Stereochemistry of Addition Reactions of Dialkaliphenylacetamides with Benzaldehydes[1]

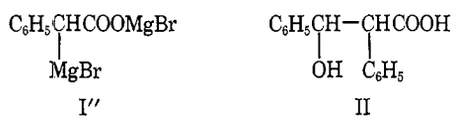
DON M. VON SCHRILTZ, EDWIN M. KAISER, AND CHARLES R. HAUSER

Department of Chemistry, Duke University, Durham, North Carolina

Received February 16, 1967

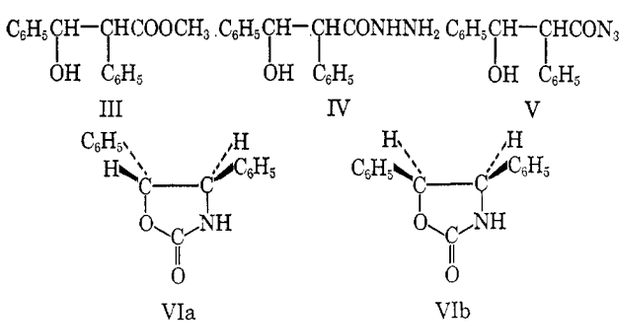
Disodiophenylacetamide, prepared from phenylacetamide and 2 mole equiv of sodium amide in liquid ammonia, underwent a carbonyl addition reaction with benzaldehyde to form the corresponding β-hydroxyamide. A mixture of the *threo* and *erythro* isomers of this product was obtained on inverse neutralization after 5 min or less, but only the *threo* isomer was isolated after 10 min or more. Dilithiophenylacetamide afforded exclusively the *threo* isomer under similar conditions after a relatively short time. Dilithiophenylacetamide, prepared by means of *n*-butyllithium, underwent the addition reaction with benzaldehyde to form exclusively the *threo* isomer in tetrahydrofuran–hexane at 0° but a mixture of the two diastereomers in refluxing ether–hexane. Similar results were obtained in certain related addition reactions. Mechanisms are suggested.

Earlier workers[2] have shown that the Ivanov reagent I''[3] undergoes an addition reaction with benzaldehyde in ether to form a mixture of *threo* and *erythro* isomers of II in 91% yield; the ratio of *threo* II to *erythro* III was shown by column chromatography to



I'' II

be approximately 3:1. The corresponding condensation of disodiophenylacetate with benzaldehyde to form II has been reported (without details) to be more stereoselective.[4] The structures of each of these isomers of II was established by stereospecific conversion through ester III, hydrazide IV, and azide V (not isolated) to the oxazolidones VIa and VIb (involving



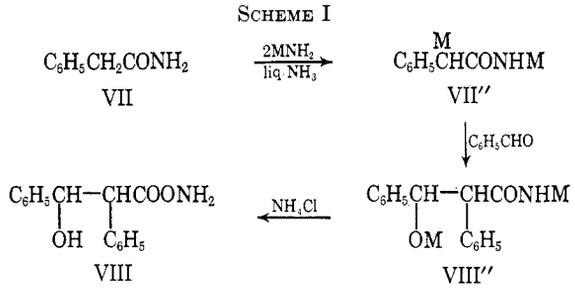
III IV V

VIa VIb

a Curtius rearrangement) whose stereochemistry had been previously determined.[5]

In the present investigation, some related addition reactions of the dialkali salts of phenylacetamide and N-substituted phenylacetamides with aromatic aldehydes were studied. First, disodio- and dilithiophenylacetamides (VII''), which were prepared by means of 2 mole equiv of the corresponding alkali amide in liquid ammonia, were condensed with benzaldehyde to form adduct VIII (Scheme I).[3] To minimize possible reversion of the condensation, the reaction mixtures were neutralized inversely with ammonium chloride. The yields of adduct VIII, the relative proportions of its *threo* and *erythro* isomers, and the percentage recovery of the benzaldehyde (by vapor phase chromatography) obtained after various condensation times are given in Table I. Although the highest total yield of the two isomers was only 54%, no other product appeared to be formed and 40% of the benzaldehyde was recovered; good material balances were also obtained in most of the other experiments (see Table I).

SCHEME I



VII VII'' VIII VIII''

TABLE I

INFLUENCE OF REACTION TIMES ON PROPORTIONS OF *threo* AND *erythro* ISOMERS OF VIII FROM DIALKALIPHENYLACETAMIDES VII'' AND BENZALDEHYDE IN LIQUID AMMONIA

Expt no.	Alkali cation	Condensation time,[a] min	Total yield, %	*threo* isomer, %	*erythro* isomer, %	Recovered C_6H_5CHO,[b] %
1	Na	0.1[c]	48[d]	...	...	42
2	Na	5	54	57	43	40
3	Na	10	52	100	0	43
4	Na	30	40	100	0	52
5	Na	360	0	...	...	80
6	Na[e]	30	47	64	36	...
7	Li	0.1[c]	15	100	0	78

[a] Condensation time after the benzaldehyde had been added to dialkaliphenylacetamide during a 5-min period. [b] Determined by vapor phase chromatography. [c] In this experiment, the reaction mixture was run into ammonium chloride immediately after the aldehyde had been added, the time being estimated as 6 sec. [d] Product was a mixture of the two isomers but their ratio was not determined. [e] Sodium amide (1 equiv) was present (see Experimental Section).

