further sublimation and collected as colorless crystals (0.02 g.), m.p. 57°. It has a faecal smell and turns pine chip soaked in concentrated hydrochloric acid cherry red. It produces a scarlet-red crystalline picrate, m.p. 134°.

Anal. Calcd. for C_9H_9N: C, 82.44; H, 6.87; N, 10.69. Found: C, 82.65; H, 6.85; N, 10.75.

It was proved to be identical with synthetic 2-methylindole, m.p. 57°, by a mixed m.p. determination and also the mixed m.p. determination of its picrate, m.p. 134°—with the picrate (which melts alone at 134°) of synthetic 2-methylindole.

(b) This fraction was separated from the adhesive gum by several fractional sublimations in higher vacuum (0.01 mm.) and was finally obtained as a colorless solid at 110° (0.01 mm.). It is an acid as it dissolves in sodium bicarbonate solution with an effervescence and the alkaline solution on acidification regenerates the original substance. It crystallizes from benzene in glistening flakes, m.p. 199° (yield 0.15 g.). The acid, when treated with soda lime, produces an oil, which has an offensive odor like skatole and responds to the pine chip test for indole. The acid produces a violet-red coloration with isatin and concentrated sulfuric acid. It decomposes at 230° producing indole, C_8H_7N, m.p. 51°. The acid and its picrate did not depress the m.p. of synthetic indole-2-carboxylic acid and its picrate (golden yellow), m.p. 178°, when mixed.

Anal. Calcd. for $C_9H_7O_2N$: C, 67.09; H, 4.35; N, 8.70. Found: C, 67.07; H, 4.34; N, 8.73.

Acknowledgment.—In conclusion, the author expresses his thanks to Dr. Asima Chatterjee (née Mookerjee) for the valuable suggestions and the laboratory facilities given. The author is also grateful to Prof. L. Zechmeister and Prof. A. J. Haagen-Smit, California Institute of Technology, for micro-analyses of the compounds.

CALCUTTA, W. BENGAL, INDIA

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Condensations of Cinchoninaldehyde. VI.[1] With the Quaternary Alkiodides of Some Heterocyclic Active Methyl Compounds

BY ARTHUR P. PHILLIPS

RECEIVED AUGUST 20, 1952

Cinchoninaldehyde has been condensed with a series of alkiodides of 2- and 4-methylpyridine and with the methiodides of 2- and 4-methylquinoline and of 2,4-dimethylthiazole. Some observations have been made concerning the relationship between structure and reactivity of the methylpyridine and quinoline alkiodides.

In a continuation of the study of the chemical reactivity of cinchoninaldehyde it has been condensed with a number of alkiodides of 2-methylpyridine and 4-methylpyridine, and with the methiodides of 2-methylquinoline, 4-methylquinoline and 2,4-dimethylthiazole. The reactions were run in methanol solution using piperidine as the catalyst. Yields were moderately good varying between 50 and 90%. Although cinchoninaldehyde belongs to the type of aldehyde for which high carbonyl reactivity is expected,[2] the reactive methyl components are of that class which gives best yields with those aldehydes such as *p*-dimethylaminobenzaldehyde and *p*-methoxybenzaldehyde, bearing strong electron release substituents, even though the carbonyl reactivity of the latter aldehydes is of a low order.[2-4]

Two points in connection with the relationship between structure and reactivity were explored semi-quantitatively: (1) The comparative reactivities of the 2- and 4-methyl groups in the methiodides of the pyridine and quinoline series using cinchoninaldehyde as the common carbonyl reactant. (2) The possible variation in the steric hindrance to the condensation depending upon the size of the N-alkyl group in the 2-methylpyridine alkiodides.[5] Any such manifestation should be more prominent with cinchoninaldehyde than with benzaldehyde because of the ortho substituent, the 5-position on the benzene ring, of the former.

Although the reactions had not been run uniformly at first, the key condensations were repeated under identical conditions employing a two-hour reaction time which gave less than optimal yields in each case. Comparison of the yields of I[6] (33%) and V[6] (22%) and of VIII (41%) and IX (27%) seems to indicate a greater reactivity for the 2-methyl methiodides with *this particular type*[2] of aldehyde. This is in spite of the fact that any hindrance to the reaction by the N-alkyl of the alkiodide should make the 2-methyl derivatives less favorable sterically than their 4-methyl analogs. It must not be overlooked that in some cases side reactions may have complicated the picture. Thus in the preparation of IX from cinchoninaldehyde and 4-methylquinoline methiodide about 25% of a highly colored by-product was obtained. This was deep greenish-black and probably is a cyanine dye, of structure as yet undetermined.

Further work is planned to compare the reactivities of the 2- and 4-methyl heterocyclic derivatives both as the tertiary bases and as their methiodides with several aldehydes of different types.[2] It is felt that the apparent "reactivity" of the methyl may depend not only upon its position on the ring (2- or 4-) but upon both the state of the hetero nitrogen and the type of aldehyde under consideration.

Comparison of the yields of I (33%, quaternizing alkyl is CH_3) and IV (25%, quaternizing alkyl is $(CH_3)_2CH$) indicates that steric interference between the aldehyde and quaternizing alkyl cannot be a very significant factor in the reaction, for changing the alkyl from methyl to isopropyl resulted in only a small decrease in the yield of product.

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[1] Paper V, THIS JOURNAL, **74**, 5230 (1952).

[2] A. P. Phillips and J. G. Murphy, *J. Org. Chem.*, **16**, 954 (1951).

[3] A. P. Phillips, *ibid.*, **12**, 333 (1947).

