TABLE I

ALKAMINE ETHERS, $ArO(CH_2)_2O(CH_2)_2NR_2$

No.	Compound Structural formula Ar	NR_2	Time, hr.	Method	Yield, %	B.p. °C.	Mm.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1	$2\text{-}C_6H_5C_6H_4$	$N(CH_3)CH_2C_6H_5$	4.5	B	[e]	218–220	1.0	$C_{24}H_{27}NO_2$	79.74	79.69	7.53	7.25
2	$2\text{-}C_6H_5C_6H_4$	$N(C_2H_5)CH_2C_6H_5$	24	A	[e]	210–211	0.45	$C_{25}H_{29}NO_2$	79.97	79.86	7.78	7.59
3	$4\text{-}CH_3C_6H_4$	$C_5H_{10}N$[a]	24	A	30	171	2.6	$C_{16}H_{25}NO_2$	72.97	72.77	9.57	9.48
4	$4\text{-}CH_3C_6H_4$	$C_6H_{12}N$[b]	24	A	39	180–181	3.1	$C_{17}H_{27}NO_2$	73.60	73.85	9.81	9.79
5	$4\text{-}CH_3C_6H_4$	$C_6H_{12}NS$[c]	24	A	57.5	190–191	1.1	$C_{17}H_{27}NO_2S$	65.98	66.17	8.79	8.67
6	$4\text{-}CH_3C_6H_4$	$N(C_4H_9)_2$	24	A	[e]	191–192	4.4	$C_{19}H_{33}NO_2$	74.22	74.36	10.82	10.56
7	$4\text{-}CH_3C_6H_4$	$NHCH_2CH(CH_3)_2$	24	A	14	156–158	2.4	$C_{15}H_{25}NO_2$	71.67	71.91	10.03	9.81
8	$4\text{-}CH_3C_6H_4$	$NH(CH_2)_4CH_3$	24	A	20	175	2.9	$C_{16}H_{27}NO_2$	72.41	73.03[d]	10.25	10.13[d]
9	$4\text{-}CH_3OC_6H_4$	$N(CH_3)CH_2C_6H_5$	3.5	B	[e]	204–205	1.4	$C_{19}H_{25}NO_3$	72.35	72.68[d]	7.99	8.05[d]

[a] 1-Piperidyl radical. [b] 2-Methyl-1-piperidyl radical. [c] 2,6-Dimethyl-4-thiomorpholinyl radical. [d] Average of two analyses. [e] Obtained in low yield.

The benzalethylimine prepared by the method of Cromwell[3,4] was obtained in 75% yield. The imine, boiling point 84–88° (10 mm.), $n^{26}D$ 1.5365, was hydrogenated at 1025 p.s.i. (80°) with Raney nickel for 1.5 hours in the absence of a solvent by G. R. Stone and Morris Freifelder. The N-ethylbenzylamine, b.p. 195–200° (747 mm.), n_D^{25} 1.5090, was obtained in 75% yield.[5]

(3) N. H. Cromwell, THIS JOURNAL, **65**, 313 (1943).

(4) H. Zaunschirm, *Ann.*, **245**, 279 (1888).

(5) (a) A. Mailke, *Bull. soc. chim.*, [4] **25**, 322 (1919); (b) O. Wallach, *Ann.*, **343**, 73 (1905); (c) F. Kraft, *Ber.*, **23**, 278 (1890).

Anal. Calcd. for $C_9H_{13}N$: C, 79.95; H, 9.69. Found: C, 80.22; H, 9.54.

All of the ethers in Table I were prepared by Method A or B described in paper II.[1b]

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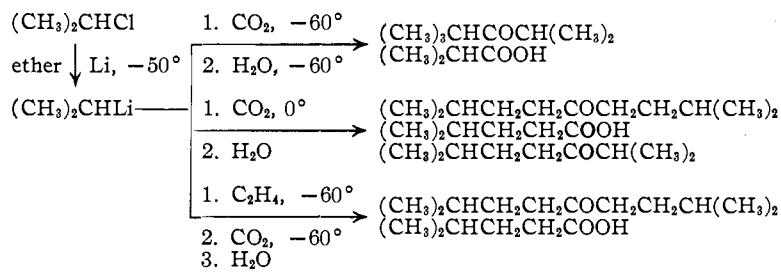
ABBOTT LABORATORIES
NORTH CHICAGO, ILLINOIS

COMMUNICATIONS TO THE EDITOR

THE REACTION OF ISOPROPYLLITHIUM AND *t*-BUTYLLITHIUM WITH SIMPLE OLEFINS

Sir:

Isopropyllithium[1] and *t*-butyllithium[2] are advantageously manipulated in ether, being much more readily prepared in this solvent than in hydrocarbons. However, they show in enhanced degree the well known tendency of organolithium compounds to decompose ether.[3,4,5,6,7,8] When isopropyllithium is prepared and carbonated in ether at temperatures below −50°, hydrolysis of the resulting solution yields the normal products, diisopropyl ketone and some isobutyric acid. When however, a solution of isopropyllithium from one mole of isopropyl chloride was allowed to warm to room temperature, a reaction was observed which caused the ether to boil, and subsequent carbonation yielded only *diisoamyl ketone* (0.25 mole, b.p. 87° (8 mm.); calcd. for $C_{11}H_{22}O$: C, 77.78, H, 13.01; found: C, 77.80, H, 13.13) and 0.05 mole of isocaproic acid. Since these products could be formed only by the addition of isopropyllithium to ethylene (resulting from decomposition of ether), an experiment was performed in which ethylene was bubbled at −60° through a solution of isopropyllithium prepared at −50°. The ethylene was readily absorbed. This solution was carbonated without allowing the temperature to rise. Hydrolysis yielded diisoamyl ketone in addition to a smaller acid fraction and residue. The diisoamyl ketone (2,4-dinitrophenylhydrazone, m.p. 53.5–54°) was identified by Beckmann degradation to isoamylamine (phenylthiourea, m.p. 105–105.5°; no depression on mixture with an authentic specimen, m.p. 104–105°)[9] and isocaproic acid (anilide, m.p. 110.5–111°; *p*-phenylphenacyl ester, m.p. 70°), and by synthesis from isoamyl chloride by carbonation of the lithium derivative.



It is clear from these experiments that iso-

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(2) P. D. Bartlett, C. G. Swain and R. B. Woodward, THIS JOURNAL, **63**, 3229 (1941).

(3) K. Ziegler and A. Colonius, *Ann.*, **479**, 135 (1930).

(4) A. Luttringhaus and G. von Saaf, *Angew. Chem.*, **51**, 915 (1938); *Ann.*, **557**, 25 (1947).

(5) A. Haubein, *Iowa State Coll. J. Sci.*, **18**, 48 (1943); *C.A.*, **38**, 716 (1944).

(6) H. Gilman and R. N. Clark, THIS JOURNAL, **69**, 1499 (1947).

(7) K. Ziegler and H. G. Gellert, *Ann.*, **567**, 185 (1950).

(8) R. L. Letsinger, A. W. Schnizer and E. Bobko, THIS JOURNAL, **73**, 5708 (1951).

(9) The melting point is given as 101–102° by M. L. Willard and M. Z. Jones, *ibid.*, **62**, 2876 (1940).

propyllithium is far more reactive toward the unsubstituted carbon-carbon double bond than any known primary organometallic reagent, and that this high reactivity disappears as soon as, by addition of one ethylene molecule, the secondary organolithium reagent has been converted into a primary one. Since the addition reaction is almost certainly of polar type, this difference in reactivity must be associated with the higher anionic instability and nucleophilic tendency of an isopropyl group as compared with an ethyl or other primary group.

We are at present exploring the implications of these observations. The behavior of *t*-butyllithium is parallel to that of isopropyllithium: it can be handled in ether without attack upon this solvent at temperatures of -40 to $-50°$; it adds ethylene readily to give neohexyllithium, which can be carbonated to dineohexyl ketone, b.p. 230–235° (2,4-dinitrophenylhydrazone, m.p. 148–149°; calcd. for $C_{19}H_{30}N_4O_4$: C, 60.3; H, 7.99; N, 14.82; found: C, 60.12; H, 7.97; N, 14.92). Solutions of isopropyl and *t*-butyl lithiums when carbonated at intermediate temperatures (about 0° for isopropyl and $-25°$ for *t*-butyl) yield, in addition to the symmetrical isoamyl and neohexyl ketones, the unsymmetrical products, isopropyl isoamyl ketone (b.p. 171°, 2,4-dinitrophenylhydrazone, m.p. 81.5–82°; calcd. for $C_{15}H_{22}N_4O_4$: C, 55.9; H, 6.88; N, 17.39; found: C, 55.57; H, 6.84; N, 16.76) and *t*-butyl neohexyl ketone (2,4-dinitrophenylhydrazone, m.p. 130–131°; oxime, m.p. 113.5–114.5°; calcd. for $C_{11}H_{23}ON$: C, 71.35; H, 12.54; N, 7.57; found: C, 71.67; H, 12.54; N, 7.51), respectively.

