,211° (278)	−1573	*b*
(*S*)-α-(1-Naphthyl)-ethylamine, hydrochloride, (*S*-**17**, HCl)	295	4·31	±0° (301)	−119,325° (283)	−1193	*b*
(*R*)-α-Benzylethylamine, (*R*)-**6**	280	4·42	−13,000° (288)	+17,500° (260)	−305	*c*
(*S*)-α-Benzylethylamine, (*S*)-**6**	280	4·38	+10,555° (290)	−14,227° (266)	+248	*c*
(*R*)-α-Benzylethylamine, hydrochloride, (*R*)-**6**, HCl	293 (EtOH)	4·47	−6180° (296)	+5420° (263)	−116	*c*
(*S*)-α-Benzylethylamine, hydrochloride, (*S*)-**6**, HCl	293 (EtOH)	4·47	+5050° (303)	−5800° (268)	+109	*c*
(*R*)-Deoxyephedrine, (*R*)-**18**	291	4·43	−10,027° (298)	+11,924° (271)	−220	*a*
(*S*)-Deoxyephedrine, (*S*)-**18**	292	4·41	+9250° (300)	−13,400° (274)	+227	*a*

* All UV and RD curves in dioxane, unless stated otherwise.

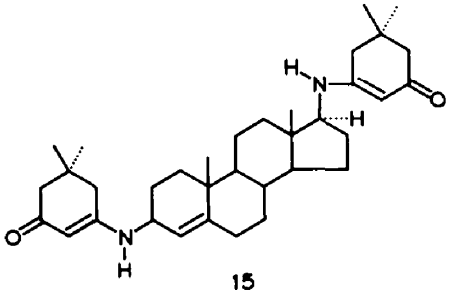
a W. Leithe, *Chem. Ber.* **64**, 2827 (1931); see also *b*.

b See Ref. 20*b* and Ref. 24 and 35*c*.

c P. Karrer and K. Ehrhardt, *Helv. Chim. Acta* **34**, 2202 (1951).

the primary or secondary nature of the amino group in a molecule of unknown structure.

In conclusion, the ORD and CD properties of the dimedonyl chromophore will be useful in stereochemical and structural studies. The 280–290 mμ UV absorption band of dimedonyl condensates of primary and secondary amines is optically active. The dimedone derivatives of all the optically active aliphatic and alicyclic amines studied thus far exhibit positive ORD and CD curves when the absolute configuration is (*R*), and negative Cotton effect curves when the configuration is (*S*). The intensity of the 280 mμ Cotton effect varies with the kind of amine under investigation. For example, the molecular amplitude of aliphatic amines is rather weak (a ~10–20), and in the case of saturated alicyclic amines the intensity of the Cotton effect is a function of the conformational rigidity of the system. In olefinic alicyclic amines and in aralkylamines, the intensity of the Cotton effects also depends on the proximity of the double bond or aromatic system to the vinylogous amide chromophore. Δ^5-3-Amino-steroids and benzylamine derivatives exhibit less intense molecular amplitudes (a ~200–300) than do the condensates of Δ^4-3-amino-steroids and of α-aralkylamines. In the case of the α-aralkylamines, the nature of the aromatic ring (i.e., the electron density of the new chromophore) acts directly on the intensity of the Cotton effect (Table 3). It should be noted, however, that the sign of the Cotton effect is inverted in aromatic amines in which the asymmetric center is separated from the aromatic ring by a methylene group. In addition, the intensity of the Cotton effect may be used to identify a double bond or an aromatic system in the close vicinity of an asymmetric center.



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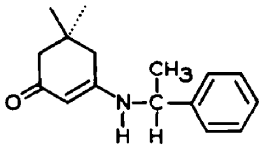
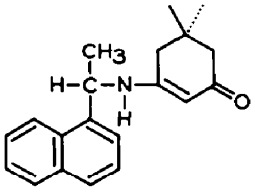


16



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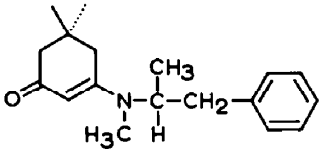

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EXPERIMENTAL

Microanalyses were performed by Dr. A. Bernhardt, Mülheim (Germany), and m.p. (corrected) were determined with a Kofler apparatus. Rotations were measured between 16° and 22° with a 1 dm tube at sodium D-light. ORD curves were taken with an automatic recording JASCO/UV-5 spectropolatimeter and CD curves were obtained with Jouan dichrograph at the University of Strasbourg, through the kind cooperation of Professor G. Ourisson. IR spectra were recorded with a Perkin–Elmer, Model 21, NaCl prism and UV absorption spectra were obtained with a Beckman spectrophotometer, Model D.U. NMR spectra were recorded at 60 Mc/s or 100 Mc/s using 5–8% w/v solns of substance in $CHCl_3$ containing TMS as an internal reference, unless stated otherwise. Resonance frequencies, are quoted as ppm downfield from the TMS reference and are accurate to ±0·1 ppm; coupling constants, *J*, are expressed in c/s units and are accurate to ±0·5 c/s. We are indebted to Dr. L. Throop, Syntex Research, Palo Alto, California, for several ORD and NMR measurements, as well as to Dr. A. Sandoval, Instituto de Química, UNAM, for NMR spectra.

General technique (A) for the preparation of dimedone condensation products. The free amine (1 equiv) was dissolved in an anhyd organic solvent ($CHCl_3$, benzene, etc), and dimedone (**1**) (1·1 equivs) was added. This soln was allowed to reflux for 24 hr using a Dean Stark separator. After cooling, the excess dimedone was removed with 5% KOHaq. After washing with water, the organic layer was dried over Na_2SO_4, filtered and then concentrated *in vacuo*.

N-(5,5-*Dimethyl*-2-*cyclohexen*-1-*on*-3-*yl*)*benzylamine* (**3**). Benzylamine **2** (1·1 g) and **1** (1·45 g) were dissolved in $CHCl_3$ and the soln was left at room temp for 24 hr. After removal of the solvent *in vacuo*, the residue was recrystallized from CH_2Cl_2–hexane yielding **3** (1·33 g): m.p. 130–131°; λ_{max}^{diox} 278 mμ (log ε 4·33); λ_{max}^{EtOH} 291 mμ (log ε 4·49); $\nu_{max}^{CHCl_3}$ 3450, 1580 and 1520 cm^{-1}; NMR 1·05 (*gem* di-Me), 2·12, 2·32; (—CH_2—CO— and —CH_2—C=C), 4·18 and 4·27 (2 benzylic H), 5·1 (vinylic H), 7·32 ppm (5 aromatic H). (Found: C, 78·83; H, 8·42; O, 7·02; N, 6·23. $C_{15}H_{19}ON$ requires: C, 78·56; H, 8·35; O, 6·98; N, 6·11%).

