TABLE I

CONVERSION OF "METHYL"-LABELED LANOSTEROL AND "METHYL"-LABELED X_1 TO CHOLESTEROL AND CO_2 IN LIVER HOMOGENATES

Substrate	$BaCO_3$, mg.	CO_2, total c.p.m.	Cholesterol, total c.p.m.	Cholesterol CO_2
Lanosterol (1500 c.p.m.)	10.85	203	929	4.6
	10.82	193	928	4.8
	10.89	184	590	3.2
	10.76	205	825	4.1
	11.83	220	848	3.9
			Av.	4.2
X_1 (1500 c.p.m.)	10.58	147	918	6.2
	10.44	133	932	7.0
	10.55	145	960	6.6
	10.17	116	921	7.9
	11.95	130	866	6.7
			Av.	6.9

In another series of 4 experiments with X_1 the total c.p.m. in cholesterol averaged 340, and in CO_2 50 c.p.m., giving a ratio of 6.8 for the two radioactivities.

carrier. The solvent was removed and the mixture oxidized with chromic acid in acetic acid at 45–50° for 1.5 hr., conditions which afford the 7-keto and the 7,11-diketo derivative of dihydrolanosteryl acetate as the principal products.[13] The neutral reaction products were chromatographed on 5 g. of alumina (Merck) and the various fractions weighed and assayed for C^{14} (Fig. 2). The combined fractions 13–24 weighing 46 mg. and having a total of 3500 c.p.m. or 6.7% of the starting radioactivity may be assumed to contain 3β-acetoxy-7-keto-Δ^8-lanostene as well as radioactive α,β-unsaturated monoketones. The peak fraction 15 had λ_{max} 255 mμ, log ϵ_{255} 3.84; reported[13] λ_{max} 255 mμ, log ϵ_{254} 4.08. The second weight and radioactivity peak (B) comprising fractions 27 to 31, contained 16.3 mg. of solid material and 1810 c.p.m. or 3.3% of the original C^{14}. On the basis of ultraviolet absorption (λ_{max} 268 mμ, log ϵ_{268} 3.87, reported for ene-diketones,[13] λ_{max} 275 mμ, log ϵ_{275} 3.94) peak B is assumed to contain 3β-acetoxy-7,11-diketo-Δ^8-lanostene and ene-diketones derived from X_1. The more polar eluates (peak C, fr. 36–42) accounted for 28% of the initial radioactivity, but contained only 3.4 mg. of unidentified solids. The introduction of a hydroxyl group at C_{14}, in addition to the 2 keto groups elsewhere in the molecule would explain the high polarity of fraction C.

4,4-Dimethylcholesterol (Expt. carried out by R. B. Clayton).—This was synthesized according to Patchett[17] starting from biosynthetic C^{14}-cholesterol. The product, m.p. 149–151°, had a specific activity of 1250 c.p.m./mg. To test the conversion to cholesterol 2 mg. was suspended in a solution containing 0.5% bovine serum albumin and incubated with 40 ml. of rat liver homogenate[22] for 4.5 hr. at 37°. The non-saponifiable fraction was isolated in the customary manner and chromatographed on alumina. The cholesterol fraction was devoid of radioactivity.

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CAMBRIDGE, MASSACHUSETTS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CARNEGIE INSTITUTE OF TECHNOLOGY]

A New Synthesis of Flavone Involving Cyclization *via* Displacement of Aromatic Chlorine

BY PHILIP L. SOUTHWICK AND JACK R. KIRCHNER

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The compound β-morpholino-2-chlorochalcone, which has been made by addition of morpholine to *o*-chlorophenylbenzoylacetylene, cyclizes when heated to yield 4-morpholinoflavylium chloride. The latter substance is readily hydrolyzed to flavone.

