TC band with the ATC band under these conditions required that the column be lengthened for their adequate separation.

Although the main effect of Sephadex is to separate molecules with respect to size, some secondary effects have been noted. Porath (9) and Gelotte (10) have found that heterocyclic and aromatic compounds interact with the Sephadex bed material which results in their delayed elution. The differences in elution rates between TC and ATC (as well as ATC and EATC) are presumed to be due to a similar adsorption phenomenon.

Of a group of about 50 tetracycline preparations analyzed on Sephadex, only about 7 of these contained degradation products in excess of 1% of the labeled amount of tetracycline. This figure of 1% represents the arbitrary amount (tentative) above which the samples were analyzed for both ATC and EATC by the partition chromatography method (7). Figure 3 shows the elution diagram of a tetracycline syrup containing an unusually high quantity of degradation products. The amount expressed as ATC was found to be 4.35 mg./ml. of syrup. The analysis of the same product by the partition chromatography method gave a gross value of 4.10 mg./ml. syrup, most of which was in the form of EATC. In general, the analysis of the TC degradation products by Sephadex analysis has been in close agreement with that by partition chromatography when appreciable quantities were present.

REFERENCES

(1) Gross, J. M., *Ann. Intern. Med.*, **58**, 523(1963).
(2) Frimpter, G. W., *J. Am. Med. Assoc.*, **184**, 111(1963).
(3) Ehrlich, L. I., and Stein, H. S., *Pediatrics*, **31**, 339 (1963).
(4) *Ibid.*, **31**, 698(1963).
(5) Rosenthal, S. M., *ibid.*, **31**, 697(1963).
(6) Benitz, K. F., and Diermeier, H. F., *Proc. Soc. Exptl. Biol. Med.*, **115**, 930(1964).
(7) Kelly, R. G., *J. Pharm. Sci.*, **53**, 1551(1964).
(8) McCormick, J. R. D., Fox, S. M., Smith, L. S., Bitler, B. A., Reichenthal, J., Origoni, V. E., Muller, W. H., Winterbottom, R., and Doerschuk, A. P., *J. Am. Chem. Soc.*, **79**, 2849(1957).
(9) Porath, J., *Biochim. Biophys. Acta*, **39**, 193(1960).
(10) Gelotte, B., *J. Chromatog.*, **3**, 330(1960).

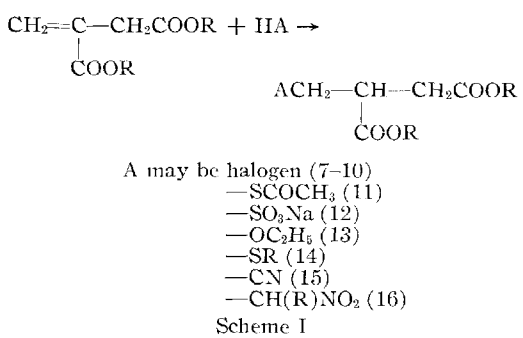
Synthesis of 1,2-Diethyl-4-(2-hydroxyethyl)pyrazolidine

By MILTON J. KORNET

The reaction of 1,2-diethylhydrazine with monomethyl itaconate has been investigated and found to give a mixture of 1,2-diethyl-4-carbomethoxymethyl-3-pyrazolidinone and its hydrolysis product, the corresponding acid. Reduction of either the ester or the acid affords 1,2-diethyl-4-(2-hydroxyethyl)pyrazolidine.

THE AUTHOR'S interest in compounds which contain both an alcoholic hydroxyl group and an alkylated hydrazine group as necessary intermediates in the synthesis of new medicinals prompted the preparation of the title compound. Recently the synthesis of 1,2-diethyl-3-hydroxymethylpyrazolidine, a molecule which embodies the above structural features, was accomplished. Esterification of the latter alcohol with several aromatic acids afforded esters whose hydrochloride salts exhibited local anesthetic activity (1). As the first step in the synthesis of 1,2-diethyl-4-(2-hydroxyethyl)pyrazolidine, it was decided to investigate the reaction of 1,2-diethylhydrazine with an itaconic acid derivative.

A large number of reagents have been added to itaconic acid and its esters (2–16). Unsymmetrical reagents add contrary to Markovnikoff's rule and the addition may be represented by Scheme I.



Scheme I

Itaconic acid reacts with primary amines to give 1-substituted-4-carboxy-2-pyrrolidinones (17). The latter are formed by the addition of the amine to the β-carbon of the double bond followed by ring closure to the 5-membered ring with the elimination of a molecule of water.

