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THE STEREOISOMERIC α,β-DIMORPHOLINYL-BENZYLACETOPHENONES

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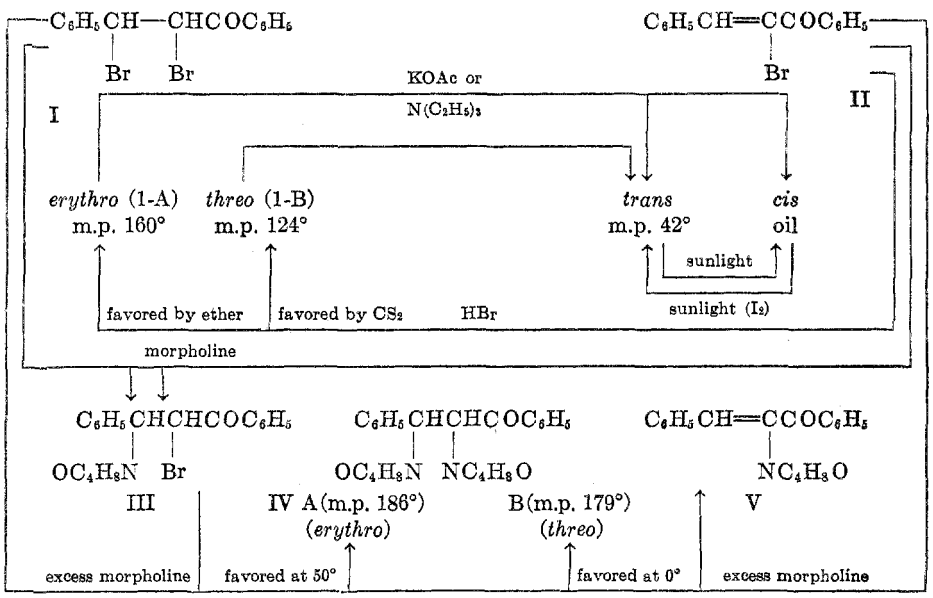
In the reaction between morpholine and benzalacetophenone dibromide (I) indication of the formation of a second stereoisomeric α,β-dimorpholinylbenzylacetophenone (IV) has been reported (1, 2). The main purpose of this investigation[2] was to extend this study sufficiently to permit a comparison with the dibenzoylethylene series where a substitution mechanism appears to be dominant in the analogous but non-stereospecific formation of a single dimorpholinyldibenzoylethane from the DL- and *meso*-dibenzoylethylene dibromides (VII) (4).

The action of morpholine on the *erythro*- and *threo*-benzalacetophenone dibromides (I) and the *cis*- and *trans*-α-bromobenzalacetophenone (II, 5) *under comparable conditions* produced in good yield the same α-bromo-β-morpholinylbenzylacetophenone (III), and it is thus shown that no consistent stereochemical guidance is involved here.



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[2] This work was originally prompted by earlier findings in the course of the program of syntheses of antimalarials (3); two nuclearly-substituted and structurally isomeric benzalacetophenone dibromides which at first were erroneously supposed to be diastereoisomers (unpublished results), had reacted with morpholine to give different α,β-dimorpholinyl ketones and had seemed at that time to support a mechanism in that particular case involving as the first step the direct displacement of at least one halogen by morpholine.

The further action of an excess of morpholine on III under the same but prolonged conditions leads to mixtures of three products, the higher-melting less-soluble α,β-dimorpholinylbenzylacetophenone (IV) (1) (now designated as isomer-A), the stereoisomer which melts at 179° (isomer-B), and small amounts of the α-morpholinylbenzalacetophenone (V) (1). Samples of the product of melting point similar to that reported earlier (1) for the supposed lower-melting form, have now been shown to be mixtures of the isomers-A and B by quantitative determination of the extent of solubility in saturated solutions of pure reference samples. The less soluble isomer-A is isolated by repeated crystallizations of the first crystalline fractions (1) from reactions carried out at slightly elevated temperatures (up to 50°). The isomer-B, which was not isolated by ordinary fractional crystallizations of the residual mixtures from such experiments, was isolated during later studies on the effect of temperature on the course of the reaction; in these experiments the proportion of the isomers in the samples comprising the bulk of the products in each experiment was estimated by determining the extent of solubilities of the samples in methanol saturated with pure isomer-A. Reactions at 0° gave the isomer-B in such high proportion that it could be obtained in nearly pure condition in the first crystal fractions. The new isomer-B is distinguished from isomer-A by its greater solubility in organic solvents and by the large mixture melting point lowering.

