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Original Scientific Paper

Aminoacetals. Syntheses of *N*,*N*-Disubstituted 4-Amino-2-butynal- and 4-Aminobutanal- acetals

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The synthesis of *N*,*N*-disubstituted 4-aminobutanal acetals (XV — XXII) was effected by the hydrogenation of the corresponding acetylenic analogues. *N*,*N*-Disubstituted 4-amino-2-butynal acetals (IV—XII) were prepared by the Mannich condensation of propargylaldehyde acetal, formaldehyde and the corresponding secondary amine. As an alternative route to *N*,*N*-disubstituted acetylenic aminoacetals, Bodroux-Tschitschibabin acetal synthesis was also applied in the preparation of 4-dibenzylamino-2-butynal acetal (VII).

It has been shown[1,2] that 4-amino- and 4-acetylamino-butanal acetals cyclize under very mild conditions and in good yields with *p*-substituted phenylhydrazine hydrochlorides into the corresponding 5-substituted tryptamines. It seemed of interest to examine whether under the same conditions *N*,*N*-disubstituted 4-aminobutanal acetals and *p*-substituted phenylhydrazines would also yield 5-substituted *N*,*N*-alkylated tryptamines. Alkylated tryptamines are compounds of wide biological interest, some of them exhibiting strong hallucinogenic activity.

Thus, our first task was to prepare some particular *N*,*N*-disubstituted 4-aminobutanal acetals. To our knowledge, from this series only the dibutylamino- compound has been reported[3] in the literature. It was prepared by the Bodroux-Tschitschibabin acetal synthesis from the corresponding Grignard reagent and ethyl orthoformate. However, our attempt to synthesize the desired acetals by this method was soon abandoned. Although Marxer[4] and Perrine[3] succeeded to obtain, under special precautions, in good yields Grignard reagents from some 3-dialkylaminopropyl halogenides, our yields on Grignard reagents from 3-dibenzylaminopropyl halogenides (II and III), as well as their readiness to react with ethyl orthoformate were not at all satisfactory.

We tried then to reach the *N*,*N*-disubstituted 4-aminobutanal acetals through the corresponding acetylenic analogues, which we intended to reduce to the saturated acetals.

N,*N*-Disubstituted 4-amino-2-butynal acetals could be obtained by two alternative routes: *A.* by a Mannich condensation of propargyl acetal, formaldehyde and a secondary amine, and *B.* by a Bodroux-Tschitschibabin condensation of ethyl orthoformate and the Grignard derivative of the corresponding *N*,*N*-disubstituted 3-amino-1-propyne:

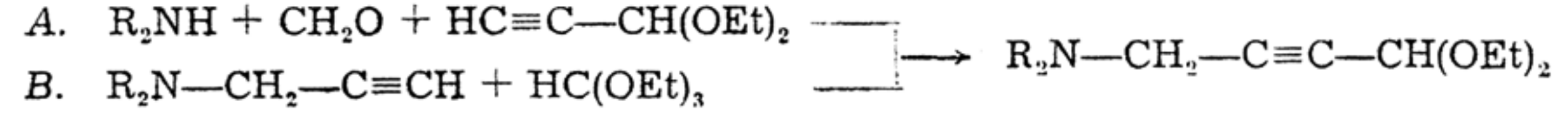
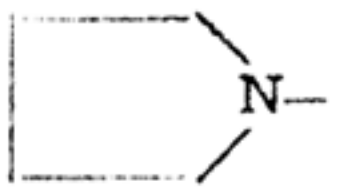