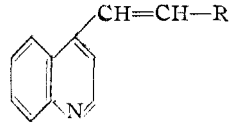
[4] A. P. Phillips, *ibid.*, **14**, 302 (1949).

[5] Any steric factor associated with the N-alkyl groups should be insignificant for the 4-methylpyridine alkiodides.

[6] See Table I for the structures of the compounds indicated here by numbers.

TABLE I

CONDENSATION PRODUCTS FROM CINCHONINALDEHYDE AND HETEROCYCLIC REACTIVE METHYL COMPOUNDS



Compound No.	R	Heating time, hr.[a]	Yield, %[b]	M.p., °C.[c]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
I	2-Pyridine·CH_3I	2	33 (80)	249–250	$C_{17}H_{15}N_2I$	54.5	54.8	4.0	4.0
		2	32 (88)						
II	2-Pyridine·C_2H_5I	5	65	250–251	$C_{18}H_{17}N_2I$	55.7	55.3	4.4	4.2
III	2-Pyridine·n-C_3H_7I	5	60	233–234	$C_{19}H_{19}N_2I$	56.7	56.7	4.8	4.8
IV	2-Pyridine·i-C_3H_7I	2	25	220–221	$C_{19}H_{19}N_2I$	56.7	56.7	4.8	4.9
		20	90						
V	4-Pyridine·CH_3I	2	23 (90)	264–265	$C_{17}H_{15}N_2I$	54.5	54.5	4.0	4.2
		2	20						
VI	4-Pyridine·C_2H_5I	7	71	225–226	$C_{18}H_{17}N_2I$	55.7	55.9	4.4	4.7
VII	4-Pyridine·n-C_4H_9I	48	70	240–241	$C_{20}H_{21}N_2I$	57.7	57.7	5.1	5.0
VIII	2-Quinoline·CH_3I	2	41 (75)	221–222	$C_{21}H_{17}N_2I$	59.4	59.3	4.0	4.3
IX	4-Quinoline·CH_3I	2	27 (50)	253–254	$C_{21}H_{17}N_2I$	59.4	59.1	4.0	3.9
X	2-(4-Methylthiazole)·CH_3I	1	70	226-227	$C_{16}H_{15}N_2SI\cdot CH_3OH$	47.9	47.8	4.5	4.2

[a] The heating times and reaction conditions have no critical significance except for the two hour times in which both the reaction period and other conditions were made uniform to allow semi-quantitative comparisons of the yields (see compounds I, IV, V, VIII and IX). [b] Yields given correspond to the total amount of product isolated after the stated reflux time plus material recovered by working up the mother liquors and filtrates. The first yields given for compounds I, IV, V, VIII and IX refer to the product isolated on cooling the reaction mixture after the two hour interval, while the figures in parentheses represent the total yield recovered after reworking the filtrates. The reworking always involves unmeasured additional heating and standing periods. [c] Melting points are uncorrected. Compounds I, II, III, V, VIII, IX and X were recrystallized from methanol, while IV, VI and VII were recrystallized from methanol-ethyl acetate mixtures.

When compound I was refluxed for 70 hours with methyl iodide in methanol solution none of the bis-methiodide was obtained and unchanged I was recovered quantitatively.

Experimental

General Condensation Method.—A mixture of 0.02 mole of 2-(or 4)-methylpyridine (or quinoline) alkiodide, 4 g. (0.022 mole) of cinchoninaldehyde (monohydrate), 50 cc. of methanol and 10 small drops of piperidine was refluxed for two hours on a steam-bath. The reaction mixture was chilled rapidly in cold water and allowed to stand for one hour in the cold. The crystalline product was collected by filtration and was purified by recrystallization from methanol.

Evaporation of the methanol mother liquors, involving another interval of heating on a steam-bath, gave an additional yield. Some of the condensations were refluxed for longer or shorter periods, but the two-hour interval and the first crop isolated were used uniformly in those cases where comparisons were made.

Details for all compounds appear in Table I.

Acknowledgment.—The microanalyses included in this paper were done by Samuel W. Blackman.

TUCKAHOE, NEW YORK

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY]

A Stereospecific Synthesis of Cantharidin

BY GILBERT STORK, EUGENE E. VAN TAMELEN, LEONARD J. FRIEDMAN AND ALBERT W. BURGSTAHLER[1]

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A total synthesis of cantharidin (I) from the butadiene adduct (X) of dimethyl 3,6-epoxy-3,4,5,6-tetrahydrophthalate (IX) is described.

Cantharidin, the potent vesicant principle found in various species of cantharides beetles,[2] was first obtained in crystalline form by the French pharmacist Robiquet in 1810.[3] The remarkable properties of the substance which had acquired a certain meretricious fame as an aphrodisiac stimulated extensive structural investigations that culminated in the proposal of the correct structure (I) by Gadamer and his school.[4] Although the cantharidin molecule possesses the somewhat unusual features of a 1,4-oxide bridge and two adjacent angular methyl groups, it is interesting to note that it consists of two tail-to-tail isoprene units and may thus be regarded as a bicyclic monoterpenoid.

Cantharidin is optically inactive and non-resolvable[4]; its anhydride ring is therefore *cis* fused. There are, nevertheless, two stereochemical arrangements which correspond to the two-dimen-

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(1) National Institutes of Health Predoctoral Fellow, Harvard University, 1951–1952.

(2) Perhaps the most familiar is *cantharis vesicatoria*, more commonly known as Spanish Fly.

(3) M. Robiquet, *Ann. chim.*, [1] **76**, 302 (1810).

(4) J. Gadamer, *Arch. Pharm.*, **252**, 609 (1914); W. Rudolph, *ibid.*, **254**, 423 (1916), and later papers.