Tetrahedron. Vol. 25, pp. 4887 to 4894. Pergamon Press 1969. Printed in Great Britain

METAL-AMMONIA REDUCTION—V
THE STEREOCHEMISTRY OF REDUCTIVE ALKYLATION[1, 2]

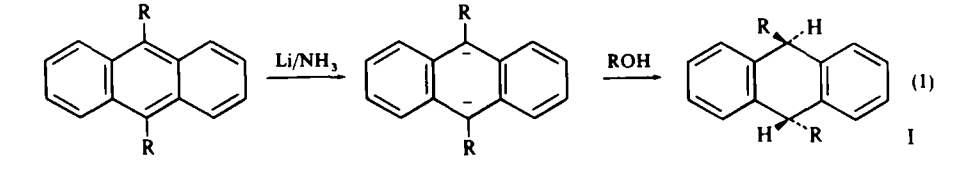
R. G. HARVEY and L. ARZADON

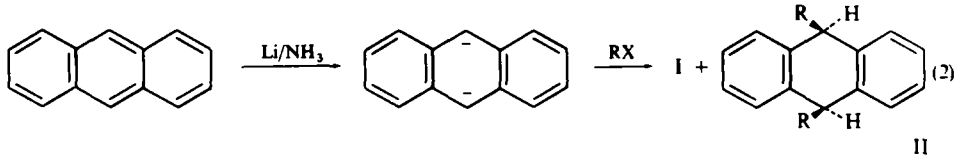
The Ben May Laboratory, University of Chicago, Chicago, Illinois 60637

(*Received in USA 24 March 1969; Received in UK for publication 30 June 1969*)

Abstract—Reductive alkylation of anthracene, 9, 10-dimethylanthracene, 1, 4-dimethylanthracene, benz(*a*)anthracene and dibenz(*a, h*)anthracene via treatment of the dilithio adducts in liquid ammonia with alkyl halides proceeds stereo selectively to furnish high yields of the corresponding *cis*-dialkyldihydro derviatives.

SINGLE-STAGE reduction of a series of representative polycyclic aromatic hydrocarbons by lithium dissolved in liquid ammonia was described in part IV.[2] The structures of the dihydro products accorded, in general, with predictions[3] based upon MO calculations of the positions of highest electron density in the corresponding anionic intermediates. Also, reduction of 9, 10-diethyl- and 9, 10-di-n-butylanthracene (Eq. 1) proceeded stereospecifically to provide the corresponding *trans*-9, 10-dialkyl-9, 10-dihydroanthracenes (I).





In principle, the anionic intermediates formed via interaction of alkali metals with hydrocarbons in liquid ammonia should be susceptible to alkylation (Eq. 2) as well as protonation (Eq. 1). This transformation, which may be termed *reductive alkylation*, has been the subject of only limited investigation.[4,*] Dialkyldihydro derivatives of anthracene,[7–9]† benz(*a*)anthracene,[7] and biphenyl[10] (of unknown stereochemistry) have been synthesized by analogous reaction in organic solvents. However, formation of metal-hydrocarbon adducts in non-polar solvents is a heterogeneous process,

* Hückel *et al.* reported reductive methylation of fluorene[5] and methylated naphthalene[6] in liquid ammonia without mention of the stereochemistry.

† It is reported,[9] for example, that interaction of methyl iodide with disodioanthracene in dioxan at 20° furnished: 9, 10-dimethyl-9, 10-dihydroanthracene and 9-methyl-9, 10-dihydroanthracene (27%); 1, 2-dimethyl-1,2-dihydroanthracene (7%); 9-methylanthracene, 9, 10-dimethylanthracene, 9-methyl-10-ethylanthracene and an unidentified alkylanthracene (11%); anthraquinone (3%); resin (8%); and recovered anthracene (44%).

requiring prolonged reaction periods (usually 2–5 days), and the products of alkylation are often complex mixtures.*

