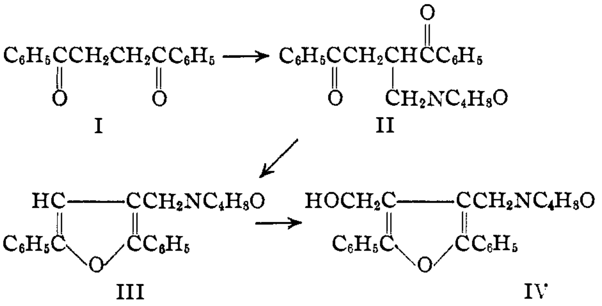
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

3-(4-Morpholinylmethyl)-2,5-diphenylfuran and 3-(Hydroxymethyl)-4-(4-morpholinylmethyl)-2,5-diphenylfuran from Mannich Reactions with 1,2-Dibenzoylethane in Benzene Medium[1]

BY PHILIP S. BAILEY, GENE NOWLIN AND HOWARD W. BOST

In the Mannich reaction with 1,2-dibenzoylethane in benzene medium the initial product is 2,3-dibenzoyl-1-(4-morpholinyl)-propane. This reacts further to give 3-(4-morpholinylmethyl)-2,5-diphenylfuran which is the principal product under slightly acidic conditions. Under more strongly acidic conditions the latter compound reacts with excess paraformaldehyde to form as the principal product 3-(hydroxymethyl)-4-(4-morpholinylmethyl)-2,5-diphenylfuran. The formation of 2,3-dibenzoyl-1-(4-morpholinyl)-propane is believed to involve first a reaction between formaldehyde and the amine hydrochloride followed by reaction of this intermediary substance with 1,2-dibenzoylethane.

In preceding papers[2] there were described the Mannich reaction with 1,2-dibenzoylethane (I) in both alcohol and benzene medium and some interesting reactions of 3-(hydroxymethyl)-4-(4-morpholinylmethyl)-2,5-diphenylfuran (IV) which is one of the principal products of the reaction in benzene medium. The present paper concerns itself with the mode of formation of the various products of the reaction, IV, 3-(4-morpholinylmethyl)-2,5-diphenylfuran (III) and 2,3-dibenzoyl-1-(4-morpholinyl)-propane (II).



The Mannich reactions were carried out in benzene medium using 1,2-dibenzoylethane (I), paraformaldehyde and morpholine hydrochloride. The addition of small amounts of hydrochloric acid was found to be necessary in order to avoid tar formation. When concentrated hydrochloric acid was added in ratios of 10–30 ml. per mole of I, the principal product was III and the minor product was IV. Using concentrated hydrochloric acid ratios of 35 ml. per mole of I and higher, the order was reversed and IV became the major product. Also, the amount of water present in the reaction mixture had to be regulated carefully in order to get consistent results. Using an acid ratio of 20 ml. per mole of I and adding water to the extent of 50 ml. per mole of I, IV became the major product, though not to as great an extent as when the acid ratio was greater. Excess paraformaldehyde was used in all reactions.

Although one would expect II to be the primary product in the Mannich reaction with I, it has been isolated only in one instance.[2a] When it was substituted, as the hydrochloride, for I in the reaction mixtures just described, however, the results were the same as when using I. The major product was III when lower acid ratios were used and IV when the acid ratios were increased. Similar results were obtained when III was substituted, as the hydrochloride, for I in the reaction mixtures. Using lower acid ratios it was recovered unchanged, whereas it reacted to give IV when higher acid ratios were employed. The possibility that III and IV were formed from I through 2,5-diphenylfuran (V) as an intermediate was discarded after 2,5-diphenylfuran (V) failed to react when substituted for I in the Mannich reaction mixture. Thus, most probably, the course of the reaction starting with 1,2-dibenzoylethane (I) is I → II → III → IV. The conversion of III to IV appears to be an acid induced hydroxymethylation and not to involve a stable chloromethyl intermediate which is hydrolyzed during the work-up period as might be suggested by earlier work,[2b] for the introduction of excess morpholine (Table I, note *n*) led to formation of no isolable 3,4-di-(4-morpholinylmethyl)-2,5-diphenylfuran.

