TABLE IV

PHYSICAL CONSTANTS AND CHARACTERISTIC INFRARED ABSORPTION BANDS OF SUBSTITUTED DEUTERIOBENZENES (C_6H_4DX)

X	B.p. °C.	B.p. Mm.	$n^{°C}_D$	Absorption peaks,[a] cm.$^{-1}$
H	79.0–79.5	Atm.	$1.5014^{25.0}$	698 (s), 780 (s), 912 (s), 980 (w), 1070 (s), 1115 (s), 1150 (w), 1344 (w), 1444 (s), 1696 (m), 1763 (m), 1883 (w), 2270 (m), 2880 (m)
2-CH_3	108.5–109.0	Atm.	$1.4931^{24.6}$	720 (m), 728 (m), 775 (s), 862 (m), 941 (m), 1040 (s), 1122 (m), 1286 (s), 1473 (ms), 1705 (s), 2255 (m)
3-CH_3	108.5	Atm.	$1.4924^{23.8}$	650 (s), 914 (w), 1045 (m), 1078 (m), 1163 (w), 1475 (s), 2275 (m)
4-CH_3	108.0	Atm.	$1.4941^{22.8}$	708 (s), 832 (s), 860 (w), 945 (w), 1284 (m), 1666 (w), 1704 (s), 1900 (m), 2285 (m)
2-$C(CH_3)_3$	57.5	13	$1.4900^{24.0}$	637 (m), 770 (m), 872 (m), 945 (w), 1040 (m), 1098 (m), 1127 (w), 1160 (w), 1278 (w)
4-$C(CH_3)_3$	58.0	13	$1.4868^{23.4}$	850 (s), 865 (w), 1040 (w)
2-OH	66–67	10	$1.5620^{25.0}$	827 (m), 913 (m), 1037 (s), 1108 (s), 1286 (s), 1450 (m)
3-OH	66–68	10	$1.5434^{32.0}$	1031 (m), 1092 (w), 1299 (w), 1437 (m)
4-OH	65–67	11	$1.5414^{25.0}$	716 (m), 845 (s), 978 (m), 1095 (s), 1290 (m), 1322 (m), 1436 (s)

[a] Principal infrared absorption peaks which are not also present in the corresponding undeuterated C_6H_5X.

experiments were increased to 3.04 g. and 8.5 g., respectively. In the deuteriobenzene experiments, quantities of all materials were increased by one third to permit recovery of sufficient material for study.

The exchange reactions in liquid ammonia at 0° were carried out in 6-oz. Coca-Cola bottles. The dry, stoppered bottle, charged with 1.8 g. of potassium and a small crystal of ferric nitrate nonahydrate, was immersed in an acetone bath which was cooled gradually to −70° by the addition of Dry Ice. Ammonia was condensed in the bottle until more than 75 ml. had been collected. The bottle was raised out of the bath and the ammonia allowed to boil off until 75 ml. remained. The bottle was again immersed in the bath and allowed to stand for 15 min. A 3-in. Pyrex test tube with a thin glass handle at the top and a 5-cm. glass rod at the bottom was charged with 3.00 g. of the deuterated compound and lowered into the reaction vessel. The bottle was removed from the bath, covered with a thin sheet of Teflon and capped. It was transferred to an ice–water bath and allowed to stand for 30 min. after which the bottle was shaken to dissolve the contents of the test tube in the liquid ammonia solution, replaced in the ice–water bath, and allowed to stand for the timed interval. The vessel was then cooled in a Dry Ice–acetone bath, uncapped, and the amide ion neutralized by the addition of 4.8 g. of ammonium chloride. The reaction mixture was treated according to the previously described procedure.[1] In the deuteriobenzene experiments, the quantities of all materials were increased by one third. Sodium-dried pentane (4 g.) was also added to the deuteriobenzene to prevent the deuteriobenzene from solidifying in the test tube.

Determination of Extent of Deuterium–Protium Exchange.—The infrared spectra of the deuteriobenzene derivatives, the nondeuterated compounds and the exchange reaction products were determined with a Beckman Model IR-4 infrared spectrophotometer. Deuteriobenzene, the deuteriotoluenes, and the deuterio-*tert*-butylbenzenes were measured neat, the deuteriophenols in carbon tetrachloride. The major absorption peaks appearing in the spectra of the deuterated compounds which were not found in the spectra of the nondeuterated substances are given in Table IV.

Measurements and determinations of the extent of deuterium–protium exchange were made according to the procedure previously described.[1]

The Condensation Products of Aldehydes and Aldol-sensitive β-Dicarbonyl Compounds[1a]

B. D. WILSON

Research Laboratories, Eastman Kodak Company, Rochester, New York

Received June 19, 1962

The noncatalyzed condensation of formalin and ethyl acetoacetate to diethyl α,α'-diacetylglutarate, discovered by Rabe, has been extended to related β-dicarbonyl compounds. With formalin, the yields are good, whereas with acetaldehyde, the yields are greatly lowered, and in the case of 2,4-pentanedione, only a 1:1 condensation product forms because of steric effects. Still higher aldehydes fail to react in the absence of a catalyst. Authentic samples of two of the three possible tautomers of 3,5-diacetyl-2,6-heptanedione have been prepared and identified by chemical and physical means.

In 1904, Rabe[1b] showed that formalin and ethyl acetoacetate reacted readily in the absence of a catalyst to give a 1:2 condensation product and that this product was not the same as that obtained by Knoevenagel[2] in a base-catalyzed reaction. Furthermore, amine bases could convert Rabe's product into Knoevenagel's. From the results of work in these laboratories (below) and of Finar's,[3] it is now known that Rabe's product is diethyl α,α'-diacetylglutarate ("methylenebisacetoacetate") (I) and that Knoevenagel's product is not I as he had claimed, but rather, it is the intramolecular aldol condensation product of I, 4,6-dicarbethoxy-3-hydroxy-3-methylcyclohexanone (II), as Rabe[4] had suggested. Finar's findings are now confirmed and further substantiated with some additional chemical data and n.m.r. analyses.

First, it should be pointed out that Finar's statement concerning the noncatalyzed condensation of ethyl

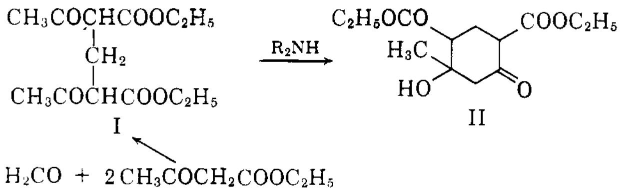
---

[1] (a) Communication no. 2275 from the Kodak Research Laboratories; (b) P. Rabe, *Ann.*, **332**, 1 (1904).

