SYNTHESIS OF SOME SUBSTITUTED 1-(2-PROPYNYL)-4-PIPERIDONES

(UDC 542.91)

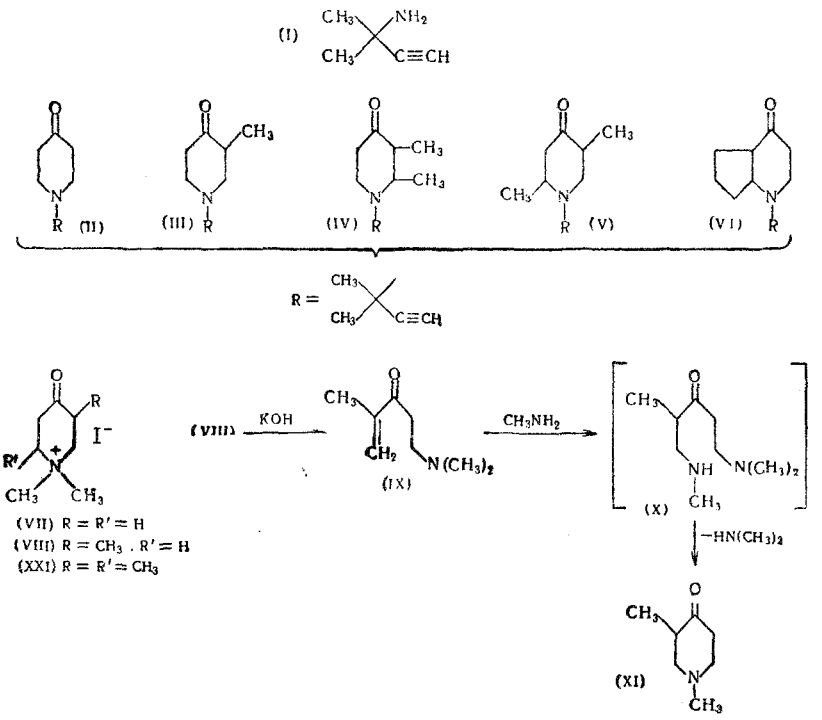
É. A. Mistryukov, N. I. Aronova, and V. F. Kucherov

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences, USSR

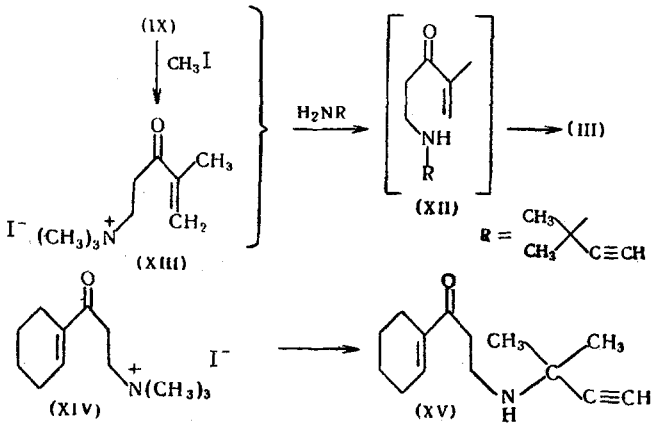
Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 3, pp. 512-519, March, 1964
Original article submitted October 4, 1962

We have previously described a method of synthesizing some 4-piperidones with bulky substituents on the nitrogen [1] and have investigated the factors determining the stability of such heterocyclic systems [2]. At the same time we showed that some 4-piperidones containing such a bulky substituent cannot be obtained in the cyclic form [2]. In view of this we thought it desirable to try to prepare 4-piperidones with a substituent on the nitrogen that could be later converted into a more bulky substituent. As such a substituent on the nitrogen we chose 1,1-dimethyl-2-propynyl [as in (II)] because of the possibility of the conversion of this group, which is less hindered than t-butyl, into the more bulky substituent t-pentyl (by hydrogenation) and because the amine required as starting material – 1,1-dimethyl-2-propynylamine (I) – is readily available [3]. Apart from this, these acetylenic piperidones may be of interest as compounds of probable pharmacological activity (cf. [4, 5]). The synthesis of the acetylenic 4-piperidones (II)-(VI) was carried out by the reaction of the amine (I) either with the methiodide of the 1-methylpiperidone [1] or with the corresponding β-dialkylamino ketone, its methiodide [2], or its hydrochloride.

