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Studies on Optical Rotatory Dispersion and Circular Dichroism. II.[1] Circular Dichroism of α-Hydroxy- and α-Amino-α-phenyl Ketones[2]

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Studies on circular dichroism of some open chain α-hydroxy-, α-amino-, and α-acylamido-α-phenyl ketones known of their absolute configurations demonstrated a good agreement between the rule of β,γ-unsaturated ketones and the experimental results in nonpolar solvents with a support of conformational analyses using their infra red spectra.

In the course of the studies, the absolute configuration of (+)-α-ethylphenylglycine (2-amino-2-phenylbutyric acid) ((+)-V) was concluded to have *S*-configuration.

Introduction

Optically active α-phenyl ketones have a dissymmetric β,γ-unsaturated ketone skeleton, which is an interesting chromophore on the optical rotatory dispersion (ORD) and the circular dichroism (CD). But, very few[4d] has been discussed for an open chain system. The present work is concerned with CD of optically active open chain α-phenyl ketones and solvent effects.

ORD and CD of dissymmetric β,γ-unsaturated ketones have been reported by many workers.[4,5,6] That is, the dissymmetric β,γ-unsaturated (including benzo) ketone is one of inherently dissymmetric chromophores characterised by the presence of relatively high molecular amplitude of the rotatory dispersion, and signs of the Cotton effect are determined by the relative disposition of the π-system and carbonyl group when suitably oriented, because the contribution to the optical activity associated with the inherently dissymmetric chromophore outweighs those that can be attributed to asymmetrically disposed substituents, such as alkyl groups and hydrogen atoms.[4d] Moreover, the sign of the Cotton effect can be correlated with the four far octants of the previously enunciated octant rule,[7] provided that the relative geometry of the π-system and carbonyl group is fixed.[4d]

The concept cited above can be extended to flexible α-phenyl ketones having the requisite structural features between the benzene ring and the carbonyl group.[8] Especially, as to open chain α-phenyl ketone derivatives, of the conformations which may exist for such ketones,

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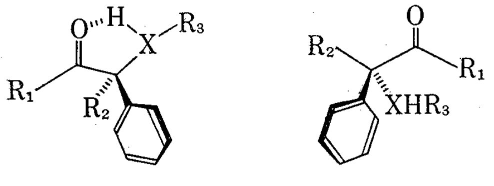
1) Part I: S. Yamada and T. Kunieda, *Chem. Pharm. Bull.* (Tokyo), **15**, 490 (1967).
2) Presented at the 89th Annual Meeting of Pharmaceutical Society of Japan, Nagoya, April, 1969.
3) Location: *Hongo, Bunkyo-ku, Tokyo.*
4) *a*) K. Mislow and C. Djerassi, *J. Am. Chem. Soc.*, **82**, 5247 (1960); *b*) K. Mislow, M.A.W. Glass, A. Moscowitz, and C. Djerassi, *ibid.*, **83**, 2771 (1961); *c*) K. Mislow, M.A.W. Glass, R.E. O'Brien, P. Rutkin, D.H. Steinberg, J. Weiss, and C. Djerassi, *ibid.*, **84**, 1455 (1962); *d*) A. Moscowitz, K. Mislow, M.A.W. Glass, and C. Djerassi, *ibid.*, **84**, 1945 (1962); *e*) K. Mislow and J.G. Berger, *ibid.*, **84**, 1956 (1962); *f*) E. Bunnerberg, C. Djerassi, K. Mislow, and A. Moscowitz, *ibid.*, **84**, 2823, 5003 (1962); *g*) D.J. Sandman and K. Mislow, *J. Org. Chem.*, **33**, 2924 (1968); *h*) D.J. Sandman, K. Mislow, W.P. Giddings, J. Dirlam, and G.C. Hanson, *J. Am. Chem. Soc.*, **90**, 4877 (1968).
5) *a*) D.E. Bays, R.C. Cookson, and S. MacKenzie, *J. Chem. Soc.* (*B*), **1967**, 215; *b*) D.E. Bays and R.C. Cookson, *ibid.*, **1967**, 226.
6) S. Watanabe, *Bull. Chem. Soc. Japan*, **46**, 1546 (1973).
7) W. Moffitt, R.B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Am. Chem. Soc.*, **83**, 4013 (1961).
8) *a*) R.C. Cookson and J. Hudec, *J. Chem. Soc.*, **1962**, 429; *b*) H.T. Thomas and K. Mislow, *J. Am. Chem. Soc.*, **92**, 6292 (1970).

only those, in which the phenyl group and the carbonyl group have a proper orientation for high optical activity, will be of interest for the purpose of the present discussion. Conformational analysis of carbonyl compounds suggests that the most stable rotamer of these compounds is the one where the carbonyl group eclipses a single bond bearing the α-carbon atom.[9] With two criteria just stated, important conformers are two rotamers depicted in Fig. 1, one (I) contributing a positive Cotton effect, the other (II) contributing to a negative one when considered in *S*-series. In particular, for α-hydroxy-, α-amino-, and α-acylamido-α-phenyl ketones discussed in the present work, intramolecular hydrogen-bonding controls the conformation. Therefore, shapes and signs of CD curves will be affected by solvents employed. We now report the CD curves of VI—XXI in polar and non-polar solvents and discuss the conformers presented in these solvents.

Syntheses and Absolute Configurations of Compounds VI—XXI

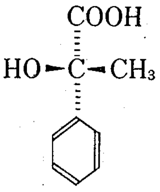
(*S*)(+)-3-Hydroxy-3-phenyl-2-butanone ((*S*)(+)-VI), (*S*)(+)-2-hydroxy-2-phenyl-3-pentanone ((*S*)(+)-VII), (*R*)(−)-3-amino-3-phenyl-2-butanone ((*R*)(−)-IX), (+)-3-amino-3-phenyl-2-pentanone ((+)-X), (*S*)(+)-3-butylamino-3-phenyl-2-butanone ((*S*)(+)-XI),(*R*)(−)-3-benzylamino-3-phenyl-2-butanone ((*R*)(−)-XII). (+)-3-benzylamino-3-phenyl-2-pentanone ((+)-XIII), (*R*)(+)-5-methyl-5-phenylpyrrolidin-2,4-dione ((*R*)(+)-XVIII), (+)-5-ethyl-5-phenylpyrrolidin-2,4-dione ((+)-XIX), (*S*)(−)-N-benzoyl-3-butylamino-3-phenyl-2-butanone ((*S*)(−)-XX), and (*R*)(+)-N-benzoyl-3-benzylamino-3-phenyl-2-butanone ((*R*)(+)-XXI) were prepared according to the methods previously reported by us.[10]



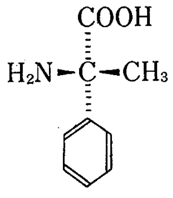
I II

X=O or N

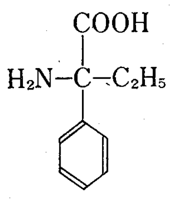
Fig. 1



(*S*)(+)−III



(*S*)(+)−IV



(+)−V

(*S*)(−)-N-Acetyl-3-amino-3-phenyl-2-butanone ((*S*)(−)-XIV), $[\alpha]_D^{17}$ −46.7° (c=1.05, EtOH), and (−)-N-acetyl-3-amino-3-phenyl-2-pentanone ((−)-XV), $[\alpha]_D^{18.5}$ −15.2° (c=1.03, EtOH), were prepared using acetyl chloride and triethylamine in chloroform from (*S*)(+)-IX and (+)-X·HCl respectively. (*S*)(+)-N-Benzoyl-3-amino-3-phenyl-2-butanone ((*S*)(+)-XVI), $[\alpha]_D^{14.5}$ +15.9° (c=1.01, EtOH), synthesised previously,[11] was used for CD measurements. Benzoylation of (+)-X·HCl by benzoyl chloride-triethylamine gave (+)-N-benzoyl-3-amino-3-phenyl-2-pentanone ((+)-XVII), $[\alpha]_D^{19}$ +50.4° (c=0.992, EtOH).

