[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MIAMI]

Synthesis of 3-Hydroxypyridines. II. Preparation of Unsaturated Cyano Esters and Their Reaction with Diazomethane[1-3]

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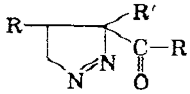
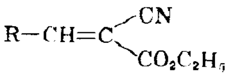
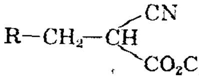
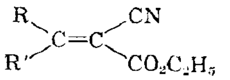
The best conditions for the condensation of a series of aldehydes, mainly aliphatic, with ethyl cyanoacetate are described. Reaction of these condensation products with diazomethane gives a product containing a methyl group on the *beta*-carbon rather than a pyrazoline.

In the course of developing a method of synthesis of 3-hydroxypyridines it was desirable to have a series of pyrazolines of the type I. A convenient route to some of the compounds in this series (I. $R' = CN$, $R'' = OC_2H_5$) would appear to be the reaction of unsaturated cyanoesters (II) with diazomethane.


I


$$R{-}CH{=}C\begin{matrix}CN\\CO_2C_2H_5\end{matrix}$$
II


$$R{-}CH_2{-}CH\begin{matrix}CN\\CO_2C_2H_5\end{matrix}$$
III


$$\begin{matrix}R\\R'\end{matrix}C{=}C\begin{matrix}CN\\CO_2C_2H_5\end{matrix}$$
IV

Alexander and Cope[4] developed an excellent method for the preparation of ethyl monoalkylcyanoacetates (III) through a reductive Knoevenagel reaction, and the reaction of ketones with ethyl cyanoacetate to give the unsaturated esters IV has been well studied.[5] With the exception of aromatic aldehydes,[1] however, only scattered reports have appeared of the condensation of aldehydes with ethyl cyanoacetate to give II. In the past[6] many compounds of the type II have been prepared by condensation of the aldehyde with cyanoacetic acid followed by esterification. Astle and Zaslowsky[7] have studied the use of anion exchange resins in the Knoevenagel reaction and include the reaction of four aldehydes with ethyl cyanoacetate in 54 to 83% yield. Other workers[8] have, however, reported lower yields and a product resulting from the condensation of two moles of the ethyl cyanoacetate with the aldehyde by using anion exchange resins.

We have studied the condensation of a group of aliphatic and heterocyclic aldehydes with ethyl cyanoacetate under a variety of conditions and find that using piperidine-acetic acid[4] or piperidine-dioxane[1] as the catalyst and solvent give the best results. The former appears to be the method of choice except when the product is a solid. The results of these condensations are shown in Table I.

A group of the compounds of type II were treated with diazomethane at 0° with vigorous evolution of nitrogen and the isolation, in good yields, of compounds of the type IV ($R' = CH_3$). Difficulty of this type has been foreseen as a result of the report of Young and co-workers[9] of the formation of methyl isopropylidenecyanoacetate from the reaction of α-cyanocrotonic acid and diazomethane. It had been hoped, however, that the use of aromatic or larger alkyl substituents might lead to pyrazoline. As speculated by Young,[9] this facile pyrazoline decomposition must be caused by the two electron withdrawing groups decreasing the electron density of the *alpha*-carbon since both methyl acrylate[10] and α-methylacrylonitrile[11] give good yields of pyrazoline with diazomethane. It might also be noted that ethyl 4-methyl-Δ1-pyrazoline-5,5-dicarboxylate is stable up to 60°[10] as compared with the lack of stability at 0° in this cyanocarboxylate series. It should be noted that the spectra of the crude reaction product after removal of ether at 20° was essentially identical with the spectra of the distilled, or recrystallized, product indicating that no pyrazoline decomposition occurred during the work-up.

Although the desired pyrazolines were not obtained, this method appears to be an excellent route to compounds of the type IV ($R' = CH_3$), particularly when the ketones needed to prepare this compound *via* a condensation reaction are not easily available. As can be seen from Table II several of

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(1) Part I, F. D. Popp, *J. Org. Chem.*, **25**, 646 (1960).