The high-melting isomer of adduct VIII was identified as *threo* and the low-melting isomer as *erythro* by independent, stereospecific syntheses from authentic *threo*- and *erythro*-2,3-diphenyl-3-hydroxypropionic acids (II), respectively (Schemes II and III). The conversion of each isomer of acid II to hydrazide IV was accomplished stereospecifically as described previously.[2] However, to avoid the Curtius rearrangement of intermediate azide V observed earlier[2] when IV was

(1) Supported by the National Science Foundation.

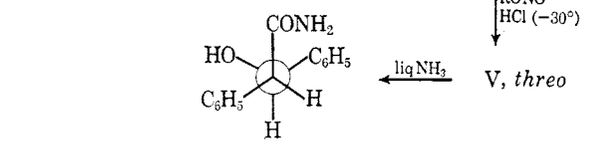
(2) H. E. Zimmerman and M. D. Traxler, *J. Am. Chem. Soc.*, **79**, 1920 (1957).

(3) For convenience, mono-, di-, and trianions are designated by prime, double prime, and triple prime, respectively.

(4) H. E. Zimmerman, L. Ahramjian, and M. D. Traxler, Abstracts of the Organic Division, 131st National Meeting of the American Chemical Society, Miami, Fla., April 1957, p 45O.

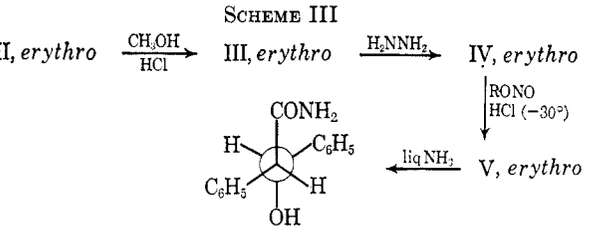
(5) M. S. Newman and A. Kutner, *J. Am. Chem. Soc.*, **73**, 4199 (1951).

SCHEME II



VIII, *threo* (high-melting isomer)

SCHEME III



VIII, *erythro* (low-melting isomer)

treated with sodium nitrite and sulfuric acid at 5–10°, we converted IV to V by means of isoamyl nitrite and hydrochloric acid at −30°; under these conditions V did not rearrange and afforded amide VIII on treatment with ammonia.[6] That the independent syntheses (Schemes II and III) were indeed stereospecific was confirmed by the fact that no *erythro* amide was formed from the *threo* acid and no *threo* amide from the *erythro* acid. Moreover, no mixtures were detected in any intermediate step.

Table I shows that a mixture of the *threo* and *erythro* isomers of adduct VIII was obtained when the condensation period was 5 min or even 6 sec (experiments 1 and 2), whereas only the *threo* isomer was isolated when the period was 10 min or more (experiments 3–5); these times were taken after the benzaldehyde had been added over a 5-min period. Although the mixture obtained in experiment 2 melted over only 2° (171–173°) and resisted separation by fractional crystallization, it was separated quantitatively by column chromatography and found to consist of approximately 53% of the *threo* and 47% of the *erythro* isomers.[7]

The formation of both isomers upon neutralization after a short reaction period but of only the *threo* isomer after a longer period indicated that the disodio salt of the *erythro* isomer was converted to the disodio salt of the *threo* isomer under the conditions employed. This was confirmed by treatment of the 53:47% mixture of *threo* and *erythro* VIII with 2 mole equiv of sodium amide in liquid ammonia for 10 min after which the *threo* isomer (70%), but not the *erythro* isomer, was obtained upon neutralization. Also, there was detected by vpc some (26%) benzaldehyde, which arose through cleavage of VIII.[8]

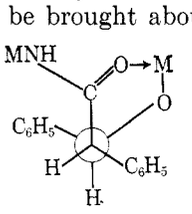
The conversion of *erythro* disodio salt VIII″ to *threo* VIII″ presumably occurred through equilibration of *erythro* VIII″ with benzaldehyde and disodiophenylacetamide (VII″) (eq 1) and/or with trisodio salt VIII‴ and monosodiophenylacetamide (VII′) or ammonia (eq 2). The equilibration of *erythro* salt VIII″ with benzaldehyde (see eq 1) would involve reversion of the original addition reaction, which was demonstrated to occur partially under similar conditions in the experiment mentioned above where some benzaldehyde was obtained when neutral adduct VIII was treated with 2 equiv of sodium amide. The equilibration of *erythro* salt VIII″ with trisodio salt VIII‴ (see eq 2) would involve ionization of the α hydrogen of *erythro* salt VIII″, which was indicated to occur at least with sodium amide.[9] Thus, when disodiophenylacetamide (VII″) was treated with benzaldehyde in the presence of 1 equiv of sodium amide followed by inverse neutralization after 30 min, a mixture of the *threo* and *erythro* isomers of adduct VIII was obtained (experiment 6, Table I). Since only the *threo* isomer of VIII was isolated in the absence of 1 equiv of sodium amide under similar conditions (experiment 4, Table I), this mixture of isomers presumably arose from the trianion VIII‴ on inverse neutralization. If the conversion of *erythro* salt VIII″ to *threo* salt VIII″ (experiments 3 and 4, Table I) occurred according to eq 2, it was apparently brought about by only a catalytic amount of sodium amide or by disodio salt VII″, which is a weaker base than the alkali amide.

