Anal. Calcd. for $C_{27}H_{22}O_2$: C, 85.68; H, 5.86. Found: C, 86.01; H, 5.76.

1,1-bis-(4-Methylthiolphenyl)-propene.—The Grignard reagent was prepared from 10 g. of 4-bromothioanisole[9] and 1.2 g. of magnesium in 130 cc. of ether and 50 cc. of benzene. Ethyl propionate (2 cc.) was added, the mixture refluxed gently for four hours, acidified, and steam distilled for three hours. The residue was extracted with benzene, and after the benzene was evaporated, 4 g. of crystals was obtained. After four crystallizations from alcohol, the compound was obtained as pale yellowish crystals, of m. p. 85.5–87.5°

Anal. Calcd. for $C_{17}H_{18}S_2$: C, 71.28; H, 6.33. Found: C, 71.34; H, 6.23.

(9) This was prepared in 95% yield by bromination of thioanisole and distilled at 138–143° (8 mm.); *cf.* Bourgeois and Abraham, *Rec. trav. chim.*, **30**, 407 (1911).

1,1-bis-(4-Methylthiolphenyl)-ethylene was prepared in the same manner as the corresponding propene. After seven crystallizations from alcohol, it was a white amorphous material, m. p. 123–126° with preliminary sintering. The analysis indicated that it was still impure.

Anal. Calcd. for $C_{16}H_{16}S_2$: C, 70.54; H, 5.92. Found: C, 67.41; H, 7.25.

Summary

A number of unsymmetrical diarylethylenes, some of them new compounds, have been prepared, and their color reactions with various toxic agents studied. Lewisite and ethyldichlorarsine give colors with most of the compounds tested.

ROCHESTER, N. Y. RECEIVED JUNE 13, 1946

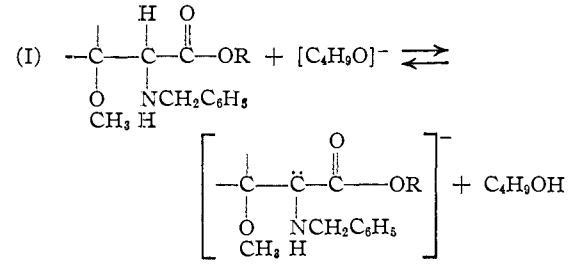
[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 1071]

The Reduction of Ethyl α-Benzylamino-β-methoxy-*n*-caproate with Sodium and Butyl Alcohol

BY CARL NIEMANN AND CARL T. REDEMANN

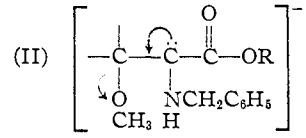
Ethyl α-benzylamino-β-methoxy-*n*-caproate when subjected to the action of sodium and butyl alcohol is converted into 2-benzylamino-1-hexanol. The loss of a methoxy group from the former compound under the conditions of the Bouveault–Blanc reduction was not anticipated. However, with the experimental observation at hand an explanation of the observed phenomena may be offered.

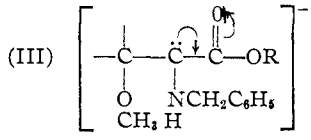
It is reasonably certain that under the conditions of the reaction the following equilibrium (I) is established



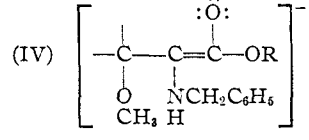
The anion formed by the reaction of butoxide ion with the ester is a resonance hybrid and the structure indicated above is but one of the contributing structures but certainly an important one. Structures in which a proton is added to the nitrogen atom cannot be significant in the presence of a base such as butoxide ion though it is true that both the benzylamino group and the carbethoxy group contribute to the activation of the hydrogen on the α-carbon atom and thereby facilitate its removal as a proton.

By analogy with the mechanism proposed for the base catalyzed dehydrohalogenation of alkyl halides[1] and the base catalyzed dehydration of β-hydroxy esters[2] one would expect that the unshared electron pair on the α carbon atom of the anion would tend to swing into the bond between the α and β carbon atoms and to thereby increase the ionic character of the carbon–oxygen bond of the β carbon atom (II). In the case at hand the





tendency also exists for the unshared electron pair on the α carbon atom to swing into the bond between the α carbon atom and the carbonyl carbon atom and thereby augment the polarization of the carbonyl carbon–oxygen bond (III). This latter tendency gives rise to another important contributing structure, of the anion resonance hybrid, in which the unshared electron pair is on the carbonyl oxygen atom (IV).



Thus while one of the contributing structures of the resonance hybrid of the anion tends to increase the ionic character of the carbon–oxygen bond of the β carbon atom and the other contributing

(1) Hauser, THIS JOURNAL, **62**, 933 (1940).