So far the mode of formation of II from I has not been considered. Of the two principal broad mechanisms suggested in earlier discussions,[3] we favor the one also favored by Alexander and Underhill[4] and Lieberman and Wagner[5] which involves a primary condensation between formaldehyde and the amine followed by reaction of this intermediate with the reactive hydrogen compound. The fact that we obtained no reaction when a tertiary amine hydrochloride was substituted for morpholine hydrochloride in the reaction mixture must mean that it is necessary for the amine to react in order for *any* condensation to occur and is, therefore, evidence against the other suggested mechanism which involves the primary interaction of I and formaldehyde.

It was desired to test further the favored mechanism by substituting (4-morpholinyl)-methanol and di-(4-morpholinyl)-methane, as hydrochlorides, for morpholine hydrochloride and paraformaldehyde in the Mannich reaction mixture. However, it was found that these compounds were not as stable as earlier work would indicate. It was

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[1] From the Ph.D. dissertation of Gene Nowlin, May, 1949, and the M.A. thesis of H. W. Bost, August, 1950.

[2] (a) P. S. Bailey and R. E. Lutz, THIS JOURNAL, **70**, 2412 (1948); (b) P. S. Bailey and G. Nowlin, *ibid.*, **71**, 732 (1949).

[3] F. F. Blicke in R. Adams, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 303. Incidentally, as pointed out by one of the referees of this paper, the stability of IV in the presence of excess morpholine or morpholine hydrochloride appears to be evidence against the proposed mechanism for Mannich condensations which involves hydroxymethylation of the active hydrogen compound followed by reaction with the amine.

[4] E. R. Alexander and E. J. Underhill, THIS JOURNAL, **71**, 4014 (1949).

[5] S. V. Lieberman and E. C. Wagner, *J. Org. Chem.*, **14**, 1001 (1949).

found impossible to prepare pure hydrochlorides or picrates of either the dimorpholinylmethane or the morpholinylmethanol. Instead, upon recrystallization of the crude salts, the corresponding morpholine salts were obtained. Likewise, upon treatment of morpholinylmethanol with phenyl isocyanate, the product was 4-morpholinylcarboxanilide.

The products of the normal reaction were obtained when the crude morpholinylmethanol hydrochloride was substituted for morpholine hydrochloride and paraformaldehyde in the Mannich reaction mixture, but no valid conclusions can be drawn from this due to the instability of the salt.

Experimental

Mannich Reactions with 1,2-Dibenzoylethane (I).—In these two-phase experiments it was found necessary to carefully control the amount of water present in order to obtain consistent results.[6] Therefore the amine salts were carefully dried under reduced pressure and ground-joint flasks with efficient mercury sealed stirrers were used. In the 0.1 and 0.2 mole experiments, 500-ml. and 100-ml. flasks were used, respectively. The reagents and products are listed in Table I. As far as possible, the same rate of vigorous stirring was used in all experiments. During the reflux period the reaction mixtures separated into two layers. At the end of the reaction period the reaction mixture was shaken with 5000 ml. of water and 2000 ml. of ether per mole of dibenzoylethane used in the reactions. Hydrochloric acid was then added until the mixture tested acid to congo red paper, and the resulting mixture was again shaken thoroughly. Any crystals which had not dissolved in either the ether or the aqueous layer were filtered off. Such material was generally the hydrochloride of III, except in those cases where I was used and did not react completely, in which case some of it was recovered at this point. The morpholinylmethylfuran hydrochloride (III) was recrystallized from water and melted at 220–222°. After III was removed, the ether and water layers of the filtrate were separated. From the ether layer unreacted dibenzoylethane was sometimes recovered. The aqueous layer was made alkaline with sodium carbonate. If material (usually semicrystalline, contaminated with a tar) separated at this point, 5–10 ml. of ether was added to dissolve the tar and the crystalline material was filtered off. This material was IV. Upon recrystallization from ethanol it melted at 166–170°. Evaporation of the 5–10 ml. ether extract usually gave an oily residue which oftentimes could be converted to the hydrochloride of III upon treatment of a dry ether solution of it with dry ethereal hydrogen chloride.