The absolute configurations of substrates VI, VII, IX, XI, XII, XIV, XVI, XVIII, XX, and XXI, prepared from atrolactic acid (III) or α-methylphenylglycine (IV), follow from that of the starting materials, (III),[12] (IV),[11] which have been clearly established, and the synthetic methods employed do not affect the asymmetric centres. The absolute configurations of others (X), (XIII), (XV), (XVII), and (XIX), synthesised from α-ethylphenylglycine (V), are unknown, since the absolute configuration of V has not been assigned yet. The absolute

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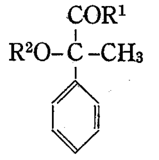
[9] *a*) G.J. Karabatsos and N. Hsi, *J. Am. Chem. Soc.*, **87**, 2864 (1965); *b*) *Idem*, *Tetrahedron*, **23**, 1079 (1967); *c*) G.J. Karabatsos and D.J. Fenoglio, *J. Am. Chem. Soc.*, **91**, 1124 (1969).

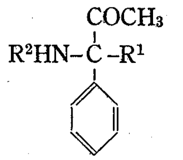
[10] H. Mizuno, S. Terashima, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **19**, 227 (1971).

[11] H. Mizuno, S. Terashima, K. Achiwa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **15**, 1749 (1967).

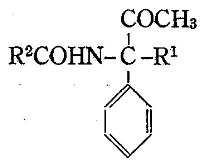
[12] *a*) K. Freudenberg, J. Todd, and R. Seidler, *Ann.*, **501**, 199 (1933); *b*) J.H. Brewster, *J. Am. Chem. Soc.*, **78**, 4061 (1956); D.J. Cram, K.R. Kopecky, F. Hauck, and Langemann, *ibid.*, **81**, 5759 (1959).



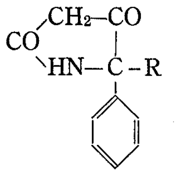
	R^1	R^2
(*S*)(+)-VI:	CH_3	H
(*S*)(+)-VII:	C_2H_5	H
(*S*)(−)-VIII:	CH_3	CH_3[a]



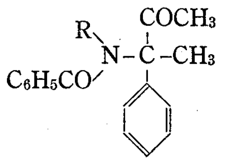
	R^1	R^2
(*S*)(+)-IX:	CH_3	H[a]
(+)-X :	C_2H_5	H
(*S*)(+)-XI:	CH_3	C_4H_9
(*S*)(+)-XII:	CH_3	$CH_2C_6H_5$[a]
(+)-XIII:	C_2H_5	$CH_2C_6H_5$



	R^1	R^2
(*S*)(−)-XIV:	CH_3	CH_3
(−)-XV :	C_2H_5	CH_3
(*S*)(+)-XVI:	CH_3	C_6H_5
(+)-XVII:	C_2H_5	C_6H_5



(*S*)(−)-XVIII: $R=CH_3$[a]
(+)-XIX: $R=C_2H_5$



(*S*)(−)-XX : $R=C_4H_9$
(*S*)(−)-XXI: $R=CH_2C_6H_5$[a]

[a] (*R*)-Isomer was used for CD measurement.

configurations of these compounds, however, will be proposed from their CD curves in this paper.

(*R*)(+)-3-Methoxy-3-phenyl-2-butanone ((*R*)(+)-VIII), α_D^{12} +21.2° ($l=0.1$, neat), was obtained from (*R*) (−)-VI, $[\alpha]_D^{12}$ −185° ($c=0.846$, C_6H_6), by a reaction with methyl iodide and silver oxide (Chart 1), and (*S*)(−)-VIII, $\alpha_D^{10.5}$ −29.4° ($l=0.1$, neat) from (*S*)(+)-VI, $[\alpha]_D^{11}$ +264° ($c=1.22$, C_6H_6) under the same reaction. (+)-VIII was, however, reported as *S*-series by Cram, *et al.*[13] In order to solve this contradiction, synthesis of (*R*)(+)-VIII was carried out by the following alternative route shown in Chart 1.

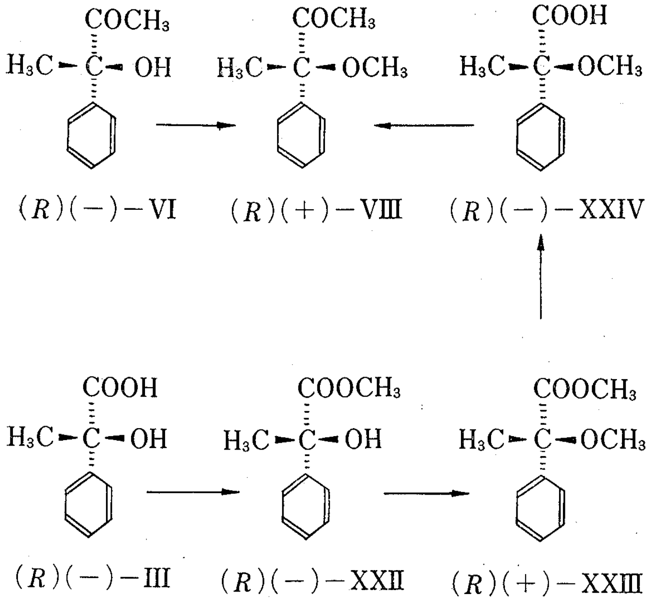


Chart 1

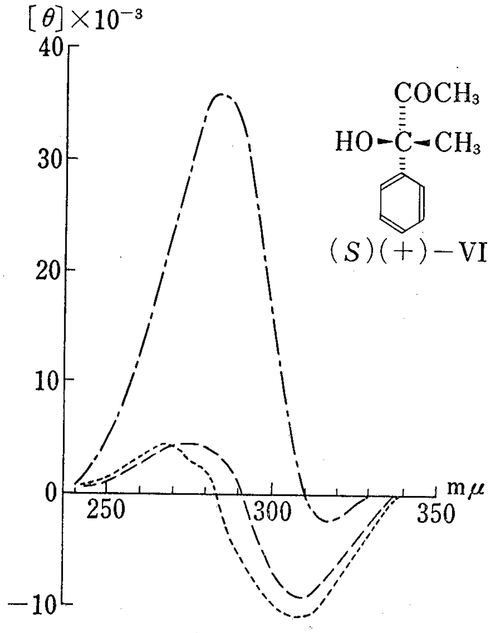


Fig. 2. CD Curves of (*S*)(+)-3-Hydroxy-3-phenyl-2-butanone ((*S*)(+)-VI)

———: in *n*-heptane
---------: in methanol
------: in dioxane ((*R*)-Isomer was used for measurement.)

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[13] D.J. Cram and K.R. Kopecky, *J. Am. Chem. Soc.*, **81**, 2748 (1959).

(*R*)(—)-Methyl atrolactate ((*R*)(—)-XXII), $\alpha_D^{21.5}$ —0.736° (l=0.02, neat), prepared from (*R*)(—)-atrolactic acid ((*R*)(—)-III), $[\alpha]_D^{18.5}$ —47.4° (c=1.06, H_2O), and diazomethane, was treated with methyl iodide in the presence of silver oxide to give (*R*)(+)-methyl 2-methoxy-2-phenylpropionate ((*R*)(+)-XXIII), α_D^{9} +5.43° (l=0.1, neat). Hydrolysis of (*R*)(+)-XXIII gave (*R*) (—)-2-methoxy-2-phenylpropionic acid ((*R*)(—)-XXIV), α_D^{11} —4.75° (l=0.1, neat), which was converted to (*R*) (+)-VIII, α_D^{11} +28.0° (l=0.1, neat), by a reaction with methyl lithium. (*R*)(+)-VIII thus obtained was identical with that obtained by the another method by elemental analysis, nuclear magnetic resonance (NMR), infrared (IR), and gas chromatography. Experiments stated above have clearly established the absolute configuration of VIII.

