Attempted Catalytic Dehydrogenation of 1. A mixture of 1 (0.4 g), mp 177–179 °C, and 10% Pd/C (40 mg) was heated at 200–210 °C in a fused salt bath for 2 h. The reaction mixture was cooled, boiled with toluene (100 ml), and filtered to remove catalyst. The filtrate was rotary evaporated and pumped to dryness to give recovered **1**, mp 174–177 °C. The same sample was heated with new catalyst (40 mg) at 300 °C for 2 h and treated in the same manner to give 0.4 g of **1**, mp 169–175 °C, and mixed with starting material, mp 174–178 °C. GLC studies showed a single major peak with a trace of trailing impurity. Individual and mixed injections of starting material and sample showed identical retention times.[17b] A second sample of **1** (401 mg), catalyst (40 mg), and 1-methylnaphthalene (40 ml) were refluxed briskly for 2 h. The warm reaction mixture was filtered and washed with 90 ml of hot toluene. This solution was rotary evaporated and Kugelrohr distilled to remove toluene and 1-methylnaphthalene. The resulting tan solid was recrystallized from isohexane. The first crop yielded 345 mg, mp 177–179 °C (mixed with starting material, mp 176–179 °C); the second crop gave 28 mg, mp 175–177 °C, with a total return of 373 mg (93%) of recovered starting material. GLC studies of this sample showed results similar to those described above.

Acknowledgments. We thank the American Petroleum Institute for support during the early part of this work. We also thank the Continental Oil Co. for some current support, and the University of Oklahoma for providing computer time. We are grateful to Dr. P. W. Flanagan for his contribution in the early work.

Registry No.—**1**, 59434-72-9; **3**, 59434-73-0; **4**, 59434-74-1; naphthalene, 91-20-3; sodium, 7440-23-5; ethylenediamine, 107-15-3.

Supplementary Material Available. A listing of temperature factor parameters (Table II) and positional coordinates of hydrogen atoms (Table III) (2 pages). Ordering information is given on any current masthead page.

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(14) See paragraph at end of paper regarding supplementary material. The structure factor table may be obtained directly from Dr. Dick van der Helm, Department of Chemistry, University of Oklahoma, Norman, Okla. 73069.
(15) D. van der Helm, S. E. Ealick, and J. E. Burks, *Acta Crystallogr., Sect. B*, **31**, 1013 (1975).
(16) J. W. Burnham, W. P. Duncan, E. J. Eisenbraun, G. W. Keen, and M. C. Hamming, *J. Org. Chem.*, **39**, 1416 (1974).
(17) (a) The GLC studies were done on a Hewlett-Packard 5750 instrument with dual flame ionization detectors using a 8 ft × 0.25 in. copper column packed with 5% UC W-98 coated on 80–100 mesh AW DMCS-treated Chromosorb G operating at 270 °C. (b) Same conditions as ref 17a at 260 °C.

Approach to the Conformational Analysis of Mannich Bases

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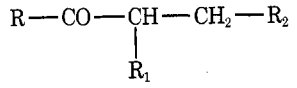
Conformational analysis of some Mannich bases and of the corresponding ammonium salts by NMR and CD indicates that in the solvents studied the hydrochlorides display a predominant conformation in which the two polar groups are gauche. In the case of the free bases, however, there is greater conformational freedom, the main factor in the equilibrium distribution of the conformers being the bulk of the substituents.

In a previous report on the stereochemistry of some α,β-disubstituted β-amino ketones[1] we observed that in solution the main factor in the distribution of the conformers at equilibrium is the bulk of the substituents, electrostatic interactions between the polar groups present in the molecule being of smaller importance. These last interactions are, on the other hand, very important in the case of the ammonium salts of the considered compounds, as other authors have demonstrated for analogous products of pharmacological and biological significance.[2]

Although there is abundant literature on the conformation of trisubstituted ethanes in solution (usually ethanes with halogens or alkyl groups),[3] no studies have been done on β-amino ketones with substituents in α or β position with respect to the carbonyl group. Continuing the studies on the reactivity and stereochemistry of Mannich bases, which are being carried out in our laboratories, in the present paper we report some aspects of NMR conformational analysis of 1-methyl- (Ia), 1-phenyl- (IIa), and 1-isopropyl-2-dimethylaminopropiophenone (IIIa) and their ammonium salts and of the NMR and CD studies of 3-methyl- (IVa) and 3-phenyl-4-dimethylaminobutan-2-one (Va), 3-phenyl- (VIa) and 3-methyl-4-piperidinobutan-2-one (VIIa), and of their hydrochlorides.

