tosyloxydiimide N-oxide in 30 ml. of THF and 6 mmoles of phenyllithium in 6 ml. of ether was carried out as described earlier. Chromatography on silica gel gave a trace of 4-chloroazoxybenzene (infrared spectrum) and 0.82 g. (71%) of phenyl *p*-tolyl sulfone, m.p. 124–126°.

Reaction of the Phenyl Grignard Reagent and Methylnitrosohydroxylamine Tosylate.—A solution of 1.15 g. (5.0 mmoles) of the tosylate in 25 ml. of methylene chloride was stirred at ice-bath temperature while 2.0 ml. of Arapahoe 3 *M* phenyl Grignard reagent was added. The mixture was stirred overnight at ambient temperature, and then was processed as usual. The residue was chromatographed on silica gel. Elution of the column was carried out with pentane–methylene chloride, methylene chloride, and ethyl acetate in methylene chloride. The first fraction eluted (after the biphenyl cut), 0.17 g., was identified as tosyl bromide by infrared spectrum, ultimate analysis, and m.p. 95–96°, lit.[21] m.p. 95–96°. The next fraction eluted, 0.365 g., was phenyl tosylate, m.p. 93–94°, lit.[22] m.p. 94–95°, identified by infrared spectrum and ultimate analysis. The last fraction from the column, eluted by ethyl acetate in methylene chloride, was recovered starting material, 0.188 g.

Reaction of the Phenyl Grignard Reagent and N-*n*-butyl-N′-tosyloxydiimide N-oxide.—A solution of 1.30 g. (5.0 mmoles) of the butylnitrosohydroxylamine tosylate in 35 ml. of methylene chloride was stirred at 3° while 12.2 ml. of 0.83 *M* phenyl Grignard in ether was added dropwise. The reaction was processed as usual and the residue was chromatographed on silica gel. The only fraction of the eluate that could be identified was that eluted by 10% ethyl acetate in methylene chloride. This was phenyl *p*-tolyl sulfone, 0.86 g., 74%, m.p. 126–127°.[20]

Reaction of N-Phenyl-N′-tosyloxydiimide N-Oxide and Sodium Methoxide.—A mixture of 5.84 g., (20 mmoles) of the above diimide N-oxide, 20 mmoles of sodium methoxide, and 75 ml. of methanol was stirred until the tosylate dissolved. The solution was refluxed for 1 hr., and then was cooled, poured into water, and extracted with methylene chloride. The residue was chromatographed on silica gel. Pentane in methylene chloride, methylene chloride, and ethyl acetate in methylene chloride were used to elute the column. The first fraction from the column was azobenzene (by infrared and melting point), 0.09 g.; the second was azoxybenzene (by infrared), 0.18 g. The infrared spectrum of the third fraction, 0.60 g., identified it as methyl tosylate (15%). Continued elution of the column gave N-phenyl-N′-methoxydiimide N-oxide, 1.24 g., 41%, m.p. 38–40° (from hexane), lit.[8] m.p. 39.5–40.5°. The infrared spectrum of this diimide was identical with that of a sample prepared from cupferron and dimethyl sulfate.[8]

When 10 mmoles of sodium methoxide in methanol was added slowly to a suspension of the tosyloxy diimide N-oxide in 50 ml. of methanol at ambient temperature, the tosylate dissolved slowly. As soon as solution was complete (*ca.* 15 min.), the methanolic solution was poured into water and processed as described before. A total of 1.48 g. (79%) of methyl tosylate and only a trace of N-phenyl-N′-methoxydiimide N-oxide was eluted from the silica gel column.

Reaction of Sodium Methoxide and N-Methyl-N′-tosyloxydiimide N-Oxide.—A mixture of 2.30 g. (10 mmoles) of the tosylate of methylnitrosohydroxylamine and 25 ml. of 0.49 *M* sodium methoxide (12 mmoles) in methanol was refluxed for 4 hr. The solution was cooled, diluted with 150 ml. of salt water, and extracted seven times with methylene chloride. The extract was dried over magnesium sulfate. After removal of all but about 2 ml. of the methylene chloride by distillation, the residual solution was distilled *in vacuo* through −30° and −80° traps. The −30° trap retained the N-methyl-N′-methoxydiimide N-oxide, 0.46 g., 51%. The sample was purified by preparative v.p.c. at 100° using a silicone (GE-SF-96) on Chromosorb column. A sample thus purified had $n^{20}D$ 1.4488; ultraviolet (cyclohexane), λ_{max} 238 mμ (ε 9730).

