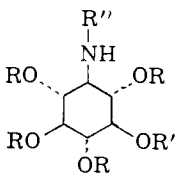
1140–960, 850, and 760 cm.$^{-1}$, and no ultraviolet absorption. Functional group determination and n.m.r. spectrum indicated one C-CH_3 and one N-CH_3 group, the latter assignable to the titrable base. Methanolysis of bluensomycin hydrochloride in anhydrous *N* methanolic hydrogen chloride at room temperature was shown by paper chromatography to result in the cleavage of the molecule into two parts. Carbon chromatography of the reaction mixture gave, by elution with water, a strong base designated bluensidine and, by elution with 10% acetone, the remainder of the molecule as a larger fragment, which is discussed in a subsequent communication.[3] In this paper I is presented as the structure for bluensidine. Bluensidine (I) was isolated as its hydrochloride, $C_8H_{16}N_4O_6 \cdot HCl$, m.p. 190–194° (dec.), $[\alpha]^{24}D$ + 0.5 to 1.5° (*c*, 1, water). The presence of a guanidino group in I was suggested by the strong basic properties, the positive Sakaguchi test and the presence of an absorption band at 1670 cm.$^{-1}$ in the infrared spectrum. In addition to the 1670 cm.$^{-1}$ absorption, the infrared spectrum showed carbonyl absorption at 1710 cm.$^{-1}$ and bands at 3500–3300 cm.$^{-1}$, indicative of the presence of hydroxyl or amino hydrogen. Hydrolysis of I under reflux with saturated barium hydroxide for 18 hr., gave two moles of carbon dioxide



I, R = H, R′ = –$CONH_2$, R″ = –C(=NH)–NH_2

II, R = R′ = R″ = H

III, R = R′ = R″ = –$COCH_3$

IV, R = R′ = H, R″ = –$COCH_3$

V, R = R′ = H, R″ = –$CONH_2$

VI, R = R′ = H, R″ = –C(=NH)–NH_2

VII, R = –$COCH_3$, R′ = –$CONH_2$, R″ = –C(=N$COCH_3$)–NH$COCH_3$

(isolated as barium carbonate), three moles of ammonia, and an optically inactive base (II), pK_a′ 7.5 (water), crystalline as its hydrochloride $C_6H_{13}NO_5 \cdot HCl$, which darkens at 265° but does not melt below 300°. Van Slyke nitrogen determination indicated one primary amino group. The base (II) consumed 6 moles of periodate per mole with no formation of formaldehyde. These data point to an amino-pentahydroxycyclohexane structure for II. The lack of infrared absorption in the 900–800 cm.$^{-1}$ region suggested[4] the all-*trans* configuration, *i.e.*, the identity of II to *scyllo*-inosamine. This was confirmed by comparison[5] of the hexaacetyl (III) and the N-acetyl (IV) derivatives of II to authentic samples[6] of hexaacetyl-*scyllo*-inosamine and N-acetyl-*scyllo*-inosamine respectively.[7,8] Mild alkaline hydrolysis of I gave two moles of ammonia, one mole of carbon dioxide and an optically inactive, neutral crystalline compound, bluensurea (V), $C_7H_{14}N_2O_6$, m.p. 244–245° (dec.). Strong alkaline hydrolysis of V afforded II together with one mole of carbon dioxide and one mole of ammonia. Acid hydrolysis of I gave one mole each of carbon dioxide and ammonia plus an optically inactive strong base (VI) isolated as its crystalline hydrochloride, $C_7H_{15}N_3O_5 \cdot HCl$, m.p. 228–230° (dec.). The infrared absorption at 1710 cm.$^{-1}$ was absent in both V and VI. Only VI gave a positive Sakaguchi test. Strong alkaline hydrolysis of VI afforded II with the formation of one mole of carbon dioxide and two moles of ammonia, and VI can thus be formulated as 1-deoxy-1-guanidino-*scyllo*-inositol. The degradation of I to VI with the simultaneous formation of one mole of carbon dioxide and one mole of ammonia, when considered with the 1710 cm.$^{-1}$ absorption, suggests the presence of a primary carbamoyl group in I. Hence, I is a guanidino-O-carbamoyl-*scyllo*-inositol. In confirmation of this structure, acetylation of I in acetic anhydride and pyridine afforded a crystalline hexaacetyl derivative, $C_{20}H_{28}N_4O_{12}$ (VII), m.p. 250–251° (dec.), $[\alpha]^{25}D$ + 5° (*c*, 0.9, chloroform), which had carbonyl absorption at 1710 cm.$^{-1}$ in addition to the ester carbonyl absorption at 1740 cm.$^{-1}$. Ammonolysis of VII in methanol afforded I. The n.m.r. spectrum[9,10] of VII showed four types of hydrogens. A broad multiplet at 780 c.p.s. of area 1 and a doublet at 551, 542 c.p.s. of total area 1 correspond to the hydrogens on N^3 and N^1 of the guanidino group. A complex multiplet at 345–275 c.p.s. of area 8 corresponds to the six ring hydrogens plus the two carbamoyl hydrogens.[11] Finally, five peaks at 128, 125, 122, 121 and 117 c.p.s. of total area 18 correspond to the 6 C-CH_3 of the acetyl groups. Aside from considerations of absolute stereochemistry, the only possible isomers of I are those having the guanidino and the carbamoyl group 1,2-, 1,3- or 1,4 to each other. From symmetry considerations, the optical activities of I and VII exclude the 1,4 arrangement. That bluensidine is 1-deoxy-1-guanidino-3-O-carbamoyl-*scyllo*-inositol was shown by periodate oxidation studies, in which I consumed 2 moles of periodate per mole, forming 1 mole of formic acid. Only the 1,3 arrangement is consistent with this, establishing I as the structure of bluensidine. The problem of determining the absolute configuration in bluensidine is under study and will be the subject of a future communication.

