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AMINO ALCOHOLS OF THE ACETYLENE SERIES.

IX. 3,3-DIPHENYL-3-OXYPROPINYL-SUBSTITUTED QUINUCLIDINES

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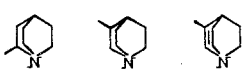
In a previous report [4] we presented results of devising methods for the production and study of synthesized acetylene amino alcohols that are piperidine derivatives. We demonstrated that the resultant preparations (arecoline model) exhibit markedly different degrees of M-cholinolytic activity. This is in accord with our notion that there must be an optimal distance between the amine nitrogen atom and the carbinol carbon atom.

The present work is concerned with the synthesis of acetylene amino alcohols (Ia-c) containing a quinuclidine residue $(C_6H_5)_2C(OH)C{\equiv}CQ$, where Q in compounds Ia-c and their HCl salts (IIa-c) is:



a b c

These compounds can be presumed to exhibit considerable cholinolytic activity. In addition, they seemed to be of particular interest for studying the structure-physiological action relationship since, on the one hand, the glycolic acid esters containing a quinuclidine residue are extremely active M-cholinolytics [12], but on the other hand, the saturated 1,3-amino alcohols of the quinuclidine series (phencarol [2]) are generally devoid of cholinolytic properties.

The amino alcohols of interest to us were obtained by various methods: 2-(3',3'-diphenyl-3'-oxy-1'-propinyl) quinuclidine (Ia) was synthesized by the method employed in the previous report to obtain piperidine analogs [4]:

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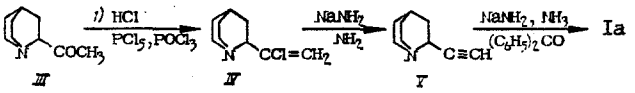
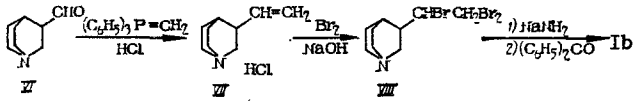
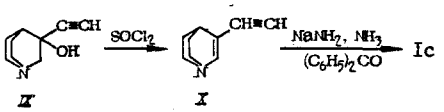


The starting compound used was 2-acetylquinuclidine (III) [6] which was converted to chlorolefin (IV) by chlorination with PCl_5 in a $POCl_3$ solution. Its dehydrochlorination led to the formation of 2-ethylquinuclidine (V). The latter was condensed with benzophenone in the presence of sodium amide in liquid ammonia into the amino alcohol Ia. The following pattern was selected to obtain 3-(3'3'-diphenyl-3'-oxy-1-propinyl)quinuclidine (Ib):



The key substance in the synthesis of this amino alcohol was 3-formylquinuclidine (VI) [7], which was converted by treatment with triphenylmethylenephosphoran into 3-vinylquinuclidine (VII) which in turn was converted into the salt and brominated in an aqueous solution. The resultant dibromide (VIII) was dehydrohalogenated by an excess of sodium amide in liquid ammonia and then converted to the sodium derivative of 3-ethynylquinuclidine which was treated with benzophenone without separation which yielded the targeted amino alcohol (Ib).

Finally, the synthesis of 3-(3,3-diphenyl-3-oxy-1-propinyl-2-quinuclidine (Ic) was accomplished by reacting the sodium derivative of 3-ethynyl-2-quinuclidene (IX) [9] with benzophenone in liquid ammonia. Ethynylquinuclidene itself was obtained from 3-ethynyl-3-quinuclidinol (IX) [8] by the method described in [9].



EXPERIMENTAL

IR-spectra were recorded on an IR-20 spectrometer (GDR). LiF prism, cell with NaCl crystal windows, cell thickness 1 mm, solutions used in CCl_4 at concentration of 1-2%. TLC performed on Silufol plates. Chromatograms developed in a water–20% aqueous ammonia (5:1) system. Spot detection by Dragendorff reagent. GLC performed on a Tsvet-6 chromatograph (Czechoslovakia). For the intermediate products we used a 2 m × 2 mm glass column with a 3% E-301 packing on chromaton. A 0.5 m × 2 mm glass column with a 1% E-301 packing on chromaton was used for the targeted amino alcohols. Melting point was determined on a Boetius instrument.