Anal. Calcd for $C_2H_6N_2O_2$: C, 26.66; H, 6.72; N, 31.10. Found: C, 27.03; H, 6.76; N, 32.35.[23]

Sodium Methoxide and N-*n*-Butyl-N′-tosyloxydiimide N-Oxide.—A mixture of 1.30 g. (5 mmoles) of the tosylate of *n*-butylnitrosohydroxylamine in 20 ml. of methanol and 12.0 ml. of 0.42 *M* sodium methoxide in methanol was refluxed for 3 hr. After the usual processing, the organic residue was chromatographed on silica gel. Methylene chloride eluted methyl tosylate, 0.08 g., 9%, identified by infrared spectrum; and 10% ethyl acetate in methylene chloride eluted N-*n*-butyl-N′-methoxydiimide N-oxide, 0.29 g., 44%, as a colorless oil. The n.m.r. spectrum is summarized in Table IV.

Anal. Calcd. for $C_5H_{12}N_2O_2$: C, 45.43; H, 9.15; N, 21.1. Found: C, 45.65; H, 9.27; N, 22.3.[23]

Potassium Phenoxide and N-Phenyl-N′-tosyloxydiimide N-Oxide.—A mixture of 2.92 g. (10 mmoles) of the tosylate of phenylnitrosohydroxylamine, 1.0 g. (11 mmoles) of phenol, 50 ml. of *t*-butyl alcohol, and 1.12 g. (10 mmoles) of solid potassium *t*-butoxide was refluxed for 3 hr. The mixture was cooled, poured into water, and extracted with methylene chloride. The methylene chloride was evaporated and the residue recrystallized from hexane yielding phenyl tosylate, 2.13 g., 86%, m.p. 94–95°.[22]

(21) R. Otto and O. Gruber, *Ann.*, **142**, 92 (1867).
(22) R. Otto, *Ber.*, **19**, 1832 (1886).
(23) As mentioned in footnote *a*, Table III, high nitrogen values were often obtained on compounds of this type in the Dumas analysis.

Synthesis of Chonemorphine Stereoisomers

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The four diastereoisomers of 3-amino-20-dimethylamino-5α-pregnane have been prepared by known reactions. One of these, the 3β,20α isomer, has been proved to be identical with the steroidal alkaloid chonemorphine. Some new observations on the stereoselectivity of reductions of 3-keto steroid oximes are reported and also some work on the preparation of $\Delta^{8(9)}$- and $\Delta^{8(14)}$-5α-pregnen-3β-ol-20-one acetates.

Chonemorphine is a steroidal alkaloid which has been isolated from the reputedly medicinal Indian herb, *Chonemorpha macrophylla*,[2] and from the similar Malayan plant, *Chonemorpha penangensis*.[3] In 1960 Chatterjee and Das[4] proposed that chonemorphine is a 3-amino-20-dimethylaminopregnene with the double bond possibly located at the 8,9-position.

Our initial work to establish the structure of this alkaloid was aimed at the synthesis of $\Delta^{8(9)}$- and $\Delta^{8(14)}$-3-amino-20-dimethylaminopregnenes having different stereochemical relationships at C-3 and C-20. 5,7-Pregnadien-3β-ol-20-one acetate, prepared by the action of N-bromosuccinimide on pregnenolone acetate with subsequent dehydrobromination,[5] was isomerized by acid to the corresponding $\Delta^{8,14}$-diene.[6] Hydrogenation

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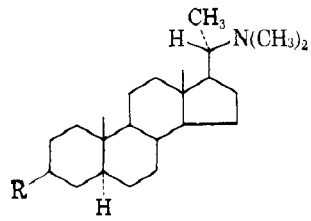
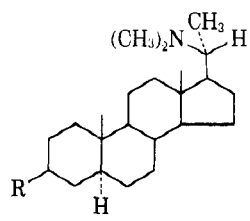
(2) K. G. Das and P. P. Pillay, *J. Sci. Ind. Res.* (India), **13B**, 602, 701 (1954).
(3) A. Chatterjee and B. Das, *Chem. Ind.* (London), 1445 (1959).
(4) A. Chatterjee and B. Das, *ibid.*, 290 (1960).
(5) R. Antonucci, S. Bernstein, D. Giancola, and K. J. Sax, *J. Org. Chem.*, **16**, 1126 (1951).
(6) L. F. Fieser and G. Ourisson, *J. Am. Chem. Soc.*, **75**, 4404 (1953).