TABLE I

N,N-Disubstituted Acetylenic Aminoacetals

$R—CH_2—C\equiv C—CH(OC_2H_5)_2$

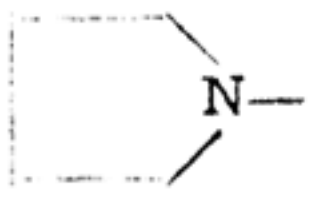
Compound No.	R	Yield %	B.p. °C/mm	Formula	Analyses Calc'd. % C	% H	% N	Found % C	% H	% N
IV*	$(C_2H_5)_2N—$	69	119—122/18	$C_{12}H_{23}NO_2$	67.56	10.87	6.57	67.75	10.80	6.76
V	$(CH_3)_2CH)_2N—$	69	74—76/0.30	$C_{14}H_{27}NO_2$	69.66	11.28	5.80	69.99	11.38	5.59
VI	$(HOCH_2CH_2)_2N—$	63	147—150/0.015	$C_{12}H_{23}NO_4$	58.75	9.45	5.71	59.00	9.38	5.66
VII	$(C_6H_5CH_2)_2N—$	56	154—157/0.01	$C_{22}H_{27}NO_2$	78.30	8.06	4.15	78.30	7.87	4.43
VIII	$C_6H_5CH_2(CH_3)N—$	71	108—110/0.01	$C_{16}H_{23}NO_2$	73.52	8.87	5.36	73.42	9.08	5.32
IX	$1\text{-}C_{10}H_7(C_2H_5)N—$	45	145—149/0.01	$C_{20}H_{25}NO_2$	77.13	8.09	4.50	76.91	8.13	4.77
X		65	68—70/0.15	$C_{12}H_{21}NO_2$	68.21	10.02	6.63	68.25	9.89	6.84
XI		70	88—90/0.20	$C_{13}H_{23}NO_2$	69.29	10.29	6.22	69.31	10.26	6.48
XII		62	99—101/0.12	$C_{12}H_{21}NO_3$	63.40	9.31	6.16	63.60	9.37	6.15

* Dornow and Ische[5] reported a 37% yield. b.p. 112–113/12 mm.

TABLE II

N,N-*Disubstituted Aliphatic Aminoacetals*

$R—CH_2—CH_2—CH_2—CH(OC_2H_5)_2$

Compound No.	R	Yield %	B.p. °C/mm	Formula	Analyses Calc'd. % C	% H	% N	Found % C	% H	% N
XV	$(C_2H_5)_2N—$	67	107—108/20	$C_{12}H_{27}NO_2$	66.31	12.52	6.44	66.60	12.47	6.82
XVI	$((CH_3)_2CH)_2N—$	41	67—71/0.01	$C_{14}H_{31}NO_2$	68.52	12.73	5.71	68.44	12.46	5.88
XVII	$(HOCH_2CH_2)_2N—$	44	103—106/0.01	$C_{12}H_{27}NO_4$	57.80	10.91	5.62	57.63	10.83	5.90
XVIII	$(C_6H_5CH_2)(CH_3)N—$	65	98—102/0.01	$C_{16}H_{27}NO_2$	72.41	10.25	5.28	72.38	10.04	5.25
XIX		82	58—59/0.15	$C_{12}H_{25}NO_2$	66.93	11.70	6.51	67.15	11.82	6.67
XX		75	75—79/0.35	$C_{13}H_{27}NO_2$	68.07	11.87	6.11	68.19	12.05	6.19
XXI		73	75—78/0.15	$C_{12}H_{25}NO_3$	62.30	10.89	6.06	62.10	10.63	6.26
XXII	$(C_6H_5CH_2)(C_6H_5C_2)N—$	53	*	$C_{22}H_{31}NO_2$	77.37	9.15	4.10	77.81	9.30	4.51

* Decomposes on distillation, sse experimental part.

The Mannich reaction was already applied by Dornow and Ische[5] who prepared by this route 4-dimethyl- and 4-diethylamino-2-butynal diethyl acetals. We used the same reaction, and worked out a general procedure by which the corresponding *N,N*-disubstituted acetylenic aminoacetals IV—XII (Table I) were obtained in good yields. All these compounds are colourless or straw-coloured oils. If not analytically pure, they show tendency to decompose and polymerize after standig for several days at room temperature.

As anticipated, because of its low basicity, diphenylamine failed to react in this type of condensation, and ethyl-1-naphthylamine reacted more sluggishly than the other secondary amines used.

The applicability of the route *B.* leading to the *N,N*-disubstituted 4-amino--2-butynal acetals was verified with 3-dibenzylamino-1-propyne (XIV) as the model substance. XIV was synthesized from 3-dibenzylamino-2-bromo-1-propene (XIII) according to the general method given by Parcell and Pollard[6]. Grignard reagent from XIV was easily obtained, but the final yield of the acetylenic acetal VII was lower than the yield obtained by the Mannich reaction.

Catalytic hydrogenation of the acetylenic acetals gave the saturated analogues XV—XXII (Table II). In all cases the first mole of hydrogen was rapidly taken up, while the second equivalent was absorbed at a markedly slower rate. The hydrogenation of acetylenic aminoacetals V, VI and VII was to a certain extend accompanied by hydrogenolysis of the *N,N*--disubstituted amino group. Consequently, lower yields of saturated aminoacetals XVI, XVII and XXII were obtained. Guermont[7] studied this cleavage with some acetylenic amino ethers of the type $Me_2N—CH_2—C{\equiv}C—C(R'R'')—OR$, where R was an alkyl group and R′ and R″ were methyl or hydrogen, and found that hydrogenation over platinum caused the formation of considerable amounts of dimethylamine.