N-(5,5-*Dimethyl*-2-*cyclohexen*-1-*on*-3-*yl*) (R)-α-*amphetamine*, (R)-**6**. To (*R*)-amphetamine sulfate (10·9 g) in water (15 ml), NH_4OH was added until the pH was >8. The mixture was extracted with ether. The organic layer was dried over Na_2SO_4, filtered and the solvent eliminated *in vacuo*. The residue was distilled under reduced press (10 mm Hg) at 80–82°, affording (R)-**4**: ν_{max} 3420, 3350, 1600, 1590 cm^{-1}. (*R*)-Amphetamine (2·75 g) was mixed with a $CHCl_3$ soln (20 ml) containing 2·8 g of **1**. The reaction mixture was allowed to stand at room temp for 16 hr. After removal of the $CHCl_3$ under reduced press, the residue was recrystallized from EtOAc–hexane to provide 4·78 g of **5**: m.p. 125–126°; $[\alpha]_D$ +5°; ORD (*c*, 0·001; dioxan):

$[\Phi]_{600}$ ±0°; $[\Phi]_{400}$ +2600°; $[\Phi]_{300}$ +3900°; $[\Phi]_{249}$ +4200°; $[\Phi]_{235}$ +3700°; $\nu_{max}^{CHCl_3}$ 3500, 2550, 1730, 1710, 1590, 1500 cm^{-1}; ν_{max}^{KBr} 3380, 2920, 2818, 2720, 2620, 2530, 2260, 1670 and 1550 cm^{-1}; NMR 1·0 (*gem* di-Me); 1·15 (doublet, J = 7 c/s, CH—CH_3), 2·16 (4H; —CH_2), 3·2 (CH—N), ~7·23 ppm (5 aromatic H). (Found: C, 74·41; H, 9·17; N, 5·20; O, 11·70. $C_{17}H_{25}O_2N$ requires: C, 74·14; H, 9·15; N, 5·09; O, 11·62%).

When 100 mg of **5** was heated in anhyd benzene the dimedonyl condensation derivative (R)-**6** was obtained quantitatively (*vide infra*).

N-(5,5-*Dimethyl*-2-*cyclohexen*-1-*on*-3-*yl*) (R)-α-*benzylethylamine hydrochloride*, (R)-6, HCl. Treatment of (R)-**4** (1·93 g) with **1** (2 g) in 50 ml anhyd $CHCl_3$ afforded the crude reaction product. This product was dissolved in acetone and the cooled solution (0°) was treated with HCl, furnishing 1·65 g of (*R*)-**6**, HCl, exhibiting, after crystallization from acetone: m.p. 202–206° (sublim); $[\alpha]_D$ −22°; ORD (*c*, 0·001; MeOH): $[\Phi]_{600}$ ±0°; $[\Phi]_{450}$ −162°; $[\Phi]_{350}$ −784°; $[\Phi]_{314}$ −2764°; $[\Phi]_{308}$ −2681°; $[\Phi]_{300}$ −3089°; $[\Phi]_{292}$ −2052°; $[\Phi]_{290}$ −2257; $[\Phi]_{287}$ ±0°; $[\Phi]_{242}$ +9917°; $[\Phi]_{224}$ +8332°; $[\Phi]_{209}$ +12,310°; (*c*, 0·0005; MeOH): $[\Phi]_{500}$ ±0°; $[\Phi]_{400}$ ±0°; $[\Phi]_{333}$ −565°; $[\Phi]_{315}$ −2160°; $[\Phi]_{280}$ −7000°; $[\Phi]_{266}$ ±0°; $[\Phi]_{252}$ +12,200°; $[\Phi]_{215}$ +10,300°; (*c*, 0·0002; dioxan): $[\Phi]_{296}$ −6180°; $[\Phi]_{278}$ ±0°; $[\Phi]_{263}$ +5420°; $[\Phi]_{252}$ +3700°; $[\Phi]_{243}$ +4940°; $[\Phi]_{233}$ ±0°; $\lambda_{max}^{CHCl_3}$ 291 mμ (log ε 4·32); λ_{max}^{EtOH} 293 mμ (log ε 4·47); ν_{max}^{KBr} 2700, 2660, 2460, 1615, 1580 and 1550 cm^{-1}. (Found: C, 69·34; H, 8·42; O, 5·24; N, 4·60; Cl, 12·30. $C_{17}H_{24}ONCl$ requires: C, 69·49; H, 8·23; O, 5·44; N, 4·77; Cl, 12·07%).

N-(5,5-*Dimethyl*-2-*cyclohexen*-1-*on*-3-*yl*) (R)-α-*benzylethylamine*, (R)-**6**. The above hydrochloride (0·5 g) was treated with 5% $NaHCO_3$ aq (10 ml). Extraction with CH_2Cl_2, and working up as above furnished the (*R*)-isomer (**6**): m.p. 82–83°; $[\alpha]_D$ −109°; ORD (*c*, 0·0002; dioxan): $[\Phi]_{600}$ −290°; $[\Phi]_{400}$ −3000°; $[\Phi]_{288}$ −13,000°; $[\Phi]_{271}$ ±0°; $[\Phi]_{260}$ +17,500°; $[\Phi]_{220}$ +17,000°; $[\Phi]_{210}$ −11,000°; λ_{max}^{dioz} 280 mμ (log ε 4·42); λ_{max}^{EtOH} 293 mμ (log ε 4·5); ν_{max}^{KBr} 3155, 2700, 1590 and 1550 cm^{-1}; NMR 1·03 (*gem* di-Me), 1·16 (doublet, J = 7 c/s, CH_3—CH), 2·17 (4H, CH_2—C═O, CH_2—C═C), 2·82 [ABX system, J_{AX} 8 c/s, J_{AB} 13 c/s, J_{BX} 6 c/s, δ_A 177 c/s, δ_B 158 c/s], 3·7 multiplet, CH—CH_3), 5·2 (vinylic H), 5·53 (NH), 7·25 ppm (5 aromatic H). (Found: C, 79·90; H, 9·20; N, 5·43. $C_{17}H_{23}ON$ requires: C, 79·33; H, 9·01; N, 5·44%).