We now wish to report the stereospecific reductive alkylation in liquid ammonia of a series of polynuclear hydrocarbons. The experimental procedure adopted was based upon that developed earlier[2, 11] for the controlled reduction of polycyclic hydrocarbons. Product distribution was determined quantitatively by gas chromatography and qualitatively by chromatography on thin layers of silica gel impregnated with *s*-trinitrobenzene.[12]

RESULTS

Reductive methylation of anthracene via treatment with 2·5 equivts of lithium in refluxing ammonia followed by methyl bromide, furnished *cis* and *trans*-9, 10-dimethyl-9, 10-dihydroanthracene (II and I: R = Me) in yields of 78% and 22%, respectively (Eq. 3). The structures of the stereoisomers were previously established by stereospecific syntheses from diacids of known configuration;[13, 14] the recently demonstrated[2] greater resistance of the *cis* isomer to catalytic dehydrogenation, equilibration and alkylation supports the correctness of this assignment. Similar reaction conducted at lower temperature (−78°) depressed the yields of II and I to 7% and 45%, respectively, and furnished 9-methyl-9, 10-dihydroanthracene as the major product.

While methyl chloride, bromide and iodide all reacted under standard conditions (Table I) to furnish II (R = Me) in 70–80% yield, differences were found in other

TABLE 1. REDUCTIVE ALKYLATION OF ANTHRACENE (A)[a]

Halide (mmole)	Product Composition (%)[b]				
	A	AH_2	*AHR*	cis-AR_2	trans-AR_2
MeCl, excess	14	0	1	77	9
MeBr, excess	0	0	0	78	22
MeBr, excess[c]	0	0	48	45	7
MeI (25)	0	0	14	72	14
EtBr (27)[d]	0	0	8	80	12
EtBr (270[e]	0	0	0	84	16
i-PrCl (55)	12	0	0	70	18
t-BuBr (44)	16	68	14	2	0

[a] Anthracene (10 mmole) and lithium (25 mmole) were employed under the standard conditions described in the experimental section, unless specified otherwise.

[b] Product composition was determined by gas chromatography on a 6′ 10% SE 30 on Chromosorb W column at 175°. A = Anthracene; AH_2 = 9, 10-dihydroanthracene; etc.

[c] Reaction was conducted at −78°.

[d] Ethyl bromide was diluted with 10 ml of THF.

[e] Tenfold scale employed.

respects. The product from the chloride contained recovered anthracene (14%), while that from the iodide invariably included appreciable monomethylated anthracene.

* See footnote * on previous page.

Employment of an increased proportion of methyl iodide led to formation of dihydroanthracene instead of a diminished quantity of the partially methylated product. This effect is apparently a consequence of the relatively high reactivity of the iodide with ammonia to provide methyl ammonium iodide;[15] the latter is an efficient protonating reagent.

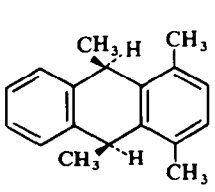
Analogous ethylation and isopropylation of the anthracene dianion proceeded readily to furnish the corresponding *cis*-9, 10-dialkyl-9, 10-dihydroanthracenes (II: R = Et, i-Pr) in yields of 80% and 70%, respectively (Eq. 4, 5). The diethyl compound, a solid melting at 58–59°, was identified as the *cis* isomer through comparison of its physical properties, particularly its integrated NMR spectrum, with those of the authentic substance; the latter was synthesized via treatment of the adduct of ethyllithium and anthracene with ethyl bromide.[16] Assignment of the *cis* structure to the diisopropyl product rests upon analogy with the diethyl example and upon the NMR spectrum: τ 6·18 (d, 2, benzylic, J = 5 Hz); τ 9·02 (d, 6, Me, J = 7·5 Hz). Also, the same isomer was obtained (55%) through alkylation with isopropyl chloride of the addition product of isopropyllithium and anthracene.[16]