(2) This investigation was supported in part by a U.S.-P.H.S. Research Grant (RG 6478) from the Division of General Medical Sciences, Public Health Service and in part by a Grant-in-Aid from Eli Lilly & Co.

(3) A portion of this material was presented at the Florida Section of the ACS Meeting-in-Miniature, May 1960.

(4) E. R. Alexander and A. C. Cope, *J. Am. Chem. Soc.*, **66**, 886 (1944).

(5) A. C. Cope, C. M. Hofmann, C. Wyckoff, and E. Hardenbergh, *J. Am. Chem. Soc.*, **63**, 3452 (1941), and A. C. Cope, *J. Am. Chem. Soc.*, **59**, 2327 (1937).

(6) See for example K. v. Auwers, *Ber.*, **56**, 1172 (1923).

(7) M. J. Astle and J. A. Zaslowsky, *Ind. Eng. Chem.*, **44**, 2867 (1952).

(8) P. Mastagli, P. Lambert, and N. Andrie, *Bull. soc. chim. France*, 796 (1956).

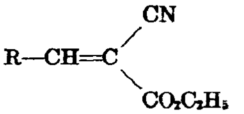
(9) W. G. Young, L. J. Anderson, S. L. Lindenbaum, and S. J. Cristol, *J. Am. Chem. Soc.*, **66**, 810 (1944).

(10) K. v. Auwers and F. Konig, *Ann.*, **496**, 27, 252 (1932).

(11) D. Gotkis and J. B. Cloke, *J. Am. Chem. Soc.*, **56**, 2710 (1934).

TABLE I

CONDENSATION OF ALDEHYDES WITH ETHYL CYANOACETATE



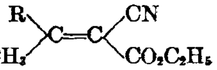
$R{-}CH{=}C(CN)(CO_2C_2H_5)$

R	Yield, %	B.P., °/mm. or (m.p., °)[a]	Method	Calcd. Carbon	Calcd. Hydrogen	Found[b] Carbon	Found[b] Hydrogen
CH_3—	52	71–72/2.4[c]	A[d]	60.42	6.52	60.35	6.44
	20		B[e]				
C_2H_5—	63	80–83/4.8[f]	A	62.74	7.18	62.43	7.11
$CH_3CH_2CH_2$—	74	68–71/2.8	A	(N 8.38)		(N 8.73)	
	47		B				
$(CH_3)_2CH$—	59	86–87/4.9	A	64.65	7.83	64.14	8.03
	53		B				
$CH_3(CH_2)_2CH_2$—	85	83–85/1	A	66.29	8.28	66.22	8.41
$(CH_3)_2CHCH_2$—	61	102–103/2.2	B	66.29	8.28	66.08	8.35
$(CH_3CH_2)_2CH$—	68	104–105/1[g]	B	67.66	8.87	67.86	8.44
$CH_3(CH_2)_4CH_2$—	85	132–134/4.8[h]	A	68.89	9.15	69.09	9.20
$CH_3(CH_2)_2CH_2CH\text{-}CH_3CH_2$	75	107–108/8.5	B	69.92	9.48	70.12	9.72
$C_6H_5CH{:}CH$—	90	(116)[i]	B	—	—	—	—
	57		A	—	—	—	—
Indole (3)	93	(165)[j]	B	—	—	—	—
Thiophene (2)	93	(93–94)[k]	B	57.90	4.38	58.02	4.48
Furan (2)	88	(90–91)[l]	B	62.82	4.74	62.94	4.97