We wish to describe the results of the initial investigation of a new cyclization reaction which can be used for the preparation of flavone (VI) and probably will prove applicable to the synthesis of some types of substituted flavones. The cyclization in question occurs when β-morpholino-2-chlorochalcone (II) is heated to the proper temperature in a solvent. The initial reaction product is not flavone itself but a related salt, 4-morpholinoflavylium chloride (V), which yields flavone upon hydrolysis. The salt is representative of a class of substances which are most conveniently referred to as 4-aminoflavylium salts, as represented in this case by the contributing form V, although other contributing forms such as Va are undoubtedly very important. Apparently such compounds have hitherto been little known[1] and never previously obtained directly from a cyclization procedure.[2]

We have found that β-morpholino-2-chlorochalcone (II) cyclizes slowly when heated in di-*n*-butyl ether to the temperatures slightly above 140° reached in refluxing solutions. In a heating period of 3.5 hr. under these conditions the salt V was obtained in 43% yield and 48% of the starting material was recovered unchanged. Compound V crystallizes from the refluxing solution in rather pure form as the reaction proceeds.

The assignment of the indicated structure to this substance is based upon its composition, its salt-like properties and its ready hydrolysis in dilute acid to flavone (VI). That the substance is a salt is indicated by its insolubility in non-polar solvents, its high melting point and the apparently ionic nature of its chlorine, which is immediately

(1) The only compounds of this type which we have found to be described in the literature are the flavone benzylimine methiodide of W. Baker, G. G. Clarke and J. B. Harborne, *J. Chem. Soc.*, 998 (1954), and the less closely similar 4-amino-5,6,7,4′-tetramethoxyflavylium picrate and chioride of R. Robinson and G. Schwarzenbach, *ibid.*, 822 (1930).

(2) Methods of preparation and reactions of flavones and flavylium salts have been reviewed recently by Wawzonek; see R. C. Elderfield, "Heterocyclic Compounds," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1951, pp. 229–342.

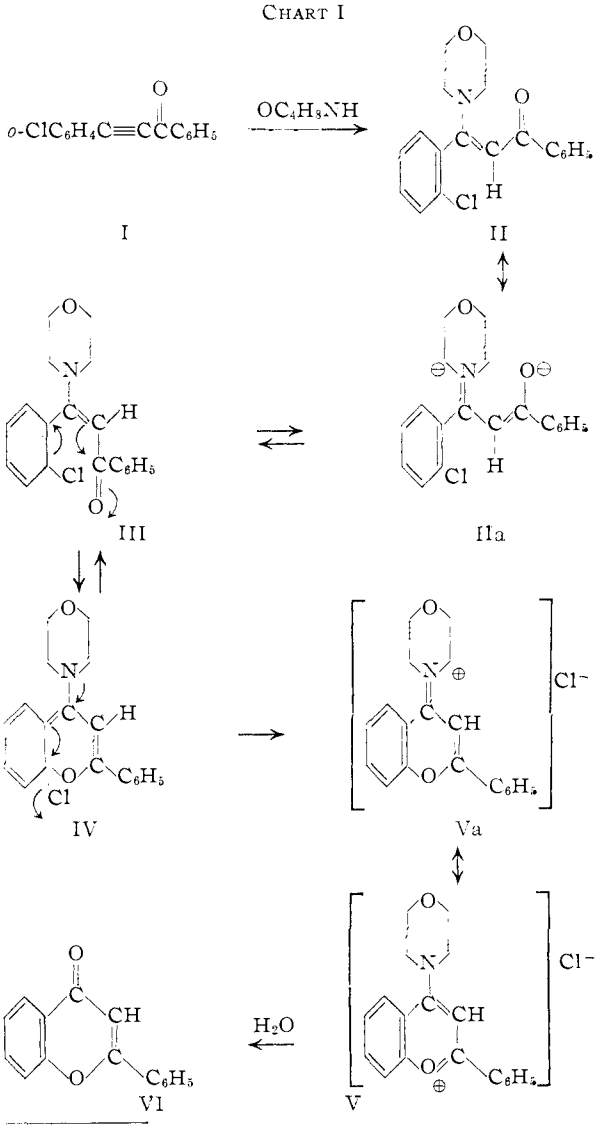
precipitated by aqueous silver nitrate solutions. The flavone produced by hydrolysis was shown to be identical with an authentic sample by the comparison of infrared spectra and by use of the mixed melting point test. The structure represented by formula V appears to be the only plausible one for a salt arising from the simple heating of compound II and convertible in the indicated manner to flavone.