Hydrochloride of the N-(5,5-*dimethyl*-2-*cyclohexen*-1-*on*-3-*yl*), (S)-α-*benzylethylamine*, (S)-**6**, HCl. (*S*)-α-Benzylethylamine sulfate (2 g) were treated with 5 ml water containing 434 mg NaOH. Extraction with $CHCl_3$ afforded the free amine **4** which was treated by method A. The crude product was dissolved in ether and treated with a stream of HCl. The ppt which formed was filtered (2·33 g) and recrystallized from CH_2Cl_2–acetone, providing (*S*)-**6** HCl: m.p. 205–210° (sublim); $[\alpha]_D$ ±0°; ORD (*c*, 0·0002; dioxan): $[\Phi]_{600}$ ±0°; $[\Phi]_{303}$ +5050°; $[\Phi]_{287}$ ±0°; $[\Phi]_{268}$ −5800°; $[\Phi]_{238}$ −2530°; (*c*, 0·001; MeOH): $[\Phi]_{600}$ ±0°; $[\Phi]_{350}$ +784°; $[\Phi]_{320}$ +5513°; $[\Phi]_{303}$ +4732°; $[\Phi]_{290}$ ±0°; $[\Phi]_{269}$ −1883°; $[\Phi]_{228}$ −735°; $[\Phi]_{216}$ −2802°; $[\Phi]_{204}$ −1470°; $\lambda_{max}^{CHCl_3}$ 289 mμ (log ε 4·28); λ_{max}^{EtOH} 293 mμ (log ε 4·47); ν_{max} 2730, 2660, 1580 and 1530 cm^{-1}. (Found: C, 69·28; H, 8·42; N, 4·92; Cl, 11·65. $C_{17}H_{24}ONCl$ requires: C, 69·49; H, 8·23; N, 4·77; Cl, 12·07%).

N-(5,5-*Dimethyl*-2-*cyclohexen*-1-*on*-3-*yl*), (S)-α-*benzylethylamine*, (S)-**6**. The hydrochloride of the dimedonyl derivative of (*S*)-amphetamine, (*S*)-**6**, HCl (300 mg) was treated with 5% $NaHCO_3$ aq (10 ml). The soln was extracted with CH_2Cl_2 and the organic layer was washed with water until neutral, dried, filtered and evaporated to dryness under reduced press. The residual material (*S*)-**6** had: m.p. 82–83°; $[\alpha]_D$ +106°; ORD (*c*, 0·001, dioxan): $[\Phi]_{600}$ +274°; $[\Phi]_{350}$ +2358°; $[\Phi]_{320}$ +5507°; $[\Phi]_{290}$ +10,555°; $[\Phi]_{280}$ ±0°; $[\Phi]_{266}$ −14,227°; $[\Phi]_{238}$ −6884°; $[\Phi]_{216}$ −14,686°; λ_{max}^{dioz} 280 mμ (log ε 4·38); $\nu_{max}^{CHCl_3}$ 3500, 1580 and 1530 cm^{-1}; NMR 1·05 (*gem* di-Me), 1·18 (doublet, J = 7 c/s, CH_3—CH), 2·15, 2·21 (CH_2—C═C, CH_2—C═O), 2·83 [ABX-system: J_{AX} 8 c/s, J_{AB} 13 c/s, J_{BX} 6 c/s, δ_A 177 c/s, δ_B 158 c/s, CH_2—CH—CH_3], 3·73 (multiplet, CH—CH_3), 5·2 (vinylic H), 5·98 (NH), 7·23 ppm (5 aromatic H).

N-(5,5-*Dimethyl*-2-*cyclohexen*-1-*on*-3-*yl*) (S)-2-*amino pentane*, (**7**). (*S*)-2-Amino pentane tartrate (0·5 g) was treated with 2% NaOH aq (50 ml) and the free amine was extracted with $CHCl_3$ (100 ml). The organic layer was washed, dried and evaporated to dryness. The amine was then treated by the above technique A. The crude product dissolved in ether was treated with a stream of HCl. The hydrochloride which formed crystallized out on cooling the soln to 0°. After filtration and crystallization from CH_2Cl_2–acetone the pure hydrochloride of **7** (290 mg) was obtained: m.p. 183–187°; $[\alpha]_D$ −7°; λ_{max}^{EtOH} 291–292 mμ (log ε 4·48); $\nu_{max}^{CHCl_3}$ 3000–3100, 1 20 and 1580 cm^{-1}; NMR (100 Mc; d_6 DMSO) 0·88 (CH_3—CH_2), 1·01 (*gem* di-Me), 1·20 (doublet, J = 7 c/s, CH_3—CH), 2·42 and 2·60 (CH_2—CO and CH_2—C═C), ~3·80 (CH—N^+), 5·99 ppm (vinylic H). (Found: C, 63·69; H, 9·93; O, 6·61; N, 5·81; Cl, 14·25. $C_{13}H_{24}ONCl$ requires: C. 63·52; H, 9·84; O, 6·51; N, 5·70; Cl, 14·43%).

A soln of the hydrochloride (100 mg) in CH_2Cl_2 (50 ml) was stirred with 5% $NaHCO_3$ aq (10 ml). The

organic layer was separated, washed with water, dried, filtered and evaporated to dryness under vacuum. The amorphous dimedonyl derivative **7** was shown to be homogeneous by TLC, exhibiting: ORD (*c*, 0·0009; dioxan): $[\Phi]_{600}$ ±0°; $[\Phi]_{350}$ −201°; $[\Phi]_{319}$ −285°; $[\Phi]_{300}$ −855; $[\Phi]_{291}$ ±0°; $[\Phi]_{276}$ +1425°; $[\Phi]_{266}$ ±0°; $[\Phi]_{256}$ −903°; $[\Phi]_{213}$ −2280°; λ_{max}^{diox} 279 mμ (log ε 4·36); $\nu_{max}^{CHCl_3}$ 3490, 1580 and 1525 cm^{-1}.

N-(5,5-*Dimethyl*-2-*cyclohexen*-1-*on*-3-*yl*) (S)-2-*amino*-3-*methylbutane* (**8**). (*S*)-2-Amino-3-methylbutane tartrate (0·5 g) treated as in the case of **7** afforded 215 mg of **8**. After recrystallization from CH_2Cl_2–hexane, the analytical sample was obtained: m.p. 138–139°; $[\alpha]_D$ −9°; ORD (*c*, 0·001; dioxan): $[\Phi]_{600}$ +12°; $[\Phi]_{400}$ −138°; $[\Phi]_{334}$ −323°; $[\Phi]_{322}$ −351°; $[\Phi]_{312}$ ±0°; $[\Phi]_{310}$ −319°; (*c*, 0·0001): $[\Phi]_{297}$ −878°; $[\Phi]_{273}$ −30°; $[\Phi]_{262}$ −928°; $[\Phi]_{253}$ ±0°; $[\Phi]_{244}$ +629°; $[\Phi]_{214}$ +779°; $[\Phi]_{210}$ +319°; λ_{max}^{diox} 279 mμ (log ε 4·42); $\nu_{max}^{CHCl_3}$ 3480, 1580 and 1530 cm^{-1}; NMR 1·06 (*gem* di-Me), 2·15, 2·25 (—CH_2—CO— and CH_2—C═C), 3·23 (multiplet, N—CH—CH_3), 5·1 (vinylic H), 5·9 ppm (N—H). (Found: C, 74·75; H, 11·22; O, 7·38; N, 6·60. $C_{13}H_{23}ON$ requires: C, 74·59; H, 11·08; O, 7·64; N, 6·69%).