Reductive ethylation and isopropylation of anthracene provided in addition to II (R = Et, i-Pr) a minor product which proved to be not the expected corresponding *trans* diastereomers, but the related 9, 9, 10-trialkyl derivatives of 9, 10-dihydroanthracene (Eq. 4, 5). These compounds were isolated by preparative gas chromatography and identified by NMR spectroscopy. The spectrum of the triethyl compound exhibited peaks at τ 9·83 (t, 3, Me, J = 7 Hz), 9·37 (t, 3, Me, J = 7 Hz), 9·23 (t, 3, Me, J = 7 Hz), 8·12 (m, 2, $C\underline{H}_2CH$), 8·05 (q, 2, CH_2, J = 7 Hz), 7·93 (q, 2, CH_2, J = 7 Hz), 6·00 (t, 1, CH, J = 6 Hz), 2·73 (m, 8, aryl), while that of the triisopropyl homolog contained characteristic peaks at τ 9·42 (d, 12, Me, J = 7 Hz), 8·33 (d, 6, Me, J = 7 Hz), 6·10 (d, 1, benzylic, J = 3 Hz). Evidence for the origin of the trisubstituted dihydroanthracenes from the *trans*-dialkyl derivatives is presented in the discussion.

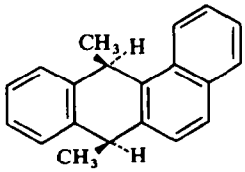
t-Butylation with t-butyl bromide proved considerably more difficult, furnishing only 14% mono-t-butyl- and 2% 9, 10-di-t-butyldihydroanthracene; the major product (68%) proved to be 9, 10-dihydroanthracene (Eq. 6). Since formation of the latter requires a proton source, and since the solvent has been demonstrated not to serve in this capacity,[11] it appears likely that hydrogen abstraction from t-butyl bromide takes place with formation of isobutylene and dihydroanthracene.

Methyl substituents in the meso region did not noticeably affect either the rate of reductive methylation or diminish the yield. Thus, a solution of 9, 10-dimethylanthracene and lithium in THF-ammonia underwent rapid decolorization upon treatment with methyl bromide to furnish 9, 9, 10, 10-tetramethyl-9, 10-dihydroanthracene (Eq. 7) (79%). The presence of Me substituents or additional fused aromatic rings in the α-positions of anthracene likewise failed to inhibit reductive methylation. Thus, 1, 4-dimethylanthracene, benz(*a*)anthracene and dibenz(*a*, *h*)anthracene underwent facile transformation to provide in each case only a single major product. These were identified as *cis*-1, 4, 9, 10-tetramethyl-9, 10-dihydroanthracene (III), d, 1-*cis*-7, 12-dimethyl-7, 12-dihydrobenz(*a*)-anthracene (IV) and *cis*-7, 14-dimethyl-7, 14-dihydrodibenz(*a*, *h*)anthracene (V), respectively. IV was readily distinguished from its *trans* isomer (prepared by lithium-ammonia reduction of 7, 12-dimethylbenz(*a*)anthracene[2]) by its NMR spectrum and melting point (Experimental). *cis* Configurations were tentatively also assigned to III and V on the basis of their

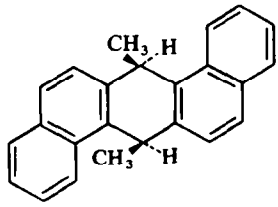
structural similarity to IV. In III and V, steric compression of substituents in the meso equatorial positions may be expected to be more severe than in IV.