While derivatives I–III (R = C_6H_5) give easily analyzable NMR spectra, they do not allow a reliable CD conformational study owing to the presence of the conjugate aryl ketone chromophore, which makes problematic the use of the "octant rule".[4]



Ia, R = C_6H_5; R_1 = CH_3; R_2 = $N(CH_3)_2$

Ib, R = C_6H_5; R_1 = CH_3; R_2 = $\overset{+}{N}H(CH_3)_2$

IIa, R = C_6H_5; R_1 = C_6H_5; R_2 = $N(CH_3)_2$

IIb, R = C_6H_5; R_1 = C_6H_5; R_2 = $\overset{+}{N}H(CH_3)_2$

IIIa, R = C_6H_5; R_1 = $CH(CH_3)_2$; R_2 = $N(CH_3)_2$

IIIb, R = C_6H_5; R_1 = $CH(CH_3)_2$; R_2 = $\overset{+}{N}H(CH_3)_2$

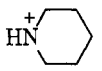
IVa, R = CH_3; R_1 = CH_3; R_2 = $N(CH_3)_2$

IVb, R = CH_3; R_1 = CH_3; R_2 = $\overset{+}{N}H(CH_3)_2$

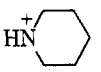
Va, R = CH_3; R_1 = C_6H_5; R_2 = $N(CH_3)_2$

Vb, R = CH_3; R_1 = C_6H_5; R_2 = $\overset{+}{N}H(CH_3)_2$

VIa, R = CH_3; R_1 = C_6H_5; R_2 = 

VIb, R = CH_3; R_1 = C_6H_5; R_2 = 

VIIa, R = CH_3; R_1 = CH_3; R_2 = 

VIIb, R = CH_3; R_1 = CH_3; R_2 = 

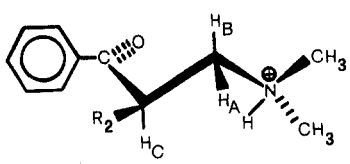
On the other hand, the NMR spectra of derivatives IV–VII are not all analyzable, while their CD spectra afford information on the conformational distribution.

Results and Discussion

NMR Studies. Examination of the NMR parameters of the ammonium salts Ib, IIb, and IIIb in a weakly polar solvent ($CDCl_3$) (see Table I) shows that the methylene protons are coupled both to the methine at C-1 and to the ammonium proton, and that this latter coupling has a different value for each of the two geminal nonequivalent protons. This shows that, at the temperature at which the spectra were recorded, the ammonium proton remains bound to the nitrogen long enough for the coupling to be observable.

A Karplus relationship between the coupling constants and the dihedral angle of CH–N^+H protons in several ammonium ions of cyclic compounds is implied in recent studies.[5,6]

On this basis, examination of the $J_{A,C}$, $J_{B,C}$, $J_{+NH,A}$, and $J_{+NH,B}$ for Ib, IIb, and IIIb leads us to assign to the system under examination, in the weakly polar solvent $CDCl_3$, a predominance of the arrangement with intramolecular interaction as shown below.



This scheme entails high values for $J_{B,C}$ and $J_{+NH,B}$ and low for $J_{A,C}$ and $J_{+NH,A}$ since the H_B, H_C, and $^+$NH protons will be approximately anti and H_A approximately gauche.

The suggested conformation also assumes an almost gauche disposition of the phenyl group and the substituent R_1, which will cause variations of J_{vic} when the bulk of R_1 changes, as found experimentally (see Table I).

Support for the idea of the suggested conformation in $CDCl_3$ is afforded by other experimental data, such as the analogous behavior of the α,β-disubstituted β-amino ketones described previously,[1] the results of the CD studies (vide infra), and the variations in the spectra of the quaternary ammonium salts in TFA (variations in all J values, marked shielding of the methine proton, and slight deshielding in the case of the two methylene protons).

In TFA, a highly polar solvent, intramolecular interactions[7] become less probable; it seems logical to assume that in this solvent the ammonium salts of I and II[8] adopt preferential conformations which are sterically favored, as is shown for example by the inversion of the relative values of $J_{+NH,A}$ and $J_{+NH,B}$ in TFA with respect to chloroform, and by the fact that in IIb the phenyl at C-1 gives a multiplet in $CDCl_3$ and approximately a singlet in TFA. Moreover, it is observed that the ammonium methyls of Ib, IIb, and IIIb and those of the isopropyl group in IIIb resonate as doublets at very different fields.

Although the nonequivalence is intrinsic for the presence of an asymmetric carbon, in the protonated compounds the relevant differences in the chemical shift of the methyls and the variations of this parameter with the solvent ($CDCl_3$ or TFA) may be interpreted on the basis of preferential steric dispositions involving different anisotropic contribution of the C_6H_5CO group.[7,9] Moreover, while the J of the H_C proton with the isopropyl methine has, in the free base IIIa, an averaged value (about 6.4 Hz), in the case of the hydrochloride IIIb in $CDCl_3$, its value is 3.45 Hz, thus confirming a different preferred conformation of the isopropyl group.

