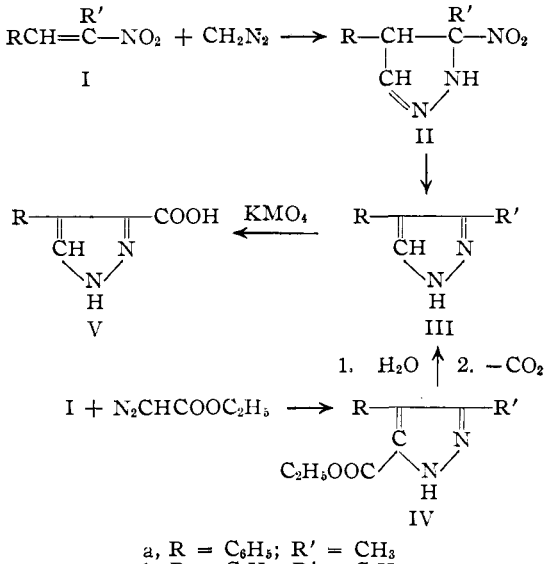
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Reactions of Diazo Compounds with Nitroölefins. I. The Preparation of Pyrazoles

BY WILLIAM E. PARHAM AND JAMES L. BLEASDALE

The condensation of aliphatic diazo compounds with olefins containing an activated double bond is known to result in the formation of pyrazolines.[1] This reaction has been studied in considerable detail, for pyrazolines are easily converted to pyrazoles by oxidation[1] or to substituted cyclopropanes by heat.[2] We were interested in determining the course of reaction between nitroölefins and diazo compounds for the possibility existed that such a reaction might lead to suitable intermediates for the preparation of 3-nitropyrazoles and nitrocyclopropanes.

When diazomethane was allowed to react with ω-nitrostyrene at room temperature, a quantitative yield of addition product was obtained; however, the product appeared to be polymeric and had no properties commensurate with those of the expected nitropyrazoline (II). It was observed that when secondary nitroölefins were used in place of ω-nitrostyrene no polymeric material was formed. This observation is not surprising since the pyrazoline formed from ω-nitrostyrene would contain an active hydrogen on the carbon holding the nitro group which, in the presence of the basic pyrazoline, could enter into reaction with ω-nitrostyrene or diazomethane. This possibility is being investigated.



a, R = C_6H_5; R′ = CH_3
b, R = C_6H_5; R′ = C_2H_5
c, R = *n*-C_3H_7; R′ = CH_3
d, R,R′ = C_2H_5

The condensation of 1-phenyl-2-nitropropene-1 (Ia) and diazomethane at room temperature resulted in a quantitative yield of 3-nitro-3-methyl-4-phenylpyrazoline (IIa). That compound IIa was not the nitrous acid salt of 3-methyl-4-phenylpyrazole (IIIa) was suggested by (a) its physical properties, (b) by the observation that IIa can be crystallized unchanged from dilute acetic acid–sodium acetate solution, whereas IIIa is recovered unchanged after treatment with sodium nitrite in cold dilute acetic acid (conditions which should convert IIIa to IIa if the latter possessed a salt structure).

When compound IIa was heated much above 100° it decomposed into oxides of nitrogen and 3-methyl-4-phenylpyrazole (IIIa). The transformation of IIa into the pyrazole (IIIa) was effected in excellent yield at room temperature by the action of hydrochloric acid or aqueous sodium hydroxide. The structure of IIIa was established by oxidation to the known 3-carboxy-4-phenylpyrazole (Va).

With secondary aliphatic nitroölefins no intermediate nitropyrazolines could be obtained, although there was evidence for their existence. The reaction product obtained from 3-nitrohexene-3 (Id) and diazomethane was soluble in ether and petroleum ether. When an ethereal solution of this product was treated with hydrogen chloride, oxides of nitrogen were eliminated and the hydrochloride of 3,4-diethylpyrazole (IIId) was obtained in 77% yield. When a petroleum ether solution of the reaction product was allowed to stand several days in a stoppered flask, the nitrate salt of 3,4-diethylpyrazole separated in high yield. All attempts to isolate a pure sample of the nitropyrazoline resulted in the isolation of the pyrazole.