A simple effective direct separation of the isomers-A and B was devised utilizing the sharp differences in basicities. Both compounds formed monohydrochlorides; however, the more basic isomer-A was retained in solution in glacial acetic acid upon dilution with water whereas the isomer-B precipitated practically completely under these conditions.

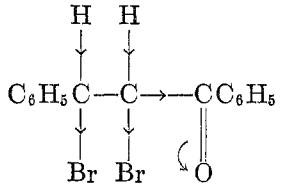
These facts outlined in the chart I–V are consistent with and support a reaction mechanism involving dehydrohalogenation of I to II followed by 1,4-addition (*cf.* 1, 2)[3] to give III. Double dehydrohalogenation is not involved here, nor is it brought about by the action of triethylamine which cannot add to II [this is in contrast with the course of the corresponding reactions in the dibenzoylethylene series (4)]; phenylbenzoylacetylene is formed only under much more drastic and strongly alkaline conditions (7, 8) and if it had been formed it would have led to the formation of β-morpholinylbenzalacetophenone only.[4]

The striking difference between the mechanism of the primary reaction of morpholine with the dibenzoylethylene and benzalacetophenone dibromides, involving displacement and dehydrohalogenation respectively, may be explainable on theoretical grounds. The two bromines of either isomeric benzalaceto-

[3] There is of course the possibility that under other conditions a competing direct-substitution might be appreciable, but the different ratios of end-products reported in earlier experiments [from I (erythro), II (*trans*) or III] (1) cannot be regarded as supporting such a contention because the conditions under which the experiments were carried out were not sufficiently comparable. The direct-substitution mechanism has been suggested but without rigorous proof in the case of the reaction between amines and α,β-dibromopropiophenone (6). [*Cf.* conclusions of Cromwell (Ref. 2, p. 559)].

[4] β-Bromobenzalacetophenone (9), $C_6H_5CBr{=}CHCOC_6H_5$, which also has an α-hydrogen and should be capable of going to the acetylene easily, is being investigated.

phenone dibromide are quite different in character; the β-bromine is a benzyl bromide type halogen and is presumably of a lower order of reactivity toward displacement than the α-bromine which is "positive" and should not only be quite active toward amine displacement (*cf.* ref. 4, 10, 11) but at the same time should facilitate enolization (or ionization) of the α-hydrogen (see VI). These



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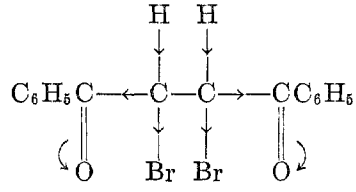

VII

influences might well concomitantly be expected to facilitate if not actually favor dehydrohalogenation. In the case of the dibenzoylethylene dibromides, however, (see VII) both bromines are similar and *alpha* to carbonyl groups, and although doubtless they increase the enolizability of the α-hydrogens, they are both "positive" in character, and each would remain so after enolization had occurred at the other α-carbon, consequently here there should be high displaceability and more than the normal resistance toward the dehydrohalogenation; furthermore the adjacency or "conjugation" of the two opposing halogeno ketone systems would presumably cause an exaggerated activity of each, in the same way though doubtless to a lesser extent that conjugation of two carbonyl groups results in increased reactivity of each.

A tentative assignment of *erythro* configuration to the isomer-A might be made on the basis of analogy in respect to its higher melting point and lower solubility which are comparable with the analogous properties of *erythro*-benzalacetophenone dibromide (*cf.* ref. 5) and *meso*-dibenzoylethylene dibromide (12).