In the reaction of 1,2-diethylhydrazine, with an itaconic acid derivative, ring closure to either a 5- or 6-membered ring is possible. Because of this possibility monomethyl itaconate was utilized. Separation of products could be more easily achieved since a mixture would consist of a 5-membered ring methyl ester and a 6-membered ring carboxylic acid. Treatment of 1,2-diethylhydrazine (I) with monomethyl itaconate (II) afforded a mixture of 43.9% of 1,2-diethyl-4-carbomethoxymethyl-3-pyrazolidinone (IV) and 44.6% of its hydrolysis product, 1,2-diethyl-4-carboxymethyl-3-pyrazolidinone (IV*a*). Both compounds gave crystalline picrate derivatives. Compound IV can be visualized as arising from an addition of I to the β-carbon of the double bond of II followed by ring closure *via* the carboxyl group with the elimination of water. The acid (IV*a*) undoubtedly arises from the hydrolysis of IV during the course of the reaction. Elemental analyses and infrared spectra are in agreement with the proposed structures for IV and IV*a*. That the isomeric acid, (III) which would arise from the addition of I to the β-carbon of the double bond of II followed by ring closure *via* the ester carbonyl with simultaneous

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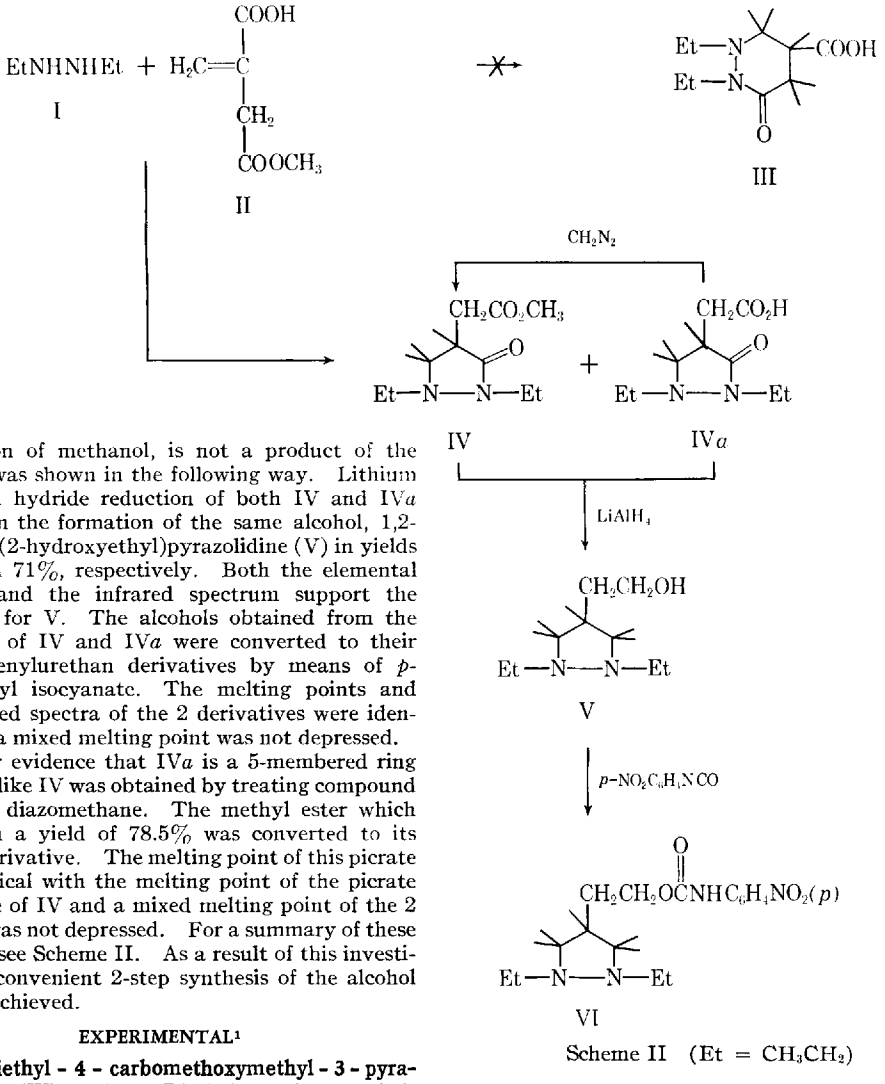

Scheme II (Et = CH_3CH_2)

elimination of methanol, is not a product of the reaction was shown in the following way. Lithium aluminum hydride reduction of both IV and IV*a* resulted in the formation of the same alcohol, 1,2-diethyl-4-(2-hydroxyethyl)pyrazolidine (V) in yields of 70 and 71%, respectively. Both the elemental analysis and the infrared spectrum support the structure for V. The alcohols obtained from the reduction of IV and IV*a* were converted to their *p*-nitrophenylurethan derivatives by means of *p*-nitrophenyl isocyanate. The melting points and the infrared spectra of the 2 derivatives were identical and a mixed melting point was not depressed.