[2] E. Knoevenagel, *ibid.*, **281**, 25 (1894).

[3] I. L. Finar, *J. Chem. Soc.*, 674 (1961).

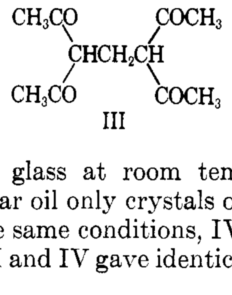
[4] P. Rabe and F. Elze, *Ann.*, **323**, 83 (1902).



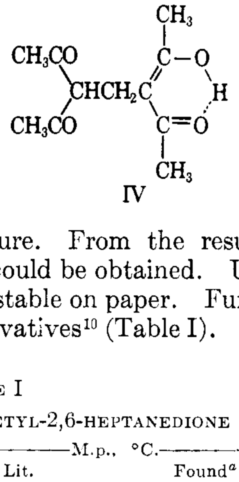
acetoacetate and formalin, as reported by Rabe,[1b] appears to be in error. The condensation does not give both diethyl α,α'-diacetylglutarate (I) and 4,6-dicarbethoxy-3-hydroxy-3-methylcyclohexanone (II). A careful translation of Rabe's articles[1b,5] indicates that I is the sole product, that it is completely stable, and that it is converted to II, its intramolecular aldol product, only on the introduction of amine bases.

Using the procedure of Scholtz[6] for the condensation of 2,4-pentanedione and formalin (with piperidine as a catalyst), Knoevenagel[7] isolated from the yellow, viscous, nondistillable reaction mixture colorless crystals melting at 87–88°, which he identified as "methylenebisacetylacetone." This same product has since been observed by others.[8,9] Rabe and Elze[4] at first did not obtain the crystalline material, but later, Rabe was able to do so.[1b]

The condensation of formalin and 2,4-pentanedione without a catalyst gave a clear, viscous oil which was readily distillable under vacuum without decomposition. From the crude oil could be obtained colorless crystals (III) melting at 41.5–42.5°; and from the distilled material, colorless crystals (IV) melting at 55–56°. That III and IV were tautomeric was indicated by the facile conversion of IV to III by standing on glass at room temperature. From the resulting clear oil only crystals of III could be obtained. Under the same conditions, IV was stable on paper. Further, III and IV gave identical derivatives[10] (Table I).



III



IV

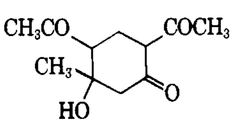
TABLE I

DERIVATIVES OF 3,5-DIACETYL-2,6-HEPTANEDIONE

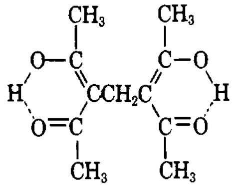
Derivative	M.p., °C. Lit.	M.p., °C. Found[a]
Bispyrazole	280[4]	285–287
Bisisoxazole	141–142[1]	142–142.5
Dihydropyridine	198[6]	207–211

[a] Prepared from either purified isomer (III and IV).

When III (or IV) was treated with piperidine, two compounds were obtained: 4,6-diacetyl-3-hydroxy-3-methylcyclohexanone (V), melting at 89–90°, which is Knoevenagel's "methylenebisacetylacetone" and a compound (A), $C_{17}H_{24}O_6$, melting at 176–177°, of yet unknown structure. This compound undoubtedly is identical to that of Rabe's[1b] of the same empirical formula and melting at 181°.



V



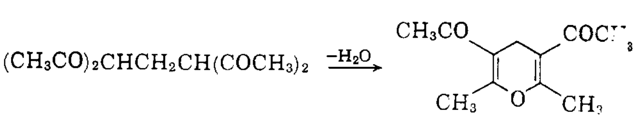
VI

The same major product (V) was also always obtained when the condensation was carried out under the Knoevenagel conditions. Further, it was found that a variety of amine bases could serve as the catalyst; diethylamine, triethylamine, piperidine, and Amberlite IR-45 ion exchange resin have been utilized. When the crude, yellowish oil was seeded, V was obtained in good yield. In some cases, particularly at shorter reaction times, small amounts of III were obtained after V had been removed. Small amounts of compound A also were obtained. The crude oil could be distilled *in vacuo* but extensive decomposition occurred.

Contrary to Finar's results for more highly substituted hydroxycyclohexanones, V was found, on treatment with hydrazine, to give only an amorphous solid, suggesting a mixture of products. This was substantiated further by the infrared spectrum. Strong bands for $>$NH, —NH_2, and —OH type bonds were detected and there was no absorption in the carbonyl region.

There are three possible keto–enol tautomers of 3,5-diacetyl-2,5-heptanedione: the all-keto form (III), the monoenol–chelate form (IV), and the dienol–chelate form (VI). By careful study of the carbonyl region of their infrared spectra, the two tautomers obtained were assigned formulae III and IV. Compound III exhibited a strong carbonyl doublet at 5.80 and 5.90 μ, with no absorption between 6 and 7 μ (where enol–chelate bands would be expected). Compound IV exhibited the same carbonyl doublet as III, but it was not as intense. It exhibited further a characteristically broad enol–chelate band centered at 6.29 μ.

Although VI should be and probably is in the reaction mixture, it has eluded all attempts at isolation. There appear to be various impurities in the oil which interfere, particularly after distillation. Mass spectrometric data indicate that an appreciable amount of the material was pyrolyzed during distillation to the pyran.



Further, the n.m.r. spectra of the tautomers substantiated the assignments made. These spectra and that of V are discussed in a separate paper.[11] The

---

(5) P. Rabe, *Ber.*, **76**, 979 (1943).

(6) M. Scholtz, *ibid.*, **30**, 2295 (1897).

(7) E. Knoevenagel, *ibid.*, **36**, 2136 (1903).

(8) R. C. Menzies and E. R. Wiltshire, *J. Chem. Soc.*, 2239 (1931).

(9) D. F. Martin and W. C. Fernelius, *J. Am. Chem. Soc.*, **81**, 1509 (1959).