N-(5,5-*Dimethyl*-2-*cyclohexen*-1-*on*-3-*yl*) (S)-1,3-*dimethylbutylamine*, (**9**). (*S*)-1,3-Dimethylbutylamine tartrate (1·5 g) was treated with 5 ml of NaOH (1·02 g) in water (15 ml). The free base was extracted with benzene. After drying the benzene soln was added to dimedone (1·1 g) and the reaction mixture treated as described in A. The crude dimedonyl derivative dissolved in ether was treated with dry HCl. This soln cooled to 0° afforded **9** HCl (740 mg), which was recrystallized from CH_2Cl_2–acetone: m.p. 178–181°; λ_{max}^{EtOH} 292 mμ (log ε 4·5); $\nu_{max}^{CHCl_3}$ 3090–3020, 2800–2500, 1580 cm^{-1}; NMR (100 Mc; d_6 DMSO) 0·87 (doublet, J = 6 c/s, CH_3 CH), 0·89 (doublet, J = 6 c/s, CH_3—CH), 1·03 (*gem* di-Me), 1·19 (doublet, J = 6 c/s, CH_3—CH), ~3·83 (CH—N^+), 5·95 ppm (vinylic H). (Found: C, 64·97; H, 10·18; O, 6·34; N, 5·60; Cl, 13·80. $C_{14}H_{26}ONCl$ requires: C, 64·73; H, 10·08; O, 6·16; N, 5·39; Cl, 13·65%).

Treatment of the hydrochloride with base, as mentioned above, followed by crystallization from non-anyydrous ether, gave the free base **9**: m.p. 96–98°; $[\alpha]_D$ −15°; ORD (*c*, 0·001; dioxan): $[\Phi]_{600}$ −34°; $[\Phi]_{530}$ −40°; $[\Phi]_{400}$ −173°; $[\Phi]_{350}$ −401°; $[\Phi]_{330}$ −835°; (*c*, 0·00003) $[\Phi]_{318}$ −171°; $[\Phi]_{303}$ −734°; $[\Phi]_{289}$ −529°; $[\Phi]_{284}$ ±0°; $[\Phi]_{272}$ +1366°; $[\Phi]_{250}$ +2356°; λ_{max}^{diox} 279 mμ (log ε 4·38); $\nu_{max}^{CHCl_3}$ 3500, 1580, 1530 cm^{-1}; NMR 0·86 (doublet, J = 6 c/s, CH_3—CH), 1·0, (doublet, J = 6 c/s, CH_3—CH), 0·97 (*gem* di-Me), 2·0 (doublet, J = 6 c/s, CH_3—CH), 4·68 ppm (vinylic H). (Found: C, 72·35; H, 10·76. $C_{14}H_{25}ON$, $\frac{1}{2}H_2O$: C, 72·47; H, 11·28%).

N-(5,5-*Dimethyl*-2-*cyclohexen*-1-*on*-3-*yl*) (3S)-β-*amino*-17β-*hydroxy*-5α-*androstane* (**11b**). 3β-Amino 17β-hydroxy-5α-androstane (400 mg) was dissolved in 10 ml MeOH. Dimedone (1·1 equiv) in 75 ml benzene was added and the mixture refluxed for 24 hr. After usual work-up followed by crystallization from MeOH–acetone, **11b** (200 mg) was obtained in the pure form: m.p. 289–290°; $[\alpha]_D$ −19°; ORD (*c*, 0·0005; MeOH): $[\Phi]_{600}$ −59°; $[\Phi]_{380}$ −392°; $[\Phi]_{312}$ −1981°; $[\Phi]_{302}$ −2551°; $[\Phi]_{299}$ −3531°; $[\Phi]_{298}$ −2747°; $[\Phi]_{295}$ −4513°; $[\Phi]_{283}$ ±0°; $[\Phi]_{282}$ +1373°; $[\Phi]_{275}$ +3728°; $[\Phi]_{270}$ +3924°; $[\Phi]_{268}$ +3531°; $[\Phi]_{263}$ +4316°; $[\Phi]_{259}$ +4218°; $[\Phi]_{249}$ +2904°; $[\Phi]_{217}$ +2099°; $[\Phi]_{213}$ +2413°; $[\Phi]_{211}$ +2296°; $[\Phi]_{201}$ +3944°; λ_{max}^{diox} 281 mμ (log ε 4·42); λ_{max}^{MeOH} 293 mμ (log ε 4·53); ν_{max}^{KBr} 3400 and 1550 cm^{-1}; NMR (100 Mc; d_6 DMSO) 0·65 (18-H), 0·80 (19-H), 0·98 (*gem* di-Me), 4·85 (vinylic H), 6·7–6·85 ppm (NH). (Found: C, 75·62; H, 10·47; O, 10·66; N, 3·19. $C_{27}H_{43}O_2N$ requires: C, 75·46; H, 10·63; O, 10·77; N, 3·14%).

N-(5,5-*Dimethyl*-2-*cyclohexen*-1-*on*-3-*yl*) (3S)-β-*amino*-*pregn*-5-*en*-20-*one* (**12b**). Holafillamine hydrochloride[37] (253 mg) was treated with 5% NaHCO aq (10 ml), and the base extracted with $CHCl_3$. After washing with water, drying and concentrating *in vacuo*, holafillamine (230 mg) was obtained. Dimedone (**1**) (102 mg) and p-toluenesulfonic acid (40 mg) were added to holafillamine (230 mg) dissolved in 100 ml anhyd benzene. The mixture was then treated as described under A. After the usual work up, **13** (150 mg) was recrystallized from acetone–hexane to provide the pure sample: m.p. 307–308°; $[\alpha]_D$ +39°; ORD (*c*, 0·0004; MeOH): $[\Phi]_{600}$ +164°; $[\Phi]_{350}$ +657°; $[\Phi]_{311}$ +3997°; $[\Phi]_{297}$ ±0°; $[\Phi]_{285}$ −15,350°; $[\Phi]_{279}$ −11,500°; $[\Phi]_{272}$ ±0°; $[\Phi]_{253}$ +3840°; $[\Phi]_{234}$ ±0°; $[\Phi]_{227}$ −6242°; $[\Phi]_{214}$ ±0°; λ_{max}^{diox} 280–281 mμ (log ε 4·43), $\nu_{max}^{CHCl_3}$ 3180, 3010, 2900, 1710, 1580, 1530 cm^{-1}; NMR 0·64 (18-H), 1·0, 1·05 (*gem* di-Me), 1·05 (19-H), 2·12 (21-H), 2·17 (CH_2—C═C, CH_2—CO), 5·15 (dimedonyl vinylic H), 5·38 (C-6 vinylic H). (Found: C, 79·42; H, 10·04; O, 7·44; N, 3·42. $C_{29}H_{43}O_2N$ requires: C, 79·58; H, 9·90; O, 7·31; N, 3·20%).

