m, 1 H; 6.61, t, J = 4 Hz, 1 H. Ir (CCl_4) 3070, 2920, 1670, 1630, 910 cm^{-1}.

Registry No.—I, 579-75-9; II (R = $CH_2CH{=}CH_2$, 38019-50-0; II (R = Pr), 59034-18-3; II (R = Pr) 2,4-DNPH, 59034-20-7; II (R = Pr-*i*), 59034-19-4; II (R = $(CH_2)_4CH_3$), 25435-63-6.

References and Notes

(1) Support of this work by National Institutes of Health Grant GM 15431 is gratefully acknowledged.
(2) G. H. Posner, *Org. React.*, **19**, 1 (1972).
(3) E. S. Binkley and C. H. Heathcock, *J. Org. Chem.*, **40**, 2156 (1975), and references cited therein.
(4) T. Harayama, H. Cho, and Y. Inubishi, *Tetrahedron Lett.*, 2693 (1975).
(5) E. J. Corey and H. S. Sachdev, *J. Org. Chem.*, **40**, 579 (1975).
(6) (a) Alkylation of cyclohexenone: J.-M. Conia and A. Le Craz, *Bull. Soc. Chim. Fr.*, 1934 (1960). (b) Alkylation of cyclohexane-1,3-dione, followed by enol ether formation, reduction, and hydrolysis: M. F. Angell and T. M. Kafka, *Tetrahedron*, **25**, 6025 (1969). (c) Bromination–dehydrobromination of a 2-alkylcyclohexanone: E. W. Warnhoff, D. G. Martin, and W. S. Johnson, *Org. Synth.*, **37**, 8 (1957). (d) Sulfenylation of a 2-alkylcyclohexanone, followed by oxidation and elimination: B. M. Trost and T. N. Salzmann, *J. Am. Chem. Soc.*, **95**, 6840 (1973). (e) Selenation of a 2-alkylcycloxanone, followed by oxidation and elimination: H. J. Reich, J. M. Renga, and I. L. Reich, *Ibid.*, **97**, 5434 (1975). (f) Reduction of a 2-alkylpyridine, followed by hydrolysis and aldol condensation: S. Danishefsky and P. Cain, *J. Org. Chem.*, **40**, 3607 (1975). (g) Oxidation of a 1-alkylcyclohexene: V. F. Belyaev, *Chem. Abstr.*, **58**, 4435d (1963).
(7) M. D. Bachi, J. W. Epstein, Y. Herzberg-Minzly, and H. J. E. Loewenthal, *J. Org. Chem.*, **34**, 126 (1969).
(8) H. Christol, M. Mousseron and F. Plenat, *Bull. Soc. Chim. Fr.*, 543 (1959).
(9) The thick white suspension is the ammonium salt of the *o*-methoxybenzoic acid. As lithium metal is added this suspension dissolves to give a pale yellow solution. As more lithium is added this color deepens to a dark orange, which deepens further to a brown before going to the blue color typical of the presence of excess lithium. On addition of 1,2-dibromethane to consume the lithium the blue color is discharged, leaving a reddish-orange solution which fades to a yellow-white suspension almost immediately on the addition of the alkylating agent.

N,N,N′,N′-Tetramethylmethanediamine. A Simple, Effective Mannich Reagent

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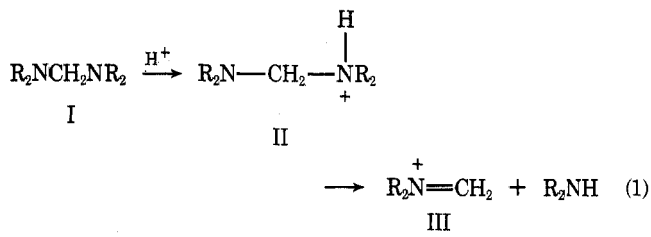
The Mannich reaction followed by β-elimination has long been used to convert a ketone into an α,β-unsaturated analogue. Under the usual reaction conditions, a methylenebisamine (I) is formed which, under acid conditions, forms the resonance-stabilized aminocarbonium ion (III) (eq 1).[1]

Ahond et al.[2,3] found that a similarly reactive intermediate formed by the treatment of trimethylamine oxide with a methylene chloride solution of trifluoroacetic anhydride proved to be an excellent Mannich reagent. Using this principle, Taylor[4] used *N,N,N′,N′*-tetramethylmethanediamine and acetic anhydride to generate an α,β-unsaturated ketone without utilizing the Mannich base.