As has been stated above both stereoisomeric dimorpholinyl ketones (IV) give monohydrochlorides. The second nitrogen in each case appears to be incapable of forming a stable salt. The striking difference of basicities of the more basic nitrogen of each isomer and its extent were confirmed by titrations with standard acid in 90% acetone using a Fisher potentiometric titrimeter. For purposes of comparison the α and β-monomorpholinyl ketones (VIII and IX), were also titrated. The β-morpholinyl ketone (IX) had the highest basicity of the four compounds (half-neutralization *p*H, 4.25) which was 20 times that of the α-mono-

$C_6H_5CH_2CH(NC_4H_8O)COC_6H_5$ VIII

$C_6H_5CH(NC_4H_8O)CH_2COC_6H_5$ IX

morpholinyl isomer (VIII) (*p*H 2.94); this difference is accounted for by the inductive effect of the carbonyl group operating in the case of the α-compound (VIII).[5] The dimorpholinyl ketone-A (IV) showed a first-nitrogen half-neutrali-

[5] In a series of substituted amines and amino alcohols it has been found (13) that the β-amino alcohols are consistently of a lower order of basicity than non-hydroxylated amines; this is in accord with expected consistent inductive effect on the nitrogen by the hydroxyl.

zation *p*H of 3.45; the second nitrogen was too weakly basic to register in any significant way. The isomer-B gave a lower first-nitrogen half-neutralization *p*H of 2.15 and no significant second level of basicity. These data indicate a 20-fold difference in first basicities, presumably involving in each case only the β-nitrogen. It is thus evident that the increased steric strains have greatly diminished the basicities of both nitrogens. If one regards the dimorpholinyl ketones as derivatives of the monomorpholinyl ketones, it is seen that one nitrogen has decreased the basicity of the other, presumably through a combination of inductive and steric effects. Incidentally, the substitution of an α-bromine in III so very greatly diminishes the basicity of the β-nitrogen that one might suspect a configurational kinship to the dimorpholinyl ketone IVB.

The striking difference of basicity and its direction in the diastereoisomers (IVA and B) must be related primarily to the configurational difference, and may be explained on the basis of relative steric strains of the postulated configurations (*cf.* 14, 15, 16). The more *trans*-like isomer (*erythro*) would presumably involve the greater freedom of the nitrogen to accommodate a proton, whereas the other isomer (*threo*) because of greater intramolecular interferences between groups would be less able to do so. Of course in the absence of the sizable steric strain factors entailed in the all-tertiary nitrogen and tertiary chain-carbon systems, one might perhaps attribute more importance to the proximity effect of one nitrogen on the other in a way somewhat analogous to the effect of one carboxyl on the acidity of another in maleic and fumaric acids (17).[6] A broad study of the configurational effects on basicity and acidity of suitably substituted *diastereo* and *cis-trans* isomeric amines, diamines, amino alcohols, dibasic and keto acids, is suggested by these results and is now in progress.

EXPERIMENTAL[7]

The α,β-dimorpholinylbenzylacetophenones (IVA and B). The isomers described in the various experiments in this paper were always identified by comparison with authentic reference samples, usually by the mixture melting point method which proved to be reliable here.

Isomer-A (higher-melting and less-soluble) (*cf.* Ref. 1); yellow hair-like needles; m.p. (initial melting-point bath temperature 40°), 167–171° when heated at 0.5° per min.; 172–174° at 1.5/min.; 175–177° at 3°/min.; mixture m.p. (with isomer-B of m.p. 171–173°), 155–165° at 3°/min. With the initial melting point bath temperature 160°; m.p. 178–180° at 3°/min.; 182–184° at 6°/min.; 184–186° at 12°/min.; mixture m.p. (with isomer-B of m.p. 177–179°) 160–168° at 6°/min. [Cromwell gave the m.p. 173–175° d. (1)]. *Solubilities*, in methanol at 25°, 0.38 g. per 100 ml.; in acetone at 0°, 1.874 g. per 100 ml. Half-neutralization *p*H in titration with one equivalent of hydrochloric acid in 90% acetone (Fisher potentiometric titrimeter), 3.45. For ultraviolet absorption see ref. 5.

The *monohydrochloride* (of IVA) was prepared by acidification to Congo Red of an ether solution of the base (IVA) with ethereal hydrogen chloride, or by the solution of the base

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[6] More closely analogous dibasic acids would be the DL and *meso* disubstituted succinic acids, but the tartaric acids constitute the only pair of stereoisomers studied in this connection and these unfortunately involve complications due to the possibility of hydrogen bonding through the alcoholic hydroxyl groups (18).