(4-Morpholinyl)-methanol was made by a variation of Henry's method[7] which Alexander and Underhill[4] used to prepare dimethylaminomethanol. The yield of crude product was 79% (n^{20}D 1.4678). Attempts to form derivatives with methyl iodide and picric acid, respectively, gave a viscous tar and a yellow crystalline material which resisted purification. Formation of the hydrochloride in dry ether solution gave crystals melting at 80–95°. Several recrystallizations from either isopropyl alcohol or ethanol gave pure morpholine hydrochloride in good yield (m.p. 175–176°, identification by mixture melting point method). Reaction with phenyl isocyanate gave colorless crystals which melted at 162–163° after recrystallization from carbon tetrachloride–chloroform solution. The compound was shown to be 4-morpholinylcarboxanilide by a mixture melting point with an authentic sample.[8]

Anal. Calcd. for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84. Found: C, 63.92; H, 7.01.

TABLE I

Principal reactant^{a}	Concd. HCl^{a}	Products^{b} III, %	IV, %
I^{c}	10	65	3
I	30	32	24
I^{c}	35	3	59
I^{c}	100	0	53
I^{d}	20	10	33
I^{e}	0	0	0
II^{f}	10	75	10
II^{f}	50	0	62
III^{g}	10	47	26
III^{h}	10	70	0
III^{g}	50	0	70
I^{i}	10	28	0^{i}
V^{j}	10	0	0
I^{k}	20	61	0
I^{l}	10	0	0
I^{m}	10	0	0
I^{n}	50	22	47

[a] Except where otherwise specified, 0.02 mole of the principal reactant, 0.04 mole of dry morpholine hydrochloride and 0.1 mole of paraformaldehyde in 100 ml. of dry benzene were used and the reflux period was 48 hours. The concentrated hydrochloric acid used is listed in column two in milliliters per mole of the principal reactant. [b] All products were identified by mixture melting points with authentic samples. [c] Similar results were obtained with runs five times the size. [d] One milliliter (50 ml./mole of I) of water was present. [e] Experiment was worked up after four hours reflux due to decomposition. Recovery of I was 68%. [f] Hydrochloride of II was used (prepared and dried in reaction flask). Water was added to extent of 0.02 mole and the morpholine hydrochloride and paraformaldehyde were decreased by 0.02 mole from that in footnote *a* in order to obtain the conditions which would have arisen by the condensation of I, morpholine hydrochloride and paraformaldehyde to give 0.02 mole of II. [g] Hydrochloride of III was used. Water was added to extent of 0.04 mole and the morpholine hydrochloride and paraformaldehyde were decreased by 0.02 mole from that in footnote *a* in order to obtain the conditions which would have arisen by the condensation of I, morpholine hydrochloride and paraformaldehyde to give 0.02 mole of III. [h] Reactants were same as in footnote *g* except only 0.43 ml. of water was added since III is produced from I only to the extent of 60% in normal reactions. [i] This was an early 0.01 mole reaction carried out without any precautions to control moisture content. At point where IV is usually obtained only an oil was found which crystallized from ethanol to give a 16% yield of 2,3-dibenzoyl-1,4-di-(4-morpholinyl)-butane (m.p. 139–142°, see reference 2b). [j] V is 2,5-diphenylfuran; 0.36 ml. of water was added to account for 0.02 mole water obtained in conversion of I to V. The only crystalline material obtained was an 88% recovery of V. [k] The crude, dry hydrochloride of morpholinylmethanol (0.02 mole) was used in place of morpholine hydrochloride and paraformaldehyde. Due to tar formation the reaction was stopped after 20 hours of reflux. No appreciable change in results was obtained in one experiment in which 0.08 mole paraformaldehyde was added and in another in which 0.02 mole of morpholine hydrochloride was added. [l] The crude, dry hydrochloride of dimorpholinylmethane (0.04 mole) was used in place of morpholine hydrochloride and paraformaldehyde; 0.02 mole of water was added to partially account for water formed in condensation of morpholine and formaldehyde to give dimorpholinylmethane. The reactions were stopped after four hours reflux due to tar formation; the recovery of I was 82%. [m] In one case triethylamine hydrochloride and in another case pyridine hydrochloride was substituted for morpholine hydrochloride. Recoveries of I were 97 and 99%, respectively. [n] In this experiment excess morpholine was added just before the regular work-up procedure and the reaction mixture was stirred for several hours. The fact that no 3,4-di-(4-morpholinylmethyl)-2,5-diphenylfuran was obtained means that no 3-(chloromethyl)-4-(4-morpholinylmethyl)-2,5-diphenylfuran was present (see footnote 2b).

