TABLE IV

RATES OF REACTION OF 2,4-DINITROCHLOROBENZENE WITH n-BUTYLAMINE AND SODIUM HYDROXIDE IN 50% DIOXANE–50% WATER AT 24.8 ± 0.1°

2,4-Dinitrochlorobenzene, mole./l.	n-Butylamine, mole/l.	Sodium hydroxide, mole./l.	$k \times 10^4$, sec. $^{-1}$	$k_4 \times 10^4$, l.^{2} mole^{-2} sec.$^{-1}$	$k_4^* \times 10^4$ l.^{2} mole^{-2} sec.$^{-1}$
0.01326	0.09816	0.0603	2.62	0	1.7
.01312	.09909	.0741	2.67	Neg.	Neg.
.01293	.09903	.1207	3.21	15.9	12.0
.01312	.09856	.1481	3.32	8.9	7.5
.01278	.09915	.1810	3.63	12.3	10.6
.01317	.09867	.2222	3.85	8.7	5.9
.01333	.09932	.2413	4.00	8.8	7.5
.01248	.04955	.2500	2.85	10.5	

6.4×10^{-4} l. mole^{-1} sec.$^{-1}$ for k_1, k_3 and k_5, respectively.

Except for the two measurements at the lowest sodium hydroxide concentrations, where one k_4 is negative and the other zero, the values obtained are appreciable and of the same order of magnitude as k_3. However, even in those cases where the k_4's are positive, the contribution of the $k_4(B_0)(C_0)$ term to the total rate, k, is small and varies from 3.9 to 6.1%. This makes the zero and negative values at the lowest sodium hydroxide concentrations understandable, since in these experiments the contribution from the k_4 term probably is less than the experimental uncertainties involved.

This, of course, brings into question the reliability of even those experiments for which k_4 is positive, for, even under the most favorable conditions, we are still trying to determine a small difference between relatively large quantities. There is the possibility that the positive k_4 that we have obtained is really the result of a positive salt effect on k_1 and k_3. The data of Table II can be used to eliminate this explanation. These measurements were at approximately the same chloride and amine concentrations as the first seven experiments of Table IV and, since a plot of the first-order rate constants *vs.* the sodium nitrate concentrations is linear, we can use these data to estimate $k_1(B_0) + k_3(B_0)^2$ at any particular sodium hydroxide concentration. This assumes that sodium hydroxide and sodium nitrate will have equivalent salt effects on k_1 and k_3. Actually, sodium hydroxide might be expected to be less dissociated in 50% dioxane–50% water than sodium nitrate, since the hydroxide ion is smaller, and its charge is less distributed. By using these values for $k_1(B_0) + k_3(B_0)^2$, the k_4's shown in the last column of Table IV were calculated. At the two lowest sodium hydroxide concentrations the k_4 values are in one case small and in the other negative. The remaining values are not appreciably lower than those given in the fifth column of Table IV. These positive values for k_4 cannot, therefore, be attributed to a salt effect on k_1 and k_3.

These results, taken at their face value, suggest that the $k_4(B_0)(C_0)$ term is significant and that the reaction of 2,4-dinitrochlorobenzene with n-butylamine is subject to catalysis by hydroxide ion. They are not, however, sufficient to constitute clear proof of these contentions. We are not prepared to claim that we have demonstrated the fact of catalysis by hydroxide ion, but we would insist that, on the basis of the available evidence, the assertion that the reaction of 2,4-dinitrochlorobenzene with primary and secondary amines is not subject to hydroxide ion catalysis is unjustified.

Acknowledgment.—I am indebted to Dr. R. C. Petersen of these laboratories for many helpful and stimulating discussions.

NORTH ADAMS, MASS.

COMMUNICATIONS TO THE EDITOR

BISMETHYLENEDIOXY STEROIDS. II. SYNTHESIS OF 9α-METHYLHYDROCORTISONE AND 9α-METHYLPREDNISOLONE[1]

Sir:

Replacement of the hydrogen atom at C-9 in adrenocortical steroids by various substituents produces a pronounced effect on biological activity.[2] We felt that knowledge of the bioactivity of 9-methyl corticoids would advance the theory of how these effects are mediated. This communication outlines a synthesis of these difficultly accessible steroids.

Jones, Meakins and Stephenson[3] have reported the preparation of a 9α-methyl-Δ^7-11-ketosteroid by alkylation of a Δ^7-11-ketone with methyl iodide–potassium t-butoxide.