β-Morpholino-2-chlorochalcone (II) readily is obtained in yields above 90% by means of the addition of morpholine to *o*-chlorophenylbenzoylacetylene (I), the expected reaction of a secondary amine with an α,β-acetylenic ketone.[3] Indeed, flavone may be prepared directly from I in a yield of 74% merely by heating the compound in an excess of refluxing morpholine and hydrolyzing the resulting crude reaction mixture.

It is not entirely clear why this unusual cyclization, which requires displacement of an aromatic chlorine atom by the oxygen of a carbonyl group, should be so facile as to proceed under conditions mild enough to allow a smooth reaction and a good yield. The intramolecular nature of the process is, of course, usually a favorable factor in reactions which close a six-membered ring. In this case, however, it is by no means certain that the initial configuration of the starting β-amino-α,β-unsaturated ketone is favorable for cyclization. In Chart I the compound has been shown as a *trans*-chalcone derivative (II), whereas a *cis* relationship between the benzoyl and *o*-chlorophenyl groups as in the *cis* form III would be needed to bring these groups into proximity for the observed cyclization. The literature appears to provide no adequate basis for predicting whether the addition of an amine to an α,β-acetylenic ketone should be expected to occur in a *cis* or a *trans* manner[4] and hence whether the configuration should correspond to II or III, but there is an indication that the interconversion of geometrical isomers of β-amino-α,β-unsaturated ketones occurs readily, possibly due to the importance of contributing forms such as IIa.[5] Thus, even if the necessary first step in the cyclization process is the change in configuration, II → III, this requirement may not seriously impede the reaction.

Once the molecule has assumed a configuration favorable for cyclization, formation of the hypothetical intermediate IV[6] in the displacement process would be expected to be facilitated to the extent that electron withdrawal from the benzene ring might occur as indicated in the formula III. It must be assumed, however, that normal electron withdrawal from a benzene ring by an attached carbonyl group would be attenuated in this instance in operating through the intervening vinyl group[7] and would be further reduced by the competition of the morpholino nitrogen in donating electrons toward the carbonyl group as in contributing form IIa. It is noteworthy that there is no indication from the results of experiments using morpholine as the reaction solvent that the chlorine is significantly activated for intermolecular displacement by morpholine. It may well be that a highly significant factor tending to promote the cyclization reaction is the capacity of the morpholino nitrogen in IV to contribute electrons toward the release of the chloride ion and the consequent formation of a stable final product by the transformation IV → V.

CHART I



(3) N. H. Cromwell, *Chem. Revs.*, **38**, 83 (1946).

(4) The nucleophilic addition of sulfhydryl compounds to substituted acetylenes recently has been shown to occur in the *trans* manner; see W. E. Truce, *et al.*, THIS JOURNAL, **78**, 2743, 2748, 2756 (1956). On the other hand, there is some evidence that the initial addition of amines to α,β-acetylenic esters may be *cis* and the similar addition to α,β-acetylenic ketones often non-stereospecific; see E. R. H. Jones and M. C. Whiting, *J. Chem. Soc.*, 1423 (1949), and ref. 5a.

(5) (a) K. Bowden, E. A. Baude, E. R. H. Jones and B. C. L. Weedon, *ibid.*, 45 (1946); (b) K. Bowden, E. A. Baude and E. R. H. Jones, *ibid.*, 945 (1946).

(6) A formula such as IV might be used to describe either a transition state for the displacement or a metastable intermediate. Which designation should be applied to IV is uncertain. For a discussion of the mechanism and other aspects of nucleophilic displacements of aromatic ring substituents see (a) J. F. Bunnett and R. E. Zahler, *Chem. Revs.*, **49**, 273 (1951), (b) J. F. Bunnett and R. J. Morath, THIS JOURNAL, **77**, 5051 (1955), and (c) J. F. Bunnett and T. K. Brotherton, *ibid.*, **78**, 155 (1956).

