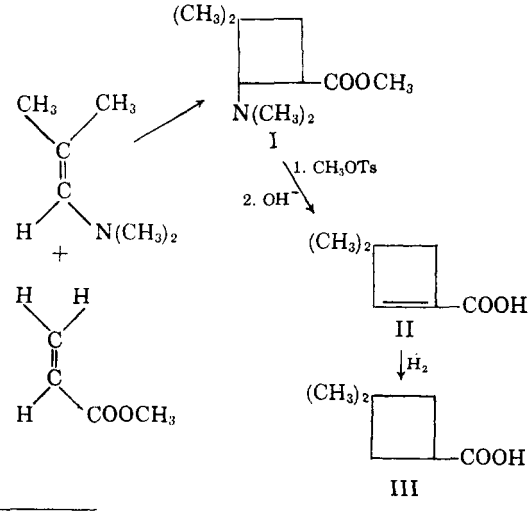
Communications TO THE EDITOR

Reactions of Isobutenylamines. I. Cyclobutane Formation

Sir:

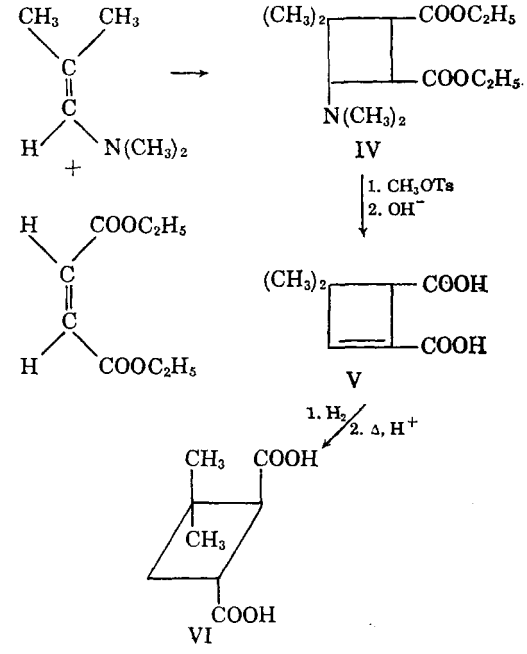
The tentative assignment of cyclobutane structures[1] to the reaction products of dimethyl maleate with enamines having no β-hydrogens prompts us to make a preliminary report of some of our work in this field. We chose as a model compound the first member of the series of enamines having no β-hydrogens: *N,N*-dimethylisobutenylamine, b.p. 87–88°, n_D^{20} 1.4221. *Anal.* Calcd. for $C_6H_{13}N$: C, 72.7; H, 13.2. Found: C, 73.0; H, 13.7. This enamine was prepared in 55% yield by reaction of isobutyraldehyde with dimethylamine in the presence of anhydrous potassium carbonate and xylene for 4 hr. at 100°.

When methyl acrylate and *N,N*-dimethylisobutenylamine were heated for 2 hr. at 170°, a 75% yield of methyl 2-dimethylamino-3,3-dimethylcyclobutanecarboxylate (I), b.p. 49–50° at 1.5 mm., n_D^{20} 1.4448, was obtained. *Anal.* Calcd. for $C_{10}H_{19}NO_2$: C, 64.8; H, 10.4. Found: C, 64.7; H 10.4. Quaternization of I with methyl tosylate followed by treatment with aqueous potassium hydroxide solution gave, after acidification, an 81% yield of 3,3-dimethyl-1-cyclobutene-1-carboxylic acid (II), m.p. (from pentane) 71.5–72.5°.[2] *Anal.* Calcd. for $C_7H_{10}O_2$: C, 66.6; H, 8.0. Found: C, 66.4; 8.0. Hydrogenation of II over palladium on alumina gave a practically quantitative yield of 3,3-dimethylcyclobutanecarboxylic acid (III), b.p. 98–99° at 9.5–10 mm., n_D^{20} 1.4363, which gave a *p*-bromophenacyl ester, m.p. 89–90°. Both the acid and its derivative were identical with authentic samples prepared by the method of Campbell and Rydon.[2]



When diethyl maleate and *N,N*-dimethylisobutenylamine were combined, a mildly exothermic reaction occurred, leading to isomerization of the maleate to the fumarate.[3] The mixture was then refluxed for 20 hr. while the temperature rose from 110° to 170°. Distillation gave diethyl 4-dimethylamino-3,3-dimethyl-1,2-cyclobutanedicarboxylate (IV), b.p. 98–99° at 0.8–0.9 mm., n_D^{20} 1.4502, in 70% yield. *Anal.* Calcd. for $C_{14}H_{25}NO_4$: C, 62.0; H, 9.3. Found: C, 61.8; H, 9.3.

Quaternization of IV with methyl tosylate followed by treatment with aqueous potassium hydroxide solution gave crude 4,4-dimethyl-2-cyclobutene-1,2-dicarboxylic acid (V) in 71% yield. After crystallization from ethyl acetate-hexane mixture, the yield was 44%, m.p. 154–155°. *Anal.* Calcd. for $C_8H_{10}O_4$: C, 56.5; H, 5.9. Found: C, 56.5; H, 6.0. Hydrogenation of V gave a mixture of *cis*- and *trans*-norcaryophyllenic acids in 98% yield, m.p. 106–115°, which was converted by heating with dilute sulfuric acid for 12 hr. at 150° to *trans*-norcaryophyllenic acid (VI), m.p. 149–150° (lit.,[4] m.p. 148–149°), in 89% yield. The



(1) A. G. Cook, doctoral dissertation, University of Illinois, 1959.

(2) A. Campbell and H. N. Rydon, *J. Chem. Soc.*, 3002 (1953), reported m.p. 54–55°.