N-(5,5-*Dimethyl*-2-*cyclohexen*-1-*on*-3-*yl*) (17R)-α-*amino*-3β-*hydroxy*-5α-*androstane* (**14a**). (17*R*)-α-Amino-3β-hydroxy-5α-androstane* (100 ml) was dissolved in 10 ml MeOH and 100 mg dimedone in 70 ml anhyd benzene were added. The reaction mixture was heated under reflux for 24 hr then worked up according to technique A. After crystallization from MeOH–acetone 117 mg of **14a** were obtained: m.p. 170°; $[\alpha]_D$ +68; ORD (*c*, 0·00005; MeOH): $[\Phi]_{600}$ +281°; $[\Phi]_{380}$ +4220°; $[\Phi]_{350}$ +7034°; $[\Phi]_{302}$

* We express our gratitude to Dr. M. Davis for providing us with a sample of this compound.

+49,238°; $[\Phi]_{292}$ ±0°; $[\Phi]_{282}$ −46,424°; $[\Phi]_{280}$ −43,611°; $[\Phi]_{279}$ +46,706; $[\Phi]_{250}$ −19,245°; $[\Phi]_{220}$ −11,648°; $[\Phi]_{208}$ −16,882°; $[\Phi]_{203}$ −18,007°; $[\Phi]_{200}$ −11,817°; λ_{max}^{MeOH} 297 mμ (log ε 4·5); ν_{max}^{KBr} 3350, 1550 cm^{-1}; NMR (100 Mc; d_6 DMSO) 0·75 (18 and 19-H), 0·97 (*gem* di-Me), 1·92 and 2·25 (CH_2—CO and CH_2—C═C), 4·40 (OH), 4·78 (vinylic H), ~6·70 ppm (NH). (Found: C, 77·94; H, 10·41; N, 3·34. $C_{27}H_{43}O_2N$ requires: C, 78·40; H, 10·48; O, 7·74; N, 3·39%).

N-(*5,5-Dimethyl-2-cyclohexen-1-on-3-yl*) (17S)-β-*amino*-3β-*hydroxy*-5α-*androstane* (**14b**). The procedure describes for the preparation of **14a** was applied to 17α-amino-3β-hydroxy-5α-androstane* (125 mg), to afford, after recrystallization from MeOH–acetone, the pure sample of **14b**: m.p. 297–298°; $[\alpha]_D$ −150°; ORD (*c*, 0·00005; MeOH): $[\Phi]_{600}$ −619°; $[\Phi]_{380}$ −2814°; $[\Phi]_{350}$ −5402; $[\Phi]_{305}$ −30,837°; $[\Phi]_{293}$ ±0°; $[\Phi]_{286}$ +29,824°; $[\Phi]_{284}$ +28,811°; $[\Phi]_{279}$ +33,200°; $[\Phi]_{277}$ +31,794°; $[\Phi]_{275}$ +32,356°; $[\Phi]_{250}$ +11,536°; $[\Phi]_{233}$ +8159°; $[\Phi]_{220}$ +10,129°; $[\Phi]_{203}$ +20,821°; $[\Phi]_{200}$ +20,258°; λ_{max}^{MeOH} 298 mμ (log ε 4·51); ν_{max}^{KBr} 3400, 1570 and 1550 cm^{-1}; NMR (100 Mc; d_6 DMSO) 0·65 (18-H), 0·73 (19-H), 0·95 (*gem* di-Me), 1·92 and 2·20 (CH_2—CO and CH_2—C═C), ~4·40 (OH), 4·93 (vinylic H), ~6·65 ppm (NH). (Found: C, 74·71; H, 10·41. $C_{27}H_{43}O_2N$, H_2O requires: C, 75·13; H, 10·51%).

Bis-N-(*5,5-dimethyl-2-cyclohexen-1-on-3-yl*) (3S;17S) 3β,17β-*diaminoandrost-4-ene* (**15**). 3β,17β-Diaminoandrost-4-ene bis-hydrochloride (450 mg) was dissolved in 100 ml $CHCl_3$ and the soln was stirred with 5% NaOH aq until alkaline pH. After extraction of the free amine and drying the $CHCl_3$ soln over Na_2SO_4, dimedone (400 mg) was added and the reaction mixture was treated according to technique A. Usual work-up gave amorphous **15**. This material was dissolved in $CHCl_3$, treated with dry HCl to provide the crystalline **15** HCl. Treatment of **15**, HCl with 5% $NaHCO_3$ aq gave, after usual procedure, the crystalline **15** (350 mg), which was recrystallized from MeOH–water: m.p. 350° (dec); $[\alpha]_D$ −33°; ORD (*c*, 0·0001; MeOH): $[\Phi]_{600}$ −171°; $[\Phi]_{400}$ −428°; $[\Phi]_{380}$ −855°; $[\Phi]_{360}$ ±0°; $[\Phi]_{350}$ +428°; $[\Phi]_{330}$ +3935°; $[\Phi]_{320}$ +13,004°; $[\Phi]_{308}$ +28,404°; $[\Phi]_{302}$ ±0°; $[\Phi]_{294}$ −91,945°; $[\Phi]_{290}$ −65,406°; $[\Phi]_{284}$ ±0°; $[\Phi]_{280}$ +20·105°; $[\Phi]_{274}$ +33,366°; $[\Phi]_{260}$ +22,672°; $[\Phi]_{250}$ +15,400°; $[\Phi]_{230}$ +8555°; $[\Phi]_{220}$ +6417°; $[\Phi]_{210}$ +8384°; $[\Phi]_{200}$ ±0°; λ_{max}^{MeOH} 295 mμ (log ε 4·81); $\nu_{max}^{CH\ Cl_3}$ 3400, 1580 and 1520 cm^{-1}; NMR (100 Mc) 0·75 (18-H), 1·05 (19H + *gem* di-Me), 4·4–4·5 (NH), ~5·16, 5·18, 5·22 (3 vinylic H). (Found: C, 78·74; H, 9·99; O, 5·92; N, 5·35. $C_{35}H_{52}O_2N_2$ requires: C, 78·90; H, 9·84; O, 6·01; N, 5·26%).