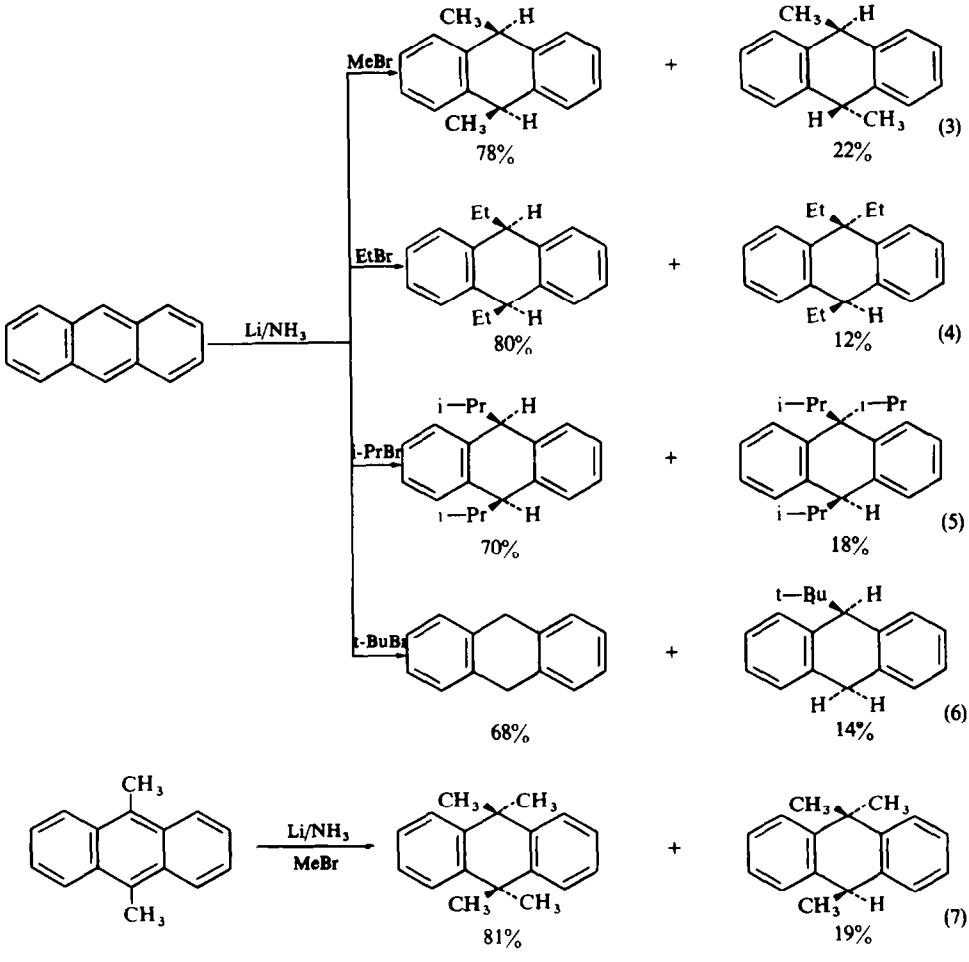
III



IV



V



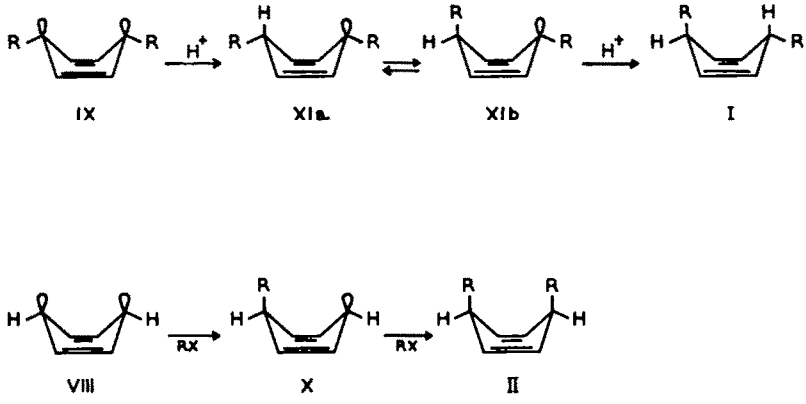
DISCUSSION

The relatively high specificity of reductive alkylation in liquid ammonia contrasts with the reported complexity of product distribution from similar reactions conducted