(7) This statement is based on analogy; the bromine of *o*-bromo-β-nitrostyrene is displaced less rapidly by piperidine than is the bromine of *o*-bromonitrobenzene; see N. Campbell, W. Anderson and J. Gilmore, *J. Chem. Soc.*, 446 (1940).

Experimental[8]

β-Morpholino-2-chlorochalcone (II).—A solution of 0.7 g. of morpholine in 1 ml. of ether was added to a solution of 1.9 g. of *o*-chlorophenylbenzoylacetylene[9] in 10 ml. of ether. The mixture was allowed to stand at room temperature while the ether evaporated. The residual solid was recrystallized from petroleum ether (b.p. 65–110°) to yield 2.4 g. (92%) of very pale yellow cubes, m.p. 113–114°.

Anal. Calcd. for $C_{19}H_{18}ClNO_2$: C, 69.61; H, 5.53. Found: C, 69.29; H, 5.37.

The ultraviolet spectrum, which was determined in ethanol solution with a Cary recording spectrophotometer, showed two maxima, λ 246 mμ, ε 11,100 and λ 340 mμ, ε 21,200.

The first time this compound was obtained it crystallized from petroleum ether (b.p. 65–110°) in white plates, m.p. 98–99°.

Anal. Calcd. for $C_{19}H_{18}ClNO_2$: C, 69.61; H, 5.53; N, 4.27. Found: C, 69.58; H, 5.64; N, 4.02.

Admixture with the latter lower-melting crystalline form did not depress the melting point of the form melting at 113–114°, and the ultraviolet spectra of the two materials were identical.

4-Morpholinoflavylium Chloride (V).—A solution of 2.3 g. of β-morpholino-2-chlorochalcone in approximately 40 ml. of *n*-butyl ether was heated under reflux for 3.5 hr. During this period a crystalline solid was gradually precipitated. After the precipitate had been removed by filtration, washed with ether and dried, there was obtained 1.0 g. (43%) of light-tan needles, m.p. 235–237° dec. Efforts to find a solvent for recrystallization of this product were unsuccessful. The compound gave an immediate precipitate with aqueous silver nitrate solution.

Anal. Calcd. for $C_{19}H_{13}ClNO_2$: C, 69.61; H, 5.53; N, 4.27. Found: C, 69.75; H, 5.88; N, 4.31.

When the filtrate from the reaction mixture and the ether used to wash the precipitate were concentrated, 1.1 g. (a 48% recovery) of crude starting material was obtained, m.p. 109–112°. Recrystallization of this material from petroleum ether (b.p. 65–110°) gave the usual light-yellow cubes, m.p. 113–114°.

Preparation of Flavone (VI) Directly from *o*-Chlorophenylbenzoylacetylene (I).—A solution of 5 g. of compound I in 30 ml. of morpholine was heated at the reflux temperature for 10 hr. Morpholine hydrochloride separated when the mixture was cooled. (The morpholine was not dried prior to use and no attempt was made to exclude water during the reaction period.) The cooled mixture was diluted with an equal volume of ether and filtered to remove the morpholine hydrochloride, which melted at 174–175° dec. after it had been washed with ether, and did not depress the melting point of an authentic sample. The filtrate was evaporated to leave a light-red oil, which was triturated first with water, then with a small amount of 6 *N* hydrochloric acid. The resulting sticky brown solid was taken up in ether, but evaporation of the ether again left an oil. The oil was triturated with petroleum ether (b.p. 65–110°), and the resulting brown solid was recrystallized from the same solvent to give two crops of crystals (total weight 2.5 g., a 74% yield) of crude flavone, m.p. *ca.* 94°. After purification by vacuum sublimation and recrystallization from low-boiling petroleum ether (b.p. 30–60°), the crystals were nearly colorless and melted at 96–97°.

Anal. Calcd. for $C_{15}H_{10}O_2$: C, 81.06; H, 4.41. Found: C, 81.23; H, 4.43.