Chart I

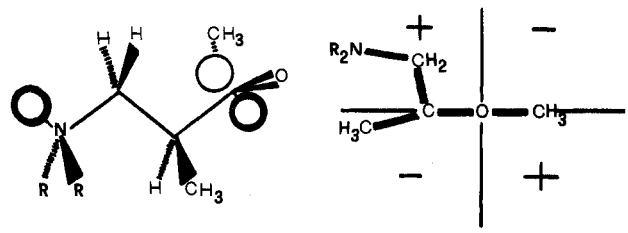
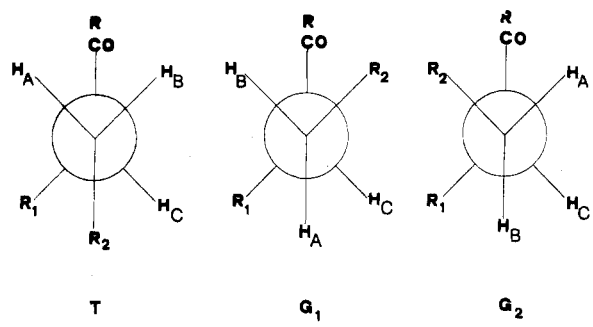


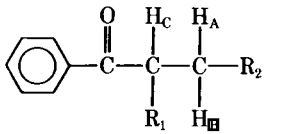
Chart II



Examination of the Newman projections along the C_1–C_2 bond of the proposed model indicates that the gauche G_1 form is predominant in $CDCl_3$, since the trans conformer T does not allow any interaction between the two polar groups, and the contribution of the gauche G_2 conformer at the equilibrium must be considered low for the steric hindrance arising from the presence of two gauche interactions.

The high experimental values of $J_{B,C}$ (which increase with the increasing bulk of R_1) and the low values of $J_{A,C}$ are in agreement with the foregoing hypothesis, and show that H_A must be gauche and H_B trans with respect to H_C in the preferred conformer G_1. The high value of $J_{B,C}$ further confirms the small weight of G_2 at the equilibrium. In the spectra of the Mannich bases I and II in TFA, the high polarity of the solvent tends to diminish the magnitude of intramolecular interactions and facilitates rotations around the bonds, as reported before; on the other hand, the G_1 rotamer remains preferred since a gauche relationship between the protons H_A and H_C (low values of $J_{A,C}$) and trans between H_B and H_C (high $J_{B,C}$) is again observed.

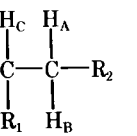
Table I.[a] NMR Parameters (δ) of Compounds Ia,b,c, IIa,b,c, and IIIa,b



Compd	R_1	R_2	Solvent	ν_A	ν_B	ν_C	ν_{R_1}	ν_{R_2}	$J_{A,B}$	$J_{A,C}$	$J_{B,C}$	$J^+_{NH,A}$	$J^+_{NH,B}$	J_{+NH,CH_3}	J_{R_1C}
			CS_2	2.23	2.61	3.54	1.11	2.15	−12.29	6.66	7.06				6.80
Ia	CH_3	$N(CH_3)_2$	Ac	2.29	2.69	3.81	1.14	2.17	−12.28	6.70	6.98				6.80
			Me_2SO	2.25	2.63	3.82	1.16	2.14	−12.08	6.73	7.27				6.90
Ib	CH_3	$\overset{+}{N}H(CH_3)_2$	$CDCl_3$[b]	3.26	3.86	4.44	1.33	2.74; 2.95	−13.00	3.90	7.90	3.48	7.55	4.95	7.20
			TFA	3.41	3.88	4.25	1.48	3.08; 3.21	−13.44	4.02	10.61	8.55	3.69	5.25	7.00
			CS_2	2.22	2.69	*c*	1.09	2.14	−12.20						
Ic	CH_3	$N(CH_3)_2$	Ac	2.27	2.61	*c*	1.09	2.17	−12.40						
			Me_2SO	2.24	2.67	*c*	1.09	2.14	−11.90						
			CS_2	2.44	3.22	4.64	*d*	2.16	−12.41	4.91	8.99				
IIa	C_6H_5	$N(CH_3)_2$	Ac	2.52	3.31	5.07	*d*	2.21	−12.42	5.11	9.01				
			Me_2SO	2.50	3.23	5.12	*d*	2.19	−12.05	5.41	9.12				
			$CDCl_3$[e]	3.36	4.13	5.91	*d*	2.73; 2.74	−12.91	3.81	7.87	3.87	6.44	5.10	
IIb	C_6H_5	$\overset{+}{N}H(CH_3)_2$	TFA	3.66	4.05	5.32	*f*	3.15; 3.18	−13.36	5.44	9.42	6.91	4.40	5.25	
			CS_2	2.45	3.23	*c*	*d*	2.17	−12.50						
IIc	C_6H_5	$N(CH_3)_2$	Ac	2.51	3.31	*c*	*d*	2.21	−12.30						
			Me_2SO	2.48	3.20	*c*	*d*	2.18	−12.00						
			CS_2	2.31	2.78	3.36	1.81 (CH); 0.90, 0.89 (2 CH_3)	2.09	−11.98	3.94	9.76				6.46
IIIa[g]	$CH(CH_3)_2$	$N(CH_3)_2$	Ac	2.38	2.86	3.64	1.86 (CH); 0.94, 0.92 (2 CH_3)	2.12	−12.01	3.84	10.10				6.40
			Me_2SO	2.31	2.81	3.65	1.89 (CH); 0.90, 0.87 (2 CH_3)	2.08	−11.92	3.72	10.25				6.45
			$CDCl_3$[h]	3.29	3.87	4.39	2.17 (CH); 0.80, 1.16 (2 CH_3)	2.58; 2.94	−12.78	0.86	9.31	2.10	7.50	5.10	3.45
IIIb[g]	$CH(CH_3)_2$	$\overset{+}{N}H(CH_3)_2$	TFA	*i*	*i*	*i*	*i* ; 0.91, 1.20 (2 CH_3)	3.04; 3.19	*i*	*i*	*i*	*i*	*i*	5.20	*i*