[a] All melting and boiling points are uncorrected. [b] Analyses by Spang Microanalytical Laboratory, Ann Arbor, Mich., and Drs. Weiler and Strauss, Oxford, Eng. [c] Reported b.p. 112°/20 mm. (from esterification of acid), Ref. 6. [d] Method A, piperidine–acetic acid, see Experimental. [e] Method B, piperidine-dioxane, see Ref. 1. [f] Reported b.p. 121–122°/25 mm. (from esterification of acid), Ref. 6. [g] Reported b.p. 122–123°/8.5 mm., see Ref. 7. [h] Reported b.p. 190°/13 mm., A. Lapworth and J. A. McRae, *J. Chem. Soc.*, **121**, 2752 (1922); reported b.p. 140–143°/7 mm., see Ref. 7. [i] Reported m.p. 114–120°, see *Beilstein*, **9**, 913. [j] Reported m.p. 165°, R. B. VanOrder and H. G. Lindwall, *J. Org. Chem.*, **10**, 128 (1945). [k] Reported m.p. 94–98°, K. Pettersson, *Arkiv. Kemi*, **7**, No. 5, 39 (1954). [l] Reported m.p. 94°, R. Heuck, *Ber.*, **27**, 2625 (1894).

TABLE II

DIAZOMETHANE REACTIONS



$(R)(CH_3)C{=}C(CN)(CO_2C_2H_5)$

R	Yield, %	B.P., °/mm. or (m.p., °)[a]	Calcd. Carbon	Calcd. Hydrogen	Calcd. Nitrogen	Found[b] Carbon	Found[b] Hydrogen	Found[b] Nitrogen
CH_3—	98	91–92/1.5[c]	62.72	7.24	—	63.07	7.54	—
C_2H_5O—	60	(74–75)[d]	—	—	7.65	—	—	7.42
$CH_3(CH_2)_4CH_2$—	65	126/1[e]	—	—	—	—	—	—
C_6H_5—	99	152–153/2.5[f]	—	—	—	—	—	—
3,4-$(C_2H_5O)_2C_6H_3$—	81	(99–100)	67.31	6.95	—	67.66	6.79	—
Furan (2)	36	142/3.5	64.38	5.40	—	64.70	5.60	—
Indole (3)	79	(128–129)	70.85	5.55	11.02	70.86	5.79	11.25

[a,b] See footnotes *a,b* respectively in Table I. [c] Reported b.p. 107°/10 mm., S. Widequist, *Acta Chem. Scand.*, **3**, 303 (1949). [d] Reported m.p. 74–75°, J. P. Vila and R. G. Jarque, *Anales fis. y quim.* (*Spain*), **40**, 946 (1944); *Chem. Abstr.*, **39**, 4329 (1945). [e] Identical in every way with material prepared from 2-octanone and ethyl cyanoacetate as described in Ref. 5. [f] Identical in every way with material prepared from acetophenone and ethyl cyanoacetate as described in Ref. 5.

these materials were identified by comparison with known compounds. In all other cases the materials exhibited correct analysis and possessed infrared spectra related to those of the known compounds. In regard to the infrared spectra, it is of interest to note that the C::C stretching vibration shifts about 15–40 cm.$^{-1}$ to lower frequency on replacing the *beta*-hydrogen of II with a methyl group. This is a shift opposite in direction to the shift, if any, normally observed on adding groups to an olefin.[12]

Since a pyrazoline could not be obtained by reaction of II with diazomethane, it was hoped that reaction of II with phenyldiazomethane might lead to a pyrazoline which could be stabilized by a phenyl group. Reaction of II (R = $(C_2H_5)_2CH$—) with phenyldiazomethane gave a 20% yield of material which was believed to be IV (R = $(C_2H_5)_2CH$—,

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(12) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd ed., J. Wiley and Sons, Inc., New York, 1958.

$R' = C_6H_5CH_2—$) on the basis of elemental analysis and analogy to the diazomethane reactions.[13] A very small amount of lower boiling material, whose infrared spectra indicated the possible presence of pyrazoline was also obtained but decomposed very rapidly. The spectra of the reaction product before distillation exhibited little difference from the combined spectra of the distillation fractions. Reaction of ethyl α-cyanocinnamate with phenyldiazomethane also gave a compound of type IV as the major product.

EXPERIMENTAL

Reagents. The authors thank Kay-Fries Chemicals, Inc., and Fisher Chemical Co., Inc., for generous gifts of ethyl cyanoacetate. The aldehydes used were obtained from commercial sources and used without further purification. Thanks to Union Carbide Chemicals Co. and Abbott Labs. for samples of some of the aldehydes. We should also like to thank the DuPont Company for a generous gift of EXR-101,[14] which was used to generate the diazomethane, and Dr. W. M. Jones for unpublished directions on the preparation of phenyldiazomethane.