(2) Hauser and Breslow, *ibid.*, **62**, 3344 (1940).

structure is without significant effect the net result would lead to an activation of the carbon–oxygen bond of the β carbon atom which is significantly greater than that obtaining in the absence of a base.

It is reasonably certain that 2-benzylamino-1-hexanol is not formed from the anion by a series of reactions involving, among others, the elimination of methoxide ion, the formation of a double bond between the α and β carbon atoms and the hydrogenation of this carbon–carbon double bond for it is well established that carbon–carbon double bonds are not reduced under the conditions of the Bouveault–Blanc reduction. It appears likely that 2-benzylamino-1-hexanol is formed by the hydrogenolysis of the activated carbon–oxygen bond of the β carbon atom of the anion derived from the ester and that the β desoxy ester, or its anion, is then reduced to the corresponding alcohol. One cannot be certain of this sequence until information is available concerning the behavior of 3-methoxy-2-benzylamino-1-hexanol with sodium and butyl alcohol. Studies are now in progress on the prepration of this compound by the reduction of ethyl α-benzylamino-β-methoxy-n-caproate under neutral or acidic conditions.

Experimental

2-Hexenoic Acid.[3]—To 200 g. (1.92 moles) of dry malonic acid in 200 ml. of anhydrous pyridine was added 158 ml. (1.76 moles) of freshly distilled n-butyraldehyde. The reaction was allowed to proceed at 25° for twenty-four hours, at 40–45° for an additional twenty-four hours and finally at 60° for three hours. The reaction mixture was chilled, acidified with 6 *N* sulfuric acid, the non-aqueous phase collected and the aqueous phase extracted with three 100-ml. portions of ether. The combined non-aqueous phase and ethereal extracts were dried over calcium chloride, filtered, the solvent removed, the residue allowed to crystallize at 0°, and the crystals collected to give 130 g. (64%) of crude 2-hexenoic acid, m. p. 30–32°.

α-Bromo-β-methoxy-n-caproic Acid.[4]—To a solution of 330 g. (1.03 moles) of mercuric acetate in 1500 ml. of methanol was added 110 g. (0.97 mole) of crude 2-hexenoic acid and the solution allowed to stand at 25° for forty-eight hours. The precipitate that had formed was collected and air-dried to give 334 g. of addition product which was then dissolved in 970 ml. of water containing 174 g. (1.46 moles) of potassium bromide. To this solution was added, with stirring in direct sunlight at 0°, over a period of thirty five minutes, 154 g. (0.97 mole) of bromine dissolved in 174 g. of potassium bromide in 280 ml. of water. The reaction mixture was allowed to stand at 0° for an additional twenty minutes, acidified with hydrobromic acid and extracted with six 150-ml. portions of ether. The combined ethereal extracts were dried over sodium sulfate and the solvent removed to give 176.5 g. (81%) of crude α-bromo-β-methoxy-n-caproic acid.

Ethyl α-Bromo-β-methoxy-n-caproate.—A solution of 22.5 g. (0.1 mole) of crude bromo acid in 100 ml. of absolute ethanol containing 3 g. of anhydrous hydrogen chloride was refluxed for two hours. The solvent was removed by distillation *in vacuo*, 75 ml. of absolute ethanol added to the residue and the process repeated. The residual oil was distilled *in vacuo* to give 19.0 g. (75%) of colorless ester, b. p. 86–87° (15 mm.).

Anal. Calcd. for $C_9H_{17}O_3Br$ (253): C, 42.7; H, 6.8. Found: C, 42.7; H, 6.7.

(3) Johnson, "Organic Reactions," **1**, 210 (1942).

(4) Carter and West, "Organic Syntheses," **20**, 101 (1940).

Ethyl α-Benzylamino-β-methoxy-n-caproate.[5]—A solution of 18 g. (0.071 mole) of ethyl α-bromo-β-methoxy-n-caproate in 20 g. (0.187 mole) of benzylamine was heated in an oil-bath at 110° for four hours. The reaction product was taken up in 75 ml. of chloroform, the suspension chilled to 10°, filtered and the precipitate washed with 10 ml. of chloroform. The filtrate and washings were combined, the solvent removed and the residual oil distilled *in vacuo*. The desired product was obtained as a pale yellow oil, b. p. 121–124° (0.03 mm.). The yield was 12.5 g. (63%). The hydrochloride was prepared by passing dry hydrogen chloride into a solution of 0.5 g. of ethyl α-benzylamino-β-methoxy-n-caproate in 5 ml. of isopropyl ether. The hydrochloride after three recrystallizations from a mixture of n-butanol and isopropyl ether exhibited a m. p. of 159.5–160.5°.