Results and Discussion

For α-hydroxy-α-phenyl ketones, such as VI and VII, the most stable conformer is assumed to be I in non-polar solvents, such as heptane or CCl_4, due to an intramolecular hydrogen-bond formation. Thus, a positive CD maximum is expected in these solvents. CD curves of (*S*)(+)-VI and (*S*)(+)-VII showed a positive CD maximum in non-polar solvents in accordance with this prediction, although a very weak negative CD maximum existed at the longer wave length region (Fig. 2 and 3). The IR spectrum of (*S*)(+)-VII suggested the existence of an intramolecular hydrogen-bonded hydroxy group, which appeared at 3465 cm^{-1} and was not affected by concentration change. This wave number agrees with the reported values,[14] and a free hydroxy group of alcohols generally shows absorption at *ca.* 3620 cm^{-1}.[14b] The conformer contributing to the negative CD maximum is assumed to correspond to II, but ν_{OH} of this rotamer could not be detected in the IR spectrum. In polar solvents, such as MeOH or dioxane,[15] (*S*)(+)-VI and (*S*)(+)-VII gave double humped CD maxima, a negative maximum and a positive one. This phenomenon suggests that II is favoured over I in polar solvents in which an intramolecular hydrogen-bonding could not exist.

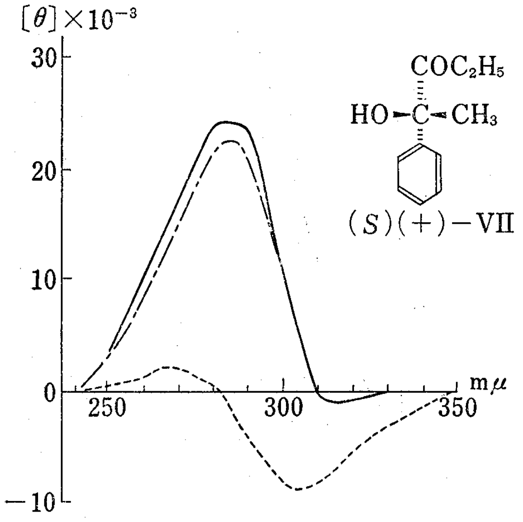

Fig. 3. CD Curves of (*S*)(+)-2-Hydroxy-2-phenyl-3-pentanone ((*S*)(+)-VII)

———: in *n*-heptane
———: in CCl_4
-----------: in methanol

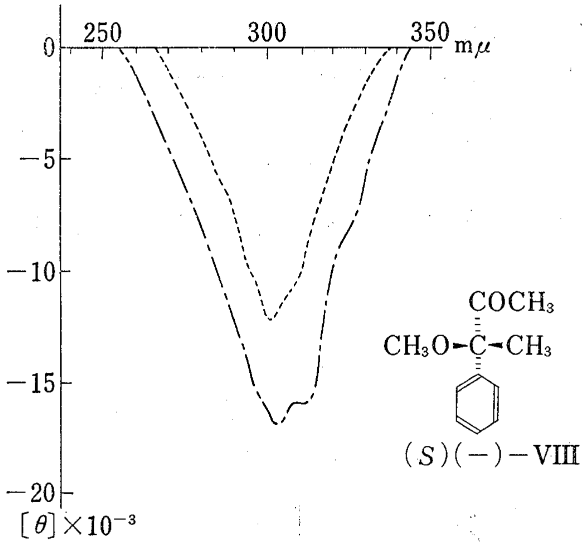

Fig. 4. CD Curves of (*S*)(—)-3-Methoxy-3-phenyl-2-butanone ((*S*)(—)-VIII)

———: in *n*-heptane, ---------: in methanol
(*R*)-Isomer was used for measurements.

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[14] *a*) T. Suga, T. Shishibori, and T. Matsuura, *J. Org. Chem.*, **32**, 965 (1967); *b*) T. Shishibori, *Bull. Chem. Soc. Japan*, **41**, 1170 (1968).

[15] Actual CD measurement was performed using (*R*)-isomer.

In order to demonstrate a rotamer (II) to be more stable when an intramolecular hydrogen-bonding can not form, CD of (*S*)(—)-3-methoxy-3-phenyl-2-butanone ((*S*)(—)-VIII) was investigated (Fig. 4).[15] (*S*)(—)-VIII showed only a negative CD maximum in any solvents in accordance with the prediction described above.

α-Amino-α-phenyl ketones, (*S*)(+)-IX,[15] (*S*)(+)-XI, (*S*)(+)-XII,[15] (+)-X, and (+)-XIII, exhibited a large positive and a small negative CD maxima in non-polar solvents, heptane and CCl_4 (Fig. 5, 6, 7, 8, and 9). This behavior suggests coexistence of two conformers, I and II. This was supported by the IR spectrum of (*S*)(+)-XI in CCl_4, which showed two maxima in the NH streching region, the weak free NH absorption (3398 cm^{-1}) and the strong hydrogen-bonded one (3340 cm^{-1}) at the concentration of the same order as the one employed for CD measurement (Fig. 10). It is assumed that a conformer corresponding to I contributes to the positive CD maximum and II to the negative one, according to the rule of β,γ-unsaturated ketones.[4d] This is supported by a coincidence of the strengths of the two CD maxima with those of the two NH absorptions.

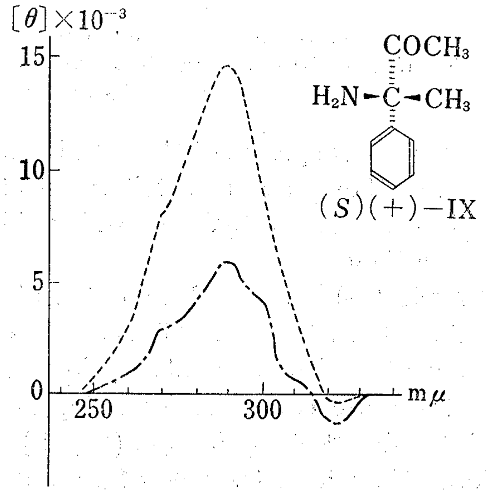


Fig. 5. CD Curves of (*S*)(+)-3-Amino-3-phenyl-2-butanone ((*S*)(+)-IX)

———: in *n*-heptane, ---------: in methanol
(*R*)-Isomer was used for measurements.

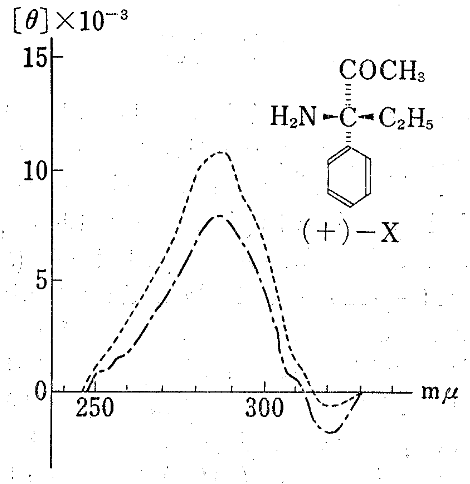


Fig. 6. CD Curves of (+)-3-Amino-3-phenyl-2-pentanone ((+)-X)

———: in *n*-heptane, ---------: in methanol

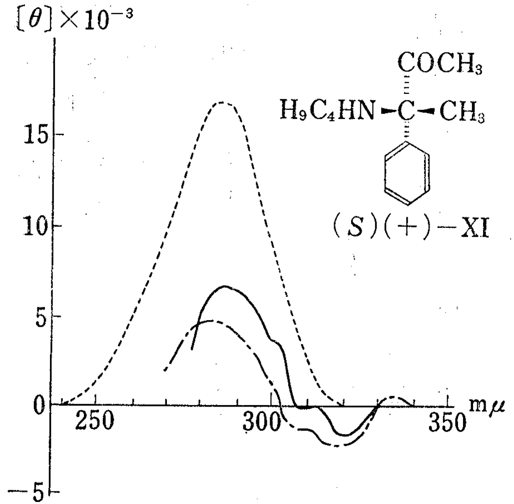


Fig. 7. CD Curves of (*S*)(+)-3-Butyl-amino-3-phenyl-2-butanone ((*S*)(+)-XI)