2-Ethynylquinuclidine (V) was obtained from 2-acetylquinuclidine (III) [6] by the method devised for piperidine analogs [4]. Yield 82%. The product is homogeneous according to GLC and TLC. IR-spectra, cm^{-1}: 2110 weak (C≡C), 3300 strong (≡C-H).

2-(3',3'-Diphenyl-3'-oxy-1'-propinyl)quinuclidine (Ia). A 4.31-g portion (32 mmoles) of 2-ethynylnuclidine (V) in 20 ml of dry ether was added to sodium amide obtained from 1.4 g (61 mmoles) of sodium in 100 ml of liquid ammonia. After 15 min, 7 g (38 mmoles) of benzophenone in 25 ml of dry ether were added and the mixture was stirred for 2 h while gradually replacing the ammonia by the ester. The ester solution was then boiled for 2 more hours. After cooling, the reaction mixture was decomposed by a saturated ammonium chloride solution, and the precipitate was filtered off, washed with water, dried, and recrystallized from nonane. Weight 7.58 g (76%), mp 192-193°C. Found, %: C 83.33, 83.59, H 7.09, 7.29. N 4.50, 4.72. $C_{22}H_{23}NO$. Calculated, %: C 83.23, H 7.32, N 4.41.

TABLE 1. Physiological Activity and Carbinol Carbon-Nitrogen Distance in Acetylene Amino Alcohols

Compound	M-cholinolytic activity – ED_{50}, mg/kg (M ± m)		Toxicity – LD_{50}, mg/kg	Nitrogen-carbinol carbon distance, nm
	peripheral	central		
IIa	1,6±0,5	0,9±0,24	1125±260	0,47
IIb	>100	0,4±0,06	2000±450	0,49
IIc	5,5±0,5	3,5±1,5	350±74	0,48
XI	8,30	2,35		0,47
XII	12,20	70		e:0,61; a:0,49*

*Distance at equatorial (e) and axial (a) position of the substituent.

The hydrochloride of Ia (IIa) was obtained by treating the alcohol suspension of the base with an alcohol solution of hydrogen chloride. It was precipitated by ether and recrystallized from dry ethanol. mp (243-244°C with decomposition). Found, %: Cl 9.99, 10.15. $C_{22}H_{34}NOCl$. Calculated, %: Cl 10.02.

3-(3'-3'-Diphenyl-3'-oxy-1'-propinyl)quinuclidine (Ib). A 5.4-g portion (13 mmoles) of pulverized triphenylmethylphosphonium iodide [11] was added to a suspension of sodium amide in liquid ammonia prepared in the usual way from 0.31 g (13 mmoles) of sodium in 100 ml of ammonia. The yellow-green colored reaction mixture was stirred for 30 min, after which 30 ml of dry ether were added and the ammonia was evaporated. A 0.93-g portion (6.7 mmoles) of VI [7] was added in a single dose to the ester solution and the resultant suspension was stirred for 2 h, left overnight, and then filtered. The precipitate was washed with ether, and the combined filtrates were extracted two to three times with 10% aqueous HCl. The acid solution was washed with chloroform and vacuum evaporated. Yield was 98 g of the solid chlorohydrate of VII. The salt was once again dissolved in water (about 50 ml) and treated with 1.6 g (0.5 ml, 20 mmoles) of bromine. The decolorized solution was made alkaline and extracted with chloroform. The extract was dried by magnesium sulfate, the solvent was thoroughly removed in a vacuum, and the crude dibromide was dissolved in tetrahydrofuran. This was added to a suspension of sodium amide in liquid ammonia obtained from 1 g (43 mmoles) of sodium in 100 ml of ammonia. After stirring for 3 h, 3.64 g (23 mmoles) of benzophenone in dry ether were added to the reaction mixture. After the ammonia was removed the remaining solution was boiled for 2 h and decomposed by water and diluted acid. After drying the magnesium sulfate, the solvent was distilled off and the residue was crystallized two times from isobutyl alcohol. Yield 0.11 g (5.2%, on the basis of the aldehyde of VI), av. mp 222-222.5°C. Found, %: C 83.48, 83.25; H 7.35, 7.47; N 4.31, 4.50. $C_{22}H_{23}NO$. Calculated, %: C 83.23; H 7.32; N 4.41.

