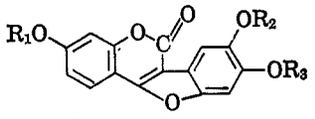
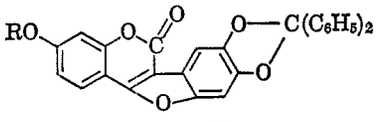


Ia, $R_1=R_2=R_3=H$
b, $R_1=Bz$, $R_2=R_3=H$
c, $R_1=Bz$, $R_2=R_3=CH_3$
d, $R_1=H$, $R_2=R_3=CH_3$



IIa, R=H
b, R=Bz

dihydroxy derivative Ib, which gave the expected bathochromic shift in the presence of boric acid for an *o*-dihydroxyl grouping[4] (355–382 mμ). Methylation of the 11- and 12-positions then gave 7-O-benzoyl-11,12-dimethoxycoumestan (Ic), identical with the benzoate prepared from the natural material. Basic hydrolysis of the synthetic benzoate gave a compound, Id, which was identical with the natural material in all respects.

Experimental Section

Purification.—The new phenolic compound was isolated from dehydrated alfalfa and purified by recrystallization from ethyl acetate, mp 306° (compound VIII in ref. 5).

Anal. Calcd for $C_{17}H_{12}O_6$: C, 65.4; H, 3.85; OCH_3, 19.8. Found: C, 65.5; H, 3.85; OCH_3, 19.6.

Acetate.—A mixture of the compound (60 mg) and anhydrous sodium acetate (250 mg) in 5.0 ml of acetic anhydride was heated at reflux for 5 min, cooled, and poured into ice–water. A white solid (69 mg) precipitated. An analytical sample, mp 213–215°, was prepared by recrystallization from acetone.

Anal. Calcd for $C_{19}H_{14}O_7$: C, 64.4; H, 3.96; OCH_3, 17.5; CH_3CO, 12.1. Found: C, 64.5; H, 4.02; OCH_3, 17.3; CH_3CO, 12.0.

Methyl Ether.—A mixture of the compound (100 mg), anhydrous potassium carbonate (300 mg), and dimethyl sulfate (0.5 ml) in 20 ml of dry acetone was heated at reflux under nitrogen for 1.5 hr, cooled, and poured into ice–water. A white solid (110 mg) precipitated. Recrystallization from methanol gave colorless crystals, mp 246°.

Anal. Calcd for $C_{18}H_{14}O_6$: C, 66.3; H, 4.30; OCH_3, 28.5. Found: C, 65.9; H, 4.35; OCH_3, 28.2.

Admixture with an authentic sample of 7,11,12-trimethoxycoumestan did not depress the melting point of the natural ether. Ultraviolet and infrared spectra were identical.

7-Hydroxy-11,12-diphenylmethylenedioxycoumestan (IIa).—Using the procedure of Jurd,[6] a mixture of 7,11,12-trihydroxycoumestan (Ia) (1.5 g) and α,α-dichlorodiphenylmethane[7] (2.8 g) was heated at 210° for 5 min. The resulting dark brown solids were purified by countercurrent distribution in a robot-operated, 100-tube instrument with Skellysolve B–methanol (2:1) as the developing system. After 250 transfers, tubes 49–80 in the instrument were combined and taken to dryness, giving 720 mg of a white solid. Recrystallization from methanol gave an analytical sample, mp 293.5–294°.

Anal. Calcd for $C_{28}H_{16}O_6$: C, 75.0; H, 3.60. Found: C, 75.0; H, 3.81.

7-O-Benzoyl-11,12-dihydroxycoumestan (Ib).—A solution of IIa (200 mg) in 10 ml of pyridine was mixed with 100 mg of anhydrous sodium acetate and 0.3 ml of benzoyl chloride. After standing for 45 min at room temperature, the reaction mixture was poured into ice-cold aqueous sodium acetate solution and the intermediate IIb was removed with chloroform. The chloroform was evaporated *in vacuo*, and the crude syrup was dissolved in 50 ml of glacial acetic acid–hydrochloric acid (15:1) and heated at reflux for 10 min. After the addition of 5.0 ml of water, the mixture was further heated on a steam bath for 5 min and cooled, and the white solids (230 mg) were collected. Recrystallization from acetic acid gave an analytical sample, mp 301–302°.

Anal. Calcd for $C_{22}H_{12}O_6$: C, 68.1; H, 3.11. Found: C, 68.5; H, 3.69.