In the preparation of the recently discovered uricosuric saluretics, (1-oxo-2,2-disubstituted-5-indanyloxy)acetic acids,[5] it was desired to introduce a methylene group under Mannich conditions α to an alkyl aryl ketone. Treatment of $ArC(=O)CH_2$-aryl with paraformaldehyde, dimethylamine hydrochloride, and acetic acid[6] did not afford high yields of α,β-unsaturated ketone in our hands.[7]

The desired transformation was successfully carried out by using *N,N,N′,N′*-tetramethylmethanediamine and acetic anhydride constituting an extension of the reaction described by Taylor. We found that the mild conditions employed allowed for the isolation of the α,β-unsaturated ketones in excellent yields with no by-products. For reaction to take place at <40°C, enhanced activation of the adjacent methylene by both the ketone and aryl moieties, $ArC(=O)CH_2$-aryl, was necessary since ketones of the type $ArC(=O)CH_2$-alkyl did not react under similar conditions. However, treatment of $ArC(=O)CH_2$-alkyl compounds with *N,N,N′,N′*-tetramethylmethanediamine and acetic anhydride at higher temperatures (90°C) did give the desired α,β-unsaturated ketones in good yields.

Experimental Section

General Procedure. Acetic anhydride (50 ml) was added dropwise to a suspension of the alkyl aryl ketone (0.1 mol) in *N,N,N′,N′*-tetramethylmethanediamine (50 ml). The reaction temperature was maintained at <40°C by ice-bath cooling. After 1 h of stirring at 25 °C, the solution was added slowly to crushed ice–water (1 l.) with stirring to precipitate analytically pure product in 80–100% yield (Table I).

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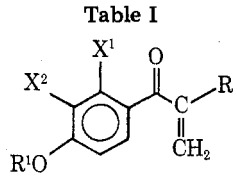
Registry No.—2,3-Dichloro-4-phenylacetylanisole, 59043-83-3; 2-chloro-3-methyl-4-phenylacetylanisole, 59043-84-4; 2,3-dichloro-4-phenylacetyl-α-carboxyanisole ethyl ester, 59043-85-5; 2,3-dichloro-4-[(*p*-bromophenyl)acetyl]anisole, 59043-86-6; 2,3-dichloro-

Table I



Registry no.	R	R^1	X^1	X^2	Mp, °C	% yield	Empirical[a] formula
57296-59-0	C_6H_5	CH_3	Cl	Cl	87–89	98	$C_{16}H_{12}Cl_2O_2$
59043-79-7	C_6H_5	CH_3	Cl	CH_3	81–85	85	$C_{17}H_{15}ClO_2$
59043-80-0	C_6H_5	$CH_2CO_2C_2H_5$	Cl	Cl	60–64	78	$C_{19}H_{16}Cl_2O_4$
57296-97-6	4-BrC_6H_4	CH_3	Cl	Cl	110–116	97	$C_{16}H_{11}BrCl_2O_2$
59043-81-1	4-FC_6H_4	CH_3	Cl	Cl	102–104	80	$C_{16}H_{11}Cl_2FO_2$
59043-82-2	C_2H_5	CH_3	Cl	Cl	46–48	86[b]	$C_{12}H_{12}Cl_2O_2$

[a] Satisfactory analytical data (±0.4% for C and H) for all compounds were submitted for review. [b] At <40 °C, no reaction; at 90 °C, 86% yield.

4-[(-*p*-fluorophenyl)acetyl]anisole, 59043-87-7; 2,3-dichloro-4-propionylanisole, 41715-70-2; *N,N,N′,N′*-tetramethylmethanediamine, 51-80-9.

References and Notes

(1) J. E. Fernandez and R. Sutor, *J. Org. Chem.*, **32**, 477 (1967).
(2) A. Ahond, A. Cavé, C. Kan-Fan, H. Husson, J. deRostolan, and P. Potier, *J. Am. Chem. Soc.*, **90**, 5622 (1968).
(3) A. Ahond, A. Cavé, C. Kan-Fan, and P. Potier, *Bull. Soc. Chim. Fr.*, 2707 (1970).
(4) E. C. Taylor and Y. Shvo, *J. Org. Chem.*, **33**, 1719 (1968).
(5) E. J. Cragoe, Jr., E. M. Schultz, J. D. Schneeberg, G. E. Stokker, O. W. Woltersdorf, Jr., G. M. Fanelli, and L. S. Watson, *J. Med. Chem.*, **18**, 225 (1975).
(6) E. M. Schultz, E. J. Cragoe, Jr., J. B. Bicking, W. A. Bolhofer, and J. M. Sprague, *J. Med. Pharm. Chem.*, **5**, 660 (1962).
(7) Under the forcing conditions required for its formation, the thermally unstable α,β-unsaturated ketone yielded a by-product presumed to be a dimer (dihydropyran) based on its ^{1}H NMR spectrum and by analogy with work previously described.[8]
(8) E. J. Cragoe, Jr., and J. J. Baldwin, U.S. Patent 3 483 227 (1969).