of the diene over Raney nickel furnished Δ^8-5α-pregnen-3β-ol-20-one acetate,[7] which could be isomerized readily to the $\Delta^{8(14)}$ isomer.[8,9]

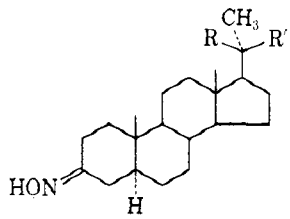
At this point Chatterjee and Das[10] reported new data showing that chonemorphine is actually a *saturated* compound and that its structure is 3β-amino-20α-dimethylamino-5α-pregnane (Ia). The evidence consisted of the observation that nitrous acid deamination of chonemorphine yields predominantly 20α-dimethylamino-5α-pregnan-3β-ol (Ib). Consequently, our efforts were shifted to prove unequivocally by synthesis the stereochemistry at C-3 of this proposed structure and also to prepare the three remaining C-3 and C-20 isomers in order to make them available for pharmacological testing of possible hypotensive or hypocholestereolemic activity.[11]



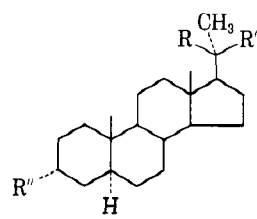
Ia, R = NH_2
b, R = OH
c, R = OAc
d, R = OTs



IIa, R = NH_2
b, R = OH
c, R = OAc
d, R = OTs



IIIa, R = H, R′ = $N(CH_3)_2$
b, R = $N(CH_3)_2$, R′ = H



IVa, R = H; R′ = $N(CH_3)_2$; R″ = NH_2
b, R = H; R′ = $N(CH_3)_2$; R″ = N_3
c, R = $N(CH_3)_2$; R′ = H; R″ = NH_2
d, R = $N(CH_3)_2$; R′ = H; R″ = N_3

The epimeric 20α- and 20β-dimethylamino-5α-pregnan-3β-ol acetates (Ic and IIc, respectively) used as starting materials in our work were prepared from 5α-pregnan-3β-ol-20-one acetate oxime by reduction and subsequent N-methylation.[12] To increase the yield of the 20α epimer (Ic) we utilized catalytic hydrogenation[13] of the oxime in acetic acid solution over Adams' catalyst in place of the sodium–alcohol reduction described by Sörm and co-workers.[12] The catalytic method gave the chromatographically separable 20α and 20β epimers (Ic and IIc) roughly in the ratio of 5:2, whereas reduction with sodium in alcohol furnished these epimers in a ratio of 1:2. Hydrolysis and oxidation of the resulting 3β-ols (Ib and IIb) to the corresponding ketones, with subsequent conversion into their respective oximes (IIIa and IIIb), was carried out as described by the Sörm group.[12] Reduction of the oximes to the corresponding equatorial 3β amines was effected with lithium aluminum hydride or by the action of sodium in amyl alcohol. It is of interest that catalytic hydrogenation of these oximes in acetic acid over Adams' catalyst gave predominantly the same 3β-amino products. This was somewhat surprising, since, according to Goutarel,[13b] catalytic hydrogenation of these oximes gives mainly the corresponding 3α-amino products.[14]

3β-Amino-20α-dimethylamino-5α-pregnane (Ia), prepared by the foregoing sequence, was found to have physical properties and derivatives identical with those of naturally occurring chonemorphine (*cf.* Table I). At about the time this phase of our work had been completed, an account of essentially the same synthesis appeared,[15] but no derivatives or direct comparisons with authentic samples were reported. Consequently, our work provides a more definitive verification of the structure of chonemorphine as 3β-amino-20α-dimethylamino-5α-pregnane (Ia).