Acknowledgment.—The authors are grateful to Dr. Ross R. Herr for helpful discussions, to Dr. R. W. Rinehart and associates for analyses, to Mr. Dennis T. Weber for titration and to Mr. K. J. Geipel for technical assistance.

(3) B. Bannister and A. D. Argoudelis, *J. Am. Chem. Soc.*, **85**, Jan. 20 (1963).

(4) S. A. Barker, E. J. Bourne, R. Stephens, and D. H. Whiffen, *J. Chem. Soc.*, 4211 (1954).

(5) Melting points, mixed melting points, infrared spectra and X-ray powder patterns.

(6) We are grateful to Dr. Laurens Anderson, Department of Biochemistry, University of Wisconsin, Madison, Wisconsin, for the samples of hexaacetyl-*scyllo*-inosamine and N-acetyl-*scyllo*-inosamine.

(7) L. Anderson and H. A. Lardy, *J. Am. Chem. Soc.*, **72**, 3141 (1950).

(8) H. E. Carter, R. K. Clark, Jr., B. Lytle, and G. E. McCasland, *J. Biol. Chem.*, **175**, 683 (1948).

(9) We are thankful to Dr. George Slomp of The Upjohn Company, Kalamazoo, Michigan, for the interpretation of the n.m.r. spectra.

(10) N.m.r. spectra were observed on a Varian A-60 spectrometer on solutions of the samples in $CDCl_3$. The spectra were calibrated downfield from tetramethylsilane (as zero).

(11) As shown by the n.m.r. spectrum of *n*-butyl carbamate.

RESEARCH LABORATORIES
THE UPJOHN COMPANY — B. BANNISTER
KALAMAZOO, MICHIGAN — A. D. ARGOUDELIS

RECEIVED NOVEMBER 30, 1962

SYNTHESIS AND STRUCTURE OF STEROIDAL 4-PREGNENO[3,2-*c*]PYRAZOLES. A NOVEL CLASS OF POTENT ANTI-INFLAMMATORY STEROIDS

Sir:

It is known that a C-3 oxygen is not required for androgenic, anabolic or progestational activity.[1,2,3] On the other hand, no potent anti-inflammatory agent has been described which lacks a C-3 oxygen.[4] For

(1) See, for instance M. S. de Winter, C. M. Siegman and S. A. Szpilfogel, *Chem. and Ind.*, 905 (1959); Z. Madjerek, J. de Visser, J. Vander and G. A. Overbeek, *Acta Endoc.*, **35**, 8 (1960).

(2) R. O. Clinton, A. J. Manson, F. W. Stonner, R. G. Christiansen, A. L. Beyler, G. O. Potts and A. Arnold, *J. Org. Chem.*, **26**, 279 (1961).

(3) J. A. Zderic, O. Halpern, H. Carpio, A. Ruiz, D. C. Limon, L. Magana, H. Jimenez, A. Bowers and H. J. Ringold, *Chem. and Ind.*, 1625 (1960).