[a] The chemical shifts are in parts per million (δ) from Me_4Si as internal standard; the *J* are in hertz. The C_6H_5CO protons resonate as multiplets in the range δ 7.0–7.7 (3 H) and 7.7–8.4 (2 H). [b] ν_{N^+H} = 12.10. [c] H_C = D. [d] The aromatic protons of R_1 are multiplets superimposed on those of the C_6H_5CO fragment. [e] ν_{N^+H} = 12.85. [f] C_6H_5 resonates as singlet (δ 7.84). [g] J_{H,CH_3} of isopropyl fragment = 6.6/6.9 Hz. [h] ν_{N^+H} = 12.35. [i] The calculation of III in CF_3COOH at 60 MHz is not possible owing to the overlap of signals.

Table II.[a] NMR Parameters of Compounds IVa, Va,b, and VIa



Compd	R_1	R_2	Solvent	ν_A	ν_B	ν_C	ν_{CH_3}	ν_{R_1}	ν_{R_2}	J_{AB}	J_{AC}	J_{BC}
			CS_2	2.07	2.44	2.65	2.01	0.96[b]	2.13	−12.00	6.13	8.89
IVa	CH_3	$N(CH_3)_2$	Ac	2.11	2.51	2.71	2.06	0.99[b]	2.14	−12.21	6.21	8.92
			Me_2SO	2.08	2.47	2.59	2.08	0.95[b]	2.11	−12.07	6.28	8.82
			CS_2	2.34	3.16	3.91	1.97	7.25[c]	2.16	−12.34	5.53	9.42
Va	C_6H_5	$N(CH_3)_2$	Ac	2.43	3.11	4.06	2.07	7.31[c]	2.19	−12.41	5.78	9.38
			Me_2SO	2.43	3.04	4.06	2.07	7.33[c]	2.16	−12.26	6.18	8.88
Vb	C_6H_5	$\overset{+}{N}H(CH_3)_2$	$CDCl_3$	3.22	4.03	4.79	2.18	7.41[c]	2.76; 2.88[d]	−13.24	4.64	7.54
VIa	C_6H_5		CS_2	2.35	3.05	3.80	1.98	7.38[c]	1.3–1.7; 2.2–2.6[e]	−12.74	5.04	9.50

[a] The chemical shifts are in parts per million (δ) from Me_4Si as internal standard; the *J* are in hertz. [b] $J_{H_CR_1}$ = 6.70/6.76 Hz. [c] C_6H_5 resanates as singlet. [d] ν_{+NH} = 12.15; $J_{+NH,A}$ = 4.99; $J_{+NH,B}$ = 4.05; J_{+NH,CH_3} = 5.00. [e] Intervals of multiplets of piperidine methylenes.