Anal. Calcd. for $C_{16}H_{26}NO_3Cl$ (316): C, 60.9; H, 8.3; N, 4.4. Found: C, 61.0; H, 8.1; N, 4.5.

Reduction of Ethyl α-Benzylamino-β-methoxy-n-caproate.[6]—In a three-necked flask equipped with a mechanical stirrer and two reflux condensers was placed a solution of 55 g. (0.197 mole) of ethyl α-benzylamino-β-methoxy-n-caproate in 500 ml. of anhydrous n-butanol. The flask was placed in an oil-bath maintained at 140°. As soon as the contents of the flask had begun to boil, the burner was removed from under the bath and the temperature of the bath permitted to fall to 115°. At this point 55 g. (2.4 g.-atoms) of sodium buck-shot was added as rapidly as possible. The butanol was kept boiling vigorously until all of the sodium had dissolved, additional n-butanol being added at intervals to keep the sodium butoxide formed in solution. After all of the sodium metal had dissolved, the flask was cooled to 25°, 100 g. of ice added and the solution acidified with 6 *N* hydrochloric acid. The solvents were then removed by distillation *in vacuo*. When an estimated 50 g. of sodium chloride had crystallized, the evaporation was interrupted, the sodium chloride removed and the distillation continued until butanol no longer appeared in the distillate. The residue solidified on cooling to 25°, the resultant paste was made strongly alkaline with 6 *N* sodium hydroxide and extracted with three 100-ml. portions of ether. The combined ethereal extracts were washed with 25 ml. of water and dried over anhydrous magnesium sulfate. The solvent was removed and the residue distilled to give 25 g. of a pale yellow oil, b. p. 130–133° (0.1 mm.). The distillate was caused to crystallize and after two recrystallizations from acetone the product was obtained as colorless needles m. p. 46.5–47.5°.

Anal. Calcd. for $C_{14}H_{23}NO_2$ (237): C, 70.9; H, 9.8; N, 5.9. Calcd. for $C_{13}H_{21}NO$ (207): C, 75.3; H, 10.2; N, 6.8. Found: C, 75.2; H, 9.7; N, 6.9.

The hydrochloride was prepared by passing a stream of dry hydrogen chloride into a solution of 0.1 g. of the purified reduction product in 1 ml. of anhydrous ether. The solid so obtained was twice recrystallized from n-butanol to give the hydrochloride, white glistening plates, m. p. 140–141°.

Anal. Calcd. for $C_{13}H_{22}NOCl$ (244): C, 64.1; H, 9.1; N, 5.7. Found: C, 64.2; H, 8.9; N, 5.7.

Debenzylation of Reduction Product Hydrochloride.[6]—The reduction product hydrochloride (4.5 g.) was added to 1.5 g. of 20% pallidized charcoal suspended in 75 ml. of methanol and the mixture shaken at 25° under 15 lb. gage pressure of hydrogen for sixteen hours. The catalyst was removed and the filtrate evaporated to dryness *in vacuo*. The residue was recrystallized three times from a mixture of methanol and ethyl ether to give large, colorless, intensely hydroscopic leaves, m. p. 92.5–94°. The reported m. p. of 2-amino-1-hexanol hydrochloride is 93–94.5°.[7]

Summary

Ethyl α-benzylamino-β-methoxy-n-caproate

(5) Bischoff, *Ber.*, **30**, 3171 (1897).

(6) Peyer, U. S. Patent No. 2,243,977 (1941).

(7) Leffler and Adams, THIS JOURNAL, **59**, 2252 (1937).

has been synthesized and it has been shown that the reduction of this compound with sodium and butyl alcohol results in the formation of 2-benzylamino-1-hexanol. An explanation of the replacement of the β-methoxy group by hydrogen under the conditions of the Bouveault–Blanc reduction has been offered.

PASADENA, CALIF. RECEIVED JUNE 6, 1946

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Antispasmodics. VIII

BY F. F. BLICKE AND FREDERICK LEONARD[1,2]

It has been found that basic-alkyl esters of certain substituted acetic acids, in which one of the substituents is a 2-thienyl group, are very potent antispasmodics.[3] Since Wagner-Jauregg, Arnold and Born[4] have shown that β-diethylaminoethyl esters of a number of aralkylacetic acids, for example those of benzylphenylacetic and benzylisopropylacetic acid, possess this activity to a high degree, we decided to synthesize a variety of β-diethylaminoethyl esters of substituted 2-thienylmethylacetic acids, $C_4H_3SCH_2(R)CHCO-OH$, in which R was represented by such radicals as alkyl, cycloalkyl, aryl, cycloalkylalkyl and aralkyl.