Comparison of the reaction of methiodides of "unhindered" 4-piperidones, such as (VII) or (VIII), with $t\text{-}C_4H_9NH_2$ and with the amine (I) reveals the considerably higher rate of the formation of 1-t-butylpiperidones. Thus, an aqueous solution of the methiodide (VIII) scarcely reacts at all with the amine (I) at 20° in the course of 24 h, i.e., under the conditions under which reaction between $t\text{-}C_4H_9NH_2$ and the methiodide (VIII) gives 1-t-butyl-3-methyl-4-piperidone in 56% yield [1]. The cause of the lower reactivity of the acetylenic amine (I) probably lies in the weakening of the basic character of this amine as a result of the inductive effect of the acetylenic grouping (–I effect). It is indeed found that if this reaction is carried out in presence of an equivalent of alkali, the yield of the piperidone (III) is increased.

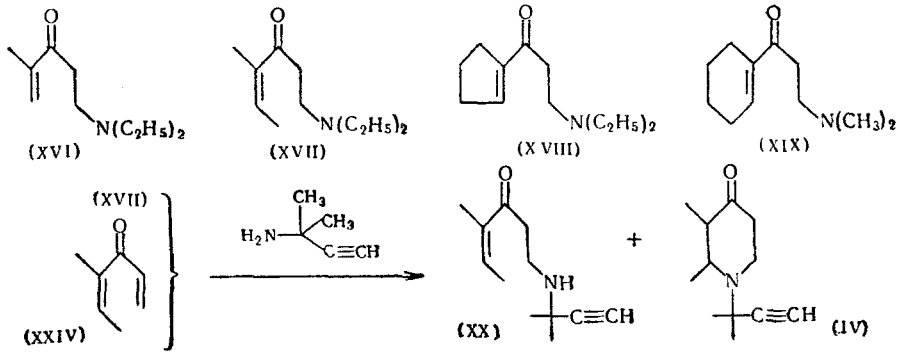


This gives us reason to suppose that in the action of alkali on the methiodide (VIII) the amino ketone (IX) is first formed (see Experimental) and that this reacts further with the amine (I) and gives the piperidone (III). It was shown previously that such unsaturated amino ketones react readily with the lower amines; the diamino ketones (type X) which are then formed are readily cyclized under the catalytic action of water into 4-piperidones, e.g. (XI) [6]. However, when hindered amines are used it would appear that the predominating direction of the reaction is direct amino exchange ["transamination" (IX) → (XII)]. Such transamination is considerably facilitated by the ammoniation of the amino group [2], as a result of which in the reaction of the acetylenic amine (I) with amino ketone methiodides at room temperature there is rapid formation of 4-piperidones or the corresponding noncyclic products (or mixtures of these), depending on the structure of the original methiodide [see, e.g. (XIII) → (III) or (XIV) → (XV)].



It was later found that hydrochloric acid can be used as the ammoniating agent, and by heating a mixture of the amino ketone (XVI) or (XVIII) [7], the amine (I), and one equivalent of HCl we obtained the 4-piperidone (III) or (VI).