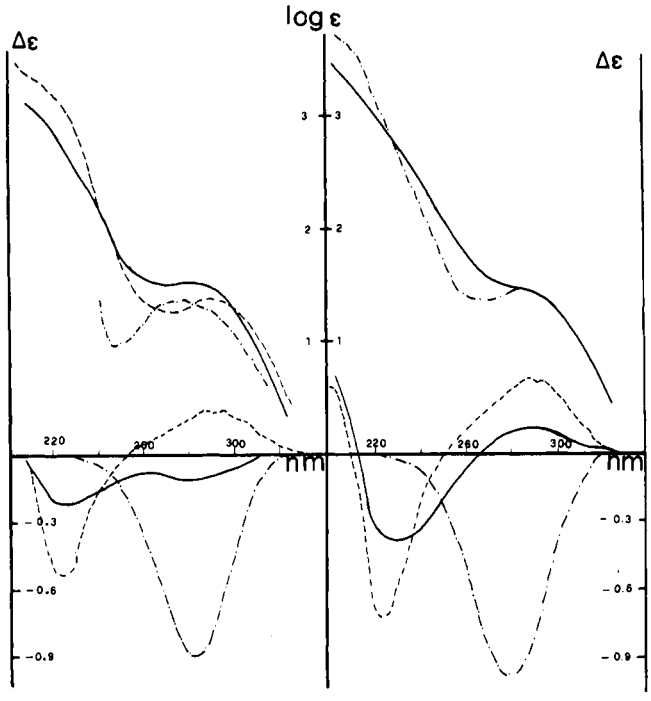


Figure 1. The absorption and circular dichroism of (−)-(*S*)-VIIa (right) and of (−)-(*S*)-IVa (left). Solvents: EtOH (—), EtOH-HCl (- · · · -), cyclohexane (- - -).

Therefore, in the case of the ammonium salts of the Mannich bases I, II, and III, attraction between the two polar groups present in the molecule is very important in the distribution of the conformers at equilibrium. Examination of the NMR parameters of the free bases Ia, IIa, and IIIa (see Table I) shows a high field shift of the order of 1 ppm for protons H_A, H_B, and H_C with respect to the corresponding protons of the ammonium salts in $CDCl_3$.[10] This effect is attributable to the absence of the positive charge on the nitrogen, and to probable variations in magnetic anisotropy resulting from different orientations of the C_6H_5CO fragment. In addition, in the three compounds, the methyls of the dimethylamino group resonate as singlets and the diastereotopic methyls of the isopropyl group in IIIa show a very slight differences (<2 Hz) of chemical shift, also in different solvents; this indicates a greater conformational freedom of the free bases as compared with the corresponding ammonium salts.

Assignment of the protons H_A and H_B in the spectra of free bases may reasonably be effected by comparison with the parameters observed in the ammonium salts. The values of the chemical shifts and coupling constants obtained from the iterative analysis of the ABC pattern of the ethane residue emphasize the importance of the steric bulk of R_1 in the conformational equilibrium of these compounds. Thus, in Ia (R_1 = CH_3) the averaged $J_{A,C}$ and $J_{B,C}$ indicate almost equal participation of the trans and gauche conformers at the equilibrium, while for IIa and IIIa [R_1 = C_6H_5 and R_1 = $CH(CH_3)_2$, respectively] the order of magnitude of the two J_{vic} is in accordance with the presence of a preferential rotamer in which one coupling constant is trans and the other gauche.

On this basis, the preferential conformer (see Chart II) will be G_1. This agrees with the experimental finding that, when the order of substituents of the ethane residue remains unchanged, an increase in the bulk of R_1 [R_1 = CH_3 → C_6H_5 → $CH(CH_3)_2$] is accompanied by an increase in $J_{B,C}$, while $J_{A,C}$ decreases, and the conformer with smaller steric hindrance becomes preferential, i.e., that in which R_1 is gauche with respect to the two methylene protons (G_1). An approximate calculation of the relative weight of the conformers at the equilibrium can be derived from the J_{vic} values ($J_{A,C}$ and $J_{B,C}$).[11] If the values used by Bailey[11] for the amphetamines (J_{trans} = 12; J_{gauche} = 2 Hz) are taken as standard values, it is found that in the three solvents used the relative weights of the conformers at equilibrium are T:G_1:G_2 = 45:50:5 for Ia, 30:70:0 for IIa, and 20:80:0 for IIIa. The fact that in these three solvents having different dielectric constants there is no appreciable variation in the conformer distribution indicates that in these compounds, contrary to the findings of other authors for different series of compounds,[12] the influence of intramolecular interaction (for example N → CO) is small compared with the influence of steric factors. The percentage of conformer G_1 increases with the steric bulk of R_1, while the weight of conformer T is reduced, the presence of conformer G_2 being negligible in all cases.

In the case of Mannich bases having R = CH_3 and of their ammonium salts (see Table II, compounds IVa, Va and Vb, VIa), the 60-MHz NMR spectra are difficult to analyze on account of the strong overlap of the signals. This makes it difficult to extend the NMR conformational analysis to these derivatives.

Only for derivative V it was possible to obtain the spectral parameters of both the free base and its hydrochloride. The data obtained show that the situation is not very different from that of derivatives having R = C_6H_5. In this case, however, the coupling constants of H_A and H_B with the ammonium proton are nearly the same. For the free bases IVa and Va, the value of J_{vic} of the ethane residue indicates that also in this case, when the steric hindrance of R_1 increases, there is a smaller conformational freedom and an increase of the G_1 conformer's population.

The spectral parameters of the free base VIa are analogous to those of Va and show that here the variation of the alkylamino group has a small effect.