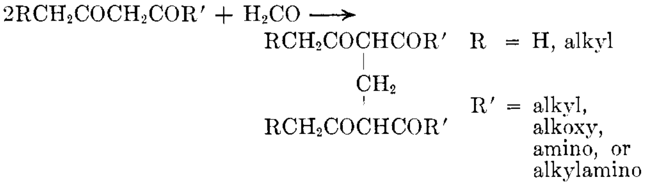
(10) Curiously enough, all of the derivatives of the "methylenebisacetylacetone" of the literature were prepared from the crude oil rather than from the crystalline solid (m.p. 88°). Knoevenagel[8] was unsuccessful in his attempt to prepare the dihydropyridine derivative from his crystalline material. He had no ready explanation, but merely stated that no solution existed with the data at hand.

(11) J. K. O'Loane, C. M. Combs, and R. L. Griffith, *J. Org. Chem.*, in press.

observed spectra agreed well with those calculated from model compounds.

The infrared spectrum of V was quite different from the spectra of III and IV, but was compatible with the assigned structure. It exhibited a single carbonyl band at 5.92 μ, a broad enol–chelate band centered at 6.24 μ, and a strong hydroxyl band at 2.94 μ, which was shifted to 2.85 μ in solution (CCl_4). These positions for the hydroxyl and carbonyl bands are reasonable for weak intramolecular bonding (chelation) of these two functional groups. The n.m.r. spectrum of V further supports the assigned structure; however, interpretation of this spectrum was much more difficult.[11]

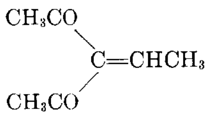
Since the Knoevenagel conditions are now known to yield cyclic products whenever an intramolecular aldol condensation can occur, it was thought that Rabe's conditions might be generally useful for the synthesis of acyclic products from aldehydes and β-dicarbonyl compounds. A large number of β-diketones, β-keto esters, and β-ketoamides of varied structure were found to condense with formalin in good yield under these conditions to form the variously substituted δ-diketones

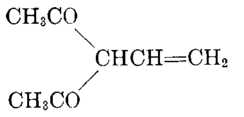


$$2RCH_2COCH_2COR' + H_2CO \longrightarrow \begin{array}{c} RCH_2COCHCOR' \\ | \\ CH_2 \\ | \\ RCH_2COCHCOR' \end{array} \quad \begin{array}{l} R = H, \text{alkyl} \\ R' = \text{alkyl, alkoxy, amino, or alkylamino} \end{array}$$

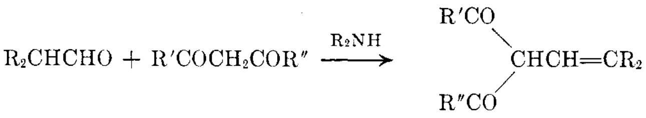
The noncatalyzed reaction proceeds much more slowly than the base-catalyzed one (qualitative observation). Thus, in the condensation of other types of reactive methylene compounds, where intramolecular aldol formation cannot occur, a base should be used. A catalyst also may frequently be used for the aldol-sensitive compounds if one operates at a lower temperature and for a shorter duration and if contamination of the δ-diketone compound by its aldol is of no concern or if the two are readily separable. In the present work, 3,5-heptanedione was condensed in this manner.

In the few cases examined where formalin was replaced by acetaldehyde in the noncatalyzed reaction, the yields dropped sharply. Surprisingly, the product from acetaldehyde and 2,4-pentanedione had a 1:1 composition. An examination of the literature, however, showed that McEntee and Pinder[12] had prepared the compound in an acid-catalyzed reaction, and assigned to it structure VII, rather than VIII which would be in analogy with higher homologs (below). Their assignment was questioned on the basis that VII, possessing a very active, conjugated double bond, should have undergone a Michael addition reaction to give the 2:1 condensation product and yet it was inert to the excess of 2,4-pentanedione in the reaction medium. On the other hand, VIII, having a terminal olefinic linkage, should have been quite susceptible to polymerization. The n.m.r. spectrum was obtained in an effort to resolve this question. The interpretation, which unequivocally favors VII, is presented in another paper.[11]


VII


VIII

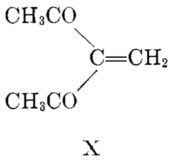
As was anticipated, propionaldehyde and butyraldehyde failed to react to any significant extent with either 2,4-pentanedione or ethyl acetoacetate in the absence of a catalyst, even over a period of several weeks. Under basic catalysis, such aldehydes possessing an α-hydrogen atom give only 1:1 condensation products whose structures (IX) are known.[12-14] Those aldehydes without the α-proton also condense only under basic catalysis, yielding hydroxycyclohexanones. Compounds corresponding to IX are stable to a base-catalyzed Michael addition reaction; compound VII, however, yields the corresponding hydroxycyclohexanone under these conditions.

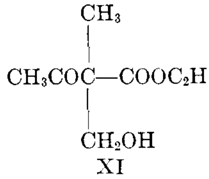

IX

A product in very low yield was formed from the noncatalyzed condensation of chloral with ethyl acetoacetate. The amount of material was too small for sufficient purification for characterization, but by all indications (*e.g.*, the boiling point), the material appeared to be a 1:1 condensation product, thus corresponding to VII.

An insight as to why VII fails to undergo the expected noncatalyzed Michael addition reaction was obtained by examination of Fisher–Taylor–Hirschfelder models. 3-Methylene-2,4-pentanedione (X) exhibits no steric hindrance. However, addition of one methyl group, to VII, produces severe interference and both carbonyls can no longer be planar with the olefinic linkage. The olefinic linkage here, then, more closely approaches that of a simple α,β-unsaturated ketone, which is known to require basic catalysis to participate in the Michael addition reaction.[15] Furthermore, the steric strain of VII is again relieved by replacement of either of the acetyl groups by a carboalkoxy group, accounting fully for the fact that α-ethylideneacetoacetates do react in the absence of a catalyst.

The condensation of formalin with ethyl α-methylacetoacetate proceeded only to the stage of the hydroxymethyl derivative (XI) and no further, even in the presence of amines.


X


XI

Experimental[16]

Intermediates. (A) Esters and Ketones.—Eastman Grade ethyl acetoacetate and benzoylacetone and Sapon ethyl propionylacetate were used as received. Eastman Grade dimethyl

---

(12) M. E. McEntee and A. R. Pinder, *J. Chem. Soc.*, 4419 (1957).