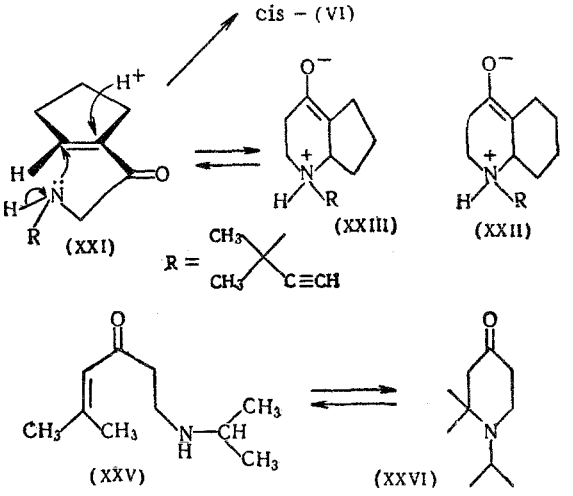
By such treatment, from the amino ketone (XIX) we obtained the noncyclic amino ketone (XV) and from the amino ketone (XVII) – a mixture of the cyclic (IV) and noncyclic (XX) transamination products. Similar results were obtained when methiodides of piperidones [e.g. (VIII) and (XXI)] were heated with the amine (I) (without the addition of alkali). Evidently, in this case also there is first formed a mixture of the unsaturated dialkylamino ketone, the amine (I), and one equivalent of acid, and this further gives the corresponding acetylenic 4-piperidone [(III) or (V)] and dimethylaminehydriodide. The choice between the first and second methods of synthesis is determined mainly by the accessibility of the starting compound. As regards the mechanism of the transamination, we must probably assume the intermediate formation of a divinyl ketone from the ammoniated form of the β-dialkylamino ketone under the action of an alkaline medium [8]. This view is supported by the identical compositions of the reaction products in the reaction of divinyl ketones or of methiodides with primary amines. It is characteristic that in absence of acid the β-dialkylamino ketone (XVI) reacts with the amine (I) extremely slowly.



As will be seen from the results discussed above, the greatest interest for the elucidation of the stereochemistry of the cyclization is presented by the cyclization of the amino ketones (XVII), (XVIII), and (XIX). Despite their similarity in the character of their substitution (cis-substituted double bond), in reaction with the amine (I) the amino ketone (XVIII) gives the cyclic product (VI) (absorption due to a conjugated keto group is absent in the ultraviolet

spectrum), but the amino ketone (XIX) gives the noncyclic amino ketone (XV) (λ_{max} 235.5 mμ, ε = 13420). The probable explanation of such a marked difference between these compounds of similar structure may be related to the different stabilities of cis-cyclic systems among N-alkylated 4-ketooctahydropyrindines and 4-ketodecahydroquinolines [9, 10] in the case when cyclization occurs as trans-dipolar addition at an activated double bond with protonization of the α-carbon atom occurring simultaneously with the formation of the $C_{(\beta)}$—N bond; then, as can be seen from the reaction scheme, cis-annelation of the piperidine ring with the carbocyclic part of the molecule must arise, and this is energetically more favorable for the pyrindine system and less favorable for the quinoline system. Another possible explanation is that, if cyclization occurs through the enolate intermediate state (XXII) and (XXIII), the enolate (XXIII) must be regarded as energetically more favored, since it contains an exo-cyclic double bond in the five-membered ring [11]. In both bases we may expect preferential cis-ketonization of the enolates (XXII) and (XXIII) (cf. [12]), which must be the energetically more favored process if the system arising is more stable.

The examination of models shows that for the ketone (XVII) and the divinyl ketone (XXIV) [13] the most favored configuration will be that with a trans arrangement of the methyl groups at the double bond, particularly in view of the fact that in the course of their synthesis they were subjected to acid and alkaline treatment at high temperatures [7, 13]. It could therefore be expected that under mild conditions the divinyl ketone (XXIV) in reaction with a hindered amine would in the first place give the noncyclic trans amino ketone (XX) (cf. [2]), and in fact the main product of the reaction of this ketone (XXIV) with the amine (I) in the cold is the noncyclic ketone (XX), which then, extremely slowly at room temperature or more rapidly when heated, gives the cyclic product (IV). However, this process is never complete, and even after long heating the mixture contains (XX) and (IV) in the proportions of about 3 : 2. When a solution of the piperidone (IV) in aqueous dioxane is heated, the same mixture is formed. It is probable that in this case the open form (XX) and the piperidone (IV) are in equilibrium with also a third component of the system — the other isomer of the piperidone, which cannot be isolated because of its instability. This unstable piperidone isomer is possibly an intermediary in the conversion (IV) → (XX). In support of this view we may advance the argument that the analogous process (XXV) ⇌ (XXVI), in which there is no possibility of the formation of isomeric cyclic products, goes very rapidly even at room temperature.