Communications

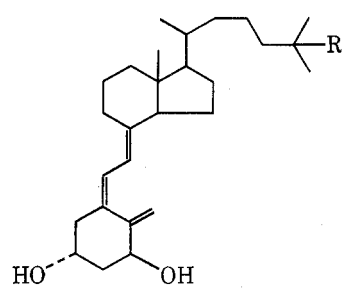
Hydroxylation with Ozone on Silica Gel. The Synthesis of 1α,25-Dihydroxyvitamin D_3

Summary: A convenient synthesis of 1α,25-dihydroxyvitamin D_3, the natural calcium regulating hormone, based on a regioselective C_{25}-hydroxylation of 1α,3β-diacetoxy-6β,7α-dibromocholestane by means of ozone absorbed on silica gel, is reported.

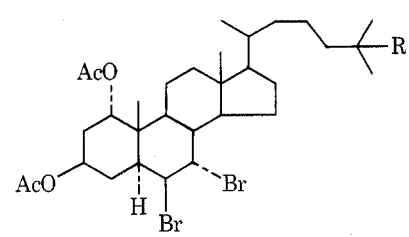
Sir: As a further development of our studies on the functionalization of unactivated carbon atoms,[1] we report on the utilization of the recently published method of dry ozonation[2] for a relatively simple synthesis of the calcium regulating hormone, viz., the 1α,25-dihydroxyvitamin D_3 (**1b**).[3]

The key step in this synthesis is the highly regioselective C_{25}-hydroxylation of a tetrasubstituted cholestane derivative, the dibromide **2a,** which is an intermediate in the preparation of a physiological useful substitute of **1b,** viz., the 1α-hydroxyvitamin D_3[4] (**1a**). We obtained this dibromide intermediate, **2a,** in a five-step synthesis from cholesterol, by the following sequence: cholesterol → **3a** → **4a** → **5a** → **5c** → **2a.**[4]

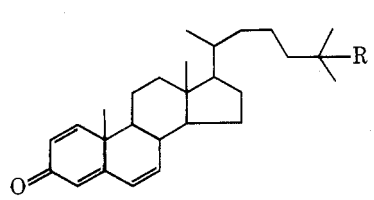
Silica gel for chromatography (Merck-Kieselgel 60, 70–220 mesh) containing 1% by weight of adsorbed **2a** was saturated with ozone (generated from Welsbach ozonizer) at −78 °C and allowed to warm to room temperature. This procedure was repeated altogether five times. Elution and chromatographic separation yielded, in addition to recovered starting material **2a,** the C_{25}-hydroxy derivative, **2b,** mp 174–175 °C, $[\alpha]_D$ −24°, as the only isolated product (11% conversion and 51% yield). The presence of OH at C_{25} in **2b** was indicated by its NMR spectrum which was similar to that of the starting compound **2a**[4] except for the signals due to the methyl protons at C_{25} appearing as a singlet at δ 1.20 ppm instead of a doublet at 0.85 and by its mass spectrum [M^+ at *m/e* 660 (^{79}Br) and 59 of $(CH_3)_2C^+OH$]. The structure of **2b** was proved by comparison of its C_{25} acetate, **2d** [NMR δ 1.41, 1.96 ppm (CH_3 and OAc at C_{25}); mass spectra M^+ at *m/e* 702 (^{79}Br) and 101 of $(CH_3)_2C^+OAc$] with a compound synthesized by us from the previously described C_{25}-hydroxy epoxide **4b.**[5,6] Reduction of the epoxide with Li/NH_3 in the presence of NH_4Cl resulted in 20% Δ^6-triol, **5b**[7] [mp 193–196 °C; $[\alpha]_D$ −62°; NMR ($CDCl_3$) δ 0.70 (s, 3, C_{18} H), 0.80 (s, 3, C_{19} H), 0.91 (d, 3, J = 7 Hz, C_{21}



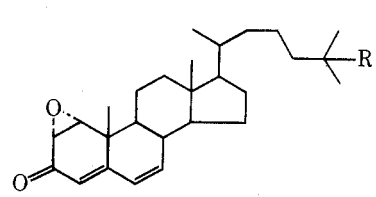
1a, R = H
b, R = OH



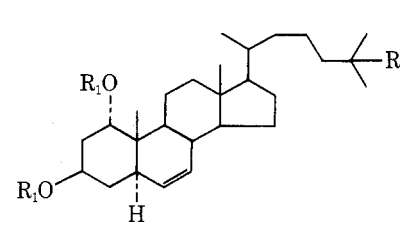
2a, R = H
b, R = OH
c, R = $OCOCF_3$
d, R = OAc



3a, R = H
b, R = OH



4a, R = H
b, R = OH



5a, R = H; R_1 = H
b, R = OH; R_1 = H
c, R = H; R_1 = Ac
d, R = OAc; R_1 = Ac