in organic solvents* (dioxan, tetrahydrofuran). In the latter case, prolonged reaction periods were necessary and the dialkylated products were contaminated with major quantities of both unreacted hydrocarbons and substances arising from competing side reactions. This solvent effect must be largely a consequence of the efficiency of anthracene 9, 10-dianion formation in the polar solvent[2, 4] relative to the slow single electron transfer from alkali metal to hydrocarbon in ethereal solvents.[17] Also, the rate of alkylation in ammonia may be expected to exceed that in organic solvents since dissociation of ionic intermediates is probable in the former medium, while aggregation is likely in the latter (e.g. n-butyllithium is hexameric in benzene solution[18, 19]).

The remarkable stereoselectivity of reductive alkylation (*cis*) in liquid ammonia, although opposite to that of reduction of 9, 10-dialkylanthracene[2] (*trans*), is explicable in similar terms (Chart 1). 9, 10-Dihydroanthracene and its *trans*-9, 10-dialkyl

CHART 1



derivatives undergo rapid ring inversion in solution at ambient temperature.[2] The corresponding 9, 10-dianions (VIII and IX) may, however, be sufficiently stabilized by orbital overlap to favor a conformation with substituents (H or alkyl) in the equatorial orientation. This would favor preferential initial alkylation (or protonation) at C-9 from the axial direction; greater accessibility from above the ring system may also aid axial attack. However, the steric preference of initial alkylation is unlikely to be a major factor in the determination of product structure. This follows since the monoanion formed upon alkylation (or protonation) is free to invert and assume a configuration offering minimum steric interaction. Alkyl groups in the equatorial orientation appear from molecular models† to be subject to considerably greater non-bonded interaction than their axial counterparts. This effect, primarily a con-

* See footnote* on p. 4887

† Space-filling molecular models (e.g. Courtauld models) are more revealing in this regard than are other types.

sequence of steric interference with the *peri* hydrogens of the adjacent aromatic rings, may be expected to increase with the steric demands of substituents in either position. On this basis, the alkyl group introduced in the initial alkylation stage may be expected to favor an axial orientation in the 9-alkyl, 10-monoanion* (X). Conversely, and for the same reasons, the inverted monoanion (XIb) should be favored during reduction. Finally, alkylation of X from the axial direction leads to the experimentally observed *cis* isomer (II); analogously, protonation of XIb provides the *trans* isomer (I).

Extrapolating to molecules wherein steric interaction should be considerably greater (i.e. the product of reductive isopropylation of anthracene and the products of reductive methylation of 1, 4-dimethylanthracene, benz(*a*)anthracene and dibenz-(*a*, *h*)anthracene), the probability of predominant *cis* geometry becomes all the more reasonable.

Formation of the triethyl and triisopropyl compounds, though unexpected, is readily explicable in terms of established facts. Reaction of excess lithium (0·5 g atoms) with excess alkyl halide may be expected to form the corresponding alkyllithium reagent. Also, the *trans*-diethyl isomer was previously demonstrated[2] to undergo virtually quantitative ethylation upon treatment with n-butyllithium in ammonia followed by ethyl bromide; the corresponding cis isomer reacted to only minor extent. If as these considerations imply, the trialkyl compounds arise through *trans*-dialkyl intermediates, there remains the question of why the *trans*-dimethyl compound fails to undergo analogous transformation. That this may be due to the relatively low efficiency of methyllithium for proton abstraction is evidenced by the diminished yield of triethyldihydroanthracene obtained upon substitution of methyllithium for n-butyllithium in the ethylation of diethyldihydroanthracene in liquid ammonia.

EXPERIMENTAL

Physical data. Mg pts were taken on a Leitz Kofler hot-stage microscope and are corrected. Proton NMR spectra were obtained on a Varian A-60 spectrophotometer; chemical shifts are reported relative to TMS in $CDCl_3$. Gas chromatographic analyses were performed on a F & M, Model 500 chromatograph; larger scale separations (100–500 mg) were achieved on a Hewlett–Packard, Model 755, preparative chromatograph.