(4) E. W. Boland, *Am. J. Med.*, **31**, 581 (1961). Indeed a C-3 ketone seemed to be required for glucocorticoid activity. The orally active 3-enol

example the [2,3-*d*]isoxazoles of cortisone[3] and of 16α-methylcortisol[5] are inactive. Very recently R. O. Clinton and his co-workers[6] have described active [3,2-*c*]pyrazoles of androstanes, 19-nor-androstanes and their unsaturated analogs. We wish to report the surprising observation that certain pyrazole derivatives, particularly 2′-phenyl and 2′-*p*-fluorophenylpyrazoles, greatly increase activity in the anti-inflammatory series.

17α,20;20,21-Bismethylenedioxy-9α-fluoro-16α-methyl-4-pregnene-3,11-dione (BMD of 9α-fluoro-16α-methylcortisone) (I), m.p. 262–265°; afforded, after treatment with ethyl formate and sodium hydride in benzene the 2-hydroxymethylene derivative II, m.p. 221–224°; λ_{max} 239 mμ[7] (log ϵ 4.29), 359.5 mμ (4.08); and III, the 5-pregnene isomer of I, m.p. 227–231°; no selective absorption in the ultraviolet in methanol; λ_{max} 5.81 μ; λ_{max} 235 mμ.[7] Refluxing II with ethanolic hydrazine gave 17α,20;20,21-bismethylenedioxy - 11 - oxo - 9α - fluoro - 16α - methyl - 4-pregneno[3,2-*c*]pyrazole (IV), dec. above 300°; λ_{max}^{MeOH} 260 mμ (log ϵ 4.0); and thence the 11β-hydroxy compound V, which was characterized as a hydrochloride,[8a] dec. *ca.* 240°; λ_{max}^{MeOH} 267 mμ (log ϵ 4.02); and converted with hot aqueous formic acid into 11β,17α,21-trihydroxy - 9α - fluoro - 16α - methyl - 20 - oxo - 4 - pregneno[3,2-*c*]pyrazole (VI), characterized as a hydrochloride, dec. above 300° with extensive previous darkening; λ_{max}^{Nj} 3–4.5, 5.87–5.91 μ. Condensation of II with *p*-fluorophenylhydrazine gave the 2′-*p*-fluorophenylpyrazole VII, m.p. 279.8–281°; λ_{max}^{MeOH} 261 mμ (log ϵ 4.20); which was reduced and then treated with dilute formic acid to give 11β,17α,21-trihydroxy-9α-fluoro-16α-methyl-20-oxo-2′-*p*-fluorophenyl-4-pregneno[3,2-*c*]pyrazole, characterized as the 21-acetate, VIII, m.p. 241–243°; λ_{max}^{MeOH} 260 mμ (log ϵ 4.19). The BMD of 16α-methylcortisol (IX), m.p. 277–279°; led to the 2-hydroxymethylene derivative X, m.p. 197–200°; λ_{max} 242.5 mμ[7] (log ϵ 4.20), 356 mμ (4.02). The latter, on treatment with hydrazine, yielded the pyrazole XI, m.p. 195–197°; λ_{max} 261 mμ (log ϵ 4.01); and with phenylhydrazine the 2′-phenylpyrazole XII, m.p. 260–260.5°; $[\alpha]^{25}D$ +25° ($CHCl_3$); λ_{max} 261 mμ (log ϵ 4.23). Acid hydrolysis of XII gave XIII, characterized as a hydrochloride,[8b] m.p. 143–145°. Similarly, condensation of X with *p*-fluorophenylhydrazine gave XIV, m.p. 154.5–155.5°; $[\alpha]^{25}D$ +38° ($CHCl_3$); λ_{max}^{MeOH} 261.5 mμ (log ϵ 4.20); which was converted into the 21-acetate XV, m.p. 186–188°.

The 2′-aryl structure assignments rest upon the following evidence: The BMD of the 2-methoxymethylene[9] derivative of 16α-methylcortisol (XVI),[8c] (obtained from IX with methanolic hydrochloric acid), dec. 257°; λ_{max}^{MeOH} 255 mμ (log ϵ 4.10), 298 mμ (3.94); was allowed to react with ethanolic phenylhydrazine at room temperature overnight and then with added acetic acid for four hours to give a mixture of XII and the isomeric 1′-phenylpyrazole (XVII), m.p. 223–224°; λ_{max}^{MeOH} 298 mμ (log ϵ 4.50). Formic acid hydrolysis of XVII gave XVIII, m.p. 209–211°; $[\alpha]^{24}D$ +61° ($CHCl_3$); λ_{max}^{MeOH} 298 mμ (log ϵ 4.50). We attribute the spectral differences between XII and XVII to steric inhibition of resonance between phenyl hydrogens and the C-4 hydrogen in XII.[10]