———: in *n*-heptane
———: in CCl_4
---------: in methanol

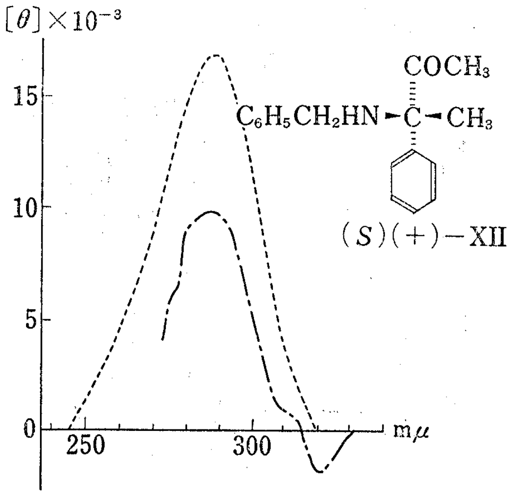


Fig. 8. CD Curves of (*S*)(+)-3-Benzyl-amino-3-phenyl-2-butanone((*S*)(+)-XII)

———: in *n*-heptane
---------: in methanol
(*R*)-Isomer was used for measurements.

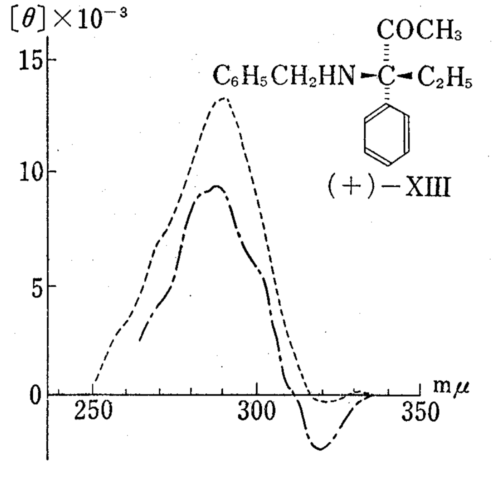


Fig. 9. CD Curves of (+)-3-Benzylamino-3-phenyl-2-pentanone ((+)-XIII)

——–——: in *n*-heptane
---------: in methanol

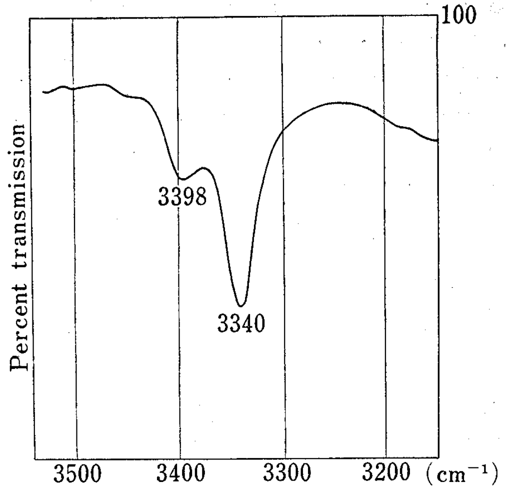


Fig. 10. ν_{NH} Spectrum on the Solution of (*S*)(+)-3-butylamino-3-phenyl-2-butanone ((*S*)(+)-XI) in CCl_4 (0.0195 M)

On the other hand, in a polar solvent, MeOH, all the CD spectra of the α-amino-α-phenyl ketones gave an only positive CD maximum which was thought to be attributed to the conformer I. These phenomena are inconsistent with the case of the α-hydroxy-α-phenyl ketones, and it is impossible to give reasonable explanations on them.

For α-acetamido-α-phenyl ketones (*S*)(—)-XIV and (—)-XV, the IR spectra of (*S*)(—)-XIV and (—)-XV in CCl_4 showed a NH absorption at 3401 cm^{-1} and at 3399 cm^{-1} respectively, at the same concentrations as those for CD measurements. These NH absorptions are found to be intramolecularly hydrogen-bonded, because these are concentration-independent and lower by *ca.* 50 cm^{-1} than that of (*R*)(+)-N-acetyl-2-amino-2-phenylbutane ((*R*)(+)-XXV)[11] (3447 cm^{-1}) corresponding to a free NH absorption. Therefore, the rule of β,γ-unsaturated ketones predicts that (*S*)(—)-XIV should give an only positive CD maximum attributed to the conformer I which is an intramolecularly hydrogen-bonded one. The experimental results agreed with the prediction (Fig. 11).

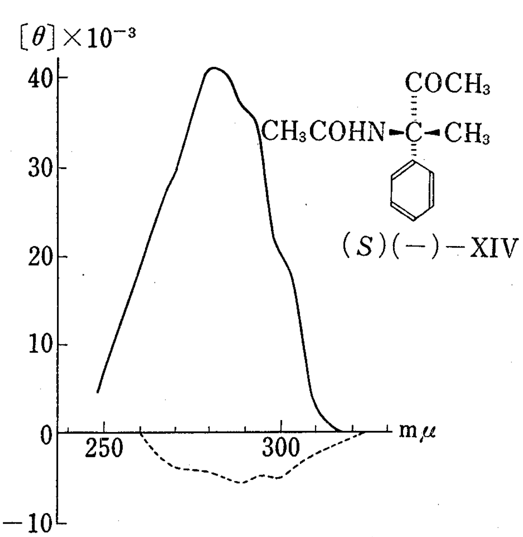


Fig. 11. CD Curves of (*S*)(—)-N-Acetyl-3-amino-3-phenyl-2-butanone ((*S*)(—)-XIV)

————: in CCl_4
-------------: in methanol

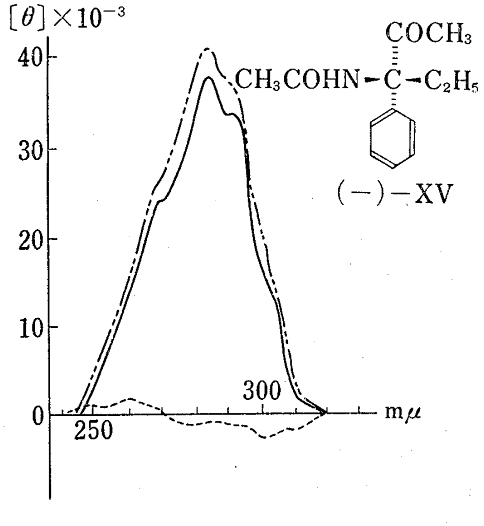
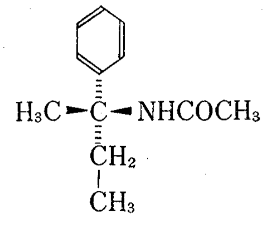


Fig. 12. CD Curves of (—)-N-Acetyl-3-amino-3-phenyl-2-pentanone ((—)-XV)

————: in CCl_4
————: in $CHCl_3$ (EtOH free)
-------------: in methanol

In a polar solvent such as MeOH, [θ] value of (*S*)(—)-XIV is markedly weaker than that of general β,γ-unsaturated ketones, and similar to that of normal α-asymmetric ketones. It is not clear whether the above behavior is due to the cancellation by a competitive contribution of the two conformers, I and II, or due to a contribution of the general ketone chromophore. CD spectra of (—)-XV were quite similar to those of (*S*)(—)-XIV (Fig. 11 and 12).



