[Contribution from the University of New Mexico, Laboratory of Pharmaceutical Chemistry and the Department of Chemistry]

CINNOLINE CHEMISTRY. II. THE CONDENSATION OF 4-METHYLCINNOLINE WITH ALDEHYDES[1]

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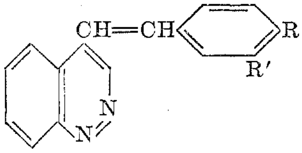
Received June 11, 1953

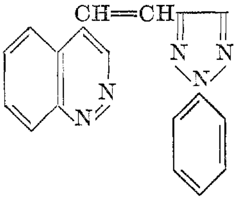
Although the methyl group in 4-methylcinnoline is highly active, only a few examples of the condensation of aldehydes with this compound have been reported. Jacobs, *et al.*, (1) prepared 4-styrylcinnoline in high yield by condensing benzaldehyde with 4-methylcinnoline in the presence of anhydrous zinc chloride. We have prepared 4-styrylcinnoline (I) by their method, except that we obtained a lower yield (62%). Atkinson and Simpson (2) prepared 4-styryl-1-cinnolinium alkiodides by condensing aldehydes with 4-methyl-1-alkylcinnolinium iodides. The methyl group is considerably more reactive when the basic nitrogen atom is quarternized.

After the present work had been completed, Albert and Hampton (3) described a novel method for the condensation of benzaldehyde with 8-hydroxy-4-methylcinnoline in concentrated hydrochloric solution. Their method obviates the large amounts of tarry materials formed when anhydrous zinc chloride is used.

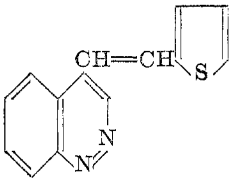
In our experiments, with the exception of the preparation of 4-styrylcinnoline (I) and 4-(*p*-methoxystyryl)cinnoline (II), the yields were very poor. In each instance large amounts of tarry materials were formed. 4-(3,4-Dimethoxystyryl)cinnoline (III) was prepared in only 10% yield. 2-Phenyl-1,2,3,2*H*-triazole-4-carboxaldehyde condensed readily, though in small yield, to produce 1-(4-cinnolyl)-2-[4-(2-phenyl)-1,2,3,2*H*-triazolyl]ethene (IV). Likewise 2-thiophenealdehyde gave 1-(4-cinnolyl)-2-(2-thenyl)-ethene (V).



I R, R' = H
II R = OCH_3, R' = H
III R, R' = OCH_3



IV



V

Salicylaldehyde, furfural, *p*-nitrobenzaldehyde, and phenylacetaldehyde produced only tars when condensations were attempted using anhydrous zinc chloride as the catalyst, while 2,4-dinitrobenzaldehyde was recovered unchanged. An attempt to condense benzaldehyde with 4-methylcinnoline using piperidine as a catalyst was unsuccessful. An attempt to condense 9-anthraldehyde produced a non-nitrogenous compound melting at 143.4–143.8°, which contained 81.29% carbon and 6.66% hydrogen. This analytical data does not

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[1] For Paper I in this series see *J. Org. Chem.*, **17**, 1571 (1952).

conform to any apparent compound. An attempt to condense acetophenone with 4-methylcinnoline using anhydrous zinc chloride was unsuccessful.

In view of the work of Albert and Hampton (3), it would be interesting to determine whether their conditions would allow the formation of the corresponding styryl compound using the aldehydes, which in our hands, produced only tars.

Acknowledgment. The authors wish to express their appreciation to the Upjohn Company for financial support. We also wish to express our appreciation to Drs. M. E. Speeter and D. I. Weisblat for their helpful suggestions.

EXPERIMENTAL

All melting points were taken with the Anschutz thermometers at total immersion, thus no stem correction was necessary, except where noted.

4-Methylcinnoline. This compound was prepared by the method of Jacobs, *et al.*, (1), m.p. 76–77°, uncorrected.

4-Styrylcinnoline. The procedure of Jacobs, *et al.*, (1) was followed on a smaller scale. There was obtained from 2.0 g. (0.014 mole) of 4-methylcinnoline, 0.9 g. (0.007 mole) of anhydrous zinc chloride, and 15 ml. of benzaldehyde, 2.0 g. (62%) of green-gold plates, m.p. 121.8–122.6° after crystallization from aqueous ethanol.