Condensation of X with methylhydrazine afforded a mixture of 17α,20;20,21-bismethylenedioxy-11β-hydroxy - 2′,16α - dimethyl - 4 - pregneno[3,2 - *c*]pyrazole (XXVII), m.p. 259–260°; $[\alpha]^{25}D$ +34° ($CHCl_3$); λ_{max}^{MeOH} 277.5 mμ (log ϵ 4.01); and the 1′-methyl isomer XIX, m.p. 240.5–242°; $[\alpha]^{25}D$ +14° ($CHCl_3$); λ_{max}^{MeOH} 266.5 mμ (log ϵ 4.12). Removal of the BMD-protecting groups of XXVII and XIX gave after acetylation respectively the 2′-methylpyrazole (XX), λ_{max}^{MeOH} 276.5 mμ (log ϵ 4.03); and the 1′-methyl isomer (XXI), λ_{max}^{MeOH} 266 mμ (log ϵ 4.08). The proposed structures of the isomeric N-methylpyrazoles are consistent with the fact that in the polarized forms a greater separation of the charges is possible with the 1′- than with the 2′-alkyl isomer (δ^- at C-5, δ^+ on N). Accordingly the former should have the higher molecular extinction.[11] The fact that the 2′-methyl isomer absorbs at longer wave length is also consistent with the proposed structure since it contains a longer conjugated system.[6b] In view of the fact that the N-unsubstituted pyrazoles IV, V and XI have log ϵ 4.0 rather than 4.10, we tentatively assign the 2′-H structures to these compounds. Both the 1′-alkyl and the 1′-aryl pyrazoles are less polar on paper and alumina chromatography than their 2′-isomers. The former pair is also characterized by a band at about 7.2 μ of strong intensity, whereas the 2′-substituted 4-pregnenopyrazoles as well as IV, VI, XI showed only weak or moderate absorption at this wave length.[12]

Allodihydrocortisol BMD (XXII), m.p. 224–225°[13]; led to the 2-hydroxymethylene derivative XXIII, m.p. 253.5–255°; $[\alpha]^{24}D$ −40° ($CHCl_3$); λ_{max} 314.5 mμ[7] (log ϵ 4.30), λ_{max}^{MeOH} 288 mμ (3.87). Unlike X, the allodihydro compound XXIII gave a mixture[14] of the 2′-phenylpyrazole[15] XXIV, m.p. 285–286°; $[\alpha]^{25}D$ −10° ($CHCl_3$); λ_{max}^{MeOH} 251 mμ (log ϵ 4.04); and the 1′-phenyl isomer XXV,[8c] m.p. 247–247.5°; $[\alpha]^{24}D$ −16°; λ_{max} 269.5 mμ (log ϵ 4.30). Acid hydrolysis of XXIV and acetylation gave XXVI, m.p. 248.5–250° (dec.); λ_{max}^{MeOH} 251 mμ (log ϵ 3.96).

Compound VI was about 10–12 times as active as cortisol in the systemic granuloma assay,[16] but only 3–4 times as active as cortisol in causing adrenal atrophy and it did not retain sodium in the adrenalectomized rat. The 2′-phenylpyrazole XIII and the 2′-*p*-fluorophenylpyrazoles XV and VIII were respectively 60, 100 and 500 times as active as cortisol in the granuloma assay, whereas the 1′-phenylpyrazole XVIII was <2

ether of cortisone [A. Ercoli and R. Gardi, *J. Am. Chem. Soc.*, **82**, 746 (1960)] may be converted into the 3-ketone *in vivo*.

(5) R. Hirschmann and S. L. Steelman, unpublished observation.

(6) (a) R. O. Clinton, *et al.*, *ibid.*, **81**, 1513 (1959); (b) R. O. Clinton, A. J. Manson, F. W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, W. B. Dickinson and C. Carabateas, *ibid.*, **83**, 1478 (1961). A 2′-phenyl derivative, 17β-hydroxy-17α-methylandrostano[3,2-*c*]-2′-phenylpyrazole, also was described but in this series the phenyl group apparently does not enhance activity.

(7) Taken in methanol containing 2% of a 2.5 *N* sodium hydroxide solution.