erythro VIII″ $\rightleftharpoons$ C_6H_5CHO + VII″ $\rightleftharpoons$ *threo* VIII″ (1)

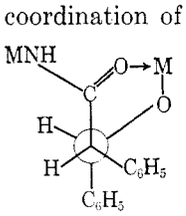
erythro VIII″ + VII″ (or $NaNH_2$) $\rightleftharpoons$ $C_6H_5CH(ONa)CCONHNa(C_6H_5)$ + VII′ (or NH_3) $\rightleftharpoons$ *threo* VIII″ + VII″ (or $NaNH_2$) (2)

VIII‴

The facile conversion of *erythro* disodio salt VIII″ to *threo* VIII″ indicates that the latter salt is more stable thermodynamically. This appears rather surprising since, on the basis of Newman projections of the free β-hydroxy amides VIII (see Schemes II and III), the free *erythro* isomer should be the more stable. The greater stability of the *threo* disodio salt VIII″ might possibly be brought about by coordination of the hydrogen-bonded type.



coordinated *threo* salt VIII″



coordinated *erythro* salt VIII″

(6) Certain other hydrazides have previously been converted stereospecifically to amides by a similar method; see E. Fischer and F. Brauns, *Ber.*, **47**, 3181 (1914).

(7) That the product melting at 171–173° was not a single isomer which was epimerized during the chromatography was indicated by its thin layer chromatogram and by the fact that the isolated *threo* and *erythro* isomers melted at 184 and 145°, respectively.

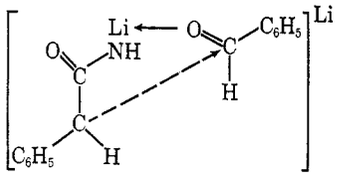
(8) A study of the equilibrium position of the addition reaction under various conditions is in progress.

(9) Similar ionization of an α hydrogen of a monosodio salt was indicated to occur in the condensation of ethyl acetate with benzophenone in the presence of excess sodium amide in liquid ammonia; see C. R. Hauser and W. R. Dunnavant, *J. Org. Chem.*, **25**, 1296 (1960).

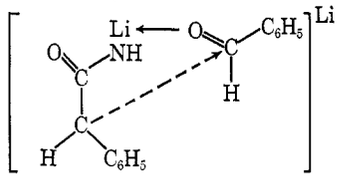
droxyl sodium atom with the oxygen or nitrogen of the amide portion of the molecule as indicated by Newman projections of these salts (M = Na). These projections suggest that the *threo* isomer, having less serious phenyl–phenyl interactions, would be the more stable.

Incidentally, the related α phenylethylations of sodiophenylacetic esters,[10] disodiophenylacetate,[11] and presumably disodiophenylacetamide,[12] which afford neutral or monosodio salts that cannot enter into such a coordination as VIII'', have been observed to afford largely the *erythro* isomers. These irreversible alkylations produce the *erythro* isomer apparently because the transition state resembles this isomer more than the *threo*.[10,12]

There is a possibility that the above reversible addition reactions similarly involved a transition state leading largely to the *erythro* isomer VIII, which was subsequently converted to the *threo* isomer through the disodio salt VIII''. Table I further shows that the condensations of dilithiophenylacetamide (VII'', M = Li) with benzaldehyde (see Scheme I) afforded exclusively the *threo* isomer of adduct VIII after only 6 sec (experiment 7). Since the disodio salt VII'' yielded a mixture of the two isomers under similar conditions after this time (experiment 1, Table I), greater stereoselectivity was observed with the dilithio salt VII''. This may be rationalized by a stronger initial coordination of the dilithio salt VII'' with the oxygen of the aldehyde so that the transition state leading to the *threo* dilithio product VIII'' (see above "coordinated *threo* VIII'') should involve lower energy than the *erythro* transition state as indicated by XIa and XIb, respectively. The latter transition state would have serious phenyl–phenyl interactions.

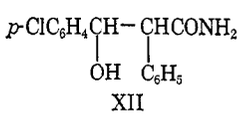


XIa (transition state)

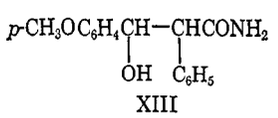


XIb (transition state)

Next, disodiophenylacetamide VII'' (M = Na) was condensed with *p*-chlorobenzaldehyde and anisaldehyde to form single isomers of adducts XII and XIII in yields of 21 and 29%, respectively.



XII



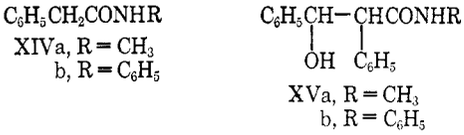
XIII

(10) W. G. Kenyon, R. B. Meyer, and C. R. Hauser, *J. Org. Chem.*, **28**, 3108 (1963).

(11) C. R. Hauser, D. Lednicer, and W. R. Brasen, *J. Am. Chem. Soc.*, **80**, 4345 (1958).

(12) R. B. Meyer and C. R. Hauser, *J. Org. Chem.*, **26**, 3696 (1961).