N-(*5,5-Dimethyl-2-cyclohexen-1-on-3-yl*) (R)-α-(*1-naphthyl*)-*ethylamine*, (R)-**17**. (*R*)-α-(1-Naphthyl)-ethylamine (1·71 g) and **1** (1·4 g) were treated in $CHCl_3$ solution, according to technique A. The crude product was chromatographed on neutral alumina. Elution with benzene–$CHCl_3$ (4–1) furnished 2 g of slightly yellow crystals (m.p. 178–179°). Recrystallization from acetone–hexane gave the pure sample of (*R*)-**17**: m.p. 185–186°; $[\alpha]_D$ +106°; ORD (*c*, 0·001; dioxan): $[\Phi]_{600}$ +312°; $[\Phi]_{450}$ +785°; $[\Phi]_{350}$ +4412°; $[\Phi]_{321}$ +14,656°; $[\Phi]_{297}$ +42,681°; $[\Phi]_{292}$ ±0°; $[\Phi]_{297}$ −114,201°; $[\Phi]_{262}$ ±0°; $[\Phi]_{255}$ +25,839°; $[\Phi]_{238}$ +36,913°; $[\Phi]_{225}$ +46,142°; λ_{max}^{diox} 224, 282 mμ (log ε 4·86, 4·40); λ_{max}^{EtOH} 224, 293 mμ (log ε 4·95; 4·53); $\nu_{max}^{CHCl_3}$ 3500, 1580 and 1520 cm^{-1}; NMR 0·93 (CH_3), 1·03 (CH_3), 1·48 (doublet, J = 6 c/s, CH_3—CH), 2·09 and 2·20 (CH_2—C═C and CH_2—CO), 4·88 (vinylic H), 5·12 (multiplet CH—CH_3), 6·21 (NH), 7·28–8·09 ppm (7 aromatic H). (Found: C, 81·86; H, 7·76; O, 5·64; N, 4·95. $C_{20}H_{23}ON$ requires: C, 81·87; H, 7·90; O, 5·45; N, 4·77%).

N-(*5,5-Dimethyl-2-cyclohexen-1-on-3-yl*) (S)-α-(*1-naphthyl*)-*ethylamine*, (S)-**17**. Similarly, condensation of (*S*)-α-(1-naphthyl)-ethylamine with **1** furnished (*S*)-**17**: m.p. 185–186°; $[\alpha]_D$ −112°; ORD (*c*, 0·001; dioxan): $[\Phi]_{600}$ −329°; $[\Phi]_{450}$ −711°; $[\Phi]_{350}$ −4334°; $[\Phi]_{321}$ −14,910°; $[\Phi]_{298}$ −37,059°; $[\Phi]_{292}$ ±0°; $[\Phi]_{278}$ +120,211°; $[\Phi]_{263}$ ±0°; $[\Phi]_{254}$ −28,721°; $[\Phi]_{229}$ −37,059°; $[\Phi]_{224}$ ±0°; λ_{max}^{diox} 224, 283 mμ (log ε 4·90, 4·44); λ_{max}^{EtOH} 224, 293 mμ (log ε 4·92; 4·48); $\nu_{max}^{CHCl_3}$ 3450, 1580 and 1520 cm^{-1}; NMR 0·90 (CH_3), 1·03 (CH_3), 1·42 (doublet, J = 6 c/s, CH_3—CH), 2·07 and 2·20 (CH_2—C═C and CH_2—C═O), 4·88 (vinylic H), 5·12 (multiplet, CH—CH_3), 6·21 (NH), 7·27–8·09 ppm (7 aromatic H). (Found: C, 82·24; H, 7·83; O, 5·36; N, 4·88. $C_{20}H_{23}ON$ requires: C, 81·87; H, 7·90; O, 5·45; N, 4·77%).

Hydrochloride of the N-(*5,5-dimethyl-2-cyclohexen-1-on-3-yl*) (S)-α-(*1-naphthyl*) *ethylamine*, (S)-**17**, HCl. A stream of dry HCl was passed through a soln of 550 mg (*S*)-**17** in 5 ml $CHCl_3$, kept at 0°. The compound which crystallized was filtered and purified by crystallization from acetone: m.p. 218–219°; $[\alpha]_D$ +128°; ORD (*c*, 0·0009; MeOH): $[\Phi]_{600}$ +428°; $[\Phi]_{400}$ +1606°; $[\Phi]_{323}$ +4174°; $[\Phi]_{320}$ +3703°; $[\Phi]_{313}$ +3371°; $[\Phi]_{316}$ ±0°; $[\Phi]_{301}$ ±0°; $[\Phi]_{291}$ +89,922°; $[\Phi]_{283}$ +119,325°; $[\Phi]_{273}$ ±0°; $[\Phi]_{212}$ +67,085°; $[\Phi]_{202}$ +43,677°; (*c*, 0·004; MeOH): $[\Phi]_{600}$ +405°; $[\Phi]_{322}$ +3600°; $[\Phi]_{299}$ ±0°; $[\Phi]_{279}$ +40,000°; $[\Phi]_{272}$ ±0°; $[\Phi]_{257}$ −72,000°; $[\Phi]_{241}$ −54,000°; $[\Phi]_{225}$ −100,000°; λ_{max}^{MeOH} 223, 245, 295, 352 mμ (log ε 4·75, 4·32, 4·31, 1·5) ν_{max}^{KBr} 3200, 2800, 1575, 1540 cm^{-1}. (Found: C, 72·43; H, 7·25; N, 4·47. $C_{20}H_{24}ONCl$, $\frac{1}{2}$ C_3H_6O: C, 72·17; H, 7·51; N, 3·91%).