However, the other acetals showed to be much more resistant to hydrogenolysis, the highest yields being obtained with the aminoacetals where nitrogen was incorporated into a ring. All the aminobutanal acetals are colourless or straw-coloured oils which could be distilled *in vacuo* without decomposition, with the exception of the dibenzylamino — derivative XXII. They are more stable than the corresponding acetylenic analogues, but still, if not very pure show tendency to decompose or polymerize after storage of several weeks.

EXPERIMENTAL

3-*Dibenzylamino-1-propanol* (I)

I was prepared from 64.5 g. (0.862 mole) 3-amino-1-propanol, 218 g. (1.72 mole) benzylchloride and 69.0 g. (1.72 mole) sodium hydroxide in 100 ml. water, in the same manner as described[8] for 2-dibenzylaminoethanol. The crude product was fractionated over a Vigreux column and 47.0 g. (61%) of colourless viscous oil, b.p. 140—143°/0.015 mm. collected. The analytical sample was redistilled, b.p. 141—142°/0.014 mm.

Anal. $C_{17}H_{21}NO$ (255.35) calc'd.: C 79.96; H 8.29; N 5.49%
found: C 79.75; H 8.41; N 5.61%

3-Dibenzylamino-1-chloropropane (II)

Following the given procedure[8], I (15.0 g., 59 mmoles) in 15 ml. chloroform was converted with thionyl chloride (6 ml. in 8 ml. chloroform) into II-hydrochloride —

a thick syrup — which was then treated with a saturated potassium carbonate solution, and the free amine extracted with benzene. After fractional distillation, 11.4 g. (71%) of a colourless viscous oil, b.p. 140—144° 0.02 mm. was obtained. The analytical sample was redistilled, b.p. 124—125°/0.012 mm.

Anal. $C_{17}H_{20}ClN$ (273.80) calc'd.: C 74.57; H 7.36; N 5.12%
found: C 74.59; H 7.32; N 4.97%

3-Dibenzylamino-1-bromopropane (III)

I (16.1 g., 63 mmoles) was converted with 47% hydrobromic acid (total 58 ml.), following the given procedure[8] into III-hydrobromide — a thick brown syrup — which was immediately treated with a saturated potassium carbonate solution and the free amine extracted with ether. Fractional distillation over a Vigreux column gave 10.8 g. (58%) of a lightly yellow oil, b.p. 144—148°/0.025 mm. The analytical sample was redistilled, b.p. 140—141°/0.015 mm., colourless oil which decomposes on standing.

Anal. $C_{17}H_{20}BrN$ (318.25) calc'd.: C 64.15; H 6.33; N 4.40%
found: C 64.11; H 6.36; N 4.50%

General procedure for the preparation of N,N-*disubstituted acetylenic aminoacetals* IV—XII

The reaction was carried out in a 100 ml. three-necked flask, equipped with a mechanical stirrer, a dropping funnel and a reflux condenser. To a stirred suspension of paraformaldehyde (0.630 g., 21 mmoles) and cupric acetate (73 mg.) in peroxide free dioxane, the appropriate secondary amine (21 mmoles) followed by propargylaldehyde diethyl acetal[9] (2.56 g., 20 mmoles) was added. The funnel was replaced by a gas inlet tube and the mixture was heated in an oil bath with stirring under nitrogen at 80—85° for 24 hours. The solution turned gradually from blue to dark brown. After cooling, dioxane was removed *in vacuo*, water (15 ml.) added to the residue and the mixture extracted several times with ether. In the case of VI, water was saturated with potassium carbonate in order to ensure better extraction. The combined extracts were dried over anhydrous potassium carbonate, the solvent was removed and the remaining oil was purified by fractional distillation. Yields and physical data are summarized in Table I. I.R. spectra (neat) of the samples exhibited absorption at 4.40—4.45 μ (C≡C).