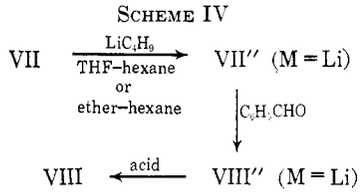
Similarly, N-methylphenylacetamide (XIVa) and phenylacetanilide (XIVb) were converted to their disodio salts in liquid ammonia and the salts condensed with benzaldehyde to afford single isomers of XVa and XVb in yields of 25 and 19%, respectively.



Presumably, these single isomers of XII, XIII, and XVa and b had the *threo* configuration. Although their yields were only fair (19–29%), good material balances were obtained (see Experimental Section).

Finally, phenylacetamide (VII), N-methylphenylacetamide (XIVa), and phenylacetanilide (XIVb) were condensed with benzaldehyde by means of *n*-butyllithium in tetrahydrofuran (THF)–hexane or ethyl ether–hexane to form VIII, XVa, and XVb, respectively. This method may be illustrated for phenylacetamide (Scheme IV).[3] The condensations

SCHEME IV



in THF–hexane were run at 0° for 5 min and those in ether–hexane at reflux for 30 min, after the aldehyde had been added over a 5-min period. The reaction mixtures were then neutralized inversely with acid. The results are summarized in Table II.

Table II shows that the reactions in THF–hexane afforded exclusively the *threo* isomer of VIII and presumably the *threo* isomers of XVa and b. The yield of the *threo* adduct VIII from dilithiophenylacetamide in THF–hexane was lower than that from disodiophenylacetamide in liquid ammonia, whereas the yields of presumed *threo* isomers of XVa and b were somewhat higher in the former solvent medium. The fact that the *threo* isomer was formed exclusively even with short reaction times may be accounted for by initial coordination as described above for lithium amide (see formulas XIa and XIb). Table II further shows that, although better yields were usually obtained from reactions carried out in refluxing ether–hexane than in cold THF–hexane, mixtures of diastereomers were produced in each case. Thus adduct VII (obtained in 19% yield) was separated by column chromatography and found to be a 79:21% (*threo*:*erythro*) mixture of diastereomers. Product XVI (obtained in 64% yield) was quantitatively separated by thin layer chromatography and found to consist of a 78:22% (*threo*:*erythro*) mixture and product XVII (obtained in 78% yield) was shown by an infrared technique to be a mixture of diastereomers in the ratio of 67:33% (*threo*:*erythro*).

The formation of mixtures in refluxing ether–hexane may be due to the use of higher temperatures and/or longer reaction times and may be accounted for by equilibration or by further ionization similar to that shown in eq 1 and 2. The possibility of equilibration

TABLE II

INFLUENCE OF REACTION TIME ON PROPORTIONS OF *threo* AND *erythro* ISOMERS OF ADDUCTS FROM DILITHIOPHENYLACETAMIDES AND BENZALDEHYDE IN ETHEREAL SOLVENTS

Amide	Solvent	Temp, °C	Condensation period,[a] min	Adduct	Total yield, %	*threo* isomer, %	*erythro* isomer, %	Recovered C_6H_5CHO,[b] %
VII	THF–hexane	0	5	VIII	20	100	0	69
XIVa	THF–hexane	0	5	XVa	37	100	0	49
XIVb	THF–hexane	0	5	XVb	53	100	0	40
VII	Ether–hexane	42	30	VIII	19	79	21	71
XIVa	Ether–hexane	42	30	XVa	64	78	22	32
XIVb	Ether–hexane	42	30	XVb	78	67	33	18

[a] Condensation time after the benzaldehyde had been added to the dilithiophenylacetamides during a 5-min period. [b] Determined by vapor phase chromatography.

was demonstrated by treatment of *threo* VIII with 1.5 equiv of *n*-butyllithium in refluxing ether–hexane. Neutralization of this mixture after 1 hr yielded 30% benzaldehyde, which arose through cleavage of VIII, and a mixture of diastereomers of hydroxyamide VIII.[8]

Experimental Section[14]

Addition Reactions of Dialkaliphenylacetamide with Benzaldehyde in Liquid Ammonia.—In Table I are summarized the yields of adduct VIII and of recovered benzaldehyde under various conditions. The details are given below.

A. Reactions of Disodiophenylacetamide (Experiments 1–5).—To a stirred suspension of 0.1 mole of sodium amide, prepared from 2.3 g (0.10 g-atom) of sodium in 300 ml of liquid ammonia,[14] was added 6.75 g (0.05 mole) of solid phenylacetamide. After 30 min, the resulting brown-green suspension, assumed to contain 0.05 mole of disodiophenylacetamide (VII'', M = Na), was treated with a solution of 5.3 g (0.05 mole) of benzaldehyde in 50 ml of anhydrous ethyl ether added during 5 min. After an appropriate time (see Table I), the resulting white suspension was poured into a mixture (magnetically stirred) of 15 g of ammonium chloride in 200 ml of liquid ammonia and the original flask was rinsed out with two 100-ml portions of ether; these washings were added to the neutralized mixture. The ammonia was allowed to evaporate and the remaining ethereal suspension was shaken with 100 ml of 10% hydrochloric acid. The resulting ether–water-insoluble solid was collected by filtration (suction) and recrystallized from 95% ethanol. Composition of the products was determined by thin layer chromatography (tlc) using silica gel G (E. Merck, AG) as the stationary phase and a solution of absolute ethanol and ether (20:80) as a developer; R_f values were compared with those of authentic samples of *erythro*- and *threo*-2,3-diphenyl-3-hydroxypropioamide (VIII). The organic portion of the original filtrate was separated from the aqueous layer and then concentrated to *ca.* 25 ml. Methyl benzoate (1 ml) was added as an internal standard and the mixture was analyzed by means of vapor phase chromatography.