CD Studies. The CD and UV spectra of the bases IVa and VIIa having *S* absolute configuration[13] are shown in Figure 1. In cyclohexane the CD of both IVa and VIIa show two bands of opposite sign at ca. 290 and 225 nm. While the first band corresponds to an isotropic absorption maximum and is assignable to the carbonyl n → π* transition, the second band does not have a corresponding absorption maximum. The CD spectrum of IVa in methanol undergoes a drastic modification with sign inversion of the low-energy band and intensity decrease of the high-energy one. The CD spectrum of VIIa, in passing from cyclohexane to methanol, shows only an intensity decrease of both bands.

Protonation of the nitrogen causes in the CD spectra of both IV and VII a sign inversion with respect to cyclohexane, an intensity increase, and disappearing of the 225-nm band. Hudec[14] has carried out detailed research on amino ketones having a fixed stereochemistry. In particular he found that, when the nitrogen lone pair is trans periplanar to the Cα–Cβ bond, when N is on the β carbon, a new band is observed at ca. 220–240 nm, having opposite CD sign to that of the n → π* transition. There is in this case a "planar zig-zag" of bonds, connecting the oxo group and the heteroatom.[15] The nitrogen atom exerts in this case an "octantlike" effect. By adding acids the high-energy band disappears. The CD spectra of derivatives IVa and VIIa (with the exception of that of IVa in methanol, for the moment) show that a situation of the type described above is present in our case.

Of the possible conformations depicted only the trans one (T) allows a connection between the nitrogen lone pair and the p orbital (depicted as circles in Chart I) of the oxo group, through a planar "zig-zag" pattern of bonds. This stereochemically restricted condition implies also a well-defined rotation around the C–C=O bond as schematized in Chart

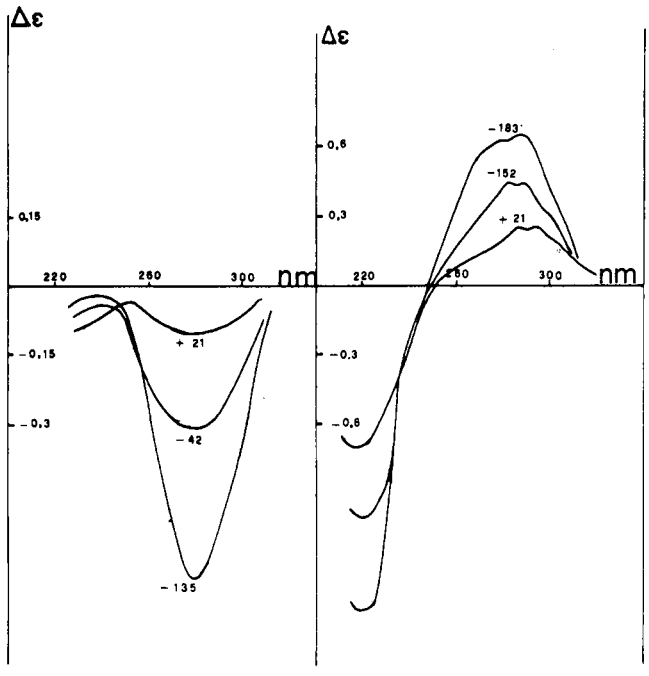


Figure 2. Low-temperature circular dichroism of (−)-(*S*)-IVa, solvent methanol–glycerol, 9:1 (v:v) (left), and methylcyclohexane–isopentane, 1:3 (v:v) (right).

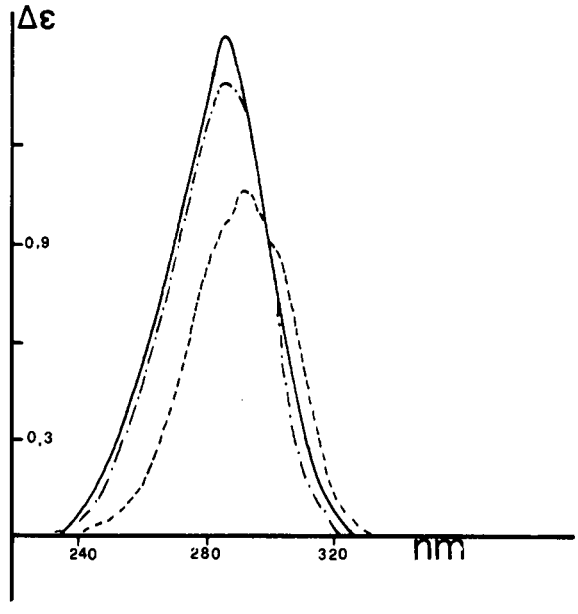


Figure 3. Circular dichroism of (+)-Va in cyclohexane (- - -) and methanol–HCl (—); circular dichroism of (+)-Vb in chloroform.

I (there are two possible rotamers having the desired "zig-zag" relation; however, the one having the methyl group pointing upwards is sterically hindered).

On the other hand, following the "octant rule"[4] this conformation should give (Chart I) for the isomer *S* a positive Cotton effect for the n → π* carbonyl transition in agreement with what is experimentally found.