[7] All melting points are "corrected." Microanalyses were by Mrs. R. L. McConnell.

in 30% hydrochloric acid (crystallization followed quickly); recrystallized from a methanol solution by addition of acetone; colorless hair-like needles; m.p. 178–180°.

Anal. Calc'd for $C_{23}H_{28}N_2O_3 \cdot HCl$: C, 66.25; H, 7.01.

Found: C, 66.16; H, 6.97.

A mixture m.p. with the free base was 170–175°.

Isomer-B (lower-melting more-soluble). M.p. (initial bath temperature 40°) 168–172° at 0.5°/min.; 171–173° at 1.5°/min.; 174–176° at 3°/min.; m.p. (initial bath temperature 160°) 176–178° at 3°/min.; 177–179° at 6°/min.; 178–180° at 12°/min. [Cromwell, 154–156° d. (1)].[8] Solubility in methanol at 25°, 0.64 g. per 100 ml.; in acetone at 0°, 2.302 g. per 100 ml. Half-neutralization *p*H in titration with one equivalent of standard hydrochloric acid in 90% acetone (Fisher potentiometric titrimeter), 2.15. For ultraviolet absorption see ref. 5.

Anal. Calc'd for $C_{23}H_{28}N_2O_3$: C, 72.62; H, 7.41; N, 7.36.

Found: C, 72.64; H, 7.56; N, 7.48.

The monohydrochloride (of IVB) did not precipitate from 30% hydrochloric acid, but crystallized from acetone upon addition of ethereal hydrogen chloride and excess ether.

An apparently *non-solvated form* (unstable) was obtained by recrystallization from benzene and petroleum ether; colorless needles, m.p. 75–85° (decomp.); after solidification; remelts at 155–160°. A typical analysis: Calc'd for $C_{23}H_{28}N_2O_3 \cdot HCl$: C, 66.25; H, 7.01 Found: C, 66.99; H, 6.96. The samples evidently had lost hydrogen chloride during drying; a sample in a test at 40° released hydrogen chloride sufficiently rapidly to turn litmus red.

A more stable *solvated form* was obtained by crystallization from acetone and ether; colorless needles; m.p. 130–133° (decomp.).

Anal. Calc'd for $C_{23}H_{28}N_2O_3 \cdot HCl \cdot CH_3COCH_3$: C, 65.73; H, 7.42.

Found: C, 65.88; H, 7.56.

That this salt actually contained a molecule of acetone of crystallization was shown by treatment in ethanol solution with 2,4-dinitrophenylhydrazine; no reaction with IVB occurred but acetone-2,4-dinitrophenylhydrazone precipitated in 80% yield (identified).

Hydrolysis of Isomer-B (IVB) (*cf.* ref. 1) was effected by heating a solution of 1 g. of the base in 10% sulfuric acid at 100° for 5 min., cooling, and extracting with ether which removed benzaldehyde; 0.2 g., identified as the phenylhydrazone. The α-morpholinylacetophenone was precipitated from the acid solution by potassium carbonate, extracted into ether and precipitated as the hydrochloride; 0.27 g. (43%), m.p. 222–225° [identified by mixture m.p. (20)].

In a *practical preparation of IVA and B*, 24 ml. (0.27 mole) of morpholine was added dropwise over 5 min. to a suspension of 24 g. (0.065 mole) of *erythro*-benzalacetophenone dibromide (1A) (21) in 210 ml. of acetone maintained at 15° in a large water-bath; the temperature rose to 18° during the addition and to 23° during the next half-hour (it would have risen much too rapidly in the absence of the water-bath). After 5 days at 0° (ice-bath kept in a refrigerator), during which time the bulk of the last steps in the reaction occurred (III → IVA and B + V), and then 3 hours at −25°, the resulting precipitate (24.95 g.) was washed with water to remove morpholine hydrobromide (96% by loss in weight). A solution of the residue of crude IVB (3.94 g., m.p. 167–173°) in 45 ml. of hot acetone was filtered and cooled; the precipitated yellow cubes were washed with cold ether; 2.30 g., m.p. 177–179°; concentration of the filtrate gave an additional 0.60 g., m.p. 175–179°.