The compound did not depress the m.p. of a sample of flavone, m.p. 96–97°, prepared by the method of Mozingo and Adkins,[10] and the infrared spectra of the two samples were identical.

Conversion of 4-Morpholinoflavylium Chloride (V) into Flavone (VI).—A 1.0-g. sample of compound V was added to 20 ml. of water which had been acidified by addition of a small amount of 6 *N* hydrochloric acid. The mixture was extracted three times with 10-ml. portions of ether. After removal of the solvent from the ether extracts and recrystallization of the residual solid from petroleum ether, 0.4 g. (59%) of flavone was obtained in the form of white needles, m.p. 96–97°. The melting point was not depressed when the product was mixed with an authentic sample of flavone.[10]

(8) Microanalyses are by Dr. G. Weiler and Dr. F. B. Strauss, Oxford, England.

(9) C. L. Bickel, THIS JOURNAL, **69**, 2134 (1947).

(10) R. Mozingo and H. Adkins, *ibid.*, **60**, 668 (1938).

PITTSBURGH 13, PENNA.

[CONTRIBUTION FROM THE DEPARTMENT OF AGRICULTURAL BIOCHEMISTRY, UNIVERSITY OF MINNESOTA]

Reduction of the Products of Periodate Oxidation of Carbohydrates. IV. Hydrogenation with Palladium–Charcoal of the Dialdehydes from Methyl Glycosides[1,2]

BY J. E. CADOTTE, G. G. S. DUTTON, IRWIN J. GOLDSTEIN, BERTHA A. LEWIS, F. SMITH AND J. W. VAN CLEVE

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Hydrogenation in the presence of a palladium–charcoal catalyst of the dialdehyde (II), D′-methoxy-D-hydroxymethyldiglycolic aldehyde, obtained from methyl α-D-glucopyranoside (I) by periodate oxidation, effects preferential reduction of one aldehyde group to give the monoaldehyde V, the properties of which indicate that it has the dioxane structure VII. The structure of V was established by bromine oxidation to the monocarboxylic acid IV which upon hydrolysis gave rise to glycerol and glyoxylic acid. The same series of reactions has been carried out with methyl β-D-glucopyranoside. The dialdehyde (D′-methoxydiglycolic aldehyde (IX)) from methyl β-L-arabopyranoside, the dialdehyde (L′-methoxy-L-methyldiglycolic aldehyde (X)) from methyl α-L-rhamnopyranoside and the dialdehyde (D′-methoxy-D-methoxymethyldiglycolic aldehyde (XI)) obtained from methyl 6-*O*-methyl-α-D-galactopyranoside, did not give rise to monoaldehydes upon hydrogenation in the presence of a palladium–charcoal catalyst. The structural significance of these findings is discussed.

When any one of the methyl α-D-hexopyranosides such as methyl α-D-glucopyranoside (I) is oxidized with periodate, D′-methoxy-D-hydroxymethyldiglycolic aldehyde (II) is formed.[3,4] Hydrogenation of the dialdehyde II in the presence of a Raney nickel catalyst under pressure at 120° has been shown in Part I of this series[2] and elsewhere[5] to give the corresponding alcohol III.

It is shown herein that hydrogenation of II under pressure in the presence of a palladium–charcoal catalyst at room temperature brings about a partial reduction and there is formed a monoaldehyde V. The structure of V rests upon the

(1) Paper No. 3581, Scientific Journal Series, Minnesota Agricultural Experiment Station, University of Minnesota, St. Paul, Minnesota.

(2) Part I, THIS JOURNAL, **77**, 3091 (1955).

(3) H. Hérissey, P. Fleury and M. Joly, *J. pharm. chim.*, **20**, 149 (1934).

(4) E. L. Jackson and C. S. Hudson, THIS JOURNAL, **58**, 378 (1936); **59**, 994 (1937).

(5) M. Abdel-Akher, J. E. Cadotte, Bertha A. Lewis, R. Montgomery, F. Smith and J. W. Van Cleve, *Nature*, **171**, 474 (1953).