The CD spectrum of derivative IVa in methanol causes some doubts, as one observes a sign inversion for the n → π* transition while the 225-nm band is still present and has the same sign of the n → π*. Low-temperature CD spectra of IVa in methylcyclohexane–isopentane and methanol–glycerol mixtures (Figure 2) contribute to clarify the case. In the hydrocarbon solvent the intensity of both bands increases with the decreasing of the temperature, showing that the most populated conformation (trans) is responsible for the observed spectrum; this is not the case for methanol–glycerol (Figure 2) where the intensity of the 280-nm n → π* transition increases, and that of the 225 nm, typical of the "zig-zag" trans conformation, decreases and practically disappears at −140 °C. This band is therefore caused by a conformer which is different from that responsible for the 280-nm band. This conformer (trans), although it gives rise to strong signals in the 220-nm region, must have higher energy, and its population is strongly reduced at low temperature. The solvent effect on derivative IVa can be understood as a passage from a predominant trans conformation in cyclohexane to a predominant "gauche" in methanol, the latter being probably stabilized by specific interactions with the solvent.

In derivative VII the presence of the bulky piperidine group destabilizes the gauche conformation and a change in CD is not observed (although the rotamers' ratio must be varied). The spectra of the base hydrochlorides have signs opposite to those of the free bases in cyclohexane, and a higher intensity. In agreement with what was previously found for aryl keto bases this seems to indicate gauche conformation, stabilized through polar interactions. Unfortunately, the use of the octant rule in this case is uncertain as "front octants" are involved. The CD spectra of derivatives V are shown in Figure 3. The CD spectrum of Va in cyclohexane has the same sign of that of Vb in methanol and chloroform. This fact indicates that in this case the gauche G_1 conformation is the most populated in all the conditions studied, in good agreement with what was found by the NMR analysis.

In conclusion, from the data reported above, one can say that in the free bases (R = alkyl or aryl) there is a great conformational freedom, and, depending on the substituents present, one passes from a dominant trans to a dominant gauche conformation. The base hydrochlorides, on the contrary, seem to exist predominantly in gauche conformations, the amount of this conformation being influenced by the polarity of the solvent.

Experimental Section

NMR spectra were run in the internal lock mode on a JEOL C 60-HL spectrometer (probe temperature 32 °C). The solutions were about 10–15% w/v. The chemical shift are in parts per million (δ) from Me_4Si as internal standard (±0.01) and the coupling constants in hertz (±0.05). The calculation of the ABC, $ABCX_3$, or ABCD patterns was carried out with iterative program LAOCN3°;[16] the root mean square error was in all cases less than 0.045. CD spectra were recorded using a Jouan II dichrograph; uv spectra, using an Unicam SP 700 spectrophotometer.

1-R_1-2-Dimethylaminopropiophenones and Hydrochlorides (Ia–IIIa, Ib–IIIb), 4-R_2-3-R_1-Butan-2-ones and Hydrochlorides (IVa–VIIa, IVb–VIIb). Ia,[17] IIa,[18] IIIa,[19] IVa,[20] Va and VIa,[21] VIIa,[22] and their hydrochlorides were prepared and purified as described in the literature.

1-R_1-1-Deuterio-2-dimethylaminopropiophenones (Ic and IIc). A complete H/D exchange in the α position to the carbonyl group occurs when a 0.5 M solution of Ia or IIa in D_2O/dioxane (1/1 v/v) was left to stand at room temperature for 48 h; after evaporation under vacuum of dioxane the deuterated compounds Ic and IIc were extracted with $(C_2H_5)_2O$ and purified by crystallization of their hydrochlorides. No H/D exchange was detected in the case of IIIa, even in more drastic conditions.

Resolution of (±)-3-Phenyl-4-dimethylaminobutan-2-one (Va). A solution of 15 g of (±)-Va in 20 ml of dry Me_2CO was added to a solution of 29.5 g of (−)-dibenzoyltartaric acid in 30 ml of dry Me_2CO. The precipitated salt was crystallized from absolute EtOH, mp 150–151 °C. The free base had $[\alpha]^{20}D$ +155° (*c* 1.1, MeOH).

Resolution of (±)-3-Methyl-4-dimethylaminobutan-2-one (IVa).[11] Working as described above a diastereoisomeric salt was obtained, which was crystallized from absolute EtOH and showed mp 135–136 °C. The free base had $[\alpha]^{20}D$ −26° (*c* 4, MeOH/HCl 10:1).

Resolution of (±)-3-Methyl-4-piperidinobutan-2-one (VIIa). Working as described above a diastereoisomeric salt was obtained;

after crystallization from dry Me_2CO it showed mp 138–139 °C. The free base had $[\alpha]^{20}D$ −28° (c 3, MeOH/HCl 10:1).