Concentration of the filtrate from the crude isomer IVB (above), washing the resulting precipitate with ether and digesting with water gave a mixture, 6.88 g., m.p. 163–170°. Evaporation of the filtrate to dryness, solution in 25 ml. of ethanol and cooling gave an addi-

[8] We had been led to investigate this because the 1° mixture melting point depression between the supposed isomer and the higher-melting form of m.p. 173–175° d. (1) seemed to us to indicate that the lower-melting material was a mixture. [*Cf.* a similar situation in the case of the supposed lower-melting stereoisomer of β-morpholinyl-α-piperidylbenzylacetophenone (19)].

tional 6.13 g., m.p. 153–160°. These samples were combined and dissolved in 25 ml. of glacial acetic acid at room temperature; the yellow solution was filtered, diluted with 100 ml. of water and iced; the precipitate (a second sample of IVB) was filtered and washed with 50 ml. of water; 4.41 g., m.p. 166–170° [This brought the total crude yield of IVB to 8.08 g. (33%)]. Solution of the fraction in hot acetone, concentration to 20 ml. followed by slow cooling gave 3.06 g. of pure IVB, m.p. 177–179°; further concentration of the filtrate to 4 ml. gave an additional 0.4 g., m.p. 176–178° [This brought the total yield of pure IVB to 6.36 g. (26%)].

TABLE I

REACTIONS OF COMPOUNDS WITH MORPHOLINE UNDER STANDARDIZED CONDITIONS[a]

COMPOUND	G.	EQUIV. OF M[b]	REAC. TIME, HRS.	YIELDS		
				M.HBr[b] *equiv.*	III, %	IVA, B, %
I (*erythro*)	5.00	2.5	12	1.15	81	5.0
I (*threo*)	5.00	2.5	3.5	1.11	89	3.0
II (*trans*)[c]	3.90	1.5	3.5	0.08	91	3.7
II (*trans*)[d]	1.95	2.0[e]	12	.33[f]	65	14.0
II (*cis*)[g]	3.90	1.5	3.5	.37	61	15.0
III[h]	2.55	1.5	9	.23	75	6.5

[a] Described above under III. [b] M = morpholine. [c] Similar results were obtained using as the solvent: acetone, methanol, ethanol, ether, benzene, chloroform, and carbon tetrachloride. No evidence of a diastereoisomer was noted. [d] This experiment demonstrates that the relatively rapid rate of reaction of II (*trans*) as compared with the much slower rate of I (*erythro*) is responsible for the higher yield of III from II (*trans*). Exposure of the rapidly-formed product [from II (*trans*)] to an excess of the amine for a length of time comparable to that involved in the case of I (*erythro*) results in further reaction of the product to give IV and V in relatively greater amounts and reduces correspondingly the yield of III. [e] Plus an additional 0.5 equivalent of morpholine hydrobromide. [f] This yield represents the excess above that added at the beginning. [g] III precipitated from solution in this experiment much more slowly than it did in the experiment on the *trans*-isomer; this showed that the *cis*-isomer was considerably the more reactive of these two. [h] This is a control experiment showing the slow conversion of the primary product (III) to the mixture (IV + V) under similar but prolonged reaction conditions.

The diluted acetic acid filtrate was neutralized with 50 ml. of 6 *N* ammonium hydroxide The precipitate of crude isomer-A was filtered and washed with 100 ml. of water [8.65 g., m.p. 165–172° (35%)]. Recrystallization from 80 ml. of ethyl acetate gave 5.00 g., m.p. 182–184°; total yield (of IVA) 6.21 g. (25%).

The ethanol filtrate from the second fraction of crude mixture (above) was concentrated to 10 ml. on a steam-bath and cooled; the resulting α-morpholinylbenzalacetophenone (V) (bright orange cubes) was filtered and washed with a little petroleum ether; m.p. 84–88°, 2.15 g. (11%); recrystallization from 5 ml. of ethanol gave 1.55 g. (8%) of m.p. 92–93.5°.

