PYRROLES FROM KETOXIMES AND ACETYLENE.

22.* DIHALOETHANES IN PLACE OF ACETYLENE IN REACTIONS WITH CYCLOHEXANONE OXIME

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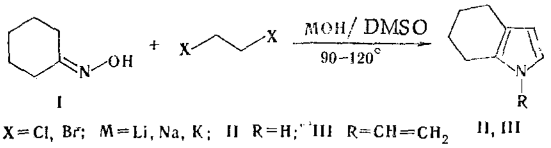
4,5,6,7-Tetrahydroindole and its 1-vinyl derivative were obtained in overall yields of 30-60% by the reaction of cyclohexanone oxime with 1,2-dichloro- and 1,2-dibromoethane in the MOH–dimethyl sulfoxide (DMSO) superbase system (M = K, Na, Li). Nucleophilic substitution of the halogen in the dihaloethanes by the oximate anion to give the corresponding ethylene glycol bis(imido ether) is a side reaction. The effect of the reaction conditions on the yields of products and the selectivity of the process was examined.

It is known [2] that pyrroles, including 4,5,6,7-tetrahydroindole, and their 1-vinyl derivatives can be obtained in high yields by the reaction of ketoximes with acetylene in an alkali metal hydroxide–dimethyl sulfoxide (DMSO) system, which has superhigh basicity.

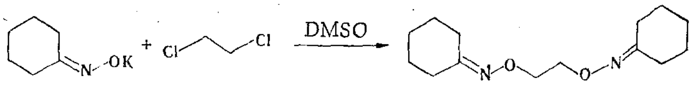
In the present paper for the first time we present the experimental details of a new synthesis of 4,5,6,7-tetrahydroindoles II and III from cyclohexanone oxime (I) and 1,2-dihaloethanes, which, as has been reported briefly [3-5], in the same superbase systems behave like acetylene upon reaction with ketoximes.



X=Cl, Br; M=Li, Na, K; II R=H; III R=CH=CH$_2$

This variant of the Trofimov reaction [2, 6, 7], despite the lower yields of pyrroles, may prove to be more acceptable for laboratories that do not have free acetylene at their disposal and experience in working with it.

Data from the analysis [by gas-liquid chromatography (GLC)] of the mixtures isolated in some characteristic experiments are presented in Table 1 to illustrate the principal tendencies in the change in the yields and the ratios of products II and III as a function of the reaction conditions. The best overall yields (52-61%) are obtained for I:dichloroethane:KOH:DMSO molar ratios of 1:1-2:7:10 at 115°C and a reaction time of 3-7 h (experiments Nos. 1-3). For the successful synthesis of pyrroles II and III it is important to add the alkali and dihaloethane to the solution of the ketoxime in DMSO in portions, for otherwise the formation of diether IV due to nucleophilic substitution of the halogen in the 1,2-dihaloethane by the oximate ion becomes appreciable.



IV

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*See [1] for communication 21.

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TABLE 1. Effect of the Conditions of the Reaction of Cyclohexanone Oxime with 1,2-Dihaloethanes on the Compositions and Yields of the Products[a]

Expt.	I:dihaloethane[b] :MOH[c] ratio, moles	Temp., °C	Time, h	Yield of the mixture of products,[d] %	Composition, %		
					I	II	III
1	1 : 1 : 7	115	3	57	1	75	24
2	1 : 2 : 7	115	6	61	Traces	83	17
3	1 : 2 : 7	115	7	52	"	89	11
4	1 : 2 : 7[e]	93	6	33	4	94	2
5	1 : 2 : 6[e]	115	4	33	Traces	95	5
6	1 : 3 : 12	115	2	51	"	61	39
7	1 : 3 : 12	115	3	53	"	51	49
8	1 : 3 : 12	115	4	53	"	37	63
9[f]	1 : 2 : 7	93	6	32	39	61	Not detected
10[g]	1 : 2 : 7	93	6	31	57	43	" "
11[g]	1 : 2 : 7	115	4	52	54	46	" "
12[h]	1 : 2 : 7	93	6	18	76	24	" "

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[a] In all of the experiments the DMSO was taken in an amount that was 10 times the mass of cyclohexanone oxime. [b] 1,2-Dichloroethane, except for experiments No. 9. [c] KOH, except for experiments Nos. 10-12. [d] On the basis of the oxime. [e] With the addition of water (∿10% of the mass of the reaction mixture). [f] The experiment was carried out with 1,2-dibromoethane. [g] With NaOH. [h] With LiOH.