In experiments 1 and 2, tlc indicated that the product was a mixture of diastereomers. A portion of the mixture from experiment 2 was recrystallized several times from 95% ethanol to give a white solid, mp 171–173°. Further recrystallization did not change this melting range. A sample of the mixture was submitted for analysis.

Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.63; H, 6.24; N, 5.67.

A 0.236-g portion of the mixture of diastereomers from experiment 2 was separated by column chromatography employing a 2.5 × 40 cm column packed with untreated 80–100 mesh absorption alumina (Fisher). Elution with 20% ethanol–80% ether afforded 0.102 g of a low-melting isomer, mp 145–146°. Next, 0.130 g of a high-melting isomer, mp 184–186°, was flushed from the column with ethanol. These isomers had identical infrared absorptions at 3400, 3300, 3180, 1650, 730, and 690 cm^{-1}, but distinctly different absorption in the 1100–1350-cm^{-1} region. In experiments 3 and 4, tlc indicated that only the high-melting, or *threo*, isomer of VIII had been formed. Several recrystallizations from 95% ethanol gave an analytical sample of *threo* VIII, mp 184–186°.

Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.77; H, 6.27; N, 5.79.

None of the ether–water insoluble VIII was isolated in experiment 5.

B. Reaction of Disodiophenylacetamide in the Presence of Sodium Amide (1 Equiv) (Experiment 6).—To a stirred suspension of 0.15 mole of sodium amide in liquid ammonia was added 6.75 g (0.05 mole) of phenylacetamide. After stirring for 30 min, the mixture was treated with a solution of 5.3 g (0.05 mole) of benzaldehyde in 50 ml of ether added during 5 min. The resulting suspension was inversely neutralized after 30 min and worked up as described in A. Thin layer chromatography showed the resulting β-hydroxyamide to be a mixture of diastereomers of VIII. These were separated by column chromatography as described in A and consisted of 64% *threo* VIII and 36% *erythro* VIII.

C. Reaction of Dilithiophenylacetamide (Experiment 7).—To a stirred suspension of 0.10 mole of lithium amide in 300 ml of liquid ammonia was added 6.75 g (0.05 mole) of phenylacetamide. After stirring for 30 min, the reaction mixture was treated with a solution of 5.3 g (0.05 mole) of benzaldehyde in 50 ml of ether added during 5 min. The resulting suspension was inversely neutralized immediately and the reaction mixture was processed as described in A to give VIII, mp 181–183°, in 15% yield. Tlc of this product indicated that none of the low-melting isomer of VIII was present.

Preparation of Authentic *erythro* and *threo* Isomers of VIII.—To a magnetically stirred suspension of 0.38 g (0.0015 mole) of *threo*-β-hydroxyhydrazide IV[2] in 3 ml of absolute ethanol and 1 ml of concentrated hydrochloric acid at −80° (Dry Ice–acetone) was added a cooled solution of 1.5 ml of isoamyl nitrite in 3 ml of absolute ethanol. The temperature of the suspension of the resulting azide V was allowed to rise to −30° at which point dissolution occurred. After 45 min at this temperature, the mixture was treated with 20 ml of anhydrous liquid ammonia to afford a white suspension initially, then a yellow solution. After allowing the ammonia to evaporate, the insoluble ammonium chloride was removed by filtration. The resulting filtrate was concentrated and the residue was shaken with 40 ml each of ether and water. The insoluble product was removed by filtration and dried overnight to give 0.02 g (64%) of *threo*-hydroxyamide VIII, mp 183–186°, undepressed upon admixture with the high-melting isomer of VIII prepared as described above by means of sodium amide. Similarly, 0.38 g (0.0015 mole) of *erythro*-β-hydroxyhydrazide IV[2] was converted to 0.18 g (58%) of *erythro* VIII, mp 145–146°, undepressed upon admixture with the low-melting isomer of VIII obtained by means of sodium amide. The infrared spectra and thin layer chromatograms of these samples of *erythro* and *threo* isomers were identical with those of the low- and high-melting isomers, respectively, of VIII prepared by means of sodium amide as described above.

Conversion of a Mixture of Diastereomers of VIII to *threo* VIII.—To a stirred suspension of 0.01 mole of sodium amide in

(13) Melting points were taken on a Thomas–Hoover melting point apparatus in open tubes and are uncorrected. Analyses were by Janssen Pharmaceutica, Beerse, Belgium, and Triangle Chemical Laboratories, Chapel Hill, N. C. Infrared spectra were obtained with a Perkin-Elmer Model 137 or 237 spectrophotometer, using the potassium bromide pellet method. Vapor phase chromatograms were obtained on an F & M Model 500 chromatograph using a 5-ft silicone oil column. Appropriate corrections were made for the differences in thermal conductivity of the unknown and the internal standard in all vpc analyses.

