TABLE I

SUBSTITUTED ALKYLTHIOUREAS, RNHCNHR′ (‖ S)

R	R′	Method of preparation	Yield, %	M.P., °C.	Analyses Nitrogen Calc'd	Found
$C_{12}H_{25}$	H	A	45	103–103.8[a]	—	—
$C_{12}H_{25}$	CH_3	B	99	68–69	10.84	10.64
$C_{12}H_{25}$	C_2H_5	B	96	55–56	10.28	10.10
$C_{12}H_{25}$	C_4H_9	B	96	61–63	9.33	9.11
$C_{12}H_{25}$	$C_{12}H_{25}$	C	93	77–78[b]	—	—
$C_{12}H_{25}$	CH_2=$CHCH_2$	B	53	56–57.5	9.85	9.72
$C_{12}H_{25}$	C_6H_5	B	79	72–76[c]	—	—
$C_{18}H_{37}$	H	A	73	114.5–115.5	8.53[d]	8.76
$C_{18}H_{37}$	CH_2=$CHCH_2$	B	82	79–80.5	7.60	7.39
$C_{18}H_{37}$	C_6H_5	B	79	84–85	6.92	6.75

[a] Reported: m.p. 104–106°,[6] 106–107°.[4] [b] Reported: m.p. 69–70°,[4] 74.5–75°,[8] 76–78°.[6] [c] Reported: m.p. 69.5–69.8°,[8] 73–76°.[6] [d] *Anal.* Calc'd: C, 69.43; H, 12.27. Found: C, 68.89; H, 12.14.

amine (two moles) in toluene. The mixture is heated on the steam-bath overnight, cooled, and filtered to yield the dialkylthiourea.

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The Preparation of Secondary Aliphatic Amines from Schiff Bases Using Lithium Aluminum Hydride

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The preparation of unsymmetrical aliphatic secondary amines from the corresponding Schiff bases by catalytic hydrogenation[1,2] and by reduction with sodium and alcohol[3] has been described.

We have found that comparable yields of these amines are obtained more conveniently by the use of lithium aluminum hydride, which has been reported to reduce also aromatic[4] and alicyclic[5] Schiff bases. This method does not require a hydrogenation apparatus, and the product is easily purified by distillation of an ether filtrate after careful hydrolysis of the reaction measure. A recent paper[6] indicates that sodium borohydride may be equal or superior to lithium aluminum hydride in effecting such reductions as those described here.

The secondary amines which were prepared are listed in Table I, together with the primary amines from which they were derived and the yields which were obtained in single experiments.

TABLE I

ALIPHATIC SECONDARY AMINES

Amine	Source	Yield, %
Methylbutyl[a]	Methylamine	55
Ethylpropyl	Propylamine	46
Propylbutyl	Propylamine	79
Propylisobutyl	Propylamine	71
Isopropylbutyl	Isopropylamine	72
Isopropylisobutyl[b]	Isopropylamine	78

[a] *α-Naphthylthiourea derivative*, m.p. 104°. *Anal.* Calc'd for $C_{16}H_{20}N_2S$: N, 10.29; Found: N, 10.31. [b] B.p. 110–111°, n_D^{25} 1.3993. *Anal.* Calc'd for $C_7H_{17}N$: N, 12.16; Found: N, 12.24. *α-Naphthylthiourea derivative*, m.p. 110°. *Anal.* Calc'd for $C_{18}H_{24}N_2S$: N, 9.33; Found: N, 9.38. British Patent 602,332, May 25, 1948, gives b.p. 109–112° for this compound prepared by catalytic hydrogenation of a mixture of acetone and isobutylamine.

EXPERIMENTAL

Schiff bases. These were prepared by the method described earlier.[2] Isopropylideneisobutylamine and butylidenemethylamine, which was prepared using 30% aqueous methylamine,[7] have been reported by Tiollais.[3] The Schiff bases were reduced immediately after distillation.

Secondary amines. The aldimine (0.3 mole) was added during one hour to a stirred solution of 11.4 g. (0.3 mole) of lithium aluminum hydride in 500 ml. of anhydrous ether under nitrogen. After another hour the mixture was hy-

(1) Henze and Humphreys, *J. Am. Chem. Soc.*, **64**, 2878 (1942).
(2) Campbell, Sommers, and Campbell, *J. Am. Chem. Soc.*, **66**, 82 (1944).
(3) Tiollais, *Bull. soc. chim. France*, 959 (1947).
(4) Nystrom and Brown, *J. Am. Chem. Soc.*, **70**, 3738 (1948); Bergmann, Lavie, and Pinchas, *J. Am. Chem. Soc.*, **73**, 5662 (1951); Stühmer and Messwarb, *Arch. Pharm.*, **236**, 19 (1953); Tai, *Dissertation Abstrs.*, **13**, 477 (1953); *Chem. Abstr.*, **47**, 12219 (1953); Castle, Aldous, and Hall, *J. Am. Pharm. Assoc.*, **42**, 435 (1953); Boothroyd and Clark, *J. Chem. Soc.*, 1499 (1953).
(5) Mousseron, Jacquier, Mousseron-Canet, and Zagdoun, *Bull. soc. chim. France*, 1042 (1952).
(6) Horii, Sakai, and Inoi, *J. Pharm. Soc. Japan*, **75**, 1161 (1955).
(7) Patrick, *J. Am. Chem. Soc.*, **74**, 2984 (1952).

drolyzed by the cautious addition of 23 ml. of water, and the milky suspension was allowed to stand overnight. It was filtered and the filtrate, including ether washings, was distilled through a 6-cm. head packed with glass helices. The boiling ranges and indices of refraction of the amines agreed with earlier values.