At the price of decreasing the yield to ∿30%, one can attain a selectivity with respect to pyrrole II of 94-95%. As in the reaction with free acetylene [8], this is achieved primarily by the addition of small amounts of water (10-20%) to the reaction mixture (experiments Nos. 4 and 5). In this case the water can be conveniently fed into the mixture by dissolving alkali in it, which simultaneously also facilitates the dispensing of both components. Thus the conditions of experiments Nos. 1-5 can be recommended as preparative conditions for the synthesis of 4,5,6,7-tetrahydroindole (II). Indole II is purified by recrystallization from hexane (starting oxime I can be removed from the mixture prior to this by washing with a concentrated aqueous solution of alkali). Thiylation of the mixture under the conditions in [9] may also help to remove 1-vinylindole III impurities. The addition of thiols to 1-vinylpyrroles proceeds quantitatively to give high-boiling sulfides, from which indole II is readily separated by distillation.

The percentage of vinyl derivative III increases when the relative amounts of the dihaloethane and alkali in the reaction mixture are increased and can be brought up to 60% or higher (experiments Nos. 6-8) vis-à-vis an overall yield of 51-53%. This mixture can also be separated by crystallization of indole II from hexane (liquid indole III remains in the mother liquor).

Somewhat poorer results are obtained with 1,2-dibromoethane (experiment No. 9) under comparable conditions (experiment No. 4) — at the same overall yield (∿30%) the reaction product contains ∿40% of the starting oxime. Replacement of KOH by NaOH and LiOH (experiments Nos. 4 and 10-12), as in the reaction with free acetylene [2], makes the process completely selective but subsequently leads to a sharp decrease in the yields of products and the conversion of the oxime. However, with NaOH the yield of indole II with respect to the converted oxime still remains satisfactory (within the limits of 30%).

EXPERIMENTAL

Chromatographic analysis was accomplished with a Khrom-4 chromatograph with a catharometer as the detector and a 2.5-m-long column with a diameter of 3 mm; the solid phase was Chromaton N-AW-DMCS, the liquid phase was 15% DS-550 silicone, the thermostat temperature was 170°C, and the carrier gas was helium.

4,5,6,7-Tetrahydroindole (II). 1. A 20-g (0.18 mole) sample of oxime I, 17.7 g of KOH powder, and 170 ml of DMSO were placed in a flask equipped wiht a stirrer, reflux condenser, thermometer, and a dropping funnel, and the mixture was stirred thoroughly at 115°C, during which a solution of 35.6 g (0.36 mole) of 1,2-dichloroethane in 30 ml of DMSO was added dropwise in the course of 7 h with the simultaneous addition each hour of a 6-8 g portion of KOH(the total amount of KOH was 53 g). The overall mass of KOH in the reaction mixture was 70.7 g (1.26 mole). The reaction mixture was cooled to room temperature and poured into ice water, and the reaction products were extracted with ether (three 150-ml portions). The ether extracts were washed with water (three 100-ml portions) and dried with K_2CO_3. The ether was removed by distillation, and the residue was fractionated *in vacuo* to give 11.4 g (52%) of a mixture [bp 60-150°C (4 hPa)] of indole II (89%) and vinylindole III (11%). Crystallization from hexane gave 8.8 g (41% based on oxime I) of 4,5,6,7-tetrahydroindole (II) with mp 55°C [10].

2. A 35.6-g (0.36 mole) sample of 1,2-dichloroethane and 70 ml of DMSO were added at 115°C in the course of 4 h to a suspension of 20 g (0.18 mole) of oxime I and 15.2 g of powdered KOH in 130 ml of DMSO. The dropwise addition of a solution of 45.4 g of KOH in 25 ml of water was begun simultaneously 1 h after the start of the addition of this mixture. Workup as described above gave 7.1 g (33%) of a mixture of indoles (95% II and 5% III); recrystallization from hexane gave 6.1 g (28.5%) of indole II.

3. The reaction of 20 g (0.18 mole) of oxime I and 35.6 g (0.36 mole) of 1.2-dichloroethane in the presence of 50.4 g (1.26 mole) of NaOH in 200 ml of DMSO (at 115°C for 4 h) gave 10.7 g (52%) of a mixture of 54% of oxime I and 46% of indole II, from which 4 g (26% based on the converted oxime I) of indole II was obtained by crystallization from hexane.

4. The reaction of 20 g (0.18 mole) of oxime I, 35.6 g (0.36 mole) of 1,2-dichloroethane, and 30.2 g (1.26 mole) of LiOH in 200 ml of DMSO (at 93°C for 6 h) gave 3.7 g (18%) of a mixture of 76% of oxime I and 24% of indole II and, subsequently, 0.6 g (3.3% based on the converted oxime I) of indole II.