4-(p-Methoxystyryl)cinnoline. A mixture of 2.0 g. (0.014 mole) of 4-methylcinnoline, 40 ml. of *p*-methoxybenzaldehyde, and 0.9 g. (0.007 mole) of anhydrous zinc chloride was heated at 150° for 4½ hours. The cooled reaction mixture was treated with 10 ml. of benzene and 10 ml. of 2 *N* hydrochloric acid and was heated on a water-bath for one hour. The dark red hydrochloride was filtered, washed with water, and dried. The hydrochloride was converted to the free base by shaking with dilute aqueous sodium hydroxide solution. There was obtained 1.5 g. (42%) of golden plates after four crystallizations from methanol, m.p. 112.2–112.6°.

Anal. Calc'd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68.
Found: C, 77.30; H, 5.44; N, 10.80.

1-(4-Cinnolyl)-2-(2-thenyl)ethene. A mixture of 2.0 g. (0.014 mole) of 4-methylcinnoline, 10 ml. of 2-thiophenealdehyde, and 0.9 g. (0.007 mole) of anhydrous zinc chloride was treated as described above. However upon regeneration of the free base a considerable quantity of methanol-insoluble material was obtained which was not identified. The desired compound crystallized from methanol as fine bright yellow needles, m.p. 113–113.6°, yield, 0.41 g. (12%).

Anal. Calc'd for $C_{14}H_{10}N_2S$: C, 70.55; H, 4.23; N, 11.75.
Found: C, 70.44; H, 4.40; N, 11.52.

1-(4-Cinnolyl)-2-[4-(2-phenyl)-1,2,3,2H-triazolyl]ethene. To a solution of 2.0 g. (0.014 mole) of 4-methylcinnoline and 4.8 g. (0.028 mole) of 2-phenyl-1,2,3,2*H*-triazole-4-carboxaldehyde [prepared by the method of Riebsomer and Sumrell (4)] in 50 ml. of dry xylene was added 0.9 g. (0.007 mole) of anhydrous zinc chloride. The mixture was refluxed for 75 minutes. After allowing the reaction mixture to cool, the supernatant liquid was decanted from a considerable amount of tar. Upon evaporation of the xylene solution a yellow residue was obtained which after crystallization from methanol gave 0.32 g. (8%) of bright yellow needles, m.p. 205.2–205.6°. Some unreacted aldehyde was also recovered from the methanol.

Anal. Calc'd for $C_{18}H_{13}N_5$: C, 72.22; H, 4.38; N, 23.40.
Found: C, 72.77; H, 4.59; N, 23.60.

4-(3,4-Dimethoxystyryl)cinnoline. To a solution of 2.0 g. (0.014 mole) of 4-methylcinnoline and 2.3 g. (0.014 mole) of 3,4-dimethoxybenzaldehyde in 40 ml. of dry xylene was added 0.9 g. (0.007 mole) of anhydrous zinc chloride. During the 4½ hour refluxing period a red semi-solid mass separated, from which was isolated some unreacted 4-methylcinnoline. The supernatant xylene solution upon evaporation yielded an oily liquid which failed to solidify upon long standing. This was distilled in a vacuum, and the red, viscous distillate solidified after it was allowed to stand for six months. After one year the solid was extracted with petroleum ether from which additional 4-methylcinnoline was recovered. The solid residue from the petroleum ether extraction was crystallized once from ethanol and twice from aqueous ethanol. There was obtained 0.4 g. (10%) of very pale yellow needles, m.p. 193–194° (uncorrected). The 10% yield does not take into account the recovered 4-methylcinnoline.

Anal. Calc'd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52
Found: C, 74.15; H, 5.75.

SUMMARY

4-Methylcinnoline has been condensed with aldehydes in the presence of anhydrous zinc chloride to give 4- "styryl-type" compounds. Of those prepared, four of these compounds have not previously been reported in the literature. Under the conditions used considerable tar formation was observed. A number of condensations of this type were unsuccessful.

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REFERENCES

(1) Jacobs, Winstein, Henderson, and Spaeth, *J. Am. Chem. Soc.*, **68**, 1310 (1946).
(2) Atkinson and Simpson, *J. Chem. Soc.*, 808 (1947).
(3) Albert and Hampton, *J. Chem. Soc.*, 4985 (1952).
(4) Riebsomer and Sumrell, *J. Org. Chem.*, **13**, 807 (1948).