(13) F. Tiemann and P. Krüger, *Ber.*, **28**, 2115 (1895).

(14) G. B. Payne, *J. Org. Chem.*, **24**, 1830 (1959).

(15) E. D. Bergmann, "*Org. Reactions*," **10**, 179 (1959).

(16) All melting points are corrected. The infrared spectra were obtained as potassium bromide pressings or as smears on sodium chloride plates, using a Baird spectrophotometer, Model AB-1, with sodium chloride optics. The assistance of Miss Thelma Davis in the interpretation of these spectra is gratefully acknowledged.

TABLE II

ACETOACETAMIDES

Name	Yield, %	Recryst. solvent[d]	M.p., °C.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Acetoacetamide[a]	91.0	P	54–55	$C_4H_7NO_2$						
N-Ethylacetoacetamide	86.0	E	*ca.* 30°[e]	$C_6H_{11}NO_2$	55.8	8.6	10.8	55.6	8.5	10.6
N-*n*-Butylacetoacetamide	75.3	E	41–42	$C_8H_{15}NO_2$	61.1	9.6	8.9	61.3	9.5	8.9
p-Fluoroacetoacetanilide	84.8	B	100.5–101.5	$C_{10}H_{10}FNO_2$	61.5	5.2	7.2	61.9	5.0	6.9
m-Trifluoromethylacetoacetanilide	94.2	A	112–113[f]	$C_{11}H_{10}F_3NO_2$	53.9	4.1	5.7	54.0	4.1	5.6
p-Sulfoacetoacetanilide (Na salt)[b]	97.1	M	>300	$C_{10}H_{10}NaO_5S$	43.0	3.6	5.0	43.2	3.6	5.1
p-Carboxyacetoacetanilide[c]	90.8	W	194 dec.	$C_{11}H_{11}NO_4$	59.7	5.0	6.3	60.1	5.1	6.5
N,N-Dimethylacetoacetamide	46.0	..	[g]	$C_6H_{11}NO_2$						
N,N-Diethylacetoacetamide	89.2	..	[h]	$C_8H_{15}NO_2$						
N-Methylacetoacetanilide	92.2	..	[i]	$C_{11}H_{13}NO_2$	69.1	6.8	7.3	68.8	6.7	7.3

[a] The general procedure was modified in that the reaction temperature was held at −35 to −30° and a slight excess of diketene used F. Chick and N. T. M. Wilsmore, *J. Chem. Soc.*, **97**, 1978 (1910), give m.p. 54°. [b] The procedure given in U.S. Patent 2,700,037 (1955) was used. [c] The procedure is the same as that used for preparation of the sulfonic acid except that the basic solution was concentrated and neutralized, precipitating out the product. [d] A = aqueous alcohol; B = benzene; E = ethyl ether; M = methanol; P = acetone–petroleum ether; W = water. [e] B.p. 85–88°/0.06 mm., $n^{25}D$ 1.4586. [f] A. E. Porai-Koshits, L. S. Efros, M. I. Krylova, D. A. Livshits, K. Yu. Maryanovskaya, I. P. Aleksandrova, and K. E. Ulman, *J. Appl. Chem. USSR* (Transl. Ed.), **28**, 921 (1955), give m.p. 110–111°. [g] The procedure of H. Bredereck, R. Gompper, H. G. von Schuh, and G. Theilig, *Angew. Chem.*, **71**, 753 (1959), was used; b.p. 85–86°/6 mm., $n^{25}D$ 1.4688; ref. gives b.p. 109°/10 mm., $n^{20}D$ 1.4710. [h] B.p. 92–94°/1.5 mm., $n^{25}D$ 1.4775. G. E. Utzinger, *Helv. Chim. Acta*, **35**, 1359 (1952), gives b.p. 123–124°/12 mm. [i] B.p. 94–101°/0.09 mm., $n^{25}D$ 1.5481. C. E. Kaslow and D. J. Cook, *J. Am. Chem. Soc.*, **67**, 1969 (1945), give b.p. 130–132°/4 mm.

3-oxoglutarate was redistilled just before use (b.p. 114–117°/7 mm., $n^{25}D$ 1.4510). Aldrich 3-pyridinealdehyde (b.p. 70–71°/7 mm., $n^{26.7}D$ 1.5471) and methyl acetoacetate (b.p. 163–164°) were redistilled. All of the aldehydes were Eastman Grade and were used as received. Diketene (Eastman Chemical Products, Inc.) was distilled (b.p. 66–68°/90 mm., $n^{25}D$ 1.4348) and stored in a freezer, where it appears to be stable indefinitely. Care should be taken in handling undiluted diketene, as it can polymerize violently in the presence of even mild base. 3,5-Heptanedione was prepared by the method of Brändström[17] (b.p. 171–172°, $n^{25}D$ 1.4533).

(B) **Amides.**—Most of the acetoacetamides commercially available were found to be contaminated by their corresponding amine. Only Eastman Grade acetoacetanilide and Union Carbide *o*-chloroacetoacetanilide were used as received. After recrystallization from alcohol or aqueous alcohol, the following melted as shown: Eastman Practical Grade *o*-acetoacetotoluidide, m.p. 106–107°; *o*-acetoacetanisidide, m.p. 84–85°; 2′,4′-acetoacetoxylidide, m.p. 91–92°; Aldrich N-cyclohexylacetoacetamide, m.p. 75.5–77°; N-benzylacetoacetamide, m.p. 102–103°; N-phenethylacetoacetamide, m.p. 54.5–55.5°; 3′,4′,5′-trimethoxyacetoacetanilide, m.p. 99–100°; and α-acetoacetamidopyridine, m.p. 112–113°. Aldrich acetoacetopiperidide was dissolved in benzene, the solution was extracted with 0.5 *N* hydrochloric acid, washed with water, dried, and distilled (b.p. 88–91°/0.1 mm., $n^{25}D$ 1.4983).

Table II contains the data for the acetoacetamides prepared. The procedure for *p*-fluoroacetoacetanilide is representative: To a solution of 36.5 g. (0.434 mole) of diketene in 200 ml. of ethyl ether was added, dropwise, at a rate which maintained refluxing, a solution of 48.2 g. (0.434 mole) of redistilled *p*-fluoroaniline in 50 ml. of ether. The resulting slurry was heated under reflux for 1 hr., the product filtered off, washed with ether, and recrystallized.