(*R*)(+)-XXV

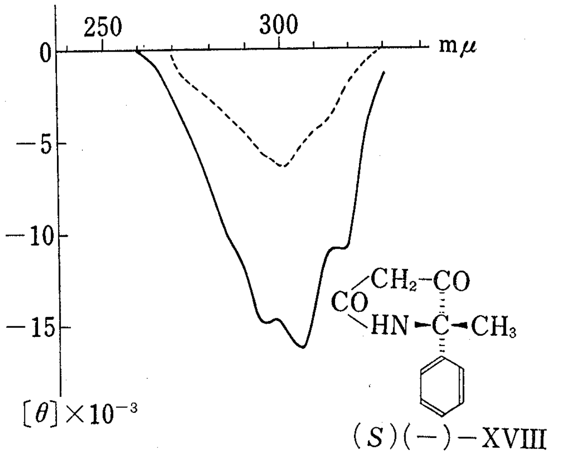


Fig. 13. CD Curves of (*S*)(—)-5-Methyl-5-phenylpyrrolidin-2,4-dione ((*S*)(—)-XVIII)

———: in CCl_4

-----------: in methanol

(*R*)-Isomer was used for measurements.

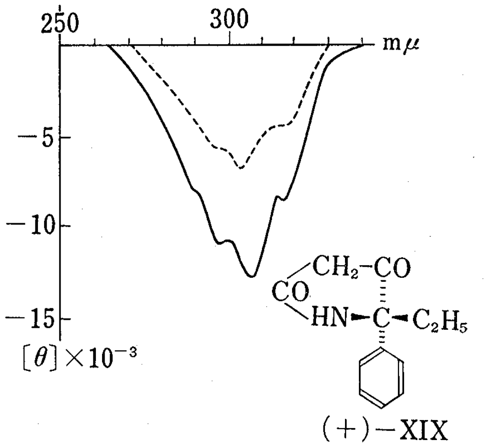


Fig. 14. CD Curves of (+)-5-Ethyl-5-phenylpyrrolidine-2,4-dione((+)-XIX)

———: in CCl_4

-----------: in methanol

(*S*) (—)-XVIII and (+)-XIX have a similar acetamide structure to those of (*S*) (—)-XIV and (+)-XV respectively, but the formers have a ring structure and these have no mobility in conformation. A molecular model of (*S*) (—)-XVIII shows that the relative composition of the benzene ring and carbonyl group is similar to that found in II. Thus, CD spectra of (*S*)(—)-XVIII$^{15)}$ are suggested to exhibit only a negative CD maximum regardless of solvents employed. The observed CD spectra were in good agreement with the prediction as shown in Fig. 13. (+)-XIX showed CD spectra similar to those of (*S*)(—)-XVIII (Fig. 14).

Different discussions from those stated hitherto should be made for α-benzamido-α-phenyl ketones. CD spectra of α-benzamido derivatives, where an interaction between a carbonyl group and a benzamide group could exist, might be attributed to the carbonyl group interacted with the benzamide group instead of the benzene ring, and not to the characteristic β,γ-unsaturated ketone chromophore. But the positions, the intensities, and the shapes of CD spectra of (*S*)(+)-XVI and (+)-XVII were similar to those of the acetamide derivatives in non-polar solvents, although the CD spectra in MeOH were found different. As a result, we may discuss (*S*)(+)-XVI and (+)-XVII in the category of the β,γ-unsaturated ketone. IR spectra of (*S*)(+)-XVI and (+)-XVII showed only an intramolecular hydrogen-bonded NH absorption at the same concentrations as those for CD measurements. Those absorptions appeared at 3403 and 3394 cm^{-1} in CCl_4 and in commercially available $CHCl_3$ (containing *ca.* 1% EtOH) respectively for (*S*)(+)-XVI, and at 3403 cm^{-1} in EtOH-free $CHCl_3$ for (+)-XVII. Therefore, nearly all the conformer of (*S*)(+)-XVI is considered to be I, and CD spectrum of the compound in non-polar solvents is suggested to show only a positive CD maximum. The experimental results are in good agreement with the prediction as shown in Fig. 15. (+)-XVII gave quite similar CD spectra to those of (*S*)(+)-XVI (Fig. 16).

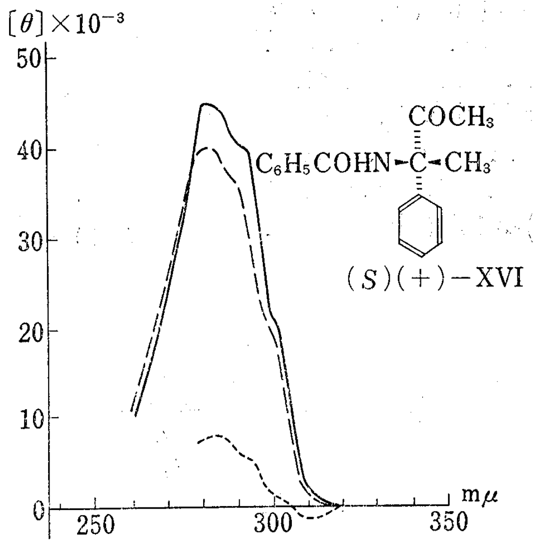


Fig. 15. CD Curves of (S)(+)-N-Benzoyl-3-amino-3-phenyl-2-butanone ((S)(+)-XVI)

———: in CCl_4
--------: in $CHCl_3$ (commecially available)
-----------: in methanol

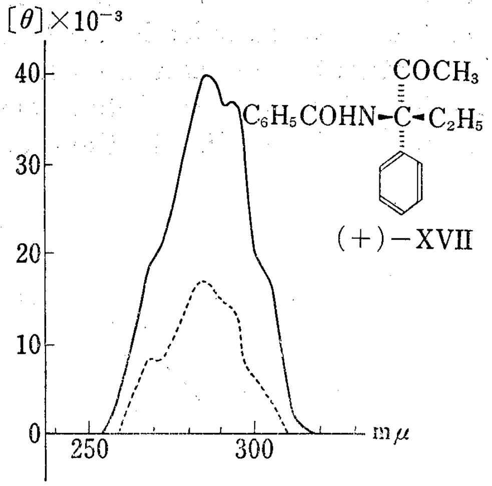


Fig. 16. CD Curves of (+)-N-Benzoyl-3-amino-3-phenyl-2-pentanone ((+)-XVII)

———: in CCl_4
-----------: in methanol

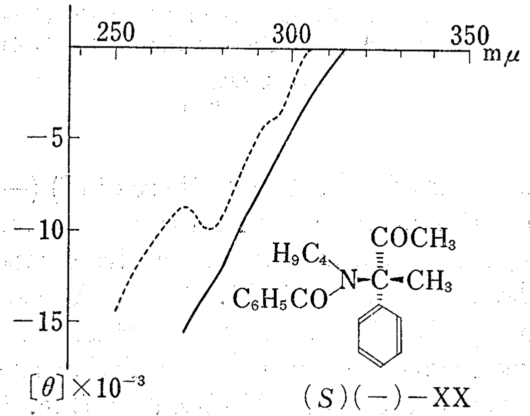


Fig. 17. CD Curves of (S)(−)-N-Benzoyl-3-butylamino-3-phenyl-2-butanone ((S)(−)-XX)

———: in CCl_4
-----------: in methanol

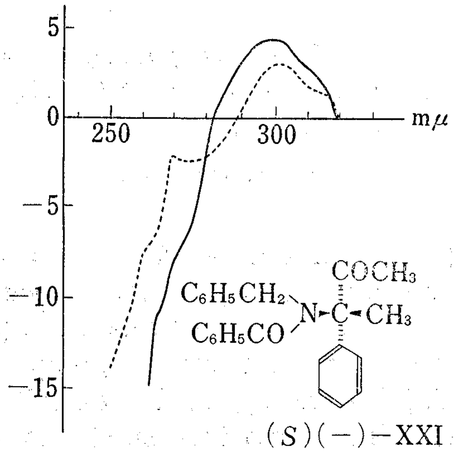


Fig. 18. CD Curves of (S)(−)-N-Benzoyl-3-benzylamino-3-phenyl-2-butanone ((S)(−)-XXI)

———: in CCl_4
-----------: in methanol
(R)-Isomer was used for measurements.