3-Dibenzylamino-2-bromo-1-propene (XIII)

To a solution of dibenzylamine (78.9 g., 0.4 moles) in 80 ml. of absolute ether, a solution of 2,3-dibromo-1-propene (40.0 g., 0.2 mole) in 40 ml. of absolute ether was added under shaking in 5 ml. portions in about 1 hour intervals. After standing overnight, dibenzylamine hydrobromide was filtered off, the filtrate refluxed for 1 hour, and after cooling a second crop of the salt removed. The bulk of ether was distilled off, the residue filtered again, the solution dried over sodium sulphate and the remaining oil fractionally distilled, yielding 45.3 g., (71.6%) of XIII, b.p. 133—137°/0.03 mm. The analytical sample had b.p. 128—129°/0.018 mm.

Anal. $C_{17}H_{18}BrN$ (316.24) calc'd.: C 64.56; H 5.74; N 4.43%
found: C 64.60; H 5.84; N 4.71%

3-Dibenzylamino-1-propyne (XIV)

In a 500 ml. three-necked flask a solution of sodamide (from 3.7 g. Na) in liquid ammonia (150 ml.) was prepared in the usual way. XIII (22.2 g., 0.07 moles) was added dropwise in one hour, and the mixture stirred and refluxed under a Dry-Ice acetone reflux condenser for additional six hours. Ammonia was evaporated, the residue treated with ether (150 ml.) and water (50 ml.) and the ethereal layer dried over sodium hydroxide. After the removal of ether, the remaining oil was distilled, yielding 13.5 g., (82.1%) of a straw-coloured oil, b.p. 109—112°/0.04 mm., which solidified after standing. For analysis a small portion was recrystallized from methanol-water (4:1), m.p. 40—41°.

Anal. $C_{17}H_{17}N$ (235.32) calc'd.: C 86.76; H 7.28; N 5.95%
found: C 86.50; H 7.34; N 6.26%

4-Dibenzylamino-2-butynal diethyl acetal (VII)

To a stirred solution of ethylmagnesium bromide under nitrogen (from 0.475 g. Mg and 2.44 g. ethylbromide) in 15 ml. of absolute ether, a solution of 3.53 g. XIV (15 mmoles) in 10 ml. of absolute ether was added and the mixture stirred and refluxed for 4 hours. Then a solution of ethyl orthoformate (2.23 g., 15 mmoles) in 5 ml. of absolute ether was added and the stirring and refluxing continued for further 24 hours. The Grignard complex was decomposed by the addition of cold saturated aqueous ammonium chloride, and the ether layer dried over anhydrous potassium carbonate. After the removal of ether some unchanged orthoformate was distilled off at 20 mm., and the remaining oil was distilled fractionally, giving 1.75 g., 35% of VII, b.p. 148—155°/0.017 mm. An analytical sample was redistilled, b.p. 149—151°/0.001 mm.

Anal. $C_{22}H_{27}NO_2$ (337.44) calc'd.: C 78.30; H 8.06; N 4.15%
found: C 78.44; H 8.14; N 4.31%

General procedure for the preparation of N,N-*disubstituted aminoacetals* XV—XXII

The appropriate acetylenic aminoacetal (13 mmoles) was dissolved in 20 ml. of absolute ethanol and shaken under hydrogen at atmospheric pressure and room temperature in the presence of 50 mg. of 10% Pd—$BaSO_4$. After consumption of two mole equivalents of hydrogen (3—10 hours), the reduction was interrupted, the catalyst removed by filtration, washed well with ethanol, and the combined filtrates evaporated *in vacuo*. The remaining oil was purified by fractional distillation. Yields and physical data are given in Table II. I.R. spectra (neat) of the samples showed the total disappearance of the 4.40—4.45 μ band (C≡C).

Isolation of 4-dibenzylaminobutanal acetal (XXII)

Since the fractional distillation failed to give pure XXII, the crude product obtained from 4.4 g. (13 mmoles) of VII, by hydrogenation till the uptake of two equivalents of hydrogen, was purified by column chromatography. Alumina (Chemapol, 100 g.) was packed with petroleumether (60—80°) in a column and the crude XXII chromatographed by successive elution with petroleumether and petroleumether-benzene (1:1). The first solvent eluted 2.35 g., (53%) of XXII. The analyses of the chromatographic fractions were slightly higher in carbon and nitrogen. Infra red spectrum showed complete absence of the 4.40 μ band (C≡C), but showed a very weak absorption at 6.30 μ (C=C) and 3.25 μ (NH), indicating that also some competing reduction of the double bond with hydrogenolysis of one *N*-benzyl group occurred. Further purification of XXII resulted in an even more contaminated product.

Petroleumether-benzene (1:1) eluted about 0.5 g. of dibenzylamine, which was identified by analysis and I.R. spectrum.

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