Materials and methods. The polycyclic aromatic hydrocarbons were obtained from commercial sources, recrystallized from absolute alcohol, and dried *in vacuo*. If chromatography on trinitrobenzene-silica gel[12] revealed impurities after crystallization, the hydrocarbons were further purified by passage through a column of activated silica gel. This procedure is essential for hydrocarbons known to form transannular peroxides (e.g. 7, 12-dimethylbenz(*a*)anthracene). Silica gel for column chromatography (Davison, Grade 950, mesh 60–200) was activated by heating overnight at 100°. THF was distilled from LAH_4 and stored over CaH_2 under N_2. Li wire (Lithium Corp. of America) was wiped free of oil and washed with hexane immediately before use. Commerical EtBr was distilled before use; MeCl and MeBr were passed through a column of activated silica gel into the reaction vessel.

All reductive alkylations were carried out employing essentially the standard conditions[11] described below for reductive methylation of anthracene, unless indicated otherwise. Precautions for the exclusion

* It was concluded[20] that the Et group of X (R = Et) was equatorial through analysis of the NMR spectra of X and the corresponding hydrocarbon. However, this assignment was based on extension of the rule that axial protons of cyclohexane absorb at higher field than their equatorial counterparts. The validity of such extension is open to question, and exceptions (e.g. in the 7, 12-dihydropleiadene series) are known. Variable temperature nmr studies currently in progress in this laboratory will, it is hoped, provide more definitive evidence.

of moisture and atmospheric O_2 were scrupulously followed; ammonia was distilled into the reaction vessel through a column of BaO (10–20 mesh); all reactions were carried out under He for reasons stated earlier.[11]

Reductive methylation of anthracene. To a stirred solution of lithium (1·74 g, 25 mmole) dissolved in liquid ammonia (250 ml) was added a solution of anthracene (1·78 g, 10 mmole) in 75 ml of THF. The resulting deep reddish-brown solution was maintained at reflux for 1 hr, then methyl bromide gas was passed into the solution for 5 min; decolorization required 2 min. Evaporation of the ammonia, followed by partition of the residue between ether and water led to recovery of a white solid. Gas chromatographic analysis revealed the *cis* (78%) and *trans* (22%) isomers of 9, 10-dimethyl-9, 10-dihydroanthracene as the sole product. NMR spectra of samples trapped off the glc column matched those of the authentic compounds.[2]

Reductive ethylation of anthracene. Analogous reaction employing a solution of EtBr (27 mmole) in 10 ml of THF instead of gaseous MeBr furnished an oily solid of the composition indicated in Table 1. Trituration with EtOH, followed by recrystallization from the same solvent, provided II (R = Et) melting at 58–59°, identified by comparison of its NMR spectrum with that of the authentic *cis*-isomer.[2]

The second product, 9, 9, 10-triethyl-9, 10-dihydroanthracene, was separated from residual *cis*-diethyl compound by preparative GLC and similarly identified by NMR spectroscopy in comparison with a previously prepared sample.[2]

Reductive isopropylation of anthracene. Similar reaction took place with i-PrCl (5 ml), except that color persisted 1 hr after addition of the halide. The oily product, which consisted of three components (Table 1), solidified upon standing. Trituration with MeOH, followed by recrystallization from alcohol, provided II (R = i-Pr) melting at 72–74°; NMR τ 6·18 (d, 2, benzylic, J = 5 Hz); τ 9·02 (d, 12, Me, J = 7·5 Hz); as well as the appropriate numbers of protons in the aryl and methine regions. 9, 10-Diisopropyl-9, 10-dihydroanthracene of uncertain stereochemistry, but closely similar m.p., has been reported by several authors.[7,9,21] Found: C, 90·90; H, 9·08. Calc. for $C_{20}H_{24}$: C, 90·85; H, 9·15%).