Finally, in order to obtain the corresponding 3α-amino isomers IVa and IVc we prepared the 3β-*p*-toluenesulfonates (Id and IId) and submitted them to nucleophilic displacement reactions with sodium azide in dimethyl sulfoxide.[16] Reduction of the resulting azides with lithium aluminum hydride readily gave the axial 3α amines (IVa and IVc), which, along with their derivatives, were found to be distinctly different from the corresponding 3β epimers (*cf.* Table I). These results thus provide additional confirmation of the assignment of the equatorial 3β-amino structure (Ia) to chonemorphine.

Experimental[17]

5α-Pregna-8,14-dien-3β-ol-20-one Acetate.—A solution of 2.0 g. of 5,7-pregnadien-3β-ol-20-one acetate (prepared according to the method of Antonucci, *et al.*,[5] from pregnenolone acetate) in 10 ml. of benzene and 40 ml. of acetic acid was refluxed in the presence of 3 drops of concentrated hydrochloric acid. Isomerization of the 5,7-diene system was found to be nearly complete after 1 hr., as indicated by the appearance of a new absorption peak at 250 mμ and the disappearance of the 282-mμ absorption of the 5,7-diene. The solution was then partially neutralized with potassium carbonate and the product isolated by extraction with ether. The residue, after evaporation of the ether, crystallized from methanol to afford 0.75 g. of 5α-pregna-8,14-dien-3β-ol-20-one acetate, m.p. 128–131°. Recrystallization from

(7) F. Gautschi and K. Bloch, *J. Biol. Chem.*, **233**, 1343 (1958).

(8) J. B. Bream, D. C. Eaton, and H. B. Henbest, *J. Chem. Soc.*, 1974 (1957).

(9) It is of interest that the n.m.r. spectrum of Δ^8-5α-pregnen-3β-ol-20-one acetate shows the C-18 and C-19 methyl proton signals at 32.5 and 58.3 c.p.s., respectively, from tetramethylsilane as an internal standard in carbon tetrachloride solution on a 60-Mc. instrument, while $\Delta^{8(14)}$-5α-pregnan-3β-ol-20-one acetate shows these signals at 42.5 and 48.7 c.p.s. These differences may offer a convenient method to distinguish $\Delta^{8(9)}$and $\Delta^{8(14)}$ steroids in the absence of other interfering C-methyl absorptions.

(10) A. Chatterjee and B. Das, *Chem. Ind.* (London), 1247 (1960).

(11) *Cf.* R. E. Counsell, P. D. Klinstra, R. E. Ranney, and D. L. Cook, *J. Med. Pharm. Chem.*, **5**, 720, 1224 (1962).

(12) V. Černý, L. Lábler, and F. Sörm, *Collection Czech. Chem. Commun.*, **22**, 76 (1957).

(13) (a) R. A. Lucas, D. F. Dickel, R. L. Dziemian, M. J. Ceglowski, B. L. Hensle, and H. B. MacPhillamy, *J. Am. Chem. Soc.*, **82**, 5688 (1960); (b) R. Goutarel, *Tetrahedron*, **14**, 126 (1961).

(14) In this connection it is perhaps pertinent to note that the stereochemistry of the reduction of a series of 3-keto steroid oximes with lithium aluminum hydride has been found to vary with the nature of the side chain as well as with the stereochemistry of the A/B ring junction [*cf.* C. W. Shoppee, D. E. Evans, H. C. Richards, and G. H. R. Summers, *J. Chem. Soc.*, 1649 (1956)].

(15) M. M. Janot, F. Laine, Q. Khuong-Huu, and R. Goutarel, *Bull. soc. chim. France*, 111 (1962).

(16) *Cf.* W. R. Hertler and E. J. Corey, *J. Org. Chem.*, **23**, 1221 (1958); H. B. Henbest and W. R. Jackson, *J. Chem. Soc.*, 954 (1962); also, A. K. Bose, J. F. Kistner, and L. Farber, *J. Org. Chem.*, **27**, 2925 (1962).