The difference in the effective bulks of the hydrocarbon groups in the acetylenic amine (I) and in t-butylamine is noteworthy; it is manifested particularly clearly in the reactions of the amine (I) and of t-butylamine with the methiodide of the amino ketone (XVIII): at room temperature only the noncyclic reaction product is formed with t-butylamine, whereas under these conditions the acetylenic amine (I) gives the piperidone (VI). When the methiodide of (XVIII) is heated with t-$C_4H_9NH_2$, the main reaction product is a ketone which corresponds in analysis to the product of the addition of two molecules of cyclopentenyl vinyl ketone to one molecule of t-$C_4H_9NH_2$.

EXPERIMENTAL

1,1,-Dimethyl-2-propynylamine (I). A solution of one mole of 3-chloro-3-methyl-1-butyne in five times its weight of dry ether was added slowly over a period of 2 h to a solution of sodamide prepared from 25 g of sodium in 1500 ml of liquid ammonia. Stirring was continued further for 3 h, ammonia was evaporated, and residual ammonia was removed by boiling with ether. The ethereal layer was filtered under pressure and was fractionated through a column. We obtained 69 g (83%) of (I); b. p. 81-82°; n_D^{20} 1.4216 (the yield of this amine is given as 41% in [3]).

1-(1,1-Dimethyl-2-propynyl)-3-methyl-4-piperidone (III). a) 2.2 ml (10% excess) of 1,1-dimethyl-2-propynylamine (I) was added with cooling to a solution of 5 g of 1,3-dimethyl-4-piperidone methiodide (VIII) [1] in 5 ml of water, and the reaction mixture was left for one day at room temperature. After ether extraction, drying of the ether layer, and removal of solvent (cf. [1]) we obtained 0.57 g of (III), identical chromatographically with the samples described below.

b) A mixture of 5 g of the methiodide (VIII), 5 ml of water, 2.2 ml of the amine (I), and 1 g of KOH was left for 24 h at room temperature and then extracted with ether. From the ether layer we obtained the piperidone (III) in 40% yield.

c) 1.2 g of KOH was added gradually with stirring to a solution of 5 g of the methiodide (VIII) in 5 ml of water, the reaction product was extracted with ether, the ether extracts were dried with potassium carbonate, ether was vacuum-distilled off, and the residue was dissolved in dry acetone. To this solution we added excess of CH_3I, and the 5-dimethylamino-2-methyl-1-penten-3-one methiodide (XIII) that came down was filtered off and washed with acetone; yield 3.1 g. 1.3 ml of 1,1-dimethyl-2-propynylamine was added to a solution of the methiodide in 6 ml of water, the mixture was left for one day at room temperature, and after treatment as under (b) we obtained 1 g of the crystalline piperidone (III) (when chromatographed [14], this product gave one spot of R_f 0.47 on alumina of activity II in 1:3 acetone-heptane). After being crystallized from heptane the piperidone (III) melted at 75-77° and gave no ultraviolet absorption characteristic for α,β-conjugated ketones. Found: C 74.12; H 9.57; N 7.66%. $C_{11}H_{17}NO$. Calculated: C 73.74; H 9.50; N 7.82%.

d) A mixture of equimolecular amounts of 5-dimethylamino-2-methyl-1-penten-3-one (XVI) [7] and the amine (I) in water was heated with stirring at 75° for 4 h. Analysis of the reaction mixture by chromatography on alumina showed that it contained only traces of the piperidone (III).