α-Acetoacetamido-N-methylpyridinium *p*-Toluenesulfonate.—A slurry of 14.6 g. (0.082 mole) of α-acetoacetamidopyridine in 50 ml. of methyl *p*-toluenesulfonate was warmed on the steam bath for several hours, then left overnight at room temperature. Cooling gave 16 g. (52%) of crude product. Recrystallization from acetone gave α-acetoacetamido-N-methylpyridinium *p*-toluenesulfonate (m.p. 134.5–135.5°).

Anal. Calcd. for $C_{17}H_{20}N_2O_5S$: C, 56.0; H, 5.5; S, 8.8. Found: C, 56.6, 55.5; H, 5.7, 5.1; S, 8.6.

1:2 Condensation Products. (A) **From β-Keto Esters. Diethyl α,α′-Diacetylglutarate** (I).—Essentially Rabe's[16] conditions were used. A 1:2 molar ratio of formalin to ethyl acetoacetate in 100 ml. of ethanol per mole of formalin was let stand at room temperature for 3–5 days, then poured into water, extracted into benzene, dried, the solvent removed, and the residue distilled. Although the material may be distilled using an ordinary vacuum pump, extensive decomposition (gassing) does occur. The use of a molecular still is preferred (b.p. about 100°/6 μ, $n^{25}D$ 1.449–1.461).

Anal. Calcd. for $C_{13}H_{20}O_6$: C, 57.3; H, 7.4; mol. wt., 272. Found: C, 57.7; H, 7.5; mol. wt., 298 (ebullioscopic in benzene).

Bispyrazolone, m.p. 329–330° dec.; lit.,[1b] m.p. 326° dec.

Bisisoxazolone, m.p. 182–183° dec.; lit.,[1b] m.p. 180–183° dec.

Dimethyl α,α′-Diacetylglutarate.—This compound was prepared analogously to the ethyl ester (above) from methyl acetoacetate, and the same comments apply here (b.p. about 90°/4 μ, $n^{25}D$ 1.456–1.462).

Anal. Calcd. for $C_{11}H_{16}O_6$: C, 54.1; H, 6.6; mol. wt., 244. Found: C, 54.2; H, 7.0; mol. wt., 238 (ebullioscopic in benzene).

Diethyl α,α′-Dipropionylglutarate.—This compound was prepared analogously to the diacetylglutarates (above) from ethyl propionylacetate (b.p. 88–91°/0.04 mm., $n^{25}D$ 1.4518).

Anal. Calcd. for $C_{15}H_{24}O_6$: C, 60.0; H, 8.1. Found: C, 60.3; H, 7.8.

Diethyl α,α′-Diacetyl-β-methylglutarate.—This compound was prepared analogously to the diacetylglutarates (just given) with acetaldehyde in place of formalin (b.p. 90–94°/0.09 mm., $n^{25}D$ 1.4527).

Anal. Calcd. for $C_{14}H_{22}O_6$: C, 58.7; H, 7.7. Found: C, 59.2; H, 7.8.

Dimethyl 4,6-Dicarbomethoxy-3,7-dioxo-1,9-nonanedioate.—Freshly distilled dimethyl 3-oxoglutarate was mixed with one equivalent of formalin; sufficient methanol was added to maintain homogeneity, the solution filtered of any dirt, and let stand for 4 days. The crystals which formed were filtered off, washed well with methanol, and air-dried, giving a 28% yield of dimethyl 4,6-dicarbomethoxy-3,7-dioxo-1,9-nonanedioate (m.p. 157–158.5°). The material decomposed on attempted recrystallization.

Anal. Calcd. for $C_{15}H_{20}O_{10}$: C, 50.0; H, 5.6. Found: C, 50.0; H, 5.8.

Dimethyl 4,6-Dicarbomethoxy-3,7-dioxo-5-methyl-1,9-nonanedioate.—This compound was prepared analogously from acetaldehyde in 8.4% yield (m.p. 171–172°). It also decomposed on attempted recrystallization.

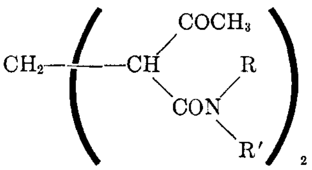
Anal. Calcd. for $C_{16}H_{22}O_{10}$: C, 51.3; H, 5.9. Found: C, 51.6; H, 5.9.

(B) **From β-Diketones. 3,5-Diacetyl-2,6-heptanedione.**—A mixture of 200 g. (2.00 moles) of 2,4-pentanedione, 70 ml. of formalin (*ca.* 37%) (1.0+ mole), and 100 ml. of absolute ethanol was let stand at room temperature for 2–5 days. The yield increased very little after the third day. The solvent was removed under vacuum. The residue (about 200 g.) was diluted with an equal volume of ethyl ether and seeded. If no seed is available, cooling an aliquot of the solution in a Dry Ice–acetone slurry usually eventually generates that seed. In several crops, 175–185 g. (82–87%) of III was obtained as colorless crystals, m.p.

---

[17] A. Brändström, *Arkiv Kemi*, **3**, 365 (1951).