The preparation of α-bromo-β-morpholinylbenzylacetophenone (III) *from I and II.* The reactions outlined in Table I were carried out under conditions in every way comparable to those of the directions given below. The times of reaction alone were varied, this in order to compensate for the different rates of the respective reactions which had been predetermined to find the time required for the maximum yield.

Morpholine (2.97 ml.; 0.034 mole) was added to a suspension of 5.00 g. of the *erythro* dibromide (IA) (21) (m.p. 159–160°) in 10 ml. of acetone. The suspension was maintained at 0° under stirring for 12 hours. The precipitate (6.70 g.) was washed with 10 ml. of iced-ether

and then with water (yield of morpholine hydrobromide, 1.15 equiv. by loss of weight); residue (III), 4.13 g. (81%) m.p. 140–141°.

Evaporation of the acetone filtrate (above) and crystallization of the residue from 3 ml. of benzene and 1 ml. of petroleum ether gave 0.25 g. of m.p. 155–163°; solution in 1 ml. of glacial acetic acid and addition of 4 ml. of water gave 0.10 g., m.p. 166–172° which on crystallization from acetone gave 0.05 g. (1.0%) of IVB, m.p. 175–178°; the acetic acid filtrate on neutralization with 6 *N* ammonium hydroxide and crystallization of the precipitate from ethyl acetate gave 0.05 g. (1.0%) of IVA, m.p. 178–182°.

Compound III is best crystallized from carbon tetrachloride; it appears to be stable in ether and ligroin, but solutions in ethanol, acetone, benzene, chloroform, and dioxane soon turn yellow; m.p. (initial bath temperature 40°) 127–128° at 1.5°/min.; with initial bath temperature 120°, m.p. 133.5–134.5° at 2°/min.; 136–138 at 6°/min.; 139–141° at 9°/min.; 141–142° at 12°/min. [Cromwell, 138–139° d. (1)]; the melt turns greenish black at 155–160°.

The conversion of III into IV and V was carried out as follows: A suspension of 5.0 g. in 10 ml. of acetone maintained at 0° was treated with 2.96 ml. of morpholine with stirring for 5 days. The product was washed with water which removed 2.27 g. (95%) of morpholine hydrobromide; the residue (IV) 3.80 g., m.p. 155–160°, was dissolved in 10 ml. of glacial acetic acid; addition of 50 ml. of water, filtering, and washing with water and 10 ml. of ether, gave 1.87 g. of IVB (m.p. 170–173°); recrystallization from 10 ml. of acetone gave 1.32 g., m.p. 177–179° (27%).

The acetic acid filtrate was neutralized with 35 ml. of 6 *N* ammonium hydroxide and the resulting precipitate (IVA), 1.61 g., m.p. 167–174°, was recrystallized from 10 ml. of ethyl acetate; 1.20 g. (24%) m.p. 182–184°.

The first filtrate (acetone) was evaporated under reduced pressure; the residual oil was dissolved in 50 ml. of ether; this solution was washed with water, dried over Drierite, filtered and evaporated; the residue was crystallized from 3 ml. of warm ethanol by addition of 1 ml. of petroleum ether and cooling: 0.23 g.; recrystallization from 1 ml. of ethyl acetate gave 0.10 g. of pure IVA, m.p. 175–179°; addition of a few drops of water and cooling precipitated V, 0.68 g. (15%), m.p. 88–91° (recrystallized, m.p. 92–93.5°, and identified).

The *stabilities of the isomers-A and B* (IV) under the above reaction conditions were shown by recoveries of materials in experiments in which the isomers were subjected to conditions comparable with those above; however, some deterioration was observed. These isomers were recovered in 94% yield after being subjected to the action of refluxing acetone containing half an equivalent each of morpholine and morpholine hydrobromide.

SUMMARY

The true diastereoisomeric α,β-dimorpholinylbenzylacetophenone has been isolated and characterized. It has been shown that there is no stereochemical guidance of the conversion of the dibromides and α-bromo derivatives of benzalacetophenone into the dimorpholinylketones; the mechanism of the reactions is discussed and contrasted with that involved in the analogous reactions in the dibenzoylethylene series. The sharp differences in basicity of the β-nitrogens of the stereoisomers is discussed in relation to probable configurations.

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