No discrepancy between in CCl_4 and in commercially available $CHCl_3$ for their IR and CD suggests that the intramolecular hydrogen-bonding is present even in a such graded polar solvent as commercially available $CHCl_3$.

Changing a solvent to a polar one such as MeOH, no inversion occurred for the CD spectra of (S)(+)-XVI and (+)-XVII (Fig. 15 and 16).

Shapes of CD curves of (S)(−)-XX and (S)(−)-XXI[15] (Fig. 17 and 18) were quite different from those associated with the typical β,γ-unsaturated ketones shown above. Therefore, this phenomenon seems to reflect the complication of the benzamide derivatives stated above.

As shown in Fig. 6, Fig. 9, Fig. 12, Fig. 14, and Fig. 16, the CD spectra of (+)-X, (+)-XIII, (−)-XV, (−)-XIX, and (+)-XVII correlated to (+)-α-ethylphenylglycine ((+)-V) are quite similar to those of the corresponding derivatives prepared from (*S*)(+)-α-methylphenylglycine ((*S*)(+)-IV), thus, the absolute configuration of (+)-α-ethylphenylglycine ((+)-V) and all the compounds prepared from (+)-V was supposed to belong to *S*-series.

Experimental[16]

(*S*)(+)- and (*R*)(−)-3-Hydroxy-3-phenyl-2-butanone ((*S*)(+)-VI and (*R*)(−)-VI)——(*S*)(+)-VI ($[\alpha]_D^{32.5}$ +222° (c=1.27, benzene)),[10] prepared from 81% optically pure (*S*)(+)-III was used for measurements. CD (c=0.251, heptane) $[\theta]^{30.5}$ (mμ): 0 (329), −1700(317)(negative maximum), 0 (310), +36100 (283) (positive maximum), +2200 (240). CD (c=0.424, MeOH) $[\theta]^{29.5}$ (mμ): 0 (335), −13000 (306) (negative maximum), 0 (283), +4220(268) (positive maximum), +600 (240). Measurement cited below was performed using (*R*)(−)-VI ($[\alpha]_D^{30}$ −198° (c=0.960, benzene))[7] prepared from 75% optically pure (*R*)(−)-III. CD (c=0.468, dioxane) $[\theta]^{27}$ (mμ): 0 (338), +9100 (308) (positive maximum), 0 (292), −5450 (276) (negative maximum), −500 (240) (Fig. 2).

(*S*)(+)-2-Hydroxy-2-phenyl-3-pentanone((*S*)(+)-VII)——(*S*)(+)-VII ($[\alpha]_D^{26}$ +211° (c=0.940, benzene)),[10] prepared from 85% optically pure (*S*)(+)-III, was used for measurements. CD (c=0.478, heptane) $[\theta]^{30}$ (mμ): 0 (335), −986 (315) (negative maximum), 0 (309), +23600 (284) (positive maximum), 0 (238). CD (c=0.406, CCl_4) $[\theta]^{29.5}$ (mμ): 0 (333), −1010 (315) (negative maximum), 0 (304) +25600 (283) (positive maximum), +5400 (250). CD (c=0.404, MeOH) $[\theta]^{29.5}$ (mμ): 0 (343), −8880 (304) (negative maximum), 0 (283), +2260 (270), +2400 (264) (positive maximum), 0 (239) (Fig. 3). IR $\nu_{max}^{CCl_4}$ cm^{-1}: (0.0231 M) ν_{OH} 3465, (0.0046 M) ν_{OH} 3461.

(*S*)(−)- and (*R*)(+)-3-Methoxy-3-phenyl-2-butanone ((*S*)(−)- and (*R*)(+)-VIII)——i) Syntheses from (*S*)(+)-VI and (*R*)(−)-VI: Silver oxide (1.62 g, 0.0210 mole) was added to a mixture of (*R*)(−)-VI ($[\alpha]_D^{12}$ −185° (c=0.846, benzene)) (1.15 g, 0.00701 mole), methyl iodide (2.99 g, 0.0210 mole), and dimethyl formamide (11 ml) with stirring in an ice bath. The mixture was stirred at room temperature for 2 days and diluted with $CHCl_3$ (40 ml). The insoluble material was filtered off and washed with $CHCl_3$. Filtrate and washings were evaporated *in vacuo* to a yellow oil. Its solution in benzene (20 ml) was washed with 5% HCl, satd. NaCl soln., 5% Na_2CO_3, and satd. NaCl soln., dried over anhydrous $MgSO_4$, and evaporated to a pale yellow oil. Column chromatography using silica gel (eluted with *n*-hexane: isopropyl ether: CH_2Cl_2= 40: 3: 3) followed by fractional distillation gave (*R*)(+)-VIII as a colourless oil (460 mg, 37%), bp 81—86° (3 mmHg), α_D^{12} +21.2° (l=0.1, neat). (lit.[13] bp 77° (0.5 mmHg), α_D^{25} +107.8° (l=1, neat)[17]). *Anal.* Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.38; H, 7.84. IR ν_{max}^{neat} cm^{-1}: 1722, 760, 702. NMR (10% solution in CCl_4) δ: 1.55 (3H, singlet, $-C-CH_3$), 1.97 (3H, singlet, $-COCH_3$), 3.28 (3H, singlet, $-OCH_3$), 7.22 (5H, singlet, aromatic proton). CD (c=0.502, heptane) $[\theta]^{17}$ (mμ): 0 (342), +176000 (302) (positive maximum) 0 (255). CD (c=0.602, MeOH) $[\theta]^{16}$ (mμ): 0 (338), +12600 (300) (positive maximum), 0 (265) (Fig. 4).

Similar treatment of (*S*)(+)-VI ($[\alpha]_D^{11}$ +264° (c=1.22, benzene)) (2.00 g, 0.00122 mole) to that for (*R*)(−)-VI described above gave (*S*)(−)-VIII as a colorless oil (640 mg, 29%), bp 121° (19.5 mmHg), $\alpha_D^{10.5}$ −29.4° (l=0.1, neat). *Anal.* Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.86; H, 7.96. IR ν_{max}^{neat} cm^{-1}: 1724, 761, 702. NMR spectrum was identical with that of (*R*)(+)-VIII.

ii) Synthesis from (*R*)(−)-III.

(*R*)(+)-Methyl 2-Methoxy-2-phenylpropionate ((*R*)(+)-XXIII)——(*R*)(−)-XXII ($\alpha_D^{21.5}$ −0.736° (l=0.02, neat)) (8.50 g, 0.0471 mole), prepared from (*R*)(−)-III ($[\alpha]_D^{13.5}$ −47.4° (c=1.06, H_2O)) and diazomethane, was treated in a similar manner to the synthesis of (*R*)(+)-VIII from (*R*)(−)-VI to give a pale yellow oil as a neutral fraction. Fractional distillation afforded (*R*)(+)-XXIII as a colorless oil (8.50 g, 93%), bp 96—98.5° (5.5 mmHg), α_D^{9} +5.43° (l=0.1, neat) (lit.[13] α_D^{24} −52.2° (l=1, neat)). NMR (10% solution in CCl_4) δ: 1.62 (3H, singlet, $-\underset{|}{\overset{|}{C}}-CH_3$), 3.23 (3H, singlet, $-OCH_3$), 3.64 (3H, singlet, $-COOCH_3$), 7.25 (5H, multiplet, aromatic proton).