The initial compound in our synthesis, 9,11β-oxido-4-pregnene-17α-21-diol-3,20-dione[4] (I), was combined with formaldehyde–hydrobromic acid to give 9α-bromohydrocortisone-BMD (IIa): m.p. 170–190° (dec.); found C, 57.35; H, 6.34; $\lambda_{\max}^{\text{MeOH}}$ 243 mμ, E 15,500; $\lambda_{\max}^{\text{Nujol}}$ 2.7, 5.98, 6.1. 8.9–9.3 (BMD)μ. Oxidation of IIa with chromic acid in tetrahydrofuran–acetic acid or pyridine gave 9α-bromocortisone-BMD (IIb): m.p. 205–210° (dec.); found C, 57.48; H, 5.97; $\lambda_{\max}^{\text{MeOH}}$ 238 mμ, E 15,800; $\lambda_{\max}^{\text{Nujol}}$ 5.80, 5.91, 6.1, 9.0–9.2μ. Reaction of IIb with ethylene glycol-p-toluenesulfonic acid yielded 9α-bromocortisone-BMD-3-dioxolane (IIIa): m.p. 190–195°, 215–220° (dec.); found C, 57.48; H, 6.04; $\lambda_{\max}^{\text{Nujol}}$ 5.87, 8.9–9.3μ.

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(1) Paper I in this series: R. E. Beyler, R. M. Moriarty, Frances Hoffman and L. H. Sarett, THIS JOURNAL, **80**, 1517 (1958).

(2) J. Fried, *Ann. N. Y. Acad. Sci.*, **61**, 573 (1955).

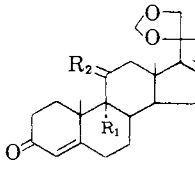
(3) E. R. H. Jones, G. D. Meakins and J. S. Stephenson, *J. Chem. Soc.*, 2156 (1958).

(4) J. Fried and E. F. Sabo, THIS JOURNAL, **79**, 1130 (1957).

This key intermediate (IIIa) was allowed to react with methylmagnesium iodide and excess methyl iodide in refluxing ether–tetrahydrofuran. The product was chromatographically separated into 9α-methylcortisone-BMD-3-dioxolane (IIIb) [m.p. 222–228°; found C, 67.85; H, 7.51; $[\alpha]^{23}\text{D}$ $-86 \pm 2°$ ($CHCl_3$); n.m.r. showed three *tertiary* C–CH_3 groups; $\lambda_{\max}^{\text{Nujol}}$ 5.86, 8.8–9.3μ; rotatory dispersion curve similar to IIIc] and cortisone-BMD-3-dioxolane (IIIc).

Reduction of IIIb with lithium aluminum hydride afforded 9α-methylhydrocortisone-BMD-3-dioxolane (IIId): m.p. 230–233°; found C, 67.61; H, 7.94; $\lambda_{\max}^{\text{Nujol}}$ 2.7, 8.8–9.2μ. The dioxolane grouping was removed using acetone-*p*-toluenesulfonic acid to give 9α-methylhydrocortisone-BMD (IIc); m.p. 295–305°; found C, 68.40; H, 8.15; $\lambda_{\max}^{\text{MeOH}}$ 244 mμ, *E* 14,800; $\lambda_{\max}^{\text{Nujol}}$ 2.7–2.9, 5.99, 6.13, 8.8–9.4μ; R_f, *ca.* 1.3 × hydrocortisone-BMD. Reversal of the BMD function with 50% acetic acid yielded 9α-methylhydrocortisone (IVa): m.p. 220–230°; found C, 70.42; H, 8.73; $\lambda_{\max}^{\text{MeOH}}$ 244 mμ, *E* 14,300; $\lambda_{\max}^{\text{Nujol}}$ 2.8, 5.80, 6.0, 6.15 μ; 21-acetate (IVb): m.p. 235–238°; found C, 69.16; H, 8.15; $\lambda_{\max}^{\text{MeOH}}$ 243 mμ, *E*, 16,500; $\lambda_{\max}^{\text{CHCl}_3}$ 2.9, 5.75, sh. 5.80, 6.04, 6.26, 8.2 μ.

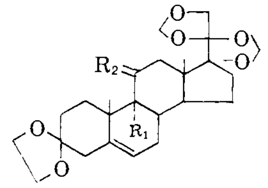
Reaction of IVb with selenium dioxide in *t*-butanol–acetic acid produced 9α-methylprednisolone 21-acetate (IVc): m.p. 220–225°; found C, 69.02; H, 7.91; $\lambda_{\max}^{\text{MeOH}}$ 245 mμ, *E* 14,000; $\lambda_{\max}^{\text{Nujol}}$ 3.0, sh. 5.75, 5.80, 6.05, 6.18, 8.05 μ.