When 1-phenyl-2-nitropropene-1 was treated with diazoacetic ester in boiling petroleum ether (100–140°) oxides of nitrogen were eliminated and the product was 3-methyl-4-phenyl-5-carbethoxypyrazole (IVa) (48% yield, 92% based on the nitroölefin used). This ester was identified by hydrolysis and decarboxylation to 3-methyl-4-phenylpyrazole (IIIa). The condensation of secondary aliphatic nitroölefins with diazoacetic ester in boiling petroleum ether (100–140°) resulted in the formation of 3,4-dialkyl-5-carbethoxypyrazoles (IV). The product from 3-nitrohexene-3 (Id) was established to be 3,4-diethyl-5-carbethoxypyrazole (IVd) by converting it by hydrolysis and decarboxylation into 3,4-diethylpyrazole (IIId).

Since the condensation of nitroölefins with diazomethane and diazoacetic ester appeared to be a suitable preparative scheme for the otherwise difficultly accessible 3,4-disubstituted pyrazoles the reactions of 1-phenyl-2-nitrobutene-1 (Ib) and 2-nitrohexene-2 (Ic) with diazo compounds were also investigated to test the generality of the re-

(1) Von Pechmann, *Ber.*, **33**, 3590 (1900).
(2) Kohler and Steele, THIS JOURNAL, **41**, 1093 (1919).

action. The expected pyrazoles were obtained. The results are summarized in the experimental section. The reactions of diazomethane with 1-phenyl-2-bromo-2-nitropropene-1 and other nitroolefins are being investigated.

Experimental

Aromatic Nitroölefins.—1-Phenyl-2-nitropropene-1[3] and 1-phenyl-2-nitrobutene-1[4] were obtained in good yield by condensation of benzaldehyde with nitroethane and nitropropane.

Aliphatic Nitroölefins.—The aliphatic nitroölefins were prepared by the removal of the elements of acetic acid from the acetates of the corresponding nitro alcohols prepared by the condensation of an aliphatic aldehyde with an aliphatic nitro paraffin. The procedure used for the preparation of the nitro alcohols was essentially that of Sprang and Degering.[5] 3-Nitrohexanol-4 was obtained in 81% yield as a pale yellow oil, b. p. 84–86° (2 mm.), $n^{25}D$ 1.4441 (reported[6] b. p. 89° (2 mm.), $n^{25}D$ 1.4441).

2-Nitrohexanol-3 was obtained in 73% yield, b. p. 83–85° (3 mm.); $n^{25}D$ 1.4455 (reported[6] b. p. 82° (2 mm.), $n^{25}D$ 1.4450).

The nitro alcohols were acetylated by action of acetic anhydride and sulfuric acid according to the general procedure of Tyndall.[7]

The acetate of 2-nitrohexanol-3 was obtained as a colorless oil in 96% yield, b. p. 95° (5 mm.), $n^{25}D$ 1.4312.

Anal. Calcd. for $C_8H_{15}NO_4$: C, 50.75; H, 7.93. Found: C, 50.92; H, 8.09.

The acetate of 3-nitrohexanol-4 was obtained in 83% yield, b. p. 84–86° (5 mm.), $n^{25}D$ 1.4320.

Anal. Calcd. for $C_8H_{15}NO_4$: C, 50.75; H, 7.93. Found: C, 50.83; H, 8.17.

The acetates were converted to the nitroölefins Ic and Id by a modification of the procedure reported by Nightingale.[6] In a 1-liter 3-necked flask, equipped with condenser and mechanical stirrer was placed 149 g. (0.79 mole) of the acetate, 252 g. (3 moles) of sodium bicarbonate and 300 ml. of benzene. The mixture was stirred vigorously for twenty-four hours at reflux temperature. The mixture was cooled and the solid removed by filtration. The benzene was removed and the residue was distilled under reduced pressure. 3-Nitrohexene-3 (Id) was obtained in 25% yield (52% recovery of unchanged acetate), b. p. 85–87° (25 mm.); $n^{25}D$ 1.4538 (reported[6] b. p. 51° (1 mm.), $n^{25}D$ 1.4521). 2-Nitrohexene-2 (Ic) was obtained in 51% yield (considerable unchanged acetate was recovered but per cent. not established), b. p. 60–62° (4 mm.); $n^{20}D$ 1.4536 (reported[6] b. p. 53° (1 mm.), $n^{25}D$ 1.4513).