TABLE III. GLUTARAMIDES



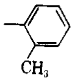
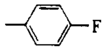
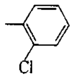
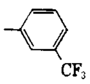
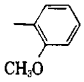
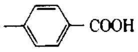
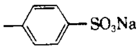
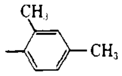
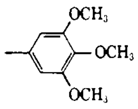
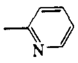
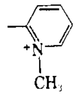
Name	R	R′	Yield, %	Recryst. solvent[c]	M.p., °C.	Formula	Calcd.			Found		
							C	H	N	C	H	N
α,α′-Diacetylglutaramide	H	H	76.2	N	161.5–162 dec.	$C_9H_{14}N_2O_4$	50.5	6.6	13.1	50.1	6.5	13.2
α,α′-Diacetyl-N,N′-diethylglutaramide	H	C_2H_5	71.3	E	170.5–171.5	$C_{13}H_{22}N_2O_4$	57.8	8.2	10.4	57.4	8.3	10.6
α,α′-Diacetyl-N,N′-di-*n*-butylglutaramide	H	*n*-C_4H_9	72.4	E	138–139	$C_{17}H_{30}N_2O_4$	62.5	9.3	8.6	62.6	9.4	8.5
α,α′-Diacetyl-N,N′-dicyclohexylglutaramide	H	C_6H_{11}	84.6	E	207 dec.	$C_{21}H_{34}N_2O_4$	66.6	9.1	7.4	66.6	9.3	7.5
α,α′-Diacetyl-N,N′-dibenzylglutaramide	H	$CH_2C_6H_5$	74.6	E	170–171	$C_{23}H_{26}N_2O_4$	70.0	6.6	7.1	70.0	6.3	7.0
α,α′-Diacetyl-N,N′-diphenethylglutaramide	H	$CH_2CH_2C_6H_5$	61.0	E	141–143	$C_{25}H_{30}N_2O_4$	71.1	7.2	6.6	71.4	6.9	6.7
α,α′-Diacetylglutaranilide[a]	H	C_6H_5	90.0	E	193 dec.	$C_{21}H_{22}N_2O_4$	68.8	6.1	7.6	69.0	6.3	7.8
α,α′-Diacetylglutar-*o*-toluidide	H		88.6	E	192 dec.	$C_{23}H_{26}N_2O_4$	70.0	6.6	7.1	69.8	7.0	7.2
α,α′-Diacetyl-4,4′-difluoroglutaranilide	H		83.6	E	221 dec.	$C_{21}H_{20}F_2N_2O_4$[e]	62.7	5.0	7.0	62.9	5.2	7.1
α,α′-Diacetyl-2,2′-dichloroglutaranilide	H		83.9	A	170–171	$C_{21}H_{20}Cl_2N_2O_4$[f]	57.9	4.6	6.4	57.8	4.7	6.7
α,α′-Diacetyl-3,3′-bis(trifluoromethyl)glutaranilide	H		63.7	B	145–146	$C_{23}H_{20}F_6N_2O_4$[g]	55.0	4.0	5.6	54.9	4.0	5.3
α,α′-Diacetylglutar-*o*-anisidide	H		72.5	E	152.5–153.5	$C_{23}H_{26}N_2O_6$	64.8	6.1	6.6	64.7	6.2	6.6
α,α′-Diacetyl-4,4′-dicarboxyglutaranilide	H		[b]	[b]	229 dec.	$C_{23}H_{22}N_2O_8$	60.8	4.9	6.2	60.3	5.2	6.0
α,α′-Diacetyl-4,4′-disulfoglutaranilide disodium salt	H		91.4	A	>300	$C_{21}H_{20}N_2Na_2O_{10}S_2$[h]	44.2	3.5	4.9	43.8	3.6	4.6
α,α′-Diacetylglutaro-2,4-xylidide	H		97.2	D	195 dec.	$C_{25}H_{30}N_2O_4$	71.1	7.2	6.6	71.2	7.4	6.9
α,α′-Diacetyl-3,3′,4,4′,5,5′-hexamethoxyglutaranilide	H		94.0	N	156–157 dec.	$C_{27}H_{34}N_2O_{10}$	59.3	6.3	5.1	59.0	6.0	5.0
α,α′-Diacetyl-N,N′-di(2-pyridyl)glutaramide	H		83.7	A	132–133	$C_{19}H_{20}N_4O_4$	61.9	5.5	15.2	61.8	5.5	15.0

TABLE III (*Continued*)

Name	R	R′	Yield, %	Recryst. solvent[c]	M.p., °C.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
α,α′-Diacetyl-N,N′-di-2-(N-methylpyridinium)-glutaramide bis-*p*-toluenesulfonate	H	 $C_7H_7SO_3^-$	87.2	[d]	[d]	$C_{35}H_{40}N_4O_{10}S_2$[i]	56.7	5.4	7.6	55.5 55.7	5.6 5.5	7.3
				$n^{25}D$								
α,α′-Diacetyl-N,N,N′,N′-tetramethylglutaramide	CH_3	CH_3	85.9	1.4910	B.p. 121–132/14–16 μ	$C_{13}H_{22}N_2O_4$	57.8	8.2	10.4	57.6	8.2	10.2
α,α′-Diacetyl-N,N,N′,N′-tetraethylglutaramide	C_2H_5	C_2H_5	89.8	1.4819	B.p. 144–151/8–10 μ	$C_{17}H_{30}N_2O_4$	62.5	9.3	8.6	62.6	8.9	8.7
α,α′-Diacetyl-N,N′-dimethylglutaranilide	CH_3	C_6H_5	*ca.* 57	1.5543	B.p. *ca.* 114/8 μ	$C_{23}H_{26}N_2O_4$	70.0	6.6	7.1	70.1	7.0	7.4
α,α′-Diacetylglutaropiperidide	—$(CH_2)_5$—		95.7	1.5062	B.p. 130–142/21–25 μ	$C_{19}H_{30}N_2O_4$	65.1	8.6	8.0	64.7	8.7	7.7

[a] C. M. Mehta and G. H. Patel, *Current Sci.* (India), **29**, 95 (1960), claim to have prepared α,α′-diacetylglutaranilide, -tolulidide, and -xylidide, but give no details or any physical constants. [b] From the crude product, a 55% recovery of starting β-ketomide was obtained by digestion with hot nitromethane. The residue could not be further purified and was analyzed directly; the yield of α,α′-diacetyl-4,4′-dicarboxyacetoacetanilide was 23%. [c] A = aqueous alcohol; B = benzene; D = 6:1:3 –ethanol–dimethylformamide–water; E = absolute ethanol; N = nitromethane. [d] The crude material was amorphous and extremely hygroscopic. It eluded all attempts at purification. [e] Calcd.: F, 9.4; Found: F, 9.2. [f] Calcd.: Cl, 16.3; Found: Cl, 16.1. [g] Calcd.: F, 22.7; Found: F, 23.1. [h] Calcd.: S, 11.2; Na, 8.1. Found: S, 10.9; Na, 8.1. [i] Calcd.: mol. wt., 740. Found: mol. wt., 677 (ebullioscopic in acetone).

37–41°. Several recrystallizations from ethyl ether raised the melting point to 41.5–42.5°.

Alternatively, the crude oil after removal of the solvent was distilled, giving about 125 g. of a colorless oil, b.p. 120–125°/0.05 mm.; $n^{25}D$ 1.4701. This oil, when treated in the same manner as the undistilled material and recrystallized from ether, gave 53 g. of IV as colorless crystals, m.p. 55–56°. *Caution:* These crystals should be dried on paper; on glass they liquefy at room temperature over a period of several hours.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.2; H, 7.6; mol. wt., 212. Found (III): C, 62.3; H, 7.5; mol. wt., 202 (ebullioscopic in alcohol). Found (IV): C, 62.4; H, 7.5.

