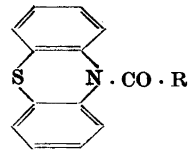
Table 2. Alkylaminoacylphenothiazines.



Compound no.	R	M. p. °C
I	$-CH_2 \cdot N(CH_3)_2$	114.5—116
II	$-CH_2 \cdot N(C_2H_5)_2$	58 —59
III	$-CH_2 \cdot$ N-ring	164—165
IV	$-CH_2 \cdot NH-$ ring	124—126
V	$-CH(CH_3) \cdot N(C_2H_5)_2$	99.5—100.5
VI	$-CH(CH_3) \cdot$ N-ring	110—111
VII	$-CH(C_2H_5) \cdot N(CH_3)_2$	98—99
VIII	$-CH(C_2H_5) \cdot N(C_2H_5)_2 \cdot HCl$	203 (dec.)
IX	$-CH(C_2H_5) \cdot$ N-ring $\cdot HCl$	216 (dec.)

An Improved Synthesis of Ethyl *Iso*propylidenecyanoacetate and the Construction of a New Water Separator

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Ethyl *iso*propylidenecyanoacetate was first prepared by Komppa [1] by condensation of acetone and ethyl cyanoacetate by means of diethylamine. The reaction mixture was kept for one month at room temperature, and the yield of ethyl isopropylidenecyanoacetate was about 8 %.

A better yield was obtained by Scheiber and Meisel [2], when a mixture of one mole of ethyl cyanoacetate, 3 moles of acetone, and 0.2 mole of zinc chloride and aniline was boiled for 8 hours, thus yielding 40 % of ethyl *iso*propylidenecyanoacetate.

These compounds have been subject to preliminary pharmacological tests (S. Wiedling). They all show a rather high local anesthetic power, for instance a 0.7 % solution of compound V has the same duration as a 2 % solution of Xylocaine-HCl (pH 5.6) but a longer time of onset when tested on rabbit cornea. The antihistaminic effect was rather weak, when tested on isolated guinea-pig intestine, for instance compound I excerted about 1/5 of the effect of Benadryl. The compounds had a good antispasmodic activity, compound V was twelve times more active than Benadryl when tested against acetylcholine on isolated guinea-pig intestine. Preliminary toxicity tests show that compound V has a Dl_{50} about 2 g/kg when injected subcutaneously on mice.

Complete chemical and pharmacological results will be reported later.

Received April 5, 1949.

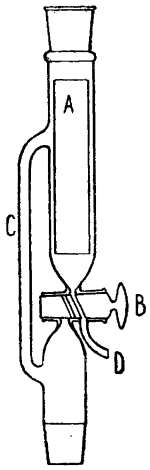

Fig. 1. The water separator.

At last Vogel [3] by using piperidine as condensing agent obtained a yield of 54 % of the ester. The reaction mixture was kept at room temperature for 60 hours, refluxed for 4 hours and again kept at room temperature for 60 hours.

Recently Cope, Hofmann, Wyckoff, and Hardenbergh [4] reported an excellent method for condensing ketones with cyanoacetic ester, in which the reactants were refluxed together with benzene, ammonium acetate, and acetic acid. The water produced during the condensation forms an azeotropic mixture with the benzene and is removed by means of a Dean and Stark constant water separator. This method is unfortunately useless for condensing ethyl cyanoacetate with acetone, as no azeotropic mixture is formed in this case. It is, however, possible to make the method useful also for condensations with acetone, when chloroform is used instead of benzene. In this way ethyl *iso*propylidenecyanoacetate was prepared in a yield of 75 %. When chloroform is substituted for the benzene, it is not possible to use the Dean and Stark separator. For this reason another separator was constructed. An ordinary simple Thielepape extractor (Fig. 1) was fitted with an inner open glass tube (A) and connected with the flask, containing the reaction mixture, and a reflux condenser. When the tap (B) is locked, an azeotropic mixture of acetone, chloroform and water distills up in the condenser and drops into the inner tube (A) in the separator. The water separates and forms the upper layer. The chloroform flows out from the bottom of the tube and up on the outside. When it reaches the side tube (C) of the separator, it flows down into the flask again. By means of the tap (B) the chloroform in the separator tube (A) may be tapped down into the reaction vessel, and the water is removed through the tap tube (D).

Experimental. A mixture of 85 g of ethyl cyanoacetate (0.75 mole), 56 g of acetone (0.97 mole), 9 g of glacial acetic acid, 6 g of ammonium acetate, and 75 ml of chloroform was boiled in a 500 ml round bottomed flask, fitted with a reflux condenser and a water separator, until no more water separated. The reaction was finished after about two hours. After cooling, the reaction mixture was washed several times with water and dried with anhydrous sodium sulfate. The chloroform was distilled off and the residue was fractionated *in vacuo* through a Widmer column. The distillate crystallized in the receiver, and it was necessary to feed the condenser with warm water in order to prevent crystallization in the condenser during the distillation. B. P. 107°/10 mm. Yield 86 g of ethyl *iso*propylidenecyanoacetate (75 %).

1. Komppa, G., *Ber.* **33** (1901) 3532.
2. Scheiber, J., and Meisel, F., *Ber.* **48** (1915) 254.
3. Vogel, I., *J. Chem. Soc.* (1928) 2019.
4. Cope, A., Hofmann, C., Wyckoff, C., and Hardenbergh, E., *J. Am. Chem. Soc.* **63** (1941) 3452.

Received May 10, 1949.