3-Methyl-3-nitro-4-phenylpyrazoline (IIa).—A solution of 13.0 g. (0.08 mole) of 1-phenyl-2-nitropropene-1 in 100 ml. of ether was cooled in an ice-bath and 300 ml. of cold ether containing about 0.1 mole of diazomethane was added. The resulting solution was allowed to stand overnight at room temperature. The ether and excess diazomethane were removed under reduced pressure at room temperature and the resulting yellow oil was heated at 25° at a pressure of 1 mm. for several hours to remove the last traces of volatile material. The resulting yellow oil, 16.4 g. (100% of theoretical), solidified; m. p. 50–53°. After several crystallizations from dilute acetic acid or petroleum ether (60–68°) the melting point was 57.5°.

Anal. Calcd. for $C_{10}H_{11}O_2N_3$: C, 58.52; H, 5.40. Found: C, 58.66; H, 5.26.

The nitropyrazoline (IIa) was soluble in ether and insoluble in water. It was recrystallized unchanged from dilute acetic acid-sodium acetate solution; m. p. and mixed m. p. 57°. 3-Methyl-4-phenylpyrazole (IIIa) was recrystallized unchanged from cold dilute acetic acid-sodium nitrite solution; m. p. and mixed m. p. 140°.

3-Methyl-4-phenylpyrazole (IIIa).—A. To the crude pyrazoline (IIa) (oil or solid) obtained from 16.3 g. of 1-phenyl-2-nitropropene-1 was added 2 ml. of 6 *N* hydrochloric acid. After the evolution of nitrous fumes had ceased, 20 ml. of 6 *N* hydrochloric acid was added and the mixture heated on a steam-cone for a short time. The resulting solution was treated with Norite and then neutralized with sodium bicarbonate. There was obtained 14.1 g. (89%) of white crystals melting at 139–140°. Crystallization from 25% ethanol in water gave a product melting at 141°.

B. A suspension of 1.09 g. of IIa in water was treated with 5 ml. of 40% potassium hydroxide. The mixture was diluted with water and the flocculent precipitate collected. There was obtained 0.71 g. (85.5%) of white solid which was identified as 3-methyl-4-phenylpyrazole; m. p. and mixed m. p. 141°.

Preparation of Pyrazoles IIIb, IIIc, IIId.—Procedure A described for 3-methyl-4-phenylpyrazole was used in the preparation of these compounds.

Attempted Isolation of Nitropyrazolines IIc and IId. Preparation of the Nitrate of 3,4-Diethylpyrazole.—When the product obtained from the condensation of 3-nitrohexene-3 (Id) and diazomethane was heated at 25° under a pressure of 1 mm. to remove the last traces of volatile material, an oil resulted. The product was soluble in ether and petroleum ether and liberated nitrous fumes when treated with hydrochloric acid. Thus it seemed likely that the nitropyrazoline (IId) was present.

A 3-g. sample of the reaction product described above was dissolved in 5 ml. of petroleum ether (60–68°) and the flask stoppered. After several days needles had formed. These crystals were collected and later combined with the solid product deposited from the filtrate. The product was recrystallized from carbon tetrachloride to give white needles, m. p. 120–121°, soluble in water, insoluble in ether.

Anal. Calcd. for $C_7H_{13}O_3N_3$: C, 44.92; H, 6.95. Found: C, 44.80; H, 7.06.

This product was identified as the nitrate salt of 3,4-diethylpyrazole (IIId). The nitrous acid liberated from the unstable condensation product was apparently oxidized by air to nitric acid. An authentic sample of the nitrate salt of 3,4-diethylpyrazole was prepared from an ethereal solution of the free base by the addition of several drops of concentrated nitric acid; m. p. and mixed m. p. 120–121°.

4-Phenyl-3-methyl-5-carbethoxypyrazole (IVa).—In a 200-ml. flask was placed 20 g. (0.122 mole) of 1-phenyl-2-nitropropene-1, 20 g. (0.175 mole) of undistilled diazoacetic ester and 40 ml. of ligroin (100–140°). The mixture was heated at the reflux temperature for ten hours during which time brown fumes of oxides of nitrogen were eliminated. The low boiling material was removed under reduced pressure and the residue was subjected to vacuum distillation. There was obtained 8.0 g. (40%) of unchanged nitroölefin, m. p. and mixed m. p. 61–62°, distilling at 98–101° at 3 mm., and 15.5 g. (55%) of light yellow oil distilling at 165–173° (3 mm.). The ester solidified after standing for twelve hours and the resulting solid was crystallized from cyclohexane and then from 50% ethanol-water. The white needles obtained melted at 122°.