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Registry No.—Ia, 91-03-2; Ib, 5400-92-0; Ic, 59434-10-5; IIa, 22563-99-1; IIb, 25287-79-0; IIc, 59434-11-6; IIIa, 2891-50-1; IIIb, 59434-12-7; (±)-IVa, 59461-64-2; (−)-IVa, 24190-15-6; (−)-IVa (−)-dibenzoyl tartrate, 24190-14-5; (±)-Va, 59434-13-8; (+)-Va, 59434-14-9; (+)-Va (−)-dibenzoyl tartrate, 59434-15-0; (+)-Vb, 59434-16-1; VIa, 27702-56-3; (−)-VIIa, 59434-17-2; (±)-VIIa, 59461-65-3; (−)-VIIa (−)-dibenzoyl tartrate, 59434-18-3; (−)-dibenzoyltartaric acid, 2743-38-6.

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Carbonyl–Alkyne Exchange of 2*H*-Pyrans. A New Aryl Annelation Method

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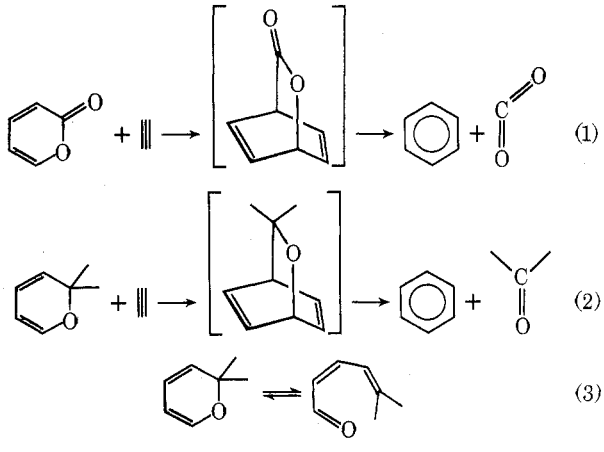
A synthesis of aryl derivatives is described which involves cycloelimination of ketones or aldehydes from the adducts obtained by cycloaddition of 2*H*-pyrans with acetylenic dienophiles. This carbonyl–alkyne exchange process is highly regiospecific. Even a 2*H*-pyran which constitutes only 20% of an equilibrium mixture with the corresponding dienone valence tautomer is shown to give good yields of the corresponding aryl derivatives upon reaction with methyl propiolate or dimethyl acetylenedicarboxylate.

Derivatives of α-pyrone react with alkynes to yield aryl derivatives and carbon dioxide (eq 1).[1] The intermediate Diels–Alder cycloadducts are generally unstable under the conditions of their formation. The analogous reaction of 2*H*-pyrans with alkynes to yield aryl derivatives and aldehydes or ketones (eq 2) has not been reported. One potential



(1)

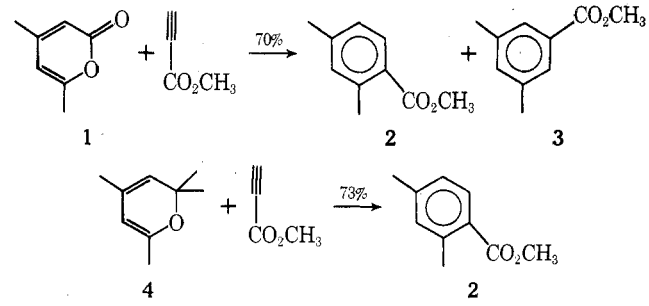
(2)

(3)

complication for such a carbonyl–alkyne exchange reaction is the fact that 2*H*-pyrans are in dynamic equilibrium with acyclic dienones (eq 3)[2] which might yield alternative products by Diels–Alder reactions. However, since 2*H*-pyrans are readily available by a variety of different synthetic routes,[3–16] it seemed worthwhile to examine the feasibility of carbonyl–alkyne exchange reactions with 2*H*-pyrans. We now report the first examples of the synthesis of aryl derivatives by the reaction of 2*H*-pyrans with acetylenic dienophiles.

Results and Discussion

In order to compare the carbonyl–alkyne exchange of α-pyrones and 2*H*-pyrans we examined the reactions of methyl propiolate with 4,6-dimethyl-α-pyrone (1) and with 2,2,4,6-tetramethyl-2*H*-pyran (4). Both reactions give good yields of



1 2 3

4 2

aryl derivatives. The α-pyrone (1) gives both methyl 2,4-dimethylbenzoate (2) and methyl 3,5-dimethyl benzoate (3) in a 4:1 ratio, respectively. The 2*H*-pyran (4) gives only **2**. The carbonyl group in **1** is expected to direct[17] the initial Diels–Alder addition to favor product **3**, while the ring oxygen and methyl groups in 1 direct the addition to favor product **2**. For 4 the exclusive formation of **2**, therefore, might be ascribed to the absence of the carbonyl group in the 2 position. However,