(14) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 122 (1954).

liquid ammonia was added 1.2 g (0.005 mole) of a 53:47 isomer mixture of VIII. After 10 min, the reaction mixture was poured into 50 ml of ammonia containing 2 g of ammonium chloride and the ammonia was allowed to evaporate. The residue remaining was shaken with 50 ml each of 10% hydrochloric acid and ether to afford 0.8 g (70%) of insoluble, high-melting VIII, mp 182–184°. Tlc indicated that none of the low-melting isomer of VIII was present. The ether layer, upon vpc analysis, was found to contain 0.0013 mole (26%) of benzaldehyde.

Condensation of Disodiophenylacetamide with *p*-Chlorobenzaldehyde and Anisaldehyde.—To a stirred suspension of 0.05 mole of disodiophenylacetamide was added 7.0 g (0.05 mole) of *p*-chlorobenzaldehyde in 50 ml of dry ether. After 10 min of stirring, the suspension was inversely neutralized and processed as described for the reactions involving benzaldehyde. Recrystallization of the product from hexane–ethanol gave 2.88 g (21%) of 2-phenyl-3-(*p*-chlorophenyl)-3-hydroxypropionamide (XII), mp 167–168°. Vpc analysis indicated the presence of 74% of the original aldehyde, The infrared spectrum of XII showed peaks at 3460, 3350, 3180, 1660, 820, 750, 750, and 690 cm^{-1}.

Anal. Calcd for $C_{15}H_{14}ClNO_2$: C, 65.34; H, 5.12; N, 5.08. Found: C, 65.22; H, 5.38; N, 5.27.

Similarly, 6.8 g (0.05 mole) of anisaldehyde was condensed with 0.05 mole of disodiophenylacetamide and inversely neutralized after a 10-min reaction period. Subsequent work-up and recrystallization from hexane–ethanol gave 3.93 g (29%) of 2-phenyl-3-(*p*-methoxyphenyl)-3-hydroxyphenylacetamide (XIII), mp 143–146°. Vpc analysis indicated the presence of 70% of the original aldehyde. The infrared spectrum of XIII showed peaks at 3400, 3350, 3180, 1675, 820, 750, and 690 cm^{-1}.

Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 71.03; H, 6.28; N, 5.33.

Condensations of the Disodio Salts of N-Methylphenylacetamide (XIVa) and Phenylacetanilide (XIVb) with Benzaldehyde.—To a stirred suspension of 0.10 mole of sodium amide in liquid ammonia was added 7.45 g (0.05 mole) of XIVa. After 30 min, the reaction mixture was treated with a solution of 5.3 g (0.05 mole) of benzaldehyde in 50 ml of ether over 5 min. The reaction mixture was inversely neutralized after 10 min and worked up as described for the condensations involving phenylacetamide. Recrystallization of the product from 95% ethanol afforded 3.19 g (25%) of N-methyl-2,3-diphenyl-3-hydroxypropionamide (XVa), mp 175–176°. Vpc analysis indicated that 70% of the original benzaldehyde remained. The infrared spectrum showed peaks at 3400, 3280, 1625, 730, and 690 cm^{-1}.

Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.14; H, 6.76; N, 5.64.

Similarly, 5.3 g (0.025 mole) of phenylacetanilide (XIVb) was added to a stirred suspension of 0.05 mole of sodium amide in liquid ammonia. After 30 min, the resulting suspension was treated with a solution of 2.65 g (0.025 mole) of benzaldehyde in 50 ml of ether added over 5 min. The reaction mixture was inversely neutralized after 10 min and processed as described previously for reactions involving phenylacetamide. Recrystallization of the product from ethyl acetate–acetone afforded 3.10 g (19%) of N-phenyl-2,3-diphenyl-3-hydroxypropionamide (XVb), mp 222–224°. Vpc analysis indicated the presence of 79% of the original aldehyde. The infrared spectrum of XVb had peaks at 3350, 3200, 1660, 740, and 690 cm^{-1}.

Anal. Calcd for $C_{21}H_{19}NO_2$: C, 79.49; H, 6.03; N, 4.41. Found: C, 79.12; H, 6.06; N, 4.35.

Condensations of Phenylacetamides VII, XIVa, and XIVb with Benzaldehyde by Means of *n*-Butyllithium.—In Table II are summarized the yields of β-hydroxyamides VIII, XVa, and XVb and of recovered benzaldehyde under various conditions. The details are given below.

A. Reactions in THF–Hexane.—To a magnetically stirred solution of 6.75 g (0.05 mole) of phenylacetamide (VII) in 100–150 ml of tetrahydrofuran (THF) cooled in an ice bath was added 62.5 ml (0.10 mole) of 1.6 *M* *n*-butyllithium[15] in hexane. The addition of the first equivalent of the reagent afforded a dense white precipitate while the second equivalent gave a yellow, light suspension. After this cooled suspension stirred for 30 min, a solution of 5.3 g (0.05 mole) of benzaldehyde in 50 ml of THF was added over a period of 5 min. The mixture was inversely neutralized after 5 more min by pouring it into 100 ml of 10% hydrochloric acid. The THF was removed under reduced pressure at room temperature on a rotary evaporator. The resulting aqueous suspension was shaken with ethyl ether and processed as described for the condensations by means of sodium amide to give the high-melting *threo* isomer of VII, mp 184–186°, undepressed upon admixture with a sample prepared by means of sodium amide. Tlc indicated that none of the *erythro* isomer was present. The amount of unreacted benzaldehyde was determined by vpc analysis.