(17) Melting points were taken in open capillaries and are uncorrected. Optical rotations were taken in chloroform solution. Analyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

TABLE I

PROPERTIES AND ANALYSES OF SYNTHETIC CHONEMORPHINE AND STEREOISOMERS

Compound	M.p., °C.	$[\alpha]_D$, deg.	Formula	Analyses: % C Calcd.	% C Found	% H Calcd.	% H Found	% N Calcd.	% N Found
3β-Amino-20α-dimethylamino-5α-pregnane (Ia)	149–149.5[a]	+25[a]	$C_{23}H_{42}N_2$	79.70	79.51	12.22	12.06	8.08	7.85
N-Benzylidene deriv.[b]	182–183[c]	+36	$C_{30}H_{46}N_2$	82.89	82.92	10.67	10.80	6.44	6.64
N-Acetyl deriv.	262–265[d]	+17	$C_{25}H_{44}N_2O$	77.26	77.07	11.41	11.52	7.21	7.21
3α-Amino-20α-dimethylamino-5α-pregnane (IVa)	153–153.5	+29	$C_{23}H_{42}N_2$	79.70	79.76	12.22	12.43	8.08	7.94
N-Benzylidene deriv.[b]	202.5–203.5	+23	$C_{30}H_{46}N_2$	82.89	82.89	10.67	10.71	6.44	6.65
N-Acetyl deriv.[e]	206–208	+31	$C_{25}H_{44}N_2O \cdot H_2O$	73.84	74.25	11.40	11.22	6.89	7.02
3β-Amino-20β-dimethylamino-5α-pregnane (IIa)	149–151	+10	$C_{23}H_{42}N_2$	79.70	79.46	12.22	12.26	8.08	8.02
N-Benzylidene deriv.[b]	153–154	+27	$C_{30}H_{46}N_2$	82.89	82.60	10.67	10.92	6.44	6.60
N-Acetyl deriv.[e]	209–212	+ 5	$C_{25}H_{44}N_2O \cdot {}^1/_2H_2O$	75.51	75.31	11.41	11.21	7.05	7.20
3α-Amino-20β-dimethylamino-5α-pregnane (IVc)	163–164	+17	$C_{23}H_{42}N_2$	79.70	79.61	12.22	11.97	8.08	8.36
N-Benzylidene deriv.[b]	117–118	+27	$C_{30}H_{46}N_2$	82.89	82.66	10.67	10.97	6.44	6.52
N-Acetyl deriv.	208–211	+30	$C_{25}H_{44}N_2O$	77.26	77.33	11.41	11.44	7.21	7.14

[a] Janot, *et al.*,[15] report m.p. 149°, $[\alpha]_D$ +25°. Our sample of natural chonemorphine melted at 147–149°, $[\alpha]_D$ +25° (lit.[3] m.p. 144–146°, $[\alpha]_D$ +25°). [b] This derivative showed λ_{max} 248, 277, and 287 mμ. [c] Chatterjee and Das[3] report m.p. 184° for this derivative of chonemorphine. [d] Chatterjee and Das[3] reported m.p. 270° for the chonemorphine derivative. [e] The indicated amount of water of crystallization was lost on prolonged drying at 130°.

ethanol afforded material with m.p. 133–134°, $[\alpha]_D$ +64° (*c* 1.54), λ_{max} 250 mμ (ε 25,500).

Anal. Calcd. for $C_{23}H_{32}O_3$ (356.49): C, 77.49; H, 9.05. Found: C, 77.76; H, 8.98.

5α-Pregna-8-en-3β-ol-20-one Acetate and 5α-Pregna-8(14)-en-3β-ol-20-one Acetate.—Hydrogenation of 0.90 g. of the foregoing product was conducted in absolute ethanol over Raney nickel in a Parr hydrogenator. After 1 hr. the catalyst was removed by filtration and the solvent evaporated. The crude hydrogenation product, m.p. 142–147°, was recrystallized from ethanol five times to give pure 5α-pregna-8-en-3β-ol-20-one acetate, m.p. 160–162°, $[\alpha]_D$ +89° (*c* 1.05). This gave a positive osmium tetroxide test[18] in about 20 min. No vinyl proton signal was observed in the n.m.r. spectrum.[19]

Anal. Calcd. for $C_{23}H_{34}O_3$ (358.50): C, 77.05; H, 9.56. Found: C, 77.30; H, 9.74.