The hydrochloride of IIb was obtained from both the base of IIa and the salt of Ib. It melted with decomposition at 253-254°C (from an alcohol-ether mixture). Found, %: Cl 10.17, 10, 19. $C_{22}H_{24}NOCl$. Calculated,%: Cl 10.02.

3-(3'-3'-Diphenyl-3'-oxy-1'-propinyl)-2-quinuclidene (Ic). This amino alcohol was obtained from 3-ethynyl-2-quinuclidene X [9] and benzophenone in the same way as the amino alcohol Ia. Yield was 57%, mp 249.5-250°C (dimethylformamide) Found, %: C 83.63; 71; H 6.81; 6.99; N 4.49; 4.61. $C_{22}H_{21}NO$. Calculated, %: C 83.76; H 6.72; N 4.44.

The hydrochloride of IIc was obtained in the same way as IIa and IIb. mp 284-285°C (with decomposition, alcohol). Found, %: Cl 10.17, 10.31. $C_{22}H_{22}OCl$. Calcualted, %: Cl 10.07.

None of the amino alcohols contained any impurities in the GLC and TLC studies.

EXPERIMENTAL – PHARMACOLOGICAL

The cholinolytic activity of the synthesized amino alcohols was studied on white mice with the help of an arecoline model [1]. Toxicity was also determined in white mice by subcutaneous injections of the preparations. The results of the tests are presented in Table 1. Also listed there for comparison are the pharmacological properties of analogous piperidine compounds [4] such as 1-methyl-2-(3',3'-oxy-3',3'-diphenyl-1'-propinyl)piperidine (XI) and 1-methyl-3-(3'-oxy-3',3'-diphenyl-1'-propinyl)piperidine (XII).

RESULTS AND DISCUSSION

The examined compounds (IIa-c) exhibit a high degree of M-cholinolytic activity with very low toxicity. These compounds have a particularly pronounced central action. The quinuclidine derivatives surpass analogous substituted derivatives of piperidine in biological activity (IIa and XI, IIb and XII). In contrast to the oxypropinyl derivatives of piperidine, these quinuclidine derivatives are characterized by a significantly greater molecular stability. Each of the three amino alcohols we synthesized exists in only one configuration (possible transpositions of the phenyl rings and hydroxyl proton were not considered). Consequently, the distance from the nitrogen atom to the carbon atom carrying the hydroxyl (the carbinol atom) was rigidly fixed. There was little difference in that distance in all of the investigated preparations, and it was very close to the same distance in the piperidine analogs of XI and XII, although markedly greater than the presumed optimal value of 0.37 nm [3]. This similarity in distance relationships means that the significant differences in the cholinolytic properties of preparations in both groups cannot be due to steric factors alone. The main reason for the higher biological activity of the examined amino alcohols is probably the special complementarity of the quinuclidine residue and the choline receptor's anion center which enhances their bonding despite the greater than optimal distance between the nitrogen and carbinol atoms. One of the reasons for that complimentarity may be the compactness of the quinuclidine residue and the greater opportunity for its nitrogen electron pair to interact with a proton than is the case in a piperidine, and especially in aliphatic amines. It is also possible that the high degree of molecular stability in the synthesized compounds potentiates their cholinolytic properties. According to data cited in [10] rigidly structured cholinolytics of the quinuclidine series of a different structure remain on the receptor for a longer period than their flexible analogs since the decomposition rate constant of the receptor-ligand complex is significantly smaller for those compounds. If this type of rule can also be justifiably applied to the preparations under examination, their stronger bonding with the receptor surface should also result in stronger cholinolytic properties.

Compound IIa's higher central M-cholinolytic activity in comparison to a peripheral amino alcohol corresponds to the same kind of relationship in the piperidine analog of XI and is in accord with the previously observed characteristic [5], i.e., the relatively intensified central effects of a preparation when the protons in the α-position towards the nitrogen atom are replaced by alkyl radicals. However, there is no rational explanation for the very strong difference in the effective doses in the center and on the periphery in the case of the 3-isomer of IIb (and to a lesser degree in the case of IIc). This is particularly so in view of the fact that the dose ratio is inverse for the 3-isomer in the piperidine series (XII).