7-O-Benzoyl-11,12-Dimethoxycoumestan (Ic). Synthetic.—A mixture of the 7-O-benzoyl derivative Ib (115 mg), dimethyl sulfate (0.2 ml), and anhydrous potassium carbonate (250 mg) in 50 ml of dry acetone was heated at reflux for 3 hr. The reaction mixture was cooled and poured into ice–water, giving 121 mg of a white solid. Recrystallization from acetone gave an analytical sample, mp 227–228°.

Anal. Calcd for $C_{24}H_{16}O_6$: C, 69.2; H, 3.87; OCH_3, 14.9. Found: C, 69.4; H, 4.11; OCH_3, 14.9.

Natural.—A mixture of the natural compound (75 mg) with benzoyl chloride (0.5 ml) in 3.5 ml of pyridine, was heated on the steam bath for 1 hr while protected from moisture. The reaction mixture was added dropwise to a well-stirred mixture of ice and saturated aqueous sodium bicarbonate solution. A white solid (80 mg) precipitated. Recrystallization from acetone gave an analytical sample, mp 227.5°, identical with the comparable synthetic derivative.

7-Hydroxy-11,12-dimethoxycoumestan (Id).—The synthetic preparation of the 7-O-benzoate of the dimethyl ether (Ic) (82 mg) was stirred with 5.0 ml of 0.5% potassium hydroxide in methanol for 0.5 hr at 0–5°. Acidification with dilute hydrochloric acid gave 48.4 mg of a tan solid. Recrystallization from ethyl acetate gave a white solid, mp 303–305°, which was identical in all respects with the natural material.

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Alkylation of N,N-Dimethylamides *via* Carbanion Intermediates

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Alkylation of several 2-aryl-N,N-dialkylacetamides[2–6] and 2,2-diaryl-N,N-dialkylacetamides[6–10] at the α-carbon *via* carbanion intermediates has been reported; however, we have found no examples in the literature of alkylation of simple N,N-dialkylamides. Generally, substitution of an activating aryl group at the 2-position has been considered a necessary condition for carbanion formation to take place in N,N-dialkylamides. We wish to report alkylation at the α-carbon *via* carbanion intermediates of three simple N,N-dimethylamides (see Table I).

Formation of carbanions of the N,N-dimethylamides was effected by refluxing the amide with finely divided sodium amide in benzene or toluene. Attempts to use lithium amide or sodium ethoxide in place of so-

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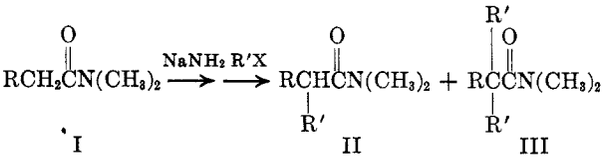
TABLE I. ALKYLATION OF N,N-DIMETHYLAMIDES



I II III

R	R'X	Moles of $NaNH_2$–R'X/ mole of amide	Solvent[a]	% recovery of I	% yield[b] II	% yield[b] III
H	CH_3I	1	B	38	44	..
H	CH_3I	1	T	24	48	..
H	n-C_4H_9Br	1	B	37	54	3
H	n-C_4H_9Br	1.5	B	8	63	15
H	n-C_4H_9Br	2.0	B	5	52	26
H	n-C_4H_9Br	1	T	28	60	7
H	$C_6H_5CH_2Br$	1	T	14	53	..
H	n-$C_{12}H_{25}Br$	1	T	14	51	..
H	i-C_3H_7Br	1	T	31	43	..
H	$C_6H_{11}Br$	1	T	61	5	..
CH_3	C_2H_5I	1	T	35	25	..
C_2H_5	CH_3I	1	T	46	25	..

[a] B = benzene; T = toluene. [b] Based on starting amide.

dium amide failed. Addition of alkyl halide to the resulting carbanion of the N,N-dimethylamide gave the corresponding 2-alkyl-N,N-dimethylamides in moderate yields. More complete conversion of starting amide and slightly higher yields of alkylated amide were obtained when the higher-boiling solvent, toluene, was used.

A dialkylated amide, 2-butyl-N,N-dimethylhexanamide, was isolated only in the reaction of N,N-dimethylacetamide with *n*-butyl bromide. When excess sodium amide was used in this alkylation (see Table I), the yield of 2-butyl-N,N-dimethylhexanamide increased, and traces of other side products were detected by glpc. Reaction of N,N-dimethylacetamide was not complete even when 2 moles of sodium amide/mole of amide was used. We believe dialkylation occurs through reaction of monoalkylated amide with excess sodium amide and alkyl halide.