The residue from the mother liquors was dissolved in acetic acid and shaken under hydrogen in the presence of palladium–charcoal for 20 hr. to effect the isomerization of double bond to the 8(14) position. The 5α-pregna-8(14)-en-3β-ol-20-one acetate thus obtained melted at 156–157°, $[\alpha]_D$ +99° (*c* 1.48) (lit.[20] m.p. 156–157°, $[\alpha]_D$ +90°). Its melting point was significantly depressed (below 130°) on admixture with the $\Delta^{8(9)}$ isomer. The n.m.r. spectrum[19] also indicated the absence of any vinyl proton.

20α- and 20β-Dimethylamino-5α-pregnan-3β-ol Acetate (Ic and IIc).—These two compounds were prepared according to the method described by Sǒrm, *et al.*,[12] or by a modification in which catalytic hydrogenation[13a] was used in the place of reduction by sodium in alcohol for the conversion of 5α-pregnan-3β-ol-20-one acetate oxime into the corresponding 20α and 20β amines. In a typical run by the hydrogenation method, with subsequent N-methylation and reacetylation of the hydroxyl group, 0.916 g. of Ic and 0.390 g. of IIc (ratio, 5:2) were obtained from 3.75 g. (0.01 mole) of 5α-pregnan-3β-ol-20-one acetate oxime. A total of more than 30 g. each of Ic and IIc was prepared.

20α- and 20β-Dimethylamino-5α-pregnan-3-one Oxime (IIIa and IIIb).—These oximes were prepared according to the method of Sǒrm, *et al.*,[12] from their respective ketones, which in turn were obtained by chromic acid oxidation of Ib and IIb in acetic acid. IIIa had m.p. 232–235° dec. (lit.[12] m.p. 241°, lit.[15] m.p. 233–235° dec.); IIIb had m.p. 240–243° dec. (lit.[12] m.p. 240–244° dec.).

3β-Amino-20α-dimethylamino-5α-pregnane (Ia) and 3β-Amino-20β-dimethylamino-5α-pregnane (IIa) from Oximes IIIa and IIIb. A. By Lithium Aluminum Hydride Reduction.—To a solution of 0.721 g. (2 mmoles) of IIIa in 200 ml. of anhydrous ether was added 2.3 g. of lithium aluminum hydride (0.06 mole). The resulting mixture was refluxed on a steam bath for 9 hr. It was then allowed to stand at room temperature overnight. Concentrated sodium hydroxide solution was added to the mixture after the excess of lithium aluminum hydride had been cautiously destroyed with water. The mixture was extracted with ether, and the combined extracts were washed thoroughly with water and dried over anhydrous potassium carbonate. The solid residue obtained by evaporation of the solvent was recrystallized from ethyl acetate. It afforded 0.185 g. (27%) of the desired amine (Ia), m.p. 145–147°, after three recrystallizations from the same solvent. The analytical sample (see Table I) melted at 149–149.5°, $[\alpha]_D$ +25° (*c* 0.43) (lit.[15] m.p. 149°, $[\alpha]_D$ +25°). A mixture melting point with chonemorphine (m.p. 147–149°) showed no depression. The infrared spectrum also was found to be superimposable with that of chonemorphine.[21]

Similarly, 0.721 g. (2 mmoles) of the oxime IIIb gave 0.197 g. (28%) of IIa, m.p. 148–150°. Purified IIa melted at 149–151°, $[\alpha]_D$ +10° (*c* 1.01). Its melting point was significantly depressed by Ia (below 125°).

The N-benzylidene and N-acetyl derivatives of both Ia and IIa were prepared in the usual manner. Those of Ia were found to be identical with the corresponding derivatives of chonemorphine.

B. By Catalytic Hydrogenation.—The oxime IIIa (1.082 g., 3 mmoles) in 20 ml. of acetic acid was reduced in a microhydrogenator in the presence of 0.25 g. of Adams' catalyst which had been prereduced in 20 ml. of the same solvent. Reduction appeared to be essentially complete in 4 hr., and after filtration the solution was neutralized and made alkaline with ammonium hydroxide, and the precipitated solid was dissolved in ether. The resulting solution was washed with water and dried over anhydrous potassium carbonate. Evaporation of the ether gave 0.956 g. of crude product (m.p. below 133°), from which 0.298 g. (29%) of Ia, m.p. 145–147°, was obtained. An additional 0.100 g. of less pure Ia, m.p. 141–143°, was recovered from the mother liquors. After recrystallization from ethyl acetate the product melted at 147–149° (not depressed by the lithium aluminum hydride reduction product), $[\alpha]_D$ +25° (*c* 1.15). Its N-benzylidene and N-acetyl derivatives also were found to be identical with those of the lithium aluminum hydride reduction product and the corresponding ones of chonemorphine.