Reductive t-butylation of anthracene. The red color faded completely 15 min after the addition of t-BuBr (5 ml). GLC on a 6 ft SE-30 column at 170° indicated the presence of the components in Table 1; retention times matched those of the authentic compounds. Recrystallization from MeOH provided 9, 10-dihydroanthracene (48%); NMR τ 6·12 (4, s, CH_2). The NMR spectrum of 9-t-butyl-9, 10-dihydroanthracene isolated from the GLC column corresponded in detailed with that reported by Carruthers and Hall.[22]

Reductive methylation of 9, 10-dimethylanthracene. GlC analysis of the product of reductive methylation of 9, 10-dimethylanthracene[2] with Li and MeBr indicated the presence of 9, 9, 10, 10-tetramethyl-9, 10-dihydroanthracene (81%) and 9, 9, 10-trimethyl-9, 10-dihydroanthracene (19%). Recrystallization from EtOH provided the tetramethyl compound (65%) as white flakes, m.p. 167–168·5° (lit.[23] 170–171·5°); NMR τ 8·32 (s, 12, Me; τ 2·75 (m, 4, β-aryl); τ 2·50 (m, 4, α-aryl). (Found: C, 91·49; H, 8·60. Calc for $C_{18}H_{20}$: C, 91·47; H, 8·53%).

Reductive methylation of 1, 4-dimethylanthracene. 1, 4-dimethylanthracene was synthesized by the method of Mosby[24] from γ-valerolactone and tetralin. Reductive methylation with Li and MeBr provided an oil containing four components according to GLC analysis. No attempt was made to characterize the three minor substances (3%, 10% and 7%); presumably those are 1, 4-dimethyl-9, 10-dihydroanthracene and its 9-monomethyl and 9, 9, 10-trimethyl derivatives. The major product (80%), obtained by preparative GLC, was identified as 1, 4, 9, 10-tetramethyl-9, 10-dihydroanthracene: m.p. 97–98°; NMR τ 8·52 (d, 6, $CHC\underline{H}_3$, J = 7 Hz); 7·60 (s, 6, CH_3); 5·79 (q, 2, CH, J = 7 Hz); 3·02 (s, 2, aryl); 2·77 (s, 4, aryl). (Found: C, 91·22; H, 8·71. Calc. for $C_{18}H_{20}$: C, 91·45; H, 8·74%).

Reductive methylation of benz(a)anthracene. Trituration of the crude product with EtOH provided *cis*-7, 12-dimethyl-7, 12-dihydrobenz(*a*)anthracene (m.p. 103–104·5°; 1·20 g from 2·28 g of benz(*a*)anthracene). Recrystallization from EtOH provided the analytical sample, m.p. 106–107°; (NMR τ 8·37 (d, 3, Me, J = 7 Hz); 8·40 (d, 3, Me, J = 7 Hz); 5·77 (q, 1, CH, J = 7 Hz); 5·17 (q, 1, CH, J = 7 Hz). Mikhailov reported[25] synthesis of two isomeric 7, 12-dimethyl-7, 12-dihydrobenz(*a*)anthracenes, m.p. 91·5–92·5 and 109–110°, respectively. A dimethyldihydrobenz(*a*)anthracene corresponding to the lower melting isomer was recently obtained through lithium-ammonia reduction of 7, 12-dimethylbenz(*a*)-anthracene;[2] the *trans* structure was assigned on the basis of the demonstrated *trans* specificity of this reaction under the conditions employed.[2] Accordingly, the *cis* structure may be assigned to the higher melting isomer. (Found: C, 93·04; H, 7·24. Calc. for $C_{20}H_{18}$: C, 92·98; H, 7·02%).