IIa, R_1 = Br, $R_2 = \langle^{OH}_{H}$

b, R_1 = Br, R_2 = O

c, R_1 = CH_3, $R_2 = \langle^{OH}_{H}$

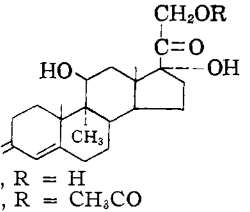


IIIa, R_1 = Br, R_2 = O

b, R_1 = CH_3, R_2 = O

c, R_1 = H, R_2 = O

d, R_1 = CH_3, $R_2 = \langle^{OH}_{H}$



IVa, R = H

b, R = CH_3CO

c, R = CH_3CO, and Δ^1 bond

In the liver glycogen test the results[5] were: IVa, about 0.1; IVb, about 0.1; IVc, about 1.6. The compounds cause slight sodium retention in adrenalectomized rats.

Acknowledgment.—The authors are indebted to Dr. L. H. Sarett for advice and encouragement during the course of this investigation.

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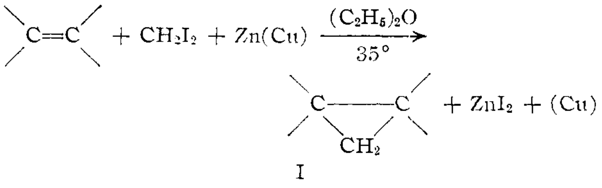
RECEIVED AUGUST 1, 1958

A NEW SYNTHESIS OF CYCLOPROPANES FROM OLEFINS

Sir:

Although the addition of a divalent carbon intermediate to carbon–carbon unsaturation would be a direct method of forming three-membered carbocyclic rings, no completely satisfactory method for the formal addition of an unsubstituted methylene group to an olefin has been recorded. We now wish to report a versatile, stereospecific synthesis of cyclopropanes of the type I by the reaction of unsaturated compounds with methylene iodide and a zinc–copper couple.



I

Thus, cyclohexene (0.30 mole), methylene iodide (0.15 mole), and zinc–copper couple[1] (0.22 mole of zinc) were stirred at reflux in anhydrous ethyl ether for 48 hours. Simple distillation gave a 48% yield of pure bicyclo[4.1.0]heptane (b.p. 116.5°, $n^{25}\text{D}$ 1.4546),[2] whose infrared spectrum was identical to that of the authentic hydrocarbon.[3] Many functionally substituted olefins have given the corresponding cyclopropanes. Yields ranged from 10–70%, depending greatly on the kind of couple employed, and in no cases were isomeric or rearranged products encountered. Thus, ethylene, cyclopentene, bicyclo[2.2.1]hept-2-ene, 3-phenylpropene, styrene and 1-(*o*-methoxyphenyl)-propene gave cyclopropane (29%), bicyclo[3.1.0]hexane (27%), tricyclo[3.2.1.0^{2,4}]octane (47%), benzylcyclopropane (49%), phenylcyclopropane (32%), and 1-(*o*-methoxyphenyl)-2-methylcyclopropane (70%), respectively. Similarly, methyl crotonate and vinyl acetate afforded methyl 2-methylcyclopropanecarboxylate and cyclopropyl acetate in yields of 9 and 31%, respectively. Conditions for optimum yields have not yet been completely determined.

Ethereal solutions obtained from the reaction of zinc–copper couple and methylene iodide are known to contain iodomethylzinc iodide.[4] It is reasonable to assume that such an intermediate would undergo displacement by the π-bond of the olefin to give a cyclopropane and zinc iodide. An alternative mechanism may involve the spontaneous elimination of zinc iodide to give a low energy methylene similar in reactivity to the dihalomethylenes described by Doering and Hoffmann.[2] Either hypothesis requires stereospecificity[5] and discrimination[2,6] in the formation of a cyclopropane. This indeed was found to be the case, for when the reaction was applied to pure

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(5) Activities are expressed relative to hydrocortisone as the reference standard. We are indebted to Dr. R. H. Silber and Dr. H. C. Stoerk of the Merck Institute for Therapeutic Research for these biological tests.

(1) F. L. Howard, *J. Research Nat. Bur. Standards*, **24**, 677 (1940).

(2) W. von E. Doering and A. K. Hoffmann, THIS JOURNAL, **76**, 6162 (1954), reported b.p. 116°, $n^{25}\text{D}$ 1.4550, for pure bicyclo[4.1.0]heptane.

(3) We are indebted to Dr. L. H. Knox, Hickrill Chemical Research Foundation, who provided us with the infrared data on pure bicyclo[4.1.0]heptane.

(4) G. Emschwiller, *Compt. rend.*, **188**, 1555 (1929).

(5) P. S. Skell and A. Y. Garner, THIS JOURNAL, **78**, 3409 (1956).

(6) W. von E. Doering and P. LaFlamme, *ibid.*, **78**, 5447 (1956).