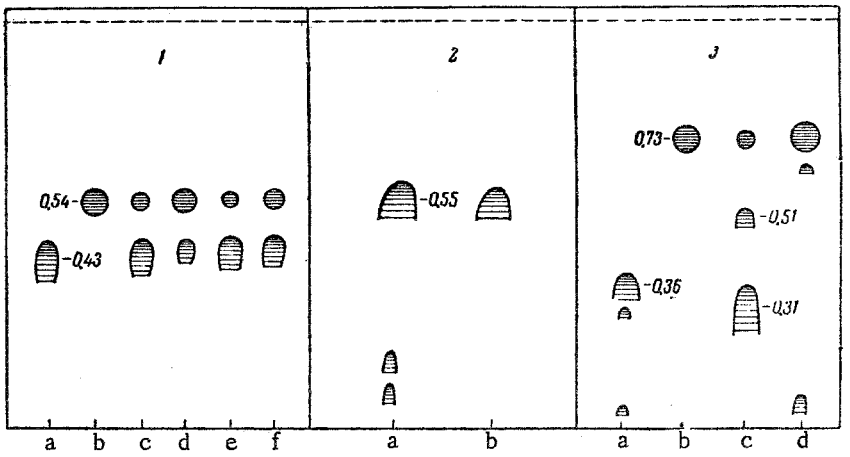
e) 30 ml of water, 16 ml of concentrated hydrochloric acid, and 18 ml of the acetylenic amine (I) were added to 26.6 g of the amino ketone (XVI); the mixture was stirred for 4 h at 75° and then left overnight. The crystals then precipitated were filtered off and crystallized from heptane. We obtained 15.7 g (56%) of 1-(1,1-dimethyl-2-propynyl)-3-methyl-4-piperidone (III), m. p. 74-75°, undepressed by admixture of the sample obtained in Expt. (c).

1-(1,1-Dimethyl-2-propynyl)octahydro-4H-1-pyrindin-4-one (VI). From 4.6 g of 1-cyclohexen-1-yl 2-diethylaminoethyl ketone (XVIII) [7], 2.6 ml of the amine (I), 5 ml of water, and 2.4 ml of concentrated hydrochloric acid under the conditions of Expt. (e) (two hours at 80°) we obtained 4.2 g of a mixture of reaction products, by the crystallization of which from heptane we isolated 1.9 g of 1-(1,1-dimethyl-2-propynyl)octahydro-4H-1-pyrindin-4-one (VI), m. p. 64°. The ultraviolet spectrum contained no maximum characteristic for α,β-conjugated ketones. Found: C 76.51; H 9.31; N 6.81%. $C_{13}H_{19}NO$. Calculated: C 76.09; H 9.27; N 6.83%.

1-Cyclohexen-1-yl 2-(1,1-dimethyl-2-propynylamino)ethyl ketone (XV). A mixture of 7.26 g of 1-cyclohexen-1-yl 2-dimethylaminoethyl ketone (XIX) [2], 7 ml of water, 4 ml of concentrated HCl, and 4.5 ml of the acetylenic amine (I) was heated under the conditions of Expt. (e) (80°, 5 h), and by purification through the hydrochloride we obtained 5.64 g (54%) of 1-cyclohexen-1-yl 2-(1,1-dimethyl-2-propynylamino)ethyl ketone hydrochloride, m. p. 193-195° (from methanol – ethyl acetate); λ_{max} in alcohol 235.5 mμ, ε = 13420. Found: C 65.76; H 8.63; N 5.76; Cl 13.90%. $C_{14}H_{22}NOCl$. Calculated: C 65.75; H 8.61; N 5.48; Cl 13.89%.

1-(1,1-Dimethyl-2-propynyl)-2,3-dimethyl-4-piperidone (IV) and 2-(1,1-dimethyl-2-propynylamino)ethyl 1-methylpropenyl ketone (XX). a) Under the above-described conditions (80°, five hours) from a mixture of 9.5 g of 2-diethylaminoethyl 1-methylpropenyl ketone (XVII) [7], 5.2 ml of concentrated HCl, 6 ml of the acetylenic amine (I), and 10 ml of water we obtained 9 g of a mixture of reaction products. This mixture was dissolved in methanol and neutralized to Congo Red with dry HCl, ethyl acetate was added, and the crystals then precipitated were filtered off and washed with ethyl acetate. We obtained 2.7 g of the hydrochloride of 1-(1,1-dimethyl-2-propynyl)-2,3-dimethyl-4-piperidone (IV), m. p. 134-135°, which contained a very small amount of admixed noncyclic product (λ_{max} in alcohol 231.5 mμ, ε = 3530). Treatment of this with potassium carbonate gave the base, which after being crystallized from isopentane had m. p. 28-29°. Found: C 74.57; H 10.05; N 7.20%. $C_{12}H_{19}NO$. Calculated: C 74.56; H 9.90; N 7.23%.