In order to obtain the acetic acid esters, we prepared, first, the monosubstituted malonic esters (Table II) either by interaction of the required ethyl arylacetate, diethyl carbonate and sodium ethylate[5] or by the malonic ester synthesis. After conversion of the mono- into the disubstituted malonic esters (Table II), the latter compounds were hydrolyzed to the corresponding disubstituted malonic acids (Table III). In some instances the malonic acids lost carbon dioxide spontaneously with the formation of the acetic acids; in other cases it was necessary to heat the malonic acids in order to bring about this conversion. The acetic acids (Table III) were esterified by the use of β-diethylaminoethyl chloride according to the general procedure of Hörenstein and Pählicke.[6]

Incidentally, we prepared β-methylaminoethyl 2-thienylmethylbenzylacetate hydrochloride by interaction of 2-thienylmethylbenzylacetyl chloride with β-methylaminoethanol to form N-methyl-N-(β-hydroxyethyl)-2-thienylmethylbenzylacetamide, and then heated the amide with hydrochloric acid, according to the general method of Reasenberg and Goldberg,[7] in order to convert it into the ester hydrochloride.

Our esters (Table IV) were studied pharmacologically in the Frederick Stearns and Company laboratories, and we are indebted to Dr. A. M. Lands and Miss Harriet McCarthy for the report (Table I). It is evident from an examination of the table that, as far as the compounds which have been reported are concerned, the anticholinergic activity is decreased when a cyclic radical, such as phenyl, 2-thienyl or cyclohexyl, is separated from the rest of the molecule by one or more aliphatic carbon atoms.

TABLE I

ANTISPASMODIC ACTIVITY,
$C_4H_3SCH_2(R)CHCOOCH_2CH_2N(C_2H_5)_2 \cdot HCl$

R	Maximum effective dilution: Acetylcholine[a] × 10^4	Barium chloride[a] × 10^4	Histamine[b] × 10^4
C_6H_5	100–200	10– 20	10–20
C_4H_3S[c]	200–400	20– 40	20–40
C_6H_{11}[d]	50–100	20– 40	20–50
C_3H_7	100–200	100–200	20–50
$C_6H_5CH_2$	20– 50	20– 50	...
$C_4H_3SCH_2$	100–200	20– 50	20–40
$C_6H_{11}CH_2$	20– 50	10– 20	50–100
$C_6H_5CH_2CH_2$	20– 40	20– 30	20–40
$C_4H_3SCH_2CH_2$	20– 40	10– 20	20–40
$C_6H_{11}CH_2CH_2$	4– 8	4– 10	4– 8

[a] Rabbit jejunum. [b] Guinea pig ileum. [c] 2-Thienyl. [d] Cyclohexyl.

Experimental Part

2-Thienylmethyl Chloride.—A rapid stream of hydrogen chloride was passed into a stirred mixture of 525 cc. of concentrated hydrochloric acid, 450 cc. of 40% aqueous formaldehyde and 465 cc. of thiophene while the temperature was maintained at 0–10°. After saturation with the gas, the material was poured into two liters of water, the oily precipitate separated, and the aqueous layer extracted several times with ether. The extracts and oil were combined, washed with water a number of times, and then dried over potassium carbonate. After removal of the ether, the product boiled at 78–82° (18 mm.); yield 373 g. (47%).

This procedure represents a variation of one described by Blicke and Burckhalter[8] who obtained the chloride in 40% yield.

The chloride should not be kept in a tightly closed container since it undergoes spontaneous decomposition, often with explosive violence. It remains undecomposed for some time if preserved in a refrigerator.

2-Thienylacetonitrile.—A mixture of 133 g. of 2-thienylmethyl chloride, 60 cc. of acetone and 74 g. of sodium

(1) This paper represents part of a dissertation to be presented to the Horace H. Rackham School of Graduate Studies by Frederick Leonard in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

(2) Frederick Stearns and Company Fellow.

(3) Blicke and Tsao, THIS JOURNAL, **66**, 1645 (1944); Lands and Nash, *Proc. Soc. Exp. Biol. Med.*, **57**, 55 (1944); Lands, Nash and Hooper, *J. Pharmacol. Exp. Therap.*, **86**, 129 (1946); Abreu and Troescher-Elam, *ibid.*, **86**, 205 (1946).

(4) Wagner-Jauregg, Arnold and Born, *Ber.*, **72**, 1551 (1939).

(5) Wallingford, Homeyer and Jones, THIS JOURNAL, **63**, 2056 (1941); Wallingford, Thorpe and Homeyer, *ibid.*, **64**, 580 (1942).

(6) Hörenstein and Pählicke, *Ber.*, **71**, 1644 (1938).

(7) Reasenberg and Goldberg, THIS JOURNAL, **67**, 933 (1945).

(8) Blicke and Burckhalter, *ibid.*, **64**, 477 (1942).