In a similar manner, there was obtained 0.235 g. (34%) of IIa, m.p. 148–150°, from 0.721 g. (2 mmoles) of the oxime IIIb.

C. By Sodium and Amyl Alcohol Reduction.—Sodium metal (3.2 g., 0.14 g.-atom) was added in small pieces over 2 hr. to a boiling solution of 0.360 g. (1 mmole) of IIIa in 50 ml. of distilled amyl alcohol. The amyl alcohol was removed by steam distilla-

(18) D. H. R. Barton and J. D. Cox, *J. Chem. Soc.*, 214 (1949).

(19) We wish to thank Dr. H. Y. Chen, U. S. Industrial Chemicals Co., Cincinnati, Ohio, for this spectrum.

(20) O. Mancera, D. H. R. Barton, G. Rosenkranz, and C. Djerassi, *J. Chem. Soc.*, 1021 (1952).

(21) Chonemorphine was isolated by N. T. I. from *Chonemorpha macrophylla* and purified as the dihydrochloride.

tion and the yellow product recovered by extraction with ether. It afforded 0.082 g. (24%) of Ia, m.p. 145–147°, still slightly yellow after three recrystallizations from ethyl acetate.

In the same manner, 0.721 g. (2 mmoles) of IIIb yielded 0.316 g. (46%) of the fairly pure but yellow IIa, m.p. 147–150°.

20α-Dimethylamino-5α-pregnan-3β-ol Tosylate (Id) and 3α-Azido-20α-dimethylamino-5α-pregnane (IVb).—A solution of 3.5 g. of recrystallized *p*-toluenesulfonyl chloride in 10 ml. of anhydrous pyridine was added in portions with cooling to 1.74 g. (5 mmoles) of Ib in 30 ml. of the same solvent. The solution immediately turned yellow, then light red. Some solid also formed. After having been kept at 0° for 13 days, the reaction mixture was poured into cold dilute sodium bicarbonate solution containing crushed ice and was then extracted with a mixture of benzene and petroleum ether (b.p. 35–60°). The combined extracts, after having been dried over anhydrous sodium sulfate, were evaporated under reduced pressure at room temperature, giving 2.10 g. of slightly yellow residue. The pure tosylate was isolated and characterized in another run. It crystallized from acetone in needles, m.p. 151–151.5°, $[\alpha]_D$ +11° (*c* 1.00).

Anal. Calcd. for $C_{30}H_{47}NO_3S$ (501.76): C, 71.81; H, 9.44; N, 2.79; S, 6.39. Found: C, 72.04; H, 9.57; N, 2.67; S, 6.17.

A mixture of the crude tosylate (2.10 g.) and 4.45 g. of sodium azide in 70 ml. of dimethyl sulfoxide was heated in an oil bath at 95–100° with stirring for 6 hr. The mixture was then poured into ice water and extracted with petroleum ether. The extracts were evaporated *in vacuo* and the residue crystallized from acetone, giving 1.00 g. of the azide IVb as needles, m.p. 153—155°. An additional 0.15 g. was obtained from the mother liquor making the total yield 62%. The purified product melted at 156–158°, $[\alpha]_D$ +17° (*c* 0.83).

Anal. Calcd. for $C_{23}H_{40}N_4$ (372.58): C, 74.14; H, 10.82; N, 15.04. Found: C, 73.99; H, 11.04; N, 14.78.

20β-Dimethylamino-5α-pregnan-3β-ol Tosylate (IId) and 3α-Azido-20β-dimethylamino-5α-pregnane (IVd).—To a solution of 4.40 g. of recrystallized *p*-toluenesulfonyl chloride in 30 ml. of anhydrous pyridine was added 1.95 g. (5.6 mmoles) of IIb with cooling. The resulting solution was allowed to stand at 0° for 5 days. No solid was formed during this period, but the solution became red. The reaction product was isolated as described for Id to yield 2.50 g. (89%) of slightly yellow tosylate, m.p. 166°. The pure tosylate formed needles (from acetone), m.p. 166–167°, $[\alpha]_D$ 0° (*c* 1.01).