(*R*)(−)-2-Methoxy-2-phenylpropionic Acid ((*R*)(−)-XXIV)——A mixture of (*R*)(+)-XXIII (α_D^{9} +5.43° (l=0.1, neat)) (9.20 g, 0.0474 mole) and 5% aq. NaOH (200 ml) was stirred at room temperature overnight to give a clear solution. The solution was washed with ether (50 ml), and the aqueous layer was acidified with concd. HCl and extracted with ether (50 ml × 3). Combined ethereal layers were washed with satd. NaCl soln., dried over anhyd. $MgSO_4$, and evaporated to give crude (*R*)(−)-XXIV as a pale yellow oil (9.0 g, 100%), α_D^{11} −4.75° (l=0.1, neat) (lit.[13] α_D^{26} +24° (l=0.1, neat)). IR ν_{max}^{neat} cm^{-1}: *ca.* 3200 (broad), 1717. This crude (*R*)(−)-XXIV was used for the following experiment without further purification.

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16) All melting points are uncorrected. IR spectra were taken with a Spectrometer, Model 402, Japan Spectroscopic Co., Ltd. Optical activities were measured on a Yanagimoto Photo Direct Reading Polarimetor, Model OR-20. CD curve measurements were performed using a Spectrometer, Model ORD/UV-5, Japan Spectroscopic Co., Ltd. NMR spectra were determined with a Spectrometer, Model 3H-60, Japan Electron Optics Lab. with tetramethylsilane as an internal standard.

17) D.J. Cram and K.R. Kopecky[13] reported (+)-VIII to belong to *S*-series.

(*R*)(+)-3-Methoxy-3-phenyl-2-butanone ((*R*)(+)-VIII)——(*R*)(−)-XXIV (α_D^{11} −4.75° (l=0.1, neat)) (5.00 g, 0.0277 mole) was added to a methanolic solution (50 ml) of Li (0.19 g, 0.0277 mole) to precipitate a colorless solid. Evaporation followed by drying *in vacuo* at *ca.* 60° gave the lithium salt of (*R*)(−)-XXIV.

Ether solution (110 ml) of methyl lithium prepared from Li (1.06 g, 0.153 mole) and methyl iodide (9.85 g, 0.0693 mole) was added to a suspension of the lithium salt of (*R*)(−)-XXIV obtained above in dry ether (40 ml). The suspension was refluxed with stirring under N_2 atmosphere for 8 hr, and treated with H_2O with stirring in an ice bath. Separated organic layer was washed with satd. NaCl soln., 5% HCl, aq. $Na_2S_2O_4$, and satd. NaCl soln., dried over anhyd. $MgSO_4$, and evaporated to a yellow oil, which was distilled under reduced pressure. The volatile fraction (3.70 g, bp 95—100° (7 mmHg)) was submitted to column chromatography using silica gel (eluted with *n*-hexane: isopropyl ether=10: 1) and distilled fractionally to give (*R*)(+)-VIII as a colorless oil (2.61 g, 53%), bp 86° (6.5 mmHg), α_D^{11} +28.0° (l=0.1, neat). *Anal.* Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.71; H, 7.87. IR ν_{max}^{neat} cm^{-1}: 1723, 760, 702. NMR spectrum was identical with that of (*R*)(+)-VIII prepared from (*R*)(−)-VI. The semicarbazone: colourless pillars (from aq. EtOH), mp 188—190°, $[\alpha]_D^{15}$ +218° (c=0.836, MeOH). *Anal.* Calcd. for $C_{12}H_{17}O_2N_3$: C, 61.25; H, 7.28; N, 17.86. Found: C, 61.38; H, 7.42; N, 18.06. The oxime: colourless needles (from aq. EtOH), mp 56—59°, $[\alpha]_D^{14}$ +139° (c=0.780, MeOH). *Anal.* Calcd. for $C_{11}H_{15}O_2N$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.62; H, 7.94; H, 7.49. IR ν_{max}^{KBr} cm^{-1}: 3265, 1602.

(*R*)(−)-3-Amino-3-phenyl-2-butanone ((*R*)(−)-IX)[10]——$[\alpha]_D^{26}$ −59.8° (c=1.17, benzene), optical purity 99%. CD (c=0.394, heptane) $[\theta]^{25}$ (mμ): 0 (333), +1300 (320) (positive maximum), 0 (315), −5990 (290) (negative maximum), 0 (247). CD measurement cited below was carried out using (*R*)(−)-IX (α_D^{31} −4.94° (l=0.1, neat), optical purity 90%). CD (c=0.480, MeOH) $[\theta]^{31.5}$ (mμ): 0 (330), +340 (322) (positive maximum), 0 (318), −14600 (289) (negative maximum), 0 (242) (Fig. 5).

(+)-3-Amino-3-phenyl-2-pentanone ((+)-X)[10]——$[\alpha]_D^{26}$ +32.6° (c=1.20, benzene), optical purity 100%. CD (c=0.624, heptane) $[\theta]^{29.5}$ (mμ): 0 (332), −1970 (320) (negative maximum), 0 (313), +7900 (288) (positive maximum), 0 (245). CD (c=0.614, MeOH) $[\theta]^{28}$ (mμ): 0 (330), −460 (319) (negative maximum), 0 (315), +11000 (288) (positive maximum), 0 (244) (Fig. 6).

(*S*)(+)-3-Butylamino-3-phenyl-2-butanone ((*S*)(+)-XI)[10]——$[\alpha]_D^{28.5}$ +114° (c=1.09, EtOH), optical purity 95%. CD (c=0.364, heptane) $[\theta]^{30.5}$ (mμ): 0 (327), −2390 (318) (negative maximum), −1600 (305), 0 (302), +4980 (281) (positive maximum), +2000 (270). CD (c=0.410, CCl_4) $[\theta]^{20}$ (mμ): 0 (339), +600 (333), 0 (327), −1850 (320) (negative maximum), 0 (314—306), +6700 (285) (positive maximum), +2900 (270). CD (c=0.460, MeOH) $[\theta]^{30.5}$ (mμ): 0 (317), +16500 (285) (positive maximum), 0 (242) (Fig. 7). IR $\nu_{max}^{CCl_4}$ cm^{-1}: (0.0195 M) ν_{NH} 3398, 3340 (Fig. 10), (0.0039 M) ν_{NH} 3398, 3340.

(*R*)(−)-3-Benzylamino-3-phenyl-2-butanone ((*R*)(−)-XII)[10]——α_D^{24} −3.61° (l=0.1 neat), optical purity 96%. CD (c=0.382, heptane) $[\theta]^{26}$ (mμ): 0 (329), +1750 (322) (positive maximum), 0 (315), −9850 (290) (negative maximum), −4400 (270). CD (c=0.736, MeOH) $[\theta]^{26}$ (mμ): 0 (320), −22700 (288) (negative maximum), 0 (245) (Fig. 8).

(+)-3-Benzylamino-3-phenyl-2-pentanone ((+)-XIII)[10]——$[\alpha]_D^{23}$ +37.0° (c=1.16, benzene), optical purity 100%. CD (c=0.416, heptane) $[\theta]^{24.5}$ (mμ): 0 (332), −2500 (320) (negative maximum), 0 (312), +9600 (288) (positive maximum), +9330 (283), +4000 (270). CD (c=0.424, MeOH) $[\theta]^{23}$ (mμ): 0 (348), +160 (330), 0 (326), −460 (319) (negative maximum), 0 (315), +13400 (288) (positive maximum), 0 (240) (Fig. 9).