(8) Obtained as a solvate: (a) 0.5 H_2O; (b) acetone; (c) 0.5 CH_3OH. The tendency of steroidal pyrazoles to crystallize as "stable reproducible solvates" has been previously recorded.

(9) It has been observed before that a hydroxymethylene compound and its enol ethers may afford different pyrazoles. See, *e.g.*, T. L. Jacobs, "Heterocyclic Compounds," Volume 5, R. E. Elderfield, Editor, John Wiley and Sons, Inc., New York, 1957, p. 51.

(10) This interpretation is in agreement with the fact that the phenyl protons in XVII are split as in aniline but not in the case of XII (B. Arison and N. Trenner, private communication).

(11) *Cf.* R. B. Turner and D. M. Voitle, *J. Am. Chem. Soc.*, **73**, 1403 (1951).

(12) R. Walker, private communication. The differences were comparatively less pronounced in the case of XX and XXI than with XIX and XXVII.

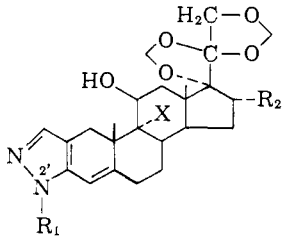
(13) This material contained <1% of cortisol BMD by ultraviolet spectroscopy.

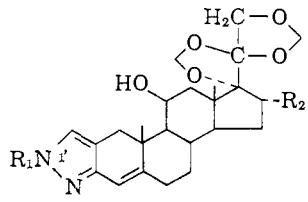
(14) The reaction of 2-hydroxymethylene-17α-methylandrostan-17β-ol-3-one with phenylhydrazine is reported[6] to give a single product, λ_{max} 262 mμ (4.15). Zderic, *et al.*,[2] however, observed that 4,5-saturated hydroxymethylene compounds react with hydroxylamine to afford two isomeric isoxazoles.

(15) That both XII and XXIV belong to a 2′-phenyl series was also shown by the fact that catalytic hydrogenation (Pd) of XII gave a 4,5-saturated product, λ_{max} 251 mμ.

(16) S. L. Steelman and E. R. Morgan, In "Inflammation and Diseases of Connective Tissue," L. C. Mills and J. H. Moyer, Editors, W. B. Saunders Co., Philadelphia, 1961, p. 350.

times cortisol. The isomeric 1′- and 2′-methylpyrazoles XXI and XX were, however, of more comparable potency (1.5 and 5.9 times cortisol, respectively). Thus the 2′-*p*-fluorophenylpyrazole function is the most powerful activity enhancing group yet reported in the anti-inflammatory field. The application of these findings to the 6-dehydro-6-methylcortisol series is described in a separate communication.[17,18]





	R_1	R_2	X
IV[a]	H	CH_3	F
V	H	CH_3	F
VI = V	with free side chain		
VII[a]	*p*-C_6H_4F	CH_3	F
VIII	*p*-C_6H_4F	CH_3	F
	free side chain 21-acetate		
XI	H	CH_3	H
XII	C_6H_5	CH_3	H
XIII = XII	with free side chain		
XIV	*p*-C_6H_4F	CH_3	H
XV = XIV	with free side chain 21-acetate		
XXVII	CH_3	CH_3	H
XX = XXVII	with free side chain 21-acetate		
XXIV	C_6H_5	H	H
	4,5α-dihydro		
XXVI = XXIV	with 4,5α-dihydro free side chain 21-acetate		

	R_1	R_2
XVII	C_6H_5	CH_3
XVIII = XVII	with free side chain	
XIX	CH_3	CH_3
XXI = XIX	with free side chain 21-acetate	
XXV	C_6H_5	H
	4,5α-dihydro	

11-keto rather than 11-β-hydroxyl.

(17) J. H. Fried, H. Mrozik, G. E. Arth, T. S. Bry, N. G. Steinberg, M. Tishler, R. Hirschmann and S. L. Steelman, *J. Am. Chem. Soc.*, **85**, Jan. 20 (1963).