Preparation of Pyrazoles IVb, IVc, IVd.—The procedure described for the preparation of 3-methyl-4-phenyl-5-carbethoxypyrazole (IVA) was used in the preparation of these compounds. The esters IVc, IVd were obtained as oils and were difficult to purify in small amounts so analytical samples were not obtained. All esters were characterized by saponification to the corresponding carboxylic acids.

Saponification of 3,4-Diethyl-5-carbethoxypyrazole.—A suspension of 0.025 mole of crude 3,4-diethyl-5-carbethoxypyrazole in 25 ml. of 10% aqueous sodium hydrox-

(3) Knoevenagel and Walter, *Ber.*, **37**, 4502 (1904).
(4) Hass and Riley, *Chem. Revs.*, **32**, 410 (1943).
(5) Sprang and Degering, THIS JOURNAL, **64**, 1063 (1942).
(6) Nightingale and Janes, *ibid.*, **66**, 352 (1944).
(7) Tyndall, *Ind. Eng. Chem.*, **33**, 65 (1941).

TABLE I

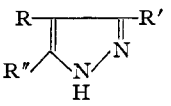
PHYSICAL PROPERTIES OF PYRAZOLES III AND IV

Compound	R	R′	M. p., °C.	B. p. °C.	Mm.	n_D	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
IIIa	C_6H_5	CH_3	141	.....	..	.....	89	76.17	76.00	6.31	6.33
IIIb	C_6H_5	C_2H_5	86–87	.....	..	.....	92	76.70	76.49	7.03	7.04
IIIc	n-C_3H_7	CH_3	.....	121	10	1.4855[a]	53, 77[b]	...	...	..	..
IIId	C_2H_5	C_2H_5	.....	98	3	1.4891[a]	57[b]	...	...	..	..
IVa	C_6H_5	CH_3	122	165–173	3	.....	92[c]	67.84	67.63	6.08	6.23
IVb	C_6H_5	C_2H_5	127–128	155–165	3	.....	68	68.87	68.72	6.55	6.81
IVc[d]	n-C_3H_7	CH_3	.....	142–144	3	1.4841[e]	48	...	...	..	..
IVd[d]	C_2H_5	C_2H_5	.....	135–140	5	1.4833[e]	25[f]	...	...	..	..

[a] $n^{20}D$. [b] The free bases were isolated as colorless oils in 53 and 57% yield as indicated. The products can be isolated more easily and in higher yields as hydrochlorides. Analytical values were obtained for the hydrochlorides. When the ethereal solution of the crude product obtained in the preparation of IIIc was treated with dry hydrogen chloride, the pure hydrochloride was obtained in 77% yield. [c] The yield was 92% based on the nitroölefin used or 55% based on the nitroölefin employed. [d] These esters were difficult to separate from the reaction mixture by the distillations employed. They were identified by conversion by hydrolysis to the corresponding carboxylic acid. It is likely that a significantly higher yield of the ester could be obtained by employing distilled diazoacetic ester. [e] $n^{25}D$. [f] This low yield does not represent a maximum yield since a considerable portion of the product was accidently lost.

TABLE II

DERIVATIVES OF PYRAZOLES III AND IV



R	R′	R″	M. p., °C. Of picrate	Of hydrochloride[b]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
C_6H_5	CH_3	H	155[a]	...	49.61	49.67	3.36	3.43
C_6H_5	C_2H_5	H	123	...	50.88	50.97	3.77	3.98
C_2H_5	C_2H_5	H	156	...	44.19	44.39	4.25	4.41
n-C_3H_7	CH_3	H	104	...	44.19	44.04	4.25	4.60
C_2H_5	C_2H_5	H	...	180	52.34	51.93	8.10	8.40
n-C_3H_7	CH_3	H	...	171	52.34	52.40	8.10	8.00
C_6H_5	CH_3	COOH[c]	265	...	67.84	67.63	6.08	6.23
C_6H_5	C_2H_5	COOH	241	...	66.67	66.43	5.56	5.66
C_2H_5	C_2H_5	COOH	194	...	57.12	57.08	7.19	7.19
n-C_3H_7	CH_3	COOH	245	...	57.12	56.88	7.19	7.27