(*S*)(−)-N-Acetyl-3-amino-3-phenyl-2-butanone ((*S*)(−)-XIV)——A solution of acetyl chloride (0.83 g, 0.0105 mole) in $CHCl_3$ (6 ml) was added to a stirred cold mixture of (*S*)(+)-IX ($[\alpha]_D^{19}$ +54.2° (c=1.04, benzene)) (0.86 g, 0.00527 mole), triethylamine (1.33 g, 0.0132 mole) and $CHCl_3$ (14 ml). The reaction mixture was washed with 5% HCl, satd, NaCl soln., 5% Na_2CO_3, and satd. NaCl soln., dried over anhyd. Na_2SO_4, and evaporated to give (*S*)(−)-XIV as slightly yellow crystals (1.12 g, 100%), mp 80—86°. Three recrystallisations from benzene–isopropyl ether–*n*-hexane gave colourless prisms, mp 87.5—88.5°, $[\alpha]_D^{17}$ −46.7° (c=1.05, EtOH). *Anal.* Calcd. for $C_{12}H_{15}O_2N$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.33; H, 7.35; N, 7.00. IR ν_{max}^{KBr} cm^{-1}: 3331, 3228, 1717, 1633, 1517, 764, 698. IR $\nu_{max}^{CCl_4}$ cm^{-1}: (0.001 M) ν_{NH} 3401. CD (c=0.230, CCl_4) $[\theta]^{20.5}$ (mμ): 0 (318) +41200 (282) (positive maximum), +5000 (250). CD (c=0.426, MeOH) $[\theta]^{20.5}$ (mμ): 0 (321), −4850 (298), −5400 (288) (negative maximum) −4350 (281), 0 (257) (Fig. 11).

(−)-N-Acetyl-3-amino-3-phenyl-2-pentanone ((−)-XV)——(+)-X·HCl ($[\alpha]_D^{19}$ +200° (c=0.658, EtOH)) (0.80 g, 0.00375 mole) was acetylated similarly to (*S*)(+)-IX with acetyl chloride and triethylamine in $CHCl_3$ to give (−)-XV as nearly colourless crystals (0.78 g, 95%), mp 101—104°. Three recrystallizations from benzene–isopropyl ether–*n*-hexane gave colourless leaflets, mp 103—104°, $[\alpha]_D^{18.5}$ −15.2° (c=1.03, EtOH). *Anal.* Calcd. for $C_{13}H_{17}O_2N$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.11; H, 7.91; N, 6.53. IR ν_{max}^{KBr} cm^{-1}: 3236, 1712, 1633, 1508. IR $\nu_{max}^{CCl_4}$ cm^{-1}: (0.018 M) ν_{NH} 3399, (0.0037 M) ν_{NH} 3399. IR $\nu_{max}^{CHCl_3(EtOH free)}$ cm^{-1}: (0.0094 M) ν_{NH} 3394. CD (c=0.201, CCl_4) $[\theta]^{24}$ (mμ): 0 (318), +34000 (293), +38100 (285) (positive maximum) +24500 (271), 0 (246). CD (c=0.206, $CHCl_3$ (EtOH free)) $[\theta]^{23}$ (mμ): 0 (313), +41500 (284) (positive maximum), 0 (244). CD (c=0.414, MeOH) $[\theta]^{23}$ (mμ): 0 (325), −2100 (308), −3240 (299) (negative maximum), −1750 (289), −790 (281), 0 (276), −440 (273), 0 (271), +1750 (263) (positive maximum), +1310 (250), 0 (242) (Fig. 12).

(*R*)(+)-5-Methyl-5-phenylpyrrolidin-2,4-dione ((*R*)(+)-XVIII)[10]——$[\alpha]_D^{27}$ +42.1° (c=1.11, benzene). CD (c=0.418, CCl_4) $[\alpha]^{21.5}$ (mμ): 0 (338), +11300 (317), +16700 (307) (positive maximum), +14900 (296), 0 (261). CD (c=0.400, MeOH) $[\theta]^{24.5}$ (mμ): 0 (331), +6480 (301) (positive maximum), 0 (273) (Fig. 13).

(+)-5-Ethyl-5-phenylpyrrolidin-2,4-dione (**(+)-XIX**)[10]——$[\alpha]_D^{19}$ +87.1° (c=1.02, EtOH). CD (c=0.410, CCl_4) $[\theta]^{24}$ (mμ): 0 (346), −8590 (318), −13000 (307) (negative maximum), −11400 (297), 0 (266). CD (c=0.404, MeOH) $[\theta]^{22.5}$ (mμ): 0 (329), −4510 (317), −6840 (304) (negative maximum), −5380 (296), 0 (271), (Fig. 14).

(*S*)(+)-N-Benzoyl-3-amino-3-phenyl-2-butanone (**(*S*)(+)-XVI**)[11]——$[\alpha]_D^{14.5}$ +15.9° (c=1.01, EtOH). CD (c=0.220, CCl_4) $[\theta]^{21}$ (mμ): 0 (315), +40500 (291), +44800 (283) (positive maximum), +8800 (260). CD (c=0.216, $CHCl_3$ (commercially available)) $[\theta]^{23}$ (mμ): 0 (311), +40700 (281) (positive maximum), +6950 (260). CD (c=0.434, MeOH) $[\theta]^{18}$ (mμ): 0 (318), −850 (309) (negative maximum), 0 (305). +8500 (282) (positive maximum), +7100 (276) (Fig. 15). IR $\nu_{\max}^{CCl_4}$ cm^{-1}: (0.0083 M) ν_{NH} 3403. IR $\nu_{\max}^{CHCl_3\,(\text{commercially available})}$ cm^{-1}: (0.0081 M) ν_{NH} 3394.

(+)-N-Benzoyl-3-amino-3-phenyl-2-pentanone (**(+)-XVII**)——(+)-X·HCl ($[\alpha]_D^{19}$ +200° (c=0.685, EtOH)) (0.60 g, 0.00281 mole) was benzoylated similarly to the acetylation of (+)–X·HCl with benzoyl chloride and triethylamine in $CHCl_3$ to give a pale yellow oil as a neutral fraction after extractive isolation. This oil was treated with a mixture of pyridine (6 ml) and H_2O (24 ml) to decompose unreacted benzoyl chloride. The mixture was worked up as usual to give (+)-XVII as pale yellow crystals (0.77 g, 97%). Three recrystallizations from ethanol–isopropyl ether–*n*-hexane gave colourless pillars, mp 115—116.5°, $[\alpha]_D^{19}$ +50.4° (c=0.992, EtOH). *Anal.* Calcd. for $C_{18}H_{19}O_2N$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.96; H, 6.84; N, 5.26. IR $\nu_{\max}^{KBr}$ cm^{-1}: 3380, 3266, 1706, 1641, 1475. IR $\nu_{\max}^{CCl_4}$ cm^{-1}: (0.0082 M) ν_{NH} 3403. CD (c=0.230, CCl_4) $[\theta]^{23.5}$ (mμ): 0 (313), +36400 (292), +40100 (285) (positive maximum), 0 (256), CD (c=0.200, MeOH) $[\theta]^{19.5}$ (mμ): 0 (310), +16400 (283) (positive maximum), +8200 (268), 0 (259) (Fig. 16).

(*S*)(−)-N-Benzoyl-3-butylamino-3-phenyl-2-butanone (**(*S*)(−)-XX**)[10]——$[\alpha]_D^{15}$ −15.9° (c=2.13, EtOH). CD (c=0.208, CCl_4) $[\theta]^{20}$ (mμ): 0 (312), −15900 (270). CD (c=0.214, MeOH) $[\theta]^{20}$ (mμ): 0 (305), −10300 (277), −7600 (269), −15000 (250) (Fig. 17).

(*R*)(+)-N-Benzoyl-3-benzylamino-3-phenyl-2-butanone (**(*R*)(+)-XXI**)[10]——$[\alpha]_D^{31}$ +4.3° (c=1.99, EtOH). CD (c=0.212, CCl_4) $[\theta]^{21.5}$ (mμ): 0 (318), −4300 (298), 0 (282). +19500 (260). CD (c=0.408 (λ>289 mμ) c=0.206 (λ<289 mμ), MeOH) $[\theta]^{20}$ (mμ): 0 (320), −3240 (299), 0 (289), +2150 (275), +14100 (253) (Fig. 18).