Similarly, 7.45 g (0.05 mole) of N-methylphenylacetamide (XIVa) was converted to the dilithio salt by means of 62.5 ml (0.10 mole) of 1.6 *M* *n*-butyllithium[15] and condensed with 5.3 g (0.05 mole) of benzaldehyde in THF at 0° as described above. Inverse neutralization immediately after the addition of benzaldehyde and subsequent processing as described above for phenylacetamide afforded the presumably *threo* isomer of XVa, mp 175–176°, undepressed upon admixture with XVa, prepared from the reaction of the disodio salt of XIVa with benzaldehyde in liquid ammonia. Tlc analysis showed that only a single isomer of XVa had been formed.

Likewise, 5.3 g (0.025 mole) of phenylacetanilide (XIVb) was converted to the dilithio salt by means of 31 ml (0.05 mole) of 1.6 *M* *n*-butyllithium[15] and was condensed at 0° as described above for phenylacetamide. Inverse neutralization immediately after the addition of benzaldehyde afforded the presumably *threo* isomer of XVb, mp 220–223°, undepressed upon admixture with a sample of XVb prepared from the reaction of the disodio salt of XIVb with benzaldehyde in liquid ammonia. Tlc analysis showed that only a single isomer of XVb had been formed.

B. Reactions in Ethyl Ether–Hexane.—To a magnetically stirred suspension of 6.75 g (0.05 mole) of phenylacetamide (VII) in 100 ml of dry ether was added 62.5 ml (0.10 mole) of 1.6 *M* *n*-butyllithium[15] in hexane. After 30 min, the reaction mixture was treated with a solution of 5.3 g (0.05 mole) of benzaldehyde in 50 ml of ether added over 5 min. After stirring at reflux for 30 min, the mixture was poured into a solution of 10 ml of glacial acetic acid and 50 ml of ether. The resulting suspension was shaken with a cold 10% sodium bicarbonate solution and processed, as described for the reactions involving sodium amide, to give a mixture of isomers of VIII. This mixture was separated by column chromatography as described above for mixtures of VIII obtained by means of sodium amide.

Similarly, 7.45 g (0.05 mole) of N-methylphenylacetamide (XIVa) was converted to its dilithio salt by means of 62.5 ml (0.10 mole) of 1.6 *M* *n*-butyllithium[15] and condensed with 5.3 g (0.05 mole) of benzaldehyde in refluxing ether–hexane, as described above for phenylacetamide. Inverse neutralization after 30 min of refluxing gave a mixture of diastereomers of XVa. A 0.072-g sample of this mixture, dissolved in acetone, was spotted on a 20 × 20 cm^2 tlc plate with a 1-mm-thick coating of Merck silica gel G. The plate was then developed with anhydrous ethyl ether. The areas corresponding to the *erythro* and *threo* isomers were located by spraying a small portion of the plate with an iodine–carbon tetrachloride solution. The appropriate areas were then scraped from the plate and extracted with chloroform which was dried over magnesium sulfate and concentrated to give solid residues. The lower spot (R_f 0.32) yielded 0.054 g (78%) of the *threo* isomer, mp 175–176°, undepressed upon admixture with XVa prepared by means of sodium amide. The upper spot (R_f 0.73) yielded 0.15 g (22%) of the *erythro* isomer, mp 144–144.5°, whose infrared spectrum was identical with that of the *threo* isomer except for differences in the region 1100–1350 cm^{-1}.

Likewise, 10.3 g (0.05 mole) of phenylacetanilide (XIVb) in 100 ml of dry ether was converted to its dilithio salt by the addition of 62.5 ml of 1.6 *M* *n*-butyllithium[15] in hexane. After the resulting yellow solution stirred for 30 min, 5.3 g (0.05 mole) of benzaldehyde in 50 ml of ether was added over a period of 5 min and the mixture was refluxed for 30 min. Upon inverse neutralization and subsequent processing as described for phenylacetamide, a mixture of diastereomers was obtained. Pure samples of *erythro*, mp 163–165°, and *threo*, mp 222–224°, isomers of XVb were isolated by repeated fractional crystallization from ethyl acetate–acetone. These isomers were indicated to be pure by tlc. A sample of the *erythro* isomer was submitted for analysis.

Anal. Calcd for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.13; H, 6.06; N, 4.43.

Although the infrared spectra of the two isomers were very similar, the *erythro* isomer had a sharp peak at 1260 cm^{-1} which was completely absent in the *threo* isomer. Both isomers had a sharp peak at 1070 cm^{-1}. A plot of isomer composition *vs.* the quotient of the heights of these two peaks (1260 cm^{-1}/1070

(15) Foote Mineral Co., Exton, Pa.

cm^{-1}) was linear. The isomer composition of the above mixture was easily determined from this plot.