If unsymmetrically substituted ethylenes were to react by addition with branched organolithium reagents, a polar mechanism might be expected to lead to a product having the lithium on the primary carbon atom. When isopropyllithium was stirred for twenty-four hours with propylene in ether below $-30°$ and the product then carbonated, a small amount of acidic material was isolated with a neutral equivalent of 308. The polymeric character of this acid suggests that the addition product is a secondary alkyl lithium with a reactivity toward olefins comparable to that of isopropyllithium itself, and that the orientation of the addition is dominated by steric factors rather than polar ones.

CONVERSE MEMORIAL LABORATORY PAUL D. BARTLETT
HARVARD UNIVERSITY SIDNEY FRIEDMAN
CAMBRIDGE 38, MASSACHUSETTS MARTIN STILES

RECEIVED MARCH 9, 1953

AN INTERMEDIATE OF THE ENZYMATIC DEGRADATION OF HISTIDINE[1]

Sir:

We wish to report the isolation of a crystalline compound with the properties of α-formamidinoglutaric acid from digests of L-histidine or urocanic acid with cat liver extracts.

(1) This work was supported in part by grants from the Rockefeller Foundation, and from the National Institute of Neurological Disease and Blindness (Grant B-226) of the National Institute of Health, Public Health Service, and by a contract between the Office of Naval Research and the Psychiatric Institute. Taken from the doctoral dissertation of Blanche A. Borek.

In a representative experiment 5 g. of L-histidine·HCl·H_2O was incubated with 1 l. of a phosphate extract of cat liver (15 mg. protein/ml.) at *p*H 8.4 at 38°. After 24 hours all the histidine had disappeared (Pauly reaction) with the liberation of one equivalent of free ammonia. A second equivalent of ammonia was liberated upon digestion of the solution with 3 *N* NaOH. After removal of protein by trichloroacetic acid the intermediate was precipitated at *p*H 6 as mercuric salt. This was collected by centrifugation and decomposed with hydrogen sulfide. Free ammonia and traces of unreacted histidine were removed by adsorption on permutit and the intermediate reprecipitated as the mercuric salt. This was decomposed with hydrogen sulfide; the filtrate was lyophilized and the residue taken up in absolute ethanol. Upon concentration of the alcoholic solution colorless crystals of the intermediate separated (yield 1.8 g., 45%). The substance is very hygroscopic and melts at 80 to 87°. *Anal.* Calcd. for $C_6H_{10}N_2O_4 \cdot H_2O$: C, 37.5; H, 6.3; N, 14.6; alkali-labile ammonia, 7.3. Found, sample I: C, 37.5; H, 6.5; N, 14.0; sample II: C, 39.6; H, 6.7; N, 14.1; alkali-labile ammonia, 7.0. Mercury salt: Calcd. for $C_6H_{10}N_2O_6Hg_2$; C, 11.9; H, 1.7; N, 4.6; Hg, 66.0. Found: C, 11.6; H, 1.5; N, 4.7; Hg, 67.0; pK'_1 2.4, pK'_2 4.7, pK'_3 11.1. Upon alkaline or acid hydrolysis, respectively, 1 mole of ammonia and 1 mole of formic acid were liberated; 0.8 mole of L-glutamic acid was isolated from the hydrolysate of the intermediate by HCl.

The properties of the intermediate correspond best to the structure of α-formamidinoglutaric acid, a compound which has been postulated as the intermediate of enzymatic histidine breakdown on the basis of the appearance of a second ionizing group in an enzymatic digest of histidine[2] in conjunction with other evidence accumulated by Edlbacher and associates.[3]

Since Sera, *et al.*,[4] and Oyamada[5] have claimed the isolation from enzymatic digests of histidine of N-formylisoglutamine this compound was synthesized by formylation[6] of L-glutamic acid-γ-benzyl ester[7] and conversion of the formylated benzyl ester into the amide by the procedure of Boissonas.[8] The benzyl group was removed by catalytic hydrogenation. N-Formyl-L-isoglutamine differed from the intermediate isolated by us not only in its solubility and the number of ionizing groups but also in its greater stability toward hydrolysis. Furthermore, the intermediate was degraded by extracts of *Pseudomonas fluorescens* at a rapid rate whereas N-formyl-L-isoglutamine was not attacked. However, it is conceivable that the intermediate was converted to N-formylisoglutamine under the conditions of isolation employed by the Japanese investigators or that guinea

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