[a] The picrates were prepared in the usual manner[8] and recrystallized from ethanol. [b] The hydrochlorides were obtained in almost quantitative yield as white, water soluble crystals when an ethereal solution of the pyrazole was treated with anhydrous hydrogen chloride. The salts were recrystallized from dioxane. [c] Calcd. for $C_{11}H_{10}O_2N_2$: neut. equiv., 202. Found: neut. equiv., 202.

ide was heated on a steam-cone for three hours. The solution was cooled, acidified with dilute hydrochloric acid, and the resulting solid collected by filtration (yield 55%). The acid was purified for analysis by crystallization from glacial acetic acid. The esters IVa, IVb, IVc were converted to the corresponding acids by the above procedure. The physical properties of all acids thus obtained are reported in Table II.

Oxidation of 3-Methyl-4-phenylpyrazole (IIIa).—In a 500-ml. flask was placed 10.5 g. (0.067 mole) of potassium permanganate, 150 ml. of water and 5.0 g. (0.0316 mole) of 3-methyl-4-phenylpyrazole. The mixture was heated very gently and the vigorous reaction was moderated by cooling. After the vigorous reaction had ceased the mixture was heated on a steam-bath for one hour. The mixture was cooled and acidified with hydrochloric acid. Sodium bisulfite was added until all the manganese dioxide had dissolved. Five milliliters of concentrated hydrochloric acid was added and the mixture was boiled until no more sulfur dioxide was liberated. The solution was cooled and extracted with ether. The ether solution was dried and the ether removed. The residue was crystallized from water, m. p. 250–251°. Reported[2] m. p. of 4-phenyl-3-pyrazolecarboxylic acid is 253° (reported[9] m. p. of 3-phenyl-4-pyrazole-carboxylic acid is 278°).

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.83; H, 4.25. Found: C, 64.11; H, 4.38.

Decarboxylation of 3-Methyl-4-phenyl-5-pyrazolecarboxylic Acid.—Five hundred milligrams of 3-methyl-4-phenyl-5-pyrazolecarboxylic acid was decarboxylated in a sublimation tube under an atmosphere of nitrogen at atmospheric pressure by heating the acid above its melting point until no more effervescence was observed. The residue was distilled under reduced pressure and the distillate solidified; m. p. 141°. A mixed melting point with a sample of 3-methyl-4-phenylpyrazole melted at 141°.

Decarboxylation of 3,4-Diethyl-5-pyrazolecarboxylic Acid.—The decarboxylation of this acid (500 mg.) was effected as described in the previous experiment. The distillate was converted to its picrate which was shown to be identical with that obtained from 3,4-diethylpyrazole (IIId). The m. p. and mixed m. p. was 155–156°.

Summary

1. The condensation of aromatic and aliphatic

(8) Shriner and Fuson, "Identification of Organic Compds.," John Wiley and Sons, Inc., New York, N. Y., 1946, p. 149.

(9) von Auwers, *Chem. Z.*, 2394 (1933).

nitroölefins, which contain no hydrogen atom alpha to the nitro group, with diazomethane and diazoacetic ester has been shown to be a useful preparative scheme for the otherwise difficultly accessible 3,4-disubstituted pyrazoles and the corresponding 5-carboxylic esters.

2. The condensation of nitroölefins with diazomethane results in the formation of products (presumably nitropyrazolines) which yield 3,4-disubstituted pyrazoles in good yields when treated with mineral acids, alkali or heat. Four new pyrazoles of this type have been prepared and characterized. In one case, the intermediate nitropyrazoline was obtained in excellent yield as a crystalline solid. Evidence is presented for its structure. Attempts to isolate the pure nitropyrazolines obtained from aliphatic nitroölefins resulted in the isolation of pyrazoles.

3. Nitroölefins were observed to react with diazoacetic ester only at elevated temperatures (boiling petroleum ether, 100–140°). Oxides of nitrogen were eliminated during the course of the reaction. The products were substituted 5-carbethoxypyrazoles. Four new pyrazoles of this type were prepared and characterized.