Treatment of *threo* VIII with 1.5 Equiv of *n*-Butyllithium.—To a magnetically stirred suspension of 4.15 g (0.0172 mole) of *threo* VIII in 50 ml of dry ether was added 16.3 ml (0.027 mole) of 1.6 *M* *n*-butyllithium[15] in hexane and the resulting suspension was heated to reflux. After 30 min, the mixture was inversely neutralized by addition to 3 ml of glacial acetic acid in ether. The mixture was shaken with two 50-ml portions of cold 10% sodium bicarbonate solution. The ether–water-insoluble material was filtered off and dried to give 2.48 g (60%) of a product shown by tlc to be a mixture of diastereomers of VIII. Vpc analysis of the ether layer indicated the presence of 0.005 mole (30%) of benzaldehyde.

Registry No.—VIII (*erythro*), 13144-04-2; VIII (*threo*), 13143-85-6; XII, 13143-86-7; XIII, 13144-05-3; XVa (*erythro*), 13143-87-8; XVa (*threo*), 13143-88-9; XVb (*erythro*), 13143-89-0; XVb (*threo*), 13143-90-3.

Notes

Alkylation of Acetylacetone with Isopropyl Alcohol by Means of Boron Fluoride[1]

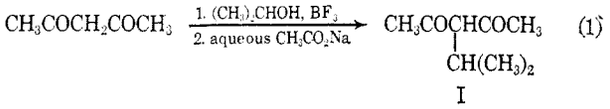
TIMOTHY F. CRIMMINS AND CHARLES R. HAUSER

Chemistry Department, Duke University, Durham, North Carolina

Received February 9, 1967

It has previously been shown that ethyl acetoacetate can be alkylated with isopropyl and *t*-butyl alcohols by means of boron fluoride to form the corresponding 3-alkyl derivatives in yields of 65 and 12%, respectively.[2]

It has now been found that acetylacetone can be alkylated similarly with isopropyl alcohol to give 3-isopropylacetylacetone (I) in 58% yield (eq 1). The

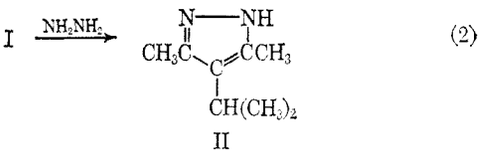


(1)

I

product was identified as I by essential agreement of its boiling point with the reported value, by identity of its vpc retention time with an authentic sample, and by its nmr spectrum. This spectrum exhibited a doublet at 0.90 ppm (assigned to the methyl hydrogens of the isopropyl group), a singlet at 2.14 ppm (assigned to the methyl hydrogens of the acetylacetone moiety), a multiplet centered at 2.41 ppm (assigned to the tertiary hydrogen on the isopropyl group), and a doublet at 3.53 ppm (assigned to the tertiary hydrogen on the acetylacetone moiety). It is not surprising that an enol signal was not observed since the nmr spectrum was determined from 0 to 8.3 ppm. Enol hydrogens resonate from 14 to 15 ppm.[3]

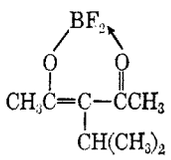
Also, I underwent cleavage with sodium hydroxide to form methyl isobutyl ketone and cyclization with hydrazine to give pyrazole II (eq 2). The nmr spectrum of II showed a doublet at 1.21 ppm (assigned to the methyl groups of the isopropyl moiety), a singlet at 2.20 ppm (assigned to the methyl groups of the pyrazole ring), and a multiplet centered at 2.70 ppm (assigned to the hydrogen of the pyrazole ring, the tertiary hydrogen of the isopropyl moiety, or possibly both).



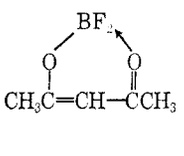
(2)

II

The isopropylation of acetylacetone evidently involved formation of the boron difluoride complex III, from which I was obtained on treatment with hot sodium acetate solution (see eq 1). Thus, III was isolated from the reaction mixture and subsequently converted to I (see Experimental Section). A possible course for the formation of boron difluoride complex III would involve initial conversion of the acetylacetone to its boron difluoride complex IV,[4] which undergoes isopropylation; however, a blank experiment with IV showed that complex III did not arise appreciably in this manner. The mechanism of formation of the boron difluoride complex III is suggested to involve a carbon–carbon condensation between enol-type intermediate VI and the isopropyl carbonium ion, followed by loss, in two steps, of hydrogen fluoride (Scheme I). As indicated in Scheme I, ionizations of boron trifluoride coordination complexes V and VII are analogous. Since the enol-type intermediate VIII loses a fluoride ion to afford difluoride complex III, enol-type intermediate VI might be expected to do likewise to afford the boron difluoride complex of acetylacetone (IV). The latter reaction may have occurred to some extent but, under the conditions employed, VI evidently underwent preferential isopropylation followed by loss of the elements of hydrogen fluoride (see Scheme I). Incidentally, enol-type intermediate VI must lose a



III



IV

(1) Supported by the National Science Foundation.

(2) J. T. Adams, B. Abramovitch, and C. R. Hauser, *J. Am. Chem. Soc.*, **65**, 552 (1943); J. T. Adams, R. Levine, and C. R. Hauser, *Org. Syn.*, **27**, 35 (1947).

(3) See J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1965, p 91.

(4) See G. T. Morgan and R. B. Tunstall, *J. Chem. Soc.*, **125**, 1963 (1924).