[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Substituted Dihydropyridines Related to Hantzsch's Pyridine Synthesis

BY ARTHUR P. PHILLIPS

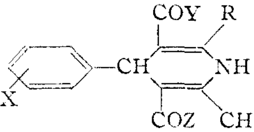
In connection with studies related to Hantzsch's dihydropyridine synthesis a few variations have been employed to produce compounds substituted on the 4-phenyl ring and with varying substituents on the dihydropyridine ring.

Suitable variations in the reactants have been employed to prepare an assortment of compounds related to the dihydropyridines obtained by the original Hantzsch[1] method.

Compounds I[2] and II (see Table I for the structures of the compounds discussed) were made by condensation of the aromatic aldehydes with two mols of acetylacetone in the presence of excess aqueous alcoholic ammonia. The difference in yields is in line with the slightly increased susceptibility to nucleophilic attack to be expected with the 3-nitrobenzaldehyde as compared with benzaldehyde.

TABLE I

MISCELLANEOUS SUBSTITUTED DIHYDROPYRIDINES



Cmpd. No.	X	Y	Z	R	Yield, %	M.p., °C.[a]	Crystn. solvent[b]	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
I[c]	H	CH_3	CH_3	CH_3	32	182–183	B·H				
II	3-NO_2	CH_3	CH_3	CH_3	50	211–212	A	65.0	65.2	5.8	5.8
III	3-NH_2	CH_3	CH_3	CH_3	70	213–214	A·B·H	71.8	71.8	7.1	7.0
IV	3-NO_2	CH_3	OC_2H_5	CH_3	80	168–169	A	62.8	62.9	5.9	5.9
V	3-NH_2	CH_3	OC_2H_5	CH_3	84	168–169	M·B·H	68.8	68.8	7.1	7.0
VI[d]	3-$(CH_3)_3$–NI	CH_3	OC_2H_5	CH_3	100	185–186	M·Ac·E	52.0	52.2	6.0	5.9
VII	4-$(CH_3)_2N$	CH_3	OC_2H_5	CH_3	35	168–169	Æ·H	70.1	70.4	7.7	7.6
VIII[d]	4-$(CH_3)_3NI$	CH_3	OC_2H_5	CH_3	85	196–197	M·Ac·E	52.0	52.4	6.0	6.0
IX	3-NO_2	OC_2H_5	OC_2H_5	C_6H_5	77	200–201	HOAc	66.0	65.9	5.5	5.4

[a] All melting points are uncorrected. [b] A = ethanol; Ac = acetone; Æ = ethyl acetate; B = benzene; E = ethyl ether; H = hexane; HOAc = glacial acetic acid; M = methanol. [c] This is a known compound, see ref. 2. [d] For evidence concerning the quaternary nature of these salts see ref. 3.

The unsymmetrical products IV and VII were readily produced by the interaction of β-aminocrotonic ester and the substituted benzylideneacetylacetone. Comparison of the yields obtained in the two cases again illustrates the lesser reactivity in the presence of the 4-dimethylamino groups as compared with the 3-nitro.

Catalytic hydrogenation, using Adams platinum oxide catalyst, of the 3-nitro derivatives II and IV yielded the corresponding primary amines III and V. Alkylation of V with excess methyl iodide in the presence of aqueous potassium carbonate gave the quaternary ammonium salt VI, while simple addition of methyl iodide to VII gave VIII.

Compound IX was obtained by the reaction of β-aminocrotonic ester with 3-nitrobenzylidenebenzoylacetic ester.

Experimental

Illustrative examples of methods of preparation are given below. The processes of catalytic hydrogenation and of alkylation are not described here as they do not differ materially from the analogous processes presented elsewhere.[3] Details for all compounds appear in Table I.

2,6-Dimethyl-3,5-diacetyl-4-(3′-nitrophenyl)-1,4-dihydropyridine (Compound II.).—A mixture of 15 g. (0.1 *M*) of *m*-nitrobenzaldehyde, 20 g. (0.2 *M*) of acetylacetone, 20 cc. of ethanol and 10 cc. of concentrated aqueous ammonia was allowed to stand for one hour at room temperature and then was heated for three hours on a steam-bath. On cooling and scratching a yellow crystalline precipitate formed and was collected. The yield of yellow prisms was 16 g. (50%) and after recrystallization from ethanol the melting point was 211–212°.

2,6-Dimethyl-3-acetyl-4-(4′-dimethylaminophenyl)-5-carbethoxy-1,4-dihydropyridine (Compound VII).—To 12 g. (0.05 *M*) of *p*-dimethylaminobenzylidene acetylacetone was added 7 g. (0.05 *M*) of β-aminocrotonic ester and the mixture was heated for 16 hours on a steam-bath. After cooling and stirring the viscous residue with ether there was isolated 6 g. (35%) of yellow crystalline solid which melted at 168–169° after recrystallization from an ethyl acetate-hexane mixture.

Acknowledgment.—The author is happy to acknowledge his indebtedness to Mr. Samuel W. Blackman who obtained the microanalytical results reported here.

TUCKAHOE 7, N. Y. RECEIVED NOVEMBER 24, 1950

---

[1] A. Hantzsch, *Ann.*, **215**, 1 (1882), and many subsequent papers.

[2] E. Knoevenagel and W. Ruschhaupt, *Ber.*, **31**, 1026 (1898).

[3] A. P. Phillips, THIS JOURNAL, **71**, 4003 (1949).