Further evidence that IV*a* is a 5-membered ring structure like IV was obtained by treating compound IV*a* with diazomethane. The methyl ester which formed in a yield of 78.5% was converted to its picrate derivative. The melting point of this picrate was identical with the melting point of the picrate derivative of IV and a mixed melting point of the 2 picrates was not depressed. For a summary of these reactions see Scheme II. As a result of this investigation a convenient 2-step synthesis of the alcohol (V) was achieved.

EXPERIMENTAL[1]

1,2 - Diethyl - 4 - carbomethoxymethyl - 3 - pyrazolidinone (IV) and 1,2-Diethyl-4-carboxymethyl-3-pyrazolidinone (IVa).—To a solution of 9.25 Gm. (0.105 mole) of 1,2-diethylhydrazine (I) (18) in 5 ml. of anhydrous methanol was added dropwise a solution of 14.4 Gm. (0.100 mole) of monomethyl itaconate (II) in 13 ml. of absolute methanol with stirring (magnetic) and ice-bath cooling. The reaction mixture was allowed to stir and come to room temperature overnight and then refluxed for 4.5 hr. The methanol was distilled *in vacuo* on a water bath and the residue was distilled under reduced pressure and gave 9.39 Gm. (43.9%) of the ester (IV), b.p. 90° (0.1 mm.), n_D^{20} 1.4724, $\lambda_{max.}^{CHCl_3}$ 5.8 μ (ester C=O), 6.0 μ (amide C=O), and 8.93 Gm. (44.6%) of the corresponding acid (IV*a*), b.p. 169° (0.18 mm.), n_D^{20} 1.4943, $\lambda_{max.}^{CHCl_3}$ 5.8–6.2 μ (carbonyl of acid and amide), 2.8–4.2 μ (associated OH of acid).

Anal.—Calcd. for $C_{10}H_{18}N_2O_3$ (ester): C, 56.05; H, 8.46; N, 13.08. Found: C, 55.74; H, 8.52; N, 12.90.

Anal.—Calcd. for $C_9H_{16}N_2O_3$ (acid): C, 53.98; H, 8.05; N, 13.99. Found: C, 53.59; H, 8.32; N, 13.90.

The ester was converted into its picrate derivative and recrystallized from absolute ethanol, m.p. 119–120.5°.

Anal.—Calcd. for $C_{16}H_{21}N_5O_{10}$: C, 43.34; H, 4.77; N, 15.80. Found: C, 43.47; H, 4.99; N, 15.91.

The acid was converted into its picrate derivative and recrystallized from absolute ethanol, m.p. 131–132°.

Anal.—Calcd. for $C_{15}H_{19}N_5O_{10}$: C, 41.96; H, 4.46; N, 16.31. Found: C, 41.73; H, 4.86; N, 16.24.

1,2-Diethyl-4-(2-hydroxyethyl)pyrazolidine (V) by Reduction of the Ester (IV).—A solution of 7.57 Gm. (0.0354 mole) of IV in 10 ml. of anhydrous ether was added dropwise to a suspension of 1.97 Gm. (0.052 mole) of lithium aluminum hydride in

[1] Melting points were determined with the Fisher-Johns melting point apparatus and are corrected. Infrared spectra were recorded on a Beckman IR 8 spectrophotometer using sodium chloride optics. Microanalyses were performed by Dr. Kurt Eder, Geneva, Switzerland.

30 ml. of ether with stirring (magnetic). After refluxing overnight the complex was decomposed with 40% KOH, and the salts were extracted with ether. The combined ether layers were dried over $MgSO_4$, and the ether was distilled on a water bath. The residue remaining was distilled and gave 4.28 Gm. (70.3%) of a colorless oil, b.p. 86° (0.33 mm.), n_D^{20} 1.4763, $\lambda_{max.}^{CHCl_3}$ 2.8–3.3 μ (OH).

Anal.—Calcd. for $C_9H_{20}N_2O$: C, 62.75; H, 11.70; N, 16.26. Found: C, 62.75; H, 11.73; N, 16.21.

A *p*-nitrophenylurethan derivative (19) was prepared and recrystallized from carbon tetrachloride, m.p. 115.5–116.5°, $\lambda_{max.}^{KBr}$ 2.94 μ (NH), 5.76 μ (C=O).

Anal.—Calcd. for $C_{16}H_{24}N_4O_4$: C, 57.13; H, 7.19; N, 16.66. Found: C, 57.20; H, 7.00; N, 16.76.