Anal. Calcd. for $C_{30}H_{47}NO_3S$ (501.76): C, 71.81; H, 9.44; N, 2.79; S, 6.39. Found: C, 71.78; H, 9.65; N, 2.78; S, 6.45.

The azide IVd was prepared in the same manner as IVd; yield, 77%. After recrystallization it formed plates (from acetone), m.p. 139–141°, $[\alpha]_D$ +8° (*c* 1.02).

Anal. Calcd. for $C_{23}H_{40}N_4$ (372.58): C, 74.14; H, 10.82; N, 15.04. Found: C, 74.35; H, 10.98; N, 15.24.

3α-Amino-20α-dimethylamino-5α-pregnane (IVa) and 3α-Amino-20β-dimethylamino-5α-pregnane (IVc).—A solution of 0.65 g. of the azide IVb in 150 ml. of anhydrous ether was reduced with 0.9 g. of lithium aluminum hydride. Nitrogen gas evolved immediately on addition of the hydride. The reaction mixture was stirred at room temperature overnight. After the excess of hydride had been consumed by slow addition of water, the mixture was treated with concentrated sodium hydroxide solution and extracted with ether. The combined extracts were washed with water and dried over potassium carbonate and evaporated. The residue crystallized from ethyl acetate to yield 0.52 g. (86%) of the desired amine IVa, m.p. 148–150°. After further recrystallization from the same solvent it melted at 153–153.5°, $[\alpha]_D$ +29° (*c* 1.00). When mixed with the 3β epimer (Ia) this melted at 120–125°.

The azide IVd (1.12 g. 3 mmoles), on reduction with an excess of lithium aluminum hydride in a similar manner, afforded 0.719 g. (69%) of IVc, m.p. 161–163°. The analytical sample melted at 163–164°, $[\alpha]_D$ +17° (*c* 1.00). The mixture melting point with IIa was depressed to below 130°.

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A New Type of Naturally Occurring Polyunsaturated Fatty Acid

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The seed oil of *Crepis foetida* L., a member of the plant family Compositae, contains 60% of a fatty acid that has been shown to be *cis*-9-octadecen-12-ynoic acid. For convenience it is called crepenynic acid. This nonconjugated polyunsaturated acid is the first known member of a new class of naturally occurring acetylenic fatty acids, analogous to linoleic acid in containing methylene-interrupted unsaturation. The new compound may find considerable importance in mechanistic studies of fatty acid biosynthesis and of fatty acid metabolism. Crepenynic acid readily autoxidizes on standing. Two derivatives have been synthesized, *cis*-9,10-epoxyoctadec-12-ynoic and *threo*-9,10-dihydroxyoctadec-12-ynoic acids.

During analytical investigation of the seed oil of *Crepis foetida* L., family Compositae, by procedures conventionally applied to seed oils,[2] it became apparent that the oil must contain compound(s) of novel structure. The presence of 88% of linolenic acid in the oil was indicated by an analysis based on conjugation developed after isomerization in alkali and measured by ultraviolet absorption.[3] However, gas–liquid chromatographic (g.l.c.) analyses of fatty acid methyl esters derived from the oil revealed no linolenic acid, but showed 60% of a component that had retention characteristics unlike those of any of the common naturally occurring fatty acids. Many of the observed properties could be rationalized by assuming a nonconjugated enynic structure for this new acid component, but precedents for this type of compound are lacking.

In this paper we report the isolation, purification, and proof of structure of this new fatty acid from *Crepis* oil, for which we suggest the name crepenynic acid, since the postulated presence of both olefinic and acetylenic unsaturation has been confirmed.

Results

Neither infrared nor ultraviolet spectral analyses provided evidence relevant to the structure of crepenynic acid since the parent oil gave spectra much like

(1) A laboratory of the Northern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) R. W. Miller and F. R. Earle, presentation before the American Oil Chemists' Society, Atlanta, Ga., April 22–24, 1963.

(3) American Oil Chemists' Society, "Official and Tentative Methods," Ed. 2, Rev., 1959, cd 7-58.