Compounds II. *Method A.* A mixture of 0.6 mole of ethyl cyanoacetate and 0.6 mole of the aldehyde in 80 ml. of glacial acetic acid was treated with a solution of 2 ml. of piperidine in 20 ml. of glacial acetic acid and allowed to stand at ambient temperature. After 24 hr. at room temperature, the mixture was diluted with 200 ml. of water and extracted with three 200-ml. portions of benzene. The combined extracts were washed with water and dried over magnesium sulfate. After removal of the solvent on the steam bath, the residue was distilled.

Compounds II. *Method B.* The reaction in dioxane was carried out as described previously.[1] If the product was not a solid, the solvent was removed *in vacuo* and the residue distilled.

Reaction of II *with diazomethane.* An ethereal solution of compound II was added to an excess of diazomethane in ether in an ice bath[15] and the solution kept for at least 16 hr. at 0 to 5°. This solution was concentrated *in vacuo* without heating and the infrared spectra obtained. Solids were then recrystallized from 95% ethanol and liquids distilled.

Reaction of II *(R' = $(C_2H_5)_2CH—$) with phenyldiazomethane.* A solution of II was added to an excess of phenyldiazomethane in petroleum ether (b.p. 35–55°) and kept at about 5° for 24 hr. The solution was concentrated at 250 ml. *in vacuo* and the precipitated azine filtered. The mixture was concentrated further and distilled to give a 20% yield of a liquid, b.p. 168–169° (2.2 mm.).

Anal. Calcd. for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12. Found: C, 75.60; H, 7.92.

Acknowledgment. We acknowledge the assistance of H. Swarz and J. Pattee in the preparation of the diazomethane.

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[13] A referee has suggested that this compound may be a cyclopropane. It has been found to decolorize potassium permanganate and to react with bromine in carbon tetrachloride at the same rate as the unsaturated starting material. In comparison, several cyclopropyl compounds reacted with the bromine at a different rate and did not decolorize permanganate. It would seem therefore that this material has the same structure as the diazomethane reaction products.

[14] Contains 70% of *N,N'*,-dinitroso-*N,N'*,-dimethylterephthalamide.

[15] Addition of the diazomethane solution to the solution of II gave identical results, as did the use of a methanol-ice bath for cooling.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS INC.]

Application of Sodium Borohydride Reduction to Synthesis of Substituted Aminopiperidines, Aminopiperazines, Aminopyridines, and Hydrazines

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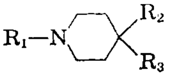
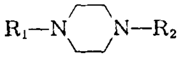
Quaternization of 4-aminopyridine with alkyl and arylalkyl halides gives 4-aminopyridinium salts, which are reduced with sodium borohydride to 1-(alkyl or arylalkyl)-4-aminopiperidines. Both 1-alkyl-4-aminopiperidines and 1-alkyl-4-aminopiperazines may be converted to Schiff bases which in turn are reduced with sodium borohydride to corresponding secondary amines. Similar reduction of appropriate Schiff bases as a means of preparing substituted 3-aminopiperidines, aminopyridines, and aminomethylpyridines, as well as reduction of dialkylhydrazones to corresponding trisubstituted hydrazines, are also described.

Piperidine and piperazine derivatives have occupied a very prominent place in medicinal chemistry and it can hardly be the purpose of this paper to review the great amount of work, much of it recorded in the patent literature, which has been done with these compounds. A host of compounds of general structure:



and



where R signifies various alkyl, arylalkyl, and oxygen-containing groups, have been prepared in a number of laboratories, and many of these have been demonstrated to have analgetic, neuroleptic, antihistaminic, hypotensive, antibacterial, or antiparasitic activity in various tests. On the other hand, far less work with similarly substituted aminopiperidines and aminopiperazines:

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[1] Mrs. Edwin L. Klett.