The mother solutions remaining after the isolation of (IV) were evaporated, and the residue was dissolved in ethyl acetate; 1.1 g of the hydrochloride of 2-(1,1-dimethyl-2-propynylamino)ethyl 1-methylpropenyl ketone (XX) crystallized out; m. p. 156-157°; λ_{max} 231.5 mμ; ε = 11400. Found: C 62.48; H 8.70; N 6.35; Cl 15.48%.



Figs. 1-3. Thin-layer chromatograms on unbound alumina of activity II; solvent systems: Figs. 1 and 2 – acetone-heptane 1 : 3; Fig. 3 – acetone-heptane 1 : 1.
Fig. 1. a) (XX); b) (IV); c) (XX) after being heated in aqueous dioxane for 2 h at 80°; d) (IV) after being heated in aqueous dioxane for 2 h at 80°; e) reaction mixture from Expt. (b) before being heated in aqueous dioxane; f) reaction mixture from Expt. (b) after being heated in aqueous dioxane.
Fig. 2. a) reaction mixture; b) analytically pure (V).
Fig. 3. a) (II) in reaction mixture; b) product of composition $C_{20}H_{31}NO_2$; c) product of reaction of (XVIII) with t-butylamine at 20°; d) reaction mixture obtained by heating in a steel tube.

$C_{12}H_{20}NOCl$. Calculated: C 62.72; H 8.78; N 6.09; Cl 15.43%. When a solution of the pure base (IV) or (XX) in aqueous dioxane was heated for 2 h at 80°, a mixture of (IV) and (XX) in the proportions of 2 : 3 approximately was again formed (Fig. 1).

b) With cooling with ice, a solution of 11.9 g of 1-methylpropenyl vinyl ketone (XXIV) [13] in ether was added gradually to a mixture of 12 ml of the amine (I) and 12 ml of water. The mixture was stirred for 30 min at 0° and then left overnight at room temperature; the ether layer was separated and vacuum-evaporated. According to chromatography (Fig. 1) the residue contained mainly the noncyclic product (XX), which was then heated for 18 h in 25 m of aqueous dioxane (1 : 4) (for the chromatography of the reaction mixture see Fig. 1). After treatment as in Expt. (a) from methanol – ethyl acetate we obtained 13.2 g of the hydrochloride of the noncyclic amino ketone (XX). From the mother solutions we prepared the base, which was vacuum distilled; b. p. 95-96° (2 mm); weight 6.3 g. According to chromatography, this product was a mixture of (XX) and (IV) in the proportions of 3 : 2 approximately.

1-(1,1-Dimethyl-2-propynyl)-2,5-dimethyl-4-piperidone (V). A mixture of 30 g of 1,2,5-trimethyl-4-piperidone methiodide [15], 30 ml of water, and 12 ml of the acetylenic amine (I) was heated with stirring for 6 h at 80° and then left overnight. The reaction products were extracted with ether, and the extract was dried (for the chromatography of this extract see Fig. 2). The residue remaining after the removal of ether (16.3 g) was vacuum-distilled. We obtained 13.8 g of a crystalline product, b. p. 65-67° (2 mm). After crystallization from heptane-isopentane we obtained 10.2 g of 1-(1,1-dimethyl-2-propynyl)-2,5-dimethyl-4-piperidone (V), m. p. 69-70°, which gave no ultraviolet absorption characteristic for an α,β-conjugated ketone. Found: C 74.12; H 9.90; N 7.41%. $C_{12}H_{19}NO$. Calculated: C 74.61; H 9.84; N 7.25%.