(3) This isomerization, which was also observed by Cook (Ref. 1), does not necessarily require that the fumarate be the reacting species since equilibrium probably exists between the maleate and the fumarate.

(4) T. L. Dawson and G. R. Ramage, *J. Chem. Soc.*, 3382 (1951).

dianilide of VI melted at 239–240° (lit.,[4] m.p. 238°).

The cycloaddition of isobutenylamines with other electrophilic olefins, such as acrylonitrile and α,β-unsaturated sulfones and nitro compounds, leads to cyclobutane formation. These reactions, as well as those described above, and some of the transformations of the cyclobutanes will be described in detail at a later date.

We are grateful to Julian H. Chaudet, of these laboratories, for the determination and interpretation of the proton magnetic resonance spectra of compounds II and V. These spectra fully substantiated the assigned structures.

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Gas Chromatographic Separations of Steroids with Polyester Phases

Sir:

The separation of steroids[1] and alkaloids[2] by gas chromatographic techniques has provided a powerful new method for the study of these natural products. The successful use of the method at moderate temperatures (180–220°) depends upon the preparation of a column packing containing a relatively small amount of liquid phase (0.1–3%) coated uniformly on a solid support with an inert surface.[3] Silicone polymer SE-30 was a particularly suitable nonpolar phase.

The value of the method has now been enhanced considerably by the use of polar phases. Preliminary experiments, together with reports[4] of the behavior of thin-film columns used for other purposes, suggested that almost any polar phase could be used in the same fashion as SE-30, provided that the "bleed" rate at 180–220° was low. Five polyesters were selected for study, and columns were prepared in each case with 0.75% phase on Gas-Chrom P.[5] The results are summarized in Table I. The effect of polar phase in each case when compared with SE-30 was an increased relative (to cholestane) retention time for steroids containing polar substituent groups. The magnitude of the effect varied with the structure of the steroid and with the polyester. It is evident that a great deal of choice exists with respect to phases suitable for these separations. The NGS, NGA, and EGIP phases have a high degree of thermal stability, and

(1) (a) W. J. A. VandenHeuvel, C. C. Sweeley, and E. C. Horning, *J. Am. Chem. Soc.*, **82**, 3481 (1960) (steroids); (b) W. J. A. VandenHeuvel, C. C. Sweeley, and E. C. Horning, *Biochem. Biophys. Res. Comm.*, **3**, 33 (1960) (sex hormones and bile acids); (c) W. J. A. VandenHeuvel and E. C. Horning, *Biochem. Biophys. Res. Comm.*, **3**, 356 (1960) (adrenal cortical steroid hormones); (d) W. J. A. VandenHeuvel, C. C. Sweeley, and E. C. Horning, *Separation of Steroids by Gas Chromatography*, Symposium on Drugs Affecting Lipid Metabolism, Milan, Italy, June 2–4, 1960 (sterols and sterol esters); (e) C. C. Sweeley and E. C. Horning, *Nature*, **187**, 144 (1960) (steroids); (f) W. J. A. VandenHeuvel, E. C. Horning, Y. Sato, and N. Ikekawa, *J. Org. Chem.*, in press (steroidal amines).

(2) H. A. Lloyd, H. M. Fales, P. F. Highet, W. J. A. VandenHeuvel, and W. C. Wildman, *J. Am. Chem. Soc.*, **82**, 3791 (1960).

(3) E. C. Horning, E. A. Moscatelli, and C. C. Sweeley, *Chem. & Ind.* (London), **1959**, 751.

(4) C. Hishta, J. P. Messerly, and R. F. Reschke, Abstracts 137th A.C.S. Meeting, April, 1960, p. 29-B; C. Hishta, J. P. Messerly, R. F. Reschke, D. H. Fredericks, and W. D. Cooke, *Anal. Chem.*, **32**, 880 (1960).

(5) Applied Science Laboratories, State College, Pa.

TABLE I

RELATIVE RETENTION TIMES OF 10 STEROIDS ON COLUMNS WITH VARYING POLARITY

	Compound	NGA[a]	NGS[b]	EGA[c]	EGS[d]	EGIP[e]
1.	Androstane	0.109	0.112	0.135	0.122	0.175
2.	Androstan-17-one	0.431	0.625	0.765	0.920	0.88
3.	Androstan-3,17-dione	2.48	5.10	7.53	12.5	9.45
4.	Pregnan-3,20-dione	3.30	6.45	9.15	13.7	10.8
5.	Allopregnan-3,20-dione	3.65	7.15	10.1	15.2	12.8
6.	Cholestane	1.00	1.00	1.00	1.00	1.00
7.	Cholestanol-3-methyl ether	2.44	2.74	2.85	2.81	2.77
8.	Cholesterol	5.15	7.30	8.55	8.25	7.20
9.	Cholestan-3-one	5.12	7.05	7.87	7.85	8.38
10.	Stigmasterol	7.30	10.0	12.0	11.4	10.0
	Column size	6′ × 3 mm.	6′ × 3 mm.	6′ × 3 mm.	6′ × 3 mm.	6′ × 3 mm.
	Temp.	210	207	198	200	215
	Inlet pressure, psi.	25	25	25	30	26
	Outlet flow rate, ml./min.	120	120	60	70	65
	Support, mesh	100–140	100–140	140–200	140–200	140–200
	Cholestane time, min.	8.1	4.8	3.5	2.9	3.5

[a] Neopentyl glycol adipate. [b] Neopentyl glycol succinate. We are indebted to Dr. Joseph Corse, Western Regional Research and Utilization Laboratory, Albany, Calif., for a sample of this polyester. [c] Ethylene glycol adipate. [d] Ethylene glycol succinate. [e] Ethylene glycol isophthalate.[1e]