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[6] In earlier experiments the products seemed to vary with the scale size of the experiments. Considerable experimentation indicated that these inconsistent results were probably caused by the accidental introduction of varying amounts of water into the reaction mixture with the morpholine hydrochloride which is very hygroscopic, and also by escape of the reaction medium around the rubber sealed stirrers used in the earlier experiments.

[7] L. Henry, *Bull. acad. roy. Belg.*, [3] **28**, 355 (1894).

[8] R. A. Henry and W. M. Dehn, THIS JOURNAL, **71**, 2297 (1949).

Di-(4-morpholinyl)-methane was prepared from crude, dry morpholinylmethanol by a modification of the method of Zief and Mason.[9] One hundred and fifty grams of morpholinylmethanol was fractionally distilled at 1-2 mm. and the 92-96° fraction was redistilled, fractionally. Thus was obtained 89 g. of material boiling at 89-92° at 1 mm. pressure. After further purification by distillation the refractive index became $n^{20}\text{D}$ 1.4818.

Anal. Calcd. for $C_{19}H_{18}N_2O_2$: C, 58.03; H, 9.74; N, 15.04. Found: C, 58.29; H, 9.45; N, 14.86.

Attempts to form a picrate gave yellow crystals which upon trituration with ether melted at 148-149° and were shown to be morpholine picrate by a mixture melting point with a known sample (m.p. 146-148°). Formation of the hydrochloride in dry ether solution gave material melting at 86-114° which upon recrystallization from isopropyl alcohol was shown to be morpholine hydrochloride (m.p. 175-176°; identification by the mixture melting point method).

Acknowledgment.—The authors wish to express their appreciation to the Research Corporation, New York, N. Y., for a grant-in-aid which helped make this work possible. We also want to acknowledge the aid of Mr. Elias E. Kawas on some of the experiments.

AUSTIN, TEXAS RECEIVED NOVEMBER 4, 1950

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[9] M. Zief and J. P. Mason, *J. Org. Chem.*, **8**, 1 (1943).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

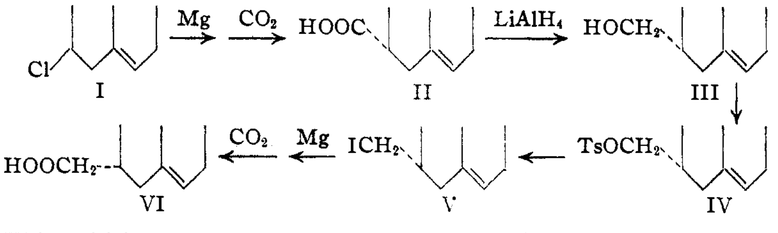
Derived Steroids. IV. 3-α-Cholesterylacetic Acid[1]

BY ROBERT H. BAKER AND QUENTIN R. PETERSEN

Nucleophilic replacement of groups at the 3-position of cholesteryl derivatives invariably leads to either 3-β or 6-derivatives. By contrast, electrophilic replacements of the 3-magnesiohalide group are shown to lead to α-products. The acid obtained by carbonation and also by degradation of other Grignard products has been converted with stereospecific reactions to cholesterylacetic acid which is different from the known β-acid.