Derivatives of III and IV were prepared by standard procedures (see Table I). A certain amount of care should be taken in handling III, IV, and especially the oils from which they are obtained, because they produce a yellow-colored stain on the skin which is removed only by normal attrition.

4,6-Diacetyl-3-hydroxy-3-methylcyclohexanone (V). (1) **Knoevenagel Conditions.**—The diethylamine-catalyzed reaction, as described by Knoevenagel,[7] could be essentially duplicated, giving V, m.p. 89–90° (from ether) in 50–60% yield. In addition to V, the 2:3 adduct (A) of formalin and 2,4-pentanedione mentioned by Rabe[1b] was found in as much as 5% yield; m.p. 176–177° (from methanol). No attempt has been made to determine its structure.

Anal. Calcd. for $C_{17}H_{24}O_6$: C, 62.9; H, 7.5; mol. wt., 324. Found: C, 63.0, 62.7; H, 7.3, 7.2; mol. wt., 324, 326 (thermometric in acetone).

It was found that if the condensation reaction was interrupted after 1–2 days, a moderate amount (up to as much as 36%) of compound III could be isolated in addition to the products already mentioned (in lower yield).

Results essentially identical to those just given were obtained when the diethylamine was replaced by piperidine. When triethylamine was used, the yield of V was improved to 70% and neither III nor A was detected. The use of Amberlite IR-45 ion exchange resin gave results slightly inferior to those obtained with triethylamine.

(2) **From 3,5-Diacetyl-2,6-heptanedione.**—A mixture of 4.0 g. of either III or IV and several drops of piperidine was melted and then held at about 45°. Crystals began appearing on the third day. These were filtered, washed with a little ether, and dried; m.p. 175–176°. (Therefore, they were crystals of A.) The filtrate and washings were cooled and seeded with III. No crystals formed. Seeding with V gave 0.72 g. of crude crystals of V; m.p. 83.5–85°. Under identical conditions but starting with V, only starting material could be recovered.

Action of Hydrazine on V.—A slurry of 5.0 g. of V in 15 ml. of absolute ethanol was treated with 2.0 ml. of hydrazine added dropwise. The mixture became warm and the solids rapidly dissolved. The clear solution was left overnight, then concentrated under vacuum without applied heat. An amorphous residue (5.27 g.) remained.

4,6-Diacetyl-3-hydroxy-3-methyl-5-(β-pyridyl)cyclohexanone.—This compound (m.p. 176–176.5°) was prepared by the procedure of Martin, Shamma, and Fernelius,[18] who reported m.p. 164–165° but incorrectly assigned to this material the structure 3,5-diacetyl-4-(β-pyridyl)-2,6-heptanedione. In the absence of piperidine, no reaction occurred.

4,6-Dipropionyl-3,7-nonanedione and 4,6-Dipropionyl-3-ethyl-3-hydroxy-2-methylcyclohexanone.—A solution of 64.1 g. (0.500 mole) of 3,5-heptanedione and 18 ml. (0.25 mole) of formalin in 40 ml. of alcohol was cooled to −10° and 10 drops of piperidine were added. The solution was kept at −10° for 40 hr., with precipitation of crystals occurring after about 25 hr. The solids (about 25 g.) were filtered off and recrystallized from alcohol (m.p. 138–139°).

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.1; H, 9.0. Found: C, 66.9; H, 8.8.

The filtrate was poured into water, the resulting solution extracted with benzene, and the benzene solution dried and fractionally distilled (b.p. 115–118°/0.02 mm., $n^{25}D$ 1.4664).

Anal. Found: C, 67.5; H, 9.4.

A small amount of solid, m.p. 135–138°, separated from the last fraction.

A solution of 2.7 g. (0.010 mole) of the oil in 15 ml. of ethanol was treated with 1.2 ml. of hydrazine. A violent reaction ensued. The next day the clear solution was diluted with water to precipitate the product, 2.6 g. (64%). Recrystallization from aqueous methanol gave methylene-4,4′-bis(3,5-diethylpyrazole) (m.p. 230–231.5°).

---

[18] D. F. Martin, M. Shamma, and W. C. Fernelius, *J. Am. Chem. Soc.*, **80**, 5851 (1958).

Anal. Calcd. for $C_{15}H_{24}N_4$: C, 69.2; H, 9.3; N, 21.5. Found: C, 69.1; H, 9.5; N, 21.5.

When treated in the same way, the crystalline product failed to give a precipitate on dilution with water. Concentration *in vacuo* left an amorphous residue of 2.76 g. Its infrared spectrum was quite similar to that obtained when 4,6-diacetyl-3-hydroxy-3-methylcyclohexanone was treated in the same manner (above). Thus, the oil and the solid are identified, respectively, as 4,6-dipropionyl-3,7-heptanedione and its intramolecular aldol product, 4,6-dipropionyl-3-ethyl-3-hydroxy-2-methylcyclohexanone.

3,5-Dibenzoyl-2,6-heptanedione.—To a stirred slurry of 48.7 g. (0.300 mole) of benzoylacetone in 250 ml. of ethanol was added 11.5 ml. (0.15 mole) of formalin. The solids dissolved during the next 45 min. After 65 hr., the solution was poured into water, extracted with benzene, dried, and the solvent removed. The oily residue (46.2 g., 91.5%) crystallized on strong cooling. Recrystallization from a small volume of methanol (with seeding) gave 3,5-dibenzoyl-2,6-heptanedione (m.p. 80–81°).

Anal. Calcd. for $C_{21}H_{20}O_4$: C, 75.0; H, 6.0. Found: C, 75.2; H, 6.2.

(C) **From β-Ketoamides.**—The same general procedure was used for all of the glutaramides prepared: The β-ketoamide was dissolved or, if it was less soluble, slurried in ethanol (a maximum of 500 ml. per mole of amide), and 0.5 equivalent of formalin was added. The slurry was stirred until solution was effected (usually within several hours, although the more insoluble amides never completely dissolved before product began to precipitate). The product usually began separating during the second day, was filtered off after 4–5 days, and purified. Those few products which failed to crystallize were concentrated *in vacuo* or diluted with water to induce precipitation. The products from the four tertiary β-ketoamides used are all oils which, on distillation, behave quite similarly to diethyl α,α′-diacetylglutarate. Table III contains the data on all these substituted diacetylglutaramides.