1-(1,1-Dimethyl-2-propynyl)-4-piperidone (II). A mixture of 2.6 g of 1-methyl-4-piperidone methiodide [1], 3 ml of water, and 1.2 ml of the acetylenic amine (I) was heated with stirring at 80°. After 30 min crystals started to separate from the initially homogeneous reaction mixture. Heating was continued further for 15 min, and then the mixture was extracted with ether. According to chromatography (Fig. 3), substantially only one product was present in this extract. Ether was driven off, and we obtained 0.86 g of 1-(1,1-dimethyl-2-propynyl)-4-piperidone (II), which after crystallization from heptane-ether had m. p. 136°. The ultraviolet spectrum showed no absorption characteristic for a conjugated ketone. Found: C 72.60; H 8.74; N 8.49%. $C_{10}H_{15}NO$. Calculated: C 72.72; H 9.09; N 8.48%.

Reaction of the methiodide of 1-cyclopenten-1-yl 2-diethylaminoethyl ketone (XVIII) with t-butylamine. t-Butylamine was added to a solution of the methiodide of the amino ketone (XVIII) [13] in water, and the reaction mixture was left for one day at room temperature. The reaction products were extracted with ether. As chromatography shows (see Fig. 3), the reaction products contained mainly the noncyclic product (for the cyclic product R_f should have been about 0.5-0.7), a very small amount of the original β-diethylamino ketone (XVIII), and a certain amount of a reaction product of composition $C_{20}H_{31}NO_2$. The unsaturated characters of all three products were confirmed by their ultraviolet spectra. The ether extract was evaporated, and the residue was crystallized from a mixture of benzene and isopentane; this gave a small amount of a product of m. p. 150-151°, which according to elementary analysis had the composition $C_{20}H_{31}NO_2$.(Found: C 75.60; H 9.49; N 4.41%; calculated: C 75.70; H 9.74; N 4.38%); λ_{max} 245 mμ, ε = 9820. When this reaction was carried out by heating the mixture of reactants in a steel tube at 80° for 3 h, the main product (see Fig. 3) was the same ketone $C_{20}H_{31}NO_2$, whose structure was not studied in detail.

SUMMARY

Some 1-(1,1-dimethyl-2-propynyl)-4-piperidones were synthesized, and the effect of substitution in the piperi dine ring on the reversible cyclization of unsaturated β-alkylamino ketones into 4-piperidones was investigated.

LITERATURE CITED

1. É. A. Mistryukov, N. I. Aronova, and V. F. Kucherov, Izv. AN SSSR. Otd. khim. n., 1961, 932.
2. É. A. Mistryukov, N. I. Aronova, and V. F. Kucherov, Izv. AN SSSR. Otd. khim. n., 1962, 870.
3. G. F. Hennion and E. G. Teach, J. Amer. Chem. Soc., 75, 1653 (1953).
4. C. Ainswarth and N. R. Easton, J. Organ. Chem., 26, 3776 (1961).
5. W. B. Luts, S. Lazarus, and R. I. Meltzer, J. Organ. Chem., 27, No. 5, 1695 (1962).
6. I. N. Nazarov and É. A. Mistryukov, Izv. AN SSSR. Otd. khim. n., 1958, 584.
7. I. N. Nazarov and É. A. Mistryukov, Izv. AN SSSR. Otd. khim. n., 1958, 460.
8. N. Ferry and F. J. McQuillin, J. Chem. Soc., 1962, 103.
9. É. A. Mistryukov, Izv. AN SSSR. Otd. khim. n., 1961, 623.
10. É. A. Mistryukov, Izv. AN SSSR. Otd. khim. n., 1963, 929.
11. H. C. Brown, J. H. Brewster, and H. Shechter, J. Amer. Chem. Soc., 76, 467 (1954).
12. H. E. Zimmerman and A. Mais, J. Amer. Chem. Soc., 81, 3644 (1959).
13. I. N. Nazarov and É. A. Mistryukov, Izv. AN SSSR. Otd. khim. n., 1958, 465.
14. É. A. Mistryukov, Collect. czechosl. chem. commun., 26, 2071 (1961).
15. I. N. Nazarov and V. A. Rudenko, Izv. AN SSSR. Otd. khim. n., 1948, 610.