Reductive methylation of dibenz(a, h)anthracene. The crude product was dissolved in a minimum volume of hot EtOAc, treated with charcoal and concentrated to 25 ml. EtOH (25 ml) was gradually added after crystallization to increase the quantity of ppt. The product (m.p. 215–216·5°; 1·38 g from 2·6 g of dibenz-

(*a*, *h*)anthracene) was identified as VI: NMR τ 8·32 (d, 6, Me, J = 7·5 Hz); 5·08 (q, 2, CH, J = 7·5 Hz). (Found: C, 93·46; H, 6·51. Calc. for $C_{22}H_{20}$: C, 92·91; H, 7·09%).

REFERENCES

[1] This investigation was supported in part by Public Health Service Grant CA-08674 from the National Cancer Institute.
[2] Part IV: R. G. Harvey, L. Arzadon, J. Grant and K. Urberg, *J. Am. Chem. Soc.* **91**, 4535 (1969).
[3] A. Streitweiser, Jr., *Molecular Orbital Theory for Organic Chemists* p. 425. Wiley, New York, N.Y. (1961).
[4] H. Smith, *Organic Reactions in liquid Ammonia* Vol. 1, Part 2. Wiley, New York, N.Y. (1963).
[5] W. Hückel and R. Schwen, *Chem. Ber.* **89**, 481 (1956).
[6] W. Hückel and J. Wolfering, *Leibigs Ann.* **686**, 34 (1965); W. Hückel and M. Wartini, *Ibid.* 40 (1965).
[7] B. M. Mikhailov and A. N. Blokhina, *Izv. Akad. Nauk SSSR, Ser. Khim.* 164 (1949); *Chem. Abstr.* **44**, 2962 (1950).
[8] G. M. Badger, M. L. Jones and R. S. Pearce, *J. Chem. Soc.* 1700 (1950).
[9] R. Gerdil and E. A. Lucken, *Helv. Chim. Acta* **44**, 1966 (1961).
[10] A. D. Petrov, E. P. Kaplan, Z. I. Letina and I. P. Egorov, *Zh. Obshch. Khim.* **28**, 608 (1958); *Chem. Abstr.*, **52**, 17169 (1958); I. P. Egorov, E. P. Kaplan, Z. I. Letina, V. A. Shliapochnikov and A. D. Petrov, *J. Gen. Chem. USSR* **28**, 3284 (1958).
[11] R. G. Harvey and K. Urberg, *J. Org. Chem.* **33**, 2206, 2570 (1968); R. G. Harvey, *Ibid.* **32**, 238 (1967).
[12] R. G. Harvey and M. Halonen, *J. Chromatog.* **25**, 294 (1966).
[13] A. H. Beckett and R. G. Lingard, *J. Chem. Soc.* 2409 (1959).
[14] L. M. Jackman and J. W. Lown, *Ibid.* 3776 (1962).
[15] G. F. White, A. B. Morrison and E. G. Anderson, *J. Am. Chem. Soc.* **46**, 961 (1924).
[16] R. G. Harvey and C. C. Davis, *J. Org. Chem.* **34**, in press (1969).
[17] D. E. Paul, D. Lipkin and S. Weissman, *J. Am. Chem. Soc.* **78**, 116 (1956).
[18] D. Magereson and J. P. Newport, *Trans. Faraday Soc.* **59**, 2058 (1963).
[19] T. L. Brown, *Accounts Chem. Res.* **1**, 23 (1968).
[20] D. Nicholls and M. Szwarc, *J. Am. Chem. Soc.* **88**, 5757 (1966).
[21] E. C. Kooijman and A. Strong, *Rec. Trav. Chim.* **72**, 329 (1953).
[22] W. Carruthers and G. Hall, *J. Chem. Soc.* (B) 861 (1966).
[23] B. Mikhailov and T. K. Kozminskaya, *Dokl. Akad. Nauk SSSR* **58**, 811 (1947).
[24] W. Mosby, *J. Org. Chem.* **18**, 964 (1953).
[25] B. Mikhailov, *Izv. Akad. Nauk SSSR, Ser. Khim.* 619 (1946).