(18) It is noteworthy that in the androgen series, the 6α-methyl and the 9α-F-substituents decrease the activity of the pyrazoles.[6b]

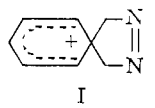
MERCK SHARP & DOHME RESEARCH LABORATORIES
DIVISION OF MERCK & CO., INC.
RAHWAY, NEW JERSEY
RALPH HIRSCHMANN
N. G. STEINBERG
PAUL BUCHSCHACHER
J. H. FRIED
G. J. KENT
MAX TISHLER
MERCK INSTITUTE FOR THERAPEUTIC RESEARCH
RAHWAY, NEW JERSEY
S. L. STEELMAN

RECEIVED NOVEMBER 30, 1962

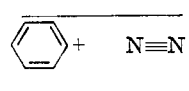
A TRACER DEMONSTRATION OF A REVERSIBLE STEP IN DIAZONIUM SALT DECOMPOSITION

Sir:

A study of the effect of thiocyanate ion concentration on the rate of decomposition of benzenediazonium ion led to the conclusion that an intermediate could revert to the diazonium ion.[1] Among the tentatively considered structures for this intermediate were some, I for example, in which the two nitrogen atoms are indistinguishable, and others, such as the caged pair II, with non-equivalent nitrogens.



I



II

A consequence of any structure (such as I) with equivalent nitrogens, or any structure in which the nitrogens are readily interconvertible, is that the isotopic rearrangement, reaction (1), should accompany the solvolysis of a labelled diazonium salt. We now show evidence for this reaction.

$$Ar^+N^*{\equiv}N \longrightarrow Ar^+N{\equiv}N^* \qquad (1)$$

Benzenediazonium-α-N^{15} fluoroborate was prepared from aniline-N^{15} (99% N^{15}) by diazotization with normal sodium nitrite. Decomposition in water at 35° to the extent of 80% (assuming the rate to be the same as that of normal diazonium salt[2]) left a solution of residual diazonium salt which was degassed and then degraded by treatment with sodium azide.[3] The "primary nitrogen" derived only from the azide ion, was discarded, except in one experiment in which it was shown to have normal isotopic abundance of N^{15}. The "secondary nitrogen," 1/4 of which is derived *via* phenylpentazole from the β-nitrogen of the diazonium salt, was collected for analysis. A second sample of nitrogen was obtained by arsenite reduction of the total phenyl azide; this contained the remainder of the β-nitrogen and none of the α-nitrogen. Mass spectrometric analysis of these samples then gives the N^{15} content of the β-nitrogen: it was found to have 2.6% N^{15} (natural abundance 0.36%). The value calculated from the phenyl azide nitrogen agreed with that from the "secondary nitrogen" if the literature value[3] for the relative amounts of reaction by the two routes (which we confirm more roughly) was used.

The quantitative specificity of labelling and the degradation were both checked by repeating the same process omitting only the prior 80% decomposition. All samples had only natural abundance of N^{15}, showing that N^{15} appears in the β position only after extensive decomposition. Reaction (1) therefore occurs during the solvolysis reaction.

If reaction (1) follows a first-order course, with the rate constant k_i, accompanying the solvolysis with rate constant k_s, it can be shown that $k_i = 0.014k_s$. This result is consistent with the existence of an intermediate which can return to diazonium ion, as well as going on to phenol; in this intermediate the initial C–N bond is nearly or totally broken.

The reaction (2) is a possible return reaction of interest in connection with nitrogen fixation. Although

$$Ar^+ + N_2 \longrightarrow ArN_2^+ \qquad (2)$$

rigorous evidence is not available, we lean toward an incompletely separated intermediate, both for the reasons previously cited,[1] and because carbon monoxide at 700 p.s.i. is not detectably incorporated into decomposing benzenediazonium ion (to give benzoic acid), even though it is more nucleophilic than the isoelectronic nitrogen molecule.

Acknowledgment.—We gratefully acknowledge support from the Robert A. Welch Foundation. The work would not have been done without the skillful and willing coöperation of Dr. E. G. Carlson and his coworkers at the Shell Oil Company, who did the mass spectrometry.

CHEMISTRY DEPARTMENT
WILLIAM MARSH RICE UNIVERSITY
HOUSTON, TEXAS
JOAN M. INSOLE
EDWARD S. LEWIS

RECEIVED NOVEMBER 14, 1962

(1) E. S. Lewis and J. E. Cooper, *J. Am. Chem. Soc.*, **84**, 3847 (1962).

(2) E. A. Moelwyn-Hughes and P. Johnson, *Trans. Faraday Soc.*, **36**, 948 (1940); D. F. DeTar and A. R. Ballentine, *J. Am. Chem. Soc.*, **76**, 3916 (1956).

(3) K. Clusius and H. Hurzler, *Helv. Chim. Acta*, **37**, 798 (1954); R. Huisgen and I. Ugi, *Chem. Ber.*, **90**, 2914 (1957).