5. The reaction of 20 g (0.18 mole) of oxime I, 67.6 g (0.36 mole) of 1,2-dibromoethane, and 70.7 g (1.26 mole) of KOH in 200 ml of DMSO (at 93°C for 6 h) gave 6.7 g (32%) of a mixture of 39% of oxime I and 61% of indole II, from which 3.5 g (19% based on the converted oxime I) of indole II was obtained.

1-Vinyl-4,5,6,7-tetrahydroindole (III). The reaction of 20 g (0.18 mole) of oxime I, 53.4 g (0.54 mole) of 1,2-dichloroethane, and 121.3 g (2.16 moles) of KOH in 200 ml of DMSO (at 115°C for 4 h) gave 12.9 g (53%) of a mixture [bp 70-150°C (4 hPa)] consisting of indole II (37%) and vinylindole III (63%). Crystallization from hexane and distillation of the mother liquor gave 7.2 g (27.7% based on oxime I) of III with bp 68°C (1.3 hPa), n_D^{20} 1.5580, and d_4^{20} 1.0010 [10].

1,2-Bis(cyclohexylideneiminoxy)ethane (IV). A 20-g (0.18 mole) sample of oxime I, 80.64 g (1.44 moles) of powdered KOH, and 170 ml of DMSO were placed in the apparatus described above (method 1), and a solution of 35.6 g (0.36 mole) of 1,2-dichloroethane in 30 ml of DMSO was added at 115°C in the course of 2 h. Workup (method 1) and vacuum distillation gave 10.2 g (44%) of a mixture [bp 60-146°C (1.3 hPa)] consisting of oxime I (3%), indole II (59%), and vinylindole III (38%), as well as 3 g (14%) of diether IV with bp 148-150°C (1.3 hPa), n_D^{20} 1.5298, and d_4^{20} 1.0281. IR spectrum (thin layer): 1050, 1075 (C—O), 1646 (C=N), 920, 930, 950 (N—O), 1450, 2860, and 2940 cm^{-1} (deformation and stretching vibrations of the cyclohexane ring CH_2 groups). PMR spectrum (CCl_4): 4.05 (CH_2O, s), 2.41, 1.59 ppm (ring CH_2, m). Found: N 10.7%, M 252. $C_{14}H_{24}N_2O_2$. Calculated: N 11.1%.

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EFFECT OF THE INCLUSION OF A CYCLIC FRAGMENT IN THE CHROMOPHORE ON THE PROPERTIES OF A SPIROPYRAN—MEROCYANINE SYSTEM

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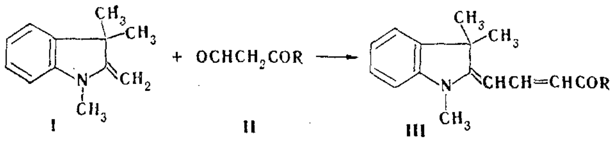
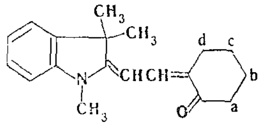
The corresponding merocyanines, which do not display a tendency to form spiropyran structures, are formed in the condensation of 1,3,3-trimethyl-2-methyleneindoline with 5-methyl-2-furoylacetaldehyde, 2-formylcyclohexanone, or 2-formyl-1-tetralone. Spiran compounds in which the spiropyran—merocyanine equilibrium is shifted markedly to favor the closed form are formed when 4a,9-dimethyl-2,3,4,4a-tetrahydrocarbazone — the cyclic analog of the Fischer base — is used in the reaction with salicylaldehydes and benzoylacetaldehydes.

We have previously shown that ω-(2-benzoylvinyl)methyleneindolines (III), which are formed in the reaction of the Fischer base (I) with benzoylacetaldehydes (II, R = aryl), have the properties that are typical for merocyanine structures and do not display a tendency to undergo conversion to the cyclic spiro form [1]. It was subsequently established that the indicated reaction also leads to the corresponding condensation products III (R = 5-methyl-2-furyl), IV, and V in satisfactory yields in the case of carbo- and heterocyclic β-keto aldehydes (5-methyl-2-furoylacetaldehyde, 2-formylcyclohexanone, and 2-formyl-1-tetralone).





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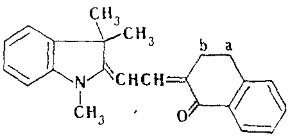

V

With respect to their properties, these merocyanine compounds do not differ fundamentally from the previously described phenyl analogs III (R = aryl) [1]. Their solutions have intense absorption in the visible region and remain unchanged when the temperature is changed or upon irradiation with visible or UV light (Table 1), which indicates the absence of rotation to the closed spiral form. Increased polarity of the medium leads to bathochromic shift (15-22 nm) of the long-wavelength absorption band for merocyanines. A sharp (~50 nm) hypsochromic blending of the band for compound IV constitutes evidence that the presence

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