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Studies on Sarkomycin. Reaction with Diazomethane

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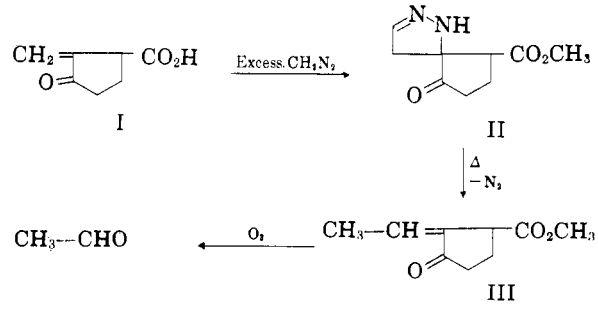
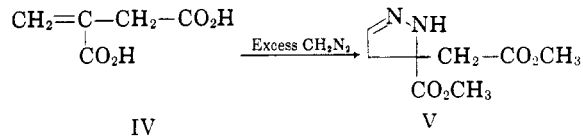
The active principle of sarkomycin, an antibiotic with suppressive action on the Ehrlich ascites tumor in mice, has been formulated as 2-methylene-3-oxocyclopentanecarboxylic acid, I.[1] We now wish to report additional experiments which are consistent with the proposed structure.

Treatment of sarkomycin with an excess of diazomethane gave a dark oil, the significant component of which appeared to be the pyrazoline ester, II. From this oil a crystalline hydrochloride was prepared, which gave an analysis in agreement with $C_9H_{12}N_2O_3 \cdot HCl$. On heating the oil to 110°, a sudden and rapid evolution of nitrogen occurred, following which an ester, III, could be distilled *in vacuo*. The analyses of this ester and its 2,4-dinitrophenylhydrazone indicated a formula of $C_9H_{12}O_3$ for III. An infrared peak at 6.1μ, similar to but sharper than that present in I[1] showed the presence of the carbon-carbon double bond. Ozonolysis of III yielded acetaldehyde, while ozonolysis of I yielded formaldehyde,[1] proving an over-all homologation at the methylene carbon.



Analogous additions of diazomethane to carbon-carbon bonds to give pyrazolines have been reported in several instances. For example, α-methylene-γ-phenyl-γ-butyrolactone has been shown to add diazomethane such that the carbon of the diazomethane becomes attached to the methylene carbon.[2] Aconic acid is first esterified, then converted to a pyrazoline by excess diazomethane.[3] This pyrazoline loses nitrogen to form the homolog of methyl aconate. We found that itaconic acid, IV, reacted with more diazomethane than was required for esterification of the two acid groups, giving a pyrazoline postulated as V by analogy with the foregoing facts. This pyrazoline did not lose nitrogen on heating up to 145°.



The authors are indebted to Dr. I. R. Hooper and his colleagues for supplying sarkomycin concentrates, and to Dr. L. C. Cheney for advice throughout this work.

EXPERIMENTAL[4]

Reaction of I with diazomethane. Fourteen liters of a Magnesol-treated methyl isobutyl ketone concentrate[1] containing a total of approximately 60 g. of sarkomycin acid were extracted with two 3.5-liter portions of water at *p*H 6.0. The aqueous extracts were concentrated slightly in a flash evaporator to remove dissolved methyl isobutyl ketone, then acidified to *p*H 3.0 with phosphoric acid. Extraction of the aqueous phase with one $^1/_5$-volume of ether followed by eight $^1/_{10}$-volumes of ether gave a total extract of about six liters, which was dried over sodium sulfate. The next day the ether solution was decanted and divided into two equal parts for esterification. Each portion was added dropwise to an ice-cold, stirred solution of diazomethane which had been prepared from 51.5 g. (0.5 mole) of N-nitrosomethylurea. After standing overnight while warming to room temperature, the two portions were combined and the solvent was distilled under reduced pressure. There remained 60 g. of dark, rather viscous oil, the crude pyrazoline ester.

Pyrazoline hydrochloride (II·HCl). The crude pyrazoline ester (2 g.) was dissolved in ether and excess dry hydrogen chloride was bubbled in. A red oil separated, from which 0.19 g. of crystalline material was obtained on disolution in *n*-butanol and dilution with ether. Several recrystallizations from methanol-ether gave pale orange crystals, m.p. 126–127° (gas evolution).

Anal. Calc'd for $C_9H_{12}N_2O_3 \cdot HCl$: C, 46.4; H, 5.6; N, 12.0; Cl, 15.2. Found: C, 46.4; H, 5.6; N, 12.5; Cl, 15.5.

Methyl 2-ethylidene-3-oxocyclopentanecarboxylate (III). Approximately 24 g. of crude pyrazoline ester was placed in a distilling flask and heated slowly to 110°. At this temperature, a vigorous evolution of nitrogen occurred. When this reaction had subsided, the material was vacuum-distilled. There was obtained 5.3 g. of III as a light yellow oil, b.p. 73–78° at 1.5 mm.

Anal. Calc'd for $C_9H_{12}O_3$: C, 64.3; H, 7.2. Found: C, 63.8; H, 7.3.

(1) Hooper, *et al.*, *Antibiotics and Chemotherapy*, **5**, 585 (1955).

(2) van Tamelen and Bach, *J. Am. Chem. Soc.*, **77**, 4683 (1955).

(3) Rekker, Brombacher, and Nauta, *Rec. trav. chim.*, **73**, 417 (1954).

(4) Melting points and boiling points are uncorrected. Analyses are by Mr. R. M. Downing; infrared data by Dr. F. M. Palermiti.