N,N-Dimethylacetamide gave better yields of 2-alkyl-N,N-dimethylamides than did N,N-dimethylpropionamide and N,N-dimethylbutyramide, in which glpc-inseparable mixtures of N-unsubstituted amides and N-alkylamides also form. These products apparently result from transamidation of the N,N-dimethylamide to yield the corresponding N-unsubstituted amide. This amide in turn is alkylated to yield the N-alkylamide. Further, when N,N,2,2-tetramethylbutyramide, which has no α-hydrogen, is treated with sodium amide followed by addition of methyl iodide, 45% of starting amide is recovered along with a mixture of inseparable transamidation products.

Secondary bromides gave lower yields than primary halides in the alkylation of N,N-dimethylacetamide, and *t*-butyl bromide and bromobenzene did not react.

This alkylation procedure[11] provides a novel method for extension of a carbon chain by two carbon atoms. It further provides a novel method for preparation of 2-alkyl-N,N-dimethylamides and their corresponding 2-alkylacids by subsequent hydrolysis.

Experimental Section[12]

Carbon, hydrogen, and nitrogen analyses were performed by Mr. L. M. White and Miss G. E. Secor of this laboratory. Infrared spectra were determined using a Perkin-Elmer Infracord 137 spectrophotometer, and nmr spectra were obtained with a Varian A-60 spectrometer on 20% solutions in carbon tetrachloride, using tetramethylsilane as internal standard. Gas chromatographic analyses were performed with an Aerograph A-90-P3 chromatograph using a 20% neopentyl glycol succinate on 60–80 mesh Chromosorb P column at 150 to 200°.

N,N-Dimethylamides were either Eastman White Label grade or were prepared by reaction of the corresponding acid chloride with dimethylamine in dry benzene. Finely divided sodium amide was purchased from Fisher Scientific Co.. Alkyl halides were Eastman White Label grade, and benzene and toluene were Baker Analyzed reagents.

Alkylation of N,N-Dimethylamides.—A mixture of 0.1 mole of N,N-dimethylamide and 3.9 g (0.1 mole) of sodium amide in 100 ml of dry benzene or toluene was heated to reflux. Vigorous evolution of ammonia began at about 65° and was essentially complete after refluxing the solution for 1 hr. Alkyl halide (0.1 mole) was added to the cooled solution, and, after any initial reaction, the solution was refluxed for an additional 1 hr. Sodium halide was removed from solution by filtration, and benzene or toluene was removed from the filtrate by distillation at reduced pressure to yield a colorless oil consisting of starting amide, alkylated amide(s), and lesser amounts of side products. In most cases, the products were separated and identified by gas chromatography (glpc). Higher boiling reaction mixtures were separated by fractional distillation at reduced pressure. Recovered N,N-dimethylamides and 2-alkyl-N,N-dimethylamides were identified by comparing their boiling points, infrared spectra, glpc retention times, and, in some cases, their nmr spectra with those from authentic samples. The previously unknown amide, 2-butyl-N,N-dimethylhexanamide, gave expected infrared bands at 1650 (amide carbonyl) and 730 cm^{-1} [$-(CH_2)_n-$] and an nmr spectrum with resonance signals at τ 7.09 and 6.97 (6 H, N–CH_3), 7.46 (1 H, α-CH), 8.77 [12 H, $(CH_2)_6$], and 9.10 (6 H, terminal CH_3).

Anal. Calcd for $C_{12}H_{25}NO$: C, 72.3; H, 12.6; N, 7.03. Found: C, 71.8; H, 12.5; N, 7.09.

When 2,2,N,N-tetramethylbutyramide was treated with sodium amide and methyl iodide in toluene by the above procedure, 6.4 g (45%) of starting amide and 6.0 g of a transamidation mixture were found. The alkylation of N,N-dimethylpropionamide and N,N-dimethylbutyramide each yielded 2.2 g of transamidation mixtures, in addition to recovered starting amide and alkylated amide. Samples of these inseparable transamidation products were prepared by glpc. They gave infrared bands at 3300–3400 (N–H) and 1640–1660 cm^{-1} (amide carbonyl) and nmr signals at τ 2.38–3.08 (N–H) and 6.82–7.31 (N–R).

(11) We learned of a similar alkylation study carried out in liquid ammonia by P. G. Gassman and B. L. Fox, Department of Chemistry, The Ohio State University, Columbus, Ohio. We thank these authors for informing us of their results prior to publication.

(12) Reference to a company or product name does not imply approval or recommendation of the product by the U. S. Department of Agriculture to the exclusion of others that may be suitable.