The high M-cholinolytic activity of acetylene amino alcohols which include a quinuclidine residue sharply distinguishes them from the analog of 3-quinuclidyldiphenylcarbinol (phencarol) which does not have a triple bond [2]. The investigated compounds therefore appear to be closer in biological properties to quinuclidine benzylate, but not to the similarly structured saturated amino alcohols. This relationship might be connected with the specific analogy of the triple bond and carbalkoxyl residue both with respect to their influence on the proton-donor properties of the adjacent hydroxyl that are essential to receptor contact and to their ability to bond with approaching groups on the receptor surface.

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CONDENSED THIENOPYRIMIDINES. VIII. SYNTHESIS OF 2-, 3-, AND 6-SUBSTITUTED TETRAHYDROBENZO[b]THIENO[2,3-d]PYRIMIDIN-4-ONES AND THEIR ANTICONVULSANT ACTIVITY

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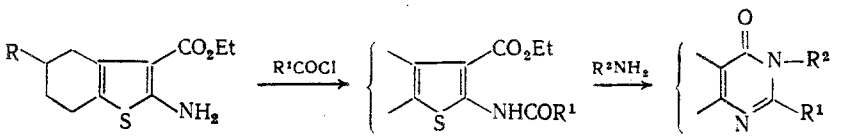
It has previously been reported [2, 3] that the anticonvulsant activity of thieno-[2,3-d]pyrimidines condensed with nitrogen-, sulfur-, and oxygen-containing six-membered saturated heterocycles is dependent on the type of heteroatom and the nature and positions of the substituents in the molecule. It was found that the presence of alkyl substituents in the 2-position and an NH_2 group in the 3-position of the prymidine ring in pyrano[4'3':4,5]-thieno[2,3-d]pyrimidin-4-one considerably increased anticonvulsant activity.

For this reason, it was of interest to synthesize some 5,6,7,8-tetrahydrobenzo[b]-thieno[2,3-d]pyrimidin-4-ones and examine their activity.

The starting materials for the synthesis were 2-amino-3-ethoxycarbonyl-(5-methyl)-4,5,6,7-tetrahydrobenzo[b]thiophenes (I) and (II) [4, 5]. Reaction of the latter with acid chlorides afforded a series of acyl derivatives (III-XVIII). Reaction of (III-XV) with hydrazine hydrate, (IV, VII, XIV) and (XVI-XVIII) with ammonia, and (IV) with methylamine gave the 2,3-substituted tetrahydrobenzo[b]thieno[2,3-d] pyrimidin-4-ones (XIX-XXXVIII).



I, II — III—XVIII — XIX—XXXVIII

R = H (I, III—IX, XVII—XXV, XXXII—XXXV), Me (II, X—XVI, XXVI—XXXI, R^1=Pr (XVI, XVII, XXXII), *i*-Pr (III, X, XIX, XXVI, XXVII), Bu (IV, XI, XX, XXXIII, XXXVIII), *sec*-Bu (V, XII, XXI, XXVIII), *tert*-Bu (VI, XIII, XXII, XXIX), Am (VII, XIV, XXIII, XXXVI), $CHCH_2OC(CH_3)_2CH_2$ (VIII, XXIV) p-(*sec*-BuO) C_6H_4 (IX, XV, XXV, XXXI), 2-benzofuryl (XVIII, XXXV); R^2 = H (XXXII—XXXVII), CH_3 (XXXVIII), NH_2 (XIX—XXXI)

EXPERIMENTAL — CHEMICAL

IR spectra were obtained on an IR-20 instrument (East Germany) in Vaseline oil, and PMR spectra on a Varian T-60 instrument (USA) with TMS as internal standard. TLC was carried out on Silufol UV-254 plates (Czechoslovakia), developer iodine vapor.

2-Substituted 3-Ethoxycarbonyl(5-methyl)-4,5,6,7-tetrahydrobenzo[b]thiophenes (III-XVIII). To a mixture of 30 ml of dry dioxane and 0.01 mole of triethylamine was added 0.01 mole of (I) or (II), followed by the dropwise addition of 0.01 mole of the acid chloride. The mixture was boiled for 4 h, then cooled, the solid filtered off, and washed with dry dioxane. The filtrate was poured into 200 ml of cold water, and the crystals which separated were

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