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Adrenergic Blocking Agents. II. N-(2-Chloroethyl)-N-(2-phenoxyethyl)-amine Hydrochlorides[1]

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The important discovery by Nickerson and Goodman[2] that N-(2-chloroethyl)-dibenzylamine ("Dibenamine")[3] hydrochloride is a specific and potent adrenergic blocking agent was followed by the syntheses and pharmacological studies of other tertiary N-(2-chloroethyl) amines.

Without reviewing here the extended literature[4] on the subject, we wish to refer only to two types of compounds which are related to the series described in this paper. Rieveschl, Fleming and Coleman[5] synthesized N-[2-(2-biphenylyloxy)-ethyl]-N-(2-chloroethyl)-alkylamines, found to be moderately active adrenergic blocking substances,[6] and Henderson and Chen[7] reported on the strong epinephrine antagonism of N-(2-*o*-benzylphenoxyethyl)-N-(2-chloroethyl)-ethylamine hydrochloride. These compounds contain either phenyl or benzyl in the ortho position of the benzene ring of the phenoxyethyl moiety; we undertook the preparation of a series of N-(2-chloroethyl)-N-(2-phenoxyethyl)-amine hydrochlorides having alkyl, dialkyl, methoxy or chlorine as ring substituents, in an attempt to find substances of higher potency and to acquire further knowledge on the relationship between structure and activity.

Our new amines belong mainly to three groups (listed in Tables IX to XI) of the configurations:

Groups I and II $ROCH_2CH_2\diagdown\atop R'\diagup\!\!>NCH_2CH_2Cl\cdot HCl$

$R' = C_2H_5$ (I) R = phenyl or phenyl substituted

$R' = C_6H_5CH_2$ (II) by alkyl, dialkyl, methoxy

Group III $(ROCH_2CH_2)_2NCH_2CH_2Cl\cdot HCl$

R = phenyl or phenyl substituted by alkyl, dialkyl, methoxy, chlorine

The properties of other tertiary N-(2-chloroethyl)-amine hydrochlorides closely related, but not exactly belonging to the types of Groups I to III, are described in Table XII.

The N-(2-chloroethyl)-amine hydrochlorides of our series are crystalline white substances, soluble in alcohols and glycols; they are practically insoluble in water, with the exception of the N-ethyl derivatives which show slight solubility. The 2-chloroethyl compounds were obtained from the corresponding N,N-disubstituted 2-aminoethanols on treating them with thionyl chloride. The 2-aminoethanols (Tables V–VIII) were synthesized in satisfactory yields by the condensation of 2-ethylaminoethanol, 2-benzylaminoethanol and 2-aminoethanol with the appropriate β-halogen phenetoles. The introduction of two phenoxyethyl groups into 2-aminoethanol required the use of the more reactive β-bromophenetoles.

In the case of some of the alcohols listed in Tables VI and VII, it was found preferable to carry out the synthesis in two steps. The secondary amino alcohols (Table IV) were prepared first and then condensed with benzyl chloride or a substituted β-halogen phenetole.

For the synthesis of the compounds listed in Table XII, the same general procedures were employed and the steps involved are evident from the formulas.

The preparation of di-(2-*o*-toloxyethyl)-amine hydrochloride (Table XIII, No. 3) was first tried

(1) Presented before the Division of Medicinal Chemistry at the 116th Meeting of the American Chemical Society, Atlantic City, September 21, 1949.

(2) Nickerson and Goodman, *Federation Proc.*, **5**, 194 (1946); *J. Pharmacol. Exp. Therap.*, **89**, 167 (1947).

(3) Trade-mark of Smith, Kline & French Laboratories, Philadelphia, Pa.

(4) Nickerson, *Pharmacological Reviews*, *J. Pharmacol. Exp. Therap.*, **95**, 27 (part 2, April, 1949).

(5) Rieveschl, Fleming and Coleman, Abstracts of Papers 112th Meeting, A. C. S., Sept. 1947.

(6) Achenbach and Lowe, *Federation Proc.*, **6**, 304 (1947); *J. Pharmacol. Exp. Therap.*, **95**, 448 (1949).

(7) Henderson and Chen, *Federation Proc.*, **8**, 301 (1949).