Discussion

Previous papers from this Laboratory[2] have shown that the cholesteryl Grignard reagents react in a stereospecific manner with such a variety of reagents as acetaldehyde, acetyl chloride and carbon dioxide. These products were converted to common derivatives, *e.g.*, the carboxylic acid or methyl ketone which appear to be of a single configuration with respect to the 3-carbon atom. We have now extended the series of derivatives from cholesterylcarboxylic acid through reactions which do not involve the configuration at 3- to cholesterylacetic acid as illustrated.



This acid is compared with three cholesterylacetic acids prepared by Kaiser[3] in Table I. Specifically it is an epimer of the 213° acid which, having been made by reaction of cholesteryl tosylate with sodiomalonic ester and subsequent hydrolysis and decarboxylation, must be of the β-configuration.[4]

TABLE I

CHOLESTERYLACETIC ACIDS

Position of Group	and Δ	Acid M.p., °C.	Acid $[\alpha]^{25}\text{D}$	Methyl ester M.p., °C.
3-α	5,6	175	−31	73
3-β	5,6	213		108
6-	-*i*-	112	+32	
6-	4,5	174	+46	

Marker[5] treated cholesterylmagnesium chloride with both oxygen and carbon dioxide. The proportion of α- and β-cholesterol so formed was not determined accurately but certainly some α-product was formed. Although Marker[5] seemed to feel that the α- and β-acids were equal in amount, it now appears that it is almost wholly α, a few crystallizations being all that is necessary to bring it to purity.[2]

This preference of reagents to attack the cholesteryl Grignard reagent preferentially at the α-side of the molecule may be attributed to the fact that this is sterically the more open of the two possible paths. It seems possible that participation by the 5,6-double bond is responsible for the stereospecificity in this reaction as it is in the case of the production of β-derivatives from the mesomeric cation.[6] Actually it is clearly demonstrated by the work of Squire[7] that opposite configurations are obtained by carbonating cholestanyl or cholesteryl Grignard reagents.

There appears to be no possibility of configurational change at C-3 during the conversion of acid II to its homolog VI. The reduction with lithium aluminum hydride has been found to be quite safe in this respect[8] and it has been shown that a halomethyl group attached to an asymmetric carbon

[1] This work was supported by a grant from the Abbott Fund of Northwestern University.

[2] R. H. Baker and E. N. Squire, THIS JOURNAL, (a) **70**, 1487 (1948); (b) **70**, 4134 (1948); (c) **71**, 1383 (1949).

[3] B. Kaiser and J. J. Svarz, *ibid.*, **67**, 1309 (1945); **69**, 847 (1947); **71**, 517 (1949). We are indebted to Dr. Kaiser for a sample of his acid.

[4] C. W. Shoppee, *J. Chem. Soc.*, 1138, 1147 (1946); R. M. Dodson and B. Riegel, *J. Org. Chem.*, **13**, 424 (1948); S. Winstein and R. Adams, THIS JOURNAL, **70**, 838 (1948).

[5] R. E. Marker, T. S. Oakwood and H. M. Crooks, THIS JOURNAL, **58**, 481 (1936); R. E. Marker, O. Kamm, T. S. Oakwood and J. F. Laucius, *ibid.*, **58**, 1948 (1936).

[6] For one explanation of this reaction see J. D. Roberts, W. Bennett and R. Armstrong, *ibid.*, **72**, 3329 (1950).

[7] E. N. Squire, *ibid.*, **73**, in press (1951).

[8] R. H. Baker and Sidney H. Jenkins, Jr., *ibid.*, **71**, 3969 (1949); D. S. Noyce and D. B. Denney, *ibid.*, **72**, 5743 (1950).