1:1 Condensation Products. Ethyl α-Hydroxymethyl-α-methylacetoacetate (XI).—A solution of 101 g. (0.700 mole) of ethyl α-methylacetoacetate and 27 ml. (0.35 mole) of formalin in 40 ml. of alcohol was let stand for 10 days. The solution was poured into water, extracted into benzene, dried, and distilled. After a forerun of starting material (35–40 g.), ethyl α-hydroxymethyl-α-methylacetoacetate distilled (b.p. 108–109°/9 mm., n^{25}_{D} 1.4411); yield, 39 g. (64.0%).

Anal. Calcd. for $C_8H_{14}O_4$: C, 55.2; H, 8.1; mol. wt., 174. Found: C, 55.5; H, 8.2; mol. wt., 185 (ebullioscopic in benzene).

The addition of piperidine or the use of a higher temperature had only a slight effect on the yield.

3-Acetyl-3-penten-2-one (VII).—A mixture of 400 g. (4.00 moles) of 2,4-pentanedione and 170 ml. (3.0 moles) of acetaldehyde was let stand for 1 week and then distilled. Distillation at aspirator pressure (about 10 mm.) appeared to be accompanied by a slow thermal decomposition. Gas chromatographic analysis of the distillate showed that 4% of 2,4-pentanedione and 4% of an unknown component were present as impurities. Distillation under a high vacuum with a low pot temperature gave 3-acetyl-4-penten-2-one as a clear liquid with a pungent odor (b.p. 44–45°/0.04 mm., n^{25}_{D} 1.4608). Gas chromatographic analysis indicated 96% purity; only 4% of the 2,4-pentanedione was found to contaminate the material. McEntee and Pinder[12] reported b.p. 80–81°/10 mm.

Anal. Calcd. for $C_7H_{10}O_2$: C, 66.6; H, 8.0; mol. wt., 126. Found: C, 66.4; H, 8.1; mol. wt., 126 (mass spectrometer).

When the condensation was carried out in the presence of piperidine, the product obtained in 89.4% crude yield was 4,6-diacetyl - 3 - hydroxy - 3,5 - dimethylcyclohexanone (m.p. 108.5–109.5°). Knoevenagel[7] reported m.p. 108° but incorrectly assigned to this material the structure 3,5-diacetyl-4-methyl-2,6-heptanedione.

3-Acetyl-4-hexen-2-one.—A mixture of 100 g. (1.00 mole) of 2,4-pentanedione and 58.1 g. (1.00 mole) of propionaldehyde was treated twice daily with 2-drop portions of diethylamine. Phase separation occurred on the third day. The next day the volatiles were removed *in vacuo* and the residue was distilled, yielding 60.2 g. (43.0%) of 3-acetyl-4-hexen-2-one (b.p. 59–61°/6 mm., n^{25}_{D} 1.4875). McEntee and Pinder[12] reported b.p. 82°/14 mm.

3-Acetyl-4-hepten-2-one.—Similarly, a mixture of 50.1 g. (0.500 mole) of 2,4-pentanedione and 22.1 ml. (0.25 mole) of butyraldehyde was treated twice daily for 5 days with 5-drop portions of piperidine, concentrated *in vacuo*, and distilled, yielding 32.8 g. (85.0%) of 3-acetyl-4-hepten-2-one (b.p. 90–92°/18 mm., n^{25}_{D} 1.4809). Payne[14] reported b.p. 83–84°/8 mm., n^{20}_{D} 1.4840.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.1; H, 9.2. Found: C, 70.3; H, 9.3.

Condensation of Chloral with Ethyl Acetoacetate.—A solution of 65.1 g. (0.500 mole) of ethyl acetoacetate and 36.7 g. (0.250 mole) of freshly distilled chloral in 25 ml. of ethanol was let stand 1 week, poured into water, extracted into ether, dried, and the volatiles, including most of the remaining ethyl acetoacetate, removed *in vacuo*. The residue (about 5 ml.) was distilled, giving about 3 g. of a colorless oil (b.p. 110–118°/0.3–0.4 mm., n^{25}_{D} 1.4730).

Anal. Found: C, 38.0; H, 4.0. Calcd. for $C_8H_9Cl_3O_3$ (ethyl α-acetyl-γ,γ,γ-trichlorocrotonate): C, 37.0; H, 3.5. Calcd. for $C_{14}H_{19}Cl_3O_6$ [diethyl α,α′-diacetyl-β-(trichloromethyl)glutarate]: C, 43.2; H, 4.9.

The Osmium Tetroxide-catalyzed Hydroxylation of Furan–Maleic Anhydride Adducts[1]

RALPH DANIELS AND JOHN L. FISCHER

Department of Chemistry, College of Pharmacy, University of Illinois, Chicago 12, Illinois

Received July 5, 1962

Diels–Alder adducts of maleic anhydride with furan, 2-methylfuran, 2-acetoxyfuran, and 2-bromofuran have been hydroxylated by osmium tetroxide in the presence of 30% hydrogen peroxide in *t*-butyl alcohol to provide the corresponding unsubstituted and 1-substituted 5,6-dihydroxy-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic acids. The probable stereochemistry of the products is discussed.

The hydroxylation of Diels–Alder adducts provides a facile route for the preparation of polyhydroxycyclohexanes. When the diene employed in the Diels–Alder reaction is a furan, then hydroxylation of the adduct affords a derivative of cyclohexane carrying hydroxyl groups or potential hydroxyl groups on at least four contiguous carbon atoms.[2] This investigation was undertaken to prepare intermediates suitable for further elaboration into naturally occurring polyhydroxycyclohexanes.

The use of furan and substituted furans as dienes in the Diels–Alder reaction, particularly with maleic an-

---

(1) This paper represents part of a thesis submitted by John L. Fischer to the Graduate College of the University of Illinois, 1959, in partial fulfillment of the requirements for the degree of Master of Science. This work was supported in part by a grant from the Research Board of the Graduate College of the University of Illinois: grant no. 05-19-82.

(2) See Yu. K. Yur'ev and N. S. Zefirov, *J. Gen. Chem. USSR*, **31**, 629 (1961) for the hydroxylation of the furan–vinylene carbonate adduct to afford derivatives of inositol.