1,2 - Diethyl - 4 - (2 - hydroxyethyl)pyrazolidine (V) by Reduction of the Acid (IVa).—The procedure for the reduction of the acid (IV*a*) was analogous to that used for reduction of the ester (IV). The alcohol (V), b.p. 80° (0.22 mm.), n_D^{20} 1.4780, was obtained in 71.5% yield. It was converted to its *p*-nitrophenylurethan derivative and recrystallized from carbon tetrachloride, m.p. 115.5–116.5°. The identity of this derivative was confirmed by a mixed melting point and comparison of infrared spectra.

Methylation of 1,2-Diethyl-4-carboxymethyl-3-pyrazolidinone.—To a solution of 7.90 Gm. (0.0395 mole) of IV*a* in 25 ml. of ether was added sufficient ethereal diazomethane to give a yellow color which persisted. The solution was dried with $MgSO_4$ and the ether was evaporated on a steam bath. The remaining residue was distilled, b.p. 90° (0.1 mm.), n_D^{20} 1.4728, to give 6.64 Gm. (78.5%) of the ester. A picrate was prepared and recrystallized from absolute ethanol, m.p. 119–120.5°. The identity of this picrate was confirmed by a mixed melting point.

REFERENCES

(1) Kornet, M. J., *J. Med. Chem.*, to be published.
(2) Swarts, T., *Z. Chem.*, **4**, 55(1865).
(3) Kekule, A., *Ann.* (*Suppl.*), **1**, 339(1860).
(4) Swarts. T , *Z. Chem.*, **12**, 583(1873).
(5) Morawski, T., *J. Prakt. Chem.*, (2), **7**, 159(1873).
(6) Read, J., and Reid, W. G., *J. Chem. Soc.*, **1928**, 745.
(7) Swarts, T., *Z. Chem.*, **5**, 721(1866).
(8) *Ibid.*, **6**, 651(1867).
(9) *Ibid.*, **5**, 722(1866).
(10) Fittig, R., and Beer, A., *Ann. Chem.*, **216**, 79(1883).
(11) Holmberg, B., and Schjanberg, E., *Arkiv Kemi, Mineral. Geol.*, 14A, **7**, 22(1940).
(12) Bougault J., and Mouchel-la-Fosse, *Compt. Rend.*, **156**, 397(1913).
(13) Coulson, E. H., and Kon, G. A. R., *J. Chem. Soc.*, **1932**, 2568.
(14) Knuth, C., Bavley, A., and Lazier, W. A., *J. Org. Chem.*, **19**, 845(1954).
(15) Hope, E., *Proc. Chem. Soc. London*, **28**, 192(1913).
(16) Leonard, N. J., and Shoemaker, G. L., *J. Am. Chem. Soc.*, **71**, 1876(1949).
(17) Paytash, P. L., Sparrow, E., and Gathe, J. C., *ibid.*, **72**, 1415(1950).
(18) Renaud, R., and Leitch, L. C., *Can. J. Chem.*, **32**, 545(1954).
(19) Shriner, R. L., Fuson, R. C., and Curtin, D. Y., "The Systematic Identification of Organic Compounds," John Wiley & Sons, Inc., New York, N. Y., 1956, p. 211.

Books

REVIEWS

Dictionary of Organic Compounds. Fourth revised edition in five volumes, and *First Supplement, 1965.* Oxford University Press, New York, N. Y., 1965. xxx + 3282 pp. 20 × 26.5 cm. Price $280.00.

The Fourth Edition of the "Dictionary of Organic Compounds" has undergone extensive revision from the preceding 3rd edition published in November 1953. The entries, which total 12,000 and represent 7,000 new compounds, are contained in five volumes instead of four.

A major change is the general policy of adopting chemical synonyms as principal entries with appropriate cross-references to popular or trivial names used predominantly in previous editions of the "Dictionary." A second important change is the inclusion of three double bonds for benzenoid rings in place of the simple hexagon to denote aromatic compounds. The implications of this revision are twofold. First, the aromatic compounds are more easily distinguished at first glance, and second a simplification of the structural formulas of saturated ring compounds has been made possible. The latter are now represented by a simple polygon and the compact structure saves considerable space alloted to the structural formula.

Improvements in the "Dictionary" are noted by the inclusion of stereochemical relationships in molecules and substantially more supplemental information for many compounds (*i.e.*, recrystallizing solvents, specific reactions, derivatives with melting points). The numbering systems for structural formulas including rings have been made to conform to the internationally accepted rules laid down by the I.U.P.A.C. A supplement to the present edition exists and further supplements are to be added annually to cover revision of existing entries and inclusion of new entries from the chemical literature.

The "Dictionary" can be improved in two respects. First by adopting the arrangement of symbols in organic formulas in strict alphabetical order following carbon and hydrogen if also present. This system typified by *Chemical Abstracts* has gained wide acceptance and allows ready comparison of formulas from multiple sources. A second area of concern pertains to the melting points included for many principal entries and certain important derivatives which are used as drugs. These melting ranges carried over from each previous