N-(*5,5-Dimethyl-2-cyclohexen-1-on-3-yl*) (S)-*deoxyephedrine*, (S)-**18**. (*S*)-Deoxyephedrine hydro-

chloride (3·5 g) was treated with $NaHCO_3$, as described above (see for example preparation of **13**) and the free base was submitted to technique A, affording after crystallization from CH_2Cl_2–hexane, (*S*)-**18** (3·5 g): m.p. 102–103°; $[\alpha]_D$ +92°; ORD (*c*, 0·0002; dioxan): $[\Phi]_{600}$ +300°; $[\Phi]_{300}$ +9250°; $[\Phi]_{294}$ ±0°; $[\Phi]_{274}$ −13,400°; $[\Phi]_{249}$ −3470°; $[\Phi]_{218}$ −17,800°; $[\Phi]_{215}$ −15,000°; (*c*, 0·0003; dioxan): $[\Phi]_{600}$ +228°; $[\Phi]_{400}$ +961°; $[\Phi]_{350}$ +2019°; $[\Phi]_{323}$ +3643°; $[\Phi]_{332}$ +5569°; $[\Phi]_{320}$ +3508°; $[\Phi]_{301}$ +13,506°; $[\Phi]_{295}$ +16,093°; $[\Phi]_{282}$ ±0°; $[\Phi]_{270}$ −9954°; $[\Phi]_{245}$ −1359°; $[\Phi]_{240}$ −2938°; $[\Phi]_{232}$ −4517°; $[\Phi]_{228}$ −3947°; $[\Phi]_{218}$ −14,865°; $[\Phi]_{210}$ −15,348°; λ_{max}^{diox} 292 mμ (log ε 4·41); $\nu_{max}^{CHCl_3}$ 3080, 1600, 1550 cm^{-1}; NMR 0·76 (CH_3—C), 0·94 (CH_3—C), 1·92 [AB system, J_{AB} 16 c/s, δ_A 124 c/s, δ_B 107 c/s, CH_2—CH—N], 2·04 (CH_2—CO and CH_2—C=C), 2.63 (CH_3—N), 5·17 (vinylic H), 4·2 (multiplet, CH—CH_3), ~7·24 ppm (5 aromatic H). (Found: C, 79·80; H, 9·25; O, 5·86; N, 5·16. $C_{18}H_{25}ON$ requires: C, 79·66; H, 9·29; O, 5·90; N, 5·16%).

N-(*5,5-Dimethyl-2-cyclohexen-1-on-3-yl*) (R)-*deoxyephedrine* (R)-**18**. (*R*)-Deoxyephedrine (1·34 g) was submitted to the above procedure A. After crystallization from acetone–hexane, (*R*)-**18** (1·02 g) was obtained: m.p. 105–106°; $[\alpha]_D$ −103°; ORD (*c*, 0·001; dioxan): $[\Phi]_{600}$ −179°; $[\Phi]_{589}$ −217°; $[\Phi]_{450}$ −596°; $[\Phi]_{400}$ −932°; $[\Phi]_{350}$ −1962°; $[\Phi]_{322}$ −3924°; $[\Phi]_{317}$ −3480°; $[\Phi]_{312}$ −6233°; $[\Phi]_{308}$ −6504°; $[\Phi]_{298}$ −10,027°; $[\Phi]_{284}$ ±0°; $[\Phi]_{271}$ +11,924; $[\Phi]_{266}$ +11,382; $[\Phi]_{250}$ +5420°; $[\Phi]_{240}$ +5528°; $[\Phi]_{226}$ +13,116°; $[\Phi]_{222}$ +14,092°; $[\Phi]_{219}$ +21,192°; $[\Phi]_{209}$ ±0°; (*c*, 0·0001; dioxan): $[\Phi]_{600}$ −281°; $[\Phi]_{400}$ −1010°; $[\Phi]_{320}$ −3673°; $[\Phi]_{305}$ −7740°; $[\Phi]_{300}$ −9033°; $[\Phi]_{279}$ ±0°; $[\Phi]_{271}$ +12,308°; $[\Phi]_{253}$ +3500°; $[\Phi]_{219}$ +18,293°; $[\Phi]_{215}$ +14,115°; (*c*,0·001; dioxan); $[\Phi]_{600}$ −195°; $[\Phi]_{500}$ −310°; $[\Phi]_{400}$ −750°; $[\Phi]_{300}$ −12,600°; $[\Phi]_{280}$ ±0°; $[\Phi]_{276}$ +16,800°; $[\Phi]_{250}$ +3000°; λ_{max}^{diox} 291 mμ (log ε 4·43); $\nu_{max}^{CHCl_3}$ 3080, 1600 and 1550 cm^{-1}; NMR 0·78 (CH_3—C), 0·94 (CH_3—C), 1·25 (doublet, J = 7 c/s, CH_3—CH), 1·95 [AB system, J_{AB} 16 c/s, δ_A 124 c/s, δ_B 107 c/s, CH_2—CH—N], 2·04 (CH_2—C=C), 2·76 (doublet, J = 7 c/s, benzylic H), 2·95 (3H, CH_3—N), 4·18 (multiplet, CH—CH_3), 5·17 (vinylic H), 7·23 ppm (5 aromatic H). (Found: C, 79·54; H, 9·09; O, 6·08; N, 5·32. $C_{18}H_{25}ON$ requires: C, 79·66; H, 9·29; O, 5·90; N, 5·16%).

REFERENCES

[1] Department of Genetics, Stanford Medical Centre, Palo Alto, California.

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[3] [a] L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*. Pergamon Press, New York (1959);
[b] N. J. Bhacca and D. H. Williams, *Applications of NMR Spectroscopy in Organic Chemistry*. Holden-Day, San Francisco (1964).

[4] [a] J. M. Bijvoet, A. F. Peerdeman and A. J. van Bommel, *Nature, Lond.* **168**, 271 (1951);
[b] See: *Advances in X-Ray Analysis* (Edited by G. R. Mallett, M. Fay and W. M. Mueller) Plenum Press, New York (1957–1965).

[5] H. Budzikiewicz, C. Djerassi and D. H. Williams, *Mass Spectrometry of Organic Compounds*. Holden-Day, San Francisco (1967).

[6] B. Halpern and J. W. Westley, *Chem. Comm.* No. 12, 246 (1965); No. 18, 421 (1965); No. 2, 34 (1966); *Biochem. Biophys. Res. Comm.* **19**, 361 (1965); *Ibid.* **20**, 710 (1965).

[7] P. Crabbé, *Applications de la Dispersion Rotatoire Optique et du Dichroisme Circulaire Optique en Chimie Organique*. Gauthier-Villars, Paris (1968).

[8] C. Djerassi, *Optical Rotatory Dispersion. Applications to Organic Chemistry*. McGraw-Hill, New York (1960).

[9] G. Snatzke, *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*, Proceedings of NATO Summer School, Heyden London (1967).

[10] L. Velluz, M. Legrand and M. Grosjean, *Optical Circular Dichroism. Principles, Measurements and Applications*. Verlag Chemie, Weinheim (1965).

[11] E. L. Eliel, *Stereochemistry of Carbon Compounds*. McGraw-Hill, New York (1962);

[12] [a] K. Mislow, *Introduction to Stereochemistry*. Benjamin, New York (1965);
[b] M. Hanack, *Conformation Theory*. Academic Press, New York (1965).

[13] *Inter alia*: [a] V. M. Potapov, V. M. Demyanovich and A. P. Terentev, *Zh. Obschch. Khim.* **35**, 1538 (1965);
[b] P. Crabbé, *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry* p. 271. Holden-Day, San Francisco (1960);
[c] See Ref. 10, p. 154.

[14] [a] C. Djerassi, E. Lund, E. Bunnenberg and B. Sjöberg, *J. Am. Chem. Soc.* **83**, 2307 (1961);
[b] G. Snatzke, H. Ripperger, C. Horstmann and K. Schreiber, *Tetrahedron* **22**, 3103 (1966);
[c] A. La Manna and V. Ghislandi, *Il Farmaco* **17**, 355 (1962).
[15] [a] S. Mitchell, *J. Chem. Soc.* 3258 (1928);
[b] S. Mitchell, *Ibid.* 1829 (1930);
[c] S. Mitchell and S. B. Cormack, *Ibid.* 415 (1932).
[16] [a] W. Kuhn and H. L. Lehmann, *Z. physik. Chem.* **B18**, 32 (1932);
[b] W. Kuhn and H. Biller, *Ibid.* **B29**, 1 (1935);
[c] H. B. Elkins and W. Kuhn, *J. Am. Chem. Soc.* **57**, 296 (1935);
[d] W. Kuhn, *Ann. Rev. Phys. Chem.* **9**, 417 (1958).
[17] [a] F. Nerdel, K. Becker and G. Kresze, *Chem. Ber.* **89**, 2862 (1956);
[b] G. Dudek, *J. Org. Chem.* **32**, 2016 (1967).
[18] [a] A. P. Terentev and V. M. Potapov, *Zh. Obschch. Khim.* **28**, 1161 (1958);
[b] *Ibid.* **28**, 3323 (1958);
[c] V. M. Potapov, A. P. Terentev and R. I. Sarybaeva, *Ibid.* **29**, 3139 (1959);
[d] V. M. Potapov and A. P. Terentev, *Ibid.* **30**, 666 (1960);
[e] V. M. Potapov, A. P. Terentev and S. P. Spivak, *Ibid.* **31**, 2415 (1961).
[19] H. E. Smith, S. L. Cook and M. E. Warren, Jr., *J. Org. Chem.* **29**, 2265 (1964).
[20] [a] J. H. Brewster and S. F. Osman, *J. Am. Chem. Soc.* **82**, 5754 (1960);
[b] H. Wolf, E. Bunnenberg and C. Djerassi, *Chem. Ber.* **97**, 533 (1964).
[21] A. La Manna and V. Ghislandi, *Il Farmaco* **19**, 480 (1964).
[22] A. La Manna, V. Ghislandi, P. M. Scopes and R. H. Swan, *Ibid.* **20**, 842 (1965).
[23] H. E. Smith, M. E. Warren, Jr., and A. W. Ingersoll, *J. Am. Chem. Soc.* **84**, 1513 (1962).
[24] [a] D. Bertin and M. Legrand, *C.R. Acad. Sci., Paris* **256**, 960 (1963);
[b] M. E. Warren, Jr., and H. E. Smith, *J. Am. Chem. Soc.* **87**, 1757 (1965);
[c] H. E. Smith and T. Ch. Willis, *J. Org. Chem.* **30**, 2654 (1965);
[d] H. Ripperger, K. Schreiber, G. Snatzke and K. Heller, *Z. Chem.* **5**, 62 (1965);
[e] H. E. Smith and R. Records, *Tetrahedron* **22**, 1813 (1965).
[25] [a] R. S. Cahn and C. K. Ingold, *J. Chem. Soc.* 612 (1951);
[b] R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia* **12**, 81 (1956);
[c] R. S. Cahn, C. K. Ingold and V. Prelog, *Angew. Chem.* (Intern. Edit.), **5**, 385 (1966).
[26] P. Haas, *J. Chem. Soc.* **95**, 421 (1909).
[27] [a] B. Halpern and L. B. James, *Nature, Lond.* **202**, 592 (1964);
[b] B. Halpern and L. B. James, *Austral. J. Chem.* **17**, 1282 (1964);
[c] B. Halpern, *Ibid.* **18**, 417 (1965).
[28] [a] A. J. Speziale and L. R. Smith, *J. Org. Chem.* **28**, 3492 (1963);
[b] G. H. Alt and A. J. Speziale, *Tetrahedron Letters* No. 2, 111 (1963); *J. Org. Chem.* **29**, 794 (1964);
[c] G. O. Dudek and E. P. Dudek, *J. Am. Chem. Soc.* **86**, 4283 (1964), and Refs therein.
[29] [a] D. L. Ostercamp, *J. Org. Chem.* **30**, 1169 (1965);
[b] G. Slomp and J. G. Lindberg, *Analyt. Chem.* **39**, 60 (1967).
[30] B. Halpern and A. D. Cross, *Chem. & Ind.* 1183 (1965).
[31] P. Crabbé, B. Halpern and E. Santos, *Bull. Soc. Chim. Fr.* 1446 (1966).
[32] G. Aguilar-Santos, E. Santos and P. Crabbé, *J. Org. Chem.* **32**, 2642 (1967).
[33] E. Santos, J. Padilla and P. Crabbé, *Canad. J. Chem.* **45**, 2275 (1967).
[34] P. Crabbé and W. Klyne, *Tetrahedron* **23**, 3449 (1967).
[35] [a] G. G. Lyle, *J. Org. Chem.* **25**, 1779 (1960);
[b] L. I. Katzin and H. E. Smith, *Abstracts of Papers, Div. Org. Chem.*; 106, Amer. Chem. Soc., Pittsburgh, March (1966);
[c] J. Cymerman Craig, R. P. K. Cahn and S. K. Roy, *Tetrahedron* **23**, 3573 (1967).
[36] [a] *Inter alia*: a. S. Yamada, K. Ishikawa and K. Achiwa, *Chem. Pharm. Bull. Japan* **13**, 892, 1266 (1965);
[b] K. Achiwa and S. Yamada, *Ibid.* **14**, 537 (1966);
[c] G. C. Barrett, *J. Chem. Soc.* 2825 (1965); *Ibid.* 1771 (1966); *Ibid.* (C), 1 (1967);
[d] E. Bach, A. Kjaer, R. Dahlbom, T. Walle, B. Sjöberg, E. Bunnenberg, C. Djerassi and R. Records, *